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Dyadic Study of Depression on Inflammation and Diurnal Cortisol Variation in Cancer Patients and Caregivers

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DYADIC STUDY OF DEPRESSION ON INFLAMMATION AND DIURNAL CORTISOL VARIATION IN CANCER PATIENTS AND CAREGIVERS

By

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Both cancer patients and their informal family caregivers develop chronic diseases earlier and more frequently than those who have not been affected by cancer. Elevated depressive symptoms, which are easily measureable and modifiable, have been linked to inflammation, dysregulated HPA axis functioning, and physical health decline in both cancer patients and healthy persons. Further, studies have shown patients' and caregivers' depressive symptoms to be correlated, and that patients' distress relates to their caregivers' poorer health, and vice versa. While it is known that one's own depressive symptoms are a risk factor for one's own inflammation and HPA axis dysregulation, and patients' depressive symptoms are a risk factor for caregivers' depressive symptoms (and vice versa), yet unknown is to what extent patients' depressive symptoms may serve as a risk factor for their caregivers' inflammation and HPA axis dysregulation, and vice versa.

In this project, a dyadic biopsychosocial model accounting for interdependence between patients' and caregivers' psychological and physiological health was proposed to fill these gaps. Data were analyzed from 84 cancer patients and 86 caregivers (81 dyads) who participated in this study around three months following the patients' cancer diagnosis. Participants reported depressive symptoms using the Center for Epidemiological Studies-Depression (CES-D) and provided blood and saliva samples for

stress biomarkers. Blood samples were analyzed to measure levels of two pro-inflammatory markers: interleukin (IL)-6 and C-reactive protein (CRP). Three saliva samples per day were taken on two consecutive days for salivary cortisol slope values. Actor-Partner Interdependence Modeling (APIM) using Structural Equation Modeling (SEM) was used to test study hypotheses.

It was hypothesized that cancer patients and their caregivers would show positively correlated depressive symptoms and stress biomarkers, which was supported for cortisol slope values only (Unstandardized estimate = 0.001, 95% CI [0 – 0.002], p = .03). It was further hypothesized that patients' and caregivers' depressive symptoms would be positively associated with both their own and their partners' stress biomarkers, after controlling for covariates of age, BMI, and sex (and patients' cancer treatment status and stage for patients only). These hypotheses were unsupported, but ability to test these hypotheses was limited by low power. Exploratory hypotheses posited that somatic depressive symptoms would be more strongly associated with own stress biomarkers, but these hypotheses were not supported.

This study remains an important first test of the dyadic biopsychosocial model of psychological and physiological health of cancer patients and their caregivers. Interdependence among patients' and caregivers' physiology underscores the importance of not only studying patients and caregivers as a unit, but treating these partners as a unit as well, to ensure optimal health outcomes among both patients and their families.

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Chapter 1. Introduction

Biopsychosocial models have shown that stressors produce psychological distress, which then can produce a physiological stress response that increases risk for physical morbidity over time. These models have tended to examine the association between psychological and physiological stress within a single individual; however, evidence has accumulated suggesting that when two people face a shared stress, these people may impact one another's psychological distress and physical morbidity. This interdependence among psychological and physical health has been documented among patients and caregivers of chronic illness, with cancer as one disease where this relationship has been found. Therefore, the current project proposes a new dyadic biopsychosocial model linking psychological risk factors with physiological morbidity among chronically ill patients and their caregivers that accounts for the interdependence of patients' and caregivers' psychological and physical health outcomes.

In support of a dyadic biopsychosocial model, first, the biopsychosocial model of how stress predicts disease at an individual level will be reviewed, with emphasis on the physiological stress responses of the immune system and hypothalamic-pituitary-adrenal (HPA) axis. Next, depressive symptoms will be reviewed as a link between stress and physiological stress responses, with evidence presented for both cancer patients and informal cancer caregivers. Finally, the interdependence between cancer patient and caregiver psychological and physical health outcomes is shown. To conclude, hypotheses testing the mutual influence between cancer patients' and their caregivers' depressive

symptoms and biological outcomes are presented as a first test of the dyadic biopsychosocial model.

Behavioral Medicine: From Intrapersonal to Interpersonal Mechanisms

Emotions were recognized as a critical determinant of physical health as early as Hippocrates c. 500 BCE and Galen c. 200 AD (Sternberg, 1997). However, philosophies of the Christian church, mind-body dualism, and reductionism contributed to the Western biomedical model that predominated from the 19th and mid-20th centuries, which shunned the idea that "psychosocial elements of human malfunction" could contribute to "the organic elements of disease" (Engel, 1977; RF Illustrated 1976). This restrictive model failed to account for phenomena linking psychological factors with medical outcomes, such as the association between neuroticism and flare-ups of rheumatoid arthritis (Solomon & Moos, 1964). Thus, through the late 20th century, support rose for a biopsychosocial model of disease, which better accounted for the complex relationship "between health and disease, [which is] diffused by cultural, social, and psychological considerations" (p. 132, Engel, 1977). The biopsychosocial model posits that psychological stress impacts disease outcomes directly through stimulating a physiological stress response and indirectly through activating psychological distress, which in turn also impacts physiological reactions directly and indirectly through altered health behavior (see Figure 1; Adler & Matthews, 1994; Cohen & Herbert, 1996).

Vast evidence has been accumulated to support the interaction between psychological, behavioral, neurological, endocrine, and immune processes, codifying the scientific discipline of behavioral medicine (Ader, Cohen, & Felten, 1995; Cohen &

Herbert, 1996; Irwin, 2008; Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002; Maier, Watkins, & Fleshner, 1994). At the individual level for a patient with chronic disease, it is appreciated that the patient's physical and psychological health interact: disease exerts pressures on one's body and environment (e.g., relationships, finances), and stress feeds back to promote disease. More recently, research has begun to examine the well-being of the family and friends within the patients' shared social environment, who provide assistance to the patient in coping with disease. The burgeoning field of chronic illness caregiving has accumulated evidence demonstrating that caregiving burden can lead to negative health consequences for the caregivers (Ji, Zöller, Sundquist, & Sundquist, 2012; Lee, Colditz, Berkman, & Kawachi, 2003; Pinquart & Sörensen, 2003; Pinquart & Sörensen, 2007; Schulz & Beach, 1999; Vitaliano et al., 2002; Vitaliano, Zhang, & Scanlan, 2003).

With evidence of the interaction between psychology and physiology, Ader and colleagues (1995) concluded that "what have been considered separate systems can be considered components of a single, integrated defense mechanism in which the interaction *between* systems is as important to an understanding of adaptation as the interactions *within* a system" (italics added; p. 102). However, most research on the interaction between systems, has been limited to *intrapersonal* processes, which fails to account for emerging evidence showing the *interdependence between* chronically ill patients' and their caregivers' psychological reactions and physical morbidity. Within the context of cancer, it has been shown that cancer patients and caregivers react as an "emotional system" to the disease (Berg & Upchurch, 2007), and the distress of one partner has been shown to affect the other partner's physical functioning (Kim, et al.,

2008a; Kim et al., 2015a; Kim, Wellisch, & Spillers, 2008b). This suggests that patients' and caregivers' psychological and physical morbidities are interdependent. Therefore, an interdependent biopsychosocial model of patient and caregiver morbidity is proposed, integrating an individual-level biopsychosocial disease model with important interpersonal determinants of physical health (see Figure 2). To begin, evidence supporting the impact of stress on physiology (see Figures 1 and 2, path A) will be reviewed.

The Physiological Stress Response

"Stress" has been defined broadly as the non-specific bodily response to demand, whether the demand is physical or psychological in nature (Selye, 1993). When a demand is perceived, the "fight or flight" physiological response is activated. This physiological stress response is designed to protect the body under life-threatening situations, by maintaining homeostasis through mobilizing energy stores and protecting the body against pathogenic invasion, tissue damage, and tumor development (Segerstrom & Miller, 2004). One pathway producing these protections is the sympathetic nervous system (SNS), which stimulates the immune and endocrine systems. When a stressor is perceived, the SNS innervates lymphoid tissues through catecholamines (Felten & Felten, 1991), stimulating the release of immune cells, which fight infection and repair tissue damage, as well as pro-inflammatory cytokines, which are immunomodulary messenger proteins that help contain bodily damage and further activate immune cells (Miller, Maletic, & Raison, 2009). The SNS also activates the endocrine system by innervating the paraventricular nucleus (PVN) of the hypothalamus to secrete corticotropin releasing factor, which stimulates the anterior pituitary gland to release adrenocorticotropin.

Adrenocorticotropin then circulates through the blood stream to prompt the adrenal gland to synthesize glucocorticoids, like cortisol. Cortisol serves two primary functions: first, to mobilize energy stores to sustain the "fight-or-flight" response; second, to downregulate the immune response (Hasler, Drevets, Manji, & Charney, 2004; Yehuda, 2002).

In a healthy, acute response to stress, a negative feedback loop exists between pro-inflammatory cytokines and cortisol—along with the SNS, pro-inflammatory cytokines also stimulate PVN to activate the HPA axis to release cortisol, thus restoring inflammatory homeostasis (Chrousos, 1995; Dentino et al., 1999; Maes et al., 1993). Cortisol also suppresses inflammation by directly communicating with immune cells to downregulate their activity (Chrousos, 1995; Elenkov & Chrousos, 2002). Endocrine homeostasis is achieved through a negative feedback loop of cortisol on the HPA axis system: cortisol downregulates the release of corticotropin releasing factor, thus reducing release of glucocorticoids downstream (Chrousos, 1995; Dentino et al., 1999; Maes et al., 1993).

Chronic activation of the physiological stress response, however, impairs these control mechanisms and leads to unchecked inflammation and HPA axis dysregulation (Segerstrom & Miller, 2004). When chronically exposed to cortisol, immune cells develop resistance to the control of glucocorticoids (Miller, Cohen, & Ritchey, 2002; Miller et al., 2008). Pro-inflammatory cytokines also contribute to glucocorticoid resistance by directly disrupting glucocorticoid receptors on immune cells (Miller, Pariante, & Pearce, 1999). Inflammation goes unchecked without glucocorticoid restraint, and this chronic inflammation then continuously activates the HPA axis resulting in hypercotisolemia, or persistently elevated cortisol levels (Chrousos, 1995; Elenkov &

Chrousos, 2002). As cortisol has neurotoxic effects on hippocampal cells (Sapolsky, Uno, Rebert, & Finch, 1990), chronically elevated cortisol damages hippocampal neurons associated with the glucocorticoid negative feedback system, further contributing to HPA axis dysregulation (Halbreich, Asnis, Zumoff, Nathan, & Shindledecker, 1984; Kling et al., 1991; Van Cauter, Leproult, & Kupfer, 1996). Therefore, the chronically activated physiological stress response causes a pathological positive feedback loop of hypercortisolemia and elevated inflammation, leading to increased risk for morbidity (see Figures 1 and 2, path B; Checkley, 1996; Segerstrom & Miller, 2004).

Inflammation produces disease. Pro-inflammatory cytokines have been described as a "double-edged sword" (Hodge, Hurt, & Farrar, 2005): under acute stress conditions, inflammation contains damage from pathogens, tumors, and tissue damage (Glaser et al., 1999; Maier et al., 1994). However, when perpetually elevated, pro-inflammatory cytokines and their downstream products increase one's risk for development and progression of disease, including atherosclerosis (Libby, Ridker, & Maseri, 2002; Di Napoli, Di Gianfilippo, Sollecito, & Bocola, 2000); coronary heart disease (Danesh et al., 2004); and cancers of the colon, lung, and breast (Helzlsouer, Erlinger, & Platz, 2006). The pathological effects of two particular pro-inflammatory markers have been well-documented: pro-inflammatory cytokine interleukin-6 and acute phase protein C-reactive protein.

Interleukin-6. The pro-inflammatory cytokine interleukin (IL)-6 is one of the strongest initiators of the inflammatory response, and is primarily responsible for rallying the acute phase response to pathogen invasion. IL-6 also is the strongest cytokine stimulator of the HPA axis: persons with high IL-6 show less cortisol diurnal variation

and higher cortisol levels overall (Dentino et al., 1999; Desantis et al., 2012). IL-6 contributes to hypertension and insulin resistance by impairing dilation of veins (Bhagat & Vallance, 1997; Chae, Lee, Rifai, & Ridker, 2001) and arteries (Hingorani et al., 2000), as well as reducing efficacy of lipoprotein lipase to store circulating fats (Greenberg et al., 1992; McCarty, 1999). These mechanisms promote the metabolic syndrome (Black, 2003), cardiovascular disease (Shlipak, Ix, Bibbins-Domingo, Lin, & Whooley, 2008; Yudkin, Kumari, Humphries, & Mohamed-Ali, 2000), and type II diabetes mellitus (Pradhan, Manson, Rifai, Buring, & Ridker, 2001). IL-6 above 3.19 pg/mL has been shown to predict doubled mortality risk among elderly persons relative to those among the lowest quartile of the cytokine (Harris et al., 1999).

IL-6 has also been implicated in the pathogenesis and progression of cancer (Grivennikov, Greten, & Karin, 2010; Hodge et al., 2005; Nilsson, Langley, & Fidler, 2005). As part of the non-specific, first-line of immune defense, pro-inflammatory cytokines confer protection to host body and immune cells against the lethal byproducts of the innate immune attack. However, tumors produce their own IL-6 to capitalize on the protective qualities of this pro-inflammatory cytokine (Galizia et al., 2002). IL-6 then contributes to tumor growth through promoting tumor vascularization (Nilsson et al., 2005) and protecting tumor cells against apoptosis (Hodge et al., 2005).

C-reactive protein. IL-6 also contributes to the development of chronic medical conditions through the activation of the hepatic acute phase response, stimulating the synthesis and release of the acute phase protein C-reactive protein (CRP; Black, Kushner, & Samols, 2004; Wilson, Ryan, & Boyle, 2006; Yudkin et al., 2000). CRP contributes to the development and progression of atherosclerotic plaques through recruitment of

monocytes and transformation of monocytes to foam cells through encouraging their uptake of low-density lipoprotein (de Ferranti & Rifai, 2007; Torzewski et al., 1998; Wilson et al., 2006). Due to its atherosclerotic and inflammatory effects, elevated CRP (≥3 mg/L; Bassuk, Rifai, & Ridker, 2004) is one of the strongest predictors of future cardiovascular disease and events (Danesh et al., 2004; de Ferranti & Rifai, 2007; Kuller, Tracy, Shaten, & Meilahn, 1996; Li & Fang, 2004; Ridker & Cook, 2004; Ridker, Hennekens, Buring, & Rifai, 2000; Shlipak et al., 2008), stroke (Di Napoli, Papa, & Bocola, 2001), peripheral artery disease (Ridker, Stampfer, & Rifai, 2001), type II diabetes mellitus (Freeman et al., 2002; Pradhan et al., 2001), and cancer incidence (Helzlsouer et al., 2006; Siemes et al., 2006) and recurrence (Wethal et al., 2010). Elevated CRP has also been associated with 50 percent greater all-cause mortality among the elderly, and elderly persons expressing both elevated IL-6 and CRP are 2.6 times more likely to die than those with low levels of inflammation (Harris et al., 1999).

HPA axis dysregulation produces disease. Cortisol increases in response to physiological and psychological stressors—healthy persons show an efficient spike and decline in cortisol from acute stressors (Adam, Hawkley, Kudielka, & Cacioppo, 2006; Burke, Davis, Otte, & Mohr, 2005; Chrousos & Gold, 1992; Dickerson & Kemeny, 2004). Among healthy persons, cortisol also shows a diurnal rhythm, with levels high in the morning (peaking 30 to 40 minutes after waking, the "cortisol awakening response"; Pruessner et al., 1997) and decreasing through the day (Kirschbaum & Hellhammer, 1989; Posener, Schildkraut, Samson, & Schatzberg, 1996; Stone et al., 2001). Among healthy adults, average waking salivary cortisol has been estimated at approximately 18

nmol/l, dropping to approximately 4 nmol/L on average by evening hours (Kirschbaum & Hellhammer, 2000).

Consequences of hypercortisolemia include: increased blood pressure through promotion of vasoconstrictor systems and salt retention and inhibition of vasodilatory systems, and insulin resistance through promotion of visceral fat cell growth, dyslipidemia, and impaired glucose disposal (Brown, Varghese, & McEwen, 2004; Chrousos & Gold, 1998). Through these physiologic changes, elevated cortisol levels have been shown to predict coronary atherosclerosis (Matthews, Schwartz, Cohen, & Seeman, 2006; Troxler, Sprague, Albanese, Fuchs, & Thompson, 1977) and acute myocardial infarction (Pereg et al., 2011), as well as increasing risk for hypertension, diabetes, and cancer (Björntorp & Rosmond, 1999). Flatter cortisol slopes and elevated overall cortisol levels due to unresponsive glucocorticoid negative feedback systems have also been associated with cognitive dysfunction (Lupien et al., 1998), cardiovascular disease incidence and complications (Nijm & Jonasson, 2009; Otte et al., 2004), and osteoporosis risk (Raff et al., 1999). Within cancer patients, low cortisol diurnal variation predicts mortality (Cohen et al., 2012; Sephton, Sapolsky, Kraemer, & Spiegel, 2000).

Utility of studying multiple biomarkers of the physiological stress response. IL-6, CRP, and diurnal cortisol variation each provide unique information about the physiological stress response, contributing to a broad risk profile to identify which persons may be at greatest risk for health decline. IL-6 and CRP are markers of inflammation, whereas diurnal variation and overall level of cortisol provides information about the endocrine system functioning. Although both inflammatory, IL-6 and CRP mark different phases of the inflammatory process: IL-6 initiates the inflammatory

response whereas CRP is a byproduct of it (Black et al., 2004). IL-6, CRP, and cortisol all influence the development of chronic diseases such as cardiovascular diseases and cancers through different biological mechanisms (Antoni et al., 2006; Lutgendorf, Sood, & Antoni, 2010; Yudkin et al., 2000) and have shown different change trajectories in cancer caregivers during the year following their patients' cancer diagnosis (Rohleder, Marin, Ma, & Miller, 2009). Information on IL-6, CRP, and cortisol together provides a better understanding of risk associated with endocrine and immune dysregulation relative to examining any single biomarker alone (Harris et al., 1999). Therefore, studying each of these stress biomarkers will provide a more comprehensive view of the role of psychological risk factors for physical health decline in cancer patients and their caregivers.

The evidence reviewed above described the physiological stress response, and how chronic psychological stress leads to increased risk for medical morbidity through dysregulation of the immune system and HPA axis, leading to elevated inflammation and hypercortisolemia (see Figures 1 and 2, paths A and B). Another pathway by which stress impacts the physiology is through the aggravation of psychological distress. One psychological state strongly influenced by stress is *depression* (see Figures 1 and 2, path C), which itself has been well-linked with physical disease outcomes through its impacts on the physiological stress response (see Figures 1 and 2, paths D and B).

Depressive Symptoms and the Physiological Stress Response

Depressive symptoms are among the most extensively studied psychological factors contributing to immune health decline and resultant increased risk for developing

major diseases, such as cardiovascular disorders (Abramson, Berger, Krumholz, & Vaccarino, 2001; Lett, Ali, & Whooley, 2008; Yusuf et al., 2004). Symptoms of depression include marked sadness and loss of interest in previously enjoyed activities, as well as disturbance of appetite and sleep, psychomotor agitation or retardation, fatigue, impaired concentration, low self-esteem, and suicidal ideation (American Psychiatric Association, 2013). Studies on depressive symptom associations, course, treatment response, and physical effects suggest these symptoms cluster into somatic symptoms (e.g., psychomotor changes, fatigue, and weight changes) and cognitive/affective symptoms (e.g., low self-esteem, guilt, and disturbed concentration; Bus et al., 2011; Capuron et al., 2002; Capuron et al., 2009; Schacht, Gorwood, Boyce, Schaffer, & Picard, 2014). Point prevalence of Americans suffering from significantly elevated and impairing depressive symptoms, a condition known as major depressive disorder, is approximately six to seven percent (Kessler et al., 2005; Reeves et al., 2011), although rates vary by sex, age, race, socioeconomic status, and geographic region (Simon, Fleck, Lucas, & Bushnell, 2004).

Stress predicts depressive symptoms. Stressful life events have been causally linked to onset of significant depressive symptoms (see Figures 1 and 2, path C; Kendler, Karkowski, & Prescott, 1999; Hammen, 2005). Although most people do not become depressed when facing a negative life event, most episodes of elevated depressive symptomatology are preceded by stressful events. In a survey of healthy persons compared to persons diagnosed with major depressive disorder, stressful life events were 2.5 times more prevalent among depressed persons, and four of five depressive episodes were preceded by a stressful life event (Mazure, 1998). As receipt of a chronic and/or

life-threatening illness is considered a stressful life event (Cella, Mahon, & Donovan, 1990; Dew, 1998), it is understandable that a disproportionately high prevalence of depression has been documented among persons with chronic medical conditions. The prevalence of major depressive disorder is two to three times greater among adults with cancer (Hodges, Humphris, & Macfarlane, 2005; Massie, 2004; Rasic, Belik, Bolton, Chochinov, & Sareen, 2008; Spiegel, 1996), as well as those with hypertension, diabetes mellitus, coronary artery disease, congestive heart failure, stroke/cerebrovascular incidents, chronic obstructive pulmonary disease, end stage renal disease (Egede, 2007).

Depressive symptoms predict disease. Depressive symptoms have been associated with both disease onset and course. Among healthy persons, numerous well-controlled and prospective investigations have linked depressive symptomatology with development of cancer (Ershler & Keller, 2000; Gross, Gallo, & Eaton, 2010; Linkins & Comstock, 1990; Penninx et al., 1998), coronary heart disease (Glassman & Shapiro, 1998; Lett et al., 2008; Nemeroff & Goldschmidt-Clermont, 2012; Pratt et al., 1996; Surtees et al., 2008; Whang et al., 2009), peripheral artery disease (Grenon et al., 2012), heart failure (Abramson et al., 2001; Joynt, Whellan, & O'Connor, 2004; van den Broek et al., 2011), heart attack (Yusuf et al., 2004), stroke (Pan, Sun, Okereke, Rexrode, & Hu, 2011), and diabetes (Knol et al., 2006; Mezuk, Eaton, Albrecht, & Golden, 2008; Renn, Feliciano, & Segal, 2011), as well as general physical decline (Penninx, Leveille, Ferrucci, Van Eijk, & Guralnik, 1999) and all-cause mortality (Herrmann et al., 1998). Among those with pre-existing disease, depressive symptoms have been associated with poorer disease outcomes. Elevated depressive symptoms have been associated with mortality and disease progression in cancer (Pinquart & Duberstein, 2010; Satin, Linden,

& Phillips, 2009), additional cardiovascular events after heart attack (Frasure-Smith, Lespérance, & Talajic, 1995), poorer cardiovascular outcomes among patients with coronary heart disease (Barth, Schumacher, & Herrmann-Lingen, 2004; Van Melle et al., 2004), higher mortality and secondary coronary events after heart failure (Rutledge, Reis, Linke, Greenberg, & Mills, 2006), mortality after stroke (Williams, Ghose, & Swindle, 2004), and greater diabetes complications (De Groot, Anderson, Freedland, Clouse, & Lustman, 2001).

Depressive symptoms predict the physiological stress response directly. Depression and medical morbidity are associated in a complex, bi-directional relationship between depression and the physiological stress response (Haapakoski, Mathieu, Ebmeier, Alenius, & Kivimäki, in press; Howren, Lamkin, & Suls, 2009; Stewart, Rand, Muldoon, & Kamarck, 2009). Depression both directly stimulates inflammation and the HPA axis (see Figures 1 and 2, path D) and indirectly stimulates these systems through increasing risk for poor lifestyle factors (see Figures 1 and 2, paths E). Pro-inflammatory cytokines and cortisol feed back to aggravate depressive symptoms by directly acting upon the central nervous system. This positive feedback loop between depression and the physiological stress response heightens risk for developing medical illnesses. To this end, depression has come to be seen as a disease of dysfunctional stress response (Sternberg, Chrousos, Wilder, & Gold, 1992), with chronic inflammation (Haapakoski et al., in press; Howren et al., 2009) and elevated cortisol (Gillespie & Nemeroff, 2005) as hallmarks of this disease.

Extensive evidence links depressive symptoms to elevated inflammation, marked by increased production and circulating levels of pro-inflammatory cytokine IL-6 and its

downstream product CRP (see Haapakoski et al., in press; Howren et al., 2009; and Maes et al., 2009 for reviews). Depressive symptoms diminish parasympathetic nervous system activity (Carney et al., 2005; Thayer, Smith, Rossy, Sollers, & Friedman, 1998), which downregulates inflammation (Tracey, 2002; Sajadieh et al., 2004; Sloan et al., 2007). Depressive symptoms also chronically activate the sympathetic-adrenal-medulla axis to release norepinephrine and epinephrine (Hughes, Watkins, Blumenthal, Kuhn, & Sherwood, 2004; Grossman & Potter, 1999; Mausbach et al., 2005), hormones that promote release of pro-inflammatory cytokines (Mohamed-Ali et al., 2001; Papanicolaou et al., 1996).

Depressive symptoms also contribute to elevated inflammation through their effects on HPA axis dysregulation, which leads to immune dysregulation through glucocorticoid resistance at both the hippocampal and immune cellular levels. Both clinically significant and subthreshold levels of persistent depressive symptoms chronically activate the HPA axis, with hypercortisolemia a well-documented biological feature of depression (Dinan, 1994; Plotsky, Owens, & Nemeroff, 1998; Posener et al., 2000; van Eck, Berkhof, Nicolson, & Sulon, 1996; Vreeburg et al., 2009). Individuals with major depression also show 'flattened' cortisol patterns: depressed persons show little diurnal variation in cortisol levels across the day (Stetler, Dickerson, & Miller, 2004) and blunted cortisol responses to stressors (Burke et al., 2005; Peeters, Nicholson, & Berkhof, 2003).

Longitudinal studies suggest that depressive symptoms produce dysregulations in the physiological stress response, with somatic depressive symptoms rather than cognitive/affective symptoms showing the strongest predictive effects. Stewart et al.

(2009) first investigated the longitudinal relationships between both cognitive and somatic depressive symptoms with IL-6 and CRP. With both cognitive and somatic symptoms combined, baseline depressive symptoms predicted change in the pro-inflammatory cytokine IL-6 across a six-year follow-up, even while controlling for known demographical, biological, and lifestyle factors. Of note, when analyses were split by depressive symptom cluster, somatic, but not cognitive, symptoms remained a significant predictor of increased inflammation (Stewart et al., 2006). Additional studies support that somatic depressive symptoms primarily drive the association between depression and both concurrent and later elevated inflammation (Copeland, Shanahan, Worthman, Angold, & Costello, 2012; Duivis, Vogelzangs, Kupper, de Jonge, & Penninx, 2013; Kupper, Widdershoven, & Pedersen, 2012), while inflammation predicts later onset of cognitive/affective depressive symptoms (Capuron et al., 2002; Gimeno et al., 2009; Kiecolt-Glaser et al., 2003).

Depression predicts the physiological stress response indirectly through health behaviors. Symptoms of depression, such as diminished interest in activities, low motivation, fatigue, cognitive difficulties, and sleep and appetite alterations also increase risk for poor health behaviors, which themselves contribute to immune dysfunction (see Figures 1 and 2, paths E; Bonnet et al., 2005; Groesz et al., 2012; Kiecolt-Glaser & Glaser, 1988). Poor health behaviors shown to be higher among depressed persons that are associated with elevated inflammation include: physical inactivity (Azevedo Da Silva et al., 2012; Barbour & Blumenthal, 2005; Katon et al., 2010; Whooley et al., 2008), obesity (Faith, Matz, & Jorge, 2002), smoking (Lasser et al., 2000; Whooley et al., 2008; Wulsin, Vaillant, & Wells, 1999), medication non-adherence (Gehi, Haas, Pipkin, &

Whooley, 2005; Rieckmann et al., 2006), poor diet (Kinder, Kamarck, Baum, & Orchard, 2002; Ziegelstein et al., 2000) and social isolation (Barefoot et al., 2003). These poor health behaviors therefore also partially contribute to increased morbidity risk.

The physiological stress response aggravates depressive symptoms. Inflammation and HPA axis dysregulation, both byproducts of the physiological stress response, promote depressive symptoms (see Figures 1 and 2, path F). Pro-inflammatory cytokines directly impact neurobiological mechanisms related to depression by reinforcing HPA axis dysfunction and hampering neurotransmitter metabolism within the brain, creating a positive feedback loop between depression and inflammation (Raison, Capuron, & Miller, 2006). Evidence from animal models suggests that pro-inflammatory cytokines access the brain directly by leaking through or active transport across the blood-brain barrier. Pro-inflammatory cytokines can also indirectly affect the brain by stimulating cells along the cerebral arteries that in turn produce inflammation within the brain, as well as stimulating peripheral afferent nerves, such as the vagus nerve (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Miller et al., 2009; Quan & Banks, 2007). Upon accessing the brain, pro-inflammatory cytokines significantly impair the metabolism of neurotransmitters such as dopamine, norepinephrine, and serotonin (Anisman, Merali, & Hayley, 2008; Felger et al., 2007), which causes symptoms of fatigue, reduced appetite, increased sleep, reduced motor activity, impaired cognition, decreased interest in one's surroundings, and increased pain sensitivity (Kent, Bluthé, Kelley, & Dantzer, 1992).

Pro-inflammatory cytokines also contribute to depressive symptoms through promotion of HPA axis dysfunction. Elevated cortisol can produce and perpetuate

depressive symptoms: corticosteroids like cortisol are able to traverse neuronal cell membranes, causing genomic changes in areas such as the hippocampus, septum, and amygdala that cause depressogenic alterations in mood, behavior, and cognition (Lewis & Smith, 1983; Pace, Hu, & Miller, 2007; Warrington & Bostwick, 2006; Wolkowitz & Reus, 1999). Long-term exposure to elevated cortisol resulting in depressive symptoms was first documented among patients with Cushing disease, a disorder marked by excess cortisol production; in this population, major depression is diagnosed in approximately two-thirds of patients (Hudson, Hudson, Griffing, Melby, & Pope Jr, 1987). Exaggerated cortisol awakening responses have also been shown to prospectively predict onset of major depressive episodes (Adam et al., 2010; Vrshek-Schallhorn et al., 2013). Evidence therefore suggests that depressive symptoms can increase release of the physiological stress response biomarkers of cortisol and pro-inflammatory cytokine release, and these biomarkers can then aggravate depressive symptoms.

Utility of depressive symptoms as a risk factor for disease development via the physiological stress response. Evidence has been reviewed that supports a bi-directional relationship between depressive symptoms and the physiological stress response: depressive symptoms, primarily the somatic cluster, produce elevated inflammation and HPA axis dysregulation through both direct and indirect pathways, and elevated inflammation and HPA axis dysregulation can feed back to produce and maintain depressive symptoms. Depressive symptoms therefore represent a useful indicator for identifying persons at elevated risk for long-term health decline and poor health outcomes, as cost-effective assessments and treatments for these symptoms are readily available.

Depressive symptoms have been suggested as the "sixth vital sign" of patient functioning (Bultz & Carlson, 2005). Depressive symptoms may be effectively assessed both quickly and cheaply (Low et al., 2009; Mitchell, 2007; Thekkumpurath, Venkateswaran, Kumar, Newsham, & Bennett, 2009), and regular depressive symptom assessment and management has been encouraged within the medical context (Nimalasuriya, Compton, Guillory, & Medicine, 2009; Orth-Gomér et al., 2005; Pignone et al., 2002). As such, depressive symptoms are an efficiently assessed indicator of risk for current and future elevated biomarkers of the physiological stress response, predicting risk for disease development or progression.

Additionally, evidence supports that when depressive symptoms are treated, the physiological stress response is mitigated. Meta-analytic findings of 22 studies showed that successful pharmacological treatment of depressed but otherwise healthy persons reduced their IL-6 (Hannestad, DellaGioia, & Bloch, 2011). Within cancer patients, those whose depressive symptoms were reduced by psychosocial interventions showed reductions in inflammation (Thornton, Andersen, Schuler, & Carson, 2009) and improved health status (Andersen et al., 2007) within the year following completion of the intervention. Both pharmacologic and psychological treatments for significantly elevated depressive symptoms have been found to be equally effective among older adults and those with medical comorbidities compared to healthy middle-aged adults (Pinquart, Duberstein, & Lyness, 2006). Addition of psychosocial treatment for depression to regular medical care has shown improved clinical outcomes at costs no greater than usual care (Katon et al., 2006), and as well as showing broad effects on improving a person's

overall quality of life (Costa, Mogos, & Toma, 1985; Ishak et al., 2011; Nicolau, Rivera, Francés, Chacártegui, & Masmiquel, 2013; Swenson et al., 2003).

In the above sections, evidence has been reviewed that supports the biopsychosocial model of disease development and progression at the individual level. First, it was shown how perceived stress contributes to disease through the physiological stress response, both directly and indirectly through depressive symptoms. Evidence was next presented supporting depressive symptoms as a useful indicator of long-term health decline, due to their associations with the physiological stress response and its regular assessment and treatment within the medical setting. In the sections to follow, research will be reviewed that suggests the biopsychosocial models linking psychological and physical health at the individual level are insufficient in the context of chronic illness, as they fail to account for interpersonal factors between patients and their informal caregivers. This argument will be presented using the disease model of cancer.

The Psychology and Physiology of Cancer

Approximately 1 in 2 men and 1 in 3 women will develop cancer over the course of their lifetimes, with approximately 1,665,540 new diagnoses expected in 2014 alone (American Cancer Society, 2014). Although the five-year relative survival rate for all cancers has increased by almost 40 percent since 1975, cancer remains the second most common cause of death in the United States (Howlader et al., 2013). As such, receipt of a cancer diagnosis can be a traumatic event, triggering intense emotional reactions (See Figures 1 and 2, path G). Risk for major depression is approximately three times greater for persons with cancer compared to those without cancer: compared to the general

population one-month point prevalence of approximately five percent, the prevalence of major depression among cancer patients in active treatment and advanced cancer patients is approximately 15 percent (Hotopf, Chidgey, Addington-Hall, & Ly, 2002; Massie, 2004; Mitchell et al., 2011; Rasic et al., 2008). Levels of depressive symptoms in cancer patients have been shown roughly comparable to those among persons with other medical conditions such as coronary artery disease, Parkinson's disease, and HIV (Evans et al., 1999), with roughly one-third reporting mild to moderate depressive symptoms (McDaniel, Musselman, Porter, Reed, & Nemeroff, 1995).

Like with other major life stressors, not all cancer patients will experience significant depressive symptoms in result of their diagnosis. However, those patients with a history of affective disorders, poor social support, and recent negative life events beyond receiving a cancer diagnosis have been shown at higher risk for developing depressive symptoms during their cancer experience (Breitbart, 1995; Bukberg, Penman, & Holland, 1984; Cassem, 1995; Massie & Holland, 1990). Additionally, although depressive symptoms tend to decrease over the course of the cancer trajectory for the majority of patients (Wood, Nail, Gilster, Winters, & Elsea, 2006), up to one-third of patients continue to experience elevated depressive symptoms beyond the acute diagnosis phase (Ell, Nishimoto, Morvay, Mantell, & Hamovitch, 1989; Howard & Harvey, 1998; Nordin & Glimelius, 1999). Patients reporting the highest depressive symptoms at diagnosis are at greatest risk for prolonged distress (Nordin, Berglund, Glimelius, & Sjöden, 2001).

Monitoring and management of depressive symptoms among cancer patients has been increasingly incorporated into regular oncological practice due to the strong

associations between elevated depressive symptoms and cancer incidence, progression, and mortality (Bultz & Carlson, 2005; Spiegel & Giese-Davis, 2003; Pinquart & Duberstein, 2010; Satin et al., 2009). Depressive symptoms contribute in part to poor clinical outcomes through behavioral mechanisms: depression is known to interfere with health behaviors such as adherence to medical regimens and recommended diet and physical activity (see section "Depression predicts the physiological stress response indirectly through health behaviors," p. 15), which are crucial for successful treatment of cancer. Additionally, depression interferes with seeking social support (Barefoot et al., 2003), which has been shown to help improve mood, reduce cancer symptom severity, and lengthen survival time (Kornblith et al., 2001; Kroenke, Kubzansky, Schernhammer, Holmes, & Kawachi, 2006). Depressive symptoms also contribute to poor clinical outcomes due to its impacts on the HPA axis and inflammation. To demonstrate, the following will review the biology of cancer, and how depressive symptoms interact with the disease of cancer.

Cancer, inflammation, and depression. Cancer is a neoplastic disease, or a disease resulting from the unchecked growth and spread of abnormal cells. A cancerous cell is differentiated from a normal cell in its abnormal ability to survive and reproduce. From multiple mutational changes to its genetic structure, these cells have the ability to avoid programmed cell death, reproduce indefinitely to the detriment of surrounding tissues, and relocate to a new anatomical locus. Genetic damage causing a single cell to spawn billions of clones typically arises from either: (a) damage to the tumor suppressor gene, impairing the cell's ability to "brake" against growth through initiating apoptosis or limiting cell reproduction, and/or (b) an increase in number or activity of oncogenes that

"accelerate" cell growth (Holland, 1998; Weinberg, 2007). Developing tumors go on to illicit an inflammatory response from the body, and are thus described as "wounds that do not heal" (Dvorak, 1986).

Although some cancers are due entirely to random carcinogenic cell mutations, over 90 percent of cancers have at least some level of environmental cause, with the majority of environmental risk factors linked with chronic inflammation (see Figures 1 and 2, path B; Aggarwal et al., 2009). Inflammation has been implicated in every stage of tumorigenesis: from tumor initiation, promotion, metastasis, and treatment resistance (Grivennikov et al., 2010). Chronic inflammation increases the risk of normal cell transforming to a cancerous cell through directly causing genetic mutations and indirectly through promoting genomic instability through the highly toxic inflammatory byproducts causing oxidative damage to cells (Kraus & Arber, 2009). Once a tumor has developed, inflammation is most influential in the promotion of established tumor growth. Cancerous cells release their own pro-inflammatory cytokines, as well as inciting an immune attack from the body (see Figures 1 and 2, path H; Galizia et al., 2002; Mantovani, Allavena, Sica, & Balkwill, 2008). These cytokines, including IL-6, serve to both promote vascularization of the tumor to increase its fuel supply of oxygenated blood as well as protect against tumor cell death from apoptosis and the innate immune response (Hodge et al., 2005; Nilsson et al., 2005). IL-6 has also been shown to accelerate proliferation of colon cancer cells in vitro (Schneider et al., 2000) and promote malignancy of colon tumors through increasing their invasiveness (Hsu & Chung, 2006).

Cancer metastasis is said to have occurred when a tumor cell has invaded the blood stream, travelled to a new location, and established a tumor colony in a different

site from the tumor origin (Holland, 1998, Weinberg, 2007). As over 90 percent of cancer deaths occur as a result of metastasis, this step in tumor progression is of high clinical importance (Grivennikov et al., 2010). Pro-inflammatory cytokines, including IL-6, promote metastasis through facilitating the transport of tumor cells into the blood stream and promoting cancer cell survival in circulation (Nguyen, Bos, & Massagué, 2009). Finally, elevated IL-6 and other pro-inflammatory cytokines released from the tumor cells reduce treatment efficacy by promoting resistance to chemotherapeutic drugs (Hodge et al., 2005; Frassanito, Cusmai, Iodice, & Dammacco, 2001).

Cancer treatments themselves also promote inflammation. Surgery, used to excise tumors and damaged tissues, incite an inflammatory response from the body to repair the tissues damaged from the procedure itself. Chemotherapy and radiation eradicate cancer cells through a necrotic process, which causes pro-inflammatory factors to be released from the dying tumor cells (Vakkila & Lotze, 2004). Although acutely inflammatory, cancer treatment aims to attenuate chronically elevated inflammation by eliminating the proinflammatory tumor (Galizia et al., 2002). Patients who do not show reduced IL-6 from treatment to a level close to healthy, demographically-matched persons have poorer prognostic outcomes, including higher risk of metastases (Chung & Chang, 2003) and death within the year following diagnosis (Chung & Chang, 2003; Knüpfer & Preiss, 2010; Roxburgh & McMillan, 2010). In cancer survivors, elevated CRP predicts development of secondary cancers and cardiovascular disease (Wethal et al., 2010) and shorter disease-free survival (Nikiteas et al., 2005). In colorectal cancer patients, elevated CRP levels after treatment have also been associated with worse survival rate (McMillan, Canna, & McArdle, 2003).

As in healthy persons, a bi-directional relationship among depressive symptoms and inflammation has been observed among cancer patients (Spiegel & Giese-Davis, 2003). Among cancer patients, depression has been reliably associated with elevated IL-6 (Jehn et al., 2006; Musselman et al., 2001), such that utilizing IL-6 values has been suggested as a prognostic marker of major depression among cancer patients (Jehn et al., 2006). Elevated inflammation then feeds back to aggravate depressive symptoms among patients, articulated in the popular cytokine theory of depression (Currier & Nemeroff, 2014; Dantzer et al., 2008; Loftis, Huckans, & Morasco, 2010). This feedback loop between depressive symptoms and elevated inflammation also negatively impacts clinical outcomes through dysregulation of patients' HPA axis functioning.

Cancer, HPA axis functioning, and depression. Blunted cortisol rhythmicity, indicating poor HPA axis functioning, has been documented among animals and humans with detectable tumors (Jehn et al., 2006; Mormont & Levi, 1997; Musselman et al., 2001; Sephton & Spiegel, 2003; Touitou, Bogdan, Levi, Benavides, & Auzeby, 1996; Touitou et al., 1995). This HPA axis dysregulation among persons with cancer is likely to derive from both psychological factors like stress and depression (Kiecolt-Glaser et al., 2003; Stetler et al., 2004), as well as from inflammation (Jehn et al., 2006; Lutgendorf et al., 2008; Musselman et al., 2001). Blunted diurnal cortisol rhythms have also been associated with poor quality of life among cancer patients: dysregulated HPA axis activity has been associated with fatigue among breast (Bower et al., 2005) and colorectal cancer patients (Rich et al., 2005), functional disability among breast cancer patients (Touitou et al., 1996), and vegetative symptoms of depression among advanced ovarian (Lutgendorf et al., 2008) and colorectal cancer patients (Rich et al., 2005).

In regards to clinical outcomes, evidence from breast cancer models show that hypercortisolemia promotes neoplastic growth (Antonova & Mueller, 2008; Sephton et al., 2009). Flattened cortisol diurnal variation was shown to predict earlier mortality among breast cancer patients, which was partially mediated by lower cell count and cytotoxicity of natural killer cells (Sephton et al., 2000). Among colorectal cancer patients, blunted cortisol rhythmicity has been associated with poorer performance status, as well as elevated pro-inflammatory cytokines, including IL-6 (Rich et al., 2005). Blunted diurnal cortisol variation has also been shown to mediate the relationship between depressive symptoms among patients with renal cell carcinoma and shorter survival times (Cohen et al., 2012).

Limitations of prior biopsychosocial research with cancer patients. Literature has been reviewed that demonstrates the utility of depressive symptoms as a risk indicator for cancer patients likely to experience poor clinical outcomes due to the strong association between these symptoms and the dysregulated physiological stress response, which contributes to cancer progression and mortality. Importantly, it has been shown that treatment of depression in cancer patients by both psychosocial and pharmacological means results in improved emotional functioning, quality of life, and clinical outcomes (McDaniel et al., 1995; Pirl, 2004). However, these interventions have only shown small to medium effects (Pirl, 2004), so identifying additional risk factors for poor patient psychological and physical health may improve patient psychosocial care and clinical outcomes.

One such factor that has been overlooked by individual-level biopsychosocial models of patient depression and health decline is the impact of informal caregivers.

Chronic illness affects not only patients, but their families as well; however, biopsychosocial studies of patient functioning have tended to focus on the patient at the individual level, with social context serving as a predictor or covariate at most. Evidence will be reviewed through the following sections that demonstrates the utility and necessity of viewing the patient-caregiver dyad as the unit of study and treatment to provide a more complete picture of risk for future health decline in both cancer patients and their families.

The Psychology and Physiology of Cancer Caregiving

It is known that chronic illnesses, such as cancer, exert challenges not only on the patients themselves, but also their families (see Figure 2, path I). Healthcare systems are increasingly shifting cancer treatment to outpatient settings, moving a greater share of caregiving burden to informal caregivers, or "family like" individuals who provide unpaid cancer care (Bailes, 1997). An estimated 4.6 million Americans provide essential emotional and instrumental support to relatives with cancer (National Alliance for Caregiving, 2009) for an average of 9 hours per day (Kim & Spillers, 2010). Cancer caregivers primarily provide emotional support for patients through the cancer experience, assisting in coping with anxiety about treatments, recurrence, and death (Carey, Oberst, McCubbin, & Hughes, 1991). Caregivers may also assist the patient with activities of daily living, including assisting with medication adherence, transportation, mobility, financial management, and healthcare navigation (Bevans & Sternberg, 2012; Kim & Schulz, 2008).

Caregivers of persons with chronic illness report significantly greater depressive symptoms and stress and lower subjective well-being compared to demographically similar non-caregivers (Pinquart & Sörensen, 2003). While it is agreed that the majority of caregivers will adapt well and are not expected to experience clinical levels of distress post-diagnosis (Hagedoorn, Sanderman, Bolks, Tuinstra, & Coyne, 2008; Neundorfer, 1991; Pitceathly & Maguire, 2003), approximately 40 percent of cancer caregivers are estimated to have clinically significant depressive symptomatology (Braun, Mikulincer, Rydall, Walsh, & Rodin, 2007). The predominant model of the development of depression among caregivers has come from the stress-appraisal-coping framework (Lazarus & Folkman, 1984; Lazarus & Folkman, 1987). Elaborated for the caregiving context by Pearlin, Mullan, Semple, & Skaff (1990) and Vitaliano, Zhang, and Scanlan (2003), this theory posits that caregiving stressors such as amount of care tasks and patients' disease factors negatively impact caregivers' psychological functioning and health behaviors, thus producing physiological changes that potentiate caregivers' physical health decline (Nijboer et al., 1998; Schulz & Sherwood, 2008).

Cancer caregivers have demonstrated an increased risk to develop coronary heart disease and have a stroke relative to age, sex, and socioeconomically comparable non-caregiving spouses (Ji et al., 2012), with similarly elevated risk for prematurely developing cardiovascular diseases among caregivers of other chronic illnesses (Lee et al., 2003; Vitaliano et al., 2002). Notably, it has been found that caregivers who report the highest level of psychological distress from caregiving, including depressive symptoms, are at highest risk for premature health decline (Pinquart & Sörensen, 2007; Schulz & Beach, 1999; Vitaliano et al., 2002). Depressive symptoms therefore may serve

as an efficiently assessed indicator of caregivers at greatest risk for premature health decline, due to the effect of depressive symptoms on the physiological stress response.

Caregiving, inflammation, and depression. Caregivers showing the highest levels of depressive symptoms early in their patient's cancer trajectory are likely to show persistently elevated distress beyond the initial diagnosis phase (Kim, Shaffer, Carver, & Cannady, 2014; Lambert, Jones, Girgis, & Lecathelinais, 2012; Palos et al., 2011), and these chronically elevated depressive symptoms put caregivers at risk for a chronically activated physiological stress response (see "Depressive Symptoms and the Physiological Stress Response", p. 10). The majority of study on caregiving and its relationship with the physiological stress response has been conducted with dementia caregivers; these studies have demonstrated caregivers' poorer immune health relative to non-caregivers. Dementia caregivers compared with non-caregivers have shown reduced cellular immunity, fewer lymphocytes, and poorer antibody responses (Vitaliano et al., 2003; Segerstrom & Miller, 2004). One study documented an increase in IL-6 in caregivers over a six-year period that was four times greater than that of non-caregivers with similar demographic characteristics (Kiecolt-Glaser et al., 2003). Among a sample of healthy women, caregivers of a parent with dementia showed higher plasma IL-6 relative to women facing a stressful relocation and to non-stressed, non-caregiving women (Lutgendorf et al., 1999). Among caregivers of elderly dependents with a variety of medical conditions, higher perceived burden from providing care was associated with higher caregiver IL-6 and CRP (Clark, Nicholas, Wassira, & Gutierrez, 2011).

Caregiving, HPA axis dysfunction, and depression. Recent research has suggested that caregivers' elevated inflammation is mediated by HPA axis dysregulation.

Research with dementia caregivers has associated caregiving with higher levels of cortisol output compared to demographically matched controls, with cortisol dysregulation comparable to that seen among persons with major depression (Da Roza Davis & Cowen, 2001; Gallagher-Thompson et al., 2006). A meta-analysis of studies examining biological markers in dementia caregivers compared to matched controls demonstrated that caregivers had 23 percent higher levels of circulating stress hormones, with authors suggesting that cortisol may be among the most responsive biomarkers to caregiving experience (Vitaliano et al., 2003).

Miller et al. (2002) published the first study examining HPA axis functioning and immune health among cancer caregivers, providing the first replication of the HPA axis dysfunction previously demonstrated in dementia caregivers specifically. Parental caregivers of a child with cancer reported greater depressive symptoms and had flatter diurnal cortisol slopes relative to age, sex, ethnicity, and marital status matched non-caregiving peers. HPA axis dysregulation contributed to an exaggerated IL-6 response to stress among the caregivers, due to impaired suppression of the pro-inflammatory response by glucocorticoids. Receipt of social support was shown to protect against the hyperinflammatory response among the caregivers; however, a measure combining both cognitive/affective and somatic depressive symptoms was not associated with the caregivers' elevated IL-6 (Miller et al., 2002).

Two later studies examining HPA axis functioning among cancer caregivers have failed to show differences in cortisol production between cancer caregivers and age, sex, ethnicity, and marital status-matched, non-stressed and non-caregiving controls. In a study by Miller and colleagues (2008), caregivers of showed similar patterns of cortisol

to matched controls; however, caregivers' monocytes demonstrated resistance to glucocorticoid downregulation. Researchers suggested this blunted glucocorticoid signaling by caregiver immune cells was the mechanism driving the higher levels of CRP observed among the cancer caregivers compared to their peers (Miller et al., 2008). In a longitudinal study, Rohleder and colleagues (2009) replicated the above findings that caregivers' cortisol output did not differ from matched non-caregivers, but caregivers' immune cells showed greater glucocorticoid resistance. Researchers suggested this mechanism drove the caregivers' profound linear increase in CRP during the year following the patients' cancer diagnosis, whereas non-caregivers showed no change in CRP across the same time period (Rohleder et al., 2009).

Limitations of prior biopsychosocial research with cancer caregivers. The above studies by Miller and colleagues (2002, 2008) and Rohleder and colleagues (2009) contributed significantly to the caregiving literature demonstrating that cancer caregiving is a risk factor for a dysregulated physiological stress response. These studies, however, are not without limitations, which may contribute to their null findings regarding differences in cortisol between caregivers and controls as well as associations between caregiver depressive symptoms and biomarkers of the physiological stress response. First, the cancer caregiver samples utilized by Miller et al. (2008) and Rohleder et al. (2009) were over four-fifths non-Hispanic white, and non-Hispanic whites have shown healthier patterns of HPA functioning relative to other racial and ethnic minorities (Chong, Uhart, McCaul, Johnson, & Wand, 2008; Cohen et al., 2006; Gallagher-Thompson et al., 2006; McCallum, Sorocco, & Fritsch, 2006). As such, studying an ethnically diverse sample

will add substantially to the generalizability of these findings to a broad range of cancer caregivers.

Second, these studies did not examine possible differential associations between depression symptoms clusters and biomarkers: Miller and colleagues (2002, 2008) failed to find an association of caregiver inflammation with a measure of depressive symptoms that collapsed cognitive, affective, interpersonal, and somatic difficulties. With evidence suggesting biomarkers are most closely associated with somatic symptoms (see section "Depressive symptoms predict the physiological stress response directly," p. 13), investigation of the relationship between separate sub-components of depressive symptoms and biomarkers of the physiological stress response will provide a clearer understanding of this association among cancer caregivers.

Despite limitations, studies by Miller et al. (2002, 2008) and Rohleder et al. (2009) have begun to provide information on the physiological ramifications of cancer caregiving, specifically. As previously noted, the majority of prior research examining psychological and physiological ramifications of caregiving has been conducted with caregivers of persons with dementia. Cancer caregiving is comparable to caring for a patient with dementia in its level of intensity and time commitment, with both conditions producing higher caregiving burden than caring for persons with diabetes or frail elders (Kim & Schulz, 2008). However, cancer and dementia caregiving differ in duration and demographic factors (Kim & Schulz, 2008; Clipp & George, 1993), suggesting that caregivers from these populations experience differing levels of vulnerability to negative consequences from caregiving.

Beyond average differences in risk factors between cancer caregivers and dementia caregivers, the nature of the patient-caregiver relationship differs significantly between those who are managing chronic illnesses with and without significant cognitive impairment. Within the context of dementia, particularly through progressive stages of illness, patients are unable to reciprocate caregivers' emotional involvement, as the disease robs patients' of their memory, communication skills, and reasoning. However, persons affected by chronic diseases such as cancer retain cognitive faculty, although some may be mildly impaired from various treatments. This allows patients to reciprocate caregivers' emotional involvement, and thus patients and caregivers may influence one another emotionally and behaviorally. This emotional interdependence between cancer patients and caregivers has been documented; however, little attention has been paid as to whether this emotional interdependence affects patients' and caregivers' physiological outcomes beyond the effects of one's own emotional reactions at the individual level. Therefore, existing biopsychosocial models linking emotional distress with physical health decline among cancer patients and caregivers at the individual level have neglected a possibly important risk factor: the partner's emotional experience. Evidence will next be reviewed that suggests the biopsychosocial models of psychological and physical morbidity among cancer patients and caregivers at the individual level fail to account for observed interdependence between patient and caregiver outcomes, thus supporting the need for a broader, dyadic framework.

Interdependence of Cancer Patient and Caregiver Psychological and Physical Health

As stated, one major limitation common to both cancer patient and caregiver research has been the focus on patients and caregivers as individuals, rather than as a dyad. This individual-level approach is problematic in that it neglects to acknowledge the *interdependence* of cancer patient and caregiver experiences through the cancer trajectory. It is now understood that cancer patients and their caregivers function as an "emotional system," reacting in tandem to the cancer experience (see Figure 2, path J; Berg & Upchurch, 2007). Evidence has begun to accumulate regarding the dyadic mutuality between cancer patients' and caregivers' distress, wherein one partner's distress impacts the other's so their distress is similar (Kim et al., 2015a; Segrin & Badger, 2014; Segrin et al., 2005; Segrin, Badger, Dorros, Meek, & Lopez, 2007).

Stress from cancer diagnosis and treatment represents a *dyadic* stress within the patient-caregiver unit (Bodenmann, 2005). The dyadic stress model posits a systems perspective, with mutual influence between each partner's stress and coping efforts (Bodenmann, 2005). Among the general population, it is known that "individuals are likely to function most adaptively both psychologically and physically if they are involved in healthy relationships" (p. 79, Baucom, Kirby, & Kelly, 2010). This dyadic stress model has been supported within cancer patients and caregivers as well. Patients and their caregivers report moderately correlated levels of distress cross-sectionally (Hagedoorn et al., 2008; Hodges et al., 2005; Kim, Duberstein, Sörensen, & Larson, 2005). Longitudinally, patient and caregiver trajectories of psychological distress are also correlated, with deterioration in one's mental health followed by decline in the other's (Segrin & Badger, 2014; Segrin et al., 2005; Segrin et al., 2007). Additionally, dyadic

effects on distress regarding cancer symptoms and adjustment to cancer have been documented. In studies of breast cancer patients and their spouses, both patient and caregiver distress regarding the patient's symptoms predicted the other's symptom distress two months later (Segrin & Badger, 2014), and patients whose husbands provided high-quality emotional support reported better emotional adjustment to their cancer (Neuling & Winefield, 1988). Accumulated evidence documenting the cross-sectional and longitudinal correlation between patient and caregiver psychological distress suggest there is interdependence among cancer patients' and their caregivers' psychological distress (see Figure 2, path J).

This mutual psychological influence between patients and caregivers has been shown to impact health outcomes. In a study of married breast and prostate cancer patient-caregiver dyads, wives' psychological distress predicted their husband's poorer physical functioning (Kim et al., 2008a). This cross-over effect was replicated among colorectal and lung cancer patient-caregiver dyads: female patients' depressive symptoms were associated with caregivers' poorer physical functioning (Kim et al., 2015a). A study of mothers with cancer and their adult daughter caregivers showed that mothers' greater psychological distress predicted their daughters' poorer physical functioning, above the effects of daughters' own distress (Kim et al., 2008b). Also supporting interdependence between cancer patient and caregiver depressive symptoms and stress biomarkers: depressed patients show more severe functional decline and require more care (Hoppe et al., 2013; Given et al., 1993), which creates greater caregiver burden and risk for caregiver health decline (Grunfeld et al., 2004; Pinquart & Sörensen, 2007; Rhee et al.,

2008) and depressed caregivers provide poorer quality care to their patients (Beach et al., 2005; Williamson & Schulz, 1990), putting patients at risk for poorer clinical outcomes.

That a cancer patient's distress could impact his/her caregiver's general physical functioning beyond the impacts of the caregiver's own distress provides evidence that there may be interdependence among cancer patients' and caregivers' physiology as well. Interdependence between cancer patient and caregiver physical outcomes may be due to one's distress impacting their partner's distress (Figure 2, path J), which incites the partner's physiological stress responses (Figure 2, path D). Impacts of social environment have even demonstrated impacts on cancer patients' immune parameters: IL-6 has been shown inversely associated to ovarian cancer patients' reports of feeling close/intimate with someone special (Costanzo, Lutgendorf, Bradley, Rose, & Anderson, 2005) and receipt of instrumental support (Lutgendorf, Anderson, Sorosky, Buller, & Lubaroff, 2000). These findings suggest that factors affecting the ability of caregivers to provide high-quality care, such as depressive symptoms, may also impact their care recipients' immune health, but this has yet to be tested empirically.

Adding to the support of the interdependence among patients and their caregivers is evidence showing improved patient and caregiver outcomes from dyadic psychosocial interventions compared to interventions delivered individually to either patients or caregivers. Martire, Lustig, Schulz, Miller, and Helgeson (2004) demonstrated that couple-based psychosocial interventions for patients of various chronic illnesses and their caregivers showed superior psychological and disease-related outcomes for patients relative to interventions for patients or caregivers only. Increased efficacy of dyadic over individual psychosocial interventions was replicated within cancer patient-caregiver

dyads, with authors suggesting that "when the patient-caregiver dyad is treated as the unit of care, important synergies are achieved that contribute to the well-being of both patients and caregivers" (p. 1229; Northouse, Williams, Given, & McCorkle, 2012).

Due to the interdependent and reciprocal nature of cancer patients' and their caregivers' distress, the cancer patient and caregiver dyad must be viewed and analyzed as a unit (Hagedoorn et al., 2008; Hodges et al., 2005; Matthews, Baker, & Spillers, 2003). However, the individual-level biopsychosocial models that have been used to examine the relationship between depressive symptoms and physiology in cancer patients and caregivers fail to account for observed interdependence between the dyad. As depressive symptoms are known to illicit the physiological stress response within healthy persons and those with cancer, and cancer patients' and caregivers' depressive symptoms are interdependent, cancer patients' depressive symptoms may represent a risk indicator for their caregivers' inflammation and HPA axis dysregulation and therefore long-term health decline risk. The same may be true in reverse: caregivers' depressive symptoms may be a risk indicator for their patients' inflammation and HPA axis dysregulation and therefore risk for patients' poor clinical outcomes through cancer treatment. These dyadic impacts of cancer patient and caregiver depressive symptoms on the other's physiology have yet to be studied empirically.

Proposed Model. Evidence has been reviewed that suggests the current individual-level biopsychosocial models of health decline among cancer patients and caregivers are insufficient, as they fail to account for the risk factor of one's partner's psychosocial functioning. Dyadic mutuality between patient and caregiver distress has also been documented among other chronic diseases, including cardiovascular diseases

(Chung, Cocchieri, Rocco, Alvaro, & Riegel, 2014; Chung, Moser, Lennie, & Rayens, 2009; Thomson, Molloy, & Chung, 2012) and multiple sclerosis (Pakenham & Samios, 2013). Therefore, a dyadic model of psychological and biological stress among patients and caregivers of non-dementia chronic illness is proposed, as seen in Figure 2.

Receiving the disease diagnosis along with demands associated with managing the illness produce stress for both the patient themselves (paths H) and for the informal caregiver (path I). Stress then "gets under the skin" for patients and caregivers by directly activating their own physiological stress response (paths A) and also by inciting psychological distress (paths C). Here, patient and caregiver psychological distress interacts (path J), such that elevations in one's distress leads to a rise in the other's distress: through this interaction between the dyad's level of distress, partners may exert influence on one another's physiological stress response and disease outcomes. Also proposed is an interaction between partner's health behaviors, as partners tend to share similar lifestyles (Jeffery & Rick, 2002; Lewis et al., 2006; Macken, Yates, & Blancher, 2000; Meyler, Stimpson, & Peek, 2007) and influence one another's lifestyle changes (Falba & Sindelar, 2008; Franks et al., 2006).

With the number of cancer patients expected to double by mid-century (Edwards et al., 2002) and overburdened healthcare systems relying ever more heavily on informal caregivers to assist with cancer care (Bailes, 1997; Blum & Sherman, 2010), identifying risk indicators for poor health outcomes both among cancer patients and caregivers is of vital importance. Depressive symptoms represent a risk indicator that is easily assessed and is modifiable; however, caregiver depressive symptoms have not been investigated as predictors of poor patient physical health, or vice versa. Evidence of dyadic impacts of

patient depressive symptoms on the other's inflammation would advocate use of dyadic frameworks for future psychoneuroimmunological research with cancer patients and their caregivers. In clinical practice, findings would indicate that early screening and intervention for both patient and caregiver depression would have significant implications for patients' treatment outcomes and risk for cancer recurrence, as well as caregivers' premature functional decline.

Proposed Project: Aims and Hypotheses

This project was the first to empirically test the interdependent biopsychosocial model of patient and caregiver morbidity among a population of cancer patients and caregivers. In a first investigation of this model, the researcher examined the impact of patient and caregiver depressive symptoms on both their own and their partner's inflammation (IL-6 and CRP) and HPA axis functioning (cortisol slope). Project analyses measured the interdependence of cancer patients' and caregivers' psychological distress (see Figure 2, path J) and how this interdependence affects both one's own stress biomarkers (see Figure 2, path D) as well as one's partner's stress biomarkers (through paths J to D and/or from shared social environment factors). Depressive symptoms were chosen due to their prevalence and documented interdependence among the cancer patient and caregiver populations, as well as these symptoms' links with the physiological stress response among both healthy adults and those with cancer. Participants for the proposed study were a racially/ethnically diverse sample of patients with colorectal cancer and their caregivers. Colorectal cancer is the third most common cancer in both men and women, and its five-year survival rate resembles the average across all types of cancer (Institute of Medicine, 2005). Furthermore, over 75% of CRC

occurs among persons 65 years of age or older (Howlader et al., 2013). Not only are older persons more vulnerable to other health concerns, but older cancer survivors are also at extreme risk for functional decline (Centers for Disease Control and Prevention, 2010).

Aim 1. The first aim measured the level of *interdependence* among cancer patients' and caregivers' depressive symptoms and stress biomarkers. When a dyad's scores are more similar to one another than any other two scores of participants who are not coupled together in a dyad, the dataset is said to show "nonindependence." Nonindependence of outcome data may come through a number of mechanisms, including *partner effects,* where a characteristic of a partner influences the other partner's outcomes. Nonindependence of cancer patient and caregiver depressive symptoms has been previously found, with small-to-moderate correlations documented (*r*s= .23-.29; Given et al., 1993; Kurtz, Kurtz, Given, & Given, 1995). Nonindependence of cancer patient and caregiver stress biomarkers, including IL-6, CRP, and cortisol variability, is suggested from prior studies showing partner effects of cancer patients and caregivers on the other's subjective physical functioning, but has yet to be tested empirically. Failing to account for nonindependence of data leads to biased significance testing, with consequences of finding too many and too few true effects possible.

It is acknowledged that several factors have been previously shown to impact immune and endocrine parameters among cancer patients and caregivers. Selection of covariates must optimize inclusion of variables known to impact outcomes of interest with acknowledging the limits of available data. Failing to account for important factors contributing to outcomes of interest may bias the associations between included predictors with the outcome. However, "asking too much from available data" by

including too many predictor variables results in an overfitted model that may produce results idiosyncratic to the sample, rather than true effects found in the population (p. 411, Babyak, 2004). Therefore, selection of covariates must balance theory and prior research indicating important factors impacting the outcome of interest with available sample size: current rules of thumb suggest that 10 to 15 observations be available per included predictor variable (Babyak, 2004).

Several factors have been related to both salivary cortisol and inflammatory markers (Chida, Hamer, Wardle, & Steptoe, 2008; Chida & Steptoe, 2009; O'Connor et al., 2009; Pearson et al., 2003), including age, socioeconomic status (captured via level of education), body mass index (BMI: kg/m^2), sex, and alcohol consumption. Socioeconomic status (SES) has been found less impactful as a covariate in the context of other covariates, suggesting that effects of SES may be accounted for by other factors such as BMI (O'Connor et al., 2009). Lastly, effects of alcohol on stress biomarkers have been found to be non-linear, suggesting a dichotomous measure of alcohol consumption as was available for the current project may not adequately capture effects (O'Connor et al., 2009). As such, final covariates of age, BMI, and sex were selected to control for both patient and caregiver stress biomarkers in analyses of the following hypotheses. For patients, cancer stage (early [stages I and II] vs. late [stages III and IV]; Chida et al., 2008; Chung & Chang, 2003; Galizia et al., 2002) and treatment status (receiving vs. not receiving cancer treatment; Chida et al., 2008; Grivennikov et al., 2010) were additional covariates.

Hypothesis 1. It was hypothesized that cancer patients' and caregivers' level of depressive symptoms would be significantly related. Therefore, patients' and caregivers' CES-D scores were expected to be positively correlated.

Hypothesis 2. It was hypothesized that cancer patients' and caregivers' level of inflammation would be significantly related. Therefore, patients' and caregivers' IL-6 values were expected to be positively correlated, controlling for covariates.

Hypothesis 3. Because it was hypothesized that cancer patients' and caregivers' level of inflammation would be significantly related, it was also expected that patients' and caregivers' CRP values would be positively correlated, controlling for covariates.

Hypothesis 4. It was hypothesized that cancer patients' and caregivers' HPA axis functioning would be significantly related. Therefore, patients' and caregivers' cortisol slopes were expected to be positively correlated, controlling for covariates.

Aim 2. The first aim examined the *intrapersonal* association between depressive symptoms and stress biomarkers: the extent to which one's own depressive symptoms at two months post-diagnosis predicted one's own concurrent stress biomarkers was measured among cancer patients and caregivers. The same set of covariates used in testing Aim 1 (age, BMI, and sex) were statistically controlled from biomarker outcomes in the following analyses.

Hypothesis 5. It was hypothesized that greater depressive symptoms would be associated with greater inflammation. Therefore, one's CES-D score was expected to be

positively associated with one's own IL-6 for cancer patients (hypothesis 5.1) and caregivers (hypothesis 5.2).

Hypothesis 6. Because it was hypothesized that greater depressive symptoms would be associated with greater inflammation, it was also expected that one's CES-D score would be positively associated with one's own CRP for cancer patients (hypothesis 6.1) and caregivers (hypothesis 6.2).

Hypothesis 7. It was hypothesized that greater depressive symptoms would also be associated with poorer HPA axis functioning. Therefore, one's CES-D score was expected to be positively associated with one's own cortisol slope for cancer patients (hypothesis 7.1) and caregivers (hypothesis 7.2).

Aim 3. The third project aim examined the *interpersonal* association between own depressive symptoms and partner stress biomarkers: the extent to which one's own depressive symptoms at two months post-diagnosis predicted one's partner's concurrent stress biomarkers was measured among cancer patients and caregivers. The same set of covariates used in testing Aim 1 (age, BMI, and sex) was statistically controlled from biomarker outcomes in the following analyses.

Hypothesis 8. It was hypothesized that one's own greater depressive symptoms would be associated with one's partner's inflammation. Therefore, patients' CES-D scores were expected to be positively associated with their caregivers' IL-6 (hypothesis 8.1) and caregivers' CES-D scores would be positively associated with their patients' IL-6 (hypothesis 8.2).

Hypothesis 9. Because it was hypothesized that one's own greater depressive symptoms would be associated with one's partner's inflammation, it was also expected that patients' CES-D scores would be positively associated with their caregivers' CRP (hypothesis 9.1) and caregivers' CES-D scores would be positively associated with their patient's CRP (hypothesis 9.2).

Hypothesis 10. It was hypothesized that one's own greater depressive symptoms would be associated with one's partner's poorer HPA axis functioning. Therefore, patients' CES-D scores were expected to be positively associated with their caregivers' cortisol slope (hypothesis 10.1) and caregivers' CES-D scores would be positively associated with their patients' cortisol slope (hypothesis 10.2).

Exploratory aims. As inflammation and HPA axis dysfunction have been shown to be most strongly associated with the somatic symptoms of depression, the researcher examined whether separate depressive symptom subscales (i.e., Somatic Complaints, Depressed Affect, Lack of Positive Affect, and Interpersonal Problems) were differentially related to stress biomarkers among cancer patients and caregivers.

Exploratory aim 1. The first exploratory aim examined *intrapersonal* associations between depressive symptom subscales and one's own biomarkers: the extent to which one's own subscales of depressive symptoms differentially impacted one's own stress biomarkers was measured among cancer patients and caregivers. It was proposed that the same set of covariates used in testing Aim 1 would be utilized in the following analyses.

Exploratory hypothesis 1. It was hypothesized that somatic depressive symptoms would be more strongly associated with inflammation compared to affective (both

depressed and Lack of Positive Affect) and interpersonal depressive symptoms. Therefore, one's own Somatic Complaints CES-D subscale score was expected to be more strongly positively associated with one's own IL-6 compared to subscale scores for Depressed Affect, Lack of Positive Affect, and Interpersonal Problems for both cancer patients (exploratory hypothesis 1.1) and caregivers (exploratory hypothesis 1.2).

Exploratory hypothesis 2. Because it was hypothesized that somatic depressive symptoms would be more strongly associated with inflammation compared to affective and interpersonal depressive symptoms, it was also expected that one's own Somatic Complaints CES-D subscale score would be more strongly positively associated with one's own CRP compared to subscale scores for Depressed Affect, Lack of Positive Affect, and Interpersonal Problems for both cancer patients (exploratory hypothesis 2.1) and caregivers (exploratory hypothesis 2.2).

Exploratory hypothesis 3. It was also hypothesized that somatic depressive symptoms would be more strongly associated with HPA axis functioning compared to affective and interpersonal depressive symptoms. Therefore, one's own Somatic Complaints CES-D subscale score was expected to be more strongly positively associated with one's own cortisol slope compared to subscale scores for Depressed Affect, Lack of Positive Affect, and Interpersonal Problems for both cancer patients (exploratory hypothesis 3.1) and caregivers (exploratory hypothesis 3.2).

Exploratory aim 2. The second exploratory aim examined the *interpersonal* association between own depressive symptoms and partner stress biomarkers: the extent to which one's own subscales of depressive symptoms differentially impacted one's

partner's stress biomarkers was measured among cancer patients and caregivers, controlling for covariates.

Exploratory hypothesis 4. It was hypothesized that there would be no difference in the effects of one's own somatic, affective, and interpersonal depressive symptoms on one's partner's inflammation. Therefore, the effects of one's own Somatic Complaints, Depressed Affect, Lack of Positive Affect, and Interpersonal Problems CES-D subscale scores were expected to be equally associated with one's partner's IL-6 for both patients to caregivers (exploratory hypothesis 4.1) and caregivers to patients (exploratory hypothesis 4.2).

Exploratory hypothesis 5. Because it was hypothesized that there would be no difference in the effects of one's own somatic, affective, and interpersonal depressive symptoms to one's partner's inflammation, it was also expected that the effects of one's own Somatic Complaints, Depressed Affect, Lack of Positive Affect, and Interpersonal Problems CES-D subscale scores would be equally associated with one's partner's CRP for both patients to caregivers (exploratory hypothesis 5.1) and caregivers to patients (exploratory hypothesis 5.2).

Exploratory hypothesis 6. It was also hypothesized that there would be no difference in the effects of one's own somatic, affective, and interpersonal depressive symptoms to one's partner's HPA axis functioning. Therefore, the effects of one's own Somatic Complaints, Depressed Affect, Lack of Positive Affect, and Interpersonal Problems CES-D subscale scores were expected to be equally associated with one's

partner's cortisol slope for both patients to caregivers (exploratory hypothesis 6.1) and caregivers to patients (exploratory hypothesis 6.2).

Chapter 2. Method

This project investigated the associations between the depressive symptoms that colorectal cancer patients and their caregivers report at two months post-diagnosis and their own and their partner's concurrent pro-inflammatory markers IL-6 and CRP as well as cortisol diurnal variation. Analyses were conducted primarily using Actor-Partner Interdependence Modeling using Structural Equation Modeling.

Participants

Participants were identified from a larger study that recruited patients diagnosed with colon or rectal cancer at study sites that include the University of Miami/Jackson Memorial Hospital (UMH) and the University of Miami Sylvester Comprehensive Cancer Center (SCCC). Eligibility criteria for the **patients** were being: (a) 21 years or older; (b) able to speak/read English or Spanish; (c) diagnosed with colon or rectal cancer (CRC: stage I to IV) within the past 3 months; and (d) having a family-like individual (family member or close friend) who is providing help to the patient with their cancer experience without being paid. Eligibility criteria for the **caregivers** were being: (a) 21 years or older; (b) self-identified as Black, non-Hispanic white, or Hispanic; (c) able to speak/read English or Spanish; and (d) nominated by the patient as a person who provide help to them with their cancer experience. Exclusion criteria for both patients and caregivers were if they have any active and untreated (a) psychotic symptoms or (b) substance dependence, or (c) reported suicidal ideation within the past year. Participants who were HIV seropositive were ineligible to provide a blood sample. All participants eligible to participate in the study were eligible to provide a saliva sample.

Procedure

This study was approved by the University of Miami Institutional Review Board and Sylvester Comprehensive Cancer Center (SCCC) Protocol Review Committee and the Jackson Health System (JHS) Institutional Review Board. Patients were identified by CRC diagnosis and date of diagnosis from their electronic medical records from a study site (SCCC and JHS). Eligible patients received a letter of invitation to the study followed by recruitment phone calls from study staff. A brief screening to determine eligibility of the patient and identified caregiver was conducted in-person or via telephone. Written informed consent was obtained individually prior to data collection. After providing informed consent, eligible patients and caregivers individually completed a questionnaire that contained measures of demographic covariates and depressive symptoms. A blood sample (10 mL) was collected from each eligible patient and caregiver by study staff, who were licensed phlebotomists. Salivary cortisol was collected by participants using salivettes with a cotton swab (Sarstedt, Rommelsdorf, Germany) at four times per day over two consecutive days: upon their personal waking time, 30 minutes after waking up, late afternoon (targeted for 4 to 5 PM), and before bedtime (targeted for 9 to 10 PM). Participants were asked to refrain from eating, drinking caffeine, exercising, and brushing their teeth within the 30 minutes prior to collecting the saliva samples. Each participant received $40 as compensation upon completion of assessment.

Measures

Center for Epidemiological Studies-Depression scale. Dejected affect, Lack of Positive Affect, lethargy, and social disconnection were assessed using the 20-item Center for Epidemiological Studies-Depression scale (CES-D; Radloff, 1977). Participants were asked to rate how often since their diagnosis they felt a certain way (e.g., "I felt depressed," "People were unfriendly," "I enjoyed life [reverse coded];" see Appendix 1 for all items). Response options range from 0 (Rarely or None of the Time) to 3 (Most or All of the Time). The sum of scores from all items after reverse-coding as appropriate indicates an overall level of depressive symptomatology (Radloff, 1977). The CES-D is one of the most widely used measures of depressive symptoms in clinical research (Santor, Gregus, & Welch, 2006; Shaffer, 2014). Construct validity of the CES-D has been established in both healthy adults (Radloff, 1977) and cancer patients (Hann, Winter, & Jacobsen, 1999) through convergent validity with other depression measures (e.g., Bradburn Negative Affect, Profile of Mood States-Depression Scale). The CES-D has also shown high internal reliability in cancer patients (Cronbach's α = .81-.87; Hann et al., 1999; Tomich & Helgeson, 2012) and cancer caregivers (Cronbach's α = .92-.97; Gaugler et al., 2008; Kim et al., 2014; Nijboer et al., 1998). The CES-D scale showed acceptable reliability in the current samples (Cronbach's αs = .82 and .90 for patients and caregivers, respectively).

Depressive symptoms measured by the CES-D cluster to four distinct subscales: Somatic Complaints (7 items; e.g., "I did not feel like eating; my appetite was poor"), Depressed Affect (5 items; e.g., "I felt sad"), Lack of Positive Affect (4 items; e.g., "I was happy," items reverse coded), and Interpersonal Problems (4 items; e.g., "I felt that

people disliked me;" see Appendix 1 for all subscale items). These subscales have been established among both healthy and chronically ill community-dwelling adults (Radloff, 1977; Sheehan, Fifield, Reisine, & Tennen, 1995) and have been utilized among cancer patient samples (Lutgendorf et al., 2008). Subscales showed lower reliability than the overall CES-D (Cronbach's αs: Somatic Complaints = .63 and .81; Depressed Affect = .74 and .90; Positive Affect = .65 and .61; Interpersonal Problems = .63 and .70, for patients and caregivers, respectively).

Pro-Inflammatory Markers. In-vivo serum level of pro-inflammatory cytokine IL-6 and acute phase protein CRP were obtained from 10 mL of blood in a coagulant tube. Blood tubes were centrifuged at four degrees Celsius at 3000 rpm for 15 minutes to separate plasma from whole blood. Next, 0.5 mL plasma were pipetted into two separate microvials (one for CRP, one for IL-6). Plasma aliquots were then stored at -80 degrees Celsius until assay, with samples analyzed in batches of 40 microvials per plate. IL-6 was measured in diluted serum or EDTA plasma using the sandwich enzyme immunoassay employing a double antibody technique manufactured by R&D Systems (Quantikine, Minneapolis, MN). The assay measures both free and receptor-bound IL-6. Intra-assay coefficient of variation (CV) is less than 7.6 percent and interassay CV is less than 9.8 percent. CRP was processed according to the high-sensitivity Luminex 200 *xMap* protocol for multiplexed cytokine analysis. Intra-assay and interassay CVs are less than 4.4 percent and 5.7 percent, respectively. Non-significant readings for IL-6 (below 0.1 pg/mL and over 10 pg/mL) and CRP (below 0.15 mg/L) were set to the detection limit.

Salivary Cortisol. Salivary cortisol is a reliable yet unobtrusive method for measuring circulating levels of unbound, biologically active cortisol for the observation

of HPA axis activity (Foley & Kirschbaum, 2010; Kirschbaum & Hellhammer, 1994). Participants completed saliva samples at four time points over the course of two consecutive days. Multiple assessment time points per day allow for examination of the diurnal fluctuations in cortisol over the course of waking. Obtaining samples on two consecutive days provides increased reliability of measurements. Samples were stored at -80 degrees Celsius until shipment for assay. All assays were completed at the Technical University of Dresden, Germany, using a commercial chemiluminescence immunoassay (IBL, Hamburg, Germany; lower detection limit 0.41 nmol/L). Inter- and intra-assay variance coefficients are less than 10% across expected range of cortisol values. Slope of salivary cortisol was utilized for analyses (see "Computing Cortisol Slope," p. 53).

Covariates. Patients' and caregivers' self-reported age and sex were collected from questionnaires. BMI was calculated from participants' height and weight obtained during a behavioral assessment. Information about patients' cancer stage and treatment status was obtained by self-report and medical records review.

Statistical Analyses

Data Descriptives. Data were inspected using quality control procedures. Descriptive statistics were computed for all study variables using SPSS software Version 22 (IBM Corp., 2013) to ensure that all data values were within expected ranges, allowing correction of any data-entry errors or out-of-range values. Box plots were used to detect outliers that were within the expected range but extreme with respect to the sample.

For cortisol sampling times, any sample taken outside four standard deviations from the mean sampling time across participants at any time point was considered an outlier and the sample was removed from analysis (as has been done previously, see Lutgendorf et al., 2008). Also as done previously (Lutgendorf et al., 2008), for cortisol values, any value four standard deviations away from the mean value across participants at any time point was considered an outlier—the value was then replaced by the most extreme allowable value (e.g., four standard deviations from the mean in the direction of deviance).

Cook's distance (D) was used to examine influence of individual observations of CES-D scores with three biomarkers (IL-6, CRP, and cortisol slope) separately. Cook's D values greater than one suggest that a single observation (an individual's score) has a high level of influence on regression parameters compared to other observations (Cook & Weisberg, 1982).

Indices of skew and kurtosis were used to examine the distribution of cortisol slope, IL-6, and CRP, as these data tend to be positively skewed (Kiecolt-Glaser et al., 2003; Pradhan et al., 2001; Sephton et al., 2000). Absolute skew values greater than three and absolute kurtosis values greater than 10 are considered markers of "extreme" data skew (Kline, 2011). It was proposed that if cortisol or pro-inflammatory markers were found to be skewed according to these criteria, the skewed data would be logarithmically transformed: first, a constant would be added to scores to ensure the lowest value was greater than 1.00. Then, the natural log (ln X) of the skewed biomarker data would be recorded and used in all following analyses (Kline, 2011; Osborne, 2002).

For all analyses, two-tailed tests were used. *P*-values less than .05 were considered significant, while *p*-values between .05 and .10 were considered marginally significant.

Computing Cortisol Slope. Because healthy HPA axis function has been described as high morning cortisol descending through the course of the day, cortisol slope is considered a good measure of HPA axis functioning (Sephton et al., 2000; Smyth et al., 1997). Per cortisol slope calculation recommendations (Kraemer et al., 2005; Nicholson, 2008; Sephton et al., 2000), thirty minute post-waking samples were excluded from the cortisol slope computation, as they violate the linearity assumption of linear regression and reduce the reliability of slope values (Kraemer et al., 2006). Regression parameters were calculated for each participant by regressing the participants' cortisol values from wake, afternoon, and evening samples from the two collection days on hour of sample collection for each cortisol value per the following:

$$Y' = bx + e$$

where *Y'* is the estimated salivary cortisol level (natural log transformed as necessary), *b* is the unstandardized cortisol slope, *x* is the hour of collection (in number of hours past midnight; e.g., 1:30 PM = 13.5), and *e* is error in prediction. This formula computes a mean regression slope across the two days of saliva sampling. Larger negative *b* values indicate more rapid decline in cortisol throughout the day (a "healthy" diurnal cortisol pattern), whereas flatter diurnal slopes typical of dysregulated HPA axis activity are represented by smaller negative or positive *b* values (Sephton et al., 2000; Turner-Cobb et al., 2000).

Missing Data Management. Patients and caregivers who completed questionnaires, saliva collection, and/or blood collection were included in analyses. However, missing data on CES-D, salivary cortisol, and pro-inflammatory markers exist. Missingness on the CES-D resulted from participants exercising their right refuse to complete questionnaires ($N = 2$). Reasons for missingness for saliva samples included: (a) participants neglecting or refusing to complete proper sample collection ($N = 10$) or (b) saliva content was not detectable on cotton swab at time of analysis ($N = 4$). Reasons for missingness for blood samples from eligible participants included: (a) refusal due to phobia, religious reasons, etc. ($N = 4$), (b) inability or lack of a phlebotomist to complete a successful venipuncture ($N = 43$), or (c) inflammatory markers were not detectable in blood sample ($N = 4$).

Patterns of missingness were examined (Hill, 1997; Enders, 2010). In a dataset, data may be missing according to three mechanisms: missing at random (MAR), missing completely at random (MCAR), or missing not at random (MNAR). If missingness of variable Y is related to Y fully through a third variable X, data are considered MAR—estimates from analyses using this partial dataset will be unbiased only if the third variable X is properly accounted for. An example of MAR data for the current project would be the following: Caregivers are more likely to miss the blood draw compared to patients, and caregivers have lower inflammation relative to patients. If among caregivers, there is no difference between the inflammation between those who did versus did not complete the blood draw, parameters would be unbiased if "caregiver/patient role" is accounted for in analyses. If missingness of variable Y is completely random (e.g., completely unrelated to Y), then data are considered MCAR—

estimates from analyses using this partial dataset would be unbiased regardless of other variables included in model. An example of MCAR data for the current project would be the following: Participants are more likely to miss the blood draw when participating on Wednesdays. If there was no difference between participants' inflammation between those who participate on Wednesdays versus other days, parameters would be unbiased.

However, if missingness of a variable Y depends on the value of Y itself, then data are considered MNAR—estimates from analyses using this missing data would be biased. An example of MNAR data for the current project would be the following: Participants who were clinically depressed were more likely to miss the blood draw and also have higher inflammation relative to non-depressed persons. It is accepted that most unplanned missingness in psychosocial research is at some level MNAR, but the extremity of the bias produced by being MNAR should be reduced through identification and inclusion of auxiliary variables (variables that are correlated with the missingness or the missing variable value; Enders, 2006; Collins, Schafer, & Kaw, 2001; Schafer & Graham, 2002).

Missing data results in loss of information, which can bias results and reduce analysis power. As such, modern missing data methods seek to reduce the impact of missing data on analyses by taking advantage of information available in the structure of available data (Collins et al., 2001; Kline, 2011; Schafer & Graham, 2002). Full Information Maximum Likelihood (FIML) estimation is one method of estimating population parameters from all observed data, without losing observations due to incomplete data (as would happen with older analytic techniques, such as listwise deletion). FIML uses an iterative process testing successive population parameters of

interest (e.g., regression coefficients) until the parameters with the best "match" to the full observed data set are found. Importantly, FIML has been shown to produce unbiased parameter estimates when data are MAR (Enders, 2006; Schafer & Graham, 2002). Therefore, analyses were completed through a Structural Equation Modeling (SEM) framework with M*plus* software (Version 7; Muthén & Muthén, 2012), which utilizes FIML estimation.

Testing Study Aims through Actor-Partner Interdependence Modeling. Actor-Partner Interdependence Modeling (APIM) using SEM was used to test study hypotheses. APIM properly accounts for nonindependence of dyadic data by correlating dyad predictor and outcome variables—these correlation parameter estimates were used to test Aim 1. Nonindependence of data often occurs in dyadic datasets, in which each individual in the dataset has a partner included in the data set (e.g., cancer patient with their family member). Data are "nonindependent" when scores of two dyad partners are more similar to one another relative to scores of two other participants who are not coupled in a dyad. In these cases, the data violate assumptions of "independence" required for most data analytic methods, in which an individuals' observation should be unrelated to any other observation. Nonindependence may arise from compositional effects (e.g., similarity on certain factors drew the dyad together), partner effects (e.g., one partner impacts the other), reciprocity or mutual influence within the dyad, and exposure to same external conditions. Importantly, failure to account for nonindependence of outcome data may lead to biased significance testing for effects of independent variables on nonindependent outcome data; significance tests may be both too liberal (e.g., too many significant results found, type I error) or too conservative (e.g.,

a "true" effect was not found to be significant, type II error) depending on the intraclass correlation of the outcome variable (Kenny, Kashy, & Cook, 2006).

It has been previously shown that cancer patients' and caregivers' depressive symptoms are significantly and positively correlated (*r*s= .23-.29; Given et al., 1993; Kurtz et al., 1995). It is also known that patients' distress negatively affects their caregivers' physical functioning, and vice versa (Kim et al., 2008a; Kim et al., 2015a; Kim et al., 2008b). Evidence therefore suggests that cancer patients and their caregivers would report similarly compromized psychological and physical functioning, representing the mutual experience of cancer in the family. However, whether nonindependence exists between partners' stress biomarkers has yet to be empirically tested.

Another attractive feature of APIM is the ability to directly model, estimate, and test the mutual influence that may exist between a dyad; e.g., whether there is a significant impact of a partner's predictor variable on one's own outcome variable above and beyond the effects of one's own predictor variable (Cook & Kenny, 2005; Kashy & Kenny, 2000; Kenny & Cook, 1999; Kenny et al., 2006). For each outcome marker, APIM was utilized to test the effect of cancer patients' depressive symptoms on their own and their partner's biomarker, while simultaneously testing the same effects for caregivers. In the APIM, the effect of one's own predictor (e.g., patient depressive symptoms) on one's own outcome variable (e.g., patient IL-6) is termed the "actor effect"—these effects were used to test Aim 2 hypotheses. The effect of one's own predictor (e.g., patient depressive symptoms) on one's partner's outcome (e.g., caregiver

IL-6) is termed the "partner effect"—these effects were used to test Aim 3 hypotheses (see Figure 3).

For the primary analyses, selected covariates were controlled in the SEM models by regressing the patient stress biomarker onto the patient covariates, and the caregiver stress biomarker onto the caregiver covariates. All exogenous variables (e.g., predictors and covariates) were allowed to covary. Both patient and caregiver CES-D scores were centered at the grand mean (e.g., mean of all CES-D scores including both patients and caregivers) to facilitate interpretation of results (Kenny et al., 2006). Equations were modeled seperately for each biological outcome variable (e.g., there was one model each for IL-6, CRP, and cortisol slope outcomes). Chi-square significance values greater than .05, comparative fit index (CFI; Bentler, 1990) values greater than .95, and standardized root mean square residual values (SRMR; Bentler, 1995) less than .08 evidenced adequate fit of a specified model to the data (Hu & Bentler, 1999; Kline, 2011).

Exploratory Analyses. Evidence further suggests that the association of inflammation and HPA axis dysfunction with somatic/neurovegetative depressive symptoms (e.g., appetite disturbance, psychomotor retardation) may be stronger than that between the biomarkers and cognitive/affective depressive symptoms (e.g., low self-esteem, feeling sad; Capuron et al., 2002; Gimeno et al., 2009; Kiecolt-Glaser et al., 2003; Stewart et al., 2006). As such, the distinct associations between the measured depressive symptom subscales of Somatic Complaints, Depressed Affect, Lack of Positive Affect, and Interpersonal Problems with the biomarker outcomes were investigated. To test whether the four subscales of depressive symptoms measured by the CES-D were differentially related to patient and caregiver biological outcomes, the four

depressive symptom subscales were all tested concurrently as exogenous predictors of patient and caregiver stress biomarkers (see Figure 4).

The first exploratory project aim tested the *intrapersonal* associations between one's own depressive symptom subscales and one's own concurrent stress biomarker outcomes, or the *actor effects* estimated in the APIM (see Figure 4, horizontal lines). It was hypothesized that somatic symptoms would have the strongest association with one's own stress biomarkers compared to affective (e.g., depressive and Lack of Positive Affect) and interpersonal symptoms. To test these hypotheses, model fit was compared between the model constraining the patient actor effect of the Somatic Complaints subscale score equal with the actor effects of the other three subscale scores (i.e., Depressed Affect, Lack of Positive Affect, and Interpersonal Problems) and the unconstrained model. Hypotheses would be supported if constraining actor effects for Somatic Complaints with the other subscale scores resulted in a significant reduction in model fit compared with that of unconstrained model, as indicated by a significant chi-square difference test. Model testing was repeated with caregiver actor effects to test caregiver exploratory aim 1 hypotheses.

The second project aim tested the *interpersonal* associations between one's own depressive symptom subscales and one's *partner's* concurrent stress biomarker outcomes, or the *partner effects* estimated in the APIM (see Figure 4, crossing dashed lines). These hypotheses were tested similarly to exploratory aim 1 hypotheses, by constraining *partner* effects equal and determining whether model fit was significantly reduced compared to the unconstrained model. It was hypothesized that there would be no difference between partner effects of the four depressive symptom subscales; therefore,

patient hypotheses were supported if the patient partner effects were able to be all constrained equal without significantly reducing model fit compared to a fully unconstrained model (and similarly for hypotheses examining caregiver partner effects).

Chapter 3. Results

In total, data from 81 dyads (84 patients and 86 caregivers) were subject to statistical analyses for this study. All but one patient-caregiver dyad completed the study questionnaire, which included a measure for depressive symptoms. Of all participants, 57 patients and 63 caregivers provided a blood sample; 77 patients and 81 caregivers provided salivary cortisol samples. As shown in Table 1, the sample was approximately two thirds Hispanic white (60.7% patients, 62.8% caregivers), with the remainder of the sample comprising non-Hispanic white (26.2% patients, 24.4% caregivers) and African American (13.1% patients, 12.8% caregivers) participants. Patients and caregivers reported comparable educational attainment, with the samples tending to be relatively well educated. Patients and caregivers also reported comparable and low adherence to health lifestyle guidelines, with a majority of participants endorsing regular alcohol consumption, lack of fruit and vegetable consumption, and sedentary lifestyle. Regarding medical characteristics, approximately one-third of the patients reported having begun receiving treatment for their cancer prior to completing assessment. Approximately two-thirds of the patients were diagnosed with advanced stage colon or rectal cancer, with patients and caregivers participating in study assessments approximately three months following the diagnosis (see Table 2).

Data Descriptives

Data were inspected using quality control procedures. For patient cortisol sampling times, two afternoon samples and two evening samples were removed due to extreme sampling time (two patients affected). For caregiver cortisol sampling times, one

afternoon sample and two evening samples were removed due to extreme sampling time (three caregivers affected). For patient cortisol values, two waking samples, one afternoon sample, and two evening samples were capped at the maximum allowable cortisol value due to being extreme relative to the sample (four patients affected). For caregiver cortisol values, one waking sample, three afternoon samples, and two evening samples were capped at the maximum allowable cortisol value due to being extreme relative to the sample (three caregivers affected). Next, one highly influential observation was excluded due to being identified as highly influential with respect to the patient or caregiver sample, respectively (one patient cortisol slope, Cook's D = 1.00).

Examining indices of skew and kurtosis showed that, among patients, CRP and afternoon and evening cortisol values were significantly positively skewed. Among caregivers, cortisol values were significantly positively skewed at all three sampling time points. All biomarker data were therefore natural-log transformed.

Descriptives for study variables are presented in Table 2. Patients and caregivers reported comparable high levels of depressive symptoms. The depressive symptoms from patients in the current study were elevated compared to a sample of metastatic renal cell carcinoma patients in the active treatment phase (M = 10.20; Cohen et al., 2012) and to a sample of older breast, colon, lung, and prostate cancer patients within six weeks of treatment initiation (M = 10.80; Kurtz, Kurtz, Given, & Given, 2004). Depressive symptoms from caregivers in the current study were also elevated compared to those reported by the caregivers of older breast, colon, lung, and prostate cancer patients within six weeks of treatment initiation (M = 10.86, Kurtz et al., 2004) and to those reported by caregivers of brain cancer patients prior to treatment initiation (M = 12.00; Rohleder et

al., 2009). For depressive symptom subscale scores from the current study, caregivers reported marginally greater Depressed Affect and significantly greater Lack of Positive Affect compared to their patients.

Regarding inflammatory markers, patients displayed significantly higher IL-6 and marginally higher CRP compared to their caregivers. Compared to prior studies of colorectal cancer patients prior to receiving treatment, the current sample of patients' IL-6 values were comparable (M = 2.98 pg/mL, Dymicka-Piekarska, Matowicka-Karna, Gryko, Kemona-Chętnik, & Kemona, 2007; M = 2.80 pg/mL; Kaminska et al., 2005), but their CRP levels were lower (M = 18.79 mg/L; Dymicak-Piekarska et al., 2007). Caregivers' IL-6 and CRP values from the current study were comparable to those seen among caregivers of patients with Alzheimer's disease ($M_{IL\text{-}6}$ = 1.38 pg/mL, M_{CRP} = 3.20 mg/L, von Känel et al., 2006). Caregivers' IL-6 values were also comparable to those seen among caregivers of patients with brain cancer (M = 1.35 pg/mL, Rohleder et al., 2009) and non-caregiving healthy adults from the Whitehall II study (M = 1.47 pg/mL, Gimeno et al., 2009). However, caregivers' CRP values were greater than those of the caregivers of patients with brain cancer (M = 1.49 mg/L; Rohleder et al., 2009) and those observed among non-caregiving healthy adults from the Whitehall II study (M = 0.81 mg/L, Gimeno et al., 2009). Twenty-seven of the 57 patients providing blood (47%) and 22 of the 63 caregivers providing blood (35%) would be considered at "high risk" for future heart attack or stroke based on CRP values $\geq$ 3 mg/L (Ridker, 2003).

Regarding HPA axis functioning, patients and their caregivers from the current study displayed comparable cortisol slopes. Patients' cortisol slopes were comparable to those documented in prior study of patients with metastatic lung cancer diagnosed during

approximately two years prior (*M* = -0.11 µg/dL/hour, Sephton et al., 2013) and patients with metastatic breast cancer diagnosed approximately three years prior (*M* = -0.10 µg/dL/hour, Turner-Cobb et al., 2000; Sephton et al., 2000). Caregivers' cortisol slopes were flatter than those documented among samples of Alzheimer's caregivers (*M* = -1.00 µg/dL/hour, Gallagher-Thompson et al., 2006), but comparable to a population of stressed older adults (*M* = -0.16 µg/dL/hour, Kraemer et al., 2006).

Regarding covariates, patients on average were older and had lower BMIs compared to caregivers, and a greater proportion of the caregiver sample was female compared to the patient sample. The current patient sample was younger than the typical population of colorectal cancer patients: whereas over 75% of colorectal cancer diagnoses occur in Americans aged 65 and older (Howlader et al. [SEER], 2003) and over 90% in Americans aged 50 and older (ACS, 2015), only 10% of the current patient sample was older than age 65 and only 67% was older than age 50. Both patient and caregiver samples were younger than samples recruited from previous dyadic psychosocial studies among colorectal cancer patients and their caregivers (*M*s = 66.75 patients, 69.37 caregivers, Grimmett, Bridgewater, Steptoe, & Wardle, 2011; *M*s = 61 patients, 61 caregivers, Northouse, Mood, Templin, Mellon, & George, 2000). Both patients and caregivers had BMI values comparable to the average adult American (*M* = 26.5, CDC, 2003). The caregiver sample was approximately three-quarters female—this was a significantly greater proportion than the patient sample, which was approximately three-fifths female. Sex distribution of the current study is as expected, with colon and rectal cancers tending to be sex neutral (ACS, 2015), whereas the majority of informal caregivers are female (National Alliance for Caregiving, 2009).

Missing Data Management

One patient was missing CES-D (1.2 percent), 27 patients were missing IL-6 and CRP (32.1 percent), and eight patients were missing cortisol slope (7.1 percent). For caregivers, one was missing CES-D (1.2 percent), 24 were missing IL-6 (26.7 percent), 25 were missing CRP (27.9 percent), and six were missing cortisol slope (7.0 percent). Little's missing completely at random (MCAR) test suggested that the data met MCAR assumptions ($\chi^2[486]= 492.07$, $p= .42$). Potential relationships of missingness on biomarker outcomes with CES-D, covariates, and a self-reported measure of physical health (Medical Outcome Survey Short-Form-12 Physical Health Component Score; Ware, Kosinski, & Keller, 1996) were also examined via bivariate correlations.

For patients, steeper cortisol slope and greater BMI were marginally related to missingness for IL-6 and CRP ($ps <.10$), but no variables were related to missingness for cortisol slope ($ps > .25$). For caregivers, steeper cortisol slope was marginally related to their missingness for CRP ($p = .09$), but no variables were related to missingness for IL-6 or cortisol slope ($ps > .12$). Therefore, to improve reliability of FIML estimation, patient cortisol slope was included as an auxiliary variable for IL-6 and CRP models, and caregiver cortisol slope was included as an auxiliary variable for the CRP model. BMI was available to FIML estimation for all models as it was included as a covariate.

Testing Study Aims: Intra- and Interpersonal Associations of Depressive Symptoms with Stress Biomarkers

Actor-partner interdependence models (APIM) were used to test study hypotheses for each of three stress biomarker outcomes. Table 6 lists results from the APIM for IL-6 (Hypotheses 2, 5, 8), Table 7 lists results for CRP (Hypotheses 3, 6, 9), and Table 8 lists

results for cortisol slope (Hypotheses 4, 7, 10). Marginal and significant paths for the three APIM models are displayed in Figures 5 through 7 for IL-6, CRP, and cortisol slope, respectively.

Testing aim 1. Aim 1 measured the level of nonindependence among cancer patients' and caregivers' depressive symptoms as well as patients' and caregivers' stress biomarkers. In the APIM, dyad members' exogenous variables are allowed to correlate, and the dyad members' outcome variable residual errors are also set to correlate (see Figure 3, curved lines). These covariances were estimated in the SEM APIM and were used to test Aim 1 hypotheses.

Hypothesis 1. It was hypothesized that patients' and caregivers' CES-D values would be positively correlated. Hypothesis 1 was not supported: the estimate of covariance between patients' and caregivers' CES-D values was not significantly different from 0 in any of the three APIM models (*p*s = .53-.54). In addition, the bivariate correlation between patients' and their caregivers' CES-D values was also was non-significant ($r = .06$, $p = .58$).

Hypothesis 2. It was hypothesized that patients' and caregivers' IL-6 values would be positively correlated, controlling for patient and caregiver depressive symptoms and covariates. Hypothesis 2 was not supported: the estimate of covariance between patients' and caregivers' IL-6 values was not significantly different than 0 ($p = .23$). When not controlling for covariates, the bivariate correlation between patients' and their caregivers' IL-6 was marginally positive ($r = .27$, $p = .07$).

Hypothesis 3. It was hypothesized that patients' and caregivers' CRP values would be positively correlated, controlling for patient and caregiver depressive symptoms and covariates. Hypothesis 3 was not supported: the estimate of covariance between patients' and caregivers' CRP values was not significantly different from 0 ($p = .88$). However, patients' and caregivers' CRP were significantly correlated when not controlling for covariates ($r = .31$, $p = .04$).

Hypothesis 4. It was hypothesized that patients' and caregivers' cortisol slopes would be positively correlated, controlling for patient and caregiver depressive symptoms and covariates. Hypothesis 4 was supported: the estimate of covariance between patients' and caregivers' cortisol slope values was significantly greater than 0 ($p = .03$). When not controlling for covariates, patients' and their caregivers' cortisol slope was also significantly positively correlated ($r = .31$, $p = .01$).

Testing aim 2. The second project aim tested the *intrapersonal* associations between one's own depressive symptoms and one's own concurrent stress biomarker outcomes, or the *actor effects* estimated in the APIM (see Figure 3, horizontal lines).

Whether actor effects significantly differed between patients and caregivers was also tested (e.g., whether the effect of patient depressive symptoms on their own IL-6 was different than the effect of caregiver depressive symptoms on their own IL-6). This research question was tested by constraining the patient and caregiver actor effects to be equal, then comparing model fit between the constrained and unconstrained models with a chi square difference test ($df_{\Delta} = df_{\text{constrained}} - df_{\text{unconstrained}}$; $\chi^2_{\Delta} = \chi^2_{\text{constrained}} - \chi^2_{\text{unconstrained}}$). These chi square difference tests have 1 degree of freedom (estimating 1 actor path value

vs. 2); therefore, chi square difference values less than 2.70 indicated equivalent model fits ($\chi^2_\Delta[1] = 2.70$, $p = .10$).

Hypothesis 5. It was hypothesized that one's CES-D score would be positively associated with one's own IL-6 for cancer patients (hypothesis 5.1) and caregivers (hypothesis 5.2). Neither hypothesis 5.1 nor 5.2 were supported: actor effects were equivalent ($\chi^2_\Delta[1] = 1.09$, $p > .10$) and not significantly different from 0 (ps = .14). When not controlling for covariates, the bivariate correlations between own CES-D and IL-6 values were also non-significant for both patients ($r = .08$, $p = .54$) and caregivers ($r = .16$, $p = .23$).

Hypothesis 6. It was hypothesized that one's CES-D score would be positively associated with one's own CRP for cancer patients (hypothesis 6.1) and caregivers (hypothesis 6.2). Neither hypothesis 6.1 nor 6.2 were supported: actor effects were equivalent ($\chi^2_\Delta[1] = 0.21$, $p > .10$) and not significantly different from 0 (ps = .46). When not controlling for covariates, the bivariate correlations between own CES-D and CRP values were also non-significant for both patients (rs = .02, $p = .89$) and caregivers ($r = .09$, $p = .49$).

Hypothesis 7. It was hypothesized one's CES-D score would be positively associated with one's own cortisol slope for cancer patients (hypothesis 7.1) and caregivers (hypothesis 7.2). Neither hypothesis 7.1 nor 7.2 were supported: actor effects were equivalent ($\chi^2_\Delta[1]= 0.53$, $p > .10$) and not significantly different from 0 (ps = .27). When not controlling for covariates, the bivariate correlations between own CES-D and

cortisol slope values were also non-significant for patients (r = .04, p = .71) and caregivers (r = -.10, p = 38).

Testing aim 3. The third project aim tested the *interpersonal* associations between one's own depressive symptoms and one's *partner's* concurrent stress biomarker outcomes, or the *partner effects* estimated in the APIM (see Figure 3, crossing dashed lines). Whether partner effects were equivalent was also tested, as well as whether partner effects were equivalent to actor effects, following the path constraint methodology addressed under "Testing aim 2" (p. 68).

Hypothesis 8. It was hypothesized that patients' CES-D score would be positively associated with caregivers' IL-6 (hypothesis 8.1) and caregivers' CES-D score would be positively associated with patients' IL-6 (hypothesis 8.2). Neither hypothesis 8.1 nor 8.2 were supported: partner effects were equivalent to one another ($\chi^2_\Delta[1] = 0.20$, $p > .10$) and to actor effects ($\chi^2_\Delta[1] = 0.20$, $p > .10$), and were not significantly different from 0 (ps = .14). The final IL-6 model fit the data according to chi square and SRMR fit indices ($\chi^2[11] = 14.76$, p = .19; SRMR = .05), yet a low CFI (.87) suggests the specified model did not improve fit relative to a baseline model with zero population covariances among variables. When not controlling for covariates, the bivariate correlations between one's CES-D with their partners' IL-6 values were also non-significant for patients to caregivers (r = .05, p = .74) and vice versa for caregivers to patients (r = .20, p =.15).

Hypothesis 9. It was hypothesized that patients' CES-D score would be positively associated with caregivers' CRP (hypothesis 9.1) and caregivers' CES-D score would be positively associated with patients' CRP (hypothesis 9.2). Neither hypothesis 9.1 nor 9.2

were supported: partner effects were equivalent to one other ($\chi^2_\Delta[1] = 2.38$, $p > .10$) and to actor effects ($\chi^2_\Delta[1] = 0.03$, $p > .10$), and were not significantly different from 0 (*p*s = .46). The final CRP model fit the data adequately ($\chi^2[11] = 11.22$, $p = .42$; CFI = 0.99; SRMR = .05). When not controlling for covariates, the bivariate correlations between one's CES-D with their partners' CRP values were also non-significant for patients to caregivers ($r = .18$, $p = .18$) and vice versa from caregivers to patients ($r = .06$, $p = .65$).

Hypothesis 10. It was hypothesized that patients' CES-D score would be positively associated with caregivers' cortisol slope (hypothesis 10.1) and caregivers' CES-D score would positively associated with patients' cortisol slope (hypothesis 10.2). Neither hypothesis 10.1 nor 10.2 were supported: partner effects were equivalent to one other ($\chi^2_\Delta[1] = 0.07$, $p > .10$), but were marginally different from actor effects ($\chi^2_\Delta[1] = 3.82$, $p = .05$), yet were also not significantly different from 0 (*p*s = .12). The final cortisol slope model fit the data adequately ($\chi^2[10] = 7.39$, $p = .69$; CFI = 1; SRMR = .04). When not controlling for covariates, the bivariate correlations between one's CES-D with their partners' cortisol slope values were also non-significant for both patients to caregivers ($r = .09$, $p = .42$) and vice versa from caregivers to patients ($r = .12$, $p = .31$).

Summary of primary analyses. It was hypothesized that colorectal cancer patients and their caregivers would show positively correlated, or *nonindependent*, depressive symptoms and stress biomarkers. Nonindependence of patients' and caregivers' data was partially supported, with dyads' cortisol slope values positively correlated. It was further hypothesized that patients' and caregivers' depressive symptoms would be positively associated with both their own and their partners' stress

biomarkers after controlling for covariates of age, BMI, and sex (and patients' cancer treatment status and stage for patients only). This hypothesis was unsupported.

Exploratory Analyses: Intra- and Interpersonal Associations of Distinct Depressive Symptom Subscales with Stress Biomarkers

Investigation of the distinct associations between the measured depressive symptom subscales of Somatic Complaints, Depressed Affect, Lack of Positive Affect, and Interpersonal Problems with the biomarker outcomes when controlling for covariates was proposed. However, reliable estimates were not able to be derived when each of the four subscales and covariates for both patients and caregivers were included in the APIM due to limited sample size. Therefore, the relationships of the distinct depressive symptom subscales with each biomarker were investigated without controlling for covariates. Table 9 lists results from the exploratory APIM for IL-6 (Hypotheses 1, 4), Table 10 lists results for CRP (Hypotheses 2, 5), and Table 11 lists results for cortisol slope (Hypotheses 3, 6). Marginal and significant paths for the three exploratory APIM models are displayed in Figures 8 through 10 for IL-6, CRP, and cortisol slope, respectively.

Testing exploratory aim 1. The first exploratory project aim tested the *intrapersonal* associations between one's own depressive symptom subscales and one's own concurrent stress biomarker outcomes, or the *actor effects* estimated in the APIM (see Figure 4, horizontal lines).

Exploratory hypothesis 1. The hypotheses that somatic depressive symptoms would be more strongly associated with one's own IL-6 compared to the other symptom subscales among both patients and caregivers were not supported. The patient actor

effects of Somatic Complaints, Lack of Positive Affect, and Interpersonal Problems subscales were equivalent ($\chi^2[2] = 0.58$, $p = .75$) and significantly greater than 0 ($ps = .01$). However, the patient actor effect of Depressed Affect was significantly different from that of the other three subscales ($\chi^2_\Delta[1] = 5.62$, $p = .02$) and was significantly less than 0 ($p = .02$). For caregivers, all actor effects of the four distinct CES-D subscales were equivalent ($\chi^2_\Delta[3] = 2.15$, $p = .54$) and not significantly different from 0 ($ps = .21$).

Exploratory hypothesis 2. The hypotheses that somatic depressive symptoms would be more strongly associated with one's own CRP compared to the other symptom subscales among both patients and caregivers were not supported. All actor effects of the four distinct CES-D subscales for both patients and caregivers were equivalent ($\chi^2[7] = 6.42$, $p = .49$) and not significantly different from 0 ($ps = .29$).

Exploratory hypothesis 3. The hypotheses that somatic depressive symptoms would be more strongly associated with one's own cortisol slope compared to the other symptom subscales among both patients and caregivers were not supported. All actor effects of the four distinct CES-D subscales for both patients and caregivers were equivalent ($\chi^2[7] = 3.25$, $p = .86$) and not significantly different from 0 ($ps = .54$).

Testing exploratory aim 2. The second exploratory project aim tested the *interpersonal* associations between one's own depressive symptom subscales and one's *partner's* concurrent stress biomarker outcomes, or the *partner effects* estimated in the APIM.

Exploratory hypothesis 4. The hypothesis that there would be no difference between the effects of one's own four distinct symptom subscales on one's partner's IL-6

for both patients and caregivers was supported. All partner effects of the four distinct CES-D subscales for both patients and caregivers were equivalent ($\chi^2_\Delta[7] = 11.00$, $p = .14$) and not significantly different from 0 ($ps = .20$). The final model constraining patient actor effects except Depressed Affect, all caregiver actor effects, and all partner effects, separately, fit the data adequately according to chi square and SRMR fit indices ($\chi^2[12] = 13.731$, $p = .32$; SRMR = .05), yet a low CFI (.82) suggests the specified model did not improve fit relative to a baseline model with zero population covariances among variables.

Exploratory hypothesis 5. The hypothesis that there would be no difference between the effects of one's own four distinct symptom subscales on one's partner's CRP for both patients and caregivers was supported. All partner effects of the four distinct CES-D subscales for both patients and caregivers were equivalent to actor effects ($\chi^2_\Delta[8] = 5.20$, $p = .74$) and not significantly different from 0 ($ps = .29$). The final model constraining all effects equal fit the data adequately ($\chi^2[15] = 11.62$, $p = .71$; CFI = 1; SRMR = .06).

Exploratory hypothesis 6. The hypothesis that there would be no difference between the effects of one's own four distinct symptom subscales on one's partner's cortisol slope for both patients and caregivers was supported. All partner effects of the four distinct CES-D subscales for both patients and caregivers were equivalent to actor effects ($\chi^2_\Delta[8] = 6.73$, $p = .57$) and not significantly different from 0 ($ps = .54$). The final model constraining all effects equal fit the data adequately ($\chi^2[15] = 9.98$, $p = .82$; CFI = 1; SRMR = .04).

Summary of exploratory analyses. It was hypothesized that one's somatic symptoms of depression would be more strongly associated with one's own stress biomarkers, for both cancer patients and their caregivers. These hypotheses were not supported. Patients' IL-6 was positively associated with their own Somatic Complaints, Lack of Positive Affect, and Interpersonal Problems to an equal degree, while their Depressed Affect was inversely associated with their IL-6. No other actor effects were significant. The hypotheses that the effects of one's depressive symptom subscales would not differ in their relations with one's partners' stress biomarkers was fully supported. For all stress biomarker outcomes, partner effects of symptom subscales were equivalent for both patients and caregivers, yet all effects were non-significant.

Chapter 4. Discussion

The current study tested the extent to which depressive symptoms related to stress biomarkers among colorectal cancer patients and their family caregivers as a first test of the dyadic biopsychosocial model of the interdependence of cancer patients' and their caregivers physiological and psychological health. It was hypothesized that dyads' data would be interdependent (Aim 1). Aim 1 hypotheses were partially supported: dyad members' depressive symptoms were unrelated, but their stress biomarkers were significantly positively correlated. Next, it was hypothesized that one's own depressive symptoms would be positively related to one's own stress biomarkers (Aim 2: actor effects) as well as positively related to one's partner's stress biomarkers (Aim 3: partner effects). Neither Aim 2 nor Aim 3 hypotheses were supported. Exploratory hypotheses with depressive symptom subscales largely corroborated findings from primary aims.

Interdependence Between Cancer Patients' and their Caregivers' Depressive Symptoms and Stress Biomarkers

Depressive symptoms. In the current study, patients and caregivers reported elevated depressive symptoms compared with other samples of cancer patients (Cohen et al., 2012; Kurtz et al., 2004) and caregivers (Kurtz et al., 2004; Rohleder et al., 2009). Patients and their caregivers did not differ from one other in levels of depressive symptoms on average. However, patients' and their caregivers' depressive symptoms were not significantly correlated, either in bivariate analyses or when controlling for covariates and stress biomarkers, failing to support hypothesis 1.

Timing of data collection may have contributed to the lack of significant correlation between cancer patients' and their caregivers' depressive symptoms around

three months following diagnosis. A meta-analysis of nine studies of patient-caregiver psychological distress (Hodges et al., 2005) showed that, although patients' and caregivers' distress was significantly correlated overall ($d = .39$, $p < .001$), the correlation was not significant around the time of diagnosis (e.g., three of nine studies: Hoskins, 1995; Kay & Gracely, 1993; Northouse et al., 2000). The study showed that as time since diagnosis progressed, however, patients' and caregivers' distress tended to become more strongly correlated. Our non-significant correlation in depressive symptoms between patients and their caregivers is also consistent with findings from Tuinstra and colleagues (2004), who reported non-significant correlations between colorectal cancer patients' and caregivers' CES-D scores cross-sectionally within the six months following diagnosis (*r*s = .19 at the week following surgery, .09 at three months post-diagnosis, and.12 at six months post-diagnosis). Although the current study did not support cross-sectional associations, examination of the longitudinal relations between these variables is yet warranted, as evidence suggests that patients' and their caregivers' depressive symptoms align over the year following diagnosis (Hodges et al., 2005; Kaye & Gracely, 1993; Segrin et al., 2005; Segrin et al., 2007; Tuinstra et al., 2004).

In practice, findings that patients and their caregivers reported elevated depressive symptoms suggest that psychosocial interventions are warranted among both of these populations. As symptoms were unrelated among dyad members, however, interventions targeting depressive symptoms in the early months following diagnosis may be most effectively delivered to distressed patients and caregivers independently to best address their unique concerns during this time.

Stress biomarkers. Compared to other samples of cancer patients, the current sample of patients' IL-6 (Dymicak-Piekarska et al., 2007; Kaminska et al., 2005) and cortisol slope (Sephton et al., 2000; Sephton et al., 2013) values were comparable, but their CRP values were lower (Dymicak-Piekarska et al., 2007). For caregivers, the current sample of caregivers' IL-6 (Gimeno et al., 2009; von Känel et al., 2006) and cortisol slope (Kraemer et al., 2006) values were comparable to those documented from Alzheimer's caregivers and stressed older adults, but their CRP values were greater than those documented among brain cancer caregivers (Rohleder et al., 2009) and non-caregiving older adults (Gimeno et al., 2009). Compared to their caregivers, patients had significantly greater levels of IL-6, marginally higher CRP, and similar cortisol slopes.

With regard to correlation in stress biomarkers, patients' and their caregivers' IL-6 were not significantly related in either bivariate analyses or when controlling for covariates and depressive symptoms, failing to support hypothesis 2. CRP levels were significantly positively correlated only in bivariate analyses, partially supporting hypothesis 3. Lastly, cortisol slopes were significantly positively associated, both in bivariate analyses and when controlling for covariates and depressive symptoms, supporting hypothesis 4. Effects were small-to-medium, which were greater than expected. Findings advance prior research that documented interdependence between patients' and their caregivers' self-reported physical health (Segrin & Badger, 2014; Shaffer, Kim, & Carver, under review).

This novel evidence of correlation between patients' and caregivers' stress biomarkers suggests that a combination of shared risk factors and cross-over effects exist between patients and caregivers (Kenny et al., 2006), supporting the dyadic

biopsychosocial model of shared vulnerability between patients' and caregivers' physical health. That interdependence between patients' and caregivers' stress biomarkers was documented during the acute diagnosis and treatment phase is notable, as patients' inflammation and endocrine dysregulation are heightened by tumor- and treatment-related factors during this time (Galizia et al., 2002; Mantovani et al., 2008; Vakkila & Lotze, 2004; Weinrib et al., 2010). Caregivers, however, tend to show stress physiology comparable to non-caregiving counterparts during the acute phase, showing blunted glucocorticoid response approximately nine months post-diagnosis (Miller et al., 2002; Miller et al., 2008) and elevated inflammation approximately 12 months post-diagnosis (Rohleder et al., 2009).

One possible explanation for interdependence between dyads' stress biomarkers during this early stage prior to the full impact of the psychosocial stress of the diagnosis may be pre-existing vulnerability factors shared by patients and caregivers. Socio-economic status may be particularly relevant, which has been associated both with more advanced cancer at stage of diagnosis (Byers et al., 2008; Clegg et al., 2008; Schwartz, Crossley-May, Vigneau, Brown, &Banerjee, 2003) and elevated stress biomarkers (Chen, Cohen, & Miller, 2009; Dowd, Simanek, & Aiello, 2009; O'Connor et al., 2009). Effects may be mediated through restricted access to medical care, greater health risk/lower health promotion behaviors, and chronic stress of poverty (O'Connor et al., 2009; Woods, Rachet, & Coleman, 2005). Further examination of shared vulnerability factors for patients' and caregivers' elevated inflammation and poor HPA axis functioning is warranted to identify patient-caregiver dyads at greatest risk for poor physical health around the time of cancer diagnosis (Chung & Chang, 2003; Cohen et al., 2012; Knüpfer

& Preiss, 2010; Roxburgh & McMillan, 2010; Sephton et al., 2000) and beyond (Björntorp & Rosmond, 1999; Danesh et al., 2004; Helzlsouer et al., 2006; Libby et al., 2000; Matthews et al., 2006; Nijm & Jonasson, 2009; Otte et al., 2004; Pereg et al., 2011).

Clinically, interdependence between patients' and caregivers' physiological health suggests that healthy lifestyle interventions aimed to improve physical health of cancer patients and/or their caregivers should target both together as a unit (Hagedoorn et al., 2008; Hodges et al., 2005; Matthews et al., 2003). Evidence from prior meta-analyses supports this assertion, with findings that lifestyle interventions provided to both patients and their family members were more beneficial to patients than those delivered to patients exclusively (Hartmann, Bäzner, Wild, Eisler, & Herzog, 2010; Martire et al., 2004; Martire, Schulz, Helgeson, Small, & Saghafi, 2010). With cancer treatments predisposing patients to secondary cancers and chronic illnesses (Carver et al., 2007; de Gonzalez et al., 2011; Yeh et al., 2004) and caregiving experience predisposing caregivers to comparable premature morbidity (Ji et al., 2012; Rohleder et al., 2009; Vitaliano et al., 2002), targeted physical health interventions will be imperative for mitigating the deleterious effects of cancer on both patients' and caregivers' physical health.

Methodologically, interdependence in patients' and caregivers' stress biomarkers suggests that a dyadic analytic approach is most appropriate to detect immune and endocrine health risk factors common between the patient-caregiver unit. Individual-level analyses for patients and caregivers separately will fail to capture shared risk factors and cross-over effects transmitting risk from one partner to the other. To properly measure

these effects, dyadic data analyses must be used, as interdependence between dyad members' outcome variables (e.g., stress biomarkers) can bias significance testing for effects of independent variables on those outcomes. Stress biomarkers represent "mixed" variables, in which mean values differ both between patients and caregivers, as well as across dyads (Kenny et al., 2006). The current analyses suggest small-to-medium interdependence between dyad members' stress biomarker values, particularly among CRP and cortisol slope values (intraclass correlation [ICC] = .26 and .23, respectively, computed via double-entry pairwise correlation [see Kenny et al., 2006 pp. 37-38; Griffin & Gonzalez, 1995; Gonzalez & Griffin, 1999]). Significance testing for the effects of a mixed independent variable with small-to-medium interdependence (e.g., depressive symptoms ICC = .05) will not be meaningfully biased (Kenny, Kashy, & Bolger, 1998). However, significance testing will be meaningfully biased for effects of mixed independent variables with medium or greater interdependence (e.g., $|ICC| > 0.5$), or for between-dyad variables (ICC = 1, same value for each dyad member, e.g., years married to dyad partner) or within-dyad variables (ICC = -1, inverse values for each dyad member, e.g., proportion of childcare provided). For independent variables with ICC of 0.5 or greater, effects on the stress biomarker outcomes with an alpha of .05 would actually indicate an alpha of .068 or higher – the test of significance would be too liberal, increasing risk of Type I error. Conversely, for independent variables with ICC of -0.5 or lower, effects on the stress biomarker outcomes with an alpha of .05 would actually indicate an alpha of .034 or lower – the test of significance would be too conservative, increasing risk of Type II error (Kenny et al., 1998). Results suggest that studies examining the impact of relational factors between patients and caregivers on their stress

biomarker outcomes must consider the interdependence between patients' and caregivers' physiological data to maximize power and precision.

Intrapersonal Associations Between Own Depressive Symptoms and Stress Biomarkers

No significant associations between own depressive symptoms and stress biomarkers were found among our samples of patients or caregivers, failing to support hypotheses 5 to 7. These results are inconsistent with existing studies showing significant positive associations between depressive symptoms with IL-6, CRP, and cortisol slope (Gillespie & Nemeroff, 2005; Haapakoski et al., in press; Howren et al., 2009; Jehn et al., 2001; Mussleman et al., 2001; Lutgendorf et al., 2008; Rich et al., 2005; Stewart et al., 2009). However, a meta-analysis by Howren and colleagues (2009) found that using self-reported measures of depressive symptoms and controlling for BMI substantially attenuates the strength of association between depressive symptoms and inflammatory markers. Effect sizes observed in the current study are comparable to the meta-analytic effect sizes from Howren et al. (2009) of studies that controlled for BMI (*d*s = 0.08 and 0.11 for IL-6 and CRP, respectively) or used self-report measures of depressive symptoms (*d*s = 0.08 and 0.12). Comparable information for cortisol slope is unavailable.

Null findings may be attributable to several factors. First, analyses were slightly underpowered (70 percent) to detect a small-to-medium effect for pro-inflammatory markers; although analyses with cortisol slope were adequately powered (79 percent). Second, prior studies linking stress biomarkers with depressive symptoms among cancer patients have been primarily conducted among more homogenous samples of cancer patients, such as those with advanced disease (Lutgendorf et al., 2008; Rich et al., 2005)

or among patients with clinically significant depression (Jehn et al., 2001; Mussleman et al., 2001). The current sample of patients, however, drew a range of cancer stages and levels of depressive symptoms, possibly reducing the ability to detect the effect of depressive symptoms on stress biomarkers. Data collection during the acute diagnosis and treatment phase may also have contributed to an obscured association, as effects of tumor- and treatment-related factors on patients' stress biomarkers are prominent during this period (Galizia et al., 2002; Mantovani et al., 2008; Vakkila & Lotze, 2004; Weinrib et al., 2010). Although cancer stage and treatment status were controlled from analyses, the diversity of the current sample of patients' tumor and treatment factors may have made variability due to depressive symptoms more difficult to detect.

Third, the timing of data collection during the acute diagnosis and treatment phase may also have affected the ability to detect a significant association between depressive symptoms and stress biomarkers for caregivers. Rohleder and authors (2009) demonstrated that cancer caregivers' IL-6, CRP, and cortisol slope did not differ from non-caregivers' at the time of diagnosis; however, caregivers, but not non-caregivers, showed a significant rise in their systemic inflammation over following year. Findings concurred with those from a study of Alzheimer's caregivers, which showed caregivers' rise in IL-6 was four times greater than that among non-caregivers (Kiecolt-Glaser et al., 2003). Additional research suggests immune and endocrine dysregulation among caregivers occurs over time due to blunted glucocorticoid signaling among caregivers' immune cells (Miller et al., 2002; Miller et al., 2008). Findings suggest that caregivers' depressive symptoms during the acute caregiving experience may prospectively predict

their later immune dysregulation, with this effect taking time to manifest (Stewart et al., 2006; Copeland et al., 2012; Duivis et al., 2014; Kupper et al., 2012).

Interpersonal Associations Between Own Depressive Symptoms and Partner's Stress Biomarkers

No significant associations between one's own depressive symptoms and one's partner's stress biomarkers were found among our samples of patients or caregivers, failing to support hypotheses 8 to 10. These results are inconsistent with existing studies using self-reported physical health (Kim et al., 2008a; Kim et al., 2008b; Kim et al., 2015a).

Factors that likely contributed to the null findings for Aim 2 hypotheses would have similarly affected Aim 3 findings. First, tests of partner effects were all underpowered, with achieved power ranging from 37 to 49 percent to detect an effect of depressive symptoms on partner stress biomarkers. Second, timing of data collection during the acute diagnosis and treatment phase may also be responsible for the lack of cross-over effects between patients' and caregivers' depressive symptoms to their partners' physiology. As aforementioned, patients' stress biomarkers were likely affected by tumor- and treatment-related factors, whereas caregivers' physiology may have not yet been impacted by the cancer experience at the time of assessment. See "Future Directions" for further discussion (p. 91).

Exploratory Analyses: Intra- and Interpersonal Associations of Distinct Depressive Symptom Subscales with Stress Biomarkers

There were no differences between the strength of relationship between own Somatic Complaints subscale scores on stress biomarkers versus effects of the other three affective/interpersonal CES-D symptom subscales, failing to support exploratory

hypotheses 1 to 3. These results are inconsistent with existing studies showing stronger relationships between somatic/neurovegetative symptoms of depression with stress physiology than affective/cognitive symptoms (Copeland et al., 2012; Duivis et al., 2013; Kupper et al., 2012; Stewart et al., 2006). Exploratory analyses largely corroborated findings from primary aims, though notably, exploratory analyses were completed without controlling for covariates due to sample size constraints. Distinct findings for depressive symptom subscales compared to overall depressive symptoms were found for interdependence of patients' and caregivers' Lack of Positive Affect and the associations between patients' symptom subscales and their own IL-6.

Findings for hypothesis 1 did not support interdependence between patients' and caregivers' overall depressive symptoms—similarly, patients' and caregivers' subscale scores for Somatic Complaints, Depressed Affect, and Interpersonal Problems were unrelated. However, patients and their caregivers reported positively correlated levels of Lack of Positive Affect. This subscale is thought to uniquely capture the affective quality of depression: whereas depressed affect is commonly reported as a symptom of both anxiety and depression, anhedonia (i.e., lack of positive affect) is considered unique to depression (Clark & Watson, 1991; Sheehan et al., 1995; Watson & Tellegen, 1985). As such, interdependence between patients' and caregivers' Lack of Positive Affect scales may capture correlation in their depressed emotional experience, whereas the lack of interdependence among the other scales may reflect dissimilarity among dyads' more generalized distress (Sheehan et al., 1995).

Supplemental analyses for patients' actor effects of depressive symptom subscales on their IL-6 also deviated from findings from primary analyses. Whereas patients'

overall level of depressive symptoms was not significantly related to their own IL-6, patients' Somatic Complaints, Lack of Positive Affect, and Interpersonal Problems were equally positively associated with their IL-6, while their Depressed Affect symptoms were inversely associated with their IL-6. Notably, these findings are exclusive to multivariate analyses controlling for covariation with other subscales, whereas all bivariate correlations between patient symptom subscales and IL-6 values are non-significant. Findings were also exclusive to patients' IL-6 and not replicated across patients' other stress biomarkers. Further study to determine whether these findings are replicable in larger samples is warranted.

Future Directions

Future studies of the dyadic biopsychosocial model should seek to address previously discussed limitations, including low power and cross-sectional study design during the acute diagnosis and treatment phase. Hypothesis testing power may be increased by first recruiting an adequate number of dyads, then minimizing missing data from these dyads. To this point, in the current analyses, actor effect analyses would have been adequately powered if no biomarker data were missing, yet partner analyses would have required twice the sample size to be adequately powered. Future studies should also strengthen power by limiting error variance in the stress biomarker outcome variables. For example, blood collection may be limited to mornings to limit effects of circadian rhythmicity on inflammatory factors, or to before treatment initiation among patients to limit effects of various treatment factors. However, placing limitations on data collection also burdens recruitment and increases the likelihood of missing data, so rigorous

methodological control must be balanced with recruitment flexibility to ensure a feasible study design.

Further, one must consider selection bias of the included sample, with 39% of eligible patients and 18% of eligible caregivers declining to participate. Of those who were eligible but refused to participate, the majority cited "no interest in research" as their refusal reason (61% of patient refusals and 43% of caregiver refusals) and "no time/too time consuming" (24% patients, 46% caregivers), as opposed to "does not want to worry about cancer" (9% patients, 11% caregivers), or "too tired to participate" (6% patients, 0% caregivers). Refusal rates among eligible patients was higher among non-Hispanic white patients (45%) as opposed to African-American (37%) and Hispanic (37%), whereas for eligible caregivers, refusal was highest among African-Americans (32%) as opposed to Hispanic (14%) and non-Hispanic white (12%). It is possible that more stressed participants chose to not participate in the study, restricting the range of stress levels in the included participants. Future studies should continue to seek to recruit a diverse participant sample to ensure external generalizability of effects.

Despite the limitations of the current study, interdependence in patients' and caregivers' stress biomarkers suggests a combination of shared risk factors and cross-over effects mutually impact dyad members' health (Kenny et al., 2006), warranting study of longitudinal processes, novel risk factors, and moderators. First, patients' and caregivers' depressive symptoms may prospectively predict their partners' physiological dysregulations, and therefore not detectable by cross-sectional study during the acute cancer stage. Patients and caregivers tend to adjust to the cancer experience in tandem, with distress levels drawing more similar between patients and caregivers as time since

the diagnosis prolongs (Hodges et al., 2005; Segrin et al., 2005; Tuinstra et al., 2004). As such, effects of psychosocial variables on stress biomarkers may take time to accumulate, in which prolonged experience of a partner's distress may be more relevant to changes in physiology than acute episodes of partner distress. Further, both individual biopsychosocial models of health (Adler & Matthews, 1994; Cohen & Herbert, 1996; Engel, 1977) and dyadic models of coping with diseases (Berg & Upchurch, 2007; Bodenmann, 2005) are understood to involve longitudinal processes. To further refine and test the dyadic biopsychosocial model, it will be necessary for future studies to examine longitudinal effects of psychosocial experiences on own and partner stress biomarkers over the course of survivorship.

Future studies may also seek to investigate other psychosocial, behavioral, and environmental mechanisms of interdependence between patients' and their caregivers' stress biomarkers. The current study tested the dyadic effects of one psychological factor (depressive symptoms), yet other psychosocial factors are known to relate to stress biomarkers, such as social support (Abercrombie et al., 2004; Costanzo et al., 2005; Lutgendorf et al., 2000;), post-traumatic stress (Maes et al., 1999; Miller et al., 2007; Yehuda, Teicher, Trestman, Levengood, & Siever, 1996), and coping (Giese-Davis, Sephton, Abercrombie, Durán, & Spiegel, 2004; Nicolson, 1992; Sjögren, Leanderson, & Kristenson, 2006). Additionally, health behaviors, such as diet, physical activity, or sleep hygiene, were also proposed as shared mechanisms of risk to patients' and caregivers' stress biomarker outcomes in the dyadic biopsychosocial model. Further elucidating psychosocial and behavioral mechanisms linking patients' and caregivers' physiological

health will both refine the dyadic biopsychosocial model and inform effective dyadic lifestyle interventions for improving both patients' and caregivers' health outcomes.

Lastly, future research may benefit from examining moderating factors of dyadic adjustment between cancer patients and their caregivers. Both distal (e.g., sociocultural) and proximal (e.g., relationship) context factors relate to the strength and success of dyadic adjustment to chronic illness (Berg & Upchurch, 2007). The sociocultural diversity in the present study represents a study strength in terms of generalizing findings for both non-Hispanic and Hispanic dyads, dyads of varying relationships (e.g., spousal, parent-child), and to persons from diverse socioeconomic backgrounds. However, this diversity may also obscure patterns of dyadic adjustment occurring within specific subgroups of patients and caregivers. Future studies may seek to determine whether moderating factors promote cross-over effects of one's distress to the partners' health outcomes, such as type and quality of the relationship between the dyad, cultural factors, or level of distress.

Conclusions

Despite limitations, this study is an important first test of the dyadic biopsychosocial model of interdependent psychological and physiological health of cancer patients and their caregivers. Interdependence was found between patients' and their caregivers' stress biomarkers, but not depressive symptoms. This first documentation of interdependence among patients' and caregivers' physiology provides empirical evidence for shared physiological health risk factors, and therefore support use of a dyadic biopsychosocial framework for future research. Identifying shared

psychosocial risk factors for patients' and caregivers' immune and endocrine dysfunction will be critical to developing effective dyadic interventions that improve patient clinical outcomes and attenuate caregiver physical health decline.

Figures

Figure 1. Biopsychosocial Model of Physical Morbidity Development (Adapted from Adler & Matthews, 1994; Cohen & Herbert, 1996)

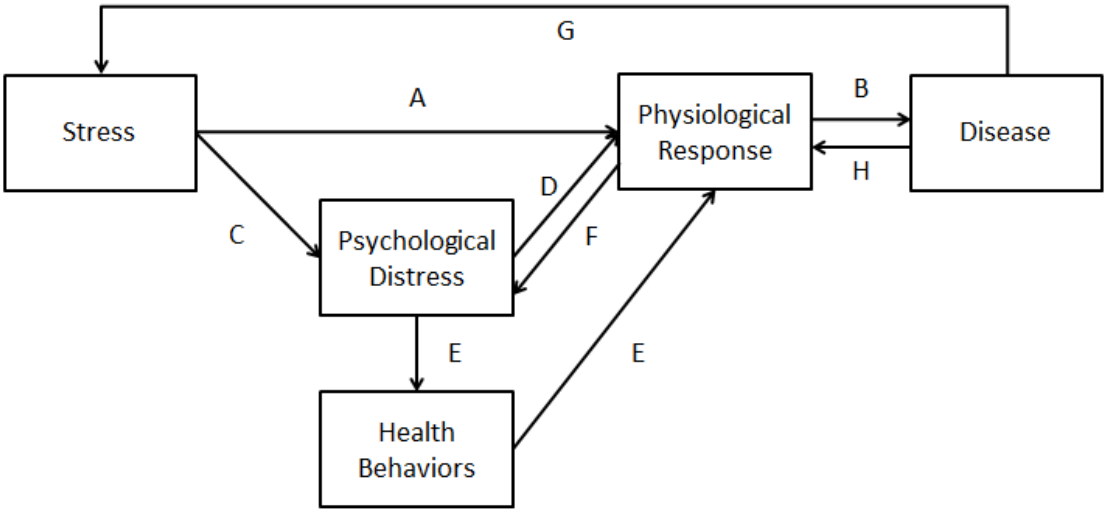
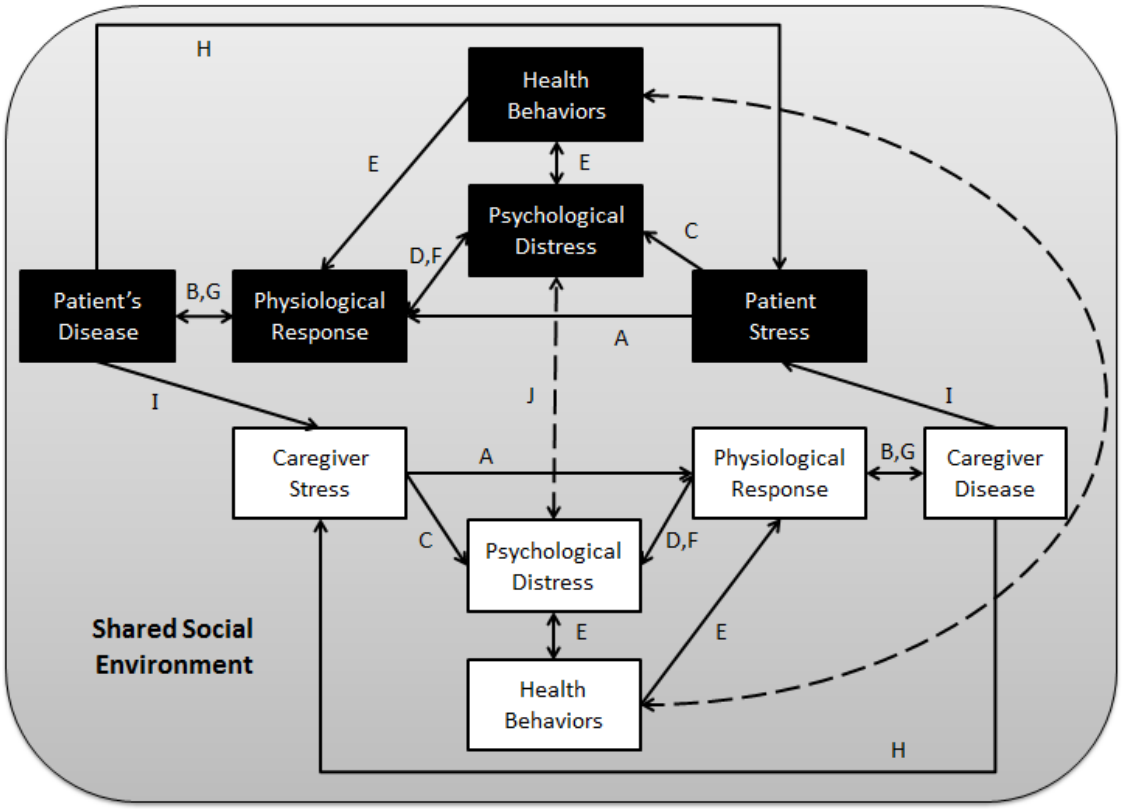
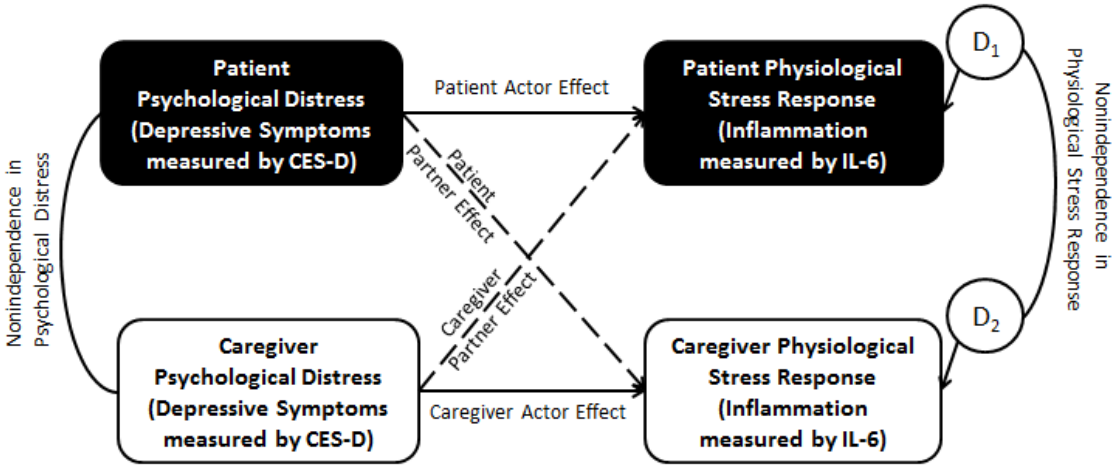


Figure 2. Interdependent Biopsychosocial Model of Patient and Caregiver Physical Morbidity Development/Progression (Adapted from Pearlin, Mullan, Semple, & Skaff, 1990; Vitaliano, Zhang, & Scanlan, 2003)



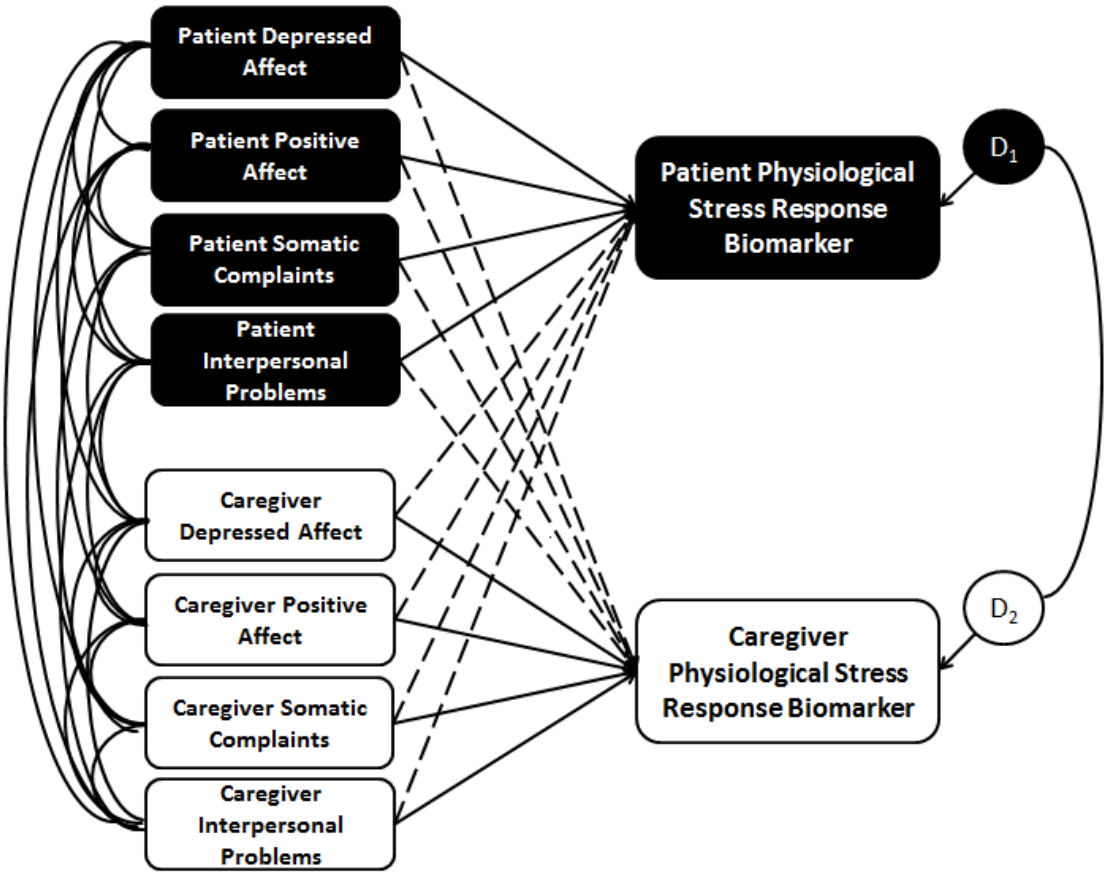
Note. Black boxes refer to processes within cancer patients; White boxes refer to processes within cancer caregivers; dotted lines indicate areas of interaction; double-headed arrows are bi-directional; path labels correspond to the text for review of evidence.

Figure 3. Study Model with Unidimensional Depressive Symptoms: Interdependent Biopsychosocial Model of Inflammation and Cortisol (Adapted from Kenny, Kashy, & Cook, 2006)



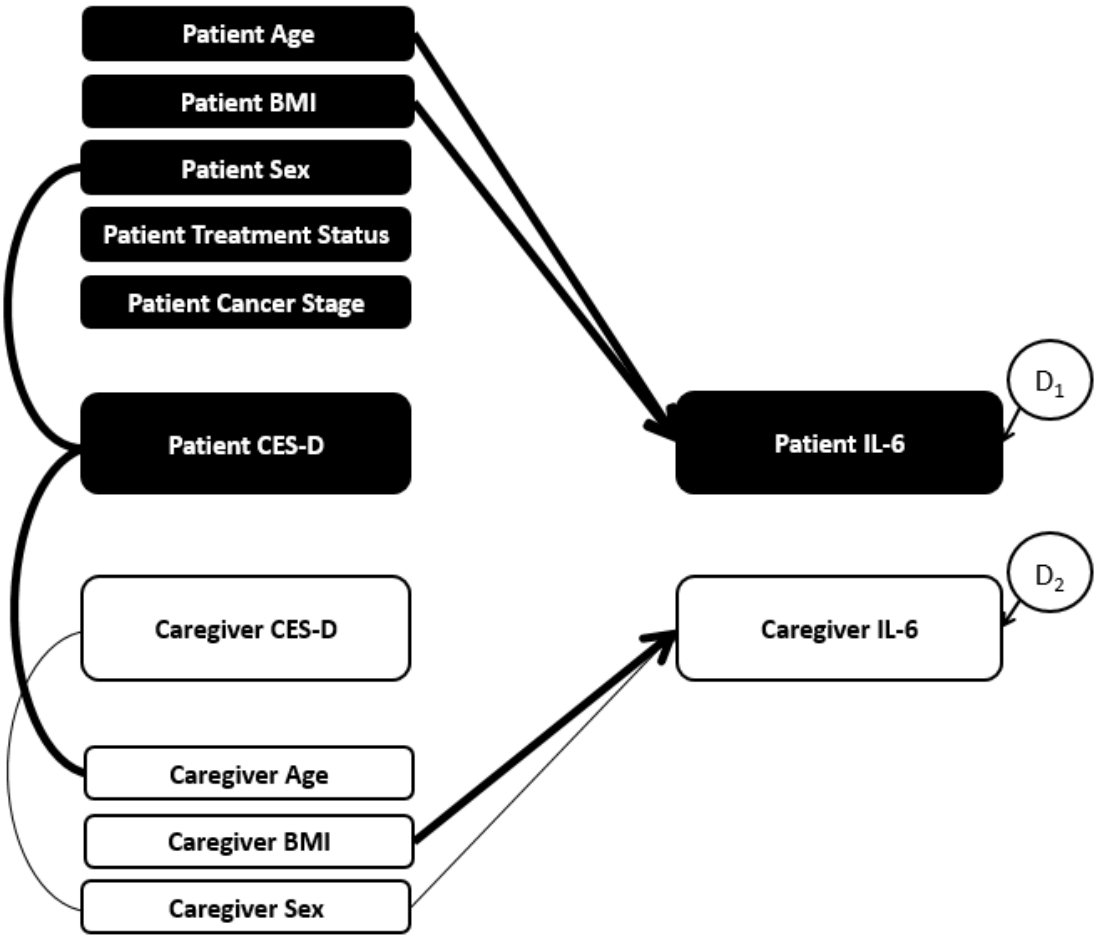
Note. Aim 1 tests significance of nonindependence among patient and caregiver depressive symptoms and stress biomarkers, respectively. Aim 2 tests significance of actor effects of one's own depressive symptoms on one's own biomarker outcomes. Aim 3 tests significant of partner effects of one's own depressive symptoms on one's partner's biomarker outcomes. Hypotheses 2, 5, and 8 will utilize the outcome biomarker of IL-6; hypotheses 3, 6, and 9 will utilize the outcome biomarker of CRP as a measure of inflammation; hypotheses 4, 7, and 10 will utilize the outcome biomarker of cortisol slope as a measure of HPA axis functioning.

Figure 4. Study Model with Multidimensional Depressive Symptoms: Interdependent Biopsychosocial Model of Inflammation and Cortisol



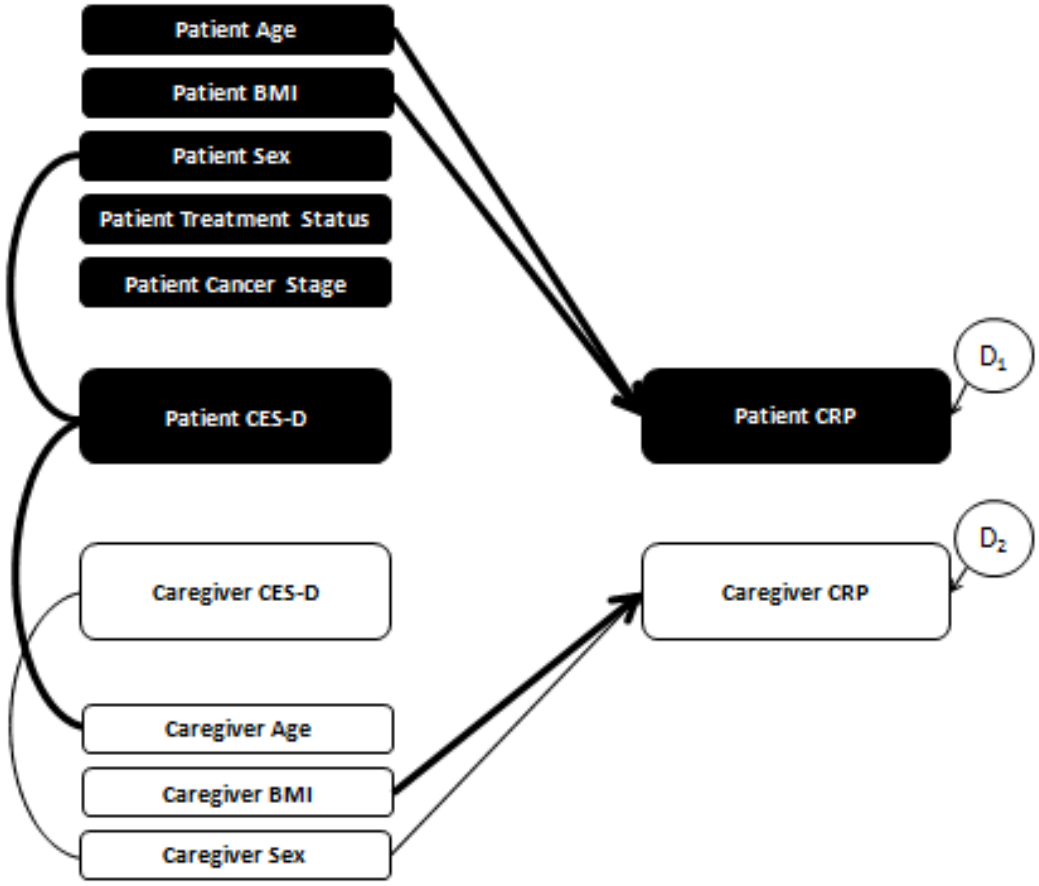
Note. Exploratory aim 1 tests significance of actor effects of one's own depressive symptoms on one's own biomarker outcomes (solid lines). Exploratory aim 2 tests significant of partner effects of one's own depressive symptoms on one's partner's biomarker outcomes (dotted lines). Hypotheses 7 and 10 will utilize the outcome biomarker of IL-6; hypotheses 8 and 11 will utilize the outcome biomarker of CRP; hypotheses 9 and 12 will utilize the outcome biomarker of cortisol slope.

Figure 5. Study Model Results with Unidimensional Depressive Symptoms: Interdependent Biopsychosocial Model of IL-6.



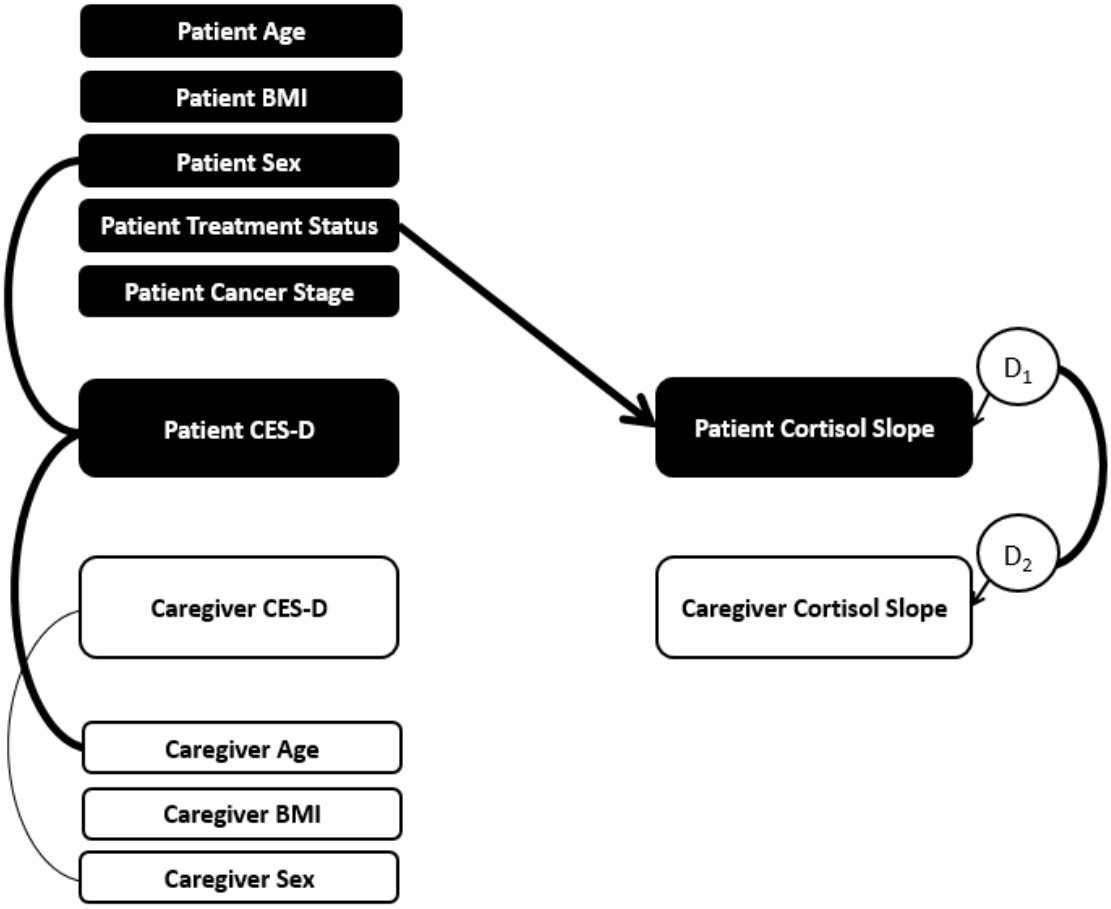
Note. Paths with $p > .10$ not shown. Significant paths ($p < .05$) bolded. All paths shown are positive.

Figure 6. Study Model Results with Unidimensional Depressive Symptoms: Interdependent Biopsychosocial Model of CRP.



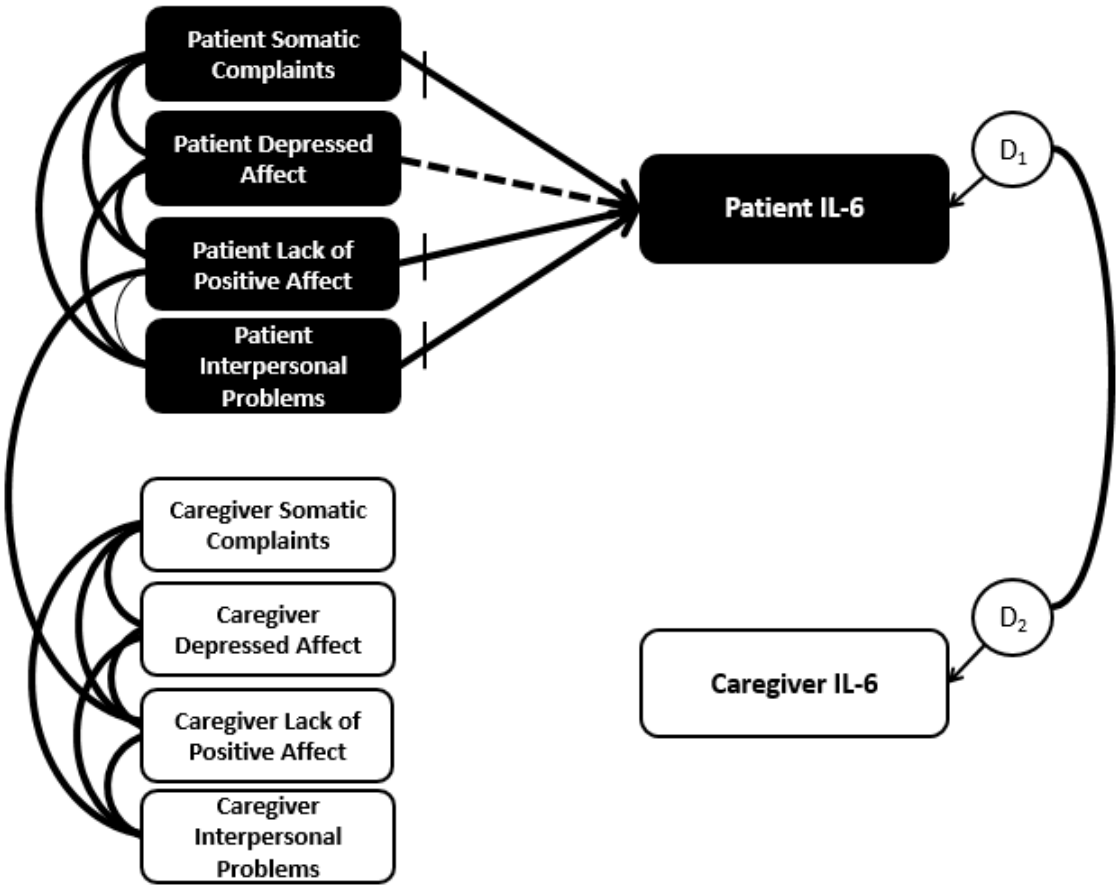
Note. Paths with $p > .10$ not shown. Significant paths ($p < .05$) bolded. All paths shown are positive.

Figure 7. Study Model Results with Unidimensional Depressive Symptoms: Interdependent Biopsychosocial Model of Cortisol Slope.



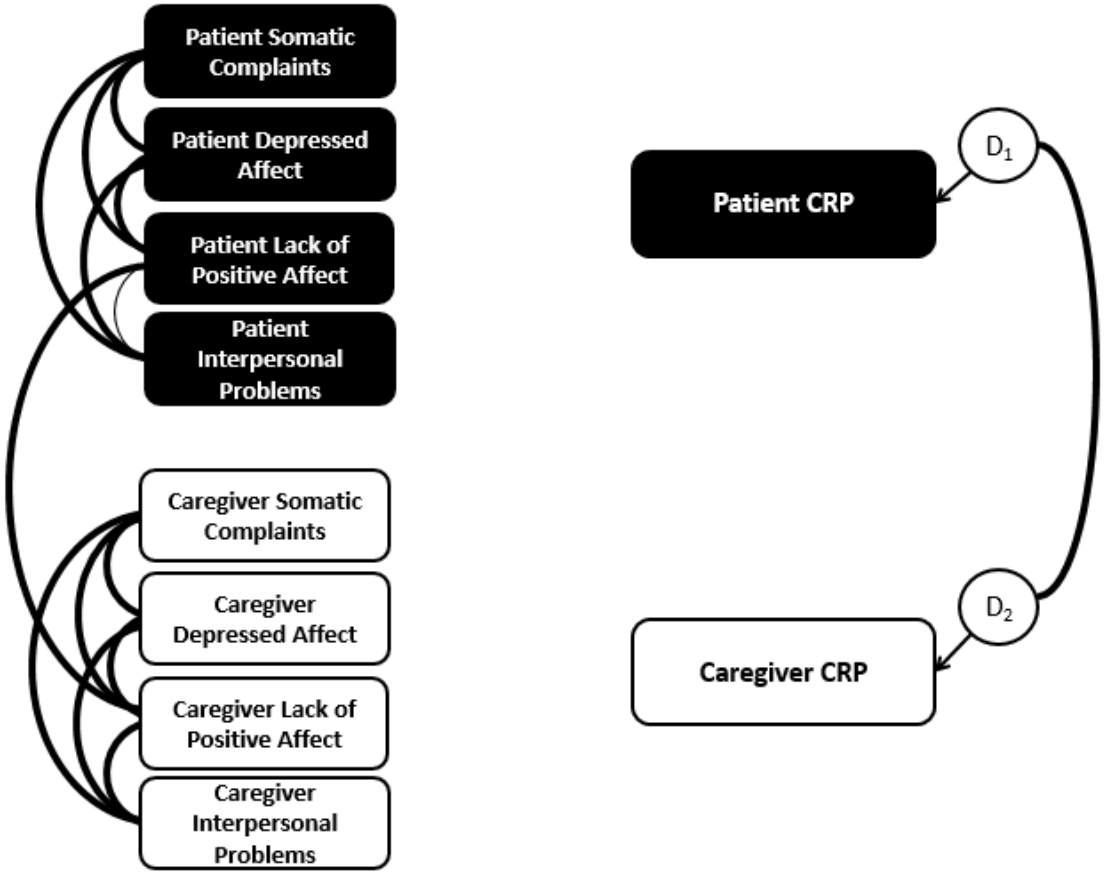
Note. Paths with $p > .10$ not shown. Significant paths ($p < .05$) bolded. All paths shown are positive.

Figure 8. Exploratory Study Model Results with Depressive Symptom Subscales: Interdependent Biopsychosocial Model of IL-6.



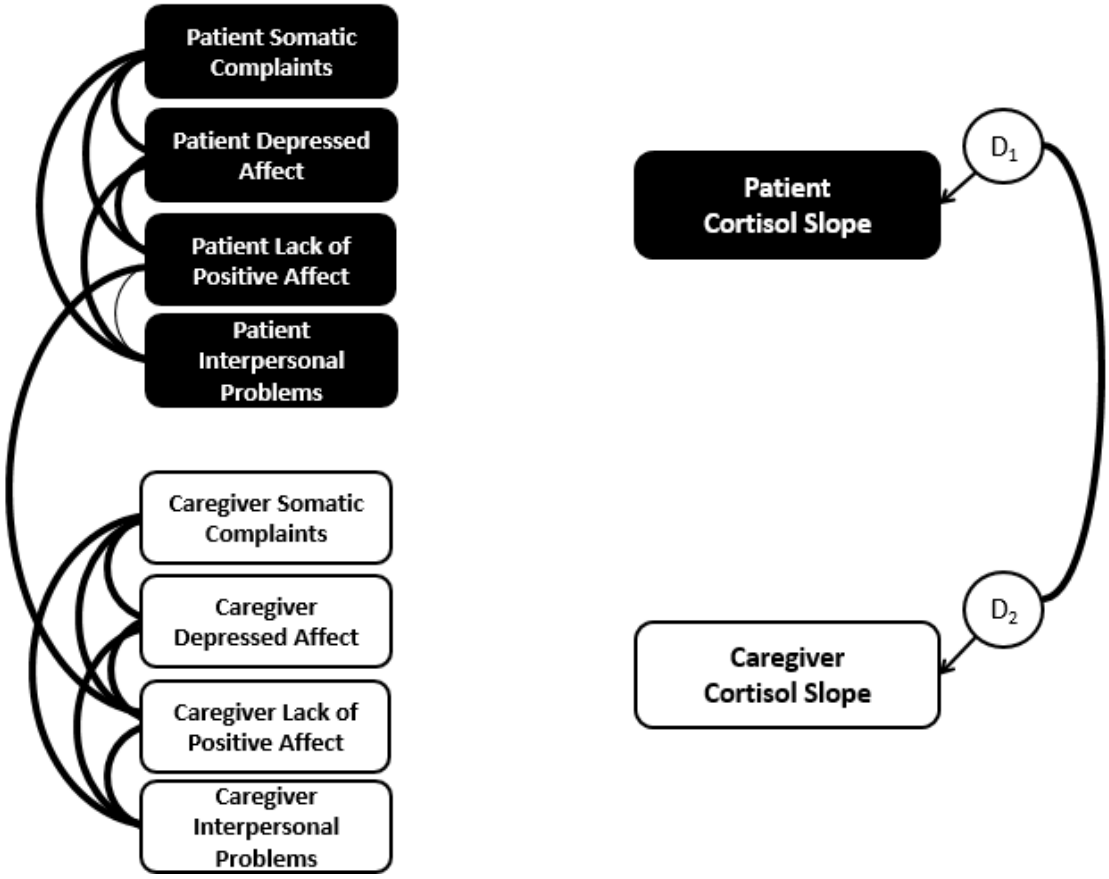
Note. Paths with $p > .10$ not shown. Significant paths ($p < .05$) bolded. Solid lines represent positive associations; dotted paths represent negative associations. Hash marked paths equal.

Figure 9. Exploratory Study Model Results with Depressive Symptom Subscales: Interdependent Biopsychosocial Model of CRP.



Note. Paths with $p > .10$ not shown. Significant paths ($p < .05$) bolded. All covariances shown are positive.

Figure 10. Exploratory Study Model Results with Depressive Symptom Subscales: Interdependent Biopsychosocial Model of Cortisol Slope.



Note. Paths with $p > .10$ not shown. Significant paths ($p < .05$) bolded. All paths shown are positive. Hash marked paths equal.

Appendix

Appendix 1. Center for Epidemiological Studies-Depression Scale Items with Respective Symptom Subscales (Radloff, 1977; Sheehan, Fifield, Reisine, & Tennen, 1995)

Item	Subscale
1. I was bothered by things that usually don't bother me.	Somatic Complaints
2. I did not feel like eating; my appetite was poor.	Somatic Complaints
3. I felt that I could not shake off the blues even with help from my family or friends.	Depressed Affect
4. I felt I was just as good as other people.	Lack of Positive Affect
5. I had trouble keeping my mind on what I was doing.	Somatic Complaints
6. I felt depressed.	Depressed Affect
7. I felt that everything I did was an effort	Somatic Complaints
8. I felt hopeful about the future.	Lack of Positive Affect
9. I thought my life had been a failure.	Interpersonal Problems
10. I felt fearful.	Interpersonal Problems
11. My sleep was restless.	Somatic Complaints
12. I was happy.	Lack of Positive Affect
13. I talked less than usual.	Somatic Complaints
14. I felt lonely.	Depressed Affect
15. People were unfriendly.	Interpersonal Problems
16. I enjoyed life.	Lack of Positive Affect
17. I had crying spells.	Depressed Affect
18. I felt sad.	Depressed Affect
19. I felt that people disliked me.	Interpersonal Problems
20. I could not get going.	Somatic Complaints

Note. Lack of positive affect items are reverse-coded.

Table 1. Descriptives for Patient and Caregiver Samples

		Patients N (%)	Caregivers N (%)	χ^2
Race/Ethnicity	Non-Hispanic white	22 (26.2%)	21 (24.4%)	0.07
	Other	62 (73.8%)	65 (75.6%)	
Educational	High school degree or less	35 (41.7%)	31 (36.0%)	0.57
Attainment	Some college or more	48 (57.1%)	54 (62.8%)	
Smoking	Current smoker	5 (6.0%)	8 (9.3%)	0.64
	Not current smoker	77 (91.7%)	77 (89.5%)	
Alcohol	Drink two or more drinks/day	17 (20.2%)	25 (29.1%)	1.67
	Drink one or fewer drinks/day	64 (76.2%)	59 (68.6%)	
Fruit & Vegetable	Five servings on four or fewer days/week	53 (63.1%)	52 (60.5%)	0.08
Consumption	Five servings on five or more days/week	26 (31.0%)	28 (32.6%)	
Physical Activity	Less than 150 minutes/week	82 (97.6%)	81 (94.2%)	1.78
	150 or more minutes/week	1 (1.2%)	4 (4.7%)	
Recent Illness	Recent illness	64 (76.2%)	71 (82.6%)	1.10
	No recent illness	19 (22.6%)	14 (16.3%)	
Patients' Cancer	Receiving treatment	30 (35.7%)	–	–
Treatment Status	Treatment not yet initiated	10 (11.9%)	–	–
	Unknown	40 (47.6%)	–	–

Patients' Cancer Stage	Stage I	5 (6.0%)	–	–
	Stage II	14 (16.7%)	–	–
	Stage III	34 (40.5%)	–	–
	Stage IV	22 (26.2%)	–	–
	Unknown	9 (10.7%)	–	–

$^{\dagger} p < .10$ $^{*} p < .05$ $^{**} p < .01$ $^{***} p < .001$

Table 2. Descriptives for Patient and Caregiver Study Variables and Covariates

	Patients N = 84			Caregivers N = 86			Paired *t*-test	
	Mean	(SD)	Range	Mean	(SD)	Range	*df*	*t*
CES-D	13.24	(8.03)	0 – 41	15.31	(11.02)	0 – 45	79	-1.39
Somatic Complaints	0.88	(0.51)	0 – 2.57	0.76	(0.61)	0 – 2.71	79	1.18
Depressed Affect	0.67	(0.57)	0 – 2.40	0.88	(0.83)	0 – 3.00	79	-1.73†
Lack of Positive Affect	0.63	(0.68)	0 – 2.75	0.99	(0.74)	0 – 2.50	79	-3.68***
Interpersonal Problems	0.33	(0.44)	0 – 2.25	0.44	(0.56)	0 – 2.00	79	-1.28
Interleukin-6 (pg/mL)	3.14	(2.56)	0.43 – 10.00	1.83	(1.71)	0.10 – 9.22	44	4.21***
C-Reactive Protein (mg/L)	6.49	(11.56)	0.15 – 64.29	3.60	(4.71)	0.10 – 19.80	45	1.83†
Cortisol Slope (µg/dL/hour)	-0.09	(0.06)	-0.20 – 0.08	-0.12	(0.07)	-0.27 – 0.06	72	1.37
Covariates								
Age	54.20	(9.88)	28.66 – 79.83	50.70	(14.43)	21.29 – 79.76	77	2.08*
Body Mass Index	26.28	(6.12)	15.36 – 52.46	28.30	(6.93)	16.83 – 51.01	62	-1.68†
Sex (N, % Female)	48	(57.1)	N/A	63	(73.3)	N/A	χ^2=	4.87*
Time Since Patient's Diagnosis (days)	103.85	(38.74)	33 – 204	103.03	(39.21)	35 – 204	80	0.21

† *p* < .10 * *p* < .05 ** *p* < .01 *** *p* < .001

Note. CES-D = Center for Epidemiology Studies-Depression scale.

Table 3. Pearson's Correlations Between Patients' and Caregivers' Depressive Symptoms and Stress Biomarkers

	Pt CES-D	Pt IL-6	Pt CRP	Pt Cortisol Slope	Cg CES-D	Cg IL-6	Cg CRP
Pt IL-6	.08	1					
Pt CRP	.02	.70***	1				
Pt Cortisol Slope	.04	.32*	.35*	1			
Cg CES-D	.06	.05	.18	.12	1		
Cg IL-6	.20	.27†	.32*	.004	.16	1	
Cg CRP	.06	.19	.31*	.05	.09	.80***	1
Cg Cortisol Slope	.09	.25†	.19	.31**	-.10	.23†	.20

† $p < .10$ * $p < .05$ ** $p < .01$ *** $p < .001$

Note. Pt = patient; CES-D = Center for Epidemiology Studies-Depression scale; IL-6 = Interleukin-6; CRP = C-Reactive Protein; Cg = caregiver

Table 4. Pearson's Correlations Between Patients' and Caregivers' Depressive Symptoms and Stress Biomarkers with Own Covariates

	Age	BMI	Sex	Treatment	Stage
Pt CES-D	-.10	-.02	.91***	.19	-.03
Pt Il-6	.24†	.29*	.33**	.07	.18
Pt CRP	.25†	.31*	.33**	.004	.16
Pt Cortisol Slope	.14	-.10	.62***	.28	.24*
Cg CES-D	.05	.05	.86***	–	–
Cg Il-6	.22†	.46***	.28**	–	–
Cg CRP	.10	.58***	.29**	–	–
Cg Cortisol Slope	.11	.10	.59***	–	–

† $p < .10$ * $p < .05$ ** $p < .01$ *** $p < .001$

Note. BMI = body mass index; Sex (1 = male, 2 = female); Treatment = patient's treatment stage (1 = treatment not initiated prior to assessment, 2 = treatment initiated prior to assessment); Stage = patient's cancer stage (1 = Early stage [stages I and II], 2 = Late stage [stages III and IV]); Pt = patient; CES-D = Center for Epidemiology Studies-Depression scale; IL-6 = Interleukin-6 (natural log transformed); CRP = C-Reactive Protein (natural log transformed); Cg = caregiver.

Table 5. Pearson's Correlations Between Patients' and Caregivers' Depressive Symptom Subscales and Stress Biomarkers

	Pt Il-6	Pt CRP	Pt Cortisol Slope	Cg Il-6	Cg CRP	Cg Cortisol Slope
Pt Somatic Complaints	.11	.08	.08	.17	.09	.07
Pt Depressed Affect	-.08	-.02	-.03	.15	.07	.10
Pt Lack of Positive Affect	.20	.09	.01	.23†	.02	.13
Pt Interpersonal Problems	.09	-.05	.12	-.01	-.02	-.03
Cg Somatic Complaints	.05	.21	.14	.14	.08	-.11
Cg Depressed Affect	.10	.25†	.10	.18	.12	-.11
Cg Lack of Positive Affect	.09	-.001	.03	.04	.04	.01
Cg Interpersonal Problems	-.21	.04	.16	.09	-.03	-.09

† $p < .10$ * $p < .05$ ** $p < .01$ *** $p < .001$

Note. Pt = patient; CES-D = Center for Epidemiology Studies-Depression scale; IL-6 = Interleukin-6; CRP = C-Reactive Protein; Cg = caregiver.

Table 6. Study Model Results: Interleukin (IL)-6

Hypo-thesis	Effect		Unstd Est	95% CI	Std Est	*p*
1	Nonindependence	Pt CES-D ↔ Cg CES-D	6.10	-12.94 – 24.96	.07	.53
2	Nonindependence	Pt IL-6 ↔ Cg IL-6	0.05	-0.03 – 0.13	.25	.23
5.1	Actor	Pt CES-D → Pt IL-6	0.01	-0.002 – 0.01	.07	.14
5.2	Actor	Cg CES-D → Cg IL-6	0.01	-0.002 – 0.01	.11	.14
8.1	Partner	Pt CES-D → Cg IL-6	0.01	-0.002 – 0.01	.08	.14
8.2	Partner	Cg CES-D → Pt IL-6	0.01	-0.002 – 0.01	.10	.14
–	Covariate	Pt Age → Pt IL-6	0.16	0.02 – 0.29	.28	.02
–	Covariate	Pt BMI → Pt IL-6	0.02	-0.001 – 0.04	.24	.07
–	Covariate	Pt Sex → Pt IL-6	-0.15	-0.45 – 0.15	-.14	.33
–	Covariate	Pt Treatment → Pt IL-6	0.13	-0.20 – 0.52	.13	.46
–	Covariate	Pt Stage → Pt IL-6	0.22	-0.13 – 0.54	.16	.19
–	Covariate	Cg Age → Cg IL-6	0.05	-0.03 – 0.13	.15	.21
–	Covariate	Cg BMI → Cg IL-6	0.03	0.02 – 0.05	.45	<.001
–	Covariate	Cg Sex → Cg IL-6	0.21	-0.01 – 0.43	.19	.06

Note. Intercorrelations between exogenous variables (CES-D and covariates) not reported. IL-6 has been natural log transformed. Pt = patient; CES-D = Center for Epidemiology Studies-Depression scale; Cg = caregiver; BMI = body mass index; Sex (1 = male, 2 = female); Treatment = patient's treatment stage (1 = treatment not initiated prior to assessment, 2 = treatment initiated prior to assessment); Stage = patient's cancer stage (1 = Early stage [stages I and II], 2 = Late stage [stages III and IV]).

Table 7. Study Model Results: C-Reactive Protein (CRP)

Hypo-thesis	Effect		Unstd Est	95% CI	Std Est	*p*
1	Nonindependence	Pt CES-D ↔ Cg CES-D	6.04	-12.94 – 25.02	.07	.53
3	Nonindependence	Pt CRP ↔ Cg CRP	0.01	-0.16 – 0.18	.03	.88
6.1	Actor	Pt CES-D → Pt CRP	0.004	-0.01 – 0.01	.03	.46
6.2	Actor	Cg CES-D → Cg CRP	0.004	-0.01 – 0.01	.05	.46
9.1	Partner	Pt CES-D → Cg CRP	0.004	-0.01 – 0.01	.04	.46
9.2	Partner	Cg CES-D → Pt CRP	0.004	-0.01 – 0.01	.03	.46
–	Covariate	Pt Age → Pt CRP	0.28	0.04 – 0.51	.29	.02
–	Covariate	Pt BMI → Pt CRP	0.05	0.01 – 0.09	.33	.01
–	Covariate	Pt Sex → Pt CRP	-0.002	-0.51 – 0.50	-.001	.99
–	Covariate	Pt Treatment → Pt CRP	-0.01	-0.66 – 0.64	-.01	.98
–	Covariate	Pt Stage → Pt CRP	0.40	-0.14 – 0.94	.19	.15
–	Covariate	Cg Age → Cg CRP	-0.03	-0.15 – 0.10	-.05	.68
–	Covariate	Cg BMI → Cg CRP	0.07	0.05 – 0.10	.61	<.001
–	Covariate	Pt Sex → Pt CRP	0.33	-0.03 – 0.69	.18	.07

Note. Intercorrelations between exogenous variables (CES-D and covariates) not reported. CRP has been natural log transformed. Pt = patient; CES-D = Center for Epidemiology Studies-Depression scale; Cg = caregiver; BMI = body mass index; Sex (1 = male, 2 = female); Treatment = patient's treatment stage (1 = treatment not initiated prior to assessment, 2 = treatment initiated prior to assessment); Stage = patient's cancer stage (1 = Early stage [stages I and II], 2 = Late stage [stages III and IV]).

Table 8. Study Model Results: Cortisol Slope

Hypo-thesis	Effect		Unstd Est	95% CI	Std Est	*p*
1	Nonindependence	Pt CES-D ↔ Cg CES-D	5.88	-13.05 – 24.80	.07	.54
4	Nonindependence	Pt Cortisol Slope ↔ Cg Cortisol Slope	0.001	0 – 0.002	.27	.03
7.1	Actor	Pt CES-D → Pt Cortisol Slope	-0.001	-0.002 – 0	-.08	.27
7.2	Actor	Cg CES-D → Cg Cortisol Slope	-0.001	-0.002 – 0	-.10	.27
10.1	Partner	Pt CES-D → Cg Cortisol Slope	0.001	0 – 0.002	.10	.12
10.2	Partner	Cg CES-D → Pt Cortisol Slope	0.001	0 – 0.002	.15	.12
–	Covariate	Pt Age → Pt Cortisol Slope	0.01	-0.01 – 0.02	.14	.24
–	Covariate	Pt BMI → Pt Cortisol Slope	0	-0.003 – 0.003	.01	.87
–	Covariate	Pt Sex → Pt Cortisol Slope	-0.002	-0.03 – 0.03	-.02	.90
–	Covariate	Pt Treatment → Pt Cortisol Slope	0.05	0.01 – 0.09	.37	.03
–	Covariate	Pt Stage → Pt Cortisol Slope	0.03	-0.01 – 0.06	.19	.12
–	Covariate	Cg Age → Cg Cortisol Slope	0.003	-0.01 – 0.01	.06	.60
–	Covariate	Cg BMI → Cg Cortisol Slope	0.001	-0.001 – 0.003	.10	.38
–	Covariate	Cg Sex → Cg Cortisol Slope	0.03	-0.004 – 0.06	.17	.09

Note. Intercorrelations between exogenous variables (CES-D and covariates) not reported. Salivary cortisol values were natural log transformed prior to calculation of cortisol slope. Pt = patient; CES-D = Center for Epidemiology Studies-Depression scale; Cg = caregiver; BMI = body mass index; Sex (1 = male, 2 = female); Treatment = patient's treatment stage (1 = treatment not initiated prior to assessment, 2 = treatment initiated prior to assessment); Stage = patient's cancer stage (1 = Early stage [stages I and II], 2 = Late stage [stages III and IV]).

Table 9. Exploratory Model Results: Interleukin (IL)-6

Hypo-thesis	Effect		Unstd Est	95% CI	Std Est	*p*
E1.1	Actor	Pt Somatic Complaints → Pt IL-6	0.19	0.05 – 0.33	.17	.01
E1.1	Actor	Pt Depressed Affect → Pt IL-6	-0.42	-0.78 – -0.07	-.42	.02
E1.1	Actor	Pt Lack of Positive Affect → Pt IL-6	0.19	0.05 – 0.33	.23	.01
E1.1	Actor	Pt Interpersonal Problems → Pt IL-6	0.19	0.05 – 0.33	.15	.01
E1.2	Actor	Cg Somatic Complaints → Cg IL-6	0.03	-0.02 – 0.08	.04	.21
E1.2	Actor	Cg Depressed Affect → Cg IL-6	0.03	-0.02 – 0.08	.06	.21
E1.2	Actor	Cg Lack of Positive Affect → Cg IL-6	0.03	-0.02 – 0.08	.05	.21
E1.2	Actor	Cg Interpersonal Problems → Cg IL-6	0.03	-0.02 – 0.08	.04	.21
E4.1	Partner	Pt Somatic Complaints → Cg IL-6	0.03	-0.03 – 0.08	.03	.20
E4.1	Partner	Pt Depressed Affect → Cg IL-6	0.03	-0.03 – 0.08	.04	.20
E4.1	Partner	Pt Lack of Positive Affect → Cg IL-6	0.03	-0.03 – 0.08	.05	.20
E4.1	Partner	Pt Interpersonal Problems → Cg IL-6	0.03	-0.03 – 0.08	.03	.20
E4.2	Partner	Cg Somatic Complaints → Cg IL-6	0.03	-0.03 – 0.08	.04	.20
E4.2	Partner	Cg Depressed Affect → Cg IL-6	0.03	-0.03 – 0.08	.05	.20
E4.2	Partner	Cg Lack of Positive Affect → Cg IL-6	0.03	-0.03 – 0.08	.04	.20
E4.2	Partner	Cg Interpersonal Problems → Cg IL-6	0.03	-0.03 – 0.08	.03	.20
–	Nonindependence	Pt Lack of Positive Affect ↔ Cg Lack of Positive Affect	0.13	0.01 – 0.24	.25	.03

–	Correlation	Pt Somatic Complaints ↔ Pt Depressed Affect	0.14	0.07 – 0.21	.48	<.001
–	Correlation	Pt Somatic Complaints ↔ Pt Lack of Positive Affect	0.09	0.01 – 0.17	.26	.02
–	Correlation	Pt Somatic Complaints ↔ Pt Interpersonal Problems	0.09	0.03 – 0.14	.38	.001
–	Correlation	Pt Depressed Affect ↔ Pt Lack of Positive Affect	0.18	0.09 – 0.27	.46	<.001
–	Correlation	Pt Depressed Affect ↔ Pt Interpersonal Problems	0.09	0.04 – 0.15	.37	.001
–	Correlation	Pt Lack of Positive Affect ↔ Pt Interpersonal Problems	0.10	0.03 – 0.16	.32	.01
–	Correlation	Cg Somatic Complaints ↔ Cg Depressed Affect	0.42	0.28 – 0.56	.84	<.001
–	Correlation	Cg Somatic Complaints ↔ Cg Lack of Positive Affect	0.17	0.06 – 0.27	.37	.001
–	Correlation	Cg Somatic Complaints ↔ Cg Interpersonal Problems	0.22	0.14 – 0.31	.65	<.001
–	Correlation	Cg Depressed Affect ↔ Cg Lack of Positive Affect	0.23	0.09 – 0.37	.38	.001
–	Correlation	Cg Depressed Affect ↔ Cg Interpersonal Problems	0.32	0.20 – 0.44	.70	<.001
–	Correlation	Cg Lack of Positive Affect ↔ Cg Interpersonal Problems	0.09	-0.01 – 0.17	.21	.06

Note. Pt = patient; Cg = caregiver; see Table 6 for patient-caregiver IL-6 non-independence; only marginal and significant CES-D subscale non-independence and correlations shown.

Table 10. Exploratory Model Results: C-Reactive Protein (CRP)

Hypo-thesis	Effect		Unstd Est	95% CI	Std Est	*p*
E2.1	Actor	Pt Somatic Complaints → Pt CRP	0.03	-0.03 – 0.09	.02	0.29
E2.1	Actor	Pt Depressed Affect → Pt CRP	0.03	-0.03 – 0.09	.02	0.29
E2.1	Actor	Pt Lack of Positive Affect → Pt CRP	0.03	-0.03 – 0.09	.02	0.29
E2.1	Actor	Pt Interpersonal Problems → Pt CRP	0.03	-0.03 – 0.09	.02	0.29
E2.2	Actor	Cg Somatic Complaints → Cg CRP	0.03	-0.03 – 0.09	.02	0.29
E2.2	Actor	Cg Depressed Affect → Cg CRP	0.03	-0.03 – 0.09	.03	0.29
E2.2	Actor	Cg Lack of Positive Affect → Cg CRP	0.03	-0.03 – 0.09	.03	0.29
E2.2	Actor	Cg Interpersonal Problems → Cg CRP	0.03	-0.03 – 0.09	.02	0.29
E5.1	Partner	Pt Somatic Complaints → Cg CRP	0.03	-0.03 – 0.09	.02	0.29
E5.1	Partner	Pt Depressed Affect → Cg CRP	0.03	-0.03 – 0.09	.02	0.29
E5.1	Partner	Pt Lack of Positive Affect → Cg CRP	0.03	-0.03 – 0.09	.03	0.29
E5.1	Partner	Pt Interpersonal Problems → Cg CRP	0.03	-0.03 – 0.09	.02	0.29
E5.2	Partner	Cg Somatic Complaints → Cg CRP	0.03	-0.03 – 0.09	.02	0.29
E5.2	Partner	Cg Depressed Affect → Cg CRP	0.03	-0.03 – 0.09	.03	0.29
E5.2	Partner	Cg Lack of Positive Affect → Cg CRP	0.03	-0.03 – 0.09	.02	0.29
E5.2	Partner	Cg Interpersonal Problems → Cg CRP	0.03	-0.03 – 0.09	.02	0.29

Note. Pt = patient; Cg = caregiver; see Table 7 for patient-caregiver CRP non-independence; see Table 9 for patient-caregiver depressive symptoms subscale significant and marginal nonindependence and correlations.

Table 11. Exploratory Model Results: Cortisol Slope

Hypo-thesis	Effect		Unstd Est	95% CI	Std Est	*p*
E3.1	Actor	Pt Somatic Complaints → Pt Cortisol Slope	0.001	-0.003 – 0.01	.01	.54
E3.1	Actor	Pt Depressed Affect → Pt Cortisol Slope	0.001	-0.003 – 0.01	.01	.54
E3.1	Actor	Pt Lack of Positive Affect → Pt Cortisol Slope	0.001	-0.003 – 0.01	.01	.54
E3.1	Actor	Pt Interpersonal Problems → Pt Cortisol Slope	0.001	-0.003 – 0.01	.01	.54
E3.2	Actor	Cg Somatic Complaints → Cg Cortisol Slope	0.001	-0.003 – 0.01	.01	.54
E3.2	Actor	Cg Depressed Affect → Cg Cortisol Slope	0.001	-0.003 – 0.01	.02	.54
E3.2	Actor	Cg Lack of Positive Affect → Cg Cortisol Slope	0.001	-0.003 – 0.01	.01	.54
E3.2	Actor	Cg Interpersonal Problems → Cg Cortisol Slope	0.001	-0.003 – 0.01	.01	.54
E6.1	Partner	Pt Somatic Complaints → Cg Cortisol Slope	0.001	-0.003 – 0.01	.01	.54
E6.1	Partner	Pt Depressed Affect → Cg Cortisol Slope	0.001	-0.003 – 0.01	.01	.54
E6.1	Partner	Pt Lack of Positive Affect → Cg Cortisol Slope	0.001	-0.003 – 0.01	.01	.54
E6.1	Partner	Pt Interpersonal Problems → Cg Cortisol Slope	0.001	-0.003 – 0.01	.01	.54
E6.2	Partner	Cg Somatic Complaints → Cg Cortisol Slope	0.001	-0.003 – 0.01	.01	.54
E6.2	Partner	Cg Depressed Affect → Cg Cortisol Slope	0.001	-0.003 – 0.01	.02	.54
E6.2	Partner	Cg Lack of Positive Affect → Cg Cortisol Slope	0.001	-0.003 – 0.01	.02	.54
E6.2	Partner	Cg Interpersonal Problems → Cg Cortisol Slope	0.001	-0.003 – 0.01	.01	.54

Note. Pt = patient; Cg = caregiver; IL-6 = Interleukin-6; see Table 8 for patient-caregiver cortisol slope non-independence; see Table 9 for patient-caregiver depressive symptoms subscale significant and marginal nonindependence and correlations.

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