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Interleukin-6, Depression, and Religious Coping in Older Seventh-day Adventists

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Interleukin-6, Depression, and Religious Coping in Older Seventh-day Adventists

by

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Each person whose signature appears below certifies that this dissertation in his/her opinion is adequate, in scope and quality, as a dissertation for the degree Doctor of Philosophy.

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ABBREVIATIONS

IL-6	Interleukin-6
CDC	Centers for Disease Control
PNI	Psychoneuroimmunology
SDA	Seventh-day Adventists
CRP	C-Reactive Protein
GR	Glucocorticoid Receptor
TNF-α	Tumor Necrosis Factor – alpha
HPA	Hypothalamic-Pituitary-Adrenal
CNS	Central Nervous System
BRHS	Biopsychosocial Religion and Health Study
AHS-2	Adventist Health Study-2
RCOPE	Brief Religious Coping Scale
CES-D	Center for Epidemiological Studies Depression Scale

ABSTRACT OF THE DISSERTATION

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Prior research suggests that depression and chronic inflammation have a bidirectional relationship. This study examined how depressive symptoms and the inflammatory marker, interleukin-6 (IL-6), interact over time in 287 older adults (54% female, 63% White, M_{age} = 66, SD_{age} = 10.9) from the Biopsychosocial Religion and Health Study and whether religious coping moderated this relationship. Depressive symptoms and IL-6 were assessed in 2006-7 and 2010-11. Results of the hierarchical multiple regressions indicate that initial depressive symptoms predicted IL-6 three to five years later, and that this relationship was moderated by positive religious coping. Moreover, negative religious coping predicted depressive symptoms three to five years later but IL-6 did not. Therefore, depression likely increases inflammation and positive religious coping may exacerbates these effects when depressive symptoms are higher. Finally, IL-6 did not predict later depressive symptoms and so the relationship between depression and inflammation may be unidirectional with depressive symptoms increasing inflammation over time. It may be that in a religious sample, any negative religious coping adversely effects inflammation. And, positive religious coping in those with

depressive symptoms also adversely effects inflammation perhaps because any negative religious coping can counteract the benefits of positive religious coping.

Keywords: religious coping, depression, IL-6, older adults.

CHAPTER 1

INTRODUCTION

Statement of Problem

As of 2013, older adults represented 14.1% of the United States, amounting to nearly 48 million persons (Center for Disease Control and Prevention & Administration on Aging, 2014). By 2040, older adults will represent 21.7% of the population and have an even longer life expectancy (CDC, 2014; Lloyd-Jones, Hong, Labarthe, Mozaffarian, Appel, et al., 2010). Although advances in science have led older adults to live fuller, longer lives, they are nonetheless still highly susceptible to chronic illness. Nearly two thirds of older adults have multiple comorbid conditions (CDC & The State of Aging and Health, 2014), which lead to a significant healthcare spending. Eighty percent of doctors' visits are dedicated to the management of chronic conditions in older adults, accounting for two thirds of the country's healthcare budget (CDC & The State of Aging and Health, 2014). Given that older adults are also more susceptible to depressive symptoms (CDC, 2014) and that mental health problems contribute to poorer health management (CDC, 2014; Lloyd-Jones et al., 2010), it becomes paramount to identify and understand risk factors of both depression and chronic illness to find novel ways to reduce mortality, morbidity, and associated healthcare costs (Parham, 2014).

Religion and Morbidity

Religion is a central part of most Americans' lives. However, while Americans were nearly unanimous in their belief of a God or universal spirit (89%), only 60% of people report having a personal relationship with God (Pew Forum, 2014). Furthermore,

while 63% are certain of God's existence, 33% are not as convinced (Pew Forum, 2014). In regards to older adults, 60% of persons report that they pray daily, that religion is the most important part of their life, and that they believe in hell. However, only 37% attend worship weekly (Pew Forum, 2014). Furthermore, it is noteworthy that earlier data demonstrated that unanimous belief in God was at 92% (Pew Forum, 2008); suggesting that belief in a higher power has decreased.

Religion is of interest to health researchers examining older adults because of its potential impact on mental and physical wellbeing. While religion has been identified as a coping strategy used successfully to confront morbidity and mortality (Aldwin, Jeon, Nath, & Park, 2014; Laubmeier, Zakowski, & Bair, 2004; Stroebe, 2004), the type of coping style used is important. Positive religious coping, or having a collaborative relationship with and loving view of God, has been shown to benefit health and reduce disease prevalence (Ano & Vasconcellas, 2005; Pargament, 2010). By contrast, negative religious coping, or seeing God as punishing, is associated with worse mental and physical health (Ano & Vasconcellas, 2005; Pargament, 2010). Understanding the role of religious coping as it relates to both depression and health outcomes merits further study.

Depression, Inflammation, and Religious Coping

Major depression is the leading cause of disability worldwide (CDC, 2012) and has a negative impact on quality of life to a degree similar to other chronic medical conditions (Dowlati et al., 2010). Like chronic medical conditions, depression is also thought to involve complex neural mechanisms and multiple etiologies. Of particular interest to health and aging, depression has been linked to inflammatory diseases

(Karakus & Patton, 2011; Miller, Stetler, Carney, Freeland, & Banks, 2002). Experts of psychoneuroimmunology (PNI), who study the effects of chronic stress on the immune system, have established that inflammation is the common denominator of multiple diseases and disorders (Irwin & Vadhara, 2005; Parham, 2004). In particular, researchers have identified bidirectional associations between depression and pro-inflammatory markers' effects on inflammatory disease risk (i.e., arthritis, type II diabetes, rheumatoid arthritis, frailty, disability, autoimmune disease, cardiovascular disease, and cancer) (Goin, Hanstoo, Kiecolt-Glaser, 2011; Maggie, Guralnik, Longo, & Ferrucci, 2006; Parham, 2004). Religious coping, which has been shown to impact mood and health, may moderate the relationship between depressive symptoms and the regulation of inflammatory markers, and subsequently alter inflammatory disease risk (Ai, Pargament, Kronfol, Tice, & Appel, 2010; Pargament, 2003).

Purpose of the Study

The present investigation examined the longitudinal relationship between depressive symptoms, IL-6, and religious coping in an older cohort of Seventh-day Adventists (SDAs). To follow-up on bidirectional relationship findings established by prior researchers (Goin et al., 2011; Maggie et al., 2006) we tested whether (2006-7) depressive symptoms predicted subsequent IL-6 (2010-11) elevations and if IL-6 (2006-7) predicted subsequent depressive symptoms (2010-11) bidirectionally. In addition, we tested whether type of baseline religious coping (positive or negative) buffered or exacerbated the bidirectional depression-inflammation relationship in 2010-11.

Research Questions

Hypothesis 1

1a. After controlling for covariates (age, gender, ethnicity, health, education, baseline levels of outcome), do depressive symptoms (2006-7) positively predict IL-6 levels (2010-11)?

1b. After controlling for covariates, do IL-6 levels (2006-7) positively predict depressive symptoms at (2010-11)?

Hypothesis 2

2a. After controlling for covariates, does positive religious coping at (2006-7) moderate the relationship between (2006-7) depressive symptoms and (2010-11) IL-6?

2b. After controlling for covariates, does positive religious coping at (2006-7) moderate the relationship between (2006-7) IL-6 and (2010-11) depressive symptoms?

Hypothesis 3

3a. After controlling for covariates, does negative religious coping (2006-7) moderate the relationship between (2006-7) depressive symptoms and (2010-11) IL-6?

3b. After controlling for covariates, does negative religious coping (2006-7) moderate the relationship between (2006-7) IL-6 and (2010-11) depressive symptoms?

Hypothesis 4

4a. After controlling for covariates, does the (2006-7) interaction between negative and positive religious coping moderate the relationship between (2006-7) depressive symptoms and (2010-11) IL-6?

4b. After controlling for covariates, does the (2006-7) interaction between negative and positive religious coping moderate the relationship between (2006-7) IL-6 and (2010-11) depressive symptoms?

CHAPTER 2

LITERATURE REVIEW

Chronic Inflammation

Chronic inflammation is associated with many age-related diseases including cardiovascular disorders, cancers, type II diabetes, rheumatoid arthritis, frailty, and Alzheimer's disease (Goin et al., 2011; Maggie et al., 2006; Parham, 2004). Inflammation is classified as either acute or chronic. Acute inflammation is an immediate physiological response to minor injuries or exposure to harmful stimuli (i.e., pain or heat). Chronic or prolonged inflammation, by contrast, is detrimental to health. Chronic low-grade inflammation has been shown to increase likelihood of disease (Ershler & Keller, 2000; Raison & Miller, 2011) by causing cellular tissue breakdown. To understand and measure chronic inflammation, researchers assess pro-inflammatory cytokines (e.g., inflammatory markers; biomarkers) that are released in response to inflammation. These are typically detected in the blood stream.

Cytokines

Cytokines are proteins released by immune cells to signal sensory information such as pain. Cytokines are activated during situations in which inflammation, infection and/or immunological alterations occur; they mediate signals between immune cells and are involved in the repair of damaged tissue and the restoration of homeostasis (Nathan, 2002; Woodroofe, 1995). Cytokines can be divided into pro-inflammatory and anti-inflammatory cytokines depending on the context. A pro-inflammatory cytokine promotes systemic inflammation that can fight acute insult (Dowlati et al., 2010).

However, after prolonged insult, these 'pro' inflammatory actions can worsen the disease process by producing fever, inflammation, tissue damage, and in some cases death (Dinarello, 2000). Although recent evidence suggests that most cytokines have pleiotropic (i.e., producing more than one effect), rather than pro- or anti-inflammatory actions, the pro-inflammatory cytokines have a crucial role in the pathophysiology of psychiatric illnesses, such as major depressive disorder (Miller et al., 2009). Related to synaptic and neural plasticity (Khairova, Machado, & Manji, 2009), pro-inflammatory cytokines play an important role in neurogenesis and neuroprotection in brain regions implicated in depressive disorders (Myint & Kim, 2014), such that an IL-6 dysfunction could maintain major depression (Khairova et al., 2009; Keohane et al., 2010; Monje et al., 2003).

Interleukin-6 (IL-6)

Given the established link between levels of interleukin-6 (IL-6) and morbidity and mortality, the present study will examine interleukin-6 (IL-6) in a cohort of SDAs (Gouin, et al., 2011; Harris et al., 1999; Maggio et al., 2006). IL-6 is a stress-related pro-inflammatory cytokine that has been found to be elevated in several chronic diseases and older age. In particular, over production of IL-6 has been associated with several age-related conditions, including depression, cancer, cardiovascular disease, arthritis, type 2 diabetes and cognitive decline (Kiecolt-Glaser, Preacher, MacCallum, Atkinson, & Glaser, 2003; Kiecolt-Glaser et al., 2011).

IL-6 and Age

Elevated IL-6 serum levels are associated with morbidity and mortality in the elderly. In fact, changes in IL-6 regulation may constitute one of the essential aging processes and contribute to a broad spectrum of age-related diseases. High functioning older adults with higher levels of IL-6 have twice the risk of mortality than those with lower levels (Ershler, 1993; Harris et al., 1999). Higher IL-6 is also associated with loss of muscle mass and strength, and accordingly, linked to frailty and health declines (Leng, Chaves, Koenig & Walston, 2002; Simonsick et al., 2002; Visser, Pahor, Taaffee, & Goodpaster). Furthermore, high levels of IL-6 have been associated with inflammatory disorders such as coronary heart disease, stroke, congestive heart failure, cancer (above 4.12 pg/mL) (Aggrawal, Shishodia, Sandur, Pandey, & Sethi, 2006), type 2 diabetes (above 4.02 pg/mL) (Pradhan, Manson, Rifai, Burging & Ridker, 2001), atherosclerotic processes, hypertension, and other cardiovascular diseases (Amar et al., 2006).

Bidirectional Relationship of Depression and Inflammation

Since inflammation is a common mechanism of disease, identifying and studying moderators such as mental health may be an important area of research for optimizing health in the elderly (Parham, 2004). Negative emotions have been consistently related to adverse immune system effects and increases in inflammatory markers (Glaser & Kiecolt-Glaser, 1994; Gouin et al., 2011; Kiecolt-Glaser, McGuire, Robles, & Glaser, 2003; Maggio et al., 2006; Parham, 2004). Too, depression has been identified as playing a role in exacerbating risk for diseases impact by IL-6 (Dowlati et al., 2009; Gouin et al., 2011; Maggio et al., 2006; Miller, Stetler, Carney, Freeland, & Banks, 2002; Parham,

2004). In particular, meta-analytic studies have found higher IL-6 levels in depressed patients compared with controls (Dowlati et al., 2009), and in those who experience anger, shame and guilt (Stewart, Janicki-Deverts, Muldoon, & Karmrak, 2008).

While both longitudinal and epidemiological studies indicate a consistent and positive relationship between depression and IL-6 (Bremmer et al., 2008; Dentino et al., 1999; Gimeno et al., 2009; Ranjit et al., 2007; Valkanova, Ebmeier, & Allan, 2013), the nature of this relationship has not been well understood in cross sectional studies. Most researchers conclude that the relationship between the two is complex and likely bidirectional (Dolwati et al., 2010; Irwin et al., 2007). However, given a scarcity of longitudinal studies, the direction of this link needs further examination.

Depression Predicts Inflammation

Studies have shown that depression may lead to inflammation by stimulating some components of the immune system while suppressing others. Stressful events and negative emotions seem to increase the production of IL-6 (Kiecolt-Glaser et al., 2002a; Maes et al., 1998; Steptoe, Hamer, & Chida, 2007), and depressive symptoms in conjunction with elevated IL-6 have been shown to be correlated with the risk of infection and inflammatory disorders (Roupe van der Voort, 2000; Zautra et al., 2004).

Major depression exacerbates and maintains inflammatory processes by reducing the sensitivity of the immune system to glucocorticoid hormones that manage the inflammatory response (Raison, Capuron, & Miller, 2006). Raison et al. (2006) propose that stressful experiences activate the hypothalamic-pituitary-adrenal (HPA) axis, responsible for regulating homeostatic systems such as the immune system. As the HPA

axis activates, IL-6 is generated at the macrophage level. In depression, the stress response may be exacerbated by an overactive HPA axis. Raison and colleagues (2006) have thus argued that depression leads to an activation of the stress response system by lowering the stress reactivity activation threshold thereby self-sustaining depression through the production of a systemic stress response that is internally regulated (see Figure 2).

Other researchers have also found that increases in stress may intensify the effect of depression on inflammatory markers. In particular, Steptoe et al. (2007) identified several other inflammatory marker mechanisms involved in repeated exposure to stress. These mechanisms include reduction in plasma volume (i.e., increased blood pressure may cause raised hydrostatic pressure forcing plasma from capillary beds into interstitial places), changes in synthesis of inflammatory marker regulation (i.e., number of cells contributing to levels is increased), and increases in cytokine-synthesizing cells that increase cytokine production (i.e., cytokines impacted by pressure may produce an increase in concentration) (Allen & Patterson, 1995; Mischler et al., 2005).

Researchers studying the bidirectional depression-cytokine relationship longitudinally have also identified important demographic moderators. For instance, Deverts et al. (2010) found that depression predicted another pro-inflammatory cytokine, C-Reactive Protein (CRP), levels five years later but only in African Americans. Others have found that depression in adolescents and young adults were associated with later levels of CRP, suggesting that risk for inflammatory diseases in middle and old age may actually originate in emotional regulation skills that develop during childhood and continue into adulthood (Copeland, Shanahan, Costello, & Angold, 2011).

Inflammation Predicts Depression

There is growing evidence that inflammation may lead to depression. The Macrophage Theory of Depression (Smith, 1991) proposes that inflammation caused by macrophages (i.e., white blood cells that detect and eliminates foreign and damaged extracellular proteins, which is mediate inflammation necessary to fight infections) will have a fundamental role in the pathophysiology of depression. Other theories propose that changes in immune system inflammation also lead to depression (i.e., Salutogenic Model, Levin, 1996; Inflammation Hypothesis, Alexoplous & Morimoto, 2011). There is some evidence that supports the idea that atherosclerotic process changes caused by elevated pro-inflammatory cytokines may change cortical brain areas responsible for emotion regulation and depression (Ross, 1999; Maes 1995; Maes et al., 1992). Specifically, resistant glucocorticoid receptors (GRs; regulators of immune response; resistant glucocorticoid receptors are created when proteins, such as cortisol, to not bind to receptors necessary to fight inflammation) in turn increase IL-6 production, which may then initiate the pathophysiology of depression (Kim, Na, Myint, & Leonard, 2016; see Figure 3).

Age itself may also predict increased inflammation. As we age, our bodies become more sensitive to immune system responses and less sensitive to central nervous system (CNS) changes, which can shift the CNS into a pro-inflammatory state (Alexopoulos & Marimoto, 2011). This leads to wear and tear on the immune system and a decreased ability to regulate negative emotions. Hence, age-related and comorbid disease-related inflammation promote changes in the neural networks that predispose older adults to depressive syndromes and higher levels of inflammation (Alexopoulos &

Marimoto, 2011). Furthermore, changes in immune function (directly relate to the onset of metabolic and behavioral changes in depression in humans and animals (Danzter & Kelly, 2007; Yaffe et al., 2004). In fact, many correlational studies have provided evidence that high levels of inflammation predispose individuals to later depression (Gimeno et al. 2009; Matthews et al., 2010; Valkanova et al., 2013).

To summarize, there is an abundance of evidence suggesting a link between inflammation and later depression, and to a lesser extent, to depression leading to inflammation. To clarify the nature of the relationship, it is of interest to examine the longitudinal relationships between inflammation and depressive symptoms.

Depression and Coping Behaviors

Depression has been conceptualized as the inability to utilize successful regulatory strategies to improve mental health (Berking & Wupperman, 2012; Cicchetti & Toth, 1998; Gross, 1998). Monat and Lazarus (1991) stated that unsuccessful coping is "an individual's efforts to master – conditions of harm, threat, challenge – that are appraised as exceeding or taxing his/her resources" (p. 5). Individuals with poor regulatory skills often select maladaptive coping strategies for the long-term management of persistent negative emotions that contribute to depression. Therefore, the use of coping strategies may either exacerbate or buffer depressive symptoms depending on the strategy chosen.

Immune system has been shown to normalize in response to interventions to treat depression and related psychological disorders. For example, antidepressant drug therapy, electroconvulsive therapy, and evidence-based psychotherapeutic interventions predict

lower pro-inflammatory cytokines (IL-6, CRP, tumor necrosis factor-alpha (TNF-α)) (Berk et al., 2015; Castanon et al., 2002; Green et al., 2009; Hannestad et al., 2011; Koenig, 2007). What is not clear is the direction of this relationship. Does improvement in coping strategies lessen depressive symptoms and subsequently reduce inflammation? Or do better coping strategies reduce inflammation, which leads to fewer depressive symptoms? Or do they occur independent of each other or simultaneously? Examining a particular form of coping in the population may lead us to better understand the nature and causal direction of these relationships.

Religious Coping

Although coping strategies vary, people facing adverse situations often turn to religion (Pargament, 1997; Park et al., 2009; Pargament, 2007). Religion is important since it plays a role in how people appraise events, which then impacts both mental and physical reactions to stress (Park & Cohen, 1993; Pargament et al., 2003; Seybold & Hill, 2001). For instance, religious beliefs and practices (i.e., religious attendance, prayer, Bible study, and high intrinsic religiosity) have been shown to prevent the onset and development of depression, increase recovery from depressive episodes through instilling hope/optimism, and serve as a way to cope by moderating depressive symptoms (Koenig, 2007; Lutgendedorf et al., 2004). While the use of religion to withstand stressors is associated with greater wellbeing in general (Gorsuch & McPherson, 1989; Hathaway et al., 1991; Trevino et al., 2010), religious coping strategies, rather than worship, are particularly strong predictors of psychological outcomes after stressful events (Hackney & Sanders, 2003).

Religion and Older Adults

Older adults report relying on religion more than any other form of coping (Koenig, 1998). Religion is naturally suited to coping as it provides a framework to understand both positive and negative events (Pargament, 1997; Roff et al., 2004). Older adults tend to have faced more life-altering existential crises (i.e., the death of a loved one, trauma, life-threatening experience) than other age groups (Gorsuch & McPherson, 1989; Greenberg, Koole, Pargament, 1997; Pyszczynski, 2004; Pyszczynski, Greenberg, Koole, & Soloman, 2010). In general, existential crises lead us to seek introspection about our existence and purpose. Relying on religion may help answer some of these big questions (Pargament, Magyar-Russell, & Murray-Swank, 2005; Pyszczynski et al., 2010). By contrast, losing one's meaning or sense of purpose are precipitants of major depression (Crystal, Sambamoorthi, Walkup & Akincigil, 2003).

Religious Coping and Mental Health

To further understand how existential crises impact wellbeing, Pargament (2005) formulated a theory for spiritual integrated psychotherapy such that spirituality is a solution to or source of psychological distress; this resource is often ignored by the scientific community and secular scholars. Pargament (2005) argued that spirituality must be integrated into our understanding of mental health because it pervades all aspects of body (physical health) and soul (mental health).

Better understanding of how religious coping may be used adaptively in times of stress can help us pinpoint how to optimize wellbeing in older adults (Pargament, 2010). The research on religious coping and its impact on mental health are abundant. For

example, after the 9/11 terrorist attacks, 90% of sampled Americans utilized religious coping (Schuster, Stein, Jaycox, Collins, Marshall, et al. 2001). Combat veterans, hospital patients, physically abused spouses, and widows have also been shown to turn to religious coping as a method of dealing with difficult life transitions (Bremmer et al., 2008). Moreover, religious coping may be useful to those already diagnosed with a mental illness. Tepper, Rogers, Coleman, and Malony (2001) found that over 80% of patients with a mental illness rely on religious coping daily to feel less distraught and frustrated.

Religious Coping and Health Outcomes

Religious coping has a fundamental role in morbidity and mortality outcomes (Hackney & Sanders, 2003). However, the impact of religious coping seems to depend on the nature of one's religious views. While holding a positive view of God can help one to feel more in control, a negative view of God can compromise one's sense of control and lead to more existential angst (Pargament, 2005; Pyszczynski et al., 2010).

Negative Religious Coping

Although most research on religion and mental health demonstrates that religious coping leads to lower rates of depression and higher self-esteem, negative religious coping does not show these benefits. Pargament et al. (2000) developed and validated a comprehensive measure of different types of positive and negative religious coping strategies, allowing for a more comprehensive understanding of religious coping and psychological adjustment to stress. Positive religious coping (i.e., I work with God to

solve my problems) involves a collaborative relationship with God. Negative religious coping (i.e., God is punishing me for my sins) involves a weak, wavering relationship with God, a punishing view of the world and a general struggle to find purpose and meaning (Pargament et al., 1998). Schaefer and Gorsuch (1991) explain that adults who use negative religious coping find God to be distant; they tend to passively wait for God to control the situation, which results in anger and resentment towards God. More specifically, those who utilize negative religious coping are more pessimistic, believe that God is punishing, and that negative outcomes will prevail.

Research on negative religious coping finds that it leads to long-term changes in stress responses (Pargament et al., 1998; Pargament, Magyar-Russell, & Murray-Swank, 2005; Thompson & Vardaman, 1997). In fact, persistent use of negative religious coping has been related to the development of depression as well as to morbidity and mortality (Ano & Vasconcelles, 2005; Fallot & Heckman, 2005). One reason for this may be that, rather than being relieved by the belief in a deity, those that rely on negative religious coping tend to instead feel burdened by this relationship (Ano & Casconcelles, 2005).

Research supports this finding and its subsequent relation to mental health. For instance, recent research revealed that negative religious coping was significantly associated higher posttraumatic stress disorder (PTSD) and depression symptoms in earthquake survivors (Feder et al., 2013). Also, negative religious coping has been associated with a greater risk for mortality, uncontrolled diabetes (Newlin, Melkus, Tappen, Chyun & Koenig, 2008), pain and reduced energy in cancer patients (Sherman, Simonton, Latif, Spohn & Tricot, 2005), longer hospitalizations (Contrada et al., 2004), and increased surgical complications (Ai et al., 2009).

Researchers explain that certain types of negative religious coping are more predictive of mortality than others (Ai et al., 2009; Ai & Noel, 2013). Specifically, feeling alienated from or unloved by God, attributing illness to the devil, and feeling that God is punishing were associated with a 28% increased risk of death (Pargament et al., 2001). While feeling burdened by God may be one reason for increased morbidity in negative religious coping, the mechanisms of this relationship are still debated. Park et al. (2009) articulated that the link between negative religious coping and poor health was attributable to reductions in motivation to preserve physical health and to avoidance in confronting an illness and its treatment (Pargament, 2010). Likewise, negative coping strategies may elicit early symptoms of depression (i.e., reduced motivation, reduced sense of purpose, etc.) and subsequently, reduced self-efficacy to manage daily life (Ano & Vasconcelles, 2005).

Negative Religious Coping and Inflammation

The influence of negative religious coping on inflammatory diseases is still developing and represents a gap in the religious coping literature. Preliminary research has shown that negative religious coping leads to increased risk for inflammatory diseases. In a longitudinal study on patients with HIV/AIDS, negative religious coping was related to declines in the function of CD4+ T cells after controlling for demographics and positive religious coping (Cotton et al., 2006). Ai et al. (2007) found that patients who faced a life-altering medical crisis and simultaneously felt an existential crisis had higher preoperative circulating IL-6 elevations (Ai et al., 2009). Negative religious coping may also mediate the relationship between medical distress and healing. Ai et al.

(2010) found that negative religious coping mediated the relationship between preoperative distress and postoperative hostility in cardiac patients, and between hostility and circulating IL-6 concentrations (Ai et al., 2010).

To summarize, stressful events may lead to existential questioning and a loss of meaning that is linked to exacerbation of inflammatory responses that promote depression. Reliance on negative religious coping may cause persons to lose a sense of purpose and meaning that not only impacts health behaviors but may have long-term impacts on recovery from medical conditions and procedures, mental illness, and response to adverse events.

Positive Religious Coping

By contrast, positive religious coping may benefit health and wellbeing. Positive religious coping involves a collaborative and loving view of God. Religious practice (i.e., church attendance, prayer, meditation) has been linked to lowered risk of autoimmune disease and death, and improved mental and physical health (Aldwin, Jeong, & Nath, 2014; Jordan, Masters, & Hooker, 2014; Koenig, 2008) (see Figures 4 and 5). This link may be explained by the use of positive religious coping to help people focus on the positive, be more optimistic, and use stressful events to generate spiritual growth (Pargament et al., 1997).

Positive Religious Coping and Inflammation

In a similar line, those who regularly attend worship are less likely to have elevated IL-6 levels, and, thus IL-6 may mediate the worship and mortality relationship in older adults (Lutgendorf et al., 2004). Specifically, attending religious services more

than once weekly predicts lower IL-6 and 12-year mortality (Lutgendorf et al., 2004). Benefits of religious practice is likely notable when examining all-cause mortality outcomes rather than specific disease incidence if inflammation is the mediator because inflammation contributes to all disease processes (Jordan et al., 2014; Powell, Shahabi, & Thorensen, 2003; Masters & Hooker, 2013).

Different theoretical models have been used to explore the relationship between religious practice, mental health, and health outcomes. The 'classical model' presented by Koenig (2008) lays the foundation for research on religious practices and health outcomes. In his model, Koenig (2008) demonstrates that religious practice impacts psychological health (i.e., connectedness, decreased incidence of depression, anxiety, etc.), which in turn impacts PNI factors (i.e., lower elevations of IL-6), and consequently health outcomes (e.g., cardiovascular disease, cancer, and mortality). He concludes that religious practices may protect one from inflammatory processes and diseases.

Similarly, Levin (1996) has demonstrated the different pathways of religious practice and their effects on health, stress, and coping. His salutogenic model establishes that strict religious commitment (i.e., frequent church attendance) has better health behavior outcomes (i.e., no smoking, drinking, etc.), thereby indirectly decreasing risk for inflammatory diseases. More specifically, the pathway for positive religious coping behaviors directly improves PNI factors. In other words, positive religious coping, like negative religious coping, has a direct effect on immune system responses.

Sapolsky's (2004) model also provides evidence that both religiously influenced health behavior habits and direct physiological effects of religious practice improve health outcomes. In a review of these three models, Aldwin et al. (2014) proposed two

different constructs that ultimately explain the impact on health outcomes. They argue that spirituality (i.e., religious coping, prayer, and meditation) has primary effects on immune system health through emotion regulation; while religiousness (i.e., church attendance) primarily affects health habits (i.e., exercise, smoking.). This model broadens the literature by finding that the effects of both positive and negative religious coping on health are primarily via the effects of emotion regulation on inflammatory processes underlying chronic illness (see Figure 5).

Most recently, the BRHS (Lee et al, 2009) investigators tested a model of religion and health (Morton, Lee, & Martin, in press) by investigating religious engagement and worship on mortality in SDAs. Morton et al. found that religious engagement operated indirectly on mortality via positive religious support and reduced negative emotionality. Further, religious engagement also reduced mortality risk indirectly by reducing negative emotionality, which in turn, increased positive health behaviors (diet, exercise). Worship directly and indirectly through health behaviors also reduced mortality risk. This model suggests that worship and religious engagement improve health via improved mental health and health behaviors to potentially reduce the stress response (Hill, Rote, Ellison & Burdette, 2014; Morton et al., in press: see Figure 6).

Understanding the role of positive religious coping as a protective factor is important considering the ample evidence linking religious practices to lower risk of morbidity and mortality. However, research on the specific role of positive religious coping on depression and inflammation is sparse. To date, Assari (2014) found that positive religious coping buffered the association between number of chronic medical conditions and major depressive disorder among Caribbean Blacks. Further research is

needed to understand the potential protective effect of positive religious coping. In particular, determining whether having a collaborative and loving view of God impacts depression and inflammation would be worthwhile.

Conclusion and Aims

Understanding risk factors of inflammation is crucial to reducing mortality and morbidity (Dinarello, 2000; American Heart Association, 2015). The current review has outlined the complex and bidirectional relationship between mental health and inflammation, or more specifically, between depression and IL-6. In short, precipitants to depression may generate enhanced physiological reactivity that leads to wear and tear on the immune system, leading to the development of inflammatory diseases. Likewise, pro-inflammatory cytokines may generate atherosclerotic changes that may induce cortical changes in brain regions responsible for the onset and maintenance of depression.

The present study will assess the relationship between depressive symptoms and IL-6 elevations, bidirectionally and longitudinally, in a cohort of older SDAs. Given that research provides evidence for the beneficial effects of some forms of religious coping but not others, and that older adults tend to rely on religious coping, the investigation will also examine the role of positive and negative religious coping as moderators of the depression and IL-6 relationship.

CHAPTER 3

METHODS

Study Design

The BRHS is a longitudinal cohort study of Seventh-day Adventist adults (Lee et al., 2009). The BRHS is a sub-study of the Adventist Health Study-2 (AHS-2), which examines the relationship between religion and health. The AHS-2 investigates cancer, diet, and lifestyle in a cohort of approximately 96,000 SDAs (Butler et al., 2008). The BRHS randomly sampled 21,000 AHS-2 participants to receive the 20-page BRHS survey. Of those, 10,988 participants responded in 2006-7 and 6,524 responded again in 2010-11. A subsample of these participants also attended a clinic on or near the campus to assess stress related biomarkers. The Institutional Review Board approved the study as minimal risk and all participants provided written consent.

Participants and Procedures

In 2006-7, 845 BRHS participants who completed the survey and who lived within 60 miles of campus were invited to participate in a clinic to assess stress biomarkers, physical functioning, and memory. Of these, 622 were scheduled, 532 attended the visit, and 511 provided complete data in 2006-7. In 2010-11, participants from time one who were over age 50, Black or White, alive, and with complete data from the initial clinics were invited to attend a second clinic, 331 attended, and 287 met other relevant inclusion criteria (having relevant data for the current study, being active or inactive SDA, being 50 years of age or more). Individuals with missing data on more than two items on the CES-D, or those who had more than one missing item on a

religious coping subscale, demographic questions, or IL-6, were excluded. Otherwise, mean replacement on the CES-D and the religious coping subscales was employed to retain the case for analysis. Outliers that were more than four standard deviations from the mean were excluded.

For the longitudinal analyses, 331 participants provided data in both 2006-7 and 2010-11. Of these, 44 persons had missing data on all relevant variables and were excluded (four cases had missing data on all variables, three on education, three on ethnicity, one on health, 15 on positive religious coping, 23 on negative religious coping, and five on multiple variables). As such, 287 participants were retained for longitudinal analyses. Participants who were included and excluded were compared based on demographics. Those included and excluded were similar on age, gender, financial difficulties, and ethnicity. However, those excluded had lower education, though both groups were relatively well educated with some college to college degrees.

The final sample consisted of 115 males (39.9%) and 173 females (60.1%) with a mean age of 67.68 years (*SD* = 11.2). The majority of the participants were White (66.0%), had some college or higher education degree (95.5%), and had little to no financial difficulties in the year prior to 2006-7 (93.4%) (see Table 1 for sample demographics).

Measures

Sociodemographic Variables

Sociodemographic factors including age, gender, ethnicity, education, general health, and difficulty meeting expenses were controlled in all analyses. We also controlled for number of days between measurement time points and for baseline levels of IL-6 and depressive symptoms depending on the models tested. Ethnicity was coded as White (non-Hispanic White) and Black (African-American, Caribbean Black, and Biracial Black). Education was obtained from the AHS-2 survey on a 9-point scale: 1 – *Grade School,* 2 – *Some High School,* 3 – *High School Diploma,* 4 – *Trade School Diploma,* 5 – *Some College,* 6 – *Associate's Degree,* 7 – *Bachelor's Degree,* 8 – *Master's Degree,* 9 – *Doctoral Degree*. Current poverty in 2010-11 was assessed by the following question: "On average how difficult was it for your family to meet expenses for financial difficulties like, food, clothing, and housing *in the last three years* on a 5-point Likert scale (1- *Not at all difficult;* 5- *Very difficult*) (Pudrovska, Schieman, Pearlin, Nguyen, 2005). General health was assessed with the question: "How is your general health?" based on a 5-point Likert scale (1- *Poor,* 2- *Fair,* 3- *Good,* 4- *Very good,* 5-*Excellent*) (Ware, Kosinski & Dewey, 2002; Short-Form Health Survey: SF-12).

Brief Religious Coping Scale (RCOPE)

Religious Coping. Religious coping was measured by the Brief Religious Coping Scale (RCOPE: Pargament, Koenig, & Perez, 2006) with these instructions: "*Thinking about how you have tried to understand and deal with major problems in your life, to what extent has each of the following been involved in the way you cope*?" with each item

rated on a 5-point Likert Scale (0= *Never*, 4= *Very often):* 1) Positive religious coping (α= .80)- *Benevolent God reappraisal* (3 items); *Collaborative Religious Coping* (3 items); *Spiritual Connection* (one item) and 2) Negative religious coping (α =.73)- *Punishing God reappraisal* (3 items); *Passive religious deferral* (3 items); and *Anger at God* (one item) .

Center for Epidemiological Studies Depression (CES-D) Scale 11-item Short Form

Depressive symptoms were measured with the CES-D 11-item Short Form (Kohout, Berkmam, Evans & Coroni-Huntley, 2003). Each item is rated on a four-point scale (0= *Rarely or none of the time;* 4= *Most or all of the time*) based on how they felt in the past week during 2006-7 (α=.79). A log transformation was performed on CES-D to normalize observed positive skew in 2006-7 (*M*= 2.98, *SD*= 1.4) and 2010-11 (*M*= 2.79, *SD*= 1.7).

Interleukin-6

IL-6 is a marker of inflammation that rises in the blood during periods of chronic stress. It has been linked to premature aging and accelerated risk of cardio-metabolic disease (Kiecolt-Glaser, 2003). Participants had 12-hour fasting blood samples taken upon arrival at the clinic. These samples were stored on ice and taken to the lab where Quantikine high-sensitivity IL-6 enzyme-linked immunosorbent assays (ELISA) were run neat according to manufacturer's instructions (R&D Systems, Minneapolis, MN). Standards ranged from 0 to 10 pg/ml. Plates were read on a plate set at 490 nm or 650 nm; correction for optical imperfections in the plate was done by determining the

difference in values between these wavelengths. Intra- and inter-assay variability was 7.4% and 7.8%, respectively. The minimal detectable level was 0.039 pg/ml. A log transformation was performed on IL-6 to normalize positive skew in 2006-7 (*M*= 0.48, *SD*= 0.44) and 2010-11 (*M*= 0.27, *SD*= 0.32).

Research Questions

Hypothesis 1a. After controlling for covariates, do depressive symptoms in 2006-7 positively predict IL-6 levels in 2010-11?

- Hierarchical linear regression with IL-6 (2010-11) as a dependent variable and CESD in 2006-7 as an independent variable. Base model included demographic variables (age, gender, ethnicity, education, financial difficulties, and IL-6 from 2006-7).

Hypothesis 1b. After controlling for covariates, do IL-6 levels in 2006-7 positively predict depressive symptoms in 2010-11?

- Hierarchical linear regression with depressive symptoms (2010-11) as a dependent variable and IL-6 in 2006-7 as an independent variable. Base model included demographic variables (age, gender, ethnicity, education, financial difficulties, and depressive symptoms from 2006-7).

Hypothesis 2a. After controlling for covariates, does positive religious coping in 2006-7 moderate the relationship between 2006-7 depressive symptoms and 2010-11 IL-6?

- Hierarchical linear regression with IL-6 (2010-11) as a dependent variable and CESD (2006-7) and positive religious coping in (2006-7) as an independent

variables. Base model included demographic variables (age, gender, ethnicity, education, financial difficulties, general health, and IL-6 from 2006-7).

Hypothesis 2b. After controlling for covariates, does positive religious coping in 2006-7 moderate the relationship between 2006-7 IL-6 and 2010-11 depressive symptoms?

- Hierarchical linear regression with depressive symptoms (2010-11) as a dependent variable and IL-6 (2006-7) and positive religious coping (2006-7) as independent variables. Base model included demographic variables (age, gender, ethnicity, education, financial difficulties, general health, and depressive symptoms from 2006-7).

Hypothesis 3a. After controlling for covariates, does negative religious coping in 2006-7 moderate the relationship between 2010-11 depressive symptoms and 2010-11 IL-6?

- Hierarchical linear regression Model 2 with IL-6 (2010-11) as a dependent variable and CESD (2006-7) and negative religious coping in (2006-7) as independent variables. Base model included demographic variables (age, gender, ethnicity, education, financial difficulties, and IL-6 from 2006-7).

Hypothesis 3b. After controlling for covariates, does negative religious coping in 2006-7 moderate the relationship between 2006-7 IL-6 and 2010-11 depressive symptoms?

- Hierarchical linear regression Model 2 with IL-6 (2010-11) as a dependent variable and CESD (2006-7) and negative religious coping in (2006-7) as independent variables. Base model included demographic variables (age, gender, ethnicity, education, financial difficulties, and IL-6 from 2006-7).

Hypothesis 4a. After controlling for covariates, does the 2006-7 interaction between negative and positive religious coping moderate the relationship between 2006-7 depressive symptoms and 2010-11 IL-6?

- Hierarchical linear regression with IL-6 (2010-11) as dependent variable and depressive symptoms (2006-7), positive religious coping in 2006-7, the interaction between depressive symptoms and positive religious coping, and the interaction between depressive symptoms and negative religious coping as independent variables. Base model included demographic variables (age, gender, ethnicity, education, financial difficulties, general health, and IL-6 from 2006-7).

Hypothesis 4b. After controlling for covariates, does the 2006-7 interaction between negative and positive religious coping moderate the relationship between 2006-7 IL-6 and 2010-11 depressive symptoms?

- Hierarchical linear regression with depressive symptoms (2010-11) as a dependent variable and IL-6 (2006-7), positive religious coping in (2006-7), and the interaction between IL-6 and positive religious coping as independent variables. Base model included demographic variables (age, gender, ethnicity, education, financial difficulties, general health, and depressive symptoms from 2006-7).

Data Analysis

An examination of the distributions of each variable indicated all were normally distributed except IL-6, which was, then square root transformed. Variables converted to

z-scores were created before calculating interaction terms. All data were analyzed using SPSS 22 (IBM Corp, 2013). The alpha level was set to .05.

Bivariate correlations were calculated to examine the relationship between covariates, depression, positive religious coping, negative religious coping, and IL-6 (see Table 2). A series of hierarchical regressions tested elevations in IL-6 in 2010-11 with the following model: (1) demographics (age, gender, ethnicity, education, financial difficulties, health, IL-6, study interval), (2) baseline IL-6 2006-7, (3) depression 2006-7, (4) religious coping 2006-7, (5) religious coping X depression. A series of hierarchical regressions tested depressive symptoms in 2010-11 with the following model: (1) demographics (age, gender, ethnicity, education, financial difficulties, health, depressive symptoms, study interval), (2) baseline depressive symptoms 2006-7, (3) IL-6 2006-7, (4) religious coping 2006-7, and (5) religious coping x depression.

CHAPTER 4

PUBLISHABLE PAPER

Journal Submission Cover Letter

Note: The formatting and referencing style below follows journal specification, not LLU dissertation guidelines.

Palak Kothari
11130 Anderson Street
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Dr. Curtis Hart
Editor-in-Chief
Journal of Religion and Health

August 22, 2016

Dear Dr. Hart:

I am currently involved in the national Biopsychosocial Religion and Health Study (BRHS), longitudinal cohort study of Seventh-day Adventist adults (Lee et al., 2009) to examine the relationship between religion and health. In that regard, we have completed the attached manuscript on how religious coping moderates the depression and IL-6 relationship.

Hence, I am pleased to submit an original research article entitled "*IL-6, Depressive Symptoms, and Religious coping in older Seventh-day Adventists*" for consideration for publication in the Journal of Religion and Health. Our study clarifies the longitudinal and bidirectional relationship of depression and the biomarker Interleukin-6, and investigated the role of religious coping as it moderates this relationship.

In this manuscript, we show that baseline depressive symptoms have a small but significant association with subsequent IL-6 elevations at follow-up; however, baseline IL-6 is not predictive of subsequent depressive symptoms at follow-up. Further, we find that the interaction between depressive symptoms and positive religious coping moderates the depression-IL-6 relationship.

This manuscript has not been published and is not under consideration for publication elsewhere. We have no conflicts of interest to disclose. The manuscript is 5,327 words long and contains 3 tables and 1 figure.

Sincerely,

Palak Kothari

Interleukin-6, Depressive Symptoms, and Religious Coping in Older Seventh-day Adventist Adults

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Abstract

Researchers suggest that depression and inflammation have a bidirectional relationship, however, few longitudinal studies have tested this conclusion. Further, in late life, it may also be that religious coping moderates the depression and inflammation relationship. This study examined how depressive symptoms and the inflammatory marker, interleukin-6 (IL-6) are related across 3-5 years in 287 older adults (54% female, 63% White, M_{age} = 66, SD_{age} = 10.9) participating in the Biopsychosocial Religion and Health Study. Depressive symptoms and IL-6 were assessed in 2006-7 and 2010-11 along with religious coping. Results of the hierarchical multiple regressions indicate that initial depressive symptoms predicted IL-6 three to five years later, and that this relationship was moderated by positive religious coping. Moreover, initial negative religious coping, not IL-6, predicted depressive symptoms three to five years later. Therefore, negative religious coping may increase depressive symptoms and depressive symptoms may increase inflammation. Further, and contrary to our hypothesis, positive religious coping exacerbates inflammation if depressed. . Finally, IL-6 was unrelated to later depressive symptoms supporting the hypothesis that depression predicts inflammation and that the relationship is not bidirectional. In a religious sample, depression does predict inflammation and positive religious coping actually exacerbates these effects. Further, because negative religious coping also predicts later depression, it could be that any amount of negative religious coping counteracts the benefits of positive religious coping.

Keywords: religious coping, depression, IL-6

Inflammation, Depressive Symptoms, and Positive Religious Coping in Older Seventh-day Adventists

Religion is of interest to health researchers because of its established relationship with mental and physical health. While religion has been identified as an often used coping strategy when facing issues of morbidity and mortality (Aldwin, Jeon, Nath, & Park, 2014; Laubmeier, Zakowski, & Bair, 2004; Stroebe, 2004); the type of religious coping often determines the health outcome. Positive religious coping, or having a collaborative relationship with and loving view of God, has beneficial health effects while negative religious coping, which involves a fearful, weak, wavering relationship with God, has detrimental health effects (Ano & Vasconcellas, 2005; Pargament, 2010).

Inflammation has been identified as an important mechanism of disease and has been related to mental health (Parham, 2004). Negative emotions have been consistently related to adverse immune system effects and increases in inflammatory markers (Glaser & Kiecolt-Glaser, 1994; Parham, 2004; Maggio et al., 2006; Gouin et al., 2011). Additionally, depression increases inflammation and subsequent disease risk though the direction of these effects are not clear (Dowlati et al., 2009; Gouin et al., 2011; Maggio et al., 2006; Miller, Stetler, Carney, Freeland, & Banks, 2002).

Studies indicate a consistent and positive relationship between depression and IL-6, a biomarker that has been linked to premature aging and accelerated risk of cardio-metabolic disease (Bremmer et al., 2008; Dentino et al., 1999; Gimeno et al., 2009; Ranjit et al., 2007; Valkanova, Ebmeier, & Allan, 2013). However, the nature of this relationship has not been well understood. Most researchers conclude that the relationship between the two is complex and likely bidirectional (Dolwati et al., 2010; Irwin et al.,

2007), however, given a scarcity of longitudinal studies, the causal direction of this relationship is not certain.

Depression Leads to Inflammation

There is evidence suggesting that depression leads to inflammation. Research supports the notion that depression exacerbates and maintains inflammatory processes by reducing the sensitivity of the immune system to glucocorticoid hormones that manage the inflammatory response (Raison, Capuron, & Miller, 2006). Accordingly, negative emotions increase the production of IL-6 (Kiecolt-Glaser et al., 2002b; Maes et al., 1998; Steptoe, Hamer, & Chida, 2007) to increase the risk of infection and inflammatory disorders (Roupe van der Voort, 2000; Zautra et al., 2004). Raison et al. (2006) posit that stressful experiences such as depression activate the hypothalamic-pituitary-adrenal (HPA) axis which is responsible for regulating homeostatic systems such as the immune system to generate the pro-inflammatory cytokine, and initiate secretion of interleukin-6 (IL-6) at the macrophage level.

Inflammation Leads to Depression

There is also evidence that inflammation leads to depression. Smith's (1991) Macrophage Theory of Depression proposes that inflammation induced by macrophages (i.e., white blood cells that metabolize proteins necessary to fight and mediate inflammation) have a fundamental role in the pathophysiology of depression. Other theorists propose that changes in inflammation leads to depression (i.e., Salutogenic Model, Levin, 1996; Inflammation Hypothesis, Alexoplous & Morimoto, 2011). These

theories are supported by evidence that changes in atherosclerotic processes responsible for emotion regulation and depression follow elevated pro-inflammatory cytokines (Ross, 1999; Maes 1995; Maes et al., 1992). Specifically, resistant glucocorticoid receptors (GRs; regulators of immune response) increase IL-6 production, which may then initiate the pathophysiology of depression (Kim, Na, Myint, & Leonard, 2016).

In sum, there is evidence suggesting a bi-directional relationship between inflammation and later depression. However, there is evidence that the pathway of depression leading to inflammation is theoretically more reasonable because of work regarding emotional functioning skills established early in life (Copeland, Shanahan, Worthman, Angold & Costello, 2011). Specifically, emotional dysregulation starting in childhood has been linked to the onset and development of depressive symptoms and depression across the lifespan (Raison et al., 2006). Further, the presence of emotion dysregulation in childhood persisting into adulthood in the form of depression and depressive symptoms uniquely predicts risk for inflammatory diseases in old age (Copeland et al., 2011).

This investigation will further examine the longitudinal depression to inflammation relationship and will further examine potential effect moderators in a religious sample. Specifically, positive and negative religious coping may potentially moderate the depression-inflammation or the inflammation-depression relationship in middle aged to older adults.

Religious Coping

Depression is conceptualized as the inability to utilize successful regulatory

strategies to improve and sustain mental health (Berking & Wupperman, 2012; Cicchetti & Toth, 1998; Gross, 1998). Individuals with poor emotional regulatory skills often select maladaptive coping strategies for the long-term management of persistent negative emotions that contribute to depression which in some cases become chronic or relapsing and remitting. Therefore, coping strategy choice may either exacerbate or buffer depressive symptoms.

People with a religious orientation who face adversities often turn to religious coping (Pargament, 1997; Park et al., 2009; Pargament, 2007). Religion is important since it plays a role in how people appraise events, which then impact reactions to stress (Park & Cohen, 1993; Pargament et al., 2003; Seybold & Hill, 2001). For instance, religious beliefs and practices (i.e., religious attendance, prayer, Bible study, intrinsic religiosity) may prevent the onset of depression and increase recovery by instilling hope and optimism (Koenig, 2007; Lutgendorf et al., 2004), or combat depression after a stressful or traumatic event (Gorsuch & McPherson, 1989; Hackney & Sanders, 2003; Hathaway and Pargament, 1991; Trevino, Pargament, Cotton et al., 2010).

Religion is often used by older adults to cope and understand and give meaning to life experience (Koenig, 1998; Pargament, 1997; Roff et al., 2004). Older adults face more life-altering existential crises (i.e., the death of a loved one, trauma, and life-threatening experience) than other age groups (Gorsuch & McPherson, 1989; Greenberg, Koole, Pargament, 1997; Pyszczynski, 2004; Pyszczynski, Greenberg, Koole, & Soloman, 2010) that leads to introspection about meaning they can address with religious engagement (Pargament, Magyar-Russell, & Murray-Swank, 2005; Pyszczynski et al., 2010).

The type of religious coping one uses has been shown to have effects on mental health and physical health outcomes as it can be adaptive or maladaptive (Hackney & Sanders, 2003; Pargament, 1998, 2010). The impact of religious coping depends on the nature of one's religious views. While a positive view of God can help one feel more in control (positive religious coping), a negative view of God can compromise one's sense of control and lead to more existential angst (negative religious coping) (Pargament, 2005; Pyszczynski et al., 2010).

The type of religious coping may moderate the relationship between depression and inflammation by serving as either a protective or an exacerbating factor. Studies have found lower production of pro-inflammatory markers (e.g., IL-6) among people who use positive religious coping strategies (Ironson et al., 2002; Tartaro et al., 2005; Chan et al., 2006) and after a spiritual intervention (Pargament, 1997;Pace et al., 2009; Berk, Bellinger, Koenig, Daher, Pearce et al., 2015) though these participants were not at high risk such as being depressed. We do know however that weekly or greater worship predicts lower IL-6 and 12-year mortality so there is certainly a possible buffering effect of positive religious engagement (Lutgendorf et al., 2004).

Similarly, positive religious coping may be protective in the complex depression-inflammation relationship, though research in this area is lacking. In one study, Assari (2014) found that positive religious coping buffered the association between chronic medical conditions and depression among Caribbean Blacks. Negative religious coping has been related to long-term changes in stress responses (Pargament et al., 1998; Pargament, Magyar-Russell, & Murray-Swank, 2005; Thompson & Vardaman, 1997). In fact, persistent use of negative religious coping has been related to the development of

depression (Ano & Vasconcelles, 2005; Fallot & Heckman, 2005), and, mortality risk, uncontrolled diabetes (Newlin, Melkus, Tappen, Chyun & Koenig, 2008), pain and reduced energy in cancer patients (Sherman, Simonton, Latif, Spohn & Tricot, 2005), longer hospitalizations (Contrada et al., 2004), and increased surgical complications (Ai et al., 2009).

Further understanding of the role of religious coping as a potential moderator of mental and physical health is still needed. Specifically, no study has looked at the unique role of positive and negative religious coping as a moderator of the depression and inflammatory relationship across time in late life.

The current investigation tested the following hypotheses in an older cohort of Seventh-day Adventists (SDA): First, we examined whether depression predicts IL-6 three to five years later and if IL-6 predicts depression three to five years later. Second, after we established the direction of effects, we examined whether religious coping moderates this relationship. Specifically, if positive religious coping moderates the IL-6-depression relationship or the depression-IL-6 relationship was tested. And, if negative religious coping moderates the IL-6-depression or the depression-IL-6 relationship was also tested.

Methods

Study Design

The Biopsychosocial Religion and Health Study (BRHS) is a longitudinal cohort study of Seventh-day Adventist (SDA) adults (Lee et al., 2009). The BRHS is a sub-study of the Adventist Health Study-2 (AHS-2) that investigates cancer and lifestyle in 96,000

SDAs over time (Butler et al., 2008). The BRHS examined stress, religion, and health by surveying a random sample of 21,000 AHS-2 participants with two 20-page questionnaires. Of those, 10,988 responded in 2006-7 and 6,524 in 2010-11. A subsample of these participants attended a clinic to assess stress related biomarkers after providing written consent. Only those who were either White or Black were resampled in 2010-2011.

Participants and Procedures

In 2006-7, 845 BRHS participants who completed the survey and who lived within 60 miles of campus were invited to participate in a clinic to assess stress biomarkers, physical functioning, and memory. Of these, 622 were scheduled, 532 attended the visit, and 511 provided complete data. At Time 2, these 511 individuals were invited to attend a second clinic, 331 attended, and 287 met relevant inclusion criteria (no missing study data at either time point, being active or inactive SDA, being 50 years of age or older). Individuals with missing data on more than two items on the CES-D, or those who had more than one missing item on a religious coping subscale, demographic questions, or IL-6, were excluded. Otherwise, a mean was calculated on the CES-D and the religious coping subscales of available items.

Of the 331 participants with longitudinal data, 44 were excluded due to missing data on study variables (four missing all variables, three on education, three on ethnicity, one on health, 15 on positive religious coping, 23 on negative religious coping, and five on multiple variables) leaving 287 for longitudinal analyses. Participants who were included and excluded were compared on demographics and found to be similar on age,

gender, financial difficulties, and ethnicity. However, those excluded had lower education, though both groups were relatively well educated with some college vs. college degrees.

The final sample consisted of 115 males (39.9%) and 173 females (60.1%) with a mean age of 67.68 years (*SD* = 11.2). The majority of the participants were White (66.0%), had some college or higher (95.5%), and had little to no financial difficulties in the year prior to 2006-7 (93.4%) (see Table 1).

Measures

Covariates

Demographic controls included age, gender, ethnicity, education, general health, and difficulty meeting expenses. We also controlled for number of days between measurement time points and for baseline levels of IL-6 or baseline levels of depression as appropriate for each hypothesis tested. Ethnicity was coded as White (non-Hispanic White) and Black (African-American, Caribbean Black, and Biracial Black). Education was assessed on a 9-point scale: 1 – *Grade School,* 2 – *Some High School*, 3 – *High School Diploma,* 4 – *Trade School Diploma*, 5 – *Some College*, 6 – *Associate's Degree*, 7 – *Bachelor's Degree*, 8 – *Master's Degree*, 9 – *Doctoral Degree*. Financial difficulties in the last three years was assessed in 2010-11 with: "On average how difficult was it for your family to meet expenses for financial difficulties like, food, clothing, and housing *in the last three years* on a 5-point Likert scale (1- *Not at all difficult;* 5- *Very difficult*) (Pudrovska, Schieman, Pearlin, Nguyen, 2005). General health was assessed with the question: "How is your general health?" based on a 5-point Likert scale (1- *Poor,* 2- *Fair*,

3- *Good*, 4- *Very good*, 5-*Excellent*) (Ware, Kosinski & Dewey, 2002; Short-Form Health Survey: SF-12). Lastly, the study interval variable was measured in number of days between each BRHS measurement as it varied by participant to be anywhere from three and five years (2006-7 to 2010-11).

Religious Coping

Religious coping was measured by the Brief Religious Coping Scale (RCOPE: Pargament, Koenig, & Perez, 2006) with these instructions: "*Thinking about how you have tried to understand and deal with major problems in your life, to what extent has each of the following been involved in the way you cope*?" with each item rated on a 5-point Likert Scale (0= *Never*, 4= *Very often):* 1) Positive religious coping (α= .80)- *Benevolent God reappraisal* (3 items); *Collaborative Religious Coping* (3 items); *Spiritual Connection* (one item) and 2) Negative religious coping (α =.73)- *Punishing God reappraisal* (3 items); *Passive religious deferral* (3 items); and *Anger at God* (one item).

Depression

Depressive symptoms were measured with the CES-D 11-item Short Form (Kohout, Berkmam, Evans & Coroni-Huntley, 2003). Each item is rated on a four-point scale (0= *Rarely or none of the time;* 4= *Most or all of the time*) based on how they felt in the past week during 2006-7 or 2010-11 depending on the analysis (α .79). A log transformation was performed on CES-D to normalize observed positive skew in 2006-7 (*M*= 2.98, *SD*= 1.4) and 2010-11 (*M*= 2.79, *SD*= 1.7).

Inflammation: IL-6

Interleukin-6 (IL-6) is a marker of inflammation that rises in the blood during periods of chronic stress. It has been linked to premature aging and accelerated risk of cardio-metabolic disease (Kiecolt-Glaser, 2003). Participants had 12-hour fasting blood samples taken upon arrival at the morning clinic in both 2006-7 and 2010-11. The samples were stored on ice and taken to the lab where Quantikine high-sensitivity IL-6 ELISAs were run neat according to manufacturer's instructions (R&D Systems, Minneapolis, MN). Standards ranged from 0 to 10 pg/ml. Plates were read on a plate set at 490 nm or 650 nm; correction for optical imperfections in the plate was done by determining the difference in values between these wavelengths. Intra- and inter-assay variability was 7.4% and 7.8%, respectively. The minimal detectable level was 0.039 pg/ml. A log transformation was performed on IL-6 to normalize observed positive skew in 2006-7 (M= 0.48, SD= 0.44) and 2010-11 (M= 0.27, SD= 0.32).

Data Analysis

An examination of the distributions of each variable indicated all were normal after transformations. Scores were transformed to z-scores before calculating interaction terms. All data were analyzed using SPSS v22 (IBM Corp, 2013). The alpha level was set to .05.

Bivariate correlations were calculated to examine the relationship between covariates, depression, positive religious coping, negative religious coping, and IL-6 at two time points (see Table 2). Hierarchical regressions tested changes in IL-6 in 2010-11 with the following model: (1) demographics (age, gender, ethnicity, education, financial

difficulties, health, study interval), (2) baseline IL-6 2006-7, (3) depression 2006-7, (4) religious coping 2006-7, and (5) religious coping x depression. Further, a hierarchical regression tested changes in depression 2010-11 with the following model: (1) demographics (age, gender, ethnicity, education, financial difficulties, health, study interval), (2) baseline depression 2006-7, (3) IL-6 2006-7, (4) religious coping 2006-7, (5) religious coping x IL-6.

Results

Bivariate Correlations

Bivariate correlations indicate baseline age is negatively correlated with baseline negative religious coping, depressive symptoms, and health as well as, positively correlated with baseline IL-6 and IL-6 (2010-11). Baseline health was negatively correlated with baseline depressive symptoms and financial difficulties. Baseline health was not significantly correlated with baseline IL-6 and IL-6 (2010-11), this finding is unusual given the empirical support connecting IL-6 and health outcomes. Baseline depressive symptoms were positively correlated with financial difficulties, baseline negative religious coping, depressive symptoms (2010-11), IL-6 (2010-11) and negatively correlated with baseline positive religious coping. Furthermore, baseline IL-6 was positively correlated with age and IL-6 (2010-11). Depressive symptoms (2010-11) were positively correlated with baseline negative religious coping (see Table 2).

Hierarchical Linear Regression

The model predicting IL-6 (2010-11) with controls, baseline IL-6, depression,

religious coping, and depression x religious coping interactions was tested using hierarchical linear regression (see Table 3); the model accounted for 25.1% of the variance in IL-6 2010-11, $R^2 = .15$, $F(2, 270) = 5.54$, $p < .001$. The controls in step 1 of the model accounted for 14.1% of the variance above and beyond all of the other steps $F(6, 276) = 5.45$, $p < .001$. Baseline IL-6 in step 2 accounted for 11.0% of the of the variance above and beyond all of the other steps, $F(1, 275) = 13.16$, $p < .001$. Depression in step 3 accounted for 5% of the variance above and beyond all of the other steps, F (8, 269) = 6.10, $p < .001$. Positive religious coping and negative religious coping accounted for 3% of the variance above and beyond all of the other steps, F (10, 267) = 5.08, $p < .001$. The interaction of positive religious coping x depression and negative religious coping x depression accounted for 2% of the variance above and beyond all other steps, F (10, 267) = 4.90, $p < .001$. Significant predictors in the model included age, baseline depression, and the interaction of baseline positive religious coping and baseline depression.

We examined the direction of the effects of the positive religious coping moderator term with the Hayes PROCESS macro. The results indicated that using positive religious coping when depressed exacerbated IL-6 levels 3-5 years later, $F(1, 286) = 6.74$, $p < .05$ (see Figure A). Specifically, higher positive religious coping (versus low) when depressed increased IL-6. Lower levels of positive religious coping had no relationship to depression and inflammation.

The model predicting depressive symptoms at 2010-11 with controls, baseline depression, IL-6, religious coping, and IL-6 x religious coping interactions was then tested using hierarchical linear regression (see Table 4). The model accounted for 34.4%

of the variance in depressive symptoms, F (5, 282) = 10.90, $p < .001$. The controls in step 1 of the model accounted for 10.2% of the variance above and beyond all of the other steps F(6, 276) = 5.05, $p < .001$. Baseline depressive symptoms in step 2 accounted for 28.0% of the variance above and beyond all of the other steps, F (7, 272) = 14.78, $p < .001$. IL-6 in step 3 accounted for .001% of the variance above and beyond all of the other steps, F (8, 268) = 9.92, $p < .001$. Positive religious coping and negative religious coping accounted for 2% of the variance above and beyond all of the other steps, F (10, 267) = 11.87, $p < .001$. The interaction of positive religious coping x depression and negative religious coping x depression accounted for 1% of the variance above and beyond all other steps, F (12, 265) = 4.17, $p < .001$. Significant predictors in the model include baseline (2006-7) depressive symptoms, and negative religious coping. Baseline IL-6 did not predict depressive symptoms in 2010-11. Negative religious coping accounted for 3.3% of the variance above and beyond all other variables in predicting depressive symptoms three to five years later.

Discussion

Our findings suggest that, in an older religious sample, depressive symptoms have a positive association with IL-6 three to five years later even after controlling for age and health which are typically predictive of IL-6 (Alexopoulos & Marimoto, 2011; Bremmer et al., 2008; Kanikowska et al., 2014; Kiecolt-Glaser et al., 2002). Our longitudinal findings are consistent with earlier cross-sectional findings demonstrating a relationship between depression and inflammation (Copeland et al., 2011; Deverts et al., 2010; Kiecolt-Glaser et al., 2002; Pace et al., 2006). We find that depressive symptoms

predicted later IL-6 elevations, potentially making individuals with depressive symptoms more prone to inflammatory diseases (Kiecolt-Glaser et al., 2002; Pace et al., 2006). However, in our study IL-6 was not predictive of subsequent depressive symptoms; although, this pathway has received some support in the literature (Gimeno et al., 2009; Matthews et al., 2010; Valkanova et al., 2013). However, our sample included community dwelling, educated, healthy older adults with less depressive symptoms so it may underestimate the effects of depression on inflammation and vice versa. Our results add to the growing body of literature that identifies religious coping as a predictor of mental and physical health outcomes (Jeong & Nath, 2014; Koenig, 2008). Although other researchers have explored this connection, our study provides novel evidence that religious coping moderates the relationship between depression and later inflammation via IL-6 in complex ways. More specifically, higher (versus low) positive religious coping in 2006-7 and who had low levels of depression had lower levels of IL-6. Conversely, those who utilized higher levels of positive religious coping and who had higher levels of depression had higher levels of IL-6 three to five years later. This finding suggests that higher use of positive religious coping when depressed exacerbates IL-6 production possibly due to chronic emotional dysregulation or the use of positive religious coping to plead with God to provide help leading to less activation and problem solving. Negative religious coping also predicted later depressive symptoms directly though had no relationship to IL-6. It may be that a sample of highly religious older adults use both negative and positive religious coping concurrently when managing depressive symptoms. In a study looking at use of religious coping and well-being in Presbyterian clergy and elders found that positive and negative religious coping were

associated with higher and lower levels of well-being respectively; moreover, the drawbacks of negative religious coping were not offset by the benefits of positive religious coping (Pargament, Tarakeshwar, Ellison & Wulff, 2001). Consistent with this study, if this is the case in our study, then the negative religious coping may not be counteracting the potential benefits of positive religious coping.

Research supports the notion that individuals facing major depression often experience existential crises or questions related to God; often relying solely on religious coping strategies to help resolve psychological distress. Research shows that in these cases existential questions may be approached from the lens of depression versus actually utilizing a positive religious coping to resolve depressive conflict (Sorenson, 2013). It is important to consider these explanations when understanding the relationship between high positive religious coping, IL-6 elevations, and depressive symptoms within a religious sample. Furthermore, to address the time lag between time 1 and time 2 in our study, research suggests that biomarkers such as IL-6 are susceptible to rapid changes in pg/ml (i.e., due to reported short half-life, influence of other agents such as caffeine, age related changes, etc.) (Maes, 2011). However, given our findings, it may be important to consider that the use of religious coping and depressive symptoms likely do not stop during the baseline period of measurement. Coping style and poor emotional regulation may continue to influence inflammatory processes on an ongoing basis over time.

Negative Religious Coping Outcomes

Our study found that negative religious coping reported in 2006-7 significantly predicted depressive symptoms in 2010-11 which is consistent with other literature

(Fallot & Heckman, 2005; Ano & Vasconcelles, 2000; Feder, Ahmad, Lee, Morgan, Singh et al., 2013). However, negative religious coping was not predictive of IL-6; nor was IL-6 predictive or negative religious coping. This suggests that negative religious coping did not play a significant role in determining changes in inflammation other than potentially indirectly through increased depressive symptoms. Likewise, we were unable to replicate prior research findings on the moderating role of negative religious coping on baseline depressive symptoms and later IL-6 elevations (Newlink, Melkus, Tappen, Chyun & Koenig, 2008; Pargament, 2010). These results may be influenced by a number of variables including the unique sample demographics of our older, religious population that tend to be healthier, to have healthier lifestyle and therefore live longer than the general population. Given these factors, this population likely differs in their use of negative religious coping compared to other groups.

Furthermore, negative religious coping may be an extension of depression that ultimately amplifies negative physical health outcomes. Accordingly, understanding how negative religious coping is used and contributes to health may help us target interventions to educate religious older adults. This is important because other research demonstrates any amount of negative religious coping can counteract positive religious coping benefits in the highly religious (Pargament et al., 2001).

Strengths

The strengths of this study are the relatively large sample size and the use of validated measures that uniquely measure religion, mental health, and physical health. Specifically, the use of IL-6 as a stress related biomarker to investigate health outcomes

reduces self-report bias. Additionally, the longitudinal nature of our design allowed us to investigate the bidirectional relationship between depression and IL-6. Based on our findings, negative religious coping may predict later depressive symptoms. Depressive symptoms effects on IL-6 elevations are also exacerbated by positive religious coping. This finding is unique and indicates the relationships between religious coping may change when the sample is at risk or that the types of coping are not independent of one another.

Limitations

First, our findings are generalizable to religious groups who are educated and financially stable. The sample is from a single denomination of Christians who promote a healthy lifestyle as part of the religious doctrine (SDAs; Fraser, 2003) who may interpret the scale items similarly. SDAs do have lower morbidity and mortality risk than other religious groups so risk effects may be underestimated here (Chaoyang, Ford, Mokdad, Jiles, & Giles, 2007; Sukala et al., 2013). Second, IL-6 was measured only once at baseline in 2006-7 and once at follow-up in 2010-11. Optimally, biomarkers should be measured at least twice within an approximate two-week interval (Pearson et al., 2003) to address factors that diminish specificity of the cytokine and due to the reportedly short half-life of IL-6, making it's detection more difficult (Maes, 2011).

Summary and Future Directions

Our hypothesis was partially supported by negative religious coping predicting later depressive symptoms, however, negative religious coping was not directly related to

IL-6. By studying the longitudinal bidirectional relationship between depressive symptoms and IL-6, we found that depressive symptoms do predict later IL-6. However, our results showed further that high positive religious coping when depressed exacerbated IL-6 levels years later. There was no relationship moderation of depression and IL-6 in those using low levels of positive religious coping. More longitudinal research is needed to better understand the causal factors embedded within the depression-cytokine relationship.

In order to better observe the bidirectional relationship between depressive symptoms and IL-6, future studies should measure participants more frequently across the study interval. It would also be beneficial to look further at the roles of both positive and negative religious coping as influences on the depression- inflammation relationship. Positive religious coping may be an attempt at combatting depression and used more frequently in such cases thereby becoming an extension of the depressive symptoms in a religious sample. Furthermore, future studies should utilize more structured methods of measuring depression (e.g., Structured Clinical Interview for DSM disorders: SCID) as research demonstrates higher reliability for structured methods versus screening measurements. Finally, to increase generalizability, it would be helpful to collect data on younger SDAs and monitor changes in emotional health and IL-6 across time.

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APPENDIX A

TABLES

Table 1. *Sample Demographics*

	N	*%*	*Mean*	*SD*
Age	287		67.68	11.20
Sex				
Female	173	40%		
Male	114	60%		
Ethnicity				
White	190	66%		
Black	96	34 %		
Financial Difficulties (last yr)				
Not at all	242	84%		
A little	26	9.0%		
Somewhat	7	2.4%		
Fairly	5	1.7%		
Very	7	2.4%		
Education (years completed)				
Some High School	3	1.0%		
High School Diploma	8	2.8%		
Trade School Diploma	2	0.7%		
Some College	46	16%		
Associate Degree	32	11%		
Bachelor's Degree	69	24%		
Master's Degree	66	23%		
Doctoral Degree	62	22%		
General Health				
Poor	2	0.7%		
Fair	27	9.4%		
Good	89	31%		
Very Good	115	40%		
Excellent	53	19%		

Table 2. *Intercorrelations, Means, and Standard Deviations for Variables of Interest*

Variable	1	2	3	4	5	6	7	8	9	M	SD
1.Depression (2006-7)	–									2.9	3.2
2. Depression (2010-11)	.55*	_								2.9	3.0
3. Positive RCOPE	-.19**	-.09	–							4.1	0.8
4. Negative RCOPE	.28**	.24**	-.39**	–						1.4	0.4
5. IL-6 (2006-7)	.03	.03	.04	-.04	_					0.5	0.4
6. IL-6 (2010-11)	.12*	.02	.04	-.01	.24**	–				0.3	0.3
7. Financial Difficulties	.18**	.04	.05	.08	-.02	.04	–			1.3	0.8
8. Age	-.06	.04	.05	.31**	.15*	.30**	-.05	–		67.0	11.0
9. Health	-.35**	.26	.05	.05	.14	.03	-.14*	-.09*	–	3.9	0.9

Table 3. *Hierarchical Regression Predicting IL-6 in 2010-11 from Baseline Depression, Positive Coping, Negative Coping and Interactions.*

	Adj. R^2	ΔR^2	b	SE	β	t	*p*	95% CI
Step 1	0.13	0.14						
Gender			0.01	0.04	0.02	0.34	0.74	[-.07, .09]
Ethnicity**			-0.03	0.04	-0.05	-0.77	0.44	[-.11, .05]
Education			0	0.01	-0.01	-0.2	0.84	[-.03, .02]
Age			0.01	0	0.29	4.82	.00*	[.01, .01]
Financial Difficulties			0.01	0.02	0.02	0.33	0.74	[-.04, .06]
General Health			0.01	0.03	0.21	1.12	0.31	[-.02, .01]
Study interval			-0.01	0.01	0.02	-0.68	0.5	[-.03, .02]
Step 2								
IL-6 2006-7	0.10	0.11	0	0	0.06	1.6	0.25	[-.01, .03]
Step 3	0.13	0.05						
Depression			0.02	0.01	0.17	2.7	.03*	[.01, .03]
Step 4	0.15	0.03						
Positive RCOPE			0.03	0.03	0.09	1.36	0.17	[-.02, .08]
Negative RCOPE			0.03	0.05	0.04	0.59	0.55	[-.07, .13]
Step 5	0.14	0.02						
Depression x Positive Religious Coping			-0.02	0.01	-0.04	4.02	.05*	[.00, .03]

Depression x Negative Religious Coping	0.01	0.13	0.08	.62	0.53	[-.02, .04]

Table 4. *Hierarchical Regression Predicting Depressive Symptoms in 2010-11 from Baseline IL-6, Positive Coping, Negative Coping and Interactions.*

	Adj. R^2	ΔR^2	b	SE	β	t	*p*	95% CI
Step 1	0.21	0.1						
Gender			-0.28	0.35	-0.05	-0.79	0.43	[-.97, .41]
Ethnicity**			-0.31	0.36	-0.05	-0.85	0.4	[-1.0, .41]
Education			0.11	0.11	0.6	1	0.32	[-.11, .33]
Age			0.02	0.02	0.06	1.02	0.31	[-.01, .05]
Financial Difficulties			0.01	0.02	0.02	0.33	0.74	[-.04, .06]
General Health			0.21	0.2	0.06	1.07	0.28	[-.18, .60]
Survey interval			-0.01	0.03	0.02	0.23	0.82	[-.03, .02]
Step 2								
Depressive Symptoms (2006-7)	0.27	0.28	0.48	0.05	0.52	9.07	.00*	[-.39, .59]
Step 3	0.28	0						
IL-6			-0.02	0.38	0	-0.04	0.97	[-.77, .74]
Step 4	0.29	0.02						
Positive RCOPE			-0.38	0.23	-0.11	-1.66	0.1	[-.83, .07]
Negative RCOPE			-1.09	0.44	-0.15	-2.48	.01*	[-1.9, .22]
Step 5	0.3	0.01						
IL-6 x PosRCOPE			1.08	1.11	-0.06	0.97	0.33	[-1.4, 3.0]
IL-6 x NegRCOPE			0.97	0.54	0.11	1.79	0.08	[.10,2.03]

Note. * $p < .05$, two-tailed. **Reference group Whites

APPENDIX B

FIGURES

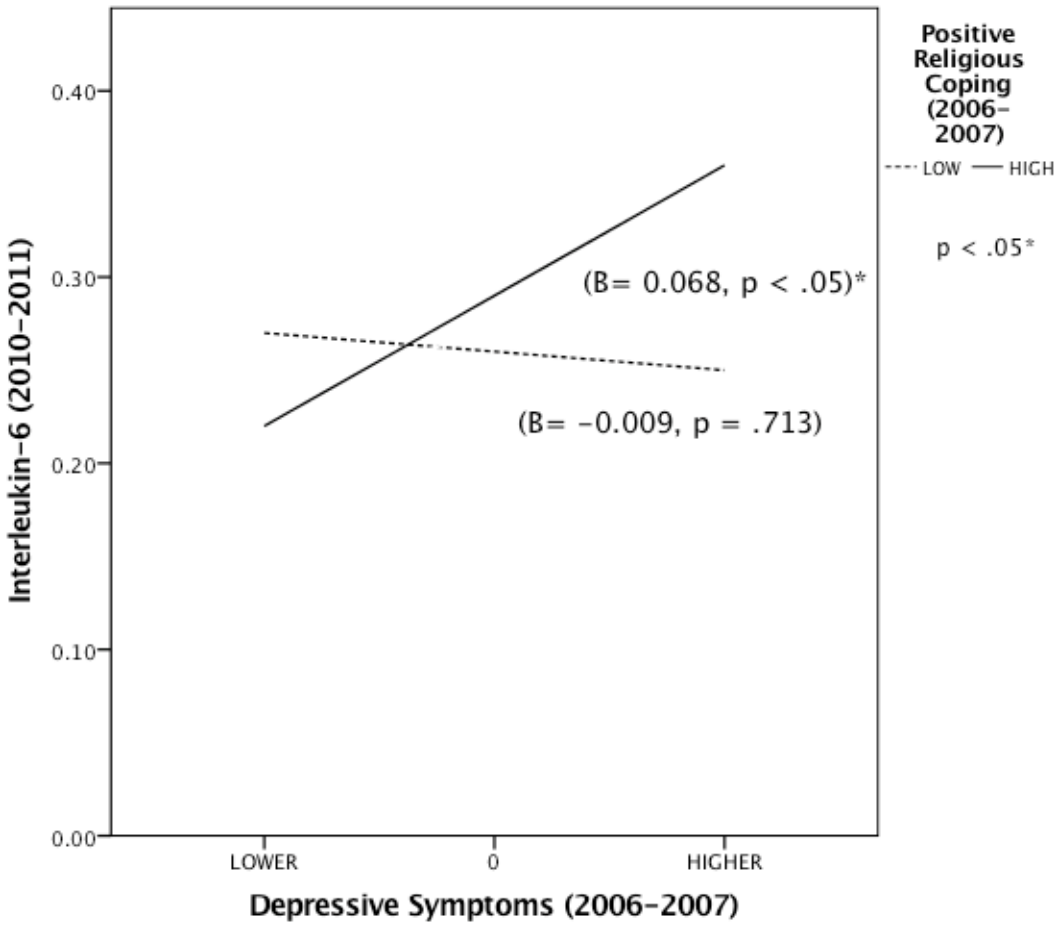

Figure A. Interaction between Low and High Positive Religious Coping and Depression on IL-6.

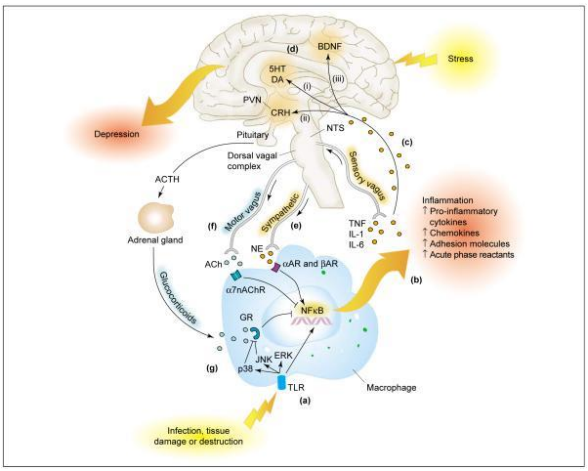

Figure 1. Stress-immune interactions and depression. Reprinted from "Cytokines sing the blues: inflammation and the pathogenesis of depression," by C. Raison, L. Capuron, & A. Miller, 2006, *Trends in Immunology, 27*, p. 29. Copyright 2005 by Elsevier. Reprinted with permission.

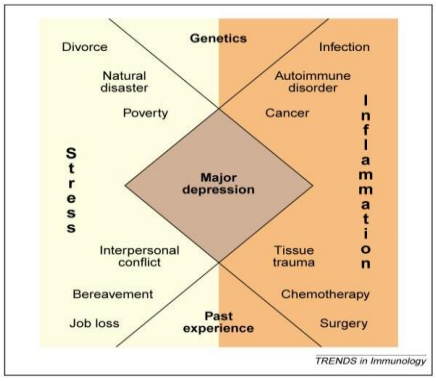

Figure 2. Acute and chronic immune and inflammatory processes, combined with relevant contributions from immunogenetics and past immune experiences (orange) interact with acute and chronic stressors combined with relevant contributions from psychiatric genetics and past emotional experiences (yellow) to promote the syndrome of major depression (brown). Reprinted from "Cytokines sing the blues: inflammation and the pathogenesis of depression," by C. Raison, L. Capuron, & A. Miller, 2006, *Trends in Immunology, 27*, p. 31. Copyright 2005 by Elsevier. Reprinted with permission.

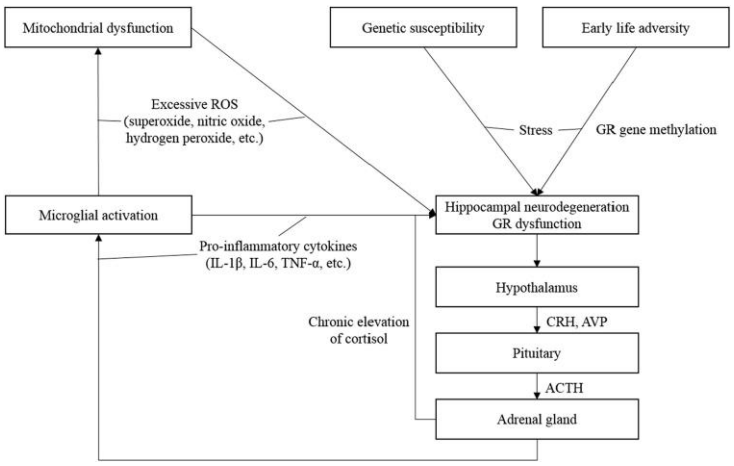

Figure 3. Schematic Representation of Relationships Among Neuroinflammation, Neurogenesis, and Neuroendocrine Systems. Reprinted from "The role of pro-inflammatory cytokines in neuroinflammation, neurogenesis and the neuroendocrine system in major depression," by Y. K. Kim, K. S. Na, A. M. Myint, and B. E. Leonard, 2016, *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *64*, p. 282 Copyright 2015 by Elsevier. Reprinted with permission.

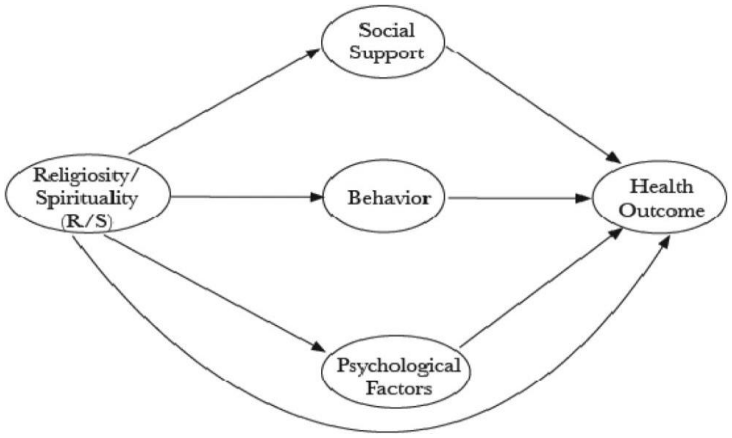

Figure 4. Mechanisms in the Relation between Religion and Health with Emphasis on Cardiovascular Reactivity to Stress. Reprinted from "Religion, spirituality, and health," by K. Masters and S. Hooker, 2013, *Handbook of the Psychology of Religion and Spirituality*, p. 538. Copyright 2013 by the Guilford Press. Reprinted with permission.

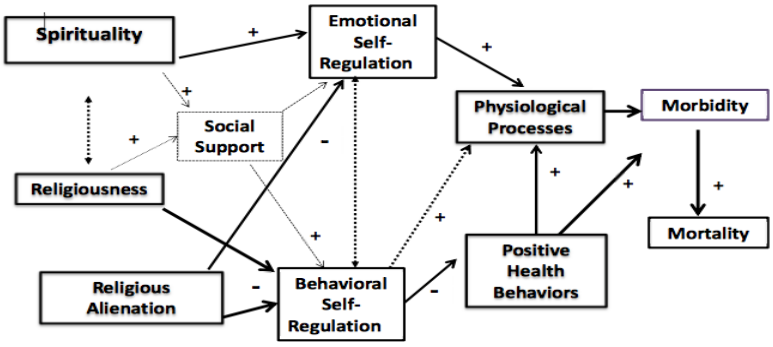

Figure 5. Proposed Model of the Differential Impact of Religiousness and Spirituality on Pathways to Morbidity & Mortality.

Figure 5. Proposed Model of the Differential Impact of Religiousness and Spirituality on Pathways to Morbidity and Mortality. Reprinted from "Differing pathways between religiousness, spirituality, and health: A self-regulation perspective," by K. M. Aldwin, C. L. Park, Y. J. Jeong, and R. Nath, 2014, *Psychology of Religion and Spirituality, 6*, p. 21. Copyright 2013 by the American Psychological Association. Reprinted with permission.

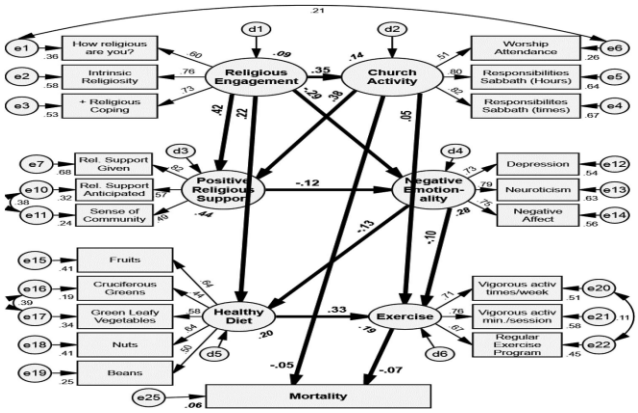

Figure 6. Final path model for Religion and Health: Mediation by Psychosocial and Lifestyle Mechanisms. Reprinted from "Pathways from Religion to Health: A mediation by Psychosocial and Lifestyle Mechanisms" (in press) by K. Morton, J. Lee, and L. Martin, 2016), *Psychology of Religion and Spirituality*, p 8. (in press). Copyright 2016 by the American Psychological Association. Reprinted with permission.

APPENDIX C

RELIGIOUS COPING

Positive Religious Coping

Benevolent God Reappraisal

1. Saw my situation as a part of God's plan
2. Tried to find a lesson from God in the event
3. Tried to see how God might be trying to strength me in this situation

Collaborative Religious Coping

1. Worked together with God as partners
2. Tried to make sense of the situation with God
3. Tried to put my plans into action together with God

Spiritual Connection

1. I thought about how my life is a larger spiritual force

Negative Religious coping

Punishing God Reappraisal

1. Felt punished by God for my lack of devotion
2. Decided that God was punishing me for my sins
3. Wondered what I did for God to punish me

Passive Deferral Coping

1. Didn't do much, just expected God to solve my problems for me
2. Didn't try much of anything; simply expected God to take control
3. Didn't try to cope; only expected God to take my worries away

Anger at God

1. Expressed anger at God for allowing the event to happen

APPENDIX D

CENTER FOR EPIDEMIOLOGICAL STUDIES DEPRESSION (CES-D)

SCALE 11-ITEM SHORT FORM

1. I did not feel like eating; my appetite was poor
2. I felt depressed
3. I felt that everything I did was an effort
4. My sleep was restless
5. I was happy
6. I felt lonely
7. People were unfriendly
8. I enjoyed life
9. I felt sad
10. I felt that people disliked me
11. I could not get “going”