HOW TO DEAL: EXPLORING THE IMPACT OF COPING, PERCEIVED CONTROL, AND STRESS ON IMMUNE FUNCTION IN PATIENTS WITH ADVANCED CANCER

by

Olutoyin L. Ola

BA, Johns Hopkins University, 2012

MA, Wake Forest University, 2014

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This thesis was presented

by

Olutoyin L. Ola

It was defended on

July 6, 2018

and approved by

Thesis Advisor:
Mary Hawk, DrPH
Associate Professor
Behavioral and Community Health Sciences, Graduate School of Public Health
University of Pittsburgh

Committee Member:
Jennifer Steel, PhD
Associate Professor
Departments of Surgery, Psychiatry, and Psychology
University of Pittsburgh

Committee Member:
Steven Albert, PhD
Professor and Chair
Behavioral and Community Health Sciences, Graduate School of Public Health
University of Pittsburgh

Mary Hawk, DrPH

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ABSTRACT

Purpose: This study sought to uncover targets for psychosocial intervention with advanced cancer patients by elucidating the three-way interactions among coping, perceived control, and perceived stress and their impact on immune function. **Background:** In recent decades, stress-related immune dysfunction—namely, chronic inflammation—has been cited as the underlying mechanism through which a variety of chronic diseases of public health significance, including type II diabetes, cardiovascular disease, and dementias, develop. There is also evidence to suggest that stress only results in serious pathology when it is long-standing and unresolved. Thus, there is an opportunity to intervene such that stress does not result in chronic disease. Coping, according to Lazarus and Folkman, is the psychological construct encompassing the numerous ways with which one can deal with situations appraised as stressful. It is important to note that there are innumerable personal factors—such as one's perceived level of control—that can influence how one appraises a situation and copes when a situation is deemed stressful. **Methods:** The present study, a secondary analysis, explored which coping strategies advanced cancer patients use to handle their diagnoses and how those coping strategies impact immune function. Peripheral blood levels of the anti-inflammatory cytokine IL-10, the regulatory cytokine IL-2, and the pro-inflammatory cytokines IL-1alpha and beta were used to

operationalize immune function as cytokines mediate the immune system's inflammatory response. Patients' self-reported coping strategies were grouped into coping profiles using PCA and cluster analysis, then linear regression models were constructed for each cytokine to assess for three-way interactions among coping, perceived control, and stress. **Findings:** Global F tests and likelihood ratio tests run on each regression model did not yield a significant p-value; however, there were several individual three-way interactions that were statistically significant. The results suggest that there is a need to investigate the person and environment variables that moderate the relationship between coping and stress and their impact on the immune system further.

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PREFACE

I am most grateful for the strong foundation and supportive environment provided by my parents and for the excellent training I received at my alma maters. I would also like to extend a special thanks to Jacob Leisey-Bartsch for executing my complex data analysis plan as a graduate student consultant in the University of Pittsburgh's statistical consulting service.

1.0 INTRODUCTION

1.1 PURPOSE, SCOPE, AND DATA COLLECTION ENVIRONMENT

The purpose of this paper is to perform a secondary data analysis in order to explore the ways in which coping, perceived control, and stress impact immune function—with the hope of identifying relevant targets for psychological intervention. To achieve this overall goal, data was obtained on patients receiving liver cancer treatment at UPMC Liver Cancer Center. It is worth noting that approximately one-third of the study sample had a diagnosis of hepatocellular carcinoma (HCC) [see Table1]. HCC is the most common primary liver cancer worldwide and "the fastest growing cause of cancer-related death in men in the United States" [El–Serag & Rudolph, 2007, p. 2559]. Nonetheless, HCC is relatively rare within the United States: Eighty percent of all cases occur in sub-Saharan Africa and eastern Asia, with more than half of all HCC cases worldwide occurring in China alone [El–Serag & Rudolph, 2007].

1.2 PUBLIC HEALTH SIGNIFICANCE

Research [Dhabhar, 2014; Cohen, Doyle, & Skoner, 1999; Cohen et al., 2012; Miller, Cohen & Ritchey, 2002] has demonstrated that stress can impede immune system functioning—leading to increased susceptibility to infectious diseases such as the common cold and other respiratory

viruses—as well as dysregulating the immune system such that an inflammatory immune response is initiated. Over time, systemic inflammation can lead to a variety of diseases of public health significance, including type II diabetes, cardiovascular disease, Alzheimer's disease and other dementias, etc. [Dantzer et al., 2008; Engelhart et al., 2004; McGeer & McGeer, 2004; Miller et al., 2002; Pickup & Crook, 1998; Sevenoaks & Stockley, 2006; Simone & Tan, 2011; Spranger et al., 2003; Sundelöf et al., 2009; Volpato et al., 2001]. These are compelling reasons to continue to explore the interplay between stress and coping and its impact on the human body.

It has been posited [Dhabhar, 2014; Moksnes & Espnes, 2016; Segerstrom & Miller,2004] that the psychological and physiological responses to stress—such as low-grade, systemic inflammation—only result in "serious pathology" [Moksnes & Espnes, 2016, para. 10] when the perceived stress is chronic and exceeds one's ability to cope. Therefore, it seems logical that, by targeting those individuals who are at risk of failing to cope sufficiently (i.e. coping maladaptively) for intervention, serious disease could potentially be prevented. In addition to the compassionate reasons that drive the desire to prevent chronic disease—namely a reduction in human suffering—there are economic considerations as well. Chronic disease treatment and management currently account for 86% of annual healthcare expenditure in the United States (U.S.) [CDC, 2017].

1.3 RESEARCH QUESTIONS AND HYPOTHESIS

In order to understand who would benefit most from intervention, there must be a better understanding of the relationship between stress and coping and its influence on immune

function (here, operationalized as levels of anti- and pro-inflammatory cytokines in peripheral blood). To that end, the following research questions guided this secondary data analysis:

(1) Which coping profiles are most prevalent among patients with advanced liver cancers?

(2) How does the three-way interaction [see Figure 1] among coping profile, perceived control, and perceived stress impact advanced liver cancer patients' blood serum levels of the regulatory cytokine Interleukin 2 (IL-2), the anti-inflammatory cytokine IL-10, and the pro-inflammatory cytokines IL-1 alpha (α) and beta (β)?

The aim of these research questions is to explore which combinations of coping strategies patients with stage III and IV liver malignancies use to handle their cancer diagnoses and to uncover how those combinations of coping strategies—or coping profiles—interact with patients' perceived levels of stress and of personal control regarding their cancer diagnoses to impact immune function. I hypothesize that, among advanced cancer patients who perceived their cancer diagnosis as highly stressful, those individuals with high perceived personal control who predominately use a coping profile characterized by high problem-focused and low emotion-focused coping will have the lowest levels of pro-inflammatory cytokines IL-1α and IL-1β in their peripheral blood.

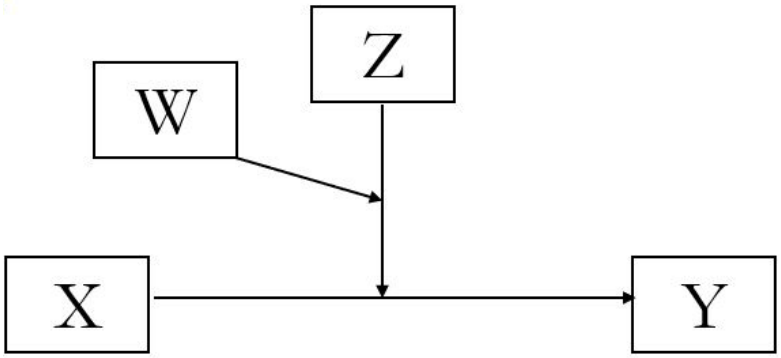

Figure 1. Conceptual Diagram of a Three-Way Interaction (Moderated Moderation)

This diagram provides a generic conceptual representation of a moderated moderation—also known as a three-way interaction—in which X, W, and Z are independent (predictor) variables interacting to influence Y, the dependent (response) variable. In the context of the present research, Y corresponds to blood levels of IL-1 α and β, IL-2, and IL-10.

1.4 CHAPTER-BY-CHAPTER SUMMARY

In this first chapter, I outlined the purpose, research questions, and hypothesis guiding this paper. In the next chapter, I define the independent and dependent variables in addition to synthesizing the literature on the relationship among coping, perceived control, and stress. In the third chapter, I detail the methods that were used to obtain the results that I present in the fourth chapter. In the fifth chapter, I discuss the key findings from this secondary data analysis as well as some limitations that could have influenced the results. In the sixth chapter, I suggest avenues that researchers might take in the future to further elucidate the complex relationship among coping, perceived control, and stress. In the seventh, and final, chapter, I list the references that are cited throughout this paper.

2.0 LITERATURE REVIEW

Over the life course, individuals are likely to encounter difficult situations that most would characterize as stressful. One theory, popularized by psychology researchers Richard Lazarus and Susan Folkman [1984], posits that situations are not inherently stressful. Instead, it is an individual's appraisal of situations and events that makes them stressful. At its most basic level, stress is "a physical and emotional response to strain" [Moksnes & Espnes, 2016, para. 1] or a "physical and psychological result of internal or external pressures" [Moksnes & Espnes, 2016, para. 4]. In their theory, Lazarus and Folkman [1984] conceive of stress as a psychological phenomenon that "involves a particular relationship between the person and the environment that is appraised by the person as taxing or exceeding his or her resources and endangering his or her well-being" [p. 19].

When an individual does appraise a situation as stressful, ze[1] must find a way to deal with that stress as rampant, unresolved stress may cause a host of unpleasant or negative psychological and physiological symptoms, dysfunction, and, eventually, diseases [Dillon, Minchoff & Baker, 1986; Kiecolt-Glaser, McGuire, Robles & Glaser, 2002; Moksnes & Espnes, 2016; Uchino, 2006]. Coping is the construct that encompasses how individuals handle situations that they perceive as stressful. In Lazarus and Folkman's [1984] theory, coping is defined as

[1] "Ze" is a singular, ungendered pronoun that is inclusive of persons who feel that the binary delineation of female and male does not adequately represent their gender identity. The other forms of the pronoun are "zir" and "zem."

"constantly changing cognitive and behavioral efforts to manage specific external and/or internal demands that are appraised as taxing or exceeding the resources of the person" [p. 141]. Note that their conceptualization does not state that coping is inherently positive or beneficial, which is often the layperson's understanding of what it means to cope with a stressful situation. There are different strategies individuals can use to cope—some of which are more adaptive and constructive than others.

According to Lazarus and Folkman's transactional theory of stress and coping [see Figure 2], a situation must first be appraised (i.e. perceived) as stressful in order for coping to occur. In other words, if an individual does not perceive a situation as stressful, then there is no need for that person to cope. Research [Bandura, 1994; Fan, Eiser, Ho & Lin, 2013; Folkman, 1984; Skinner, 1995; Thompson, Cheek, & Graham, 1988] has shown that one's perceived level of personal control over a challenging situation can impact the way in which one appraises a situation (i.e. whether one believes that a situation is stressful). Therefore, if Lazarus and Folkman's understanding of stress and coping is taken as fact, it stands to reason that one's perceived level of personal control should also influence, or moderate, how one copes with the situations that one appraises as stressful [see Figure 2].

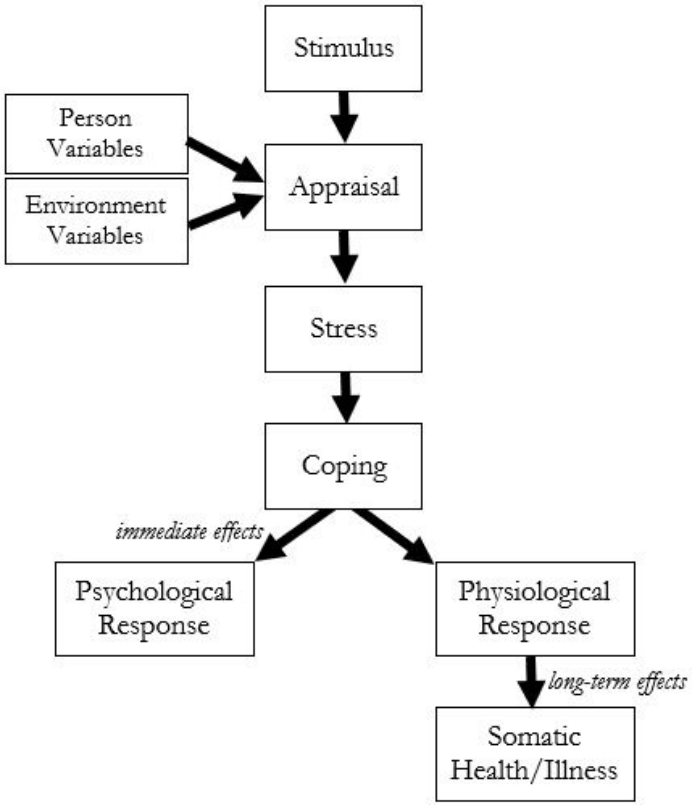

Figure 2. Diagrammatic Rendition of Lazarus and Folkman's Transactional Model of Stress and Coping

The content of this figure was adapted from Lazarus & Folkman [1984] and Caltabiano et al. [2008] in Moksnes & Espnes [2016]. Note that perceived control can be thought of as an individual-level, or person, variable that could influence how one appraises an environmental stimulus.

It is important to keep in mind that stress is not inherently harmful [Dhabhar, 2014; Lazarus & Folkman, 1984; Moksnes & Espnes, 2016]. Individuals often encounter situations that challenge their current coping capacity and grow (e.g. enhance their threshold for what will be appraised as a stressful situation in the future) as a result of said situations. Nevertheless, as mentioned above, uncontrolled stress can have serious, damaging effects on both mind and body that could lead to acute and, eventually, chronic disease.

2.1 COPING

As noted above, coping consists of the myriad of the ways in which an individual manages a situation that ze perceives as stressful. Among coping researchers, there are essentially two camps: Those who believe that coping is a stable trait akin to personality, and those who believe that coping is an ever-evolving process [Carver, Scheier & Weintraub, 1989; Folkman et al., 1986; Folkman & Lazarus, 1985; Folkman & Moskowitz, 2004; Litman, 2006]. In the Lazarus and Folkman [1984] tradition, coping is a process that can vary as one's interactions with the environment—and one's appraisals of those interactions—change due to a variety of internal and external factors. For the sake of research, coping must be operationalized. This has been done with a variety of coping instruments that generally include several subscales that can be grouped into two broad categories of coping: emotion-focused coping and problem-focused coping [Ben-Zur, 2017; Carver, Scheier & Weintraub, 1989; Dunkel-Schetter, Feinstein, Taylor & Falke, 1992]. Emotion-focused coping strategies are usually geared toward "[making] life more bearable by avoiding realities which might prove to be overwhelming if directly confronted" [Goldstein, 1980 in Lazarus & Folkman, 1984, p. 154]. Conversely, problem-focused coping strategies tend to be more concerned with systematically solving problems in order to alter the environment [Lazarus & Folkman, 1984]. While these two broad categories are convenient ways to differentiate ways of coping, they are by no means mutually exclusive: "Theoretically, problem- and emotion-focused coping can both facilitate and impede each other in the coping process" [Lazarus & Folkman, 1984, p. 153]. Some researchers [Moksnes & Espnes, 2016; Lazarus, 1999; Lazarus and Folkman, 1984; Taylor and Stanton, 2007] have noted that individuals are more likely to utilize problem-focused coping strategies when they perceive that

they have the capacity to influence the stressful situation itself (i.e. when they have a high level of perceived personal control).

2.2 PERCEIVED CONTROL

Perceived control refers "to the extent to which people feel confident of their powers of mastery over the environment" [Lazarus & Folkman, 1984, p. 65]. Individuals with a high level of perceived control believe that they can influence their environment. Refer back to Figure 1 to see how perceived control could influence the relationship between stress and coping. When an individual believes that ze has a high level of personal control, ze is endorsing a strong sense of self-efficacy (i.e. a belief that ze is capable of producing the desired effects on the situations around them) [Bandura, 1994]. Possessing a high level of perceived control or self-efficacy can have numerous benefits: "People with high assurance in their capabilities approach difficult tasks as challenges to be mastered rather than as threats to be avoided" [Bandura, 1994, p. 71]. In other words, they are more likely to persist and to apply additional effort in situations that they appraise as stressful. When they encounter failure or setbacks, people with a high sense of internal control or self-efficacy redouble their efforts with a belief that, if they work harder or acquire more knowledge, they will be successful. These perceptions of efficacy have the potential to impact how one appraises situations and, then, which strategies one employs to cope with those situations that are deemed stressful. An individual's perceived level of personal control also has implications for treatment: A fairly recent meta-analysis [Tamagawa et al., 2012] revealed that psychosocial interventions conferred more benefits to patients with low

perceived control compared to their counterparts with a higher level of perceived personal control.

Though research [Bonanno & Burton, 2013; Doron et al., 2014; Folkman, 1984; Folkman et al., 1986; Lazarus & Folkman, 1984; Skinner, Edge, Altman & Sherwood, 2003; Skinner, 1995; Richardson et al., 2017] has demonstrated the benefits of a high level of perceived personal control, there is a point at which perceiving a high level of personal control can be detrimental [Lazarus & Folkman, 1984; Stowell, Kiecolt-Glaser & Glaser, 2001]. Those with a high level of perceived personal control may take responsibility (or blame) for situations over which they have little influence. This can lead to excessive self-criticism that negatively impacts functioning and enhances negative appraisals of a challenging situation.

2.3 IMMUNE FUNCTION

The immune system has a host of challenging roles. First and foremost, it must distinguish between self and non-self (i.e. those foreign substances that could potentially lead to disease) [Banchereau, Pascual & O'Garra, 2012]. Once a foreign substance has been deemed non-self, there are a series of immune responses that can be mounted. If there are flaws in determining which substances are non-self or in ascertaining whether a foreign substance is potentially pathogenic, there are serious consequences, including infectious disease, autoimmune diseases, allergies, etc. [Banchereau, Pascual & O'Garra, 2012]. In recent decades, researchers [Capuron et al., 2008; Dowlati et al., 2010; Miller, Maletic & Raison, 2009; Picardi, Tarolla, Tarsitani & Biondi, 2009] have also cited immune dysfunction as a key step in the development of mental health conditions (e.g. major depressive disorder) and chronic diseases that are often associated

with lifestyles factors, such as cardiovascular disease and type II diabetes. The many complicated functions of the immune system are orchestrated through the use of cytokines. At their most basic level, cytokines are signaling molecules that aid in regulating the immune system processes that, if dysregulated, can lead to a series of adverse effects and chronic mental and physical health conditions [“Cytokine,” 2010].

2.3.1 Pro-Inflammatory cytokines: IL-1α and IL-1β

Pro-inflammatory cytokines are those signaling molecules in the immune cascade that help initiate an inflammatory response [Glaser et al., 1999]. In the short term, inflammation is an important function of the immune system that can help prevent life-threatening infection (e.g. fever in response to a bacterial infection, localized redness and swelling in response to a cut or abrasion, etc.) [Glaser et al., 1999; U.S. National Library of Medicine, 2015]. However, in the long term, persistent inflammation—even low-grade, subclinical inflammation—has been shown [Forti et al., 2010; Kronfol & Remick, 2000; Maes, 1999; Raison, Capuron & Miller, 2006] to play a role in the development of mental and physical pathologies.

Interleukin 1 alpha and beta are two inflammatory cytokines whose role in the inflammatory cascade and impact on adverse health outcomes has been well-studied [Balak et al., 2015; Banerjee & Saxena, 2012; Dinarello, 2009; Dinarello, 2013]. For instance, there is evidence to suggest that they may be the link between immune system dysfunction, depression, and cardiovascular disease as they are biological molecules that are capable of crossing the blood-brain barrier [Baune, 2015]. One study [Thomas et al., 2005] went so far as to conclude that an individual’s level of IL-1β is predictive of the severity of zir depressive symptoms. Moreover, the importance of inhibiting the action of certain members of the IL-1 family has been

translated from bench to bedside. For example, IL-1β is the target of several therapies used to treat autoinflammatory conditions (e.g rheumatoid arthritis and psoriasis) [Braddock, Quinn & Canvin, 2004; Dinarello, 2014; Palomo et al., 2015]. In oncology, IL-1β is an essential mediator of the inflammatory response that can provide insight into tumor growth and metastases [Berghella et al., 1994; Clary, Coveney & Phillip, 1997; Klund & Kuzel, 2004].

2.3.2 Anti-Inflammatory cytokines: IL-10

In addition to inciting inflammation, cytokines can also inhibit or dampen the inflammatory immune response [Dhabhar et al., 2009]. These cytokines that impede the inflammatory immune cascade are called anti-inflammatory cytokines. IL-10 is one such cytokine that works to temper the action of certain inflammatory cytokines and to prevent their downstream effects [Mocellin et al., 2003; Xiu et al., 2015; Dhabhar et al., 2009]. Though the classification of cytokines as either primarily anti-inflammatory or pro-inflammatory is useful, it is not perfect. In the context of context of cancer, IL-10 has been shown [Xiu et al., 2015] to both enhance and impede tumoral actions.

2.3.3 Regulatory cytokines: IL-2

Interleukin 2 plays important roles in regulating the immune system. It does this by activating other immune cells (e.g. regulatory T cells and natural killer cells) that are, then, responsible for initiating various immune response cascades [Capobianco, et al., 2016; Nelson, 2004]. Research [Capuron, Ravaud & Dantzer, 2000; Maes, Meltzer & Bosmans, 2008] has found associations between psychological disorders, such as schizophrenia and obsessive-compulsive disorder, and

blood serum levels of IL-2. In oncology, IL-2 has been used as immunotherapy for patients with a variety of cancer types to inhibit tumor growth, the development of metastases, and the onset of other immune disorders [Jiang, Zhou, and Ren, 2016; Sim & Radvanyi, 2014]. It is important to note that some [Capobianco, et al., 2016] primarily classify IL-2 as a pro-inflammatory cytokine while others [Banchereau, Pascual & O'Garra, 2012] classify it as an anti-inflammatory cytokine.

3.0 METHODS

3.1 PARTICIPANTS

The data used for this secondary analysis were originally gathered from patients seeking treatment at the medical clinics of the UPMC Liver Cancer Center between 2008 and 2015. In order to be included in the original study (n = 543), patients had to have a biopsy or imaging confirming a cancer diagnosis impacting the hepatobiliary or pancreatic system, be at least 21 years old, be fluent in English, and be able to provide informed consent. Patients also had to have no evidence of a thought disorder, hallucinations or delusions, or chronic steroid use. Patients who had received any immunizations or contracted any infectious illnesses in the past month were also excluded from participation since a recent immunization or infectious illness could impact the detectable levels of circulating cytokines in patients' peripheral blood. For the purposes of the present secondary analysis, any patients who had missing coping, perceived control, stress, or biomarker data were excluded, which left a sample size of 285 patients.

3.2 MATERIALS

3.2.1 Revised Ways of Coping Questionnaire

Throughout their careers, Lazarus and Folkman, in conjunction with other researchers, developed several instruments designed to measure and categorize coping in an attempt to operationalize the elusive construct. To gather the data analyzed here, the 1985 revision of the Ways of Coping Questionnaire (WOCQ) was utilized. This revision of the instrument consists of 67 items, each with a 5-point, Likert-style response scale. Generally, the instrument is divided into 8 subscales: Confrontative Coping, Distancing, Self-Controlling, Seeking Social Support, Accepting Responsibility, Escape-Avoidance, Planful Problem Solving, and Positive Reappraisal [see Appendix A]. These subscales were devised through a study Lazarus et al. [1986] conducted on a sample of healthy, community-dwelling, Caucasian, Christian, married couples who were, on average, in their early forties and had at least one child living at home. The sample was obtained through random-digit dialing, a probability-based sampling method. In their study, Lazarus et al. [1986] administered the WOCQ to the participants a total of five times. These data were then "analyzed using alpha and principal factoring with oblique rotation" [p. 994]. Across the five administrations, the average coefficient alphas (also called Cronbach's alpha) were .70, .61, .70, .76, .66, .72, .68, and .79 for Confrontative Coping, Distancing, Self-Controlling, Seeking Social Support, Accepting Responsibility, Escape-Avoidance, Planful Problem Solving, and Positive Reappraisal, respectively [Lazarus et al., 1986].

Traditionally, the eight WOCQ subscales are further grouped into emotion-focused or problem-focused, with Planful Problem Solving being the only scale that is entirely problem-focused. Nonetheless, Lazarus and Folkman [1984] note that there is no concrete rule regarding

what constitutes problem-focused or emotion-focused coping since coping is a process rather than a stable style or trait. For the original study from which the data were obtained for this secondary analysis, the Confrontative Coping, Distancing, and Positive Reappraisal subscales were not administered to participants.

3.2.2 Perceived Stress Scale

The Perceived Stress Scale (PSS) was designed to be a global measure of one's perceived level of stress, meaning the scale can be used to assess a respondent's perceived level of stress for a variety of situations. The instrument is intended for the examination of "the role of nonspecific appraised stress in the etiology of disease and behavioral disorders and as an outcome measure of experienced levels of stress" [Cohen, Kamarck & Mermerlstein, 1983, p. 385]. There are several versions of the PSS, which primarily differ in length. This data set included responses from the 14-item version [see Appendix B]. It is important to note that the PSS itself does not prompt respondents to consider a specific situation as it is meant to be widely applicable in a variety of situations that individuals may perceive as stressful. For the original study from which data were used for the present analysis, participants were prompted to recollect their "feelings and thoughts for the past month" as they completed the 14-item instrument.

The PSS is structured such that a composite score can be calculated. Respondents provide an answer to each of the items using a 5-point scale ranging from 0 to 4, where 0 is equivalent to "never" and 4 is equivalent to "very often." Once positively worded items are reverse scored, respondents scores for each item can be summed to calculate a composite score. The higher the score, the more stress the respondent perceives. The 14-item version of the PSS was validated using three samples, two of which were comprised of college students and one of which

consisted of smoking-cessation program attendees [Cohen, Kamarck & Mermerlstein, 1983]. For the two college-student samples, the coefficient alpha of the PSS was .84 and .85; similarly, the coefficient alpha for the smoking-cessation sample was .86 [Cohen, Kamarck & Mermerlstein, 1983].

3.2.3 Brief Illness Perception Questionnaire

The Brief Illness Perception Questionnaire (Brief-IPQ) is an abbreviated version of its namesake instrument: the Illness Perception Questionnaire. It is "designed to rapidly assess the cognitive and emotional representations of illness" [Broadbent et al., 2006, p. 631]. In its entirety, the Brief-IPQ is nine items. To assess the validity of the instrument, Broadbent et al. recruited a sample of individuals with diverse acute and chronic illnesses (e.g. renal disease, type II diabetes, and minor seasonal allergies). They [Broadbent et al., 2006] administered the Brief-IPQ was administered a total of three times in order to ascertain the test-retest reliability. Three weeks after the initial administration, the test-retest reliability of each of the nine items ranged from .48 to .70; at six weeks, the test-retest reliability ranged from .42 to .72. For the personal control item—the only item used in the present analysis—the three-week test-retest reliability was. 63, and the six-week test-retest reliability was .42.

As was the case for all of the questionnaires administered in the original study from which the data for the present analysis were obtained, the Brief-IPQ was administered to participants as part of a mailed packet of questionnaires. Though participants completed all nine of the Brief-IPQ's items, only the responses to item three were used for the purposes of the present secondary analysis. Item three asks individuals, "How much control do you feel you have over your illness?" [Broadbent et al., 2006]. Respondents are provided with a scale from one to

ten to rate their level of perceived personal control, where one is “absolutely no control” and 10 is “extreme amount of control.”

3.3 PROCEDURE

3.3.1 Data collection

The data used for this secondary analysis were originally gathered from patients seeking treatment at the medical clinics of the UPMC Liver Cancer Center between 2008 and 2015. Data collection did not commence until the original investigators received approval from the University of Pittsburgh’s institutional review board. Patients were referred by the medical teams providing their liver cancer care and were included for participation only after they had provided written informed consent.

3.3.2 Operationalizing the coping process

In an attempt to operationalize participants’ coping processes in a nuanced way, principle components analysis (PCA) and cluster analysis were used to create four coping profiles. As will be detailed in the following section, PCA was used rather than exploratory or confirmatory factor analysis (EFA and CFA, respectively) because the primary objective was to reduce the number of items, not uncover latent constructs. A varimax orthogonal rotation was used to complete the PCA in an attempt to minimize redundancy in the resulting components. There were seven components with an eigenvalue greater than one. There was no obvious elbow pattern [see

Figure 4], and none of the seven components' factor loadings had an absolute value greater than 0.5, so only the first two components—which accounted for more than half of the variance observed—were kept for to the next phase of the analysis: cluster analysis. For the cluster analysis, a k-means algorithm was used to differentiate four coping profiles [see Figure 5]. This first phase of the analytic plan was heavily influenced by the work of Rood, McConnell and Pantalone [2015]. All inferential analyses were performed using R, an opensource statistical package, with the aid of the University of Pittsburgh's statistical consulting service that is offered by graduate students in the Department of Statistics.

3.3.3 Operationalizing stress

First, participant's responses on the 14-item PSS were aggregated according to the scoring instructions—reverse coding items as appropriate—to create a composite score. The instrument is scored such that an increase in composite score corresponds with an increase in the respondent's level of perceived stress. To facilitate the three-way interaction analysis using multiple linear regression, the stress data was categorized into low stress, moderate stress, and high stress. Per the creators of the instrument [Carnegie Mellon University, n.d.; Cohen & Williamson, 1988], are no standard cut-off scores for low, moderate, and high stress, so standard deviations were used to group the PSS data. PSS scores that were one SD or below (less than 27.64) the mean were categorized as "low stress." PSS scores within one SD of the mean (between 27.64 and 35.47) were deemed "moderate stress." Finally, those PSS scores that were one SD or above (greater than 35.47) the mean were categorized as "high stress."

3.3.4 Operationalizing perceived control

Given that only one item of the Brief-IPQ was used for the present analysis, few steps were taken to prepare the perceived personal control variable for the next phase of analysis. To facilitate interpretation of the three-way interactions using multiple linear regression, control was also treated as a categorical variable. This was done by categorizing a self-rated level of personal control of one to four as "low control," of five or six as "moderate control," and of seven to ten as "high control."

3.3.5 Operationalizing immune function

Blood serum levels of IL-1α, IL-1β, IL-2, and IL-10 were used as indicators of immune function for reasons detailed above. Looking at the Q-Q plots and residual graphs for each of the cytokines indicated that there were some potential multiple linear regression model violations, namely a lack of normality. For this reason, the cytokine data were further investigated using histograms. These histograms indicated that there were several outliers that were having undue influence. In order to alleviate these issues, the cytokine data were log-transformed—a remedy proposed in the oft-cited Aiken & West [1991]. Since some of the cytokine values were zero, the data were log-transformed as log (biomarker level + 1) in order to avoid producing results of negative infinity. Transforming the data in this way enabled the cytokine data to be left as continuous variables.

3.3.6 Assessing three-way interactions

After all the independent variables and the dependent variables were transformed as described above, four multiple linear regression models were created—one for each cytokine—using global F tests. Once a series of reference groups was selected [see section 4.0] for the purposes of dummy-coding the categorical predictor variables, global F tests were used to ascertain whether there was a significant interaction among the three independent variables in their influence on the dependent variables. The F test does this by assessing the significance of the permutations of two-way interactions among the independent variables and whether the introduction of the third independent variable impacts the effect of those two-way interactions [see Figure 3]. The global F tests were followed by likelihood ratio tests to further explore the statistical significance of any observed interactions. Lastly, the results of the global F tests were used to construct the regression equations for the three-way interactions, which were then used to plot the three-way interactions for each cytokine. This phase of the analysis, particularly the decision to plot the interaction results, was heavily influenced by Stowell, Kiecolt-Glaser, and Glaser [2001].

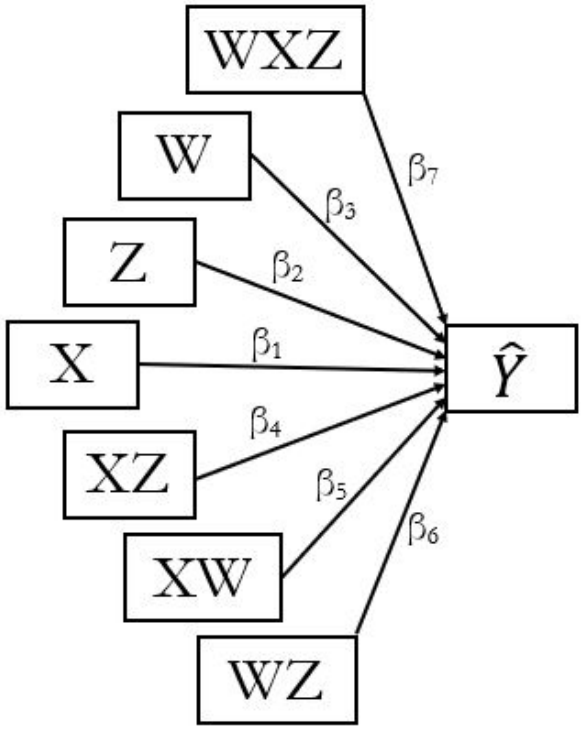

Figure 3. Statistical Diagram of a Three-Way Interaction

This diagram provides a generic statistical representation of a three-way interaction. In order to explore the ways in which the three independent variables (W, X, and Z) interact to influence the dependent variable (Y), the main effects of each predictor and the two-way interactions between the predictors must first be examined. The beta coefficients indicate the magnitude and direction of the predictors' influence on the response variable.

3.3.7 Rationale for use of principle components analysis

Since I did not feel it was appropriate to use the subscales that were previously devised using a healthy sample of married couples, PCA was used to reduce the amount of coping data. There is debate among statisticians regarding the best use of PCA (compared to EFA) [Costello & Osborne, 2005]. In the present analysis, PCA was only used to reduce the amount of data, while retaining as much of the variance as possible. Though PCA is statistically similar to both EFA and CFA, there is a theoretical difference: EFA and CFA are intended to uncover latent constructs, which often results in a reduced number of variables grouped into discrete dimensions or subscales [Byrne, 2005; River-Medina, 2015]. I sought to reduce the number of

variables by removing redundancy without removing the variance (i.e. complexity) in coping strategies—a task better suited for PCA [O'Rourke & Hatcher, 2013]. By using PCA, I was coming from a place of unknowing about the coping processes used by patients with advanced liver cancers:

> Principal component analysis makes no assumptions about the underlying causal structures; it is simply a variable reduction procedure that (typically) results in a relatively small number of components accounting for, or capturing, most variance in a set of observed variables (i.e., groupings of observed variables versus latent constructs). [O'Rourke & Hatcher, 2013, p. 7]

3.3.8 Rationale for use of multiple linear regression

Some statisticians [Aiken & West, 1991; Cohen, Cohen, West & Aiken, 2003] maintain that the use of multiple linear regression is not as common as the use of analysis of variance, or ANOVA, in social science disciplines. Nonetheless, ANOVA is not necessarily the statistical method that is well-suited to explore the complex relationships that are often hypothesized by social sciences researchers [Aiken & West, 1991; Cohen, Cohen, West & Aiken, 2003]. For the present analysis, the most important feature of multiple linear regression is its ability to tolerate relationships among predictor variables that are somewhat curvilinear [Aiken & West, 1991; Cohen, Cohen, West & Aiken, 2003] as there is some evidence in the literature [Stowell, Kiecolt-Glaser & Glaser, 2001; Thompson, Cheek & Graham, 1988] that the relationship between perceived control and perceived stress is not entirely linear.

4.0 FINDINGS

4.1 SECONDARY ANALYSIS SAMPLE

As noted in a previous section (see 3.1), patients from the original study who had any missing data were excluded from this secondary analysis. This was primarily done to facilitate execution of the complex data analysis plan. I felt that this exclusion would not significantly bias the results given that a sensitivity analysis conducted by the original principal investigator and her consultant statistician determined that the missing data was missing at random, not as a result of a systematic error (or bias) [J.L. Steel, personal communication, February 15, 2018].

Of the 285 participants whose data were included, 117 identified as women and 168 identified as men. The sample's mean age at time of cancer diagnosis was 62 years (±11 years), and the median age at time of cancer diagnosis was 61 years. Though all participants had malignancies in their liver, not all participants had primary liver tumors [see Table 1]. Approximately one-third of the sample had a primary liver cancer called hepatocellular carcinoma (HCC)—which, as was described in the introduction, is a relatively rare cancer type in the U.S. Eighty-six percent of the sample had a least one comorbid condition. The sample was rather homogenous in terms of race and ethnicity: 91.5% of the sample identified as "White," and 98.2% of participants identified as non-Latino. The homogeneity continued for a variety of key sociodemographic variables: At the time of consent for participation in the original study,

73.7% of the sample was currently married or widowed, and 95.2% had at least a high school diploma or GED. Though it threatens the external validity of the findings, the homogeneity of the sample was an advantage when it was time to conduct regression analyses as demographic variables could be controlled statistically without fear of suppressing crucial information.

Table 1. Sample Characteristics (n=285)

	Frequency	Percent
Sex		
Female	117	41
Male	168	59
Age at Diagnosis (years)		
30 – 39	6	2.1
40 – 49	33	12
50 – 59	78	27.6
60 – 69	96	33.7
70 – 79	57	20.3
80 – 89	14	5.1
90 – 99	1	0.4
Race		
American Indian	1	0.4
Asian	2	0.7
Black or African American	19	6.7
Other	1	0.4
Unknown	1	0.4
White	260	91.5
Latino		
No	279	98.2
Yes	5	1.8
Highest Degree Completed		
Less than 8th Grade	1	0.4
Less than High School	12	4.4
High School Graduate/GED	110	40.6
Some College	69	25.5
College Graduate	57	21
Master's Degree	16	5.9
Doctoral Degree/MD	6	2.2
Employment Status		
Full-Time	76	27
Part-Time	12	4.3
Unemployed, but looking	5	1.8

Table 1 Continued

Unemployed, but not looking	4	1.4
Retired, not working at all	107	38.1
Retired, but working part- or full-time	5	1.8
Disabled/Unable to Work	51	18.1
Full-Time Homemaker	7	2.5
Student	1	4
Other	13	4.6
Marital Status		
Currently Married	182	63.9
Divorced	33	11.6
Living with Partner	10	3.5
Never Married	25	8.8
Separated	3	1.1
Widowed	28	9.8
Other	4	1.4
Cancer Diagnosis		
Breast with Metastases	14	4.9
Cholangiocarcinoma	22	7.7
Colorectal with Metastases	80	28.1
Hepatocellular Carcinoma	92	32.3
Neuroendocrine	33	11.6
Pancreatic	14	4.9
Other	30	10.9
Hepatocellular Carcinoma Etiology		
Alcohol	11	12.1
Cryptogenic	13	14.3
Hepatitis B	6	6.6
Hepatitis C	25	27.5
Hepatitis C + Alcohol	10	11
Non-Alcoholic Steatohepatitis	15	16.5
Other	11	21.1
Treatment at Time of Consent		
None	57	20
Regional Therapies	61	21.4
Systemic Chemotherapies	46	16.2
Resection	82	28.8
Radiofrequency Ablation	39	13.7

4.2 PRINCIPLE COMPONENTS ANALYSIS

As noted above, upon conducting PCA with varimax rotation on the available WOCQ items, seven components were found to have an eigenvalue over one. Moreover, none of the components with an eigenvalue of one had factor loadings with an absolute value greater than 0.5. Collectively, the seven components accounted for 53% of the variance observed; however, the first two components accounted for 17.25% and 10.93% of the variance, respectively [see Figure 4]. For this reason—in conjunction with the fact that there was no clear elbow pattern in the scree plot [see Figure 4]—the analysis continued using only the first two components.

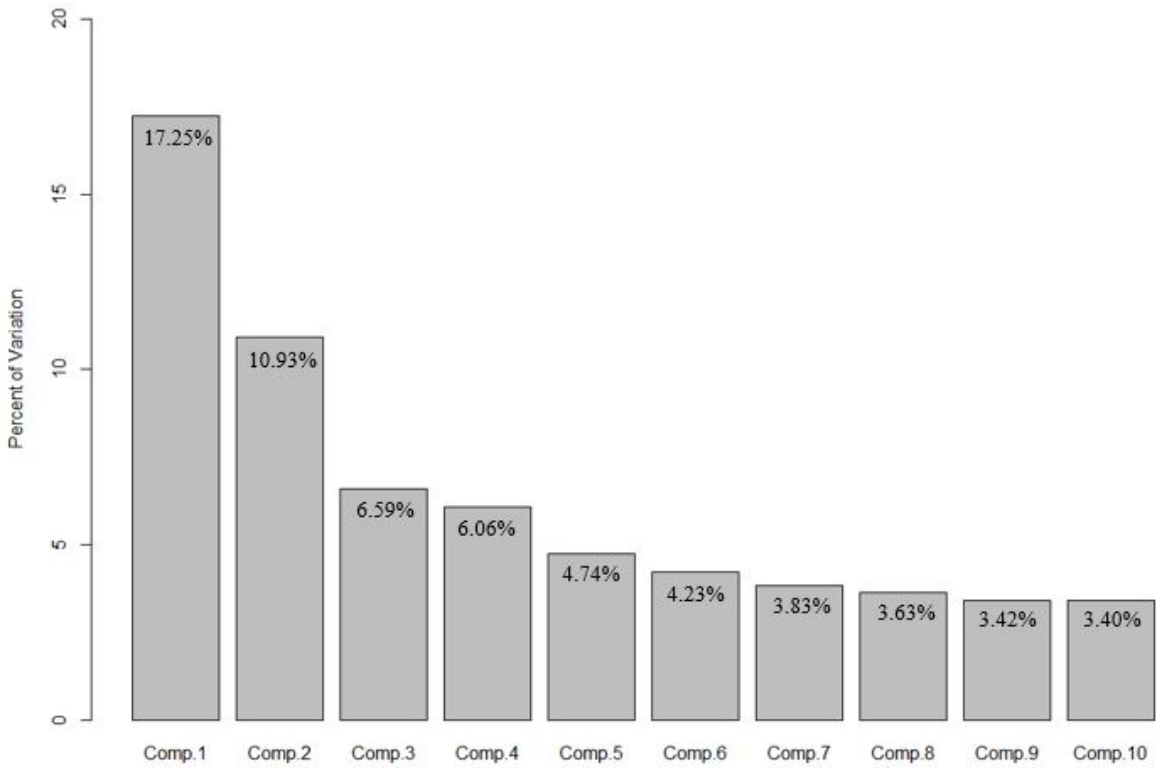

Figure 4. Scree Plot for WPCQ Principle Components Analysis

The following WOCQ items were accounted for in Component 1:

Item 11: Hoped a miracle would happen

Item 26: I made a plan of action and followed it

Item 31: Talked to someone who could do something concrete about the problem

Item 39: Changed something so that things would turn out all right

Item 42: I asked a relative or friend that I respected for advice

Item 45: Talked to someone about how I was feeling

Item 49: Knew what had to be done, so I doubled my efforts to make things work

Item 52: Came up with a couple different solutions to the problem

Item 63: I thought about how a person I admire would handle the situation and used that as a model

Item 64: I tried to see things from another person's point of view

All of the factor loadings for Component 1 were negative, meaning that Component 1 was inversely correlated with all of the WOCQ items that comprised it [see Table 2].

Table 2. Principle Components Analysis: Component 1 Factor Loadings

	Component 1
Item 11	-0.251
Item 26	-0.221
Item 31	-0.253
Item 39	-0.273
Item 42	-0.26
Item 45	-0.215
Item 49	-0.226
Item 52	-0.236
Item 63	-0.222
Item 64	-0.227

The following WOCQ items were accounted for in Component 2:

Item 1: Just concentrated on what I had to do next-the next step

Item 8: Talked to someone to find out more about the situation

Item 9: Criticized or lectured myself

Item 1: Hoped a miracle would happen

Item 26: I made a plan of action and followed it

Item 31: Talked to someone who could do something concrete about the problem

Item 43: Kept others from knowing how bad things were

Item 45: Talked to someone about how I was feeling

Item 58: Wished that the situation would go away or somehow be over with

Item 59: Had fantasies or wishes about how things might turn out

For Component 2, half of the factor loadings were negative, indicating negative associations [see Table 3].

Table 3. Principle Components Analysis: Component 2 Factor Loadings

	Component 2
Item 1	-0.204
Item 8	-0.202
Item 9	0.219
Item 11	0.255
Item 26	-0.322
Item 31	-0.276
Item 43	0.242
Item 45	-0.209
Item 58	0.374
Item 59	0.254

4.3 CLUSTER ANALYSIS

A k-means clustering alogrithim was run with the assumption that there were four groups [see Figure 5]. The first group (Group 1) was characterized by a low Component 2 score. The second group (Group 2) consisted of a low Component 1 score. The third group (Group 3) was characterized by a high Component 2 score. The fourth group (Group 4) consisted of a high Component 1 score.

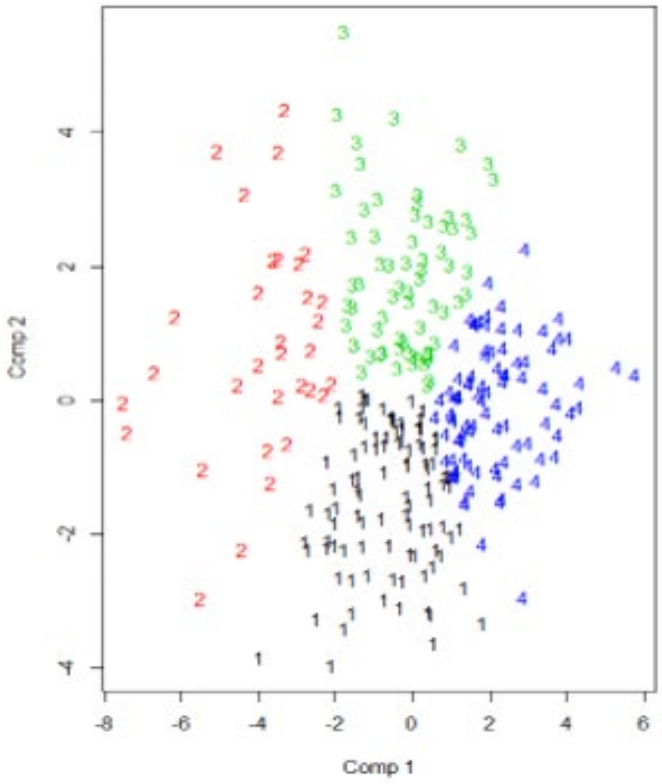

Figure 5. Cluster Analysis of Components 1 and 2 Using K-Means Clustering

In the present sample, 100 patients used coping strategies characterized by Group 1 (hereafter, the Action-Oriented Coping Profile). Thirty-four patients primarily used coping strategies in Group 2 (hereafter, the Planful Advice-Seeking Coping Profile). Sixty-nine patients primarily used coping strategies in Group 3 (hereafter, the Wishful Internal Struggle Coping

Profile). Eighty-nine patients primarily used coping strategies in Group 4 (hereafter, the Avoidant Self-Reliance Coping Profile).

4.4 MULTIPLE LINEAR REGRESSION

The four coping profiles devised from PCA followed by cluster analysis were then used to assess whether stress, perceived control, and coping moderate one another to impact the mean log-transformed levels of four biomarkers in peripheral blood.

Please see Table 4 on the next page.

Table 4. IL-10 Regression Model

Interaction Term	$\widehat{\beta}_i$	Standard Error	t value	Pr(>|t|)
Two-Way				
Low Control*Low Stress	-0.99773	1.56667	-0.637	0.5248
Moderate Control*Low Stress	-2.12364	1.79485	-1.183	0.2379
Low Control*Moderate Stress	-1.45501	0.96801	-1.503	0.1341
Moderate Control*Moderate Stress	-2.02213	1.10032	-1.838	0.0673
Low Control* Planful Advice-Seeking Coping	-2.39882	1.32558	-1.810	0.0716
Moderate Control*Planful Advice-Seeking Coping	0.04273	0.81338	0.053	0.9581
Low Control*Wishful Internal Struggle Coping	0.34338	1.55831	0.220	0.8258
Moderate Control* Wishful Internal Struggle Coping	-0.83333	1.79485	-0.464	0.6428
Low Control*Avoidant Self-Reliance Coping Profile	0.43042	1.24977	0.344	0.7308
Moderate Control*Avoidant Self-Reliance Coping Profile	-1.53763	1.49843	-1.026	0.3058
Low Stress* Planful Advice-Seeking Coping	-2.36328	1.92603	-1.227	0.2210
Moderate Stress*Planful Advice-Seeking Coping	-1.98015	1.09355	-1.811	0.0714
Low Stress*Wishful Internal Struggle Coping	-1.18784	1.98838	-0.597	0.5508
Moderate Stress* Wishful Internal Struggle Coping	-0.18975	1.42895	-0.133	0.8945
Low Stress*Avoidant Self-Reliance Coping Profile	-0.44804	1.72552	-0.260	0.7953
Moderate Stress*Avoidant Self-Reliance Coping Profile	-1.15615	1.00379	-1.152	0.2505
Three-Way				
Low Control*Low Stress*Planful Advice-Seeking Coping	N/A	N/A	N/A	N/A
Moderate Control* Low Stress*Planful Advice-Seeking Coping	N/A	N/A	N/A	N/A
Low Control*Moderate Stress*Planful Advice-Seeking Coping	2.96284	1.53380	1.932	0.0545
Moderate Control*Moderate Stress*Planful Advice-Seeking Coping	N/A	N/A	N/A	N/A
Low Control*Low Stress*Wishful Internal Struggle Coping	-0.31178	2.24570	-0.139	0.8897
Moderate Control* Low Stress*Wishful Internal Struggle Coping	2.01568	2.57647	0.782	0.4348
Low Control*Moderate Stress*Wishful Internal Struggle Coping	0.25927	1.67372	0.155	0.8770
Moderate Control*Moderate Stress*Wishful Internal Struggle Coping	1.69398	1.92777	0.879	0.3804
Low Control*Low Stress*Avoidant Self-Reliance Coping Profile	-0.31629	2.03731	-0.155	0.8768
Moderate Control* Low Stress*Avoidant Self-Reliance Coping Profile	1.37562	2.33811	0.588	0.5568
Low Control*Moderate Stress*Avoidant Self-Reliance Coping Profile	0.56548	1.36545	0.414	0.6791
Moderate Control*Moderate Stress*Avoidant Self-Reliance Coping Profile	2.451	1.63021	1.503	0.1341
$F(32, 250) = 0.842$, $p = 0.713$, Adjusted $R^2 = -0.018$				

Table 5. IL-1α Regression Model

Interaction Term	β_i	Standard Error	t value	Pr(>|t|)
Two-Way				
Low Control*Low Stress	-1.39596	2.22697	-0.627	0.53133
Moderate Control*Low Stress	-5.53091	2.55131	-2.168	0.03111
Low Control*Moderate Stress	-1.64796	1.37599	-1.198	0.23219
Moderate Control*Moderate Stress	-3.89425	1.56407	-2.490	0.01343
Low Control* Planful Advice-Seeking Coping	-0.86379	1.88427	-0.458	0.64705
Moderate Control*Planful Advice-Seeking Coping	0.73816	1.15619	0.638	0.52377
Low Control*Wishful Internal Struggle Coping	1.18182	2.21507	0.534	0.59414
Moderate Control* Wishful Internal Struggle Coping	-2.88247	2.55131	-1.130	0.25964
Low Control*Avoidant Self-Reliance Coping Profile	-1.26967	1.77650	-0.715	0.47546
Moderate Control*Avoidant Self-Reliance Coping Profile	-4.61586	2.12995	-2.167	0.03117
Low Stress* Planful Advice-Seeking Coping	-5.20240	2.73778	-1.900	0.05855
Moderate Stress*Planful Advice-Seeking Coping	-2.42437	1.55444	-1.560	0.12011
Low Stress*Wishful Internal Struggle Coping	-3.56979	2.82640	-1.263	0.20776
Moderate Stress* Wishful Internal Struggle Coping	-0.11599	2.03120	-0.057	0.95451
Low Stress*Avoidant Self-Reliance Coping Profile	-4.43462	2.45277	-1.808	0.07181
Moderate Stress*Avoidant Self-Reliance Coping Profile	-4.35135	1.42684	-3.050	0.00254
Three-Way				
Low Control*Low Stress*Planful Advice-Seeking Coping	N/A	N/A	N/A	N/A
Moderate Control* Low Stress*Planful Advice-Seeking Coping	N/A	N/A	N/A	N/A
Low Control*Moderate Stress*Planful Advice-Seeking Coping	2.73418	2.18024	1.254	0.21099
Moderate Control*Moderate Stress*Planful Advice-Seeking Coping	N/A	N/A	N/A	N/A
Low Control*Low Stress*Wishful Internal Struggle Coping	0.19980	3.19217	0.063	0.95014
Moderate Control* Low Stress*Wishful Internal Struggle Coping	6.74235	3.66236	1.841	0.06681
Low Control*Moderate Stress*Wishful Internal Struggle Coping	-0.01708	2.37913	-0.007	0.99428
Moderate Control*Moderate Stress*Wishful Internal Struggle Coping	3.44848	2.74026	1.258	0.20940
Low Control*Low Stress*Avoidant Self-Reliance Coping Profile	1.88139	2.89596	0.650	0.51651
Moderate Control* Low Stress*Avoidant Self-Reliance Coping Profile	5.97453	3.32354	1.798	0.07344
Low Control*Moderate Stress*Avoidant Self-Reliance Coping Profile	3.44290	1.94093	1.774	0.07731
Moderate Control*Moderate Stress*Avoidant Self-Reliance Coping Profile	6.22143	2.31728	2.685	0.00774
$F(32, 250) = 1.34$, $p = 0.12$, Adjusted $R^2 = 0.037$				

Table 6. IL-1β Regression Model

Interaction Term	$\hat{\beta}_i$	Standard Error	t value	Pr(>|t|)
Two-Way				
Low Control*Low Stress	-1.37557	2.22478	-0.618	0.5369
Moderate Control*Low Stress	0.07773	2.54880	0.030	0.9757
Low Control*Moderate Stress	-2.50979	1.37464	-1.826	0.0691
Moderate Control*Moderate Stress	-0.49677	1.56253	-0.318	0.7508
Low Control* Planful Advice-Seeking Coping	-3.43444	1.88242	-1.824	0.0693
Moderate Control*Planful Advice-Seeking Coping	0.71655	1.15506	0.620	0.5356
Low Control*Wishful Internal Struggle Coping	0.06759	2.21290	0.031	0.9757
Moderate Control* Wishful Internal Struggle Coping	2.13677	2.54880	0.838	0.4026
Low Control*Avoidant Self-Reliance Coping Profile	-1.57968	1.77476	-0.890	0.3743
Moderate Control*Avoidant Self-Reliance Coping Profile	-0.39699	2.12786	-0.187	0.8522
Low Stress* Planful Advice-Seeking Coping	-0.66177	2.73509	-0.242	0.8090
Moderate Stress*Planful Advice-Seeking Coping	-2.14865	1.55291	-1.384	0.1677
Low Stress*Wishful Internal Struggle Coping	-1.64106	2.82362	-0.581	0.5616
Moderate Stress* Wishful Internal Struggle Coping	0.18169	2.02920	0.090	0.9287
Low Stress*Avoidant Self-Reliance Coping Profile	0.89474	2.45036	0.365	0.7153
Moderate Stress*Avoidant Self-Reliance Coping Profile	-0.99985	1.42544	-0.701	0.4837
Three-Way				
Low Control*Low Stress*Planful Advice-Seeking Coping	N/A	N/A	N/A	N/A
Moderate Control* Low Stress*Planful Advice-Seeking Coping	N/A	N/A	N/A	N/A
Low Control*Moderate Stress*Planful Advice-Seeking Coping	4.07874	2.17810	1.873	0.0623
Moderate Control*Moderate Stress*Planful Advice-Seeking Coping	N/A	N/A	N/A	N/A
Low Control*Low Stress*Wishful Internal Struggle Coping	0.13354	3.18904	0.042	0.9666
Moderate Control* Low Stress*Wishful Internal Struggle Coping	-0.83509	3.65876	-0.228	0.8196
Low Control*Moderate Stress*Wishful Internal Struggle Coping	0.52456	2.37679	0.221	0.8255
Moderate Control*Moderate Stress*Wishful Internal Struggle Coping	-1.70320	2.73756	-0.622	0.5344
Low Control*Low Stress*Avoidant Self-Reliance Coping Profile	0.16294	2.89311	0.056	0.9551
Moderate Control* Low Stress*Avoidant Self-Reliance Coping Profile	-2.54115	3.32027	-0.765	0.4448
Low Control*Moderate Stress*Avoidant Self-Reliance Coping Profile	1.79087	1.93902	0.924	0.3566
Moderate Control*Moderate Stress*Avoidant Self-Reliance Coping Profile	0.81557	2.31501	0.352	0.724
F(32, 250) = 1.03, p = 0.43, Adjusted R^2 = 0.003				

Table 7. IL-2 Regression Model

Interaction Term	$\widehat{\beta}_i$	Standard Error	t value	Pr(>|t|)
Two-Way				
Low Control*Low Stress	-0.53914	1.27764	-0.422	0.6734
Moderate Control*Low Stress	-2.34872	1.46372	-1.605	0.1098
Low Control*Moderate Stress	-0.66199	0.78942	-0.839	0.4025
Moderate Control*Moderate Stress	-2.22878	0.89732	-2.484	0.0137
Low Control* Planful Advice-Seeking Coping	-0.94926	1.08103	-0.878	0.3807
Moderate Control*Planful Advice-Seeking Coping	-0.16363	0.66332	-0.247	0.8054
Low Control*Wishful Internal Struggle Coping	0.76819	1.27081	0.604	0.5461
Moderate Control* Wishful Internal Struggle Coping	-1.88899	1.46372	-1.291	0.1981
Low Control*Avoidant Self-Reliance Coping Profile	0.69055	1.01920	0.678	0.4987
Moderate Control*Avoidant Self-Reliance Coping Profile	-1.99104	1.22198	-1.629	0.1045
Low Stress* Planful Advice-Seeking Coping	-1.03661	1.57069	-0.660	0.5099
Moderate Stress*Planful Advice-Seeking Coping	-1.43542	0.89180	-1.610	0.1088
Low Stress*Wishful Internal Struggle Coping	-0.80304	1.62154	-0.495	0.6209
Moderate Stress* Wishful Internal Struggle Coping	-0.17729	1.16532	-0.152	0.8792
Low Stress*Avoidant Self-Reliance Coping Profile	-0.86289	1.40718	-0.613	0.5403
Moderate Stress*Avoidant Self-Reliance Coping Profile	-1.16605	0.81860	-1.424	0.1556
Three-Way				
Low Control*Low Stress*Planful Advice-Seeking Coping	N/A	N/A	N/A	N/A
Moderate Control* Low Stress*Planful Advice-Seeking Coping	N/A	N/A	N/A	N/A
Low Control*Moderate Stress*Planful Advice-Seeking Coping	1.48315	1.25083	1.186	0.2369
Moderate Control*Moderate Stress*Planful Advice-Seeking Coping	N/A	N/A	N/A	N/A
Low Control*Low Stress*Wishful Internal Struggle Coping	-0.29358	1.83139	-0.160	0.8728
Moderate Control* Low Stress*Wishful Internal Struggle Coping	2.64633	2.10114	1.259	0.2090
Low Control*Moderate Stress*Wishful Internal Struggle Coping	-0.14501	1.36493	-0.106	0.9155
Moderate Control*Moderate Stress*Wishful Internal Struggle Coping	2.97337	1.57212	1.891	0.0597
Low Control*Low Stress*Avoidant Self-Reliance Coping Profile	-0.23841	1.66144	-0.143	0.8860
Moderate Control* Low Stress*Avoidant Self-Reliance Coping Profile	1.91772	1.90675	1.006	0.3155
Low Control*Moderate Stress*Avoidant Self-Reliance Coping Profile	0.02444	1.11353	0.022	0.9825
Moderate Control*Moderate Stress*Avoidant Self-Reliance Coping Profile	2.34635	1.32945	1.765	0.0788
$F(32, 250) = 0.92$, p =059, Adjusted $R^2 = -0.009$				

To facilitate interpretation of the results, the coefficient estimates ($\hat{\beta}_i$) reported in Tables 4 through 7 were used to create the regression equations for the interaction between each category of perceived control and each category of stress under the influence of each coping profile for each of the four cytokines. Plotting three-way interactions is accomplished by plotting two-way interactions at the levels of the third independent variable [Aiken & West, 1991, p. 61]. In general, the linear regression equation for a three-way interaction is: $\hat{Y} = \beta_0 + \beta_1 X + \beta_2 Z + \beta_3 W + \beta_4 XZ + \beta_5 XW + \beta_6 ZW + \beta_7 XZW$, where $\hat{Y}$ is the observed value(s) of the dependent variable in the sample and W, X, and Z are the independent variables that (in theory) moderate each other's effect on the dependent variable [Aiken & West, 1991, p. 49]. In the present analysis, $\hat{Y}$ is equivalent to log(biomarker level +1). Given that high control, high stress, and the Action-Oriented Coping Profile were used as the reference groups, the linear regression equation summarizing the predicted three-way interaction, where X = coping, Z = perceived control, and W = stress, is:

$$\hat{Y} = \beta_0 + \beta_1 * \text{CopingProfile2} + \beta_2 * \text{CopingProfile3} + \beta_3 * \text{CopingProfile4} + \beta_4 * \text{LowControl} + \beta_5 * \text{ModerateControl} + \beta_5 * \text{LowStress} + \beta_7 * \text{ModerateStress} + \beta_8 * \text{CopingProfile2} * \text{LowControl} + \beta_9 * \text{CopingProfile2} * \text{ModerateControl} + \beta_{10} * \text{CopingProfile3} * \text{LowControl} + \beta_{11} * \text{CopingProfile3} * \text{ModerateControl} + \beta_{12} * \text{CopingProfile4} * \text{LowControl} + \beta_{13} * \text{CopingProfile4} * \text{ModerateControl} + \beta_{14} * \text{CopingProfile2} * \text{LowStress} + \beta_{15} * \text{CopingProfile2} * \text{ModerateStress} + \beta_{16} * \text{CopingProfile3} * \text{LowStress} + \beta_{17} * \text{CopingProfile3} * \text{ModerateStress} + \beta_{18} * \text{CopingProfile4} * \text{LowStress} + \beta_{19} * \text{CopingProfile4} * \text{ModerateStress} + \beta_{20} * \text{LowControl} * \text{LowStress} + \beta_{21} * \text{ModerateControl} * \text{LowStress} + \beta_{22} * \text{LowControl} * \text{ModerateStress} + \beta_{23} * \text{ModerateControl} * \text{ModerateStress} + \beta_{24} * \text{CopingProfile2} * \text{LowControl} * \text{LowStress} + \beta_{25} * \text{CopingProfile2} * \text{ModerateControl} * \text{LowStress} + \beta_{26} * \text{CopingProfile2} * \text{LowControl} * \text{ModerateStress} + \beta_{27} * \text{CopingProfile2} * \text{ModerateControl} * \text{ModerateStress} + \beta_{28} * \text{CopingProfile3} * \text{LowControl} * \text{LowStress} + \beta_{29} * \text{CopingProfile3} * \text{ModerateControl} * \text{LowStress} + \beta_{30} * \text{CopingProfile3} * \text{LowControl} * \text{ModerateStress} + \beta_{31} * \text{CopingProfile3} * \text{ModerateControl} * \text{ModerateStress} + \beta_{32} * \text{CopingProfile4} * \text{LowControl} * \text{LowStress} + \beta_{33} * \text{CopingProfile4} * \text{ModerateControl} * \text{LowStress} + \beta_{34} * \text{CopingProfile4} * \text{LowControl} * \text{ModerateStress} + \beta_{35} * \text{CopingProfile4} * \text{ModerateControl} * \text{ModerateStress}$$

Regression lines were created for each of the four biomarkers in this fashion, then the lines were plotted to produce the graphs in Figures 6 through 9. Recall that Coping Profile 1 is the Action-Oriented Coping Profile, Coping Profile 2 is the Planful Advice-Seeking Coping Profile, Coping Profile 3 is the Wishful Internal Struggle Coping Profile, and Coping Profile 4 is the Avoidant Self-Reliance Coping Profile.

4.4.1 Graphical representation of IL-10 regression model

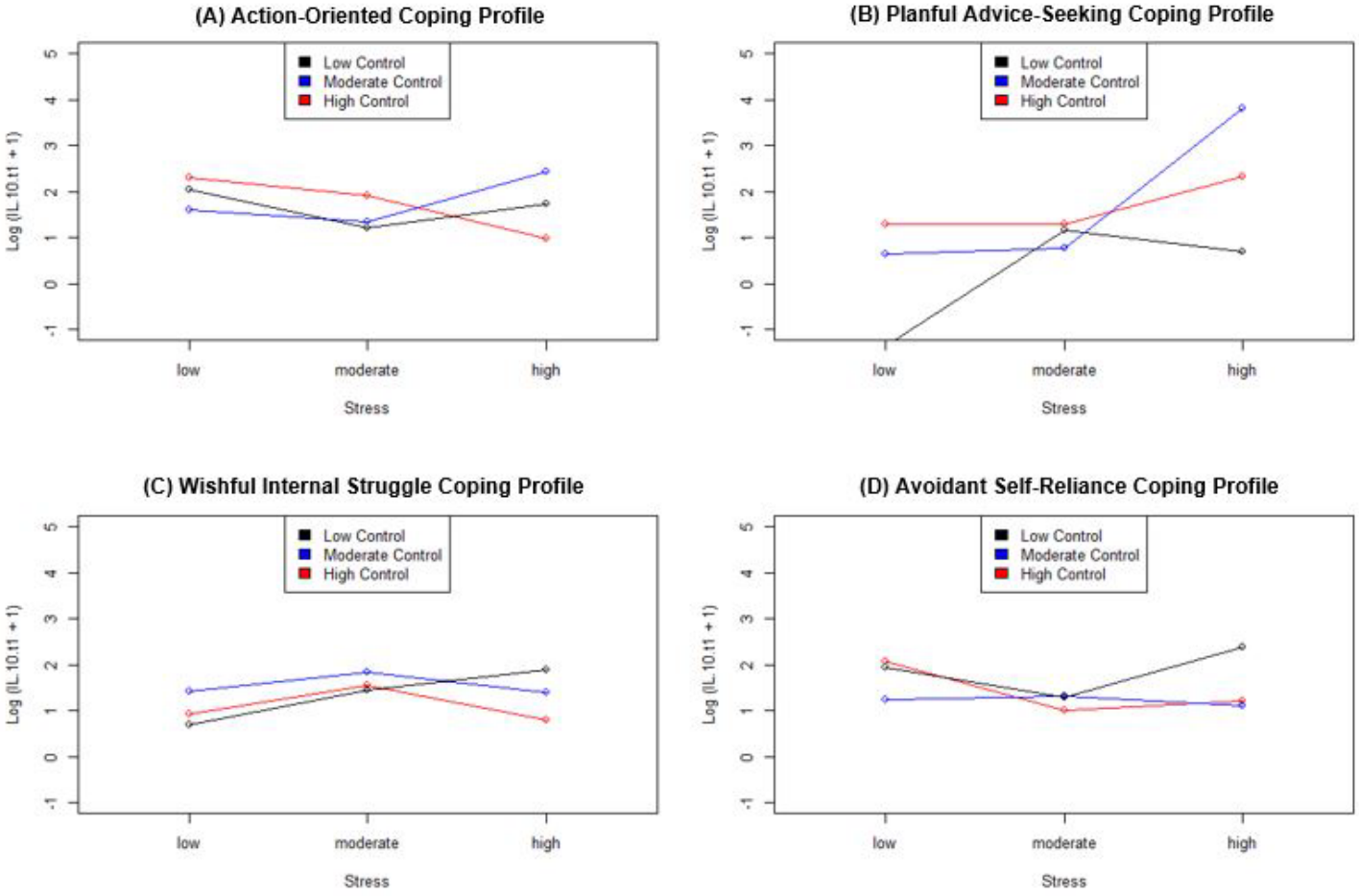

Figure 6. Graphical Representation of IL-10 Regression Model

The fact that plotting the equations from the IL-10 regression model results in graphs [Figure 6] that differ from one another indicates that there is a three-way interaction among the coping, control, and stress variables [The University of North Carolina at Chapel Hill, 2008]. These graphs also illustrate the utility of observing the two-way interaction between control and stress in order to ascertain the three-way interaction among the independent variables [Aiken & West, 1991]. Though the p-values associated with the global F test do not provide sufficient evidence to suggest that the interactions among the three independent variables are not simply due to chance, it is still possible to explore these interactions graphically since the majority of the estimated β coefficients (i.e. the slopes of the regression lines) are non-zero. The notable exception is the interaction model depicted in Figure 6B. Though there appear to be substantial interactions based on this graphical representation, no interpretable coefficients could be calculated for the interactions among low control, low stress, and the Planful Advice-Seeking Coping Profile; low control, moderate stress, and the Planful Advice-Seeking Coping Profile; or moderate control, moderate stress, and the Planful Advice-Seeking Coping Profile [see Table 4]. These singularity warnings suggest that the variables are associated in a non-linear fashion. It is unlikely that these singularity warnings indicate the complete absence of interactions among the variables given that the interaction among low control, moderate stress, and the Planful Advice-Seeking Coping Profile was the only statistically significant three-way interaction for the IL-10 regression model. Despite these singularity warnings, this is the best-fitting multiple linear regression model based on the Q-Q and residuals plots of the dependent variable.

4.4.1.1 Exploring interactions within graphical representation of IL-10 model

Control and stress in Action-Oriented Coping Profile users

Figure 6A depicts the impact of stress and control on the mean log-transformed blood serum level of the pro-inflammatory cytokine IL-10 among individuals who use the Action-Oriented Coping Profile. For individuals who perceive their diagnosis as a low-stress situation, it appears that the mean level of log(IL-10 + 1) is lowest among those who also perceive that they have moderate control over the situation. The mean level of log(IL-10 + 1) is highest among individuals who perceive the situation as low-stress and believe that they have a high level of personal control. When users of the Action-Oriented Coping Profile perceive their advanced cancer diagnosis as a moderately stressful situation, a low level of perceived personal control appears to result in the lowest mean levels of log(IL-10 + 1). However, the difference in the mean levels of log(IL-10 + 1) between a low and a moderate level of perceived personal control is almost imperceptible to the naked eye. Mean levels of log(IL-10 + 1) are the highest among individuals who believe that they have high personal control over a situation they perceive as moderately stressful. For individuals utilizing the Action-Oriented Coping Profile to process what they perceive as a highly stressful initial cancer diagnosis, having a high level of perceived personal control results in the lowest mean levels of log(IL-10 +1). The highest mean levels of log(IL-10 + 1) are seen among those who have moderate levels of perceived personal control in what they believe is a high stress situation.

It is worth noting the parallel nature of the blue (moderate control) regression line and the red (high control) regression line when stress is low to moderate. This parallelism suggests that the interaction among control, stress, and coping is less evident when a situation is appraised as low- or moderate-stress—particularly when an individual believes ze has moderate or high

personal control. In contrast, the fact that all the regression lines intersect when a situation is perceived as moderately to highly stressful suggests a more robust interaction between control and stress among Action-Oriented Coping Profile users.

Control and stress in Planful Advice-Seeking Coping Profile users

Figure 6B depicts the impact of stress and control on the mean log-transformed blood serum level of the pro-inflammatory cytokine IL-10 among individuals who use the Planful Advice-Seeking Coping Profile. As indicated above, there were singularity warnings associated with several of the interactions terms depicted in this graph. On the other hand, the interaction among low control, moderate stress, and the Planful Advice-Seeking Coping Profile (see the black circle at moderate stress in Figure 6B) was the only statistically significant three-way interaction for the IL-10 regression model. Incidentally, the graph reveals that the mean level of log(IL-10 +1) is almost identical when a situation is perceived as moderately stressful among the Planful Advice-Seeking Coping Profile users who believe that they have either low or moderate personal control.

Control and Stress in Wishful Internal Struggle Coping Profile users

Figure 6C depicts the impact of stress and control on the mean log-transformed blood serum level of the pro-inflammatory cytokine IL-10 among individuals who use the Wishful Internal Struggle Coping Profile. The parallel nature of the blue (moderate control) regression line and the red (high control) regression line across all three categories of perceived stress is noteworthy. This parallelism suggests that the interaction among control, stress, and coping is less evident for Wishful Internal Struggle Coping Profile users who perceive that they have moderate or high control, regardless of the perceived stressfulness of the cancer diagnosis. In contrast, having low

perceived personal control results in the lowest mean level of log(IL-10 +1) when the situation is perceived as low-stress and in the highest mean level of log(IL-10 +1) when the situation is perceived as high-stress.

Control and stress in Avoidant Self-Reliance Coping Profile users

Figure 6D depicts the impact of stress and control on the mean log-transformed blood serum level of the pro-inflammatory cytokine IL-10 among individuals who use the Wishful Internal Struggle Coping Profile. For individuals who perceive their cancer diagnosis as a low-stress situation, it appears that the mean level of log(IL-10 + 1) is lowest among those who also perceive that they have moderate control over the situation. When cancer diagnosis is perceived as a moderate-stress situation, having high perceived personal control results in the lowest mean level of log(IL-10 +1). The mean level of log(IL-10 +1) when the situation is perceived as high-stress is lowest among Avoidant Self-Reliance Coping Profile users who perceive they have a low level of personal control. However, the difference in the mean levels of log(IL-10 + 1) when one perceives a low versus a high level of perceived personal control is almost imperceptible to the naked eye when the cancer diagnosis is perceived as a high-stress situation.

4.4.2 Graphical representation of IL-1α regression model

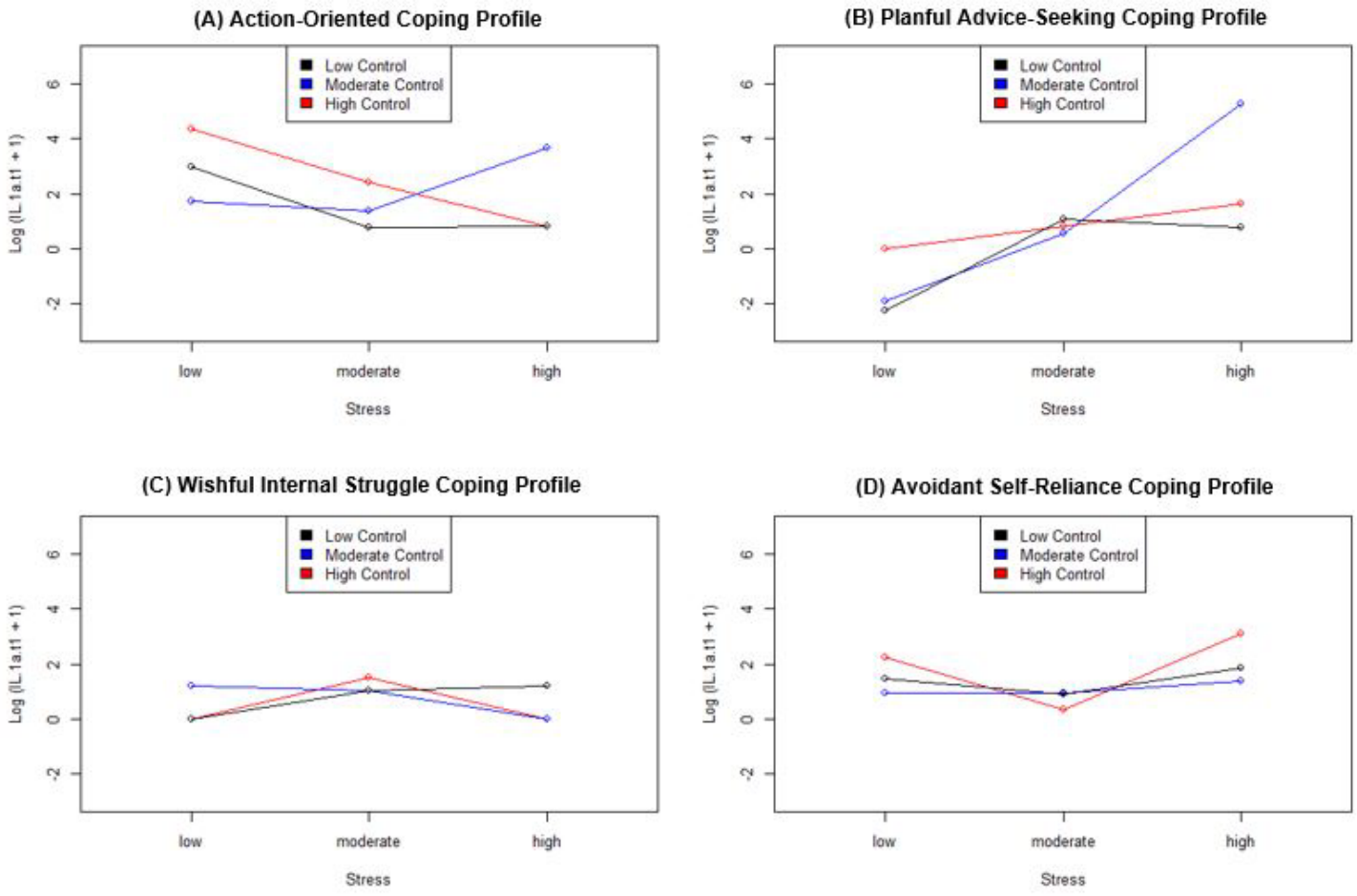

Figure 7. Graphical Representation of IL-1α Regression Model

The fact that plotting the equations from the IL-1α regression model results in graphs [Figure 7] that differ from one another indicates that there is a three-way interaction among the coping, control, and stress variables [The University of North Carolina at Chapel Hill, 2008]. Though the p-values associated with the global F test do not provide sufficient evidence to suggest that the interactions among the three variables are not simply due to chance, it is still possible to explore these interactions graphically since the majority of the estimated β coefficients (i.e. the slopes of

the regression lines) are non-zero. The notable exception is the interaction model depicted in Figure 7B. Though there appear to be three-way interactions for each category of control and stress based on this graphical representation, no interpretable coefficients could be calculated for the interactions among low control, low stress, and the Planful Advice-Seeking Coping Profile; low control, moderate stress, and the Planful Advice-Seeking Coping Profile; or moderate control, moderate stress, and the Planful Advice-Seeking Coping Profile [see Table 5]. These singularity warnings could indicate that the variables are associated in a non-linear fashion. These singularity warnings may also suggest that there are no interactions among the independent variables in their influence on IL-1α given that the only three-way interaction detected by the regression model was not statistically significant. Despite these singularity warnings, this is the best-fitting multiple linear regression model based on the Q-Q and residuals plots of the dependent variables.

4.4.2.1 Exploring interactions within graphical representation of IL-1α model

Control and stress in Action-Oriented Coping Profile users

Figure 7A depicts the impact of stress and control on the mean log-transformed blood serum level of the pro-inflammatory cytokine IL-1α among individuals who use the Action-Oriented Coping Profile. For individuals who perceive their diagnosis as a low-stress situation, it appears that the mean level of log(IL-1α + 1) is lowest among those who also perceive that they have moderate control over the situation. The mean level of log(IL-1α + 1) is highest among individuals who perceive the situation as low-stress and believe that they have a high level of personal control. When users of Action-Oriented Coping Profile perceive their advanced cancer diagnosis as a moderately stressful situation, a low level of perceived personal control appears to

result in the lowest mean levels of log(IL-1α + 1). Mean levels of log(IL-1α + 1) are the highest among individuals who believe that they have high personal control over a situation they perceive as moderately stressful. For individuals utilizing the Action-Oriented Coping Profile to process what they perceive as a highly stressful cancer diagnosis, the difference in the mean level of log(IL-1α + 1) is visually indistinguishable for those who perceive either a high or a low level of personal control.

Control and stress in Planful Advice-Seeking Coping Profile users

Figure 7B depicts the impact of stress and control on the mean log-transformed blood serum level of the pro-inflammatory cytokine IL-1α among individuals who use the Planful Advice-Seeking Coping Profile. As indicated above, there were singularity warnings associated with several of the interactions terms depicted in this graph. Incidentally, the graph reveals that the mean level of log(IL-1α +1) is almost identical in a situation perceived as moderately stressful among Planful Advice-Seeking Coping Profile users who believe that they have low, moderate, or high personal control over the situation.

Control and stress in Wishful Internal Struggle Coping Profile users

Figure 7C depicts the impact of stress and control on the mean log-transformed blood serum level of the pro-inflammatory cytokine IL-1α among individuals who use the Wishful Internal Struggle Coping Profile. For this model, when the cancer diagnosis is perceived as low-stress, a belief in either a low or high personal control results in the lowest mean level of log(IL-1α + 1). The difference in the mean levels of log(IL-1α + 1) between those who perceive low personal control and those who perceive high personal control is visually indistinguishable. Recall from Table 5 that the interaction among moderate control, low stress, and the Wishful Internal

Struggle Coping Profile is nearly statistically significant with a two-tailed p-value of 0.067. When Wishful Internal Struggle Coping Profile users believe that their diagnosis is moderately stressful, perceiving a low or a moderate level of personal control results in the same mean level of log(IL-1α + 1). There is, once again, an overlap in the mean level of log(IL-1α + 1) when the situation is perceived as high-stress: A perception of either a moderate or a high level of personal control has the same impact on the mean level of log(IL-1α + 1) among Wishful Internal Struggle Coping Profile users.

Control and stress in Avoidant Self-Reliance Coping Profile users

Figure 7D depicts the impact of stress and control on the mean log-transformed blood serum level of the pro-inflammatory cytokine IL-1α among individuals who use the Avoidant Self-Reliance Coping Profile. For individuals who perceive their diagnosis as a low-stress situation, it appears that the mean level of log(IL-1α + 1) is lowest among those who also perceive that they have moderate control over the situation. When cancer diagnosis is perceived as a moderately stressful situation, having high perceived personal control results in the lowest mean level of log(IL-1α +1). The mean level of log(IL-10 +1) when cancer diagnosis is perceived as high-stress is lowest among Avoidant Self-Reliance Coping Profile users who perceive they have a moderate level of personal control. It is worth noting that the interaction among low stress, moderate control, and the Avoidant Self-Reliance Coping Profile was nearly significant according to the global F test with a two-tailed p-value of 0.073. Similarly, the interaction among moderate stress, low control, and the Avoidant Self-Reliance Coping Profile were nearly significant with a two-tailed p-value of 0.077. According to the global F test, moderate stress, moderate control, and Avoidant Self-Reliance Coping Profile was significant with a two-tailed p-value of 0.073.

4.4.3 Graphical representation of IL-1beta regression model

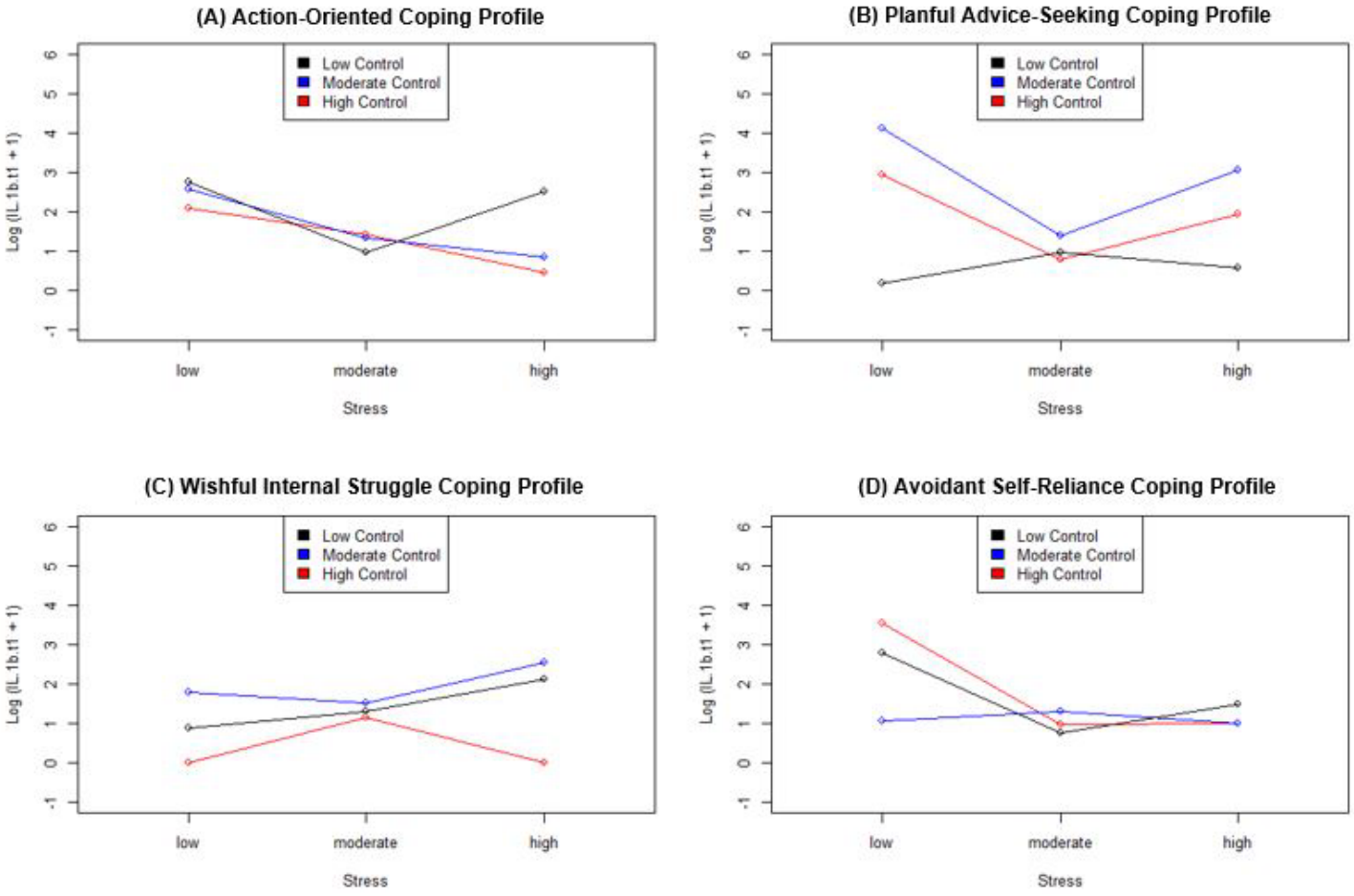

Figure 8. Graphical Representation of IL-1β Regression Model

The fact that plotting the equations from the IL-1beta regression model results in graphs [Figure 8] that differ from one another indicates that there is a three-way interaction among the coping, control, and stress variables [The University of North Carolina at Chapel Hill, 2008]. Though the p-values associated with the global F test do not provide sufficient evidence to suggest that the interactions among the three variables are not simply due to chance, it is still possible to explore these interactions graphically since the majority of the estimated β coefficients (i.e. the

slopes of the regression lines) are non-zero. The notable exception is the interaction model depicted in Figure 8B. Though there appear to be three-way interactions for each category of control and stress based on this graphical representation, no interpretable coefficients could be calculated for the interactions among low control, low stress, and the Planful Advice-Seeking Coping Profile; low control, moderate stress, and the Planful Advice-Seeking Coping Profile; or moderate control, moderate stress, and the Planful Advice-Seeking Coping Profile [see Table 6]. These singularity warnings could indicate that the variables are associated in a non-linear fashion. These singularity warnings may also suggest that there are no interactions among the independent variables and their influence on IL-1beta given that the only three-way interaction detected by the regression model was not statistically significant. Despite these singularity warnings, this is the best-fitting multiple linear regression model based on the Q-Q and residuals plots of the dependent variables.

4.4.3.1 Exploring interactions within graphical representation of IL-1beta model

Control and stress in Action-Oriented Coping Profile users

Figure 8A depicts the impact of stress and control on the mean log-transformed blood serum level of the pro-inflammatory cytokine IL-1β among individuals who use the Action-Oriented Coping Profile. For individuals who perceive their diagnosis as a low-stress situation, it appears that the mean level of log(IL-1β +1) is lowest among those who also perceive that they have a high level of personal control over the situation. The mean level of log(IL-1β +1) is highest among individuals who perceive the situation as low-stress and believe that they have a low level of personal control. Conversely, when users of Action-Oriented Coping Profile perceive their advanced cancer diagnosis as a moderately stressful situation, a low level of perceived personal

control appears to result in the lowest mean levels of log(IL-1β +1). For individuals utilizing the Action-Oriented Coping Profile to process what they perceive as a highly stressful cancer diagnosis, the lowest mean level of log(IL-1β +1)) is among those who believe they have a high level of personal control.

Control and stress in Planful Advice-Seeking Coping Profile users

Figure 8B depicts the impact of stress and control on the mean log-transformed blood serum level of the pro-inflammatory cytokine IL-1β among individuals who use the Planful Advice-Seeking Coping Profile. As indicated above, there were singularity warnings associated with several of the interactions terms depicted in this graph. On the other hand, the interaction among low control, moderate stress, and the Planful Advice-Seeking Coping Profile was nearly statistically significant with a two-tailed p-value of 0.062. Incidentally, the graph reveals that the mean level of log(IL-1β +1) is quite similar in a situation perceived as moderately stressful among Planful Advice-Seeking Coping Profile users who believe that they have either low or moderate personal control.

Control and stress in Wishful Internal Struggle Coping Profile users

Figure 8C depicts the impact of stress and control on the mean log-transformed blood serum level of the pro-inflammatory cytokine IL-1β among individuals who use the Wishful Internal Struggle Coping Profile. For this model, when cancer diagnosis is perceived as low-stress, a belief in a high level of personal control appears to result in the lowest mean level of log(IL-1β + 1). When Wishful Internal Struggle Coping Profile users believe that their diagnosis is moderately stressful, the differences in the mean levels of log(IL-1β + 1) for those who perceive moderate, low, or high personal control are barely distinguishable—although individuals who

believe they have a high level of personal control appear to have the lowest mean level of log(IL-1β + 1). The pattern continues when those using the Wishful Internal Struggle Coping Profile to process their cancer diagnosis assess the situation as highly stressful: The mean levels of log(IL-1β + 1) are lowest among individuals who perceive a high level of personal control.

Control and stress in Avoidant Self-Reliance Coping Profile users

Figure 8D depicts the impact of stress and control on the mean log-transformed blood serum level of the pro-inflammatory cytokine IL-1β among individuals who use the Avoidant Self-Reliance Coping Profile. For individuals who perceive their diagnosis as a low-stress situation, it appears that the mean level of log(IL-1β +1) is lowest among those who also perceive that they have moderate control over the situation. The difference in the mean level of log(IL-1β + 1) is visually indistinguishable for those who perceive either a moderate or a high level of personal control.

4.4.4 Graphical representation of IL-2 regression model

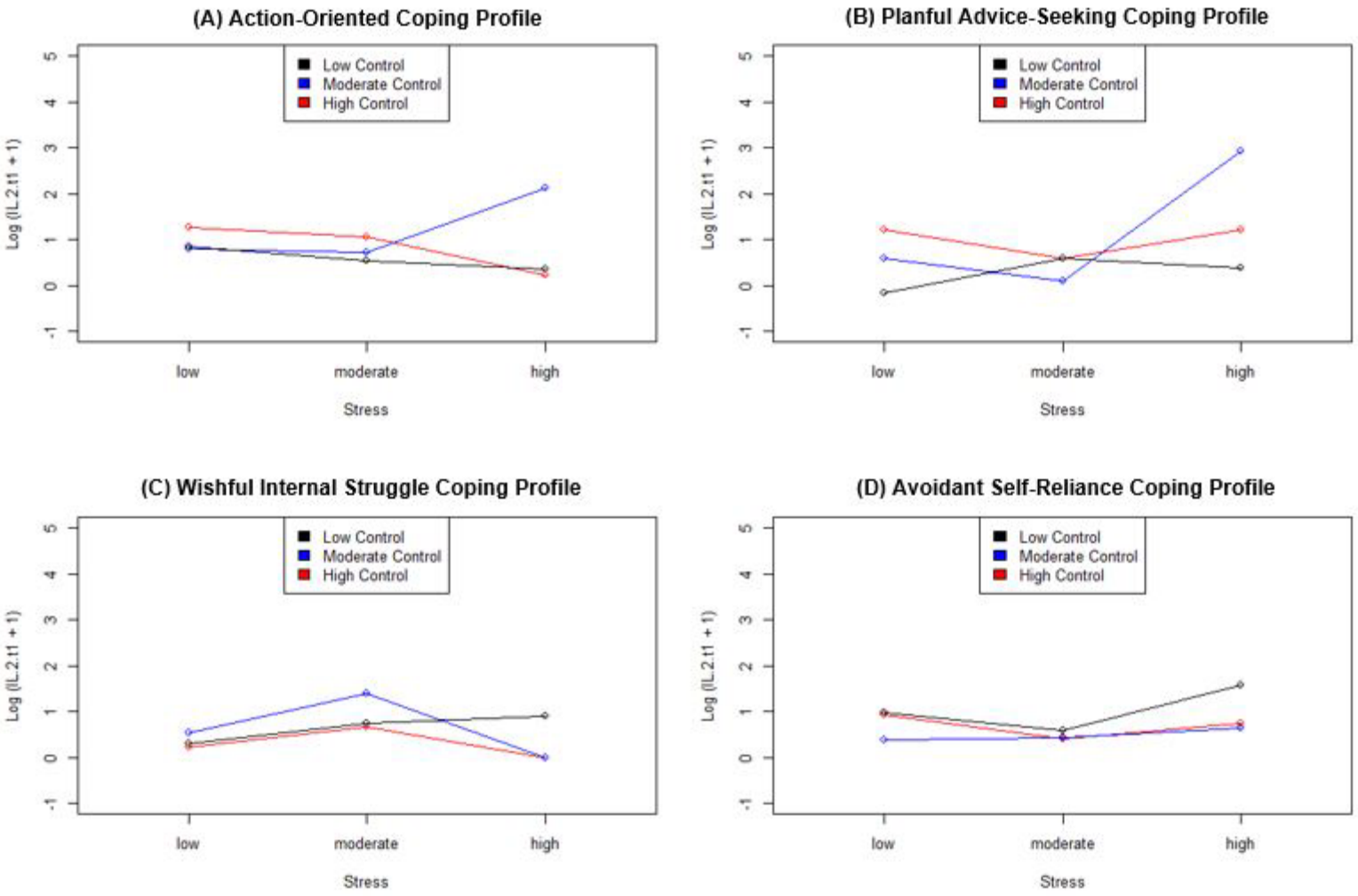

Figure 9. Graphical Representation of IL-2 Regression Model

The fact that plotting the equations from the IL-2 regression model results in graphs [Figure 9] that differ from one another indicates that there is a three-way interaction among the coping, control, and stress variables [The University of North Carolina at Chapel Hill, 2008]. Though the p-values associated with the global F test do not provide sufficient evidence to suggest that the interactions among the three variables are not simply due to chance, it is still possible to explore these interactions graphically since the majority of the estimated β coefficients (i.e. the slopes of

the regression lines) are non-zero. The notable exception is the interaction model depicted in Figure 9B. Though there appear to be three-way interactions for each category of control and stress based on this graphical representation, no interpretable coefficients could be calculated for the interactions among low control, low stress, and the Planful Advice-Seeking Coping Profile; low control, moderate stress, and the Planful Advice-Seeking Coping Profile; or moderate control, moderate stress, and the Planful Advice-Seeking Coping Profile [see Table 7]. These singularly warnings could indicate that the variables are associated in a non-linear fashion. These singularity warnings may suggest that there are no interactions among the independent variables in their influence on IL-2 given that the only three-way interaction detected by the regression model was not statistically significant. Despite these singularity warnings, this is the best-fitting multiple linear regression model based on the Q-Q and residuals plots of the dependent variables.

4.4.4.1 Exploring interactions within graphical representation of IL-2 model

Control and stress in Action-Oriented Coping Profile users

Figure 9A depicts the impact of stress and control on the mean log-transformed blood serum level of the pro-inflammatory cytokine IL-2 among individuals who use the Action-Oriented Coping Profile. For individuals who perceive their diagnosis as a low-stress situation the difference between the mean levels of log(IL-2 + 1) when they perceive either a low or a moderate level of personal control cannot be discerned by the naked eye. Similarly, when users of the Action-Oriented Coping Profile perceive their advanced cancer diagnosis as a moderately stressful situation, the mean level of log(IL-2 +1) is only slightly lower among those who perceive a low level of personal control compared to those who perceive a moderate level of control. For individuals utilizing the Action-Oriented Coping Profile to process what they

perceive as a highly stressful cancer diagnosis, the lowest mean level of log(IL-2 +1) is among those who believe they have a high level of personal control.

Control and stress in Planful Advice-Seeking Coping Profile users

Figure 9B depicts the impact of stress and control on the mean log-transformed blood serum level of the pro-inflammatory cytokine IL-2 among individuals who use the Planful Advice-Seeking Coping Profile. As indicated above, there were singularity warnings associated with several of the interactions terms depicted in this graph. Incidentally, the graph reveals that the mean level of log(IL-2 +1) is almost identical in a situation perceived as moderately stressful among Planful Advice-Seeking Coping Profile users who believe that they have low, moderate, or high personal control over the situation.

Control and stress in Wishful Internal Struggle Coping Profile users

Figure 9C depicts the impact of stress and control on the mean log-transformed blood serum level of the pro-inflammatory cytokine IL-2 among individuals who use the Wishful Internal Struggle Coping Profile. For this model, when cancer diagnosis is perceived as low-stress, a belief in a high or a low level of personal control appears to result in the same mean level of log(IL-2 + 1). When Wishful Internal Struggle Coping Profile users believe that their diagnosis is moderately stressful, the differences in the mean levels of log(IL-2 + 1) for those who perceive a low or a high personal control are barely distinguishable—although individuals who believe they have a high level of personal control appear to have the lowest mean level of log(IL-2 + 1). Similarly, the mean level of log(IL-2 + 1) appears to be identical for those who perceive their cancer diagnosis as a highly stressful event and believe they have either a moderate or a high level of personal control. It is worth noting that, based on the global F test, the interaction among

moderate control, moderate stress, and the Wishful Internal Struggle Coping Profile is nearly statistically significant with a two-tailed p-value of 0.0597.

Control and stress in Avoidant Self-Reliance Coping Profile users

Figure 9D depicts the impact of stress and control on the mean log-transformed blood serum level of the pro-inflammatory cytokine IL-2 among individuals who use the Avoidant Self-Reliance Coping Profile. For individuals who perceive their diagnosis as a low-stress situation, it appears that the mean level of log(IL-2 +1) is lowest among those who also perceive that they have moderate control over the situation. It is impossible to distinguish the mean levels of log(IL-2 + 1) when cancer diagnosis is perceived as a moderately stressful situation with the naked eye—though the value seems to be slightly higher for those who believe they have low personal control. Despite the fact that the impact seems identical based on the graphical representation, only the interaction among moderate control, moderate stress, and Avoidant Self-Reliance Coping Profile was nearly statistically significant with a two-tailed p-value of 0.079 from the global F test. For those who believe that their situation is highly stressful, having either a high or a moderate level of perceived control appears to have the same impact on mean levels of log(IL-2).

4.5 LIKELIHOOD RATIO TEST

As indicated by the p-values in the Tables 4 through 7, none of the three-way interaction models were statistically significant according to the global F tests run on the multiple regression models created for each of the four biomarkers. Nonetheless, the graphs constructed using the linear

regression equations derived from these statistically insignificant models clearly depict an interaction among the independent variables as they influence each dependent variable—as evidenced by the non-parallel lines in Figures 6 through 9 and the non-zero beta coefficients in Tables 4 through 7. For this reason, I opted to conduct post-hoc probing to ascertain whether the slopes of the regression lines were significantly different. Likelihood ratio tests revealed that the differences in the slopes of the regression lines were not statistically significant [see Table 8].

Table 8. Likelihood Ratio Test for Each Cytokine's Regression Model

Regression Model	p-value
IL-10	0.53
IL-1α	0.12
IL-1β	0.49
IL-2	0.36

5.0 DISCUSSION AND LIMITATIONS

Though neither the global F tests nor the likelihood ratio tests had p-values less than or equal to 0.05, the regression models for three of the four cytokines did detect several three-way interactions that were statistically significant or nearly statistically significant. For instance, the regression model for the proinflammatory cytokine IL-1α revealed that there were nearly statistically significant interactions (with p-values of 0.073, 0.077, and 0.73) among varying levels of perceived control and of perceived stress and the high emotion-focused, low problem-focused Avoidant Self-Reliance Coping Profile. These findings indicate that the use of the Avoidant Self-Reliance Coping Profile—which is characterized by coping strategies that have traditionally been deemed maladaptive—could be associated with a lower level of the inflammation-triggering IL1-α in certain circumstances.

Recall that I hypothesized that blood serum levels of the pro-inflammatory cytokines IL-1α and IL1-β would be lowest among those advanced cancer patients who use a high problem-focused, low emotion-focused coping profile (i.e. the Action-Oriented Coping Profile) to handle what they perceive as a high-stress situation over which they have high personal control. The graphical representation of the IL-1β regression model (see Figure 8) demonstrated that this was indeed the impact that high perceived control and high perceived stress had on IL-1β among Action-Oriented Coping Profile users; however, the three-way interaction was not statistically significant. Moreover, none of the cytokine regression models, including those for IL-1α and

IL1-β, were statistically significant based on the global F tests and the likelihood ratio tests, so there is not sufficient evidence to support this hypothesis. Still, not all of the three-way interactions tested for each cytokine were deemed statistically insignificant. Furthermore, graphing the regression lines reveals compelling three-way interactions among the independent variables—despite the lack of statistical significance. "Unfortunately…tests of interactions often have low statistical power and may fail to detect small but true interaction effects that exist in the population" [Aiken & West, 1991, p. 103-4]. In the future, it may be worthwhile to refine the experimental design and to attempt to elucidate the impact that coping, stress, and perceived control have on blood serum levels of key biomarkers. Though this study's findings are not universally statistically significant, they are sufficiently compelling to suggest that researchers should continue to challenge the good (problem-focused) versus bad (emotion-focused) coping dichotomy.

In a similar vein, it seems noteworthy that there was overlap in the items included in Components 1 and 2, despite the use of varimax rotation for the PCA. Similarly, there were no starkly distinct groups as a result of the cluster analysis. Taken together, these facts indicate that there was poor differentiation among the coping profiles created for use in the regression models. On one hand, this lack of differentiation supports the notion that coping is not a concrete trait that can be readily categorized—which substantiates the supposition that emotion- and problem-focused strategies are used in combination rather than in isolation. Nonetheless, this is not ideal for the purposes of conducting analyses with categorical predictor variables using multiple linear regression.

The issues with effectively creating nuanced coping profiles were not the only measurement issues. The one-item measure of perceived personal control may not have been

sufficiently robust to represent the complexities of perceived personal control accurately for the purposes of detecting the subtle interplay among control, coping, and stress. In a similar vein, using peripheral blood to monitor the serum levels of cytokines may not be the most accurate way to operationalize immune function. In the past, a study [Stowell, Kiecolt-Glaser, and Glaser, 2001] had lackluster results when measuring levels of biomarkers in peripheral blood but significant results when cells in culture were used to measure immune function. Finally, the homogeneity of the sample further limits the conclusions that can be drawn from this analysis given that differences in person variables, such as perceived control, have been shown [Dunkel-Schetter, Feinstein, Taylor & Falke, 1992; Yuan et al., 2014] to vary by race, ethnicity, gender, age, and socioeconomic status.

6.0 CONCLUSION

While the results of the present secondary analysis were not statistically significant, they are sufficiently compelling to encourage future investigations of the ways in which person and environment variables moderate the relationship between stress and coping and, consequently, impact immune function. Future research into the complex relationship among coping, perceived control, and stress and their impact on immune function (or dysfunction) may benefit from the inclusion—or exclusive use—of qualitative methods. While the results of such studies would not be generalizable, they might provide a richer understanding of the ways in which individuals cope with advanced cancer and suggest new avenues for investigation that have, heretofore, remained unexplored.

APPENDIX A: WAYS OF COPING QUESTIONNAIRS SUBSCALES ADMINISTERED

Scale 3: Self-Controlling

Item 10: Tried not to burn my bridges but leave things open somewhat

Item 14: I tried to keep my feelings to myself

Item 35: I tried not to act too hastily or follow my first hunch

Item 43: Kept others from knowing how bad things were.

Item 54: I tried to keep mu [*sic*] feelings from interfering with other things too much

Item 63: I thought about how a person I admire would handle the situation and used that as a model.

Item 63: I tried to see things from the other person's point of view

Scale 4: Seeking Social Support

Item 8: Talked to someone to find out more about the situation

Item 18: Accepted sympathy and understanding from someone

Item 22: I got professional help

Item 31: Talked to someone who could do something concrete about the problem

Item 42: I asked a relative or friend I respected for advice.

Item 45: Talked to someone about how I was feeling.

Scale 5: Accepting Responsibility

Item 9: Criticized or lectured myself

Item 25: I apologized or did something to make up

Item 29: Realized I brought the problem on myself

Item 51: I made a promise to myself that things would be different next time

Scale 6: Escape-Avoidance

Item 11: Hoped a miracle would happen

Item 16: Slept more than usual

Item 33: Tried to make myself feel better by eating, drinking, smoking, using drugs, medications, etc.

Item 40: Avoided being with people in general.

Item 47: Took it out on other people

Item 50: Refused to believe that it had happened

Item 58: Wished that the situation would go away or somehow be over with

Item 59: Had fantasies or wishes about how things might turn out

Scale 7: Planful Problem Solving

Item 1: Just concentrated on what I had to do next-the next step

Item 26: I made a plan of action and followed it

Item 39: Changed something so that things would turn out all right.

Item 52: Came up with a couple different solutions to the problem

Item 48: Drew on my past experiences; I was in a similar situation before.

Item 49: Knew what had to be done, so I doubled my efforts to make things work

Please note that Scale 1 (Confrontive), Scale 2 (Distancing), and Scale 8 (Positive Reappraisal) were not administered to participants in the original study from which data were obtained.

APPENDIX B: PERCEIVED STRESS SCALE (14-ITEM)

(1) Been upset because of something that happened unexpectedly?

(2) Felt that you were unable to control the important things in your life?

(3) Felt nervous and stressed?

(4) Dealt successfully with irritating life hassles?

(5) Felt that you were effectively coping with important changes that were occurring in your life?

(6) Felt confident about your ability to handle your personal problems?

(7) Felt that things were going your way?

(8) Found that you could not cope with all the things that you had to do?

(9) Been able to control irritations in your life?

(10) Felt that you were on top of things?

(11) Been angered because of things that happened that were outside of your control?

(12) Found yourself thinking about things that you have to accomplish?

(13) Been able to control the way you spend your time?

(14) Felt difficulties were piling up so high that could not overcome them?

BIBLIOGRAPHY

Aiken, A. S., & West, S.G. (1991). *Multiple Regression: Testing and Interpreting Interactions*. Newbury

Skinner, E. A., Edge, K., Altman, J., & Sherwood, H. (2003). Searching for the structure of coping: a review and critique of category systems for classifying ways of coping. *Psychological Bulletin*, *129*(2), 216..

Ballak, D. B., Stienstra, R., Tack, C. J., Dinarello, C. A., & van Diepen, J. A. (2015). IL-1 family members in the pathogenesis and treatment of metabolic disease: Focus on adipose tissue inflammation and insulin resistance. *Cytokine, 75*(2), 280-290.

Banchereau, J., Pascual, V., & O'Garra, A. (2012). From IL-2 to IL-37: the expanding spectrum of anti-inflammatory cytokines. *Nature Immunology, 13*(10), 925.

Bandura, A. (1994). Self-efficacy. In V. S. Ramachaudran (Ed.), *Encyclopedia of Human Behavior* (Vol. 4, pp. 71-81). New York: Academic Press. (Reprinted in H. Friedman [Ed.], *Encyclopedia of Mental Health*. San Diego: Academic Press, 1998).

Banerjee, M., & Saxena, M. (2012). Interleukin-1 (IL-1) family of cytokines: Role in type 2 diabetes. *Clinica Chimica Acta, 413*(15-16), 1163-1170.

Baune B.T. (2015) Immunology, Inflammation, Mental Disorders, and Cardiovascular Risk. In: Alvarenga M., & Byrne, D. (Eds.) *Handbook of Psychocardiology*. Singapore: Springer.

Ben-Zur, H. (2017). Emotion-focused coping. In: Zeigler-Hill, V., & Shackelford, T. (Eds.) *Encyclopedia of Personality and Individual Differences*. Cham, Switzerland: Springer International Publishing. https://doi.org/10.1007/978-3-319-28099-8_512-1

Berghella, A. M., Pellegrini, P., Piancatell, D., Maccarone, D., Del Beato, T., Giubilei, D., ... & Casciani, C. U. (1994). Progression mechanisms in colon cancer: soluble interleukin-2 (IL-2) receptor, IL-2 plus anti CD3 proliferative response and tumour stage correlations. *Cancer Immunology, Immunotherapy, 38*(3), 160-166.

Blake, G. J., & Ridker, P. M. (2002). Inflammatory bio-markers and cardiovascular risk prediction. *Journal of Internal Medicine, 252*(4), 283-294.

Bonanno, G. A., & Burton, C. L. (2013). Regulatory flexibility: An individual differences perspective on coping and emotion regulation. *Perspectives on Psychological Science, 8*(6), 591-612.

Braddock, M., Quinn, A., & Canvin, J. (2004). Therapeutic potential of targeting IL-1 and IL-18 in inflammation. *Expert Opinion on Biological Therapy, 4*(6), 847-860.

Broadbent, E., Petrie, K. J., Main, J., & Weinman, J. (2006). The brief illness perception questionnaire. *Journal of Psychosomatic Research, 60(*6), 631-637.

Byrne, B. M. (2005). Factor analytic models: Viewing the structure of an assessment instrument from three perspectives. *Journal of Personality Assessment, 85*(1), 17-32.

Capobianco, M.P., Cassiano, G.C., da Cruz Furini, A.A., Sorti de Melo, L.M., Domingos, C.R.B., & Machado, R.L.D. (2016). Human interleukin 2 (IL-2) promotion of immune regulation and clinical outcomes: A review. *Journal of Cytokine Biology 1*(2), e1000109. doi: 10.4172/2576-3881.1000109

Capuron, L., Ravaud, A., & Dantzer, R. (2000). Early depressive symptoms in cancer patients receiving interleukin 2 and/or interferon alfa-2b therapy. *Journal of Clinical Oncology, 18*(10), 2143-2151.

Capuron, L., Su, S., Miller, A. H., Bremner, J. D., Goldberg, J., Vogt, G. J., ... & Vaccarino, V. (2008). Depressive symptoms and metabolic syndrome: is inflammation the underlying link?. *Biological Psychiatry, 64*(10), 896-900.

Carnegie Mellon University. (n.d.). Laboratory for the study of stress, immunity, and disease. Retrieved from: http://www.psy.cmu.edu/~scohen/index.html

Carver, C. S., Scheier, M. F., & Weintraub, J. K. (1989). Assessing coping strategies: a theoretically based approach. *Journal of Personality and Social Psychology, 56*(2), 267-283.

Clary, BM, Coveney, EC, Philip, R, et al. (1997). Inhibition of established pancreatic cancers following specific active immunotherapy with interleukin-2 gene-transduced tumor cells. *Cancer Gene Therapy*, 4, 97-104.

Cohen, S., & Williamson, G.M. (1988). Perceived stress and in a probability sample of the United States. In S. Spacapan, & S. Oskamp (Eds.), *The Social Psychology of Health: Proceedings of the Claremont Symposium on Applied Social Psychology* (pp. 31-68). Newbury Park, CA: SAGE Publishing.

Cohen, S., Doyle, W., & Skoner, D. (1999). Psychological stress, cytokine production, and severity of upper respiratory illness. *Psychosomatic Medicine*, 61, 175-180.

Cohen, S., Janicki-Deverts, D., Doyle, W. J., Miller, G. E., Frank, E., Rabin, B. S., & Turner, R. B. (2012). Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk. Proceedings of the National Academy of Sciences, 109(16), 5995-5999.

Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of perceived stress. *Journal of Health and Social Behavior*, 385-396.

Cytokine. (2010). *Webster's New World College Dictionary* (4th ed). Retrieved from: https://www.collinsdictionary.com/us/dictionary/english/cytokine

Dantzer, R., O'Connor, J. C., Freund, G. G., Johnson, R. W., & Kelley, K. W. (2008). From inflammation to sickness and depression: When the immune system subjugates the brain. *Nature*, 9, 46–57

Dhabhar, F. S. (2014). Effects of stress on immune function: The good, the bad, and the beautiful. *Immunologic Research, 58*(2), 193-210. doi:10.1007/s12026-014-8517-0

Dhabhar, F. S., Burke, H. M., Epel, E. S., Mellon, S. H., Rosser, R., Reus, V. I., & Wolkowitz, O. M. (2009). Low serum IL-10 concentrations and loss of regulatory association between IL-6 and IL-10 in adults with major depression. *Journal of Psychiatric Research, 43*(11), 962-969. doi:10.1016/j.jpsychires.2009.05.010

Dillon, K. M., Minchoff, B., & Baker, K. H. (1986). Positive emotional states and enhancement of the immune system. *The International Journal of Psychiatry in Medicine*, 15(1), 13-18.

Dinarello, C. A. (2009). Immunological and inflammatory functions of the interleukin-1 family. *Annual Review of Immunology*, 27, 519-550.

Dinarello, C. A. (2013). Overview of the interleukin-1 family of ligands and receptors. In *Seminars in Immunology* (Vol. 25, No. 6, pp. 389-393). Academic Press.

Dinarello, C. A. (2014). An expanding role for interleukin-1 blockade from gout to cancer. *Molecular Medicine, 20*(Suppl 1), S43.

Doron, J., Trouillet, R., Maneveau, A., Neveu, D., & Ninot, G. (2014). Coping profiles, perceived stress and health-related behaviors: a cluster analysis approach. *Health Promotion International, 30*(1), 88-100.

Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E. K., & Lanctôt, K. L. (2010). A meta analysis of cytokines in major depression. *Biological Psychiatry, 67*(5), 446-457.

Dunkel-Schetter, C., Feinstein, L. G., Taylor, S. E., & Falke, R. L. (1992). Patterns of coping with cancer. *Health Psychology, 11*(2), 79.

El–Serag, H. B., & Rudolph, K. L. (2007). Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. *Gastroenterology, 132*(7), 2557-2576.

Engelhart, M. J., Geerlings, M. I., Meijer, J., Kiliaan, A., Ruitenberg, A., van Swieten, J. C., ... & Breteler, M. M. (2004). Inflammatory proteins in plasma and the risk of dementia: the rotterdam study. *Archives of neurology*, *61*(5), 668-672.

Folkman, S. (1984). Personal control and stress and coping processes: A theoretical analysis. *Journal of Personality and Social Psychology*, *46*(4), 839.

Folkman, S., & Lazarus, R. S. (1985). If it changes it must be a process: Study of emotion and coping during three stages of a college examination. *Journal of Personality and Social Psychology*, 48, 150–170.

Folkman, S., & Moskowitz, J. T. (2004). Coping: Pitfalls and promise. Annual Review of *Psychology*, 55, 745–774.

Folkman, S., Lazarus, R. S., Dunkel-Schetter, C., DeLongis, A., & Gruen, R. J. (1986). Dynamics of a stressful encounter: Cognitive appraisal, coping, and encounter outcomes. *Journal of Personality and Social Psychology*, 50, 992–1003.

Forti, P., Rietti, E., Pisacane, N., Olivelli, V., Mariani, E., Chiappelli, M., . . . Ravaglia, G. (2010). Blood inflammatory proteins and risk of incident depression in the elderly. *Dementia and Geriatric Cognitive Disorders, 29*(1), 11-20. doi:10.1159/000261644

Glaser, R., Kiecolt-Glaser, J. K., Marucha, P. T., MacCallum, R. C., Laskowski, B. F., & Malarkey, W. B. (1999). Stress-related changes in proinflammatory cytokine production in wounds. *Archives of General Psychiatry, 56*(5), 450-456.

Henriques, J.B (2010, June 19). Factor analysis versus PCA. Retrieved March 4, 2018 from: http://psych.wisc.edu/henriques/pca.html

Jiang, T., Zhou, C., & Ren, S. (2016). Role of IL-2 in cancer immunotherapy. *Oncoimmunology, 5*(6), e1163462.

Kiecolt-Glaser, J. K., McGuire, L., Robles, T. F., & Glaser, R. (2002). Psychoneuroimmunology: psychological influences on immune function and health. *Journal of Consulting and Clinical Psychology, 70*(3), 537.

Klund JW, & Kuzel TM. (2004). A review of recent findings involving interleukin-2-based cancer therapy. *Current Opinion in Oncology*, 16,542-6.

Kronfol, Z., & Remick, D. G. (2000). Cytokines and the brain: implications for clinical psychiatry. *American Journal of Psychiatry, 157*(5), 683-694.

Lazarus, R.S., & Folkman, S. (1984). *Stress, Appraisal, and Coping*. New York: Springer Publishing

Litman, J. A. (2006). The COPE inventory: Dimensionality and relationships with approach-and avoidance-motives and positive and negative traits. *Personality and Individual Differences, 41*(2), 273-284.

Maes, M. (1999). Major depression and activation of the inflammatory response system. In *Cytokines, Stress, and Depression* (pp. 25-46). Springer, Boston, MA.

Maes, M., Meltzer, H. Y., & Bosmans, E. (2008). Psychoimmune investigation in obsessive compulsive disorder: Assays of plasma transferrin, IL-2 and IL-6 receptor, and IL-1β and IL-6 concentrations. *Neuropsychobiology, 30*(2-3), 57-60. doi:10.1159/000119136

McGeer, P. L., & Mcgeer, E. G. (2004). Inflammation and the degenerative diseases of aging. *Annals of the New York Academy of Sciences, 1035*(1), 104-116.

Miller, A. H., Maletic, V., & Raison, C. L. (2009). Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biological Psychiatry, 65*(9), 732-741.

Miller, G. E., Cohen, S., & Ritchey, A. K. (2002). Chronic psychological stress and the regulation of pro inflammatory cytokines: a glucocorticoid-resistance model. *Health Psychology, 21*(6), 531.

Miller, G. E., Stetler, C. A., Carney, R. M., Freedland, K. E., & Banks, W. A. (2002). Clinical depression and inflammatory risk markers for coronary heart disease. *The American Journal of Cardiology, 90*(12), 1279-1283.

Mocellin, S., Panelli, M. C., Wang, E., Nagorsen, D., & Marincola, F. M. (2003). The dual role of IL-10. *Trends in Immunology, 24*(1), 36-43. doi:10.1016/S1471-4906(02)00009-1

Moksnes, U.K. & Espnes, G.A. (2015) Stress: Concepts, models, and measures. In M. Alvarenga, & D. Byrne. (Eds) *Handbook of Psychocardiology*. Singapore: Springer International Publishing. doi: 0.1007/978-981-4560-53-5_11-1

Nelson, B. H. (2004). IL-2, regulatory T cells, and tolerance. *The Journal of Immunology, 172*(7), 3983-3988.

O'Rourke, N. & Hatcher, L. (2013). A step-by-step approach to using SAS for factor analysis and structural equation modeling (2nd edition). SAS Institute. Retrieved from: https://www.sas.com/store/books/categories/usage-and-reference/a-step-by-step-approach-to-using-sas-for-factor-analysis-and-structural-equation-modeling-second-edition/prodBK_61314_en.html

Palomo, J., Dietrich, D., Martin, P., Palmer, G., & Gabay, C. (2015). The interleukin (IL)-1 cytokine family Balance between agonists and antagonists in inflammatory diseases. *Cytokine, 76*(1), 25-37.

Picardi, A., Tarolla, E., Tarsitani, L., & Biondi, M. (2009). Links between immunity and conditions leading to psychotherapy. *Rivista di Psichiatria, 44*(3), 149-163.

Pickup, J. C., & Crook, M. A. (1998). Is type II diabetes mellitus a disease of the innate immune system?. *Diabetologia, 41*(10), 1241-1248.

Raison, C. L., Capuron, L., & Miller, A. H. (2006). Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends in Immunology, 27*(1), 24-31.

Richardson, E. M., Schüz, N., Sanderson, K., Scott, J. L., & Schüz, B. (2017). Illness representations, coping, and illness outcomes in people with cancer: a systematic review and meta-analysis. *Psycho-oncology, 26*(6), 724-737.

Rivera-Medina, C.L. (2015). Retrieved from: https://www.researchgate.net/post/Factor_analysis_Vs_PCA

Rood, B. A., McConnell, E. A., & Pantalone, D. W. (2015). Distinct coping combinations are associated with depression and support service utilization in men who have sex with men living with HIV. *Psychology of Sexual Orientation and Gender Diversity, 2*(1), 96.

Segerstrom, S. C., & Miller, G. E. (2004). Psychological stress and the human immune system: a meta analytic study of 30 years of inquiry. *Psychological Bulletin, 130*(4), 601.

Sevenoaks, M. J., & Stockley, R. A. (2006). Chronic Obstructive Pulmonary Disease, inflammation and co morbidity–a common inflammatory phenotype?. *Respiratory Research, 7*(1), 70.

Sim, G. C., & Radvanyi, L. (2014). The IL-2 cytokine family in cancer immunotherapy. *Cytokine and Growth Factor Reviews, 25*(4), 377-390. doi:10.1016/j.cytogfr.2014.07.018

Simone, M. J., & Tan, Z. S. (2011). The role of inflammation in the pathogenesis of delirium and dementia in older adults: a review. *CNS Neuroscience & Therapeutics, 17*(5), 506-513.

Skinner, E. A. (1995). *Perceived control, Motivation, & Coping* (Vol. 8). Sage.

Skinner, E. A., Edge, K., Altman, J., & Sherwood, H. (2003). Searching for the structure of coping: a review and critique of category systems for classifying ways of coping. *Psychological Bulletin*, *129*(2), 216.

Spranger, J., Kroke, A., Möhlig, M., Hoffmann, K., Bergmann, M. M., Ristow, M., ... & Pfeiffer, A. F. (2003). Inflammatory cytokines and the risk to develop type 2 diabetes. *Diabetes, 52*(3), 812-817.

Stowell, J. R., Kiecolt-Glaser, J. K., & Glaser, R. (2001). Perceived stress and cellular immunity: When coping counts. *Journal of Behavioral Medicine, 24*(4), 323-339.

Sundelöf, J., Kilander, L., Helmersson, J., Larsson, A., Rönnemaa, E., Degerman-Gunnarsson, M., … & Basu, S. (2009). Systemic inflammation and the risk of Alzheimer's disease and dementia: a prospective population-based study. *Journal of Alzheimer's Disease, 18*(1), 79-87.

Tamagawa, R., Garland, S., Vaska, M., & Carlson, L. E. (2012). Who benefits from psychosocial interventions in oncology? A systematic review of psychological moderators of treatment outcome. *Journal of Behavioral Medicine, 35*(6), 658-673.

Taylor, S. E., & Stanton, A. L. (2007). Coping resources, coping processes, and mental health. *Annu. Rev. Clin. Psychol.*, 3, 377-401.

The University of North Carolina at Chapel Hill. (2008, February 14). Understanding and Interpreting Interactions [Lecture]. Retrieved from: https://www.unc.edu/courses/2008spring/psyc/270/001/interact.html

Thomas, A. J., Davis, S., Morris, C., Jackson, E., Harrison, R., & O'Brien, J. T. (2005). Increase in interleukin-1β in late-life depression. *American Journal of Psychiatry, 162*(1), 175-177.

Thompson, S.C., Cheek ,P.R., & Graham, M.A. (1988). The other side of perceived control: Disadvantages and negative effects. In S. Spacapan, & S. Oskamp (Eds.), *The Social Psychology of Health: Proceedings of the Claremont Symposium on Applied Social Psychology* (pp. 69-94). Newbury Park, CA: SAGE Publishing.

U. S. Department of Health and Human Services, Centers for Disease Control and Prevention. (2017, June 28). Chronic Disease Prevention and Health Promotion: Chronic Disease Overview. Retrieved from: https://www.cdc.gov/chronicdisease/overview/index.htm

U.S. National Library of Medicine. (2015, January 7). "What is an inflammation?." Retrieved from: https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0072482/

Uchino, B. N. (2006). Social support and health: a review of physiological processes potentially underlying links to disease outcomes. *Journal of Behavioral Medicine, 29*(4), 377-387.

Volpato, S., Guralnik, J. M., Ferrucci, L., Balfour, J., Chaves, P., Fried, L. P., & Harris, T. B. (2001). Cardiovascular disease, interleukin-6, and risk of mortality in older women. *Circulation, 103*(7), 947- 953.

Xiu, B., Lin, Y., Grote, D. M., Ziesmer, S. C., Gustafson, M. P., Maas, M. L., . . . Ansell, S. M. (2015). IL-10 induces the development of immunosuppressive CD14+HLA-DRlow/− monocytes in B-cell non-hodgkin lymphoma. *Blood Cancer Journal, 5*(7), e328. doi:10.1038/bcj.2015.56

Yuan, C., Wei, C., Wang, J., Qian, H., Ye, X., Liu, Y., & Hinds, P. S. (2014). Self-efficacy difference among patients with cancer with different socioeconomic status: Application of latent class analysis and standardization and decomposition analysis. *Cancer Epidemiology, 38*(3), 298-306.