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2014

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UNIVERSITY OF CALIFORNIA, SAN DIEGO

SAN DIEGO STATE UNIVERSITY

Longitudinal Examination of Mood Disturbance, Inflammation and Acute Illness Outcomes
in Spousal Alzheimer's Disease Caregivers

A dissertation submitted in partial satisfaction of the
requirements for the Degree of Doctor of Philosophy

in

Clinical Psychology

by

Elizabeth Anne Chattillion

Committee in charge:

University of California, San Diego

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Professor Igor Grant
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San Diego State University

Professor Linda C. Gallo
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2014

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2014

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ACKNOWLEDGEMENTS

The present study was supported by award AG15301 (Igor Grant, M.D., Principal Investigator) from the National Institutes of Health, National Institute of Aging. I would like to express my gratitude to Professor Brent Mausbach for his guidance and support as the Chair of my committee.

Chapters 1-4, in part, are currently being prepared for submission for publication of the material. Chattillion, Elizabeth; Grant, Igor; Gallo, Linda C.; Mills, Paul J.; Roesch, Scott C.; Mausbach, Brent T. Elizabeth Chattillion was the primary investigator and author of this material.

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ABSTRACT OF THE DISSERTATION

Longitudinal Examination of Mood Disturbance, Inflammation and Acute Illness Outcomes
in Spousal Alzheimer's Disease Caregivers

by

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Doctor of Philosophy in Clinical Psychology

University of California, San Diego, 2014

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Over 15 million Americans provide unpaid care for a family member with Alzheimer's disease. Dementia caregiving can have detrimental effects on caregivers' physical health, including increased risk for cardiovascular disease (CVD) and mortality. Inflammation, evidenced by elevated plasma interleukin-6 (IL-6) and C-reactive protein (CRP), may play a fundamental role in the initiation and progression of CVD. Dementia caregivers may also be at increased risk for acute illness or infection, such as cold or flu. Evidence suggests that caregivers with mood disturbance may be particularly vulnerable to these health outcomes. Existing research indicates that depression is linked with both elevated inflammation and increased CVD risk, and may also be associated with immune dysfunction and susceptibility to acute illness. Caregivers experience greater mood disturbance compared with noncaregivers, but investigation of the relationship between mood disturbance and health outcomes in caregivers has been minimal and largely cross-sectional. The present study addresses gaps in the current literature by using mixed models regression to investigate associations between

mood disturbance [i.e., depressive symptoms, positive affect (PA), and negative affect (NA)] and caregiver health (i.e., inflammation and symptoms of acute illness) over time. Spousal caregivers (N=116) completed annual in-home assessments for up to five years, including a semi-structured psychosocial interview and blood draw. Caregivers were primarily female (69.0%) and Caucasian (87.9%) with a mean age of 74.6 years (SD=7.8). Multilevel analyses revealed that caregivers with higher average levels of NA over the course of the study had higher levels of IL-6 and CRP. No other mood predictors were significantly related to inflammation, including within-caregiver yearly fluctuations in mood. With regard to acute illness symptoms, caregivers with higher average levels of depressive symptoms and NA throughout the study were significantly more likely to report flu symptoms. Yearly fluctuations in depressive symptoms within caregivers were also associated with higher likelihood of experiencing flu symptoms. This study provides preliminary evidence that mood disturbance, particularly increased NA, is associated with inflammation and acute illness symptoms in dementia caregivers. Chronic mood disturbance appeared to have a stronger association with caregiver health, highlighting the need for timely intervention to treat caregiver mood disturbance.

INTRODUCTION

Alzheimer's Disease Caregiving and Health

An estimated 35.6 million people suffer from Alzheimer's disease (AD) worldwide, and this number is expected to double every 20 years (World Alzheimer Report, 2009). In the United States, one in eight adults over the age of 65 has Alzheimer's disease (AD) (Alzheimer's Association, 2012). The number of Americans with AD is expected to increase by 30% by 2025, and may triple by 2050. AD is the sixth leading cause of death in the United States and the number of deaths resulting from AD rose by 66% from 2000 to 2008. However, it is not only those with AD who are impacted by the disease. Over 15 million Americans provide unpaid care for persons suffering from AD or other dementias (Alzheimer's Association, 2012). These informal caregivers, primarily family members, represent a vital national health care resource: in 2011 informal caregivers provided over 17 billion hours of unpaid care, valued at over \$210 billion. Family caregivers provide over 80% of in-home care to patients with AD (Alzheimer's Association, 2012). As the number of persons with AD grows, so will the number of unpaid family caregivers.

The negative impact of AD extends beyond the affected patient, as caregiving can take a toll on one's physical health, increasing caregivers' risk for physical morbidity (Vitaliano, Zhang, & Scanlan, 2003), and all-cause mortality (Schulz & Beach, 1999) compared with noncaregiving adults. One study found that caregivers whose spouse was hospitalized and had AD were more likely to die in the following year than caregivers of spouses who were hospitalized but did not have dementia (Christakis & Allison, 2006). Caregivers have been shown to have poor health compared with noncaregivers in a variety of domains, including slowed wound healing (Kiecolt-Glaser, Marucha, Malarkey, Mercado, & Glaser, 1995), altered

immune functioning (Esterling, Kiecolt-Glaser, & Glaser, 1996; Kiecolt-Glaser et al., 1987; Mills et al., 2004; Mills et al., 1997; Mills, Yu, Ziegler, Patterson, & Grant, 1999), and poorer response to vaccination (Glaser, Sheridan, Malarkey, MacCallum, & Kiecolt-Glaser, 2000; Kiecolt-Glaser, Glaser, Gravenstein, Malarkey, & Sheridan, 1996; Vedhara et al., 1999). Caregivers also show signs of metabolic dysregulation (i.e., increased fasting insulin levels) compared to non-caregivers (Vitaliano, Scanlan, Krenz, Schwartz, & Marcovina, 1996). Caregivers exhibit worse self-reported health, worse general health, report more illness symptoms, and have increased health care utilization compared with noncaregivers (Vitaliano, Zhang, & Scanlan, 2003). AD and dementia caregivers have higher health care costs than noncaregivers, a difference totaling \$8.7 billion in 2011 (Alzheimer's Association, 2012).

Alzheimer's Disease Caregiving and Cardiovascular Disease Risk

Recently, a growing body of research has focused on impairments in caregivers' cardiovascular health relative to noncaregivers (Lee, Colditz, Berkman, & Kawachi, 2003; Mausbach, Patterson, Rabinowitz, Grant & Schulz, 2007; Schulz et al., 1995; Vitaliano et al., 2002; von Känel et al., 2008). Cardiovascular disease (CVD) is the leading cause of death worldwide, with an estimated 17.3 million deaths from CVD occurring globally in 2008 (World Health Organization [WHO], 2011). CVD refers to a group of disorders of the heart and blood vessels, including coronary heart disease (CHD) and cerebrovascular disease, which can cause conditions such as heart failure and acute events such as myocardial infarction or stroke (WHO, 2011). In the United States in 2007, CVD caused approximately one out of every three deaths, with CHD accounting for one out of every six deaths, stroke accounting for one out of every eighteen deaths, and heart failure mentioned in one out of every nine death certificates (Roger et al., 2011). Recent evidence suggests that dementia caregivers may be at

even greater risk for CVD than their noncaregiving peers. Specifically, spousal dementia caregivers show elevated Framingham CHD risk scores compared to non-caregivers (von Känel et al., 2008) and may have higher incidence of CHD (Vitaliano et al., 2002). Lee and colleagues (2003) found in a four-year prospective study that caregivers providing nine or more hours of care per week to a spouse with dementia had an almost two-fold increase in their risk of developing CHD, even after controlling for various CHD risk factors. Dementia caregivers also have an increased risk compared with non-caregivers for developing hypertension (Grant et al., 2002; Roepke et al., 2011; Shaw et al., 1999), and caregivers display impaired endothelial functioning (Mausbach et al., 2010), both of which may be associated with increased risk of CVD (McEwen & Stellar, 2003).

The Role of Inflammation in Caregiver CVD Risk

Inflammation and CVD

Cardiovascular disease (CVD) is primarily a result of atherosclerosis, a progressive disease in which lipids and fibrous elements accumulate in large arteries (Libby, 2002). Previous models of atherosclerosis characterized the disease as primarily a lipid storage disease, involving the collection of cholesterol in the arteries and the proliferation of smooth muscle cells (Libby, Ridker, Hansson, The Leducq Transatlantic Network on Atherothrombosis, 2009). More recently, however, a substantial body of research has demonstrated that inflammation plays a fundamental role in the initiation and progression of atherosclerotic CVD (Hansson, 2005; Libby, 2002; Libby et al., 2009). Immune and inflammatory mechanisms interact with metabolic risk factors to develop and activate atherosclerotic lesions (i.e., atheromata). Immune cells, such as macrophages and T cells, are involved in the development of fatty streaks, which are accumulations of lipid-laden cells

under the endothelium. Fatty streaks are common in younger people, and may disappear, or can progress into atheromata, of which blood-borne inflammatory and immune cells form an important component (Hansson, 2005). These atheromata (i.e., atherosclerotic lesions) may progress into unstable plaques, which, when activated or ruptured can cause ischemia and myocardial infarction. Myocardial infarction is suspected to result not from stenosis of the artery but from activation of plaques, which often results from the formation of an occluding thrombus on the plaque's surface.

Various immune cells (e.g., macrophages activated within coronary plaques) and inflammatory molecules (e.g., Th1 cytokines produced by activated T cells) are intimately involved in destabilizing plaques, and promoting prothrombotic and procoagulant processes that cause thrombus formation (Hansson, 2005). The activation of immune cells within a plaque triggers a powerful inflammatory cascade, both within the atherosclerotic lesion and systemically. Activated immune cells produce inflammatory cytokines such as interferon-gamma, interleukin-1 (IL-1), and tumor necrosis factor (TNF), which elicit the production of large amounts of interleukin-6 (IL-6). IL-6 then induces the production of acute-phase reactants, such as C-reactive protein (CRP) (Hansson, 2005). Importantly, with each step of this cytokine cascade, the amount of cytokines produced is amplified, therefore, elevated levels of downstream mediators such as IL-6 and CRP may be more easily detected in peripheral circulation, making these markers more useful for clinical assessment of CVD risk (Hansson, 2005). For this reason, IL-6 and CRP are often used as biomarkers of inflammation used for evaluating risk for CVD. CRP in particular has recently emerged as the leading inflammatory biomarker of CVD risk used for clinical application (Libby et al., 2009).

Indeed, increased systemic levels of IL-6 and CRP have been associated with cardiovascular morbidity and mortality. IL-6 and CRP levels are elevated in patients with

unstable angina and myocardial infarction, with higher levels predicting worse prognosis (Biasucci et al., 1996; Lindahl, Toss, Siegbahn, Venge, & Wallentin, 2000). Increased plasma IL-6 is also associated with increased risk of future myocardial infarction in healthy men, after controlling for CVD risk factors (Ridker, Rifai, Stampfer, & Hennekens, 2000), and increasing concentrations of IL-6 have been associated with greater risk of nonfatal myocardial infarction and fatal CHD in longitudinal studies of population-based cohorts (Danesh et al., 2008). Long-term prospective cohort studies suggest that CRP levels, measured by a highly sensitive assay, predict incident myocardial infarction, CHD, stroke, and vascular mortality, even after adjusting for conventional risk factors (e.g., Framingham Risk Score predictors) (The Emerging Risk Factors Collaboration, 2010; Ridker, 2007). However, it remains unclear whether CRP and IL-6 are causally linked to CVD (Danesh & Pepys, 2009; Rattazzi et al., 2003; Ridker, 2007). Whether CRP and IL-6 are merely markers reflecting local inflammation in arteries, and thus indicate the clinical course of acute coronary syndromes, or whether these markers play a causal role in the atherothrombotic process (e.g., via effects on endothelial and smooth muscle cells) remains a matter of debate and warrants future investigation. However, substantial evidence indicates that IL-6 and CRP reflect inflammation that is relevant to increased CVD risk.

Inflammation in Dementia Caregivers

Given the evidence that dementia caregivers are at increased risk for CVD and related conditions, caregivers might also be expected to display increased levels of inflammatory markers such as IL-6 and CRP. Indeed, accumulating evidence demonstrates that caregivers have higher levels of IL-6 compared with non-caregiving controls (Mills et al., 2009; Lutgendorf et al., 1999; von Känel, Dimsdale, Ancoli-Israel et al., 2006; von Känel, Dimsdale,

Mills et al., 2006). Although aging has been associated with increases in IL-6 production (Ershler, 1993), the aforementioned research demonstrates that caregivers display elevated IL-6 even compared with non-caregiving adults of similar age. Furthermore, in a six-year longitudinal study, family dementia caregivers' rate of increase in IL-6 over time was on average four times higher than that of noncaregivers (Kiecolt-Glaser et al., 2003). The evidence to date regarding dementia caregiver elevations in CRP is more mixed. Although one study found no differences between spousal dementia caregivers and non-caregiving controls with respect to plasma CRP levels (von Känel et al., 2012), among caregivers, longer duration of providing care was associated with increased CRP. Another study did find elevated CRP in caregivers as compared to noncaregivers (Gouin, Glaser, Malarkey, Beversdorf, & Kiecolt-Glaser, 2012). Other evidence suggests that caregivers show a stronger correlation between decreased sleep and increased circulating CRP, as well as IL-6, compared with non-caregiving controls (von Känel et al., 2010). Caregivers' increased systemic inflammation, as indicated by IL-6 and CRP levels, may serve as an indicator of increased CVD risk before the occurrence of cardiovascular events, therefore, factors associated with increased levels of these biomarkers in caregivers warrant further investigation.

Alzheimer's Disease Caregiving and Risk of Acute Illness

Not only are caregivers at increased risk of chronic health consequences such as CVD and hypertension, dementia caregivers may also be at increased risk for more acute illness or infection, such as cold or flu. Indeed, previous research shows that caregivers report poorer overall health than noncaregivers (Legg, Weir, Langhorne, Smith, & Stott, 2013) as well as more symptoms of physical illness (Vitaliano, Zhang, & Scanlan, 2003). Dementia caregivers' increased risk of CVD and related conditions is important given the chronic, serious nature of

these diseases and their impact on mortality; however, caregivers' experience of acute infectious illness (e.g., cold, flu) also represents an important, though less thoroughly studied health outcome. The presence of acute illness has societal and public health implications, as well as consequences for individual caregivers and care recipients. First, acute illnesses such as cold or flu have a substantial public health impact and monetary cost to society. For example, research estimates that in the United States, annual influenza epidemics result in an average of over 600,000 life-years lost, 3.1 million hospitalized days, and 34.1 million outpatient medical visits, with associated direct medical costs totaling \$10.4 billion annually (Molinari et al., 2007). Additionally, indirect costs associated with projected earnings loss due to influenza illness and loss of life are estimated at \$16.3 billion annually. The common cold is estimated to result in 75-100 million physician visits each year in the United States for an estimated cost of \$7.7 billion. The total estimated direct medical cost of the common cold is \$17 billion, including \$4.8 billion spent treating complications and over \$1.1 billion spent on unnecessary antibiotic prescriptions, which has implications for antibiotic resistance (Fendrick, Monto, Nightengale, & Sarnes, 2003). Estimated indirect costs of lost productivity due to the common cold and allergic rhinitis due to absenteeism and reduced at-work productivity range from \$25 million (Bramley, Lerner, & Sames, 2002) to \$601 million (Crystal-Peters, Crown, Goetzel, & Schutt, 2000). Not only are these illnesses expensive, they can also result in hospitalization and even death due to complications, both of which are more likely among adults over age 65 (Thompson, Comanor, & Shay, 2006; Castle, 2000).

Second, just as acute illness results in decreased productivity in the workplace for working adults, acute illness can impair the productivity of family dementia caregivers in providing care to their loved one. Spousal dementia caregivers provide an important societal resource by providing free care that would otherwise burden the healthcare system

(Alzheimer's Association, 2012), however, if a caregiver is acutely ill, the quality of the care provided to the care recipient will likely be decreased. Depending on the caregiver's level of illness, it may be necessary to obtain outside care for the care recipient while the caregiver recovers. Increased frequency and duration of illness episodes can interfere not only with the quality of life of the caregiver, but also the quality of care provided to the patient with dementia.

Caregivers may be at greater risk for acute illness or infection due to immune downregulation or dysregulation. The human immune system is generally divided into two arms: innate and adaptive (alternatively, natural and specific). Innate (natural) immunity refers to the more "primitive" and earlier-evolved system, which mounts a rapid, all-purpose response to perceived foreign invaders. This innate immune response is nonspecific, responding not to any particular pathogen and recognizing only a limited number of foreign structures (Libby, Ridker, & Hansson, 2009; Segerstrom & Miller, 2004). Cellular participants in innate immunity include mononuclear phagocytes, macrophages, and neutrophils, which engulf their targets, and natural killer (NK) cells which lyse their targets (Libby, Ridker, & Hansson, 2009; Miller, 1998; Segerstrom & Miller, 2004). The adaptive (specific) immune system is more recently evolved and mounts a slower but more specific response, recognizing millions of specific structures on invading pathogens. Cells involved in adaptive immunity include T lymphocytes (T cells; including T-helper and T-cytotoxic cells) and B lymphocytes (B cells), which are programmed to respond to specific antigens via receptor sites on their cell surfaces (Libby, Ridker, & Hansson, 2009; Segerstrom & Miller, 2004). This specific adaptive response requires "education" of the immune system and proliferation of these antigen-specific cells, therefore it can take weeks or months to mount an immune response. Adaptive (specific) immunity has a cellular response (mounted against intracellular pathogens) and a humoral

response (mounted against extra cellular pathogens) (Segerstrom & Miller, 2004).

Previous research suggests that caregivers experience alterations and impairments in both innate and adaptive immune functioning relative to noncaregivers. For example, compared to noncaregivers, caregivers display reduced NK cell cytotoxicity to cytokine stimulation (Esterling, Kiecolt-Glaser, & Glaser, 1996), alterations in sensitivity and density of lymphocyte β 2-adrenergic receptors (Mills et al., 2004; Mills et al., 1997), deficits in circulating CD62L- T lymphocytes (Mills, et al., 1999), reduced levels of T lymphocytes and helper T lymphocytes (Kiecolt-Glaser et al., 1987), diminished antibody response to influenza virus vaccination (Kiecolt-Glaser et al., 1996; Vedhara et al., 1999), and deficits in antibody response to pneumococcal bacterial vaccine (Glaser et al., 2000). Importantly, although dysregulation in both innate and adaptive immunity occurs with aging (Agarwal & Busse, 2010; Castle, 2000; Gouin, Hantsoo, & Kiecolt-Glaser, 2008), the aforementioned studies all found that dementia caregivers evidenced immune dysregulation relative to age-matched comparison groups.

This dysregulation in immune functioning in caregivers may be expected to result in increased susceptibility to influenza virus and other infections, compared with age-matched peers (Burns & Goodwin, 1997; Kiecolt-Glaser & Glaser, 2002). Indeed, adults who show poorer responses to vaccines also experience higher rates of clinical illness and longer-lasting illness (Kiecolt-Glaser & Glaser, 2002). Therefore, caregivers are likely to experience increased rates of infection and symptoms of acute illness. Pinquart and Sorensen (2003) found in their aforementioned meta-analysis that dementia caregivers had poorer health (as measured by symptom checklists and/or a single-item subjective health rating) than noncaregivers across 34 studies. For example, Kiecolt-Glaser and colleagues (1991) found that caregivers reported more days of infectious illness, including upper respiratory tract infections, than noncaregivers.

The Role of Depression in Caregiver Health

Depression, Inflammation and CVD Risk

Evidence suggests that caregivers have increased risk for CVD and mortality (e.g., Lee et al., 2003; Schulz et al., 1995) and may also have increased inflammation (e.g., elevated IL-6 and CRP), considered a marker of CVD risk (Hansson, 2005; Libby, 2009). A number of behavioral and physiologic factors (e.g., physical inactivity, smoking, diabetes, obesity, high blood pressure) may increase risk for CVD (Roger et al., 2011; U.S. Department of Health and Human Services [USDHHS], 2006; WHO, 2011). However, there has been a great deal of recent research investigating psychosocial factors that might contribute to CVD risk (e.g., Das & O'Keefe, 2008; von Känel, 2012). The worldwide INTERHEART case-control study evaluated traditional CHD risk factors and psychosocial stressors in over 12,000 MI patients and over 14,000 age and gender matched controls across 52 countries, finding that almost one third of the attributable risk of MI was due to psychosocial factors including depression, work or family stress, financial stress, major life events, and lack of perceived control over life (Yusuf et al., 2004). A great deal of prospective evidence also demonstrates that psychosocial factors may contribute to the incidence and progression of CVD (Rozanski et al., 2005).

One of the most extensively studied psychosocial factors in predicting CVD risk is depression. Depression is often diagnosed using clinical or structured interviews based on criteria detailed in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (American Psychiatric Association, 2000). For an individual to meet criteria for a major depressive episode (often referred to as clinical depression), the individual must endorse five or more symptoms of depression that are present for most of the day, almost every day, for a period of two weeks or longer. One of these symptoms must be either depressed mood or diminished interest or pleasure in all or most activities. Other symptoms of depression include

fatigue, feelings of worthlessness or guilt, hopelessness, changes in sleep or appetite, fatigue or loss of energy, difficulty concentrating or making decisions, and recurrent thoughts of death. Importantly, patients can experience clinically meaningful symptoms of depression that cause distress or interfere with functioning even if patients do not meet criteria for a diagnosis of a major depressive episode (Judd et al., 2000). Research to date regarding depression as a psychosocial factor impacting CV health has examined “depression” in terms of both depression diagnosis as well as clinically significant depressive symptoms that are below the diagnostic threshold for major depressive episode or major depressive disorder.

Depression is a significant problem in many patients with CVD (Rutledge, Reis, Linke, Greenberg, & Mills, 2006; Thombs et al., 2006). Not only is depression more prevalent in those with CVD, substantial evidence suggests that the presence of depression or depressive symptoms may play a role in the development and progression of CVD. Meta-analytic results demonstrate that depression predicts the development of CHD in healthy subjects (Rugulies, 2002) and depressive symptoms are associated with cardiac events and mortality among patients with various types of CVD (e.g., heart failure, coronary heart disease, recent myocardial infarction) (Barth, Schumacher, & Herrmann-Lingen, 2004; Nicholson, Kuper, & Hemingway, 2006; Rutledge et al., 2006; van Melle et al., 2006). Depression is also associated with increased risk of all-cause mortality in older adults (Penninx et al., 1999; Schulz et al., 2000).

As might be expected, increased levels of the inflammatory biomarkers IL-6 and CRP, which may be upstream indicators of CVD risk, have also been associated with depression. In a recent meta-analysis, Howren and colleagues (2009) found that across 51 studies, CRP was positively associated with depression, with an overall small but significant effect size (standardized mean difference, $d = 0.22$). The meta-analysis found that across 62 studies, IL-6

was also positively associated with depression, with an aggregated small but significant effect size (standardized mean difference, $d = 0.25$). The association between increased depression and both elevated CRP and IL-6 was stronger in clinically depressed samples, but was still significant in samples with subthreshold depressive symptoms. The relationship between CRP and depression across studies was not affected by age, but the relationship between IL-6 and depression became smaller as the mean age of the sample increased.

Additional cross-sectional evidence since the time of that meta-analysis has corroborated the associations between depression and IL-6 and CRP in healthy adults (Baune et al., 2012; Elovainio et al., 2009; Kobrosly & van Wijngaarden, 2010; Ma et al., 2010; Uddin et al., 2011), and adults with cardiovascular morbidity (Bankier, Barajas, Martinez-Rumayor, & Januzzi, 2009; Frasure-Smith, Lesperance, Irwin, Talajic, & Pollock, 2009; Johansson et al., 2011). Furthermore, in a six-year prospective cohort study of healthy adults, self-reported depressive symptoms predicted change in IL-6, though not CRP, over the six-year study (Stewart, Rand, Muldoon, & Kamarck, 2009). IL-6 did not predict six-year change in depressive symptoms, suggesting that depressive symptoms may precede and augment inflammatory processes relevant to coronary artery disease in healthy, older adults. In a large prospective study of adults over 65 years of age, greater self-reported depressive symptoms were also associated with increased IL-6 over a six-year period, but not with CRP (Milaneschi et al., 2011). Greater depressive symptoms were associated with a steeper increase in IL-6 over time. Increased depressive symptoms have also been associated with increased IL-6 production in response to an acute laboratory stressor, and these elevations in IL-6 persisted among depressed individuals for several hours after stressor, compared with less depressed individuals (Fagundes, Glaser, Hwang, Malarkey, & Kiecolt-Glaser, 2013).

Depression in Caregivers

Accumulating evidence suggests that caregivers are more likely to be depressed than their noncaregiving peers. In a meta-analysis of 81 studies assessing depression in caregivers and noncaregivers, Pinquart and Sorensen (2003) found that older adult caregivers were more likely to have depression (both self-rated and clinician-rated) than noncaregivers, with a medium effect size across all studies. Furthermore, differences in depression between caregivers and noncaregivers were significantly larger in the 60 studies that examined only dementia caregivers, compared with older adults caring for a loved one with other physical or mental health problems. More recent evidence has confirmed that dementia caregivers report more depressive symptoms than noncaregiving adults (e.g., Adams, 2008). Estimates of the rate of depression among dementia caregivers range from just over 10% (Mahoney, Regan, Katona, & Livingston, 2005; Watson, Lewis, Moore, & Jeste, 2011) to 28-55% (Schulz, O'Brien, Bookwala, & Fleissner, 1995). Other estimates suggest that 40-55% of caregivers have clinically significant levels of depressive symptoms, while 20-25% of caregivers have major depression (Lavretsky, 2005; Schulz & Martire, 2004; Taylor, Ezell, Kuckibhatla, Ostbye, & Clipp, 2008).

In light of this evidence, it seems that depression may be an important factor contributing to increased inflammation (and potentially downstream CVD risk) in caregivers. In fact, although substantial evidence suggests that overall, dementia caregivers are at increased risk for CVD compared to noncaregivers, not all caregivers experience negative health consequences (Brown et al., 2009; Fredman, Cauley, Hochberg, Ensrud, & Doros, 2010). In particular, caregivers experiencing emotional distress or depressive symptoms may be at increased risk for negative health effects. For example, in Schulz and Beach's (1999) seminal paper establishing caregiving as a risk factor for mortality, it was only caregivers who

reported experiencing mental or emotional strain who displayed increased risk for mortality compared to noncaregivers. Furthermore, Mausbach and colleagues (2007) found that both depressive symptoms and emotional reactivity to care recipient problem behaviors predicted shorter time to CVD diagnosis in dementia caregivers.

Despite evidence demonstrating that caregivers have higher rates of depression and depressive symptoms than noncaregivers, as well as evidence suggesting that caregivers experience greater levels of systemic inflammation, very little research has directly examined the relationships between depression and inflammation in dementia caregivers. Dementia caregivers experiencing greater psychological distress (in the form of subjective burden related to caregiving activities) have been shown to display increased levels of IL-6 (Mausbach et al., 2011). Caregivers' elevations in CRP may be associated with greater experience of daily stressful events (Gouin et al., 2012). One study found that increased subjective caregiving burden predicted both depression and increased proinflammatory cytokine levels, but did not directly examine whether increased depression predicted cytokine levels (Clark, Nicholas, Wassira, & Gutierrez, 2013). Greater depressive symptoms in dementia caregivers over a three-year period have also been linked with platelet hyperactivation, which may also be associated with increased risk for cardiovascular events (Aschbacher et al., 2009). Additional research is needed to directly examine whether the established links between depressive symptoms and inflammatory markers (IL-6 and CRP), which may indicate downstream CVD risk, hold true in caregivers.

Furthermore, a great deal of research to date examining the associations between depressive symptoms and inflammation has been cross-sectional. Longitudinal research thus far has generally established that greater depression predicts accelerated increases in inflammation levels over time (Milaneschi et al., 2011; Stewart, Rand, Muldoon, & Kamarck,

2009). However, depressive symptoms are likely to fluctuate over time within a given individual. Even small changes in depressive symptoms (i.e., a 5-point increase in self-reported depressive symptoms using the Center for Epidemiologic Studies-Depression [CESD-10] scale) are associated with physiological changes such as increased risk for CVD in dementia caregivers (Mausbach et al., 2007) and increased risk for CHD and mortality in healthy adults (Ariyo et al., 2000). However, little is known about how exacerbation or attenuation of depression over time in dementia caregivers relates to changes in markers of inflammation such as IL-6 and CRP.

Depression and Caregiver Risk for Acute Illness

Again, it is important to note that not all caregivers experience the negative health consequences associated with caregiving (Brown et al., 2009; Fredman, Cauley, Hochberg, Ensrud, & Doros, 2010). Although evidence suggests that, overall, caregivers have a greater risk for immune dysfunction compared with noncaregivers, many studies find that it is particularly caregivers experiencing emotional distress who appear display dysregulated immune functioning. For example, alterations in functioning of lymphocyte β 2-adrenergic receptors, which are important for T cell and NK cell functioning (Sanders & Straub, 2002), have been observed only in caregivers who experienced stressful life events and associated emotional distress (Mills et al., 1997). Additional alterations in lymphocyte β 2-adrenergic receptor density and sensitivity have been observed only in “vulnerable” caregivers (determined by the amount of care required by the spouse relative to the amount of respite the caregiver received) (Mills et al., 2004). Vulnerable caregivers experienced emotional distress, including higher rates of depression, than noncaregivers and nonvulnerable caregivers. Vedhara and colleagues (1999) found that caregivers displayed poorer antibody response to

influenza vaccine than noncaregivers over a six-month period, as well as increased emotional distress, including increased depressive symptoms, compared to noncaregivers. In a recent study of immune function in older adults, caregiving status alone had less of an effect on immune response to influenza vaccine than did negative repetitive thought (i.e., rumination). Negative repetitive thought predicted both greater depressive symptoms and poorer response to vaccine among caregivers (Segerstrom, Schipper, & Greenberg, 2008).

Although none of these studies directly examined the links between increased depressive symptoms and immune functioning in dementia caregivers, the results suggest that depressive affect is present among caregivers with immune dysfunction. A few studies have directly examined this link, finding that older adults (caregivers and controls) with chronic, mild depressive symptoms had poorer T cell responses to two mitogens compared to nondepressed adults, over a period of 18 months (McGuire, Kiecolt-Glaser, & Glaser, 2002) and that depression in dementia caregivers was associated with impaired T cell proliferation and a reduction in NK cells (Castle, Wilkins, Heck, Tanzy, & Fahey, 1995). The association of depression with T cell and NK cell function in the latter study was stronger than the association between these immune markers and other measures of psychological distress (e.g., caregiver subjective burden).

Given that poorer response to vaccination and other immune dysregulation is likely to result in greater risk of acute illness or infection (Kiecolt-Glaser & Glaser, 2002), it may be expected that caregivers experiencing emotional distress or depressive symptoms would have increased rates of acute illness or infection (Segerstrom & Miller, 2004). In a review of noncaregiving populations, Cohen and Williamson (1991) found that overall, psychological stress (which included difficult life events and emotional distress such as depressive symptoms) was associated with increased upper respiratory infection symptom reporting,

greater health care utilization, and higher rates of verified infection. However, they noted that further research is necessary in order to draw definitive conclusions about the role of psychological stress in the onset of these infections. Additional investigations have demonstrated that dysphoric mood increases risk of infection after experimentally administered respiratory viruses (Cohen, Tyrell, & Smith, 1993; Cohen et al., 1995). Spousal dementia caregivers, often viewed as an exemplar of a chronically stressed population (Segerstrom & Miller, 2004), and also at increased risk of functional immune impairment due to advanced age (Agarwal & Busse, 2010), may represent a population in which it is especially important to further examine the links between depressed affect and meaningful outcomes such as acute illness susceptibility.

Initial evidence suggests that, indeed, depressive symptoms may correlate with increased prevalence of acute illness among dementia caregivers. For example, in dementia caregivers, increased self-reported depressive symptoms are associated with worse self-reported physical health and increased presence or history of self-reported illness (Cucciare, Gray, Azar, Jimenez, & Gallagher-Thompson, 2010). Interestingly, in a recent meta-analysis of correlates of physical health in caregivers, depressive symptoms were more strongly associated with physical health outcomes than were objective caregiving stressors (e.g., amount of daily care provided, problem behaviors exhibited by the care recipient) (Pinquart & Sorensen, 2008). The physical health outcomes in these analyses included, but were not limited to, measures of infectious illness, however, the overall pattern of results suggests that depressive symptoms may be an important correlate of health and illness in caregivers. Depressed caregivers may also be more likely to visit the hospital or emergency room, though the reason for hospital visits may vary widely (Schubert et al., 2008).

Evidence directly examining the effects of depressed affect or mood disturbance on

acute illness or infection in dementia caregivers is lacking. Not only is it important to understand whether increased depressed mood is associated with more frequent experience of acute illness, but it may also be beneficial to investigate whether fluctuations in depressed mood over time are associated with changes in acute illness. In noncaregiving populations, some evidence suggests that chronic psychological stressors (i.e., lasting longer than 1 month), but not acute psychological stressors, may increase susceptibility to the common cold in healthy adults (Cohen et al., 1998). It may be useful to investigate both overall levels of mood disturbance as well as more acute changes in mood with respect to their impact on symptoms of acute illness or infection in caregivers as well.

It is important to note that although substantial evidence exists indicating that depression and emotional distress may play a role in morbidity through immune dysregulation and inflammation, this relationship is undoubtedly bidirectional in nature (Kiecolt-Glaser & Glaser, 2002; Segerstrom & Miller, 2004). For example, immune activation, particularly cytokine release, has effects on the central nervous system and can induce “sickness behavior” that includes reduction in activity, social isolation, lethargy, fatigue, decreased appetite, and depressed mood (e.g., Maier & Watkins, 1998). Although the present study focuses on the impact of depression on inflammation and acute illness, there is reasonable evidence that the immune system plays a role in neuroendocrine and behavioral components of depression (Miller, 1998). The present study examines the associations between depressive symptoms and caregiver health outcomes over time, but cannot determine causality in these relationships.

Summary of Depression and Caregiver Health Risk

Caregivers are at increased risk for a variety of health consequences compared with noncaregivers, including chronic, serious conditions such as CVD, as well as inflammation,

which is often viewed as a risk marker for CVD. Caregivers may also be at increased risk for health problems that are less chronic or life-threatening in nature, such as acute infection (e.g., cold, flu), but which nonetheless impact the quality of life of both the caregiver and care recipient. Each of these unique but important categories of health outcomes may be associated with psychological distress, particularly depression or depressive symptoms. Preliminary evidence has examined linkages between depressive symptoms and these two categories of health outcomes among caregivers, but much remains unknown about these relationships. Particularly, these relationships have most often been examined cross-sectionally. Less is known about how sustained elevations in depression over time, or fluctuations in depression over time, might impact these two categories of health outcomes in dementia caregivers.

Affective Components of Depression: Positive and Negative Affect in Caregiver Health

A substantial body of research links depression and health outcomes. Although this research has typically focused on depressive symptoms or formal diagnoses of depressive disorders, other research suggests that depression comprises two separate affective domains: positive affect (PA) and negative affect (NA) (Clark & Watson, 1991). Positive affect reflects a person's level of joy, energy, enthusiasm, and interest, whereas negative affect reflects feelings of fear, sadness, guilt, and irritability (Watson, Wiese, Vaidya, & Tellegen, 1999). Based upon their seminal review of psychometric data from measures of anxiety and depressive symptoms, Clark and Watson (1991) developed a "tripartite" model of depression and anxiety. According to this model, increased NA is a shared feature of both depression and anxiety, while depression is uniquely characterized by the presence of low PA. Depression is conceptualized as a combination of high NA with low PA, wherein NA and PA are viewed as distinct, orthogonal dimensions, rather than opposite ends of a continuum (Watson et al., 1999). The

validity of Clark and Watson's "tripartite" model has been supported in multiple studies (Brown, Chorpita, & Barlow, 1998; Cook, Orvaschel, Simon, Hersen, & Joiner, 2004; Watson, Clark, et al., 1995; Watson, Weber, et al., 1995; Watson et al., 1999). Support for the model of depression as a combination of low PA and high NA has been demonstrated in older adults as well. In one study, PA was inversely correlated with depressive symptoms (measured by the Beck Depression Inventory) in older adults, whereas greater NA was associated with higher depression scores (Cook et al., 2004). Older adults categorized as having "major" or "other" depression using the Centers for Epidemiologic Studies Depression (CES-D) scale reported more NA and less PA on a day-to-day basis (Chepenik et al., 2006). In dementia caregivers specifically, low PA and high NA have also been shown to uniquely predict depressive symptoms (Mausbach, Roepke, Depp, Patterson, & Grant, 2009). Depressive symptoms, measured by the short form CES-D, were correlated with increased NA ($r = .66$) and decreased PA ($r = -.55$). However, PA and NA are generally not highly correlated with each other [e.g., Watson and colleagues (1999) reported a correlation between NA and PA of $-.19$ in a sample of over 4,400 people], further supporting the notion that they are distinct dimensions of affect.

Measures of affect usually differ from measures of depressive symptoms with regard to the breadth of emotions reflected in the measures, as well as the time frame of the specific emotions assessed (Skaff et al., 2009). Measures of depression are often based on DSM-5 (or previously, DSM-IV-TR) criteria for depressive disorders, and assess for mood-related symptoms (e.g., depressed mood, sadness, hopelessness, guilt) as well as symptoms such as sleep disturbance and decreased appetite. Measures of affect exclusively assess mood states, most often explicitly including both PA and NA, and measure constructs that encompass a broader range of subjective moods and feelings (Denollet & de Vries, 2006). Additionally, depression measures often assess symptoms over clinically-relevant time periods associated

with DSM-IV-TR diagnoses (i.e., two weeks), while affect can either reflect a relatively fleeting mood (state affect; measured currently or within the last day) or a more stable characteristic of the individual (trait affect; measured generally or over a period of a few weeks) (Pressman & Cohen, 2005). In summation, PA and NA are both conceptually related to depression in that depression is theorized to result from a combination of high NA and low PA, however, measuring affect can reflect a broader range of subjective mood states than measuring depression.

Just as depression and depressive symptoms have been linked with health outcomes, recent evidence suggests that the specific affective components of depression, PA and NA, may also be associated with various health outcomes. Increased trait NA has been associated with lower secondary antibody response to immunization, especially among older adults (Cohen, Miller, & Rabin, 2001), as well as increased objective and subjective symptoms of respiratory and viral illness (Cohen et al., 1995). Increased NA has also been associated with greater complaints of cold and flu symptoms in older adults (Leventhal et al., 1996). However, in one study, daily fluctuations in NA were not related to changes in heart rate, although arousal of any sort (regardless of valence) was associated with heart rate changes (Kamarck et al., 2005). In adults with Type II diabetes who reported NA, PA, and glucose monitoring results daily over 21 days, greater NA on one day was associated with higher blood glucose levels measured the following morning (Skaff et al., 2009). Greater average NA over the 21 days was also associated with higher morning glucose levels. No relationship was observed between PA and blood glucose levels. In adult men, increased NA is associated with attenuated procoagulant reactivity to an acute laboratory stressor, while increased PA was associated with enhanced procoagulant response (von Känel et al., 2005). There is limited evidence regarding NA and inflammation. Some evidence suggests that NA induced via a laboratory stressor task

is associated with acute increases in IL-6 (Carroll et al., 2011), and that induced NA over a period of one week is associated with increases in other proinflammatory cytokines (not including IL-6) (Dickerson et al., 2004). Other studies have demonstrated positive associations of NA with both IL-6 (Miyamoto et al., 2013) and CRP (Marsland et al., 2008), though these associations may be present only in Western cultures (Miyamoto et al., 2013). Another study found an inverse association between PA and IL-6 observed no association between NA and IL-6 (Prather et al., 2007).

Slightly more research to date has examined the influence of PA on health. In a summary of the literature, Pressman and Cohen (2005) found that, in general, higher PA is related to lower mortality and morbidity. For example, studies indicated that increased PA is associated with fewer reported illness symptoms, may be protective against future occurrence of stroke or infectious illness, and is associated with less rehospitalization after acute cardiac events. Additional research has supported that greater levels of PA are associated with decreased risk of mortality (Chida & Steptoe, 2008) and lower risk for coronary heart disease (Kubzansky & Thurston, 2007), even when controlling for levels of NA, suggesting that PA, rather than a mere lack of NA, may have a protective effect on health. Steptoe and Wardle (2005) found that PA was significantly associated with lower salivary cortisol, reduced fibrinogen stress response, and lower ambulatory heart rate in men, analyzing data from the Whitehall study. Preliminary research suggests that IL-6 may be inversely associated with PA (Friedman et al., 2007), even after controlling for lifestyle confounds and depressive symptoms (Brouwers et al., 2013; Prather et al., 2007). Evidence for an association between CRP and PA has been more mixed (Brouwers et al., 2013). One study found inverse associations of PA with both IL-6 and CRP, even after controlling for covariates such as age, ethnicity, BMI and smoking status, though this association was observed in women but not men (Steptoe et al.,

2008). Andreasson and colleagues (2013) found in women that PA was positively associated with subjective health. Additional evidence suggests that higher PA is associated with lower risk of developing illness after exposure to rhinovirus and influenza A virus (Cohen et al., 2003; Cohen et al., 2006).

The evidence examining the impact of subjective mood states related to PA and NA on health outcomes in dementia caregivers is lacking. However, as previously described, high NA and low PA are conceptualized to be components of depression, and evidence suggests that depression may be associated with poor health in caregivers. The subjective mood states associated with the dimensions of PA and NA have also been independently linked with health outcomes in noncaregiving populations. Therefore, the potential impact of positive and negative affective states on caregiver health warrants investigation. The present study will investigate whether levels of PA and NA are associated with two types of health outcomes in caregivers: inflammation, which may reflect risk for chronic, serious illness such as CVD, and symptoms of acute illness, which may be less serious but still cause impairment for caregivers.

In addition to examining how overall level of depressive symptoms might impact caregiver health, investigating the role of PA and NA, two distinct components of depressive affect, may provide valuable information about the impact of mood on caregiver health, which could potentially be useful in identifying relevant treatment targets for caregivers. PA and NA are conceptualized as orthogonal dimensions of mood (i.e., an increase in PA does not necessarily result in a decrease in NA, it is possible to simultaneously experience high PA and high NA). If depression results from high levels of NA and low levels of PA, treatment for depression could theoretically target increasing patients' PA [e.g., through behavioral activation (Mazzucchelli, Kane, & Rees, 2009), that is, increasing engagement in enjoyable activities], treatment could target decreasing patients' level of NA [e.g., through cognitive

behavioral therapy (CBT) techniques such as restructuring of negative thoughts (Beck, 2005)], or treatment could target both dimensions of affect. Indeed, preliminary evidence in dementia caregivers suggests that negative cognitions are uniquely associated with levels of NA, but not PA, and caregivers' frequency of engagement in social and recreational activities is uniquely associated with PA, but not NA (Mausbach et al., 2009). Investigating the contributions of PA and NA in influencing health outcomes in caregivers could aid in identifying specific treatment targets for improving mood disturbance that may yield maximal benefit for caregivers' overall well-being, including health improvements. Furthermore, the present study will not only examine whether levels of PA and NA are correlated with health outcomes in caregivers, but will also explicitly examine whether fluctuations in PA and NA over time are associated with concomitant changes in these health outcomes.

Repeated Measures Analyses

The evidence to date supporting an association between depression, or depressive symptoms, and both chronic and acute health outcomes (i.e., inflammation, an indicator of CVD risk, and presence of acute illness) in dementia caregivers has been largely cross-sectional. The current study attempts to augment the knowledge regarding these relationships in dementia caregivers by examining these relationships longitudinally, using data collected during repeated annual assessments within individual participants for a period of up to five years. These repeated measurements allow for many opportunities for analysis beyond the traditional cross-sectional analyses. Cross-sectional analyses can examine a "snapshot" of a group of individuals and examine whether two constructs are associated at a particular point in time (e.g., do caregivers with elevated depressive symptoms at a given time point also have elevated inflammation?). However, with data collected repeatedly over time within the same

individual, data from multiple time points within the same person can be aggregated to obtain a measure of the individual's average level of depression (Singer & Willet, 2003). Aggregating data from the same individual over time to examine these between-person effects (i.e., between-person differences in average levels of depression) can provide a better picture of the effects of *chronic* elevations in depressive symptoms on health outcomes. Information regarding the detrimental impact of chronic mood disturbance on caregiver health could suggest the need for prevention or early intervention to address mood disturbance in caregivers in order to protect caregiver well-being. Indeed, one study examining both persistent and transient depression found that sustained elevations in depressive symptoms over a three-year period predicted platelet hyperactivation in dementia caregivers, whereas depressive symptoms in any given year were not associated with platelet activation (Aschbacher et al., 2009).

Although it is useful to determine whether chronic mood disturbance impacts health outcomes, even in caregivers with chronic elevations in depression, or caregivers with low average levels of depression, mood disturbance is likely to show some variation over time. That is, an individual caregiver's level of mood disturbance is likely to fluctuate from year to year, relative to that caregiver's personal mean. The present study examines whether yearly variations in mood disturbance are also associated with more acute changes in health outcomes (inflammation or acute illness symptoms). That is, we can directly examine whether caregivers with elevated mood disturbance relative to their personal mean level of mood disturbance also show a concomitant elevation in inflammation or illness symptoms. These analyses allow for more direct investigation of the effects of both acute (i.e., year to year) and chronic (i.e., across several years of study enrollment) mood disturbance on caregiver health.

Additionally, examination of changes in mood and health within the same individual caregiver can yield valuable information regarding potentially modifiable factors that could

serve as intervention targets for improving caregiver mental and physical health. As is common in the literature, much of the research to date regarding depression and health outcomes has inferred causal relationships or made within-person inferences by comparing differences in depressive symptoms and health outcomes *across* individuals (Affleck, Zautra, Tennen, & Armeli, 1999). At a basic level, this traditional analytic approach of examining differences between individuals assumes that if two individuals differ by ten points on some variable (e.g., depression score) and also show a significant difference in some outcome (e.g., inflammation), then if one individual's depression score changes ten points, that individual's inflammation level should also significantly change. However, this inference cannot be made without observing individuals when they are experiencing high depression and when they are experiencing low depression (Affleck et al., 1999). Observed differences *between* individuals are often taken to indicate the potential effects of change *within* individuals, without directly testing the effects of fluctuation of a given variable in an individual. Affleck and colleagues (1999) argue that multilevel analyses examining within- *and* between-person effects provide novel contributions to the literature in clinical psychology by explicitly examining these within-person correlations, which can help answer intraindividual questions that may be of particular importance to clinicians (e.g., for informing interventions). The present study collected repeated measures of mood and health variables over time within the same caregivers, allowing for analyses that further elucidate the true effects of change in mood and health over time within caregivers. Although causation cannot be inferred from these analyses, directly testing whether depression and inflammation or illness symptoms covary over time within the same person can provide greater knowledge about whether these health outcomes are modifiable in caregivers, which can provide information about whether these variables may be appropriate targets for interventions to improve caregiver well-being.

Specific Aims of the Current Study

The aims of the current study attempted to elucidate the relationships between mood disturbance and caregiver health over time, focusing on both chronic and acute caregiver health outcomes, namely, inflammation, which is likely associated with risk for CVD, and acute illness symptoms experienced within the past month, in a population of spousal Alzheimer's disease caregivers. Specifically, the study aimed to:

Aim 1. Examine the within-person effects of mood disturbance on biomarkers of inflammation in spousal Alzheimer caregivers

The overall question addressed in this aim was, do caregivers with increased mood disturbance in one year of the study have concomitant elevations in inflammatory biomarkers? Alternately stated, are mood disturbance and inflammatory biomarkers positively associated over time within the same caregiver? The outcome variables of interest were IL-6 and CRP. First, level of depressive symptoms (i.e., CESD-10 score) were examined as a predictor of these inflammatory markers. The analysis was repeated with levels of positive and negative affect examined as predictors.

Hypothesis 1.1. Depressive symptoms were expected to be positively associated with IL-6 and CRP over time. That is, caregivers with higher CESD-10 scores at a given assessment were expected to have higher levels of IL-6 and CRP at that assessment point.

Hypothesis 1.2. Negative affect was expected to be positively associated with IL-6 and CRP over time such that caregivers with higher negative affect at one assessment would have higher IL-6 and CRP at that assessment. Positive affect was expected to be negatively associated with these inflammation markers over time, such that caregivers with higher positive affect at a given assessment would show lower IL-6 and CRP at that assessment.

Aim 2: Examine the between-person effects of mood disturbance on biomarkers of inflammation in spousal Alzheimer caregivers

The overall question addressed in this aim was, do caregivers with higher average levels of mood disturbance throughout the course of the five-year study also have higher average levels of inflammation markers? Specifically, the outcome variables were IL-6 and CRP, markers of inflammation that have been associated with CVD risk throughout the literature. First, the effect of level of depressive symptoms (i.e., CESD-10 score) was examined as a predictor of these inflammatory outcomes. Levels of positive and negative affect were also examined with respect to these outcomes.

Hypothesis 2.1. Caregivers with higher mean CESD-10 scores across all study assessments were expected to have higher levels of IL-6 and CRP.

Hypothesis 2.2. Caregivers with higher mean negative affect were also expected to have higher levels of IL-6 and CRP, whereas caregivers with higher mean positive affect were expected to have lower levels of IL-6 and CRP.

Aim 3: Examine the within-person effects of mood disturbance on acute illness symptoms in spousal Alzheimer caregivers

The overall question addressed in this aim was, do caregivers' yearly variations in mood disturbance influence their experience of illness symptoms? Alternately stated, are mood disturbance and symptoms of acute illness positively associated over time within the same caregiver? First, level of depressive symptoms (i.e., CESD-10 score) was examined as a predictor of acute illness symptoms, then levels of positive and negative affect were examined as predictors of acute illness symptoms.

Hypothesis 3.1. Depressive symptoms were expected to be positively associated with

acute illness symptoms over time. That is, caregivers with higher CESD-10 scores at a given assessment would be more likely to report acute illness symptoms at that assessment point.

Hypothesis 3.2. Negative affect was expected to be positively associated with illness symptoms over time such that caregivers with higher negative affect at one assessment would be more likely to report illness symptoms at that assessment. Positive affect was expected to be negatively associated with illness symptoms over time, such that caregivers with higher positive affect at a given assessment would be less likely to report illness symptoms at that time point.

Aim 4: Examine the between-person effects of mood disturbance on acute illness symptoms in spousal Alzheimer caregivers

The overall question addressed in this aim was, are caregivers with higher average levels of mood disturbance throughout the course of the five-year study also more likely to experience acute illness symptoms? First, the effect of level of depressive symptoms (i.e., CESD-10 score) was examined as a predictor of illness symptoms. As a follow up, levels of positive and negative affect were examined with respect to acute illness symptoms.

Hypothesis 4.1. Caregivers with higher mean CESD-10 scores across all study assessments were expected to be more likely to report experiencing acute illness symptoms.

Hypothesis 4.2. Caregivers with higher mean negative affect were also expected to be more likely to report experiencing illness symptoms, whereas caregivers with higher mean positive affect were expected to be less likely to report illness symptoms.

This chapter is currently being prepared for submission for publication of the material. Chattillion, Elizabeth; Grant, Igor; Gallo, Linda C.; Mills, Paul J.; Roesch, Scott C.; Mausbach, Brent T. The dissertation author was the primary investigator and author of this material.

METHODS

Participants

Participants included 116 community-dwelling older adults providing care to a spouse with AD enrolled in the University of California, San Diego (UCSD) Alzheimer Caregiver Study, a five-year longitudinal project examining the effects of stress on physical and psychological health. Eligibility in the UCSD Alzheimer Caregiver Study required that at the time of study enrollment caregivers were at least 55 years of age, married, and living in the same home as their spouse who had a diagnosis of probable AD. Caregivers were excluded from participation in the study if they were diagnosed with or receiving treatment for a serious medical illness (e.g., Parkinson's disease, cancer) or had received cancer treatment within the past five years. Caregivers were also excluded from the study if they had severe hypertension (i.e., blood pressure exceeding 200/120 mm Hg) at enrollment or if they were taking anticoagulant medications, non-selective beta blockers, or steroids for a period of longer than two weeks. Caregivers were recruited for participation in the UCSD Alzheimer Caregiver Study through referrals from the UCSD Alzheimer's Disease Research Center (ADRC), community caregiver support groups, health fairs, local senior centers, flyers, and by recommendation of other participants in the study. All caregivers provided written informed consent to participate in the study, and the study protocol was approved by the UCSD Institutional Review Board (IRB).

Study Design and Procedures

All assessments for the Alzheimer Caregiver Study were administered in participants' homes by a trained research assistant and research nurse. After obtaining written informed

consent, the research assistant administered a semi-structured interview assessing demographic information, medical history (e.g., current diagnoses, recent health symptoms, current medications), health behaviors (e.g., physical activity, smoking history), psychosocial variables (e.g., depressive symptoms, levels of positive and negative affect), and caregiving variables (e.g., number of years providing care). Within approximately one week, the study nurse returned to the participant's home to administer biological assessments, which included blood pressure readings and a blood draw. In order to minimize the effects of diurnal variations in study biomarkers, blood draws were conducted between the hours of 8:00 and 10:00am for all participants. The nurse first inserted a 22-gauge indwelling venous catheter into the forearm with participants resting in a supine position. After catheter insertion, participants rested for a period of five minutes while keeping the hand level with the heart to control for hydrostatic differences. The first blood pressure measurement was taken, participants rested for an additional 10 minutes, and then the second blood pressure measurement was taken. Next, a total of 15 minutes after catheter insertion, the blood sample was drawn, with the first 2 ml discarded. Blood samples for the inflammatory marker assays were dispensed into EDTA tubes and centrifuged at 3,000 g for 10 minutes at 4-8°C. Samples were placed on crushed ice and then processed for storage in a -80°C freezer until assayed. The blood draw was followed by the final blood pressure recording.

Caregivers enrolled in the UCSD Alzheimer Caregiver Study completed psychosocial and biological assessments annually for up to five years. In addition to formal yearly assessment, research staff made brief phone calls to participants every three months to check for changes in participants' caregiving status (i.e., whether the spouse with AD was placed into long-term care outside the home, or the spouse with AD was deceased). Participants were also encouraged to call and notify research staff if these caregiving transitions occurred. If

participants experienced either of these transitions (i.e., placement or death of the spouse with AD), staff documented the incident and set up an assessment appointment approximately three months after the transition. For caregivers who placed their spouse into formal care or whose spouse was deceased, post-transition assessments were conducted at three months after the transition, and in yearly increments after that (i.e., 15, 27, and 39 months post-transition). During the post-transition assessments, study staff gathered the same biological data as during the yearly assessments, and gathered psychosocial data related to the caregiver (e.g., health behaviors, mood variables), but excluded assessments related to the care recipient (e.g., care recipient level of functioning).

Caregivers enrolled in the study may have up to five yearly assessments. One participant completed six assessments, due to experiencing a transition (i.e., bereavement) shortly after completing a yearly assessment. Caregivers enrolled during year two or three of the study completed fewer than five assessments. Only caregivers with two or more completed assessments were included in the analysis. Each participant's total number of completed assessments throughout the study was included in the present analysis, regardless of whether the assessments were yearly or post-transition visits.

Measures

Depressive Symptoms

Depressive symptoms were assessed using the short-form of the Center for Epidemiological Studies-Depression scale (CESD-10) (Andresen, Malmgren, Carter, & Patrick, 1994). The CESD-10 asks participants to rate 10 statements indicating how often they felt the way described in each statement over the past week. Statements include “You felt depressed,” “You had trouble keeping your mind on what you were doing,” “You felt hopeful

about the future,” and “Your sleep was restless.” Participants rated each statement on a 4-point scale from 0 = “Rarely or none of the time (<1 day)” to 3 = “Most or all of the time (5-7 days).”

Positive and Negative Affect

Positive and negative affect were assessed using the Positive and Negative Affect Scale (PANAS) (Watson, Clark, & Tellegen, 1988). The PANAS consists of 20 mood descriptors (10 positive and 10 negative). Caregivers rated each item on a 5-point Likert-type scale from 1 = “very slightly or not at all” to 5 = “Extremely” to indicate to what extent they felt each mood state “in the past few weeks.” Positive affect (PA) scale items included: interested, excited, strong, enthusiastic, proud, alert, inspired, determined, attentive, and active. Negative affect (NA) scale items were distressed, upset, guilty, scared, hostile, irritable, ashamed, nervous, jittery, afraid. Watson and colleagues (1988) reported high reliability and validity for both the PA and NA scales.

Caregiver Self-Reported Illness Symptoms

Caregivers were provided with a list of 21 symptoms (e.g., “temperature of 100 degrees F or more,” “headache lasting more than 1 hour,” “sore throat,” “toothache,”) and were asked to indicate (yes or no) whether they experienced each symptom within the last month preceding the assessment. Thirteen of these 21 symptoms are associated with acute infectious diseases such as cold and flu, or are associated with conditions that can arise as complications from cold or flu, such as pneumonia, bronchitis and ear infection (Centers for Disease Control and Prevention, 2011). Primary analyses will examine outcomes related to symptoms associated with cold, flu and other respiratory infections. Secondary analyses will examine

outcomes in the remaining 8 “other” (non-flu) symptoms. See Appendix A for a full list of symptoms and those specifically associated with cold, flu and other respiratory infection. Given that participants reported experiencing no flu symptoms on 40.5% of the measurement occasions in the study and reported experiencing no non-flu (“other”) illness symptoms on 61.9% of the measurement occasions in the study, the flu symptom and “other” symptom variables were dichotomized for these analyses (“yes” experienced any symptoms and “no” experienced zero symptoms).

Inflammatory Markers

Circulatory levels of the proinflammatory cytokine IL-6 were assessed by high-sensitive ELISA (Quantikine, R&D Systems, Minneapolis, MN, USA). Circulating CRP was assessed in plasma using the high-sensitivity Denka-Seiken assay. Intra- and interassay coefficients of variation were <10% for all assays.

Time-varying Covariates

Additional caregiver variables were assessed as part of the UCSD Caregiver Study that could impact caregiver’s levels of inflammatory biomarkers or acute illness symptoms, including age, body mass index, sleep quality, physical activity, smoking status, use of antihypertensive medications, use of cholesterol-lowering medications, and use of antidepressant medications, and caregivers’ level of perceived burden using the Role Overload scale. All of these variables were entered as time-varying covariates when included in the statistical models tested for this study.

Body Mass Index (BMI)

BMI was computed as the ratio between participant-reported weight in kilograms and height in square meters.

Subjective Sleep Quality

Caregiver sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). This 19-item self-report questionnaire assesses sleep quality over the past month and creates an overall sleep quality rating, summarizing sleep quality in seven domains: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. The overall sleep quality score ranges from 0–21, with higher scores indicating poorer sleep quality. Overall scores greater than five are considered to indicate disturbed sleep.

Physical Activity

Caregivers' level of physical activity was assessed using the Rapid Assessment of Physical Activity (RAPA) questionnaire, which was designed for use with older adults (≥ 50 years of age) (Topolski et al., 2006). Participants responded to nine 'yes' or 'no' items assessing the frequency and duration of their engagement in light, moderate, and vigorous exercise (the RAPA provided descriptions and examples of each of these three levels of physical activity). Based on their responses to these nine items, participants were assigned a score of 0-6, with higher scores indicating a greater level of physical activity.

Medications

Caregivers were asked to report a list of all medications they were taking at the time of

each assessment. Caregivers' use of antihypertensive, cholesterol-lowering, and antidepressant medications were entered as three separate dichotomous (yes/no) variables into the analyses.

Role overload

The Role Overload scale (Pearlin et al., 1990) was used to assess participants' perceived level burden, an indicator of subjective stress. Participants rated their agreement with four statements such as, "I have more things to do than I can handle" on a 4-point scale (0 = "not at all"; 3 = "completely"). Items were summed in order to derive a total overload score, with higher scores indicating a greater level of perceived burden.

Smoking status

Participants were asked about their current cigarette smoking and whether they had been a former cigarette smoker. Smoking status was entered as a dichotomous variable (0 = never smoked; 1 = current or former smoker). At baseline assessment, only one participant was a current smoker.

Person-level Covariates

Other demographic variables that may impact inflammatory markers or acute illness symptoms, included gender, years of education, and ethnicity (dichotomized into Caucasian vs. other ethnicity, given the high percentage of Caucasian caregivers in the sample). The number of years a caregiver has been providing care to their spouse (measured at baseline assessment) was also measured. Years spent caregiving has been shown to be associated with CRP (von Känel et al., 2012) and measures of atherosclerotic burden (Roepke et al., 2012). Caregivers were asked to report the year that their spouse was diagnosed with Alzheimer's disease (i.e.,

the year that caregiving began). The time elapsed between the diagnosis year and the time of the baseline assessment is considered the duration (in years) of providing care. When included in statistical models, the above variables were entered as person-level (or time-constant) variables given that they do not change from year to year.

Data Analysis

Data were analyzed using IBM SPSS Statistics 22.0 software package (IBM Corp., Armonk, NY, USA). Given the nested structure of the data (i.e., yearly assessments are nested within individual participants), multilevel modeling (i.e., mixed models regression) was used to test the relationships described in the study aims. Mixed models regression allows for the estimation of an intercept and a slope for each participant based on all data points available for that individual, augmented by data from the entire sample (Singer & Willett, 2003). Importantly, this analytic approach allows for missing data points, such that even participants who did not complete all five yearly assessments can be included in the analysis. Boxplots and histograms of IL-6 and CRP values were examined to identify outliers that were removed from analysis. Non-normal distributions were transformed. Descriptive statistics were calculated to describe sample characteristics and study variables. Statistical significance was defined as $p < .05$. Remaining analyses were conducted as described in the Specific Aims below.

Creation of Within and Between Variables

Each measure of mood disturbance (i.e., CESD-10 score, PA, NA) was separated into two predictors: (a) a between-person measure representing the individual's mean across the total number of study assessments completed, and (b) a within-person measure representing the individual's deviation for a given assessment from their personal mean across all assessments.

The between-person variables were centered around the grand mean. The within-person variables were centered around each participant's mean such that a higher or lower level at a given assessment point represents a higher or lower difference at that assessment from the individual's mean. Creating within and between mood disturbance variables in this way allows for direct examination of how between-person and within-person differences in mood are related to health outcomes (Skaff et al., 2009).

Analytic Plan for Aims 1 and 2: Examine the within-person and between-person effects of mood disturbance on inflammatory biomarkers

A series of multilevel regression models was used to examine the relationships described in Aims 1 and 2. All models were fit with a random intercept and used maximum likelihood estimation (ML). All within- and between-person mood disturbance variables and all time-varying and person-level covariates were entered into the model as fixed effects (Skaff et al., 2009). Level 1 predictors and covariates were person mean-centered and level 2 covariates were grand mean-centered (Peugh & Enders, 2005). A separate model was tested for each of the two inflammatory outcomes (IL-6 and CRP). Additionally, for each outcome, one model was tested using depressive symptoms (i.e., CESD-10-between and CESD-10-within) as the primary predictors. A separate model was then tested with both PA and NA entered as predictors (i.e., PA-between, PA-within, NA-between, and NA-within). Variables were added stepwise into the models. Separate models were run with primary predictors (within-person and between-person mood variables). Covariates were then added to the models to evaluate whether any significant findings of primary predictors were robust to the addition of covariates, given the relatively small sample size of the current study and concerns about reduced power with the addition of predictors. Pseudo R^2 effect sizes were examined for each model.

Several covariates were included *a priori* in all models examining inflammatory outcomes, based on prior research findings from meta-analyses or large population-based studies demonstrating that these variables impact inflammatory markers IL-6 and CRP. These variables were BMI (e.g., Howren et al., 2009), age (Ershler, 1993; Hemmerich, et al., 2006; Marques-Vidal et al., 2011) and smoking status (e.g., Wanamethee et al., 2005; Yanbaeva et al., 2007), added as time-varying covariates, and gender (Hemmerich, et al., 2006; Herd, Karraker, & Friedman, 2012; Marques-Vidal et al., 2011; Khera et al., 2005) included as a person-level covariate. Several other variables collected as part of the study may also impact inflammatory biomarker levels, including sleep quality (Liu et al., 2012; Miller, 2011; Mullington et al., 2009; von Känel et al., 2010), physical activity (Swardfager et al., 2012), education level (Gruenewald et al., 2009; Herd et al., 2012), ethnicity (Herd et al., 2012; Khera et al., 2005; Paalani, Lee, Haddad & Tonstad, 2011), use of medication (Kenis & Maes, 2002; Laffer & Eljovich, 2010), role overload (i.e., a measure of subjective stress; Mausbach et al., 2011; Roepke et al., 2011), and years caregiving (von Känel et al., 2012). Each of these covariates was examined statistically to determine their influence on inflammatory biomarker outcomes in this study. A series of bivariate mixed models regressions were run with each covariate as a single (fixed effect) predictor of each inflammatory biomarker outcome (IL-6 and CRP). Significant predictors in bivariate analyses were included as covariates in the final model.

Analytic Plan for Aims 3 and 4: Examine the within-person and between-person effects of mood disturbance on acute illness symptoms

To investigate Aims 3 and 4, a series of multilevel logistic regression models was used, similar to the process described above for Aims 1 and 2. Analyses were consistent with

procedures for conducting multilevel modeling with categorical outcomes using IBM SPSS described by Heck and colleagues (2012). All models were fit with a random intercept and were estimated using active set method (ASM) with Newton-Raphson estimation. All mood predictors and covariates were entered as fixed effects. Level 1 predictors and covariates were person mean-centered and level 2 covariates were grand mean-centered. Primary analyses examined the presence flu symptoms (i.e., the 13 symptoms that are associated with acute infectious diseases such as cold and flu, or related complications). Additional analyses were conducted examining the presence of non-flu illness symptoms (i.e., the remaining 8 illness symptoms not specifically associated with cold or flu, such as toothache or discomfort with hemorrhoids). See Appendix A for a full list of symptoms and those specifically associated with cold, flu and other respiratory infection. Separate models were tested for flu symptoms and for other symptoms. Again, for each outcome one model was tested using depressive symptoms (i.e., CESD-10-between and CESD-10-within) as the primary predictors and a separate model was tested with both PA and NA entered as predictors (i.e., PA-between, PA-within, NA-between, and NA-within). For illness symptom outcomes, age and gender were included as covariates in all models and other potential covariates (smoking status, BMI, sleep quality, physical activity, education level, ethnicity, use of medications, role overload, and years caregiving) were statistically tested for inclusion in models as described in the analytic plan for Aims 1 and 2. Separate models were run with only primary predictors (within-person and between-person mood variables) and additional models were then run with covariates included. Pseudo R^2 effect sizes were examined for each model.

This chapter is currently being prepared for submission for publication of the material. Chattillion, Elizabeth; Grant, Igor; Gallo, Linda C.; Mills, Paul J.; Roesch, Scott C.; Mausbach, Brent T. The dissertation author was the primary investigator and author of this material.

RESULTS

Participant Characteristics

Table 1 presents demographic characteristics of the study sample at baseline. Caregivers were primarily female and Caucasian with a mean age of 74.6 years. One hundred twenty-six caregivers were recruited as part of the study; however, only caregivers who completed two or more annual assessments were included in the present analyses.

Table 1. Caregiver Characteristics at Baseline (N=116)

Age in years, mean (SD)	74.6 (7.8)
Female gender, n (%)	80 (69.0)
Caucasian ethnicity, n (%)	102 (87.9)
Years of education, mean (SD)	15.1 (3.1)
Monthly household income in dollars, median*	4,000
Years caregiving, mean (SD)	4.5 (3.5)
Body Mass Index, mean (SD)	26.5 (4.7)
Overall PSQI sleep quality score, mean (SD)	6.5 (3.5)
Rapid Assessment of Physical Activity (RAPA) score, mean (SD)	3.4 (1.6)
Role overload score, mean (SD)	5.1 (3.2)
Taking antihypertensive medication, n (%)	70 (60.3)
Taking antidepressant medication, n (%)	28 (24.1)
Taking cholesterol-lowering medication, n (%)	56 (48.3)
CESD-10 score, mean (SD)	8.6 (5.8)
Positive Affect, mean (SD)	32.1 (7.3)
Negative Affect, mean (SD)	17.8 (6.1)
Interleukin-6 in pg/mL, median (IQR) ‡	1.01 (0.77)
C-reactive protein in mg/L, median (IQR) ¶	1.43 (3.12)
Reported flu symptoms in past month, n (%)	69 (59.5)
Number of flu symptoms for those who reported any, mean (SD)	2.4 (1.5)
Reported non-flu illness symptoms in past month, n (%)	45 (38.8)
Number of non-flu symptoms for those who reported any, mean (SD)	1.4 (0.6)

SD=standard deviation; PSQI=Pittsburgh Sleep Quality Index; CESD-10=Center for Epidemiologic Studies Depression Scale-10-item short form; IQR = interquartile range.

*Median monthly income was based on data from 104 participants because 12 declined to report their income

**Only 1 participant was a current smoker at baseline assessment

‡IL-6 was based on data from 110 participants included in the final analysis

¶C-reactive protein was based on data from 109 participants included in the final analysis

Table 2 shows the number of assessments completed by the 126 enrolled caregivers and the caregivers included in the final analyses. As shown in Table 2, 116 caregivers were included in the analyses examining illness symptom outcomes (measured at the psychosocial assessment visit) and 110 and 109 caregivers were included in analyses of inflammatory biomarker outcomes (IL-6 and CRP, respectively). The 10 excluded participants were compared with the 116 participants included in the final analysis and were found to be less likely to report flu symptoms ($p=.011$). Participants excluded from the final analyses did not differ significantly from the final sample on any other demographic or outcome variable.

Table 2. Sample sizes for study assessments

Assessment	# Psychosocial Assessments Completed (# Analyzed)	# IL-6 Assessments Completed (# Analyzed)	# CRP Assessments Completed (#Analyzed)
Assessment 1 (baseline)	126 (116) 10 CGs removed due to only 1 total completed visit	113 (110) 3 CGs removed due to only 1 completed IL-6 assessment	112 (109) 3 CGs removed due to only 1 completed CRP assessment
Assessment 2	115	109 (108) 1 assessment removed as outlier	108 (107) 1 assessment removed as outlier
Assessment 3	109	100	101 (100) 1 assessment removed as outlier
Assessment 4	100	97	95
Assessment 5	50	46 (45) 1 assessment removed as outlier	45
Assessment 6*	1	1	1
Total assessments completed (analyzed)	501 (491)	466 (461)	462 (457)

CG = caregivers.

*Extra assessment completed by 1 caregiver

Missing Data

As shown in Table 2, for psychosocial outcome variables, a total of 491 assessments were analyzed across the five-year study. Inflammatory biomarker data were collected and assayed for a total of 466 assessments for IL-6 and 462 assessments for CRP. As described below in the results for Aims 1 and 2, distributions of IL-6 and CRP values were examined to identify outliers. This resulted in the exclusion of two IL-6 assessments and two CRP assessments. Additionally, three participants who completed more than one psychosocial assessment completed only one assessment of inflammatory biomarkers, thus those three participants were removed from the inflammatory biomarker analyses. Therefore, the final numbers of assessments included in the present analyses were 461 and 457 for IL-6 and CRP, respectively.

Table 3 displays the total number of missing assessments throughout the study for each outcome variable. For caregivers enrolled in the first two years of the study there was a maximum of five yearly assessments that could be completed. For caregivers enrolled after 2009, the maximum number of annual assessments that could be completed was four. The mean number of assessments completed per caregiver was 4.23 ($SD=0.83$). Based on the time of study recruitment, 73 caregivers had the potential to complete all five annual assessments. Thirty-nine caregivers had a maximum of four annual assessments that could be completed and four caregivers had a possible maximum of three assessments. One caregiver completed six assessments due to experiencing a transition (i.e., bereavement) shortly after completing a yearly assessment. Out of a maximum 578 total assessments possible, 77 psychosocial assessments were not completed due to participant dropout. All participants who completed a study assessment reported data regarding health symptoms (that is, there were no participants who completed a study assessment but were missing health symptom data). One-hundred

twelve and 116 assessments were not completed for IL-6 and CRP, respectively. Missingness of inflammatory data included dropout (i.e., failure to complete a study biological assessment), failure to collect blood samples during biological assessment, or failure for collected samples to be assayed for IL-6 or CRP levels. A total of 73 caregivers completed the maximum possible number of psychosocial study assessments (i.e., had no missing assessments due to dropout), and 59 caregivers completed the maximum possible number of assessments resulting in inflammatory data.

Table 3. Missing Data

	Outcome Variable		
	Illness Symptoms	IL-6	CRP
Maximum Possible Assessments	578	578	578
Observed Assessments	501	466	462
Total Assessments Missing	77	112	116
% of Assessments Missing	13.3	19.4	20.1

Note. “Missing” refers to assessments that were not completed due to study dropout as well as cases in which an annual assessment was completed but the outcome variable was not measured/assayed.

Missingness of psychosocial data (i.e., caregivers who did not complete the maximum possible number of psychosocial assessments) was significantly associated with experiencing other (non-flu) illness symptoms at baseline ($X^2 = 6.83, p=.009$) such that caregivers who reported experiencing “other” health symptoms at baseline were more likely to have missing psychological data. Missingness of psychosocial data was not significantly associated with any other study variable (measured at baseline). Missingness of inflammatory data (i.e., caregivers

who did not complete the maximum possible number of IL-6 and CRP assessments) was significantly associated with experiencing other (non-flu) illness symptoms at baseline ($\chi^2 = 5.31, p=.021$) such that caregivers experiencing non-flu symptoms at baseline were more likely to be missing inflammatory data. Missingness of inflammatory data was not significantly associated with any other study variable at baseline.

Additionally, neither missingness of psychosocial data nor missingness of inflammatory data were significantly associated with caregivers' average levels of depression (CESD-10 score), IL-6, CRP, or the number of flu symptoms throughout the duration of the study (i.e., caregivers' personal mean of CESD, IL-6, CRP, flu symptoms across all assessments completed). Missingness of psychosocial data was significantly associated with caregivers' average number of "other" (non-flu) health symptoms [$t(124) = -2.07, p=.040$] such that caregivers experiencing more non-flu health symptoms over the course of the study were more likely to have some missing psychosocial assessments. Missingness of inflammatory data was also significantly associated with caregivers' average number of "other" (non-flu) health symptoms throughout the study [$t(124)=-1.99, p=.049$] such that caregivers experiencing more non-flu health symptoms over the course of the study were more likely to have missing inflammatory biomarker assessments.

Mood Variables and Inflammatory Biomarker Outcomes (Aims 1 and 2)

For inflammatory biomarker outcomes IL-6 and CRP, boxplots and histograms were examined for normality. For each variable, two cases were removed as outliers that were greater than four standard deviations above the mean. Both variables had positively skewed distributions so the variables were log transformed to approximate normality.

Outcome: log IL-6

As stated above, all predictors were entered as fixed effects. However, additional models which included within-person mood variables as random effects were also explored. Adding a variable as a random effect allows for each participant to have a different (stronger or weaker) correlation between the predictor and the outcome variable. However, the addition of random effects can reduce power (Heck et al., 2012). When within-person mood predictor variables (CESD-10, PA, NA) were included as random effects, model fit measured by Akaike's Information Criterion (AIC) did not improve relative to a model with only fixed effects; in fact, model fit worsened. Additionally, the residual variance in slope was not significant, indicating that mood variables did not correlate differently with IL-6 across individuals. Therefore, all models examining IL-6 as an outcome included only fixed effects predictors.

Results of bivariate analyses of potential covariates revealed that physical activity level ($B=-.022, p=.036$) and use of antihypertensive medication ($B=-.110, p=.006$) were significantly associated with log transformed IL-6 values. Thus, these variables were included with age, gender, BMI, and smoking status as covariates in all models examining IL-6 as an outcome. Years of education, ethnicity, use of depression medication, use of cholesterol-lowering medications, role overload and years caregiving at baseline, were not significantly associated with log IL-6 in bivariate analyses (all $ps > .28$). The association of sleep quality and log IL-6 approached statistical significance ($p=.053$). These variables were not included as covariates in the models examining IL-6.

Table 4 displays the parameter estimates for the effects in the multilevel regression models for log IL-6. Model A examines the effects of the between-person CESD-10 variable (a caregiver's average CESD-10 score across all annual assessments) and the within-person

CESD-10 variable (the deviation of an individual's annual assessment score from their personal mean across all assessments). Results indicate that neither the CESD-10 within ($p=.588$) or between ($p=.135$) variables were significantly associated with log IL-6. Model B includes the effects of covariates. Age was significantly positively associated with log IL-6 ($p<.001$). Antihypertensive use was significantly associated with lower IL-6 ($p=.021$). CESD-10 within ($p=.400$) and CESD-10 between ($p=.164$) variables were not significantly associated with IL-6. Model C examines the effects of between-person and within-person positive affect and between-person and within-person negative affect on log IL-6. For positive affect, neither between-person ($p=.991$) nor within-person ($p=.844$) variables were significantly associated with log IL-6. Within-person negative affect was not significantly associated with IL-6 ($p=.732$), but between-person negative affect was significantly associated with IL-6 ($p=.029$) such that caregivers with higher average negative affect across all annual assessments had significantly higher IL-6 levels, controlling for positive affect. This pattern of significance for the within-and between-person positive and negative affect variables remained when Model D was tested with the addition of covariates. In Model D, age was also a significant predictor of increased IL-6 ($p<.001$) and antihypertensive use was again associated with lower IL-6 ($p=.028$). In the present data, there were small to moderate correlations of PA and NA (within-person $r = -0.25$; between-person $r = -0.33$).

Table 4. Predictors of logIL-6 Concentrations (Unstandardized Regression Coefficients With Standard Errors)

Variable / Effect	Model A (CESD-10 variables only)		Model B (Covariates included)	
	Estimate	SE	Estimate	SE
Intercept	.096*	.024	.19**	.038
Gender	--	--	-.062	.051
Age	--	--	.048**	.010
Body Mass Index	--	--	.011	.008
Smoking status	--	--	-.082	.041
Physical Activity	--	--	-.004	.012
Antihypertensive Use	--	--	-.091*	.039
CESD-10 Within	.002	.004	.003	.004
CESD-10 Between	.007	.005	.006	.005
	Pseudo R ² = .011		Pseudo R ² = .075	
Variable / Effect	Model C (Affect variables only)		Model D (Covariates included)	
	Estimate	SE	Estimate	SE
Intercept	.096**	.024	.19**	.038
Gender	--	--	-.063	.050
Age	--	--	.048**	.010
Body Mass Index	--	--	.011	.008
Smoking status	--	--	-.080	.041
Physical Activity	--	--	-.003	.012
Antihypertensive Use	--	--	-.086*	.039
PA Within	-.001	.004	-.001	.004
PA Between	-.00004	.004	-.0004	.004
NA Within	-.001	.004	.002	.004
NA Between	.011*	.005	.009*	.005
	Pseudo R ² = .027		Pseudo R ² = .086	

* $p < .05$; ** $p < .001$

Outcome: log CRP

All mood predictors were entered as fixed effects in the models examining CRP. As with IL-6, models were explored testing within-person mood variables as random effects, however, this did not improve model fit and the residual variance in slope was not significant, indicating that mood variables did not correlate differently with CRP across individuals. Therefore, all models examining CRP included only fixed effects.

Results of bivariate analyses of potential covariates revealed that physical activity level ($B=-.041, p=.013$) and use of antihypertensive medication ($B=-.159, p=.009$) were significantly associated with log transformed CRP values. Thus, these variables were included with age, gender, BMI, and smoking status as covariates in all models examining CRP as an outcome. Years of education, ethnicity, use of depression medication, use of cholesterol-lowering medications, role overload, sleep quality and years caregiving at baseline, were not significantly associated with log CRP in bivariate analyses (all $ps > .17$) and were not included as covariates in the models.

Table 5 displays the parameter estimates for the effects in the multilevel regression models for log CRP. Model E examines the effects of the between-person CESD-10 variable (a caregiver's average CESD-10 score across all annual assessments) and the within-person CESD-10 variable (the deviation of an individual's annual assessment score from their personal mean across all assessments). Results indicate that neither the CESD-10 within ($p=.961$) or CESD-10 between ($p=.092$) variables were significantly associated with log CRP. Model F includes the effects of covariates. Age was significantly positively associated with CRP ($p=.004$) and antihypertensive use was significantly associated with lower CRP ($p=.011$). CESD-10 within ($p=.772$) and between ($p=.130$) variables were again not significantly associated with CRP. Model G examines the effects of between-person and within-person

positive affect and between-person and within-person negative affect on CRP. For positive affect, neither between-person ($p=.387$) nor within-person ($p=.847$) variables were significantly associated with CRP. Within-person negative affect was not significantly associated with CRP ($p=.367$), but between-person negative affect was significantly associated with CRP ($p=.008$) such that caregivers with higher average negative affect across all annual assessments had significantly higher CRP levels, controlling for positive affect. This pattern of significance for the within-and between- positive and negative affect variables remained when Model H was tested with the addition of covariates. In Model H, age was also a significant predictor of increased CRP ($p=.007$) and antihypertensive use was significantly associated with lower CRP ($p=.012$).

Table 5. Predictors of logCRP Concentrations (Unstandardized Regression Coefficients With Standard Errors)

Variable / Effect	Model E (CESD-10 variables only)		Model F (Covariates included)	
	Estimate	SE	Estimate	SE
Intercept	.27**	.035	.38**	.055
Gender	--	--	-.11	.072
Age	--	--	.049*	.017
Body Mass Index	--	--	-.006	.014
Smoking status	--	--	-.039	.062
Physical Activity	--	--	-.018	.021
Antihypertensive Use	--	--	-.15*	.060
CESD-10 Within	-.0003	.007	.002	.007
CESD-10 Between	.011	.007	.010	.006
	Pseudo R ² = .013		Pseudo R ² = .066	
Variable / Effect	Model G (Affect variables only)		Model H (Covariates included)	
	Estimate	SE	Estimate	SE
Intercept	.27**	.034	.37**	.054
Gender	--	--	-.12	.071
Age	--	--	.047*	.018
Body Mass Index	--	--	-.006	.014
Smoking status	--	--	-.031	.061
Physical Activity	--	--	-.018	.021
Antihypertensive Use	--	--	-.15*	.059
PA Within	.001	.006	.001	.006
PA Between	.005	.006	.005	.005
NA Within	-.006	.006	-.002	.006
NA Between	.019*	.007	.017*	.007
	Pseudo R ² = .032		Pseudo R ² = .081	

* $p < .05$; ** $p < .001$

Mood Variables and Illness Symptoms (Aims 3 and 4)

Outcome: Flu symptoms

Results of bivariate analyses of potential covariates revealed that higher BMI (OR=1.08, $p=.007$), poorer sleep quality (OR=1.14, $p<.001$), use of antidepressant medications (OR=1.71, $p=.028$) and use of antihypertensive medications (OR=1.66, $p=.047$) were all associated with increased likelihood of experiencing flu symptoms. These variables were included with age and gender in all models examining flu symptoms as an outcome. Years of education, ethnicity, smoking status, physical activity, role overload, use of cholesterol-lowering medications, and years caregiving at baseline were not significantly associated with likelihood of experiencing flu symptoms in bivariate analyses (all $ps > .06$) and were not included as covariates in the models.

Table 6 displays the odds ratios and 95% confidence intervals for the effects in the multilevel logistic regression model predicting the presence of flu symptoms. Model 1 examines the effects of the between-person CESD-10 variable (the average CESD-10 score across all annual assessments) and the within-person CESD-10 variable (the deviation of an individual's annual assessment score from their personal mean across all assessments). Results indicate that both the CESD-10 within and between variables were significantly associated with likelihood of flu symptoms. Caregivers with higher average CESD-10 score across all annual assessments had a greater likelihood of experiencing flu symptoms ($p<.001$). Caregivers with greater annual fluctuation of CESD-10 score (relative to their own personal mean across all assessments) had a greater likelihood of experiencing flu symptoms ($p=.006$). Model 2 tested CESD score variables with the inclusion of covariates. Both CESD-10 within ($p=.010$) and CESD-10 between ($p<.001$) variables remained significant predictors of flu symptoms in

this model. Additionally, increased BMI ($p=.042$) was associated with the presence of flu symptoms, as was use of antihypertensive medications ($p=.021$).

Model 3 tested the effects of the between- and within-person affect variables. Results indicated that between-person NA was significantly positively associated with an increased likelihood of experiencing flu symptoms ($p=.002$). Between-person PA was associated with decreased likelihood of flu symptoms ($p=.044$). Neither within-person NA ($p=.778$) nor within-person PA ($p=.056$) was significantly associated with flu symptoms. Model 4 examines these relationships with the addition of covariates. BMI ($p=.040$) and antihypertensive medication use ($p=.041$) were both positively associated with flu symptoms. When covariates were added to the model, between-person negative affect remained a significant predictor of flu symptoms ($p=.002$), but the relationship of between-person positive affect to flu symptoms was no longer significant ($p=.065$).

Table 6. Predictors of Flu Symptoms

Variable / Effect	Model 1	Model 2
	(CESD-10 variables only)	(Covariates included)
Intercept	Odds Ratio (95% CI) 1.63* (1.23; 2.16)	Odds Ratio (95% CI) 0.94 (0.50; 1.76)
Age	--	1.17 (0.98; 1.39)
Gender	--	1.21 (0.65; 2.26)
BMI	--	1.16* (1.01; 1.34)
Sleep Quality	--	0.99 (0.87; 1.12)
Antidepressant use	--	1.34 (0.77; 2.30)
Antihypertensive use	--	1.76* (1.09; 2.84)
CESD-10 Within	1.09* (1.02; 1.16)	1.10* (1.02; 1.18)
CESD-10 Between	1.18** (1.11; 1.25)	1.17** (1.11; 1.25)
Pseudo R ² = 0.35		Pseudo R ² = 0.33
Variable / Effect	Model 3	Model 4
	(Affect variables only)	(Covariates included)
Intercept	Odds Ratio (95% CI) 1.59* (1.20; 2.11)	Odds Ratio (95% CI) 0.89 (0.45; 1.74)
Age	--	1.18 (0.99; 1.41)
Gender	--	1.29 (0.68; 2.47)
BMI	--	1.16* (1.01; 1.34)
Sleep Quality	--	1.01 (0.90; 1.14)
Antidepressant use	--	1.52 (0.91; 2.55)
Antihypertensive use	--	1.64* (1.02; 2.62)
PA Within	0.95 (0.91; 1.00)	0.96 (0.91; 1.01)
PA Between	0.95* (0.91; 0.99)	0.96 (0.91; 1.00)
NA Within	1.01 (0.95; 1.08)	1.02 (0.95; 1.10)
NA Between	1.11* (1.04; 1.19)	1.11* (1.04; 1.19)
Pseudo R ² = 0.37		Pseudo R ² = 0.39

* $p < .05$; ** $p < .001$

Outcome: Other symptoms

Results of bivariate analyses of potential covariates revealed that taking antidepressants (OR=2.54, $p=.001$) and poorer sleep quality (OR=1.13, $p=.001$) were significantly associated with increased likelihood of experiencing other (non-flu) symptoms.

These variables were included with age and gender in all models examining other symptoms as

an outcome. Years of education, smoking status, BMI, role overload, physical activity, taking antihypertensive or cholesterol-lowering medications, years caregiving at baseline, and ethnicity were not significantly associated with likelihood of experiencing other symptoms in bivariate analyses (all p s > .09) and were not included as covariates in the models.

Table 7 displays the odds ratios and 95% confidence intervals for the effects in the multilevel logistic regression model predicting presence of non-flu illness symptoms. Model 5 examines the effects of the between-person CESD-10 variable (the average CESD-10 score across all annual assessments) and the within-person CESD-10 variable (the deviation of an individual's annual assessment score from their personal mean across all assessments). Results indicated that neither the CESD-10 within ($p=.065$) nor the CESD-10 between ($p=.072$) variables was significantly associated with likelihood of experiencing non-flu illness symptoms. These predictors remained non-significant after the addition of covariates in model 6. Use of antidepressants ($p=.002$) and female gender ($p=.030$) were significantly associated with increased likelihood of experiencing non-flu illness symptoms.

Model 7 tested the effects of the between- and within-person affect variables. Results indicated that neither between-person PA ($p=.333$) nor between-person NA ($p=.068$) were significantly associated with non-flu illness symptoms. Within-person NA was significantly associated with increased presence of non-flu illness symptoms ($p=.042$), such that yearly increases in NA relative to one's personal mean level of NA throughout the study were associated with greater likelihood of experiencing flu symptoms. Within-person PA was not significantly associated with non-flu symptoms ($p=.313$). Model 8 examines these relationships with the addition of covariates. Use of antidepressants ($p=.001$) and female gender ($p=.031$) were significantly associated with experiencing non-flu symptoms. When covariates were added to the model, within-person NA remained a significant predictor of other symptoms

($p=.047$). Within-person PA ($p=.385$), between-person PA ($p=.593$), and between-person NA ($p=.086$) were again not significantly associated with experiencing non-flu illness symptoms.

Table 7. Predictors of Non-Flu (Other) Illness Symptoms

Variable / Effect	Model 5	Model 6
	(CESD-10 variables only)	(Covariates included)
	Odds Ratio (95% CI)	Odds Ratio (95% CI)
Intercept	0.57** (0.42; 0.77)	0.27** (0.15; 0.50)
Age	--	1.01 (0.87; 1.17)
Gender	--	2.10* (1.07; 4.10)
Antidepressant Use	--	2.26* (1.35; 3.78)
Sleep Quality	--	1.08 (0.96; 1.21)
CESD-10 Within	1.07 (0.99; 1.14)	1.05 (0.98; 1.13)
CESD-10 Between	1.06 (0.99; 1.12)	1.03 (0.97; 1.10)
	Pseudo R ² = 0.35	Pseudo R ² = 0.38
Variable / Effect	Model 7	Model 8
	(Affect variables only)	(Covariates included)
	Odds Ratio (95% CI)	Odds Ratio (95% CI)
Intercept	0.57** (0.42; 0.77)	0.27** (0.15; 0.50)
Age	--	1.04 (0.89; 1.21)
Gender	--	2.11* (1.07; 4.18)
Antidepressant Use	--	2.33* (1.39; 3.91)
Sleep Quality	--	1.08 (0.97; 1.20)
PA Within	0.97 (0.92; 1.03)	0.97 (0.91; 1.03)
PA Between	0.98 (0.93; 1.02)	0.99 (0.94; 1.04)
NA Within	1.05* (1.00; 1.11)	1.05* (1.00; 1.11)
NA Between	1.06 (0.99; 1.12)	1.05 (0.99; 1.11)
	Pseudo R ² = 0.34	Pseudo R ² = 0.40

* $p < .05$; ** $p < .001$

This chapter is currently being prepared for submission for publication of the material. Chatillion, Elizabeth; Grant, Igor; Gallo, Linda C.; Mills, Paul J.; Roesch, Scott C.; Mausbach, Brent T. The dissertation author was the primary investigator and author of this material.

DISCUSSION

The present study aimed to investigate the impact of mood disturbance on acute and chronic health outcomes (i.e., flu symptoms and biomarkers of inflammation) in elderly spousal Alzheimer's disease (AD) caregivers. Although existing evidence from cross-sectional studies provides preliminary support for associations among mood disturbance and increased risk for acute and chronic illness in caregivers, the present study examined these relationships longitudinally. Longitudinal analysis allowed for aggregation of data over time to examine between-person differences in depression and positive and negative affect, which may provide insight into the effects of chronic mood disturbance on health outcomes. This analysis also allowed for examination of individual fluctuations in mood disturbance (i.e., within-person effects) on health outcomes. In a sample of 116 spousal Alzheimer caregivers who completed annual assessments for up to five years, between-person and within-person effects of mood disturbance (depressive symptoms, positive affect, and negative affect) were examined as predictors of inflammatory markers IL-6 and CRP, and the presence of acute illness symptoms.

Depressive Symptoms and Caregiver Health

Depressive Symptoms and Inflammation

The primary hypotheses regarding depressive symptoms and inflammatory outcomes were not supported in these analyses. Results indicated that caregivers' average level of depressive symptoms across the five years of study (i.e., between-person CESD-10 score) was not significantly associated with either IL-6 or CRP levels. Caregivers' yearly fluctuations in depressive symptoms relative to their own personal mean (i.e., within-person CESD-10 score) were also not significantly associated with IL-6 or CRP levels. These findings are unexpected given the large body of literature associating depressive symptoms with increased levels of

inflammatory biomarkers including IL-6 and CRP in noncaregiving populations (Baune et al., 2012; Bankier, et al., 2009; Elovainio et al., 2009; Frasure-Smith, et al., 2009; Howren et al., 2009; Johansson et al., 2011; Kobrosly & van Wijngaarden, 2010; Ma et al., 2010; Stewart, Rand, Muldoon, & Kamarck, 2009; Uddin et al., 2011) as well as preliminary support for these associations in caregivers (Clark, Nicholas, Wassira, & Gutierrez, 2013; Gouin et al., 2012; Mausbach et al., 2011). One possible explanation for the lack of observed associations of depressive symptoms with inflammatory biomarkers could be related to the measurement of depressive symptoms in the current study. In Howren and colleagues' (2009) meta-analysis demonstrating relationships among depressive symptoms and IL-6 and CRP, they observed much stronger associations between depression and inflammatory outcomes in studies that used clinical interview to assess depressive symptoms ($d=0.52$ for IL-6; $d=0.26$ for CRP), compared with studies that measured depressive symptoms using self-report questionnaires ($d=0.08$ for IL-6; $d=0.12$ for CRP). It is possible that a more thorough assessment of depressive symptoms using clinical interview may have resulted in significant associations with inflammatory outcomes in this sample. Additionally, Howren and colleagues' (2009) meta-analysis found that associations between depressive symptoms and both IL-6 and CRP were stronger when measured in samples of clinically depressed patients ($d=0.71$ for IL-6; $d=0.40$ for CRP) compared with community samples ($d=0.09$ for IL-6; $d=0.11$ for CRP). In the current study, caregivers' average CESD-10 score was slightly above eight, which is two points below the CESD-10 suggested cutoff score for determining clinically significant symptoms of depression. It is possible that additional research in a sample of caregivers diagnosed with Major Depressive Disorder could reveal significant associations between depression and inflammatory biomarkers that were not evident in this sample of caregivers with mild to moderate levels of depressive symptoms. However, in Howren and colleagues' meta-analysis,

significant associations between depressive symptoms and inflammation were observed even in non-clinically depressed samples, although associations were weaker. Another possible explanation for the lack of significant associations of depressive symptoms with inflammation in the present study could be related to the timing of measurement of depressive symptoms and inflammation. Depressive symptoms in the current study were measured over the past week. Basal plasma levels of IL-6 and CRP may not be expected to fluctuate as quickly as depressive symptoms and may be influenced by affective experiences occurring outside the time period during which depressive symptoms were measured in the study. In light of the unexpected findings in the present study, the relationship between depression and inflammation in dementia caregivers warrants additional investigation. Future longitudinal research is needed using larger samples, as increased power may aid in detecting significant effects. Research with a sample of caregivers exhibiting a wider range of depressive symptoms may also be better able to detect significant associations between depression and inflammation.

Consistent with prior research, age and antihypertensive use were significantly associated with both IL-6 and CRP in these analyses, suggesting that IL-6 and CRP increased throughout the duration of the study, and caregivers who reported using antihypertensive medications had lower levels of IL-6 and CRP (Howren et al., 2009). In light of prior research, it is somewhat surprising that BMI, gender, and smoking status were not significantly associated with inflammatory markers in these analyses. It is possible that the lack of significant associations of BMI and inflammation in the present study is related to measurement error in BMI, as caregivers' weight was obtained through self-report. Prior findings regarding the moderating impact of gender on the associations of depression and inflammation have been mixed, with some studies finding no significant effect of gender as in the present study (Howren et al., 2009). The present study included only one caregiver who

was a current smoker at the baseline assessment, which may account for the lack of significant associations of smoking status with inflammation.

Depressive Symptoms and Acute Illness Symptoms

As hypothesized, depressive symptoms were associated with the presence of flu symptoms in the current analyses. Results indicated that both between-person and within-person depressive symptoms were significantly positively associated with experiencing flu symptoms. Caregivers with a higher average level of depressive symptoms across the five years of study were 1.17 times more likely to report experiencing flu symptoms, controlling for covariates. Additionally, caregivers reporting an increase in depressive symptoms in a given year relative to their personal mean level of depressive symptoms were also 1.10 times more likely to experience flu symptoms in that year. Although these effects are small in magnitude, these results suggest that chronic elevations in depressive symptoms sustained over a period of years, as well as more acute (yearly) fluctuations in depressive symptoms, are both associated with an increased likelihood of experiencing flu symptoms. These findings are consistent with prior research demonstrating links between elevated depressive symptoms and poorer subjective health, including more self-reported illness symptoms (Cucciare et al., 2010; Pinquart & Sorensen, 2008). However, the current study is the first to directly examine the link between depressive symptoms and infectious illness symptoms in dementia caregivers. Furthermore, the longitudinal design of the present study allows for examination of both chronic elevations in depressive symptoms and yearly fluctuations in depressive symptoms over time (within the same caregiver), and found that both significantly predict increased likelihood of flu symptoms.

Based on prior research, the observed links between depressive symptoms and acute

illness symptoms are likely mediated by changes in immune functioning. Emotionally distressed caregivers display evidence of immune dysregulation including alterations in lymphocyte β 2-adrenergic receptor functioning (Mills et al., 1997; 2004), poorer antibody response to influenza vaccine (Segerstrom, Schipper, & Greenberg, 2008; Vedhara et al., 1999), impaired T cell proliferation and a reduction in NK cells (Castle et al., 1995). The present study provides support for a link between depressive symptoms and symptoms of acute infectious illness, but further research is required to directly test potential immune mechanisms of these effects. It is important to note that although the present analyses are longitudinal in nature, they do not establish causality. These results suggest that depressive symptoms and flu symptoms covary over time within caregivers, but they do not indicate whether increases in depressive symptoms cause increases in flu symptoms. Although substantial evidence suggests that depression contributes to morbidity through immune dysregulation, this relationship is likely bidirectional (Kiecolt-Glaser & Glaser, 2002; Segerstrom & Miller, 2004). Immune activation during acute illness, in particular the release of cytokines, impacts the central nervous system and can induce “sickness behavior” such as reduction in activity, social isolation, lethargy, fatigue, decreased appetite, and depressed mood (e.g., Maier & Watkins, 1998). It is possible that the presence of flu symptoms causes behavioral and affective changes which contribute to higher self-report of depressive symptoms. The causality of these relationships cannot be determined by the present study.

With regard to non-flu illness symptoms (e.g., toothache, skin rash) neither between-person nor within-person depressive symptoms were significantly associated with likelihood of experiencing non-flu illness symptoms. This finding may not be surprising given that the majority of research to date regarding depression and illness symptoms has focused on overall subjective health or symptoms of acute infectious illness such as cold and flu. Additionally, the

non-flu illness symptoms examined in the present study varied widely (e.g., skin rash, toothache, discomfort with hemorrhoids; see Appendix A for a full list of symptoms), thus, this set of symptoms may not represent a single underlying illness as did the set of flu symptoms. In fact, the set of “other” non-flu symptoms examined in the present study may represent a “control” with which to compare the results of flu symptom analyses. That is, the lack of association of “other” symptoms with depressive symptoms may indicate that caregivers reporting increased depressive symptoms are not endorsing increased illness symptoms of any type, but only flu-related symptoms. This may, in fact, further support the idea that caregivers with depressed affect undergo specific immunologic changes that increase susceptibility to cold and flu-like infections, rather than depressive affect leading to an increase in reporting of any somatic complaints. However, the results of the non-flu symptom analyses should be interpreted with caution given that experiencing “other” symptoms at baseline was significantly associated with missingness of later study assessments. Future research may wish to further examine the impact of mood disturbance on rates of non-flu illness symptoms in caregivers, though the impact of the presence of these “other” symptoms on the dementia caregiving experience is unclear.

Positive Affect and Caregiver Health

Positive Affect and Inflammation.

Hypotheses regarding positive affect (PA) and health outcomes were largely unsupported in the present study. Contrary to hypotheses, neither average PA throughout the study (between-person effects), nor yearly individual fluctuations in PA (within-person effects), were associated with biomarkers of inflammation (IL-6 and CRP). These findings are somewhat surprising given the growing body of literature suggesting an association between

PA and health (Pressman & Cohen, 2005), including decreased risk of mortality (Chida & Steptoe, 2008) and lower risk for coronary heart disease (Kubzansky & Thurston, 2007), even when controlling for levels of NA. There is growing support for the idea that PA, rather than a mere lack of NA, may have a protective effect on health. Accumulating evidence suggests that the protective influence of PA on health may be mediated through biological processes, including activation of neuroendocrine, autonomic, and immune systems (Dockray & Steptoe, 2010). However, direct associations between PA and systemic inflammation have not been thoroughly studied to date. Preliminary research suggests that IL-6 may be inversely associated with PA (Friedman et al., 2007), even after controlling for lifestyle confounds and depressive symptoms (Brouwers et al., 2013; Prather et al., 2007). Evidence for an association between CRP and PA has been more mixed (Brouwers et al., 2013). One study found inverse associations of PA with both IL-6 and CRP, even after controlling for covariates such as age, ethnicity, BMI and smoking status, though this association was observed in women but not men (Steptoe et al., 2008). The present study is the first to directly examine PA and inflammation in dementia caregivers. Given the surprising lack of association of PA and inflammation in this sample, further research investigating these relationships is warranted, including research with larger sample sizes, as limited power may have contributed to the lack of significant findings in the present study. Average levels of PA in the current sample, as measured by PANAS scores, were similar to those observed in a large non-clinical normative sample of adults in the UK (Crawford & Henry, 2004).

Positive Affect and Acute Illness Symptoms

Support for hypotheses regarding PA and illness symptoms in the present study was mixed. Yearly fluctuations in PA (within-person effects) were not associated with experiencing

illness symptoms, however, average PA over the course of the five-year study was associated with a lower likelihood of experiencing flu symptoms (but not non-flu illness symptoms). Caregivers with lower average PA were 1.05 times more likely to experience flu symptoms, controlling for their level of NA. This effect was quite small in magnitude, and additionally, when relevant covariates were included in the model, the association between average level of PA and flu symptoms became nonsignificant. Prior research has found that greater PA is associated not only with better subjective health, but also with lower risk of developing illness after exposure to rhinovirus and influenza A virus (Cohen et al., 2003; Cohen et al., 2006). The findings from the current investigation begin to extend these findings to caregivers, demonstrating that high levels of PA over time are associated with decreased likelihood of flu symptoms. However, these effects disappeared with the addition of covariates, suggesting that before drawing definitive conclusions about PA and acute illness in caregivers, these results require replication, likely with larger samples. Although preliminary, our study provides some indication that sustained high levels of PA over time may be associated with reduced flu symptoms, but yearly fluctuations are not associated with experiencing flu symptoms. This could suggest that sustained PA, or trait PA, is more strongly associated with acute illness outcomes than are fluctuations in PA, or state PA. Given that between-person effects of PA were not robust after the addition of covariates, these conclusions cannot be definitively drawn from these data. Additional longitudinal work is needed to continue to disentangle the relative contributions of sustained vs. acute increases in PA on the experience of illness in dementia caregivers. Non-flu illness symptoms were not associated with PA in the current study, which again, may not be surprising given the variety of “other” symptoms examined, and the fact that the immune mechanisms linking PA with symptoms of flu-like infectious (Dockray & Steptoe, 2010) illness may be unrelated to the presence of the non-flu symptoms examined in this study.

Negative Affect and Caregiver Health

Negative Affect and Inflammation

With regard to NA, support for hypotheses in the present study was mixed. Between-person NA was significantly positively associated with both IL-6 and CRP levels in this analysis. That is, caregivers with higher average NA across all annual assessments had significantly higher IL-6 and CRP levels, controlling for PA. The effect of between-person NA on IL-6 and CRP remained significant with the addition of relevant covariates, and indicated that a one-point increase in NA as measured with the PANAS scale was associated with a 0.009 *log* pg/mL increase in plasma IL-6 concentration and a 0.017 *log* mg/L increase in plasma CRP concentration. However, yearly fluctuations in NA (within-person effects) were not significantly associated with inflammatory outcomes. The existing literature examining affect and inflammation has focused more on PA than NA. The limited evidence regarding NA and inflammation is mixed with some studies finding that greater NA is associated with increased levels of inflammatory cytokines (Carroll et al., 2011; Dickerson et al., 2004; Marsland et al., 2008; Miyamoto et al., 2013) and other investigations finding no association between NA and IL-6 (Prather et al., 2007). To our knowledge, no studies to date have directly examined the associations between NA and inflammation in dementia caregivers, although a recent trial of a behavioral activation intervention for dementia caregivers observed significant improvements in both NA and IL-6 levels immediately after the 6-week intervention (Moore et al., 2013). The current study adds to the existing literature by demonstrating that caregivers exhibiting higher NA over a period of five years show higher levels of IL-6 and CRP. Lack of significant within-person effects for NA may suggest that more transient NA, such as that measured over a period of weeks, is not associated with changes in inflammatory markers in dementia caregivers. However, this finding is inconsistent with some prior research

demonstrating associations between IL-6 and NA over a 30-day period, even after controlling for more stable personality characteristics (Miyamoto et al., 2013). Other investigations support a greater role of trait NA in predicting inflammation (Marsland et al., 2008). It is also possible that the present study was unable to detect significant within-person effects due to power limitations. The relative contribution of within- and between-person NA to inflammation in dementia caregivers warrants additional investigation.

Negative Affect and Acute Illness Symptoms

Between-person NA, but not within-person NA, was significantly associated with experiencing flu symptoms in the present study. Caregivers with higher average NA were 1.11 times more likely to report experiencing flu symptoms, controlling for their level of PA and other covariates. These between-person effects are consistent with prior research demonstrating associations between increased NA and poorer subjective health, including report of more cold and flu symptoms (Leventhal et al., 1996) and with increased reported illness symptoms after exposure to respiratory virus (Cohen et al., 1995). The present investigation provides preliminary support for these findings in caregivers, suggesting that sustained increases in NA over a period of years is associated with high report of flu symptoms in dementia caregivers. This increase in reported flu symptoms may result from changes in immunity associated with NA. Indeed, in noncaregiving populations, higher levels of NA have been associated with alterations in immune functioning that may increase risk for acute infections, such as poorer secondary antibody response to vaccination (Cohen, Miller, & Rabin, 2001). Within-person fluctuations in NA from year-to-year were not associated with flu symptoms in the present study. This could indicate that chronic elevations in NA impact acute illness in dementia caregivers more than fluctuations in NA. However, other evidence from noncaregiving

populations has found that state NA was more strongly associated with somatic symptom complaints than trait NA (Leventhal et al., 1996). Power limitations may also account for the lack of significant within-person effects of NA on flu symptoms, reiterating the need for additional research investigating these relationships.

However, non-flu illness symptoms were significantly associated with yearly increases in NA in the current study. Although higher average levels of NA (between-person effects) were not associated with increased likelihood of experiencing non-flu illness symptoms, caregivers who showed an increase in NA in a given year relative to their mean level of NA were more 1.05 times more likely to report experiencing non-flu illness symptoms in that year. This effect is small, though findings could indicate that increases in NA measured over a period of “a few weeks” are associated with non-flu illness symptoms or somatic complaints. Given that within-person depressive symptoms were not associated with experiencing non-flu symptoms, it is possible that other components of NA not captured by the CESD-10 (e.g., anxiety) could be driving increased reporting of non-flu somatic complaints. However, as previously mentioned, results of the non-flu symptom analyses should be interpreted with caution given that experiencing “other” symptoms at baseline was significantly associated with missingness of later study assessments. The relationship of NA and non-flu illness symptoms may warrant additional research in caregivers, including investigation of how experiencing these non-flu illness symptoms might impact the caregiving experience.

Implications

This study is the first to directly examine associations of mood disturbance with symptoms of acute infectious illness in a sample of dementia caregivers. Although the consequences of acute infectious illness may be less severe or of shorter duration than cardiovascular consequences associated with caregiving, the presence of acute infectious

illness can significantly impact the caregiving experience. Spousal dementia caregivers provide an important societal resource by providing free care that would otherwise burden the healthcare system (Alzheimer's Association, 2012). When family dementia caregivers experience acute illness, this can impair their ability to provide quality care to their loved one. Depending on the caregiver's level of illness, it may be necessary to obtain outside care for the care recipient while the caregiver recovers. Additionally, acute illnesses such as cold or flu have a substantial public health impact (e.g., risk of serious complications or death among adults over age 65) and a large monetary cost to society (e.g., costs of hospitalization and outpatient medical visits). The current study demonstrates that elevated depressive symptoms are associated with greater likelihood of experiencing flu-related symptoms among dementia caregivers. The association of depressive symptoms with acute illness provides support for the notion that treating or preventing depressive symptoms in dementia caregivers may also reduce rates of acute illness. The longitudinal nature of the present analyses provides additional information about the links between depressive symptoms and acute illness that may be particularly relevant to interventions. Examination of between-person and within-person depressive symptoms across the five years of the study revealed that both sustained elevations in depressive symptoms over time and yearly fluctuations in depressive symptoms were associated with risk of experiencing flu symptoms. Demonstrating that changes in depressive symptoms over time *within the same individual* are associated with changes in that caregiver's experience of illness symptoms provides additional support for the idea that intervening to reduce depressive symptoms could lead to reductions in acute illness. This could not be inferred simply from examining between-person differences. We are not aware of any studies to date that have examined acute illness symptoms as an outcome of a psychosocial intervention, though the present work suggests that reduced experience of acute illness may be

an additional health benefit of psychosocial interventions for depression in dementia caregivers. Self-report measures of acute illness may be easier to measure as health outcomes of caregiver intervention trials and may require less participant burden compared with measurement other health outcomes (e.g., blood markers of cardiovascular risk). We encourage future investigations of psychosocial interventions targeting caregiver mood disturbance to include measures of physical illness as clinical outcomes.

This study also investigated the longitudinal associations of mood disturbance chronic health outcomes, in this case, inflammatory markers IL-6 and CRP, which are linked with downstream risk for cardiovascular disease. The lack of significant associations of depressive symptoms with inflammatory markers in this sample of dementia caregivers was surprising in the context of a large body of research demonstrating linkages between depression and inflammation. Another important aspect of the current study is the examination of PA and NA and their unique associations with health outcomes. PA and NA represent distinct dimensions of affect, each of which have been associated with health in research with noncaregiving populations. Measuring affect has the potential to capture a broader range of mood states than is typically included in measures of depression. Additionally, examining two distinct components of affect may be useful in identifying specific treatment targets for improving caregiver wellbeing. The present study found no significant relationship between PA and inflammation, but did find significant associations between NA and inflammation. The effects of NA on inflammation markers in the present study were small in magnitude. With regard to clinical significance, there are no well-established cutoffs for levels of IL-6 associated with elevated risk for CHD. Danesh and colleagues (2008) found that in patients without known CHD at baseline an increase of approximately 2 pg/mL in IL-6 concentration over 5 years was associated with an odds ratio of 1.94 for developing CHD, after adjusting for other established

CHD risk factors. With regard to CRP, established clinical guidelines suggest that values below 1 mg/L are considered low risk. CRP levels over 3 mg/L are considered high risk and represent a hazard ratio of 1.4 for experiencing an incident cardiovascular event (compared with CRP below 1), after adjusting for other risk factors (Pearson et al., 2003). It is possible that even small increases in inflammatory biomarker levels associated with increased NA, coupled with additional risk factors for inflammation in a population of elderly caregivers, may translate to meaningful increases in risk for long-term cardiovascular consequences.

The observed association of NA with inflammation in the present study could indicate that targeting reductions in NA as part of psychosocial interventions for caregivers may have maximal benefit for not only mood outcomes, but also cardiovascular health risk. Prior research suggests that dementia caregivers' level of NA is uniquely linked with negative cognitions, whereas caregivers' engagement in pleasurable activities is uniquely linked with PA (Mausbach et al., 2009). This suggests that perhaps treatments targeting reduction in caregivers' negative cognitions, such as CBT, could result in improvements in mood as well as inflammation. However, caregiver treatments aimed at reducing NA need not be confined to CBT. A recent pilot study evaluated a group intervention for dementia caregivers using meditation and guided imagery and found that this intervention significantly reduced anxious and depressive affect (Jain, Nazarian, & Lavretsky, In Press). Another recent intervention trial for caregivers of persons with early dementia found that a six-session problem-solving therapy (PST) treatment resulted in significant reductions in anxiety and depression (Garand et al., In Press). Additionally, a mindfulness-based stress reduction (MBSR) intervention has been recently shown to significantly reduce perceived stress and state anxiety (Whitebird et al., 2012). Even a recent trial of behavioral activation for dementia caregivers, a treatment specifically targeting increasing levels of engagement in pleasurable activities and not directly

addressing negative cognitions, demonstrated significant reductions in NA (as measured by PANAS) for caregivers participating in the intervention compared with controls (Moore et al., 2013). This intervention also observed concomitant improvement in IL-6 levels. A variety of psychosocial interventions are available that may improve dementia caregivers' NA. However, very few intervention trials aimed at improving caregiver mood have also measured changes in physical health outcomes post-intervention. The present study adds to accumulating evidence supporting the link between caregiver mood and health, suggesting that health variables, including systemic inflammation, could be additional outcomes measured as part of caregiver interventions in order to more fully assess the broad impact these interventions might have on caregiver mental and physical wellbeing.

Additionally, the results of the current study demonstrated that sustained elevations in NA, but not yearly changes in NA, were associated with increased inflammation in dementia caregivers. This particular finding may suggest that chronic health consequences associated with caregiving are associated with chronically elevated NA, and could therefore be prevented through early intervention to reduce caregiver NA or even prevention efforts aimed at protecting caregivers from increases in NA as they adjust to the caregiving role. Guided imagery, meditation, and maintaining engagement in pleasurable activities, all interventions shown to reduce NA in caregivers (Jain, Nazarian, & Lavretsky, In Press; Moore et al., 2013; Whitebird et al., 2012), could lend themselves particularly well to prevention interventions and might be easy to disseminate via caregiver community resource agencies. More research is needed regarding prevention and early intervention to address potential mood disturbance in dementia caregivers and the results of the current study suggest that such interventions could impact both acute and potentially chronic health outcomes.

Limitations

The present study has several limitations that should be considered. As previously mentioned, the results of the current study do not establish causality in the relationships among mood and health outcomes in caregivers. These longitudinal results add to the current literature on caregiver mood and health outcomes by examining the relative contributions of chronic mood disturbance on caregiver health and can investigate whether within-caregiver changes in mood are accompanied by changes in health. The results do not indicate whether fluctuations in mood cause changes in inflammation or report of illness symptoms, and do not establish mechanisms for these effects. Additional research is needed to investigate the causality of these relationships among mood and health, including prospective studies and controlled intervention trials targeting changes in mood and measuring health-related outcomes in caregivers. The present study helps lay the foundation for this important future work. Another method for preliminary exploration of causality in longitudinal designs would be to examine lagged correlations, e.g., examining whether mood measured at one time-point in a longitudinal design is associated with health outcomes measured at a later time point. In the present study, assessments were one year apart and mood variables were measured for a period of one to several weeks, thus examination of lagged correlations was not appropriate in this study. Future studies could measure mood and health outcomes at closer intervals (e.g., monthly) and examine lagged correlations. Another limitation of the present study is that the sample is predominantly Caucasian (88%), well-educated (43% were college graduates) and had a relatively high income (median reported monthly income was \$4,000). Therefore, the results of the present study may not be generalizable to the larger population of dementia caregivers. Future research would benefit from examining these relationships between mood and acute and chronic health outcomes in a sample of caregivers that is more diverse with regard to ethnicity,

education and socioeconomic status. A large body of research suggests that low socioeconomic status (SES), low education levels, and racial and/or ethnic minority status are associated with poorer health outcomes, including increased inflammation (Gruenewald et al., 2009; Herd et al., 2012; Khera et al., 2005; Paalani, Lee, Haddad & Tonstad, 2011) and these factors interact in complex ways to influence health (e.g., Reagan & Salsberry, 2014). The results of the present study may not extend to dementia caregivers of lower SES or to ethnic minority caregivers. Another significant limitation of the current study is the relatively small sample size for conducting mixed models regression with repeated measures. The present research requires replication within a larger sample of dementia caregivers, especially given that the level 2 sample size (in this case, number of caregivers) has a greater impact on power than the level 1 sample size (number of annual assessments) (Heck et al., 2012; Snijders, 2005). Some power may have been preserved given that the present analyses did not examine random effects in the models tested (Heck et al., 2012; Snijders, 2005), however, the relatively small sample size as well as the large number of models tested necessitates replication of these results in larger samples before definitive conclusions can be drawn about the longitudinal relationships among mood disturbance and health in dementia caregivers. The present results can be viewed as preliminary and support the need for additional research. Additionally, although the present sample of caregivers is small with regard to mixed models analyses, it is relatively large considering the difficulty of recruitment in this highly burdened population.

Conclusions

Despite the aforementioned limitations, the present study provides new insight into the potential links between mood and physical health in spousal dementia caregivers, with regard to both chronic and acute health outcomes. Although the results require replication, they suggest that sustained elevations in depressive symptoms and NA over several years are linked

with increased symptoms of acute flu-like illness. More acute (yearly) increases in depressive symptoms within an individual caregiver may also be associated with experiencing flu symptoms. In this study, NA was uniquely associated with inflammatory biomarkers in this sample of caregivers. Although causal inferences cannot be made from the current study, the associations observed in these analyses highlight the potential for improving caregiver acute and chronic health through intervention targeting improvements in depressive symptoms and NA. Additional longitudinal research with larger and more diverse samples of dementia caregivers is needed to further elucidate the relationships between mood and health assessed in this study. The current analyses highlight another important direction for future behavioral medicine research with dementia caregivers, that is, incorporating health outcomes into psychosocial intervention trials to directly examine the impact of treating mood on caregiver mental *and* physical health. Although preliminary, the present study helps lay the groundwork for future research aimed at improving the wellbeing of dementia caregivers.

This chapter, in part, is currently being prepared for submission for publication of the material. Chattillion, Elizabeth; Grant, Igor; Gallo, Linda C.; Mills, Paul J.; Roesch, Scott C.; Mausbach, Brent T. The dissertation author was the primary investigator and author of this material.

APPENDIX A

Assessment of Acute Illness Symptoms

The following items assessed caregivers' illness symptoms. Caregivers responded "yes" or "no" to the question, "In the past month, have you experienced the following symptoms?" For each item answered "yes," caregivers reported the number of days during the last month during which they experienced the symptom(s).

1. *Temperature of 100 degrees F (37.7 C) or more
2. *Headache lasting more than 1 hour
3. Skin rash or hive
4. *Painful, irritated, or burning eyes
5. *Ear ache or ear infection
6. Toothache
7. *Sore throat
8. *Sneezing, stuffy, or runny nose
9. *Dry cough (more than occasional)
10. *Coughing up substances other than saliva, or thin phlegm
11. *Wheezing (from chest)
12. *Unusual shortness of breath
13. Unplanned weight loss
14. *Nausea and/or vomiting
15. *Stomach pain or abdominal cramps
16. Heartburn
17. Chest pain other than heartburn
18. Unanticipated Rapid or pounding heart (not associated with exercise)
19. *Diarrhea
20. Bloody or black stools
21. Discomfort with hemorrhoids

The 13 items with an * indicate symptoms associated with cold or flu, or conditions that can arise as complications from cold or flu, such as bronchitis or pneumonia.

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