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Positive Emotions and Immune Respose to Influenza in Medically Stable Older Adults

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POSITIVE EMOTIONS AND IMMUNE RESPONSE TO INFLUENZA IN MEDICALLY STABLE OLDER ADULTS

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To Emily, Matt, and Rick

Hope is the Thing with Feathers

Hope is the thing with feathers
That perches in the soul,
And sings the tune without the words,
And never stops at all,

And sweetest in the gale is heard;
And sore must be the storm
That could abash the little bird
That kept so many warm.

Emily Dickinson

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ABSTRACT

Influenza results in substantial human suffering and health care costs. Evidence from psychoneuroimmunology suggests that emotions influence the immune system and may alter susceptibility to infectious diseases, like influenza. The purpose of this investigation was to evaluate the influence of psychological factors, health behaviors circulating levels of proinflammatory cytokines, and the development of influenza-like illness in older adults. Medically stable participants, 55 years of age and over, were enrolled from the general community and an elderly community. Psychological factors (emotions and perceived stress), health behaviors (sleep and activity) and plasma cytokine levels (IL-6 and IL-1β) were evaluated with respect to the development of influenza like-illness over the course of the influenza season (October to March 31, 2011). Findings revealed that individuals reporting influenza-like symptoms were significantly younger than those who did not report symptoms (60 versus 72 years). These individuals reported lower positive trait emotion scores on the Positive and Negative Affect Scale (PANAS), with significantly lower scores for the calm subscale for trait emotions. Those with influenza-like symptoms reported significantly higher levels of perceived stress and physical activity and less sleep disturbance. For cytokine measurements, significantly lower circulating IL-6 levels were observed at initial assessment for those with influenza-like symptoms. No differences were observed between groups for IL-1β. Lower calm trait subscales approached significance for

predicting increased IL-1β in plasma, suggesting a role for lower positive emotions and stress perception as risk factors for influenza-like illness in older adults. Further, these results support the need for additional study to evaluate potential mechanisms that may underlie these risks. Significant increases in positive trait emotion scores were associated with increasing age, higher Ego Resiliency Scale scores, fewer reported sleep problems and lower Perceived Stress scores. An ad hoc mediator analysis was significant for positive trait emotion scores mediating the relationship between scores for ego resiliency and perceived stress. This finding supported a direct and indirect role for positive emotions to reduce perceived stress.

CHAPTER ONE

PURPOSE OF STUDY

Influenza, a viral disease of the upper respiratory tract, extracts high costs in terms of human suffering and economic burden. The Centers for Disease Control (2009) reported average annual hospitalizations for influenza to be 36,000 for the period during 1979 to 2001, and average annual deaths from influenza of approximately 226,000 during 1990 to 1999. Direct medical costs of $1 billion to $3 billion were reported for influenza in the United States, with indirect costs, including lost earnings due to illness and lost future earnings due to death, estimated to be $10 billion to $15 billion annually (Office of Technology Assessment US Congress, 1981). More recent studies have attributed much higher costs ranging from $87 billion to $167 billion when considering the impact of epidemic influenza (Molinari et al., 2007; World Health Organization, 2003). It was estimated that 9% of the world population could contract symptomatic influenza annually (Ghendon, 1992).

Elderly individuals carry a higher risk for influenza, and higher risk for complications associated with influenza (Centers for Disease Control and Prevention, 2009). Approximately 90% of deaths from influenza occur in individuals over aged 65 (Thompson et al., 2003). Of the total economic burden of influenza, 64% was borne by individuals over age 65 (Thompson et al., 2003). As more Americans reach age 65, they will amplify the ranks of this group at high risk for influenza and its complications, and

influenza will exert an even greater impact on a greater number of individuals, the healthcare system, and the US economy.

Vaccination is cited as the most effective method for preventing influenza virus infection and its complications (Centers for Disease Control and Prevention, 2009) and remains the cornerstone of public health efforts to control influenza. The efficacy of Influenza vaccine has been estimated to be between 70 to 90% in young adults when there is a close match between the vaccine and circulating influenza strains (Couch, 1981). Unfortunately, influenza vaccine response in the elderly is less vigorous than in young adults, due to age related declines in the immune system (Cook, Barr, Hartel, Pond, & Hampson, 2006; Rivetti et al., 2009). Efficacy of influenza vaccine in the elderly has been shown to be 17-53% depending on circulating virus strains (Goodwin, Viboud, & Simonsen, 2006), with one review reporting the effectiveness of vaccine against influenza-like illness to be 23% for individuals living in homes for the elderly (Jefferson et al., 2005). A major review of 64 studies concluded that the effectiveness of influenza vaccine in elderly individuals was modest, and below decision making levels quoted for economic modeling irrespective of setting, outcome, population, and study design (Rivetti et al., 2009).

After considering these sobering statistics, the need to improve influenza outcomes among the elderly becomes evident. Turning to the topic of positive emotions may seem incongruous. Yet recent research into the field of positive emotions and psychoneuroimmunology suggest some interesting links for improving health outcomes,

especially related to immune response to vaccination. Positive emotions are an area in which nursing actions may exert an impact, either through the context or timing of interventions, or through application of techniques to increase positive emotions. If these interactions positively affect vaccination outcomes, this would add to the value of these nursing actions. The broad, long term objective of this dissertation is to explore positive emotions as they relate to health outcomes. This objective will be addressed by a research study to examine the role of positive emotions in affecting immune response to influenza in a medically stable population of adults aged 65 years of age and over.

This exploration of positive emotions and health outcomes will synthesize findings from psychology, psychoneuroimmunology, and immunology. A number of epidemiological studies on positive emotions and health outcomes will be reviewed. Background information on the pathology of influenza, vaccine components, and declines in immunity among the elderly will be provided. The implications of public health initiatives aimed at influenza vaccination for the elderly will be briefly discussed. The overall aim will be to apply knowledge from these diverse fields, using a psychoneuroimmunology model, to proposed research examining the impact of positive emotions on immune response to influenza within a healthy population of older adults.

CHAPTER TWO

REVIEW OF THE LITERATURE

In order to present information pertinent to positive emotions and immune response to influenza in the elderly, research on positive emotions and health outcomes will first be reviewed in five separate sections. The first section will focus on positive emotions and health outcomes beginning with definitions of the concept from psychology. This will be followed by a review of findings from the positive psychology movement, as well as research on positive emotions and beneficial health outcomes. In the next section, research from the field of psychoneuroimmunology, especially as it pertains to positive emotions and immune response to vaccination will be reviewed. After discussion of these conceptual approaches, influenza disease, virus, vaccine, and immunity will be briefly discussed in the next section. This will be followed with section providing a brief summary of age related declines in immunity. The final section of this literature review will discuss research on influenza in the elderly, ending with behavioral factors and emotions.

Research on Positive Emotions

Overview

Positive emotions have always been an important topic of human inquiry. Early interest was evidenced in Aristotle's discussion of the concept of eudemonia in

Nicomachean Ethics. Eudemonia is often translated as happiness in English. Even a brief review of Aristotle's discussions on eudemonia, however, reveal complex levels of meaning ranging from simple enjoyment of pleasurable activity, through the well lived life, to pride and virtue in accomplishments, and toward the concepts of duty and human flourishing (Ryff & Singer, 2008; Tefler, 1980). The pursuit of happiness has been cherished as the ultimate goal for Aristotle, successive philosophers, the United States government, the positive psychology movement, self-help books and innumerable talk shows. When positive emotions were entered into a major internet search engine on the World Wide Web on October 23, 2009, the number of hits generated was 2,130,000. While there is evidence for great depth and breadth of interest in positive emotions, going back 2,000 years and moving to the present day, this interest is not evident in healthcare literature.

In the United States, healthcare typically focuses on the treatment of illness and minimizing the effects associated with the progression of disease. Healthcare resources may be viewed as valuable commodities. The expenditure of these resources is prioritized to those areas where need is most pronounced; preserving life, curing illness, preventing disease. Nursing practice works within these priorities, but also supports patients in their emotional responses to health crises. Nursing practice acknowledges emotional components of disease processes, focusing efforts to help patients cope with stress, for example, or die with dignity. Despite the attention nursing gives to patient's emotions, nursing science has not emphasized the potential impact of positive emotions.

A notable exception to this inattention are nursing interventions aimed at promoting patient comfort.

The nursing profession is not alone in focusing attention on negative rather than positive emotions. Medicine, psychiatry, and other health professions share this propensity. The focus on negative emotions in health disciplines may be due to pathology associated with negative emotions. These include depression, anti-social behavior, overeating, violence, disease, and suicide. With the notable exceptions of sexual promiscuity, manic behavior, and addiction, there are relatively few problems/pathologies associated with positive emotions. There is mounting evidence, however, that there are potential health benefits of positive emotions. Healthcare researchers are beginning to investigate these emotions and the role they play in health and illness.

Definitions of Positive Emotions

Any examination of positive emotions requires that the term be defined. The ancients, modern literature, and especially the field of psychology, provide insight into the meaning of positive emotions. These insights and definitions are essential to any study of the concept.

Aristotle's distinction between *hedonia*, the momentary experience of pleasure, and *eudemonia*, a more reasoned valuation of life's quality and worth (Tefler, 1980), continues to be used by researchers on positive emotions (Diener, Lucas, & Scollon, 2006; Ryan & Deci, 2001; Ryff & Singer, 2008; Seligman & Csikszentmihalyi, 2000).

Modern day distinctions in positive emotions range from emotional responses which reflect momentary pleasurable engagement with the environment, through stable longer lasting trait characteristics, to psychological constructs used to characterize abilities within individuals, and finally to complex measures that provide global life evaluations.

Behavioral scientists, who use quantitative self-report measures of emotions, typically describe the moment to moment experience of positive emotions as short affective conditions characterized by feelings such as joy, happiness, enthusiasm, and contentment. These pleasurable experiences may be referred to as *state* emotions and are distinguished by the transitory nature of their experience (Stone, 1995). These momentary emotional experiences are contrasted with *mood* or *trait* emotions which describe a more enduring portrayal of how individuals typically feel (Seligman, Steen, Park, & Peterson, 2005). These are important distinctions relating to positive emotions, and certainly significant for any research (Janda, Markowski, Derlega, Nezlek, & McCain, 2006; Ong, Bergeman, Bisconti, & Wallace, 2006). Despite this importance, terms such as mood, trait, affect, and emotional state are frequently used interchangeably in the literature (Kemeny, 2007; Marsland, Pressman, & Cohen, 2007; Pressman & Cohen, 2005). This presents many challenges to the researcher of positive emotions who may be seeking to compare results or expand upon past findings. In contrast, studies differentiating and analyzing both state and trait emotions provide evidence that the interaction between fleeting emotional states and more stable mood valence within

individuals impacts responses to events (Janda et al., 2006; Zautra, Johnson, & Davis, 2005).

In seeking to define positive emotions for quantitative studies, several authors (Chesney et al., 2005; Cohn, Fredrickson, Brown, Mikels, & Conway, 2009; Diener, 2000; Diener & Emmons, 1984; Diener & Larsen, 1984; Diener et al., 2006; Fredrickson, Cohn, Coffey, Pek, & Finkel, 2008; Lucas, Clark, Georgellis, & Diener, 2003; Ostir, Ottenbacher, & Markides, 2004; Ryan & Deci, 2001; Watson, Clark, & Tellegen, 1988, Zautra et al., 2005) argued that positive emotions are distinct from negative emotions. This argument is in contrast to common perceptions that positive and negative emotions exist along a single continuum, that positive emotions are the polar opposites of negative emotions, or that positive emotions are defined by the absence of negative emotions. The co-occurrence of positive and negative emotions during even the most stressful experiences has been cited as evidence of their distinct natures (Folkman, 2008; Penninx et al., 2000).

Stone (1995) acknowledged that mood is an intrinsically difficult construct to measure, citing the importance of frequency, intensity, recall, situation, and bias in measuring emotions. Psychophysical responses must be defined by the researcher (Nunnally & Bernstein, 1994) and can often be situation specific. Psychology is still in the early stages of developing definitions for positive emotions, which presents challenges to the health care researcher looking for clearly objective variables and criteria. Any research on positive emotions should clearly define the positive emotions

under consideration as well as provide differentiation between positive transitory state emotions and more enduring trait emotions.

Complex Constructs of Positive Emotions

Both transitory emotions and stable mood conditions are distinct from more complex, positive psychological constructs. These more complex constructs are differentiated into two general groups: Cognitive and motivational constructs such as self-esteem, optimism, extraversion, purpose, and mastery; and, complex measures such as quality of life and subjective well-being that combine positive affect with other constructs in an undifferentiated manner (Marsland et al., 2007).

There are a number of complex emotional constructs that represent a constellation of abilities within individuals. These complex constructs were shown to have a positive impact on individual's lives. Examples include coping (Carver, Schneider, & Weintraub, 1989), resilience (Cohn et al., 2009), sense of coherence (Lutgendorf, Vitaliano, Tripp-Reimer, Harvey, & Lubaroff, 1999), optimism (Hoodin, Uberti, Lynch, Steele, & Ratanatharathorn, 2006), social support, and self-esteem. Many of these constructs are interrelated with positive emotions. Positive emotions, for example have been shown to predict increased ego resilience, which in turn predicted increased life satisfaction (Cohn et al., 2009). Resilience was characterized as a complex skill which ultimately determined life satisfaction and involved emotion regulation, problem solving, as well as the ability to change perspective (Cohn et al., 2009). Additional links between positive emotions, resilience, and adapting to change have been demonstrated (Pauquet, Kergoat,

& Dube, 2005; Zautra, Smith, Affleck, & Tennen, 2001; Zautra, Affleck, Tennen, Reich, & Davis, 2005). Since these links have application to the proposed study, they will be explored in greater detail in a following section.

Review of the research on emotions raises the question of whether, in addition to differing emotional experiences, individuals vary in their ability to experience emotions; that is, their emotional intelligence. In seeking to measure emotional intelligence, the developers of the Trait Meta-Mood Scale (Salovey, Mayer, Goldman, Turvey, & Palfai, 1995) noted that a starting point was an individual's willingness to attend to feelings and to experience these feelings clearly. The developers noted the usefulness of identifying differences in emotional complexity that characterized emotionally intelligent individuals who were capable of disclosing their feelings to themselves and others. These researchers concluded that mood experiences could be understood based on three primary domains within individuals; attending to moods, experiencing them clearly, and trying to regulate them (Salovey et al., 1995; Salovey, Rothman, Detweiler, & Steward, 2000). Emotional complexity has been shown to increase with age (Paquet, Kergoat, & Dube, 2005; Ready, Carvalho, & Weinberger, 2008). Insights into emotional intelligence have potential application for researchers seeking to examine mood, or the impact of emotion on health outcomes. Research has demonstrated that mindfulness is closely related to emotional intelligence and complexity due to improvements in one's ability to attend to present experiences (Cohn, Fredrickson, Brown, Mikels, & Conway, 2009; Fredrickson, Cohn, Coffey, Pek, & Finkel, 2008; Ong, Bergeman, Bisconti, & Wallace, 2006).

Researchers also discussed the concept of a hedonic treadmill (Lucas et al., 2003), a set point of emotional neutrality that people return to after briefly reacting to good and bad events (Dykens, 2006). The inevitability of individuals reverting to pre-established emotional set points has been generally disproved. Adaptation of positive emotional trait is thought to be a dynamic process with changes occurring over time in response to important events (Lucas et al., 2003). There are gaps in the literature regarding time frames for this adaptation, as well as the types of experiences which enhance or suppress its development. The hedonic treadmill concept remains useful to describe an individual's tendency to return to a general emotional mean valence, though it has been noted that experiences such as chronic pain, illness, or emotional loss can cause adaptive changes in emotional traits.

In the Circumplex Model (Larsen & Diener, 1992; Russell, 1980), emotions have been characterized along four dimensions; positive and negative valence, and high and low activation (or aroused and unaroused). A high arousal positive emotion would be excitement, while contentment would be a low arousal positive emotion. This model is proposed to be of use for health researchers interested in aspects of physiological arousal, such as the sympathetic or parasympathetic nervous systems (Marsland et al., 2007), which are considered to be pathways through which emotions may influence immunity and health.

There are a number of complex positive emotion constructs within the field of psychology, which involve subjective evaluation of life satisfaction, similar to quality of

life appraisals, and which have bearing on the understanding of positive emotions. Subjective well-being, for example, was defined as people's emotional and cognitive evaluation of their lives, including happiness, peace fulfillment and life satisfaction (Diener, Oishi, & Lucas, 2003). Another construct is psychological well being, which Ryff and Singer (2008) maintained was comprised of self-acceptance, positive relations with others, personal growth, life purpose, environmental mastery, and autonomy. In an excellent review of these constructs, Ryan and Deci (2001) defined well-being as a complex construct that concerns optimal experience and functioning, and noted that the field is a burgeoning one within psychology. Ryan and Deci subsumed these measures under the umbrella of lifespan perspectives on well-being and cautioned that the definition of well-being is controversial and unresolved. In noting the correspondence between chronic personality styles and individual differences on satisfaction with life, Ryan and Deci highlighted the emotional interrelatedness of several measures: Neuroticism, defined as negative affect, and extraversion, characterized by positive affect, were two examples of measures which correlated with negative and positive affect, and also correlated with life satisfaction. This interrelatedness confounds findings associated with these complex measures, and makes it difficult to identify the impact of factors such as personality on positive and negative affect. Researchers should be wary of this interrelatedness of measures when using multiple emotional scales in studies of positive emotions. Caution is especially warranted if separate measures of positive

emotions, emotional constructs, or evaluations of well-being are included as both independent and dependant variables in research designs.

Positive Emotion Studies from Positive Psychology

Seligman and Csikszentmihalyi (2000) identified positive psychology as a unique area of inquiry within psychology. The territory they staked out for the positive psychology movement ranged from subjective individual experiences to institutional characteristics. A central tenant of positive psychology was a focus away from negative emotions and pathology and toward positive emotions and flourishing. Positive psychology seeks a constructive human functioning, illuminated by scientific understanding, and fostered through effective interventions, that would build thriving individuals, families, and communities. Seligman and Csikszentmihalyi maintained that a side effect of this endeavor would be knowledge in how to prevent mental, and to a lesser degree, physical illnesses. These positive psychology goals where translated into a theory proposed by Fredrickson in 1998, which she labeled the broaden-and-build model of positive emotions.

The broaden-and-build model focused on the role of positive emotions to broaden individual's momentary thought action repertoires, and to build individual's social bonds and resources. Broadening occurred when positive emotions such as joy, interest, contentment and love expanded an individual's scope of attention, enlarged the cognitive context, and promoted flexibility, elaboration, and creativity in thinking. In addition to broadening cognitive repertoires, Fredrickson also cited evidence that positive emotions

broadened the scope of actions exhibited by individuals. Individuals exhibiting positive affect were better able to carry out problem solving tasks, sought more variety in foods, and demonstrated more variety and longer play activity. Building occurred through an increase in physical, intellectual, and social resources that emerged as a result of broadened thinking and activity. For example, broadening options to consider and act to help others, led to altruism and gratitude, eventually building beneficial co-operative relationships. More varied playful activities led to greater physical stamina. Shared play built enduring social bonds. Fredrickson concluded that positive emotions broadened attention, thinking, and action which in turn built physical, intellectual and social resources (Fredrickson, 1998).

The broaden-and-build theory was tested in a series of experiments. In one, students demonstrated faster return to baseline heart rates when sad or fearful films were followed by films that induced contentment or amusement. In another experimental manipulation, students who spontaneously smiled while viewing a sad film showed faster recovery from cardiovascular changes than students who did not smile. These findings supported the researchers' hypothesis that positive emotions would dismantle, or undo, the effect of negative emotions. This undoing hypothesis was used to demonstrate the adaptive value of positive emotions (Fredrickson, 1998).

Fredrickson's landmark study (Fredrickson & Levenson, 1998) provided support for the broaden-and-build theory and demonstrated physiological links between emotions and cardiovascular findings. The methodology generates questions, however, as to the

meaning of the cardiovascular findings which were used as proxy measures to demonstrate recovery from negative emotions. While the authors extrapolated findings from the study to the development of cardiac diseases, to do so was an oversimplification of disease etiology and may have gone beyond the applicability of the research design. The outcomes demonstrated in the study, return to resting heart rate and discrepancies between cardiac and peripheral measures of heart rate, may have been affected by factors other than the transition from negative emotional states.

Further testing of the broaden-and-build theory provided additional support for the model as well as insight into the mechanisms through which positive emotions impact complex emotional constructs. A study of college students (Fredrickson & Joiner, 2002) who provided self-assessments of positive affect on the PANAS (Watson & Clark, 1994), found that initial positive affect improved broad minded coping, and initial broad minded coping predicted increased positive affect. Broad minded coping was defined as taking a broad perspective toward problems and generating multiple possible solutions to them. Step-wise mediational analysis indicated that positive affect and broad-minded coping serially enhanced each other, with significant outcomes demonstrated between the predictors and the mediators (positive affect and broad minded coping). Based on these findings, the authors hypothesized that positive emotions initiated upward spirals toward enhanced emotional well-being. These upward spirals where characterized as the accumulative and compounding effects of positive emotions to facilitate coping with adversity, and predict future positive emotions in a cyclic manner. This cycle was

thought to build resilience and enhance emotional well-being (Fredrickson & Joiner, 2002).

A field study of the broaden-and-build theory was performed in 2003, following 46 college student's reactions to the terrorist attacks of September 11, 2001. Fredrickson, Tugade, Waugh, & Larkin (2003) explored the interrelationship of resilience and positive emotions, demonstrating the linkages between resilience, humor, cognitive exploration, relaxation, optimism, amusement, interest, contentment, hope, and coping. The students' positive emotions in the weeks following the terrorist attacks accounted for the difference between pre-crisis resilience and post-crises depression or growth. Positive emotions were shown to mediate the pathway from high trait resilience to low depressive symptoms (Fredrickson et al., 2003). The concept of upward spirals of positive emotions and their association with coping was reinforced in subsequent studies on 185 undergraduates (Burns et al., 2008). Positive affect and broad-minded coping, interpersonal trust and social support predicted one another, both reciprocally and prospectively, over a two month period (Burns et al., 2008).

The build hypothesis, inherent in the broaden-and-build theory, was investigated in a study that involved 139 employees at a computer software firm who were randomly assigned to a seven week course in loving kindness meditation or a wait list condition (Fredrickson et al., 2008). The authors noted that time of day positively predicted positive emotions, which underscores the importance on temporal consistency when collecting data on positive emotions. More specific to Fredrickson et al.'s research aims,

findings indicated that the meditation increased positive emotions over the course of the study. In addition, meditation produced positive emotions during meditation practice and these emotions persisted after meditation sessions were completed. Repeated meditation produced a cumulative increase in positive emotions that appeared on subsequent days, regardless of whether the individual meditated on that day or not. The authors performed a path analysis to determine if initial positive emotions, and changes in positive emotions, predicted changes in personal resources, which in turn, predicted changes in life satisfaction over the course of the study. They found that paths from (a) changes in positive emotions to changes in resources, and (b) from changes in resources to changes in life satisfaction, were significant for nine resources; mindfulness, pathways thinking, savoring the future, environmental mastery, self-acceptance, purpose in life, social support received, positive relations with others, and illness symptoms. The authors concluded that the practice of loving kindness meditation increased participant's experience of a wide range of positive emotions, and that this increase in positive emotions took time to manifest itself. Over the course of nine weeks, these increases in positive emotions were linked to increases in personal resources including mindful attention, self-acceptance, positive relations with others, and good physical health. Positive emotions emerged as the mechanism through which people built resources and became more satisfied with their lives (Fredrickson et al., 2008). The study stands apart from many performed within positive psychology in that the subjects were employed

adults, rather than college students. The use of randomization, a wait list control group, and multiple self report measures of trait and state emotions lend strength to this study.

These studies provide additional evidence to support the broaden-and-build model, which is a middle range theory describing the relationship between positive emotions, adaptive outcomes, and well-being. As discussed, the theory has undergone hypothesis testing in experimental designs utilizing random participant selection and random assignment to treatment groups. The model has successfully predicted the relationship between positive emotions and the building of resources. Theory testing included experimental manipulation of interventions (e.g. emotional affect stimulated through watching films). While the studies cited support the broaden-and-build theory, and provide insight into the interrelationship between positive emotions and complex emotional constructs, more research is indicated. Extrapolation of findings to the development or prevention of diseases, for example, is an oversimplification of the complex etiologies underlying these processes and beyond the scope of the research. Additional research is needed to more clearly demonstrate links between positive emotions, emotional abilities, and health outcomes.

An important limitation is the frequent use of college students in the studies on positive emotions from psychology. There are serious questions regarding the generalization of findings from this specialized population to other groups, especially elderly individuals and those with health risks or concerns.

Beyond the Broaden-and-Build Model

By 2005, the positive psychology movement had gained momentum (Seligman, Steen, Park, & Peterson, 2005). Fredrickson and Losada (2005) quantified the relationship between positive affect and human flourishing in a study of 188 undergraduates in which a ratio of positive to negative affect greater than or equal to 2.9, characterized flourishing mental health in individuals. The practical application of such a ratio to healthcare appears dubious. The importance of the relationship between the levels of positive and negative emotions was relevant, however, to research on positive emotions, as well as understanding interrelationships between stress and emotions.

Ongoing research continued to provide insight into the utility of positive emotions. Tugade and Fredrickson (2004) used a broaden-and-build framework to examine how resilient individuals use positive emotions to bounce back from stressful events, and find meaning in negative events. In this study, resilience was defined as coping and adaptation despite loss, hardship, or adversity, and was found to be highly correlated with positive emotions. Resilient individuals used positive emotions to effectively cope with stressful situations and to find meaning in negative events. Coexisting conditions within resilient individuals allowed them to recognize the effects of stressful situations, and to experience positive emotions amidst the negative emotions surrounding the situation. Experiences of positive emotions appeared to be critical to undergraduates' ability to find positive meaning in negative situations. Trait resilience was correlated with positive emotions, and at-the-moment experiences of positive

emotions appeared to fuel participant's ability to take positive meaning from stressful tasks. While Tugade and Fredrickson studied undergraduates faced with the task of preparing a speech, or writing an essay on a negative experience, the utility of positive emotions in both recovering and finding meaning from negative events has potential application for patients facing difficult diagnoses, unpleasant treatment regimens, or painful recovery from illness. Of relevance to this paper, is whether these findings can be extended from the stressful academic tasks assigned to these undergraduates in this experimental condition, to individuals who face stress in everyday life and are exposed to pathogens in their everyday environment. Can positive emotions aid in recovery from illness and help individuals buffer physical ailments and enhance coping ability? Does resilience improve immune response?

Ong et al. (2006) moved research further along toward answering this question in their studies of resilience, positive emotions and successful adaptation to stress in later life. Instead of undergraduates, these authors studied men and women aged 57-85. In three separate experiments, groups of participants underwent preliminary testing to measure trait resilience and neuroticism, then recorded their emotions and responses to daily stressful events in diaries for periods ranging from 14 days to 48 months. The authors found that positive emotions moderated reactions to stress and aided in recovery from stress for these later life adults. The effects of positive emotions were greatest when participants were experiencing stress. When comparing day-to-day emotions and stress responses, participants who experienced more positive daily emotions leading up to

stressful events displayed fewer negative emotions associated with these stressful events. Positive emotions accounted for differences in trait resilience, and those individuals with lower trait resilience tended to have more difficulty regulating negative emotions and displayed greater reaction to stresses. At the same time, positive emotions appeared especially helpful to low resilient individuals responding to stressful events. Ong et al. concluded that two pathways aided individuals in adapting to stress, one at the level of within person variation (daily experiences of positive emotions) and the other at the trait level of psychological resilience. Positive emotions were associated with trait resilience, but also served a spiraling effect to build greater resilience. The applicability of findings for persons experiencing intense stress was investigated when these authors' examined responses for widows at intervals ranging from one to 48 months after the loss of a spouse (Ong et al., 2006). This was the only group of the three studied in which participants reported greater negative emotions than positive emotions. While findings for this group where consistent with those reported above, key differences distinguished high-resilient widows: They were more likely to experience a range of both positive and negative emotions throughout the bereavement process, and they were able to maintain separation of positive and negative emotions while under stress. Ong et al. identified this as the ability to preserve emotional complexity. These findings were consistent with those reported by Zautra and the Dynamic Model of Affect (Zautra, Smith, Affleck, & Tennen, 2001), which supported the importance of emotional clarity and emotional intelligence. Ong et al. (2006) suggested that an adaptive outgrowth of resilience was an

increase in emotional complexity during times of stress. They noted the widows in their study showed greater control over their positive emotions and could selectively mobilize these emotions to recover and bounce back from daily stresses. Strengths of these studies include measurement of emotions over several weeks, and older participants reacting to real life events. These studies by Ong et al. (2006) have implications for how individuals with various state and trait emotions react to illness, the effect of chronic and acute illness on emotions, and the interactions between positive and negative emotions.

Research into how positive emotions impact responses to stress, moves this discussion into the role of positive emotions for individuals with chronic health problems. The Dynamic Model of Affect proposed by Zautra et al. (2001) maintained that stress reduced the degree of complexity in awareness of one's own emotions. This effected a narrowing of the range of emotional experiences, leading to an inverse relationship between positive and negative emotions. As a result, the individual has ever decreasing access to positive emotions, which are believed to be critical to preserving well being during times of stress. This domino effect results in a downward spiral and increasing vulnerability to negative emotions. According to Zautra et al. (2001) the Dynamic Model of Affect focused on changes within a person's current state of emotions, independent of trait affect, and predicted that the timing of emotions were critical, since positive emotions during times of stress were particularly important. Zautra, Johnson, & Davis (2005) applied the Dynamic Model of Affect in examining pain experiences for 124 women with fibromyalgia, osteoarthritis, or both. They found that deficits in positive

affect when experiencing pain led to increased vulnerability to negative emotions, while more positive affect led to lower levels of negative emotions during times of stress and pain. This demonstrated the use of positive emotions to regulate pain in individuals with chronic health conditions. Research by Paquet, Kergoat, and Dube (2005) also supported the role of emotional complexity in pain regulation for hospitalized adults.

In examining positive and negative events, as well as positive and negative affect, Zautra et al. (2005) found that negative events tended to narrow affect. Negative affect increased during negative experiences. Emotional complexity decreased when positive affect decreased. Positive events, on the other hand, increased positive affect and broadened affective experience. One explanation offered was that stressful events generated the need to process information efficiently, rather than engage in an evaluation of complex emotional stimuli. Attention was narrowed and judgments became more rapid and simple, in order to adapt to a threatening situation. In these situations, individuals focused on negative information at the expense of positive input. Positive events, on the other hand, relaxed informational demands, and allowed the individual to engage in greater emotional evaluation and complexity (Zautra et al., 2005). Emotional complexity assisted individuals to marshal resources and utilize positive emotions during times of stress. Zautra's findings support the importance of positive emotional stimuli during stressful experiences, including stresses such as coping with illness or hospitalization. They may also have application to ameliorating the stress of mounting an immune response to influenza vaccine, influenza illness, or other respiratory diseases.

Researchers applying these findings to prospective designs must be mindful of the importance of measuring negative emotions, even when the concept of interest is positive emotions. Multiple measures of emotions are necessary, because of the transient nature of the data, and the ability for state and trait emotions to affect perception of each. Interactions between positive and negative emotions, state and trait emotions should be considered when analyzing findings. Data on state emotions should be collected at the same time each day. When performing research on positive emotions, it is also important to collect data on the subject's experience of stressful events. These suggestions will be incorporated into the proposed research.

Interventional Studies

Given that stress and negative life events reduce emotional complexity, several studies evaluated meditation as a mechanism for individuals to improve emotional complexity (Creswell, Way, Eisenberger, & Lieberman, 2007; Davidson et al., 2003; Fredrickson et al., 2008; Kabat-Zinn, Lipworth, & Burney, 1985; Teasdale et al., 2002) By increasing awareness and acceptance of present moment experiences, mindfulness and other forms of meditation were believed to raise an individual's sensitivity and acknowledgement of emotions. Becoming more aware of the range of experienced emotions improved an individual's emotional complexity. Several authors cited the importance of emotional complexity as a desirable trait, demonstrating the contribution of emotional complexity to resilience (Cohn et al., 2009; Fredrickson et al., 2008; Zautra et al., 2001; Zautra, Affleck, Tennen, Reich, & Davis, 2005; Zautra et al., 2005)

Increases in the awareness and incidence of positive emotions have been demonstrated with Coping Effectiveness Training, a method that draws attention to positive emotions through acknowledgement of these emotions in treatment groups and daily life. Recording positive emotions at the end of the day, using humor, and identifying sources of meaning in life, was also shown to increase the knowledge and incidence of positive emotions (Chesney et al., 2005). Journaling about cognition and emotions has been recommended as a method to develop greater awareness of the positive benefits of a stressful event (Ullrich & Lutgendorf, 2002).

The work of Cohn et al. (2009) demonstrated that moment-to-moment positive emotions led to greater resilience. Zautra et al. (2005) supplemented findings that individuals with less neuroticism coped with stress more effectively, also demonstrating that positive emotions had greater utility for neurotic individuals during times of stress. These findings underscore the importance of positive emotions for individuals facing immune challenges such as vaccination or exposure to pathogens circulating within the community. While interventional studies have demonstrated a number of approaches to engender positive emotions, more research is needed to evaluate the effectiveness of these methods for various healthy and sick populations.

Positive Emotions and Health Outcomes

Research linking positive emotions and specific health outcomes has just begun to emerge. A number of these are large epidemiological studies. The association between emotional well-being and incidence of stroke in adults 65 years of age and older was

examined in a 6-year prospective cohort study of 2,478 mixed race residents of North Carolina (Ostir, Markides, Peek, & Goodwin, 2001). Emotional well being was measured using a modified version of the CES-D (Radloff, 1977). There was a significant and inverse association between positive affect and incidence of stroke for both men and women in the study. Each unit increase in positive affect was associated with a 32% decrease in risk of stroke for whites and a 27% decrease in risk for blacks (Ostir et al., 2001). A similar study (Ostir et al., 2004) examined associations between positive affect and frailty in 1,558 Mexican Americans over seven years and found that high positive affect significantly lowered the risk of frailty. Each unit increase in baseline positive affect scores was associated with a 3% decrease in risk of frailty. Other studies demonstrated significant correlations with gains in functional status after stroke (Ostir, Berges, Ottenbacher, Clow, & Ottenbacher, 2008) and between positive emotions and lower blood pressures in Mexican Americans (Ostir, Berges, Markides, & Ottenbacher, 2006). These studies are cited frequently in the literature on positive emotions. With the exception of the last, they have the added strength of being prospective studies.

A two year study of 97 older women demonstrated positive affect decreased glycosylated hemoglobin, an indicator of glycemic control (Tsenko, Love, Singer, & Ryff, 2008). Positive emotions were found to be protective of adverse health outcomes for 1002 moderately to severely disabled, community dwelling women aged 65 years and older followed in another longitudinal study (Penninx et al., 2000). A review of 19

published reports on the effect of psychosocial variables on survival after adult stem cell transplant concluded that pre-transplant optimism about the transplant affected survival in the short term (Hoodin, Uberti, Lynch, Steele, & Ratanatharathorn, 2006).

Another two year study, this time involving 1,041 patient records and emotions measured through a mailed questionnaire, examined two specific positive emotions: hope and curiosity. Hope was associated with a lower likelihood of developing the three disease outcomes measured: hypertension, diabetes mellitus, and respiratory tract infections. Higher levels of curiosity were associated with decreased likelihood of hypertension and diabetes mellitus (Richman et al., 2005).

Critical Analysis of Research on Positive Emotions within Psychology

This research cited suggests interesting possibilities for the role of positive emotions in improving health outcomes. Much of the research linking positive emotions and health are largely correlational designs, with a few prospective studies. Positive psychology provided a directional hypothesis for the relationships identified, but the limitations of nonexperimental research in identifying causal relationships were sometimes ignored. Instead, caution was warranted to avoid faulty interpretation of findings, given the complex interrelationships between emotions and health, especially given the ex post facto research designs used in a number of studies. Additional criticism is directed toward the circular logic sometimes used to describe these causal relationships, and the confounding effect of positive emotions within measures for dependant and independent variables.

Another limitation in much of the research on positive emotions is self selection into the independent variable. Participants typically provide self ratings of positive or negative mood, which determine their emotion grouping which serves as the independent variable for these correlational studies. This approach limited the strength of the research findings. In contrast, the experimental designs in the broaden-and-build theory, as well as the interventional studies cited had greater utility for predicting the relationship between positive emotions and health outcomes. They provided a means to further identify significant functions and relationships between positive emotions, and resource building. More research is needed to link these theories with health outcomes such as longevity, better symptom control, or higher functionality beyond psychological measures such as resilience. The body of research on resilience invites further investigation of this trait, which researchers have shown is related to positive emotions, and impacts reaction to life events. Does increased resilience also make an individual less susceptible to developing disease?

While the correlational designs discussed have inherent shortcomings, correlational research is useful in collecting large amounts of data regarding a large number of interrelationships in real life situations (Polit & Hungler, 1983). The large sample sizes in the epidemiological studies, as well as the prospective designs used in a number of these studies give this research greater rigor. The research on positive emotions and health has given us important clues regarding positive emotions, warranting further examination in more controlled studies.

The research done within psychology provides valuable insights into the complex relationships between positive emotions, resilience, and coping. The broaden-and-build theory provides a framework to predict relationships between positive emotions and health outcomes. What is missing in this body of research, for the healthcare professional seeking to use this research in practice settings, is how positive emotions may impact health outcomes. To provide insight into these mechanisms, the focus of this discussion shifts slightly from psychology to a more interdisciplinary approach used within the field of Psychoneuroimmunology.

Positive Emotions and Psychoneuroimmunology

In the preface to the fourth edition of Psychoneuroimmunology, Ader (2007) described psychoneuroimmunology as a convergence of disciplines, which included behavioral sciences, neurosciences, endocrinology and immunology, to achieve a more complete understanding of the way interactions among these systems serve homeostatic ends and influence health and disease. Ader cited the importance of current trends toward interdisciplinary integration to provide a better understanding of the psychosocial, social and biological interactions in health and disease. In the mid 1990's, psychoneuroimmunology (PNI) was proposed as a framework for nursing research, especially suited to nursing's holistic approach to care. PNI was suggested as a methodology for nurse researchers to use in examining relationships between behavioral and biological phenomena and their influences on health outcomes (McCain & Smith, 1994; Zeller, McCain, & Swanson, 1996).

Zeller et al. (1996) provided a description of the PNI model to provide a framework for nurse researchers. PNI examines mechanisms of bidirectional neuroendocrine and immune system interactions. Inherent in this model is bidirectional communication between the nervous system and chemicals, hormonal regulators, endocrine factors and immunological markers that have measurable outcomes for health (Zeller, McCain, McCann, Swanson, & Colletti, 1996).

While psychobehavioral issues are inherent to psychoneuroimmunology, much of the research within PNI focuses on stress or coping with stress. In contrast, the focus for this paper continues to be positive emotions and health. Landmark PNI studies examining the relationship between positive emotions and health, as well as a number of theoretical and methodological publications, are provided to illustrate psychoneuroimmunology concepts. Of particular relevance to the proposed research, several PNI studies of positive emotions involve immune response to vaccination, and these will be discussed.

Cold Studies

A landmark PNI study compared positive and negative emotions in 334 quarantined individuals who were exposed to rhinovirus via nasal drops. In that study, Cohen, Doyle, Turner, Alper, & Skoner (2003) found that increases in positive emotional style were associated significantly and linearly with a lower risk of developing a cold. Trait emotions were measured six times prior to the start of the study and again at screening. Self rated mood scores were recorded daily during the seven day quarantine

period. Trait positive emotions were associated with greater resistance to developing a common cold based on either objective signs or subjective symptoms. The association was not mediated by health practices, or stress hormone measures of epinephrine, norepinephrine in serum, or cortisol measured in the urine. These authors considered both activated (defined within their study as vigor and well being) and unactivated emotions (defined as calm within their study) in the analysis, finding the same associations between illness and both of these subscales and total positive emotional styles. Thus, these findings did not support the role of differing emotional arousal levels (e.g. calm and excited) for effecting health outcomes as proposed within the circumplex model (Larsen & Diener, 1992; Russell, 1980). This study was important in demonstrating a link between positive emotions and a definitive health outcome—avoiding the common cold. This cold study was replicated and expanded to 193 participants exposed to either rhinovirus, or influenza A virus given via nasal drops (Cohen, Alper, Doyle, Treanor, & Turner, 2006). Trait measurements of optimism, mastery, purpose, self-esteem and extraversion, were also incorporated to address the possibility that these constructs may be spurious factors that might influence both affect and health. Findings again confirmed that positive emotional style was associated with fewer infections. Positive emotional style was moderately correlated with self-esteem, optimism, purpose, and mastery. Adding these variables as covariates had little impact on the association between positive emotional style and health outcomes. The authors concluded that positive emotional style was the independent variable that accounted for the relationship between positive

emotions and health (Cohen et al., 2006). In both studies (Cohen et al., 2003; Cohen et al., 2006), it was noted that positive emotional style was associated with reporting fewer symptoms than expected given objective indications of disease. This last finding underscores the need to include both subjective and objective measures of disease when studying positive emotions and health outcomes. These cold studies have direct relevance to the topic of the proposed research since positive emotions were the independent variable and the outcome was a viral disease.

A secondary analysis (Janicki-Deverts, Cohen, Doyle, Turner, & Treanor, 2007) of the cold study replication (Cohen et al., 2006), examined the role of "sickness behaviors". Sickness behaviors included; fatigue, malaise, loss of interest in pleasurable activities such as eating and socializing, inability to concentrate, and disturbed sleep. Proinflammatory cytokines have been implicated as a cause for sickness behavior (Kelley et al., 2003). Behaviors such as lethargy and loss of appetite that typically accompany illnesses are considered an adaptive function that encouraged the ill individual to withdraw and recuperate. Proinflammatory cytokines such as IL-6 and TNF-α were noted to be significantly correlated with increased anxiety, reduced positive affect, and depressed mood, suggesting a role in sickness behavior (Janicki-Deverts et al., 2007). Because of the independence of positive and negative affect discussed in experiential and physiological studies, the authors hypothesized that proinflammatory cytokines related differently to positive and negative mood states. The 153 participants who experienced infections in this study reported less positive affect on days characterized by greater IL-6

production. Positive affect was not related to concurrent production of IL-1β or TNF-α. There was no association between cytokine levels and negative affect. Each of the three cytokines, IL-6, IL-1β and TNF-α, were independent predictors of positive affect as evaluated on the following day. The lag times in this study suggested that nasal cytokines predicted level of positive affect, and the authors postulated that this was due to the production of secondary mediators that influenced mood. These findings have numerous implications for research on positive emotions and health, including the importance of measuring IL-6. A study of cytokine and influenza vaccination in the elderly, however, showed extremely high levels of IL-6 in a few individuals pre-vaccination, and noted an association between IL-6 and arthritis (Bernstein, Gardner, Abrutyn, Gross, & Murasko, 1998).

Immune Response Studies

Conducting research with direct application to the proposed study, Lutgendorf and Costanzo (2003) hypothesized that interactions between mood, age-related processes, health behaviors, and stress may impact the robustness of immune response to vaccination. Research has shown that vaccination prevented influenza in less than 50% of adults over 60 years of age, compared to 70-90% prevention rates in younger adults (Gardner, Bernstein, Dran, & et al., 2001; Govaert et al., 1994; Palache et al., 1993). Costanzo and Lutgendorf (2004) studied relationships between mood, optimism, stress, and cytokine response to live influenza virus and vaccine in eighteen older adults. Peripheral blood mononuclear cells were stimulated in vitro with live viruses from the

previous influenza season and trivalent influenza vaccine. The levels of T-helper type 1 (interleukin-2 and interferon - γ) and type 2 (interleukin -10) cytokines were measured in culture supernatants. In response to live viruses, greater vigor (both positive mood and vitality) correlated with significantly greater IL-2 levels in response to A/Beijing/262/95, and B/Yamanashi/166/98 influenza viruses. Greater optimism correlated with significantly greater IFN-γ to A/Beijing/262/95 virus. For the trivalent vaccine response, greater optimism was correlated with significantly higher IL-2 levels. Further, optimism and vigor were associated with significantly greater cytokine responses to the live viruses and vaccines, with stronger TH1 cytokine responses demonstrated (Costanzo et al., 2004). These TH1 responses favor a cell-mediated immune response, rather than a humoral response (Lucey, Clerici, & Shearer, 1996). The elderly often show decreased immune responses, with greatest decreases in TH1 immune responses, which play a role in immunity to viral diseases. Costanzo and Lutgendorf (2004) concluded that optimism protected participants against age-related decreases in immune response and hypothesized that positive mood and optimism may buffer decreases in T-lymphocyte functioning associated with aging. These results support the importance of positive emotions to optimize immune responses to vaccination and, in turn, reduce the morbidity and mortality associated with influenza for the elderly. Participants rated their emotions based on how they felt over the previous week, immediately prior to having blood drawn. This blood drawing occurred one week before receiving influenza vaccination. Limitations of the study included the small sample size of 18 individuals. Use of in vivo

measures of immune response would lend further strength to the findings demonstrating the relationships between emotions and immune response.

A study of alterations in brain and immune function produced by mindfulness meditation (Davidson et al., 2003) supported previously discussed findings demonstrating the relationship between positive affect and response to influenza vaccination. Davidson et al. suggested that mindfulness meditation may serve to increase positive affect and, in turn, promote a greater antibody response to vaccination. Increases in left-sided anterior brain activation, a pattern previously seen with positive affect, were seen in the 48 (right-handed) participants who completed an 8 week mindfulness meditation course. Furthermore, significant increases in antibody response to influenza vaccination were seen in participants in the meditation group compared with those randomized to the wait-list control group. In addition, the magnitude of increase in left-sided brain activation predicted the magnitude of antibody titer rise to vaccine (Davidson et al., 2003). This study is significant in that it employed a control group and used random assignment to treatment. In addition, it is perhaps the only study in PNI that included a measure of brain activation in addition to self-report of affect and an in vivo measure of immune function in humans.

A study of positive affect and antibody response to hepatitis B vaccination reinforced the association between trait positive affect and immune response (Marsland, Cohen, Rabin, & Manuck, 2006). The in vivo response to hepatitis B virus was evaluated in 81 graduate students 3.5 months after receiving the second of the three Hepatitis B

vaccination series. At the time of their laboratory visit, participants completed psychosocial questionnaires evaluating trait affect, optimism, depression, and health behaviors. An 88 item adjective rating scale was used, composed of subscales from: Profile of Mood States (POMS, McNair, Lorr, & Droppleman, 1992); Goldberg's Big-5 Factor Scales (Goldberg, 1992); Larsen and Diener Circumplex (Larsen & Diener, 1992); and Mackay Circumplex (Mackay, Cox, Burrows, & Lazzerini, 1978). Participants were asked to rate nine positive emotional traits (lively, full of pep, energetic, happy, pleased, cheerful, at-ease, calm and relaxed), and nine negative emotional traits (sad, depressed, unhappy, on-edge, nervous, tense, hostile, resentful, and angry) in terms of how accurately these emotional traits reflected their usual emotional status. Health practices such as smoking, alcohol use, and physical activity were also measured to determine whether these factors influenced the relationships being evaluated. Higher levels of trait positive affect were correlated with significantly higher antibody responses to hepatitis B vaccination. Aroused and calm subscales were similarly associated with higher antibody responses suggesting that the association between positive mood and antibody response were equivalent irrespective of activation/arousal dimensions. Level of antibody response was primarily predicted by positive mood. Results supported the conclusion that positive and negative affect are distinct, though related, concepts. Findings in this study contradicted previous work reporting that trait negative affect was significantly related to lower antibody response. The authors concluded that previous findings supporting a relationship between trait negative affect and antibody response may have

been due to evaluating the absence of positive affect, rather than the presence of negative affect. The association between trait positive affect and antibody response was found to be largely independent of the related constructs of optimism and extraversion. Finally, there was a significant correlation found between positive affect and time spent exercising each week. Examination of the interaction led the authors to conclude that low positive affect was associated with lower antibody response among those exercising fewer hours but not among those exercising longer. Physical activity appeared to be protective (through enhanced immune response) for those who characterized themselves as low in positive affect. The authors postulated that both positive affect and physical activity might activate the same physiological pathways, such as the sympathetic nervous system. The authors noted that causation could not be attributed solely on the basis of this cross sectional data, and thought that the single measurement of affect was a study limitation, even though their purpose was to measure trait affect (Marsland et al., 2006).

Psychoneuroimmunology Studies of Healthy Populations

The PNI framework was used to evaluate the role of sense of coherence, a complex emotional construct, on the relationship between life stress and natural killer cell activity (NKCA) in a population of healthy adults voluntarily moving to a group living situation (Lutgendorf et al., 1999). Sense of coherence was conceptualized as an individual's sense of comprehensibility, manageability, and meaningfulness about their environment and life circumstances. Study participants anticipating relocation reported

lower vigor and more intrusive thoughts, as well as lower NKCA than individuals not relocating. The authors reported a positive association between vigor and NKCA and observed that this association appeared to operate independently of negative affect. There was a lack of association between negative mood and intrusive thoughts with NKCA, supporting a stronger relationship between positive mood and innate immune function than for negative mood. Poorer immune function was most evident in individuals with low sense of coherence (Lutgendorf et al., 1999). This study reinforced other research demonstrating that mood and sense of coherence contributed to immune function, and therefore health outcomes.

Psychoneuroimmunology Studies with Clinical Populations

While the PNI model would seem to lend itself to outcomes that focus on the presence or absence of disease, there are a limited number of PNI studies examining positive affect in populations with identified diseases. Exceptions include a study of 407 men who were HIV positive at baseline (Moskowitz, 2003). For these participants, positive affect was significantly associated with lower risk of AIDS mortality. Robins et al. (2006) examined the effects of a ten week tai chi class on stress management for persons with HIV. Upon completing the class, participants demonstrated higher overall quality of life with higher emotional and social well being, lower HIV-related psychological distress, and more frequent use of appraisal-focused coping. The authors stated that altering perception of stress may be the key component in ultimately impacting neuroendocrine-immune responses and health outcomes (Robins et al., 2006),

though they did not provide any neuroendocrine-immune measures or health outcomes in their study.

Critical Analysis of Research on Positive Emotions and PNI

There are shortcomings in the research on positive emotions and PNI, consistent with the problems identified in the review of psychological research on positive emotions. These included failure to manipulate the independent variables, and a lack of random assignment. The research designs are predominantly correlational studies, though many of these are prospective in the PNI literature. Only two studies reviewed, one examining alterations in brain and immune function associated with meditation (Davidson et al., 2003) and a study examining tai chi as a stress management approach for individuals with HIV (Robins et al., 2006) included random assignment of participants. Both of these studies were interventional, so random assignment into a positive emotion enhancing intervention group was possible. Unless such experimental manipulation is present in the research design, the problem of individuals self selecting into groups based on positive and negative emotions is inherent to research examining health outcomes for individuals experiencing positive emotions. For non-interventional study designs, this problem would need to be addressed through baseline comparisons of the participants at the start of the study and statistical analysis that included within person changes in emotions over the course of the study.

In general, researchers who used PNI methodology controlled many extraneous variables through use of baseline measurements and more rigorous exclusion criteria

when enrolling participants. Sample sizes were limited and as a result, these studies may have been underpowered. There was less of a reliance on college students as study participants in the PNI studies. This allowed for greater generalization of findings to other populations than was possible for many of the studies in positive psychology. Of special concern to the issue of immune response, but also problematic within all the PNI studies, was identification of the end point or outcome. For example, the link between less robust immune responses and incidence of disease was never demonstrated. The PNI studies assumed the emotion related changes in PNI measurements translated to changes in health and disease, but this relationship was not always demonstrated. A method to address this shortcoming, in the proposed study to examine the role of positive emotions on immune response to influenza, is to include a post vaccination follow-up period during which individuals are assessed for influenza like illness.

The design of the cold studies (Cohen et al., 2003; Cohen et al., 2006; Janicki-Deverts et al., 2007) enabled the researchers to provide a clearly defined end point to evaluate health; development of a cold or influenza. The cold study by Cohen et al. (2003) also provided exemplary models for baseline screening, data collection, and statistical analysis, and future researchers would be well served in following these models. Baseline screenings for emotional style, medical and psychiatric illness, as well as antibody titers, demographics, height, weight, urine catecholamine, saliva cortisol and health practices were completed. Variables that were studied included measures of total symptoms, mucus weight, mucociliary clearance, cortisol, epinephrine, norepinephrine,

cigarettes per day, alcoholic drinks per day, zinc and vitamin C intake. (These which were log transformed to better approximate a normal distribution.) Stepwise logistic regression was used to predict the binary outcome, which was presence or absence of a cold, with multiple linear regressions used to predict continuous outcomes. In Cohen's cold study, positive and negative emotional styles were initially treated as continuous variables. The regression coefficient, its standard error and probability were reported. To provide an estimate of relative risk, odds ratios (OR) and 95% confidence intervals (CI) for emotional style scales were categorized by percentile. To determine whether the association between emotional style measures and susceptibility to cold was substantially modified after controlling for the other variables, emotional style was entered alone in the second step of the logistic regression, and the other variables were added sequentially to the first step of the regression analysis. Interaction terms were entered in a third step (Cohen et al, 2003).

Cohen et al.'s cold study was well controlled with an ingenious design. The authors controlled for prechallenge antibody titer, age, body mass, race, sex, virus type, month of exposure and education. The five day quarantine period allowed the investigators to control exposure to exogenous viruses. Inoculating the participants with a cold virus provided a mechanism to measure a real health outcome i.e. development or failure to develop a cold. It is doubtful that methodology which included a quarantine period or administration of a virus inoculum to elderly participants would satisfy either a researchers' personal ethics or those of an IRB within most research environments.

Information on circulating levels and strains of influenza within communities is usually available, however, and should be considered when evaluating findings related to influenza research.

Suggestions to be applied from the Cold studies, to the proposed influenza study of the elderly include clear definitions for influenza and influenza like illness and self rating of objective symptoms including fever, cough, or rhinorrhea. One limitation of Cohen's landmark study, that participants were removed from their everyday life, will not occur in the proposed study. Findings from Cohen et al.'s study were limited to trait rather than state emotions. The proposed research will include measures of trait emotions at the start of the study and at least once over the course of the study, with daily self reports of state emotions for two weeks after vaccination. Emotions during the two weeks following immune challenges have been reported to have important impact on the development of viral infections (Doyle, Gentile, Cohen, 2006; Cohen et al., 2006).

Janicki-Deverts et al.'s analysis (2007) provided additional replication data of cold study findings, while also examining the effect of increased negative mood and decreased positive mood. Such comparisons of negative and positive state and traits will be included in the proposed research, since findings from the psychology literature point to the importance of these interactions. Because random assignment to experimental group was lacking in all the cold studies (Cohen et al., 2003; Cohen et al., 2006; Janicki-Deverts et al., 2007) they are classified as quasi-experimental research. Causal relationships can be asserted with more strength than in the retrospective correlational

studies discussed, but these assertions carry less weight than those obtained via true experimental designs which require the manipulation of at least one independent variable, the random selection of participants, and the random assignment of treatments to groups (Kerlinger & Lee, 2000). The researcher must be mindful of these limitations for the proposed study.

Findings from PNI provide additional support for the beneficial impact of positive emotions on health outcomes, while also providing insight on how this impact occurs, and suggestions of how it can be measured. The studies on immune response to vaccination (Costanzo et al., 2004; Marsland et al., 2006) are especially enlightening, and provided the impetus for the proposed research.

At this point, discussion will turn to influenza, influenza vaccination, and immunity to influenza. This will be followed by a brief summary of age related declines in immunity. Next, studies of immune response to influenza vaccination in the elderly with be presented, focusing on research that pertains to investigating the role of positive emotions and their impact on the immune response to influenza vaccination.

Influenza Disease, Virus, Vaccine, and Immunity

Influenza Disease

Influenza virus may result in asymptomatic infections or severe disease depending on the influenza strain, host immunity, and other factors. Individuals who are more likely to experience severe disease include those with underlying respiratory disease, immune deficiency, smokers, and the elderly. Influenza virus first establishes an upper respiratory

infection which can develop into an infection of the lower respiratory tract. The virus initially targets and kills mucus-secreting, ciliated, and other epithelial cells in the upper respiratory tract, causing the loss of these innate immune mechanisms. If the virus spreads to the lower respiratory tract, the infection can cause severe destruction of the bronchial or alveolar epithelium. While influenza can directly cause pneumonia, it more frequently promotes a secondary bacterial infection that leads to bronchitis or pneumonia. Because the elderly are less able to quickly initiate a new immune response, repair damaged tissue, and recover, they are more susceptible to complications of influenza. (Murray, Rosenthal, & Pfaller, 2009).

The influenza virus typically incubates for 1-4 days before producing a short prodrome of malaise and headache (Murray et al., 2009). The short incubation time is related to the fact that the final target organ for influenza is the respiratory tract which is the same as the portal of entry for the virus (Roitt & Delves, 2001). The prodrome is followed by the abrupt onset of fever, chills, severe body aches, loss of appetite, weakness, fatigue, sore throat and usually a non-productive cough (Murray et al., 2009). The fever typically lasts 3-8 days, with recovery within 7 to 10 days, unless a complication ensues (Murray et al., 2009).

Diagnosis of influenza is usually based on symptoms and the seasonal presence of the virus in the community. When necessary, typically for epidemiological purposes, laboratory confirmation is usually obtained from respiratory secretions. Testing methods for influenza include: Detecting the presence of the virus on a cell culture;

hemagglutination testing for virus presence; hemagglutination inhibition (HI) to determine type, strain or antibody specificity; antibody inhibition of hemadsorption which identifies type and strain, immunofluorescence and ELISA (enzyme-linked immunosorbent assay) which identifies influenza virus antigens; serology testing which can include HI, hemadsorption inhibition, ELISA, immunofluorescence, or complement fixation; and reverse transcriptase polymerase chain reaction to identify the type and strain of influenza (Murray et al., 2009).

Symptoms of influenza infection are caused by the interferon and lymphokine response to the virus, initially characterized by the inflammatory cell response of the respiratory mucosa. Interferon and cytokine responses peak with the presence of the virus in nasal washes, occurring at the same time as the febrile response. The classic flu symptoms of fever, malaise, headache and myalgia are associated with interferon induction (Murray et al., 2009). Because there is so little time for a primary antibody response to be mounted, the rapid production of interferon is extremely important in countering influenza infections (Roitt & Delves, 2001).

Influenza Virus

Influenza is a member of the Orthomyxoviridae family which includes Influenza A, Influenza B, as well as Influenza C. All three influenza viruses cause disease in humans but health research has focused on influenza A, which causes more severe illness and has been the causative agent for recurrent epidemics which can be large and associated with high mortality. Influenza A virus is characterized by its surface antigens,

Hemagglutinin and Neuraminidase, which have resulted in 16 and 9 different subtypes respectively. Influenza B virus also causes disease and epidemics, with associated mortality, especially among the elderly, but wide ranging pandemics to not occur with influenza B. There is only one influenza B subtype. Influenza C is not a serious human pathogen (Strauss & Strauss, 2008).

Orthomyxoviruses have segmented, single strand, RNA genomes which result in high rates of gene reassortment in mixed infections as well as mutation during replication in host cells. As a result, influenza viruses undergo constant changes that affect pathogenicity and disease epidemiology. These antigenic changes allow the influenza virus to overcome immunity in individuals who have been previously infected with influenza, and result in the need for annual reformulation of influenza vaccines to ensure effectiveness against newly evolved influenza strains (Maassab, Herlocher, & Bryant, 1999).

Influenza Vaccine

Current influenza vaccines available in the United States include trivalent inactivated influenza vaccine which can be used for any person 6 months of age or older and live attenuated influenza vaccine recommended for healthy non pregnant individuals aged 2-49 years (Centers for Disease Control and Prevention, 2009). Since live attenuated influenza vaccine is not recommended for the elderly, this paper will focus exclusively on the trivalent inactivated influenza vaccine.

The annual trivalent inactivated influenza vaccine contains three strains of influenza viruses. These include two influenza A viruses and one Influenza B virus. Each year, one or more virus strains in the vaccine might be changed on the basis of global surveillance and anticipated circulating influenza strains for that year. For the 2009-2010 influenza season, the influenza A vaccine strains were H1N1 and H3N2, and the B vaccine virus strain was B/Brisbane/60/2008 (Centers for Disease Control and Prevention, 2009). In order to allow sufficient vaccine production time, the vaccine strains are chosen from those circulating in late spring, anticipating that these viruses will cause epidemics the following winter. The final selection of vaccine components is made by individual health agencies, based on choices and supply seed virus provided by the World Health Organization. While these choices are usually correct, there is always a risk involved in the selection of vaccine components (Strauss & Strauss, 2008). The selected influenza viruses for the 2010-2011 influenza season contain an A/California/7/09 (H1N1)-like virus, an A/Perth/16/2009 (H3N2)-like virus, and a B Brisbane/60/2008-like virus. The A/California/7/09 (H1N1)-like virus is the pandemic (H1N1) 2009 influenza virus. The A/Perth/16/2009 (H3N2)-like virus will also be a change from the 2009-2010 influenza vaccine formulation (FDA, 2010). Research on influenza vaccine effectiveness must consider the vaccine components for that year, as well as circulating strains of influenza virus during the research period. For the proposed study, information on circulating strains will be obtained at the time the study is conducted from local health departments and laboratories.

While it is known that protection afforded by vaccination is not lifelong, research on the duration of vaccine protection is lacking (Longo, 2003). One review concluded that, while antibody levels decreased in the elderly post vaccination, this decrease was not below levels generally accepted to be protective at 4 or even 6 months post vaccination (Skowronski, Tweed, & De Serres, 2008). Numerous studies have documented that immune response to influenza vaccination is poorer in the elderly when compared to the response of younger vaccine recipients (Bernstein et al., 1999; de Bruijn et al., 1999; Fireman et al., 2009; Gardner, Gonzalez, Nogusa, & Murasko, 2006; Goodwin et al., 2006; Goronzy, Lee, & Weyand, 2007; Gulati, Keitel, & Air, 2007; Jefferson et al., 2005; Joshi, Shaw, & Quagliarello, 2009; K. L. Nichol, Nordin, Nelson, Mullooly, & Hak, 2007; Nichol, 2009; Rivetti et al., 2009; Wang, Wang, Lai, Lin, & Chou, 2007).

Influenza Immunity

Immunity following influenza infection is long lived but may not be complete and is subtype and strain specific. New strains of Influenza A that arise from antigenic drift and new subtypes that emerge as a result of antigenic shift have led to the continuing development of new influenza epidemics. Antigenic drift has been identified as the process by which mutations occur in the influenza genome, usually because of immune selection, that results in new virus strains. These new strains are partially resistant to immunity developed from previous influenza disease. Changes in the virus strain brought about by antigenic drift over 2 to 3 years may be sufficiently different to cause

disease in a person previously infected with the earlier strain. When these illnesses develop they are usually less severe due to partial immunity to the new strain (Strauss & Strauss, 2008).

New strains of influenza that are capable of causing serious disease can arise as a result of antigenic shift. Antigenic shift occurs with reassortment of the surface glycoproteins of the virus. Reassortment can result in a new virus subtype that can cause serious illness. This occurred with the emergence of Influenza A H2N2 in the late 1950s which was associated with high mortality during the 1957 influenza epidemic (Strauss & Strauss, 2008), as well as the novel H1N1 virus seen during the 2009-2010 influenza season (Joshi et al., 2009). It is a worthwhile clarification to note that the 1957 virus did not differ significantly from epidemic viruses from the 1930s and 40s except in degree of antigenic difference (Kilbourne & Arden, 1999). Antigenic drift and antigenic shift result in gradual mutations of the virus that result in strains for which humans have varying degrees of immunity, based on previous exposure to earlier strains.

The immune system employs a complex interaction between innate and adaptive immune functions to first clear primary infection from the body, and later provide ongoing protection from the same pathogen. In the case of influenza, these mechanisms are effected through Immunoglobulin A (IgA), CD8 killer cells, and Immunoglobulin G (Janeway, Travers, Walport, & Shlomchik, 2005).

Age Related Declines in Immunity

When functioning optimally, the innate and adaptive immune systems interact closely to defend against disease. Longo (2003) noted the aging process is very individual specific, with a wide variety of body systems affected in unique ways. Within this large continuum of individual diversity, the consensus that immune system functioning declines with age is widely accepted (Bernstein et al., 1999; Costanzo et al., 2004; Gardner et al., 2006; Keylock et al., 2007).

Changes in the Innate Immune System with Age

The innate immune system includes host defense mechanisms that first respond to antigens and which do not develop antigen-specific responses. Longo (2003) noted declines in innate immune responses were believed to be less severe in the elderly than declines in the other branch of the immune system, adaptive immunity. Declines in innate immunity, that have been noted and are clinically relevant to respiratory diseases in the elderly, include defects in swallowing, decreased gag reflex, decreased mucociliary clearance, decreased cough strength, increased alveolar duct diameter, and smaller airway size. While Langerhans cell density is preserved in oral mucosa with aging, salivary flow rates have been shown to decrease with decreased levels of IgA. Evidence indicates that macrophage, neutrophils and natural killer cell responses in the elderly are less effective against pathogens (Longo, 2003).

Patterns of cytokine and chemokines production, which regulate immune cells and immune cell functioning, are characteristically different in the elderly. Generally, the

elderly produce more Th2 type cytokines (IL-4 and IL-10) than Th1 type cytokines (IL-2, interferon γ, IL -12). This shift to Th2 type response has specific application to cell-mediated responses to influenza, and will be discussed below. Higher levels of proinflammatory cytokines such as IL-1, Il-6, IL-8 and TNF-α are typically seen in the elderly. In addition, the pro-inflammatory response is often prolonged in the elderly. The pro-inflammatory cytokines, IL-1, Il-6 and TNF-α, are typically seen in responses to tissue damage, and characterize acute responses to disease, often evidenced by the presence of fever. The goal of the pro-inflammatory response is to destroy pathogen and rebuild damaged tissue. In normal immune response, the proinflammatory actions are countered by anti-inflammatory cytokines such as IL-10, that limit the duration of TNF and IL-1 effects (Longo, 2003).

One of the most common sites of infection in the elderly was reported to be the lung (Longo, 2003). The respiratory nature of influenza disease, the virus' propensity to destroy protective mechanisms such as pulmonary cilia, and viral changes that come about due to antigenic shift and drift, result in a considerable threat to the elderly, from influenza. This threat is augmented by major changes that occur in the adaptive immune system with ageing.

Age Related Changes in Adaptive Immunity

Adaptive immunity refers to antigen specific pathogen response that involves T cells and B cells. These cells protect against pathogens and immunogens through specific

antigen recognition and activation of effective immune responses. It is adaptive immunity that is most affected by aging (Longo, 2003).

The major route for T cell maturation is through the thymus. Thymopoietic tissue shrinks with age, with a 70 year-old exhibiting about 10% of the thymopoietic space of a child (Longo, 2003). The aging thymus continues to generate T-cells, but at a reduced rate. There is also a reduced capacity to increase T-cell production in response to a decline in peripheral T-cells. Subsets of T-cells also change in the elderly: CD4+ T cells decrease with naïve CD4+ T cells being more greatly reduced than memory CD4+ T cells. T-cell receptors are frequently altered in older individuals with CD8+ T cells being affected. CD8+ T cells are essential to combating viral diseases such as influenza. T-cell proliferation is decreased in the elderly and stimulated T-cells produce less IL-2, and lower levels of IL-2 receptors (Longo, 2003).

While the total numbers of B cells and serum immunoglobulin concentrations are not significantly affected by aging, the nature of humoral immunity is changed. Changes have been noted in B-cell development, antibody repertoire, and B-cell subsets (Longo, 2003).

In summary, aging impacts the immune system in diverse ways. Longo (2003) identified the most notable changes were increased levels of inflammatory cytokines, especially IL-6, a decrease in the generation of CD4+ T cells due to thymic changes, and a decreased response of T-cells to antigen. These changes are exacerbated by the decreases in physiologic reserve and slower restoration of homeostasis within the

immune system as well as other organ systems within elderly individuals. These changes can be ameliorated by exercise, improved nutrition and, especially applicable to the topic of this paper, vaccination (Longo, 2003).

Research on Influenza in the Elderly

There is a large amount of research documenting the greater morbidity and mortality risk from influenza among the elderly, as well as the greater difficulty for the elderly in mounting a protective response to influenza vaccine (Bernstein et al., 1999). This body of research provides numerous resources for methodology when planning to examine immune response to influenza vaccination. These will be discussed in this section, as well as questions that have arisen regarding immune response to influenza, controversies regarding the effectiveness of influenza vaccination in the elderly, and research specifically linking positive emotions and immune response to influenza vaccination and influenza disease.

Approaches for Evaluating Influenza Vaccine Effectiveness

Numerous factors contribute to the presence of immunologic memory against influenza in the elderly. One of these is the prevalence of influenza disease worldwide, affording naturally acquired immunity among those who have encountered the virus during their lifetime. The other source of immunologic memory against influenza is a result of influenza vaccination which has been recommended in developing countries for the elderly on an annual basis. Influenza vaccination provides a prophylaxis that involves a killed, trivalent influenza vaccine tailored each year to specific strains of the influenza

virus (Corsini et al., 2006). It is important to consider immunologic memory when evaluating influenza vaccine effectiveness in the elderly (Beyer et al., 1996; Keitel, Cate, Couch, Huggins, & Hess, 1997).

A common method of assessing immune response to vaccination is to examine hemagglutination inhibition antibody titers. Titers > 40 are usually considered to be protective. The elderly frequently do not achieve these levels due to decreased immune response. Researchers on influenza vaccine effectiveness question the utility of HI as a single evaluative measure (Bernstein et al., 1999; Corsini et al., 2006; Feng et al., 2009; McElhaney et al., 2006). The relevance of HI titers for the elderly is complicated by findings that levels of antibody considered predictive of protection in the young are not necessarily predictive of protection against influenza in the elderly (Bernstein et al., 1999). Individuals with high titers have gone on to develop confirmed influenza infections (Gravenstein, Drinka, & Duthie, 1990). Virus-specific antibodies measured by ELISA testing are greater than those measured by HI test. In addition, ELISA testing measures antibodies against denatured protein, thereby providing measures against antibodies which are potentially protective, as well as those that are not protective. (Gulati, Kumari, Wu, Keitel, & Air, 2005; Gulati et al., 2007). Mean antibody levels post vaccination, rather than increases in antibody levels post vaccination, are more reflective of protective antibody response in the elderly (Gulati et al., 2005). Measurements of cell mediated immunity, coupled with HI titer have been proposed as being more useful in defining a relevant response to influenza vaccination in the elderly. A study of 233

healthy elderly individuals living in a group of continuing care centers assessed the interaction between cell-mediated and humoral immune responses to influenza vaccine (Bernstein et al., 1999). Only 48.9% of these elderly had intact humoral immune systems and only 30% demonstrated intact cell-mediated immune responses, with no association observed between the two. Measures of IFNγ, however, were significantly correlated with both antibody and cell-mediated responses to influenza vaccination (Bernstein et al., 1999).

Cytokines refer to a collective group of cellular mediators which regulate the immune system. Interleukins are cytokines that mediate signals between leukocytes. In regulating the immune system, cytokines may behave antagonistically to inhibit each other's actions. The differentiation of Th0 cells into Th1 and Th2 cells provides an example of the regulation of cell differentiation. Th1 cells and Th2 cells each produce a variety of regulatory cytokines. Th1 cells, for example, produce IL-1, IL-2, IL-12, THF and IFNγ, while Th2 cells produce IL-4, IL-5, IL-10 and IL-13. While cytokines perform a variety of immune, regulatory, and feedback mechanisms, the primary effects of Th1 cytokines is to activate macrophages, and the primary effects of Th2 cytokines is B cell activation and antibody production.

Th1 cells develop when IL-12 is present during antigen stimulation of T cells. IL-12 is manufactured by dendritic and other cells early in virus response. Th1 cell development is contrasted to Th2 cell development which occurs in the early response to viruses when IL-4 is present (Coico, Sunshine, & Bnjamini, 2003).

Th1 and Th2 subsets can regulate one another's growth and effector functions. As a result of the activity of cytokines produced by one subset, it can become difficult for the immune system to shift the response to the others subset. The effect of IL-10 or IFNγ, for instance, may allow either a Th2 or Th1 response to dominate (Coico & Sunshine, 2009).

Cytokines play a vital role in regulating immune response. TH2 cytokines (IL-4, IL-5, IL-6, and IL-10) produced by CD4+ cells are essential for the development of antibody production, and TH1 cytokines (IL-2, IL-12, and IFNγ) affect both B-cell and T-cell production (Bernstein et al., 1998). Since age related declines in the immune system are most dramatic at the level of T-cell responses, examination of cytokine production may be viewed as a significant contributor to decreased antibody production seen after influenza vaccination in the elderly. To examine cell-mediated immune response to influenza vaccination in 30 young healthy volunteers and 270 healthy elderly living in retirement communities, the production of IL-2, Il-4, IL-6, IL-10 and IFNγ was measured in vitro after stimulation with trivalent influenza vaccine. Lower levels of IL-10 and IFNγ were associated with poorer immune response in the elderly (Bernstein et al., 1998). These findings were expanded upon in a group of 90 community dwelling older adults with congestive heart failure who developed laboratory confirmed influenza illness and whose ex vivo cellular response demonstrated a 10-fold lower IFNγ:IL-10 ratio compared to study subjects who did not develop influenza (McElhaney et al., 2006). The question must be raised as to whether this ratio would be similarly predictive of

influenza illness in an elderly population who did not have congestive heart failure. Examination of the ratio for Th1 and Th2 cytokines to evaluate type of immune response will be used in the research proposed in the next section of this paper.

Roitt and Delves (2001) cited studies in mice which demonstrated that, after an early peak of interferon production, titers of live influenza virus in the lungs fell rapidly. They postulated that antibody arrived too late to be of value in aiding recovery. This placed greater importance for antibodies which may be present in nasal mucosa and the lung, despite low serum titers. Discussing the major cytotoxic roles of CD4 and CD8 T-cells, Roitt and Delves emphasized the importance of CD8 cell's cytokine producing actions. The importance of cytokine release in interfering with viral replication, and increasing the nonspecific cytotoxicity of natural killer cells for cells already infected, was noted to be especially valuable for protection against viruses (Roitt & Delves, 2001).

Longo (2003) reported that the aging immune system is characterized by producing more TH2 type cytokines (IL-4, and IL-10) than TH1 type cytokines (IL-2 and IFNγ, IL-12). IL-4 functions as a growth factor for B cells and TH2 CD4+T cells, promotes IgG synthesis, and inhibits TH1CD4+ helper cells. IL-2 functions as a T-cell growth factor. IL-10 inhibits production of TH1 cells and macrophage function. IL-12 activates natural killer cells and promotes generation of Th1 CD4+ T cells. (Coico & Sunshine, 2009). Table 1 identifies a number of cytokines and their actions. These include IL-2, IL-4, IL-6, IL-10, IL-12, INFγ, and INFα.

Table 1. Selected Cytokines, Producer Cells and Functions
adapted from Janeway, Travers, Walport, & Shlomchik, M. J. (2005).

Cytokine	Producer Cells	Major Functions
IL-2	T cells	T-cell proliferation
IL-4	T cells, mast cells	B-cell activation, IgE switch, induces differentiation in Th2 cells
IL-6	T cells, macrophages, endothelial cells	T- and B-cell growth and differentiation, acute phase protein production, fever
IL-10	T cells, macrophages	Potent suppressant of macrophage functions
IL-12	Macrophages, dendritic cells	Activates natural killer cells, induces CD4 T-cell differentiation in Th1 like cells.
IFN-α	Leukocytes, dendritic cells	Antiviral, increased MHC class 1 expression
IFN-γ	T cells, natural killer cells	Macrophage activation, increased expression of MHC molecules and antigen processing components, Ig class switching, suppresses TH2

Influenza Vaccine Effectiveness: Criteria and Controversies

A study by McElhaney et al. (2006) highlighted another important measure in evaluating immunity as well as the goal for influenza vaccination; prevention of disease. This prospective study conducted surveillance for influenza-like illness when influenza was circulating in the community. Influenza like illness (ILI) was defined as either 2 respiratory symptoms, or one respiratory and one system symptom. Respiratory symptoms included cough, shortness of breath, sore throat, nasal congestion. Systemic

symptoms included fatigue, myalgia, malaise, feverishness, or fever of greater than 37.3oC. Nasopharyngeal swabs were collected for virus culture if symptoms were reported within 72 hours of onset. Laboratory diagnosed influenza was defined as ILI associated with a positive influenza virus culture and/or seroconversion (4-fold rise in Ab titers from pre-to post-illness (McElhaney et al., 2006). In the proposed study, sera will be frozen and stored, if additional testing is indicated. Surveillance for influenza like illness, using criteria similar to McElhaney et al.'s will be ongoing for the duration of the influenza season.

McElhaney et al.'s (2006) criterion for influenza disease is more specific than that provided by the Centers for Disease Control (CDC). Uncomplicated influenza illness is characterized by the abrupt onset of constitutional and respiratory signs and symptoms, for example; fever, myalgia, headache, malaise, nonproductive cough, sore throat, and rhinitis (Centers for Disease Control and Prevention, 2009). The CDC cautioned that clinical definitions have performed poorly in some studies of older patients, advising that the presence of fever, cough, and acute onset had a positive predictive value of 30% for influenza in patients 60 and older. They highlighted the challenges of identifying influenza illness in the absence of laboratory confirmation and indicated that the diagnosis should be considered in patients with respiratory symptoms or fever during influenza season (Centers for Disease Control and Prevention, 2009).

A systemic review of 64 studies assessing efficacy of influenza vaccine against influenza disease included the following outcomes: Influenza confirmed by viral

isolation, serology or any other type of laboratory testing; influenza-like illness that arose in the winter or epidemic periods; pneumonia; admission to a hospital for complication associated with influenza-like illness or influenza; and all-cause mortality. The review concluded that the aims of vaccination programs are met in preventing disease for residents of long-term care facilities. The effectiveness of influenza vaccination for elderly living in the community, however, was modest (Jefferson et al., 2005). These findings were reiterated in a subsequent review of influenza research (Rivetti et al., 2009) in which effectiveness of influenza vaccination programs where found to be 23% effective against ILI, and non-significant against laboratory confirmed influenza for residents of extended care facilities, when there was a good vaccine match and high viral circulation. Well matched vaccines prevented pneumonia, hospital admission, and deaths from influenza or pneumonia for residents of nursing homes. For elderly individuals living in the community, however, vaccines were found to not be significantly effective against influenza or pneumonia (Rivetti et al., 2009).

These findings were in contrast to a ten year observational study of vaccine effectiveness that included 713,872 person-seasons of observation and concluded that vaccination was associated with a 27% reduction in the risk of hospitalization for pneumonia or influenza and a 48% reduction in the risk of death among community-dwelling elderly persons (Nichol et al., 2007). A historical cohort study of individuals over 64 years of age from 1989 to 1999 in England and Wales and linking influenza vaccination to subsequent hospitalization and death found vaccination was 21% effective

against hospitalization for acute respiratory infection and 12% effective against death (Mangtani et al., 2004). These findings were countered in a study of 1952 elderly Australians for whom influenza vaccination provided no benefit against hospital admissions for community acquired pneumonia with influenza (Skull et al., 2007). Citing problems with estimates of influenza vaccine effectiveness in preventing deaths, given that influenza mortality estimates are only 5-10%, a Kaiser Permanente study in Northern California used an alternative model to examine the vaccine effectiveness. Employing a "difference in differences" model (often used by economists) yielded a 4.6% reduction in all cause mortality during nine influenza seasons (Fireman et al., 2009). Nichol (2009) summarized the numerous challenges in evaluating influenza vaccine effectiveness and mortality and concluded that, even taking into account the potential for residual bias and confounding, most studies confirmed the benefits of vaccination among the elderly for reducing hospitalization and death. The controversy regarding vaccine effectiveness extends well beyond academic interest, since 40 out of 51 developed or rapidly developing countries recommended vaccination for all persons aged 65 or older (van Essen, Palache, Forleo, & Fedson, 2003). Such large scale public health initiatives call for meaningful evaluation.

In the proposed research, findings for study participants who live in more restricted assisted living situations within the elderly community will be examined separately from those who live independently in apartment settings within the same elderly community. In this way, it will be possible to evaluate the role of independent

living, vs. assisted living situations on immune responses for residents within the same community experiencing similar circulating virus exposures.

2009 H1N1 Influenza Pandemic

The 2009 H1N1 influenza pandemic resulted in extraordinary influenza activity in the United States and provided a real life demonstration of influenza immunology for the general population and the elderly (Centers for Disease Control and Prevention, 2010b). In April 2009, a new Influenza A (H1N1) virus was determined to be the cause of influenza in two children in the United States and outbreaks of respiratory illness in Mexico. By May, 2009, this virus emerged in communities across North America and in many areas of the world. On June 11, 2009, the World Health Organization declared a worldwide pandemic, indicating uncontained community-level transmission of the novel influenza A virus. In contrast to seasonal influenza, evidence indicated that relatively few severe cases of novel Influenza A (H1N1) virus infection had occurred among older persons, and the highest hospitalization rates for illness caused by this virus occurred among persons aged <65 years (Centers for Disease Control and Prevention, 2010b). This finding was attributed to partial immunity to the virus among the elderly due to earlier exposures to a similar strain, the Novel H1N1 virus being the result of a reassortment from 4 earlier strains (Joshi et al., 2009).

Because current seasonal influenza vaccines did not provide protection against novel influenza A (H1N1) virus, specific vaccines were manufactured during the summer of 2009 (Centers for Disease Control and Prevention, 2010b). Since initial supplies of

these vaccines were not sufficient to meet the demand, the CDC's Advisory Committee on Immunization Practices (ACIP) recommended that groups at highest risk for infection or influenza-related complications should be the initial targets for vaccination. These included: pregnant women, individuals who lived with or provided care for infants aged <6 months, health-care and emergency medical services personnel, children and young adults aged 6 months to 24 years, and persons aged 25 to 64 years with medical conditions that put them at higher risk for influenza-related complications. Among adults, cross-reactive antibody to novel influenza A (H1N1) virus at titers that correlated with protection from illness was detected in 6% to 9% of those aged 18 to 64 years and in 33% of those aged >60 years (Centers for Disease Control and Prevention, 2010b). Influenza disease incidence correlated with these antibody findings. In contrast to seasonal influenza in previous years, the median age of persons in the U.S. who developed laboratory-confirmed Novel H1N1 virus infections was 12 years, with the highest infection incidence occurring among persons aged 5--24 years. The incidence of infection was lowest among persons aged ≥65 years. The age distribution of hospitalized persons with laboratory-confirmed novel influenza A (H1N1) was also strikingly different from seasonal influenza with a median age of 20 years for the novel strain. The incidence of hospitalization was highest among young children aged <4 years. Only 282 (5%) of 5,514 hospitalizations and 29 (8%) of the 353 reported deaths occurred among persons aged ≥65 years. The median age among persons who died with novel influenza A (H1N1) virus infection was 37 years (Centers for Disease Control and Prevention,

2010b). These findings contrast with multiple studies of seasonal influenza in which hospitalization and mortality rates are typically highest among persons aged ≥65 years. In contrast to the novel H1N1 influenza season, an estimated 90% of seasonal influenza-related deaths and 60% of seasonal influenza-related hospitalizations were reported among adults aged ≥65 years in a typical influenza season (Centers for Disease Control and Prevention, 2010b). The trends seen in novel H1N1 virus continued until the early fall. During October and November 2009, CDC received reports of 2009 H1N1 outbreaks in Long Term Care Facilities in Colorado, Maine, and New York (Centers for Disease Control and Prevention, 2010a). Despite a lower risk of infection for 2009 H1N1, vulnerable elderly patients still succumbed to the virus.

Approaches to Improve Vaccine Effectiveness

There have been a number of suggestions to improve the effectiveness of influenza vaccines for the elderly. These include the addition of adjuvants which are substances that enhance the immunogenity of antigens (Janeway et al., 2005), changing the route of vaccine administration from subcutaneous to intramuscular (Cook et al., 2006), ongoing annual vaccinations and better vaccine program strategies (de Bruijn et al., 1999; Keitel et al., 1997; Nichol et al., 2007), more immunogenic vaccines (Nichol et al., 2007), and strategies to improve vaccine protection such as oral administration of dehydroepinrosterone (DHEA;Corsini et al., 2006). Increasing the vaccine components from 30 µg to 60 µg for each component (A/H3N2, A/H1N1, B) was shown to induce a higher frequency of serum antibody increases for all three viruses in elderly vaccine

recipients (Couch et al., 2007). Consistent with these findings, the U.S. Food and Drug Administration announced approval of a high dose seasonal influenza vaccine specifically intended for people ages 65 years and older on December 23, 2009 (FDA, 2010). Inquiries regarding the cost of the high dose vaccine for the elderly, on March 10, 2010, made by a community hospital pharmacy purchasing department determined that the cost of the high dose vaccine was $25.75 per dose compared with a cost of $8.00 per dose for the traditional influenza vaccine. The CMS reimbursement rate for vaccination in this same locality was $22.57, which was established to include the cost of vaccine reimbursement (set at 95% of wholesale price) and compensation for vaccine administration (Centers for Medicare & Medicaid Services, 2010).

In 1994, the last year for which census data was available, there were 33.2 million individuals in the United States, aged 65 and older (Centers for Disease Control and Prevention, 2010b). As previously discussed, the elderly are more greatly affected by mortality and morbidity associated with influenza. This increased vulnerability underscores the importance of public health initiatives aimed at decreasing influenza among this age group. Census changes, with the rate of growth for individuals aged 65 years and over exceeding the growth rate of the country as a whole (by a factor of 11 to a factor of 3;Centers for Disease Control and Prevention, 2010b) also underscore the impact of public health initiatives that focus on the elderly. The combined consequences of these factors increase the need for better understanding of variables which affect immune response to influenza among the elderly.

Behavioral Factors and Emotions

A basic, underlying assumption to this paper is that obtaining annual influenza vaccination is a behavioral factor with important health outcomes. Other behavioral factors which have been found to affect immune response to influenza vaccine include physical activity (Keylock et al., 2007), diet and vitamins (Burns, Carroll, Ring, & Drayson, 2003), smoking, drinking, exercise, and sleeping (Miller et al., 2004; Cohen, Miller, & Rabin, 2001; Phillips et al., 2006). In contrast to student populations, social support was found to be not related to influenza vaccine response in the elderly. Being married, and having higher marital satisfaction, however, was associated with a higher peak response to influenza A, one month post vaccination in a study of 184 community dwelling seniors (Phillips et al., 2006).

When positive emotions have been studied within the context of stress and negative emotions (Lutgendorf & Costanzo, 2003; Cohen et al., 2003; Costanzo et al., 2004; Doyle, Gentile, & Cohen, 2006), positive emotions have demonstrated beneficial health outcomes. These include benefits for antibody response to vaccines (Gallagher, Phillips, Ferraro, Drayson, & Carrol, 2008), and cytokine production (Prather, Marsland, Muldoon, & Manuck, 2007) in studies of healthy adults. As discussed in this paper, immunosenescense in the elderly results in unique challenges to mounting an effective immune response. Costanzo et al. (2004) have argued that positive mood and optimism may buffer decreases in T-lymphocyte function associated with ageing by moderating hypothalamic-pituitary-adrenocortical and sympathodrenomedullary activation. Their

study evaluating in vitro TH1 response through the measurement of IL-2 and IFNγ, and TH2 response through the measurement of IL-10 to both live virus and vaccine in elderly individuals, supported this hypothesis with higher IL-2 and IFNγ for participants who scored higher in measurements of vigor and optimism (Costanzo et al., 2004).

The research proposed in this paper seeks to expand upon these findings through a study of a healthy elderly population, comparing measurements of immune response for elderly individuals based on self reported measures of trait and state positive affect. The study design proposed provides an opportunity to examine psychosocial factors, immune regulators and health outcomes within one study. This will be accomplished through the examination of positive trait emotions as predictors of less influenza like illness for 120 medically stable elderly individuals followed throughout the influenza season. For a subset of the study population self-reporting higher and lower levels of positive trait emotions, immune mediators (IL-4, IL-6, and IL-12) will be measured to determine Th1, Th2 and proinflammatory responses to immune system challenges represented by influenza immunization and circulating respiratory viruses including circulating influenza strains within the community.

CHAPTER THREE

DISCUSSION OF PROPOSED RESEARCH METHODOLOGY: POSITIVE EMOTIONS AND IMMUNE RESPONSE TO INFLUENZA IN MEDICALLY STABLE ELDERLY INDIVIDUALS

The research question to be investigated is: Do positive emotions impact immune response in medically stable individuals aged 65 years and older? The broad aim is to investigate the relationship between positive emotions and health outcomes related to influenza vaccination for medically stable, older adults. There are two specific aims: One is to evaluate the relationship between positive emotions and the development of influenza like illness for a group of medically stable older adults who have received influenza vaccination. The second aim is to evaluate the relationship between positive emotions and cytokine measurements for medically stable older adults vaccinated for influenza. The research question will be investigated using theoretical frameworks from psychology and psychoneuroimmunology. The hypothesis for the first aim is that medically stable elders with higher state positive emotions will demonstrate lower incidence of influenza-like illness following influenza vaccination. The hypothesis for the second aim is that medically stable older adults with higher positive emotions will demonstrate different cytokine responses to influenza vaccination and influenza like illness

The independent variable is positive emotion trait defined as an enduring emotional state consisting of pleasant dispositional characteristics such as happy, energetic and pleased, as measured by self-report on the PANAS (Watson & Clark, 1994). The PANAS will be used to self-report both state and trait emotions, and positive and negative emotions. Because the PANAS is designed to measure both momentary affective states, as well as long term mood, daily measures of state emotions ("rate how you felt today") and trait emotions ("rate how you generally feel") can be obtained. The dependant variables are responses to immune challenges defined as development of influenza like illness over the duration of the influenza season, and cytokine measures at baseline, following vaccination, and during the initial development of influenza like illness during the influenza season.

The hypothesis is specified as follows:

1. Medically stable individuals aged 65 years and older who report higher trait positive emotions, will demonstrate lower incidence of influenza like illness over the course of the influenza season (October through March) after receiving influenza immunization from clinics, healthcare providers or other vaccination sources.
2. Participants who self report higher positive trait emotions will demonstrate different cytokine responses:
    a. Positive trait emotions will affect cytokine measurements, resulting in differing cytokine profiles.

b. Positive trait emotions will affect the cytokine response to respiratory viruses circulating within the community exhibited during the initial period of influenza like illness during the influenza season.
c. Higher positive emotions will result in a greater Th1 than Th2 response to influenza vaccine and influenza like illness as evidenced by higher levels of IL-12 and lower levels of IL-4 when measured post vaccination and during the initial period of influenza like illness during the influenza season.
d. Higher positive emotions will result in lower levels of pro-inflammatory cytokines (as measured by IL-6).

In seeking to demonstrate the impact of positive emotions on health outcomes of influenza vaccination among a healthy elderly population, the objective of this study is to provide evidence, using a psychoneuroimmunology model, that positive emotions play a role in immune response to influenza in the elderly. The Psychoneuroimmunology model proposes that psychobehavioral variables (i.e. positive emotions) impact health outcomes (i.e. influenza-like illness) via neurological and immunological mechanisms (cytokine responses). This study seeks to provide insight into the role of positive emotions in influenza outcomes post vaccination with the goal of improving these outcomes for elderly patients.

Research Design and Methods

Sample

The study will include a prospective design to measure the impact of positive emotions on immune response to influenza vaccination in a sample of residents from a faith based community for the elderly located in a large metropolitan suburb. These residents will include individuals who are 65 years of age and older who are living independently in community apartments, or living in assisted living settings which provide extended care services. Participants must agree to influenza vaccination and receive vaccination through during the study period according to their own preferences, physician recommendations or other criteria. Those who refuse vaccination or cannot be vaccinated (e.g. due to allergy or severe reaction to vaccine) will be excluded.

Participants will be medically stable. Individuals who have been hospitalized within the last month, or demonstrate symptoms of infection within the previous week will be excluded. Participants with medical conditions that are controlled or regulated via medication will be included in the study. Examples of controlled medical conditions include: Diabetes controlled by diet, exercise, or medication; hypertension controlled by medication. Individuals with the following conditions will be excluded from the study: Immunocompromised individuals (HIV or AIDS, post transplant, autoimmune disorders or malignancy); individuals on immunosuppressive therapy (chemotherapy, steroids, and other immunosuppressive therapies); and individuals with asthma. Participants who smoke will be excluded from the study. Information for exclusion criteria will be obtained via participant self report on a Health Assessment Survey.

Participants will need to have sufficient cognitive ability to self-report emotional affect on the PANAS (Watson & Clark, 1994) and other measures, as well as follow through with daily PANAS reporting, and self monitoring for respiratory symptoms or systemic symptoms. Orientation to person, place and date will be assessed when study consents are obtained. Ability to read and reply to questionnaires will be assessed after consent is obtained. Elderly individuals who are not oriented, or do not have the physical capacity to complete questionnaires will be excluded from the study. Elderly individuals who have difficulty reading or writing, but have sufficient mental capacity to respond to items, as well as access to an individual capable of filling out the questionnaires will be eligible for participation if the support individual agrees to study training and parameters.

After obtaining necessary approvals, from Loyola University's Medical Center investigational review board (IRB), and the community's corporate administrators, the study will be announced via flyers and posters. Informed consent will be obtained from all interested individuals who meet the study criteria of age 65 or older, as described above. It is anticipated that this will include more women than men, since the demographics of the elderly do not include equal representation from both genders. It is also anticipated that participants will be predominantly Caucasian, since the faith based community facility primarily draws from that racial group. The demographics question will include a question regarding race, based on US census categories, because research has demonstrated a decreased immune response to influenza vaccination in elderly African Americans (Gardner et al., 2006).

Power Analysis

Data to be used for power analysis was identified in the a study of 18 older adults for whom peripheral blood mononuclear cells were stimulated in cultures for influenza vaccine strains, in which the level of T-helper type 1 (interkeukin-2 and interferon γ) and type 2 cytokines (interleukin-10) were measured in culture supernatants (Costanzo et al., 2004). This study found greater vigor was associated with significantly greater IL-2 levels in response to an A influenza ($r = .64$, $p = .004$) and a B influenza ($r = .57$, $p = .01$). Greater optimism was associated with significantly greater IFN-γ response to A influenza vaccine components ($r = .48$, $p = .049$; Costanzo et al., 2004). G* power online software (Buchner, Franz, & Erdfelder, 1996) was used to calculate recommended sample size (Faul, Erdfelder, Lang, & Buchner, 2007) for the proposed study. Results for a correlation of $r = .64$, $p = .004$ as seen in the patients with greater rigor tested for IL-2 with the A influenza strain yielded a sample size of 15 (one-tailed). For the correlation of $r = .5$, $p = .01$ as seen in the patients with greater rigor tested for IL-2 with the B influenza strain yielded a sample size of 34 (one-tailed), and for the correlation of $r = .48$, $p = .049$ as seen in the patients with greater optimism testing IFN-γ with the A influenza strain yielded a sample size of 38 (one-tailed). A second study was used for power analysis, with 334 participants assessed for level of positive emotions and subsequent development of a cold after inoculations with nasal drops containing rhinoviruses (Cohen et al., 2003). Using G* power to calculate sample size for a correlation of .48 with a power of .80 and $p = .05$ yielded a sample size of 23.

Addressing concerns about statistical power, Cohen, Miller, and Rabin (2001) recommended a sample size of approximately 120 subjects to have sufficient statistical power to detect differences in antibody responses in studies of influenza vaccine effectiveness for stressed and non-stressed groups. While the differences between stress and positive emotions, or differences in antibody and cytokine response may account for the disparity between the two sample size recommendations, it seems prudent to plan for a larger sample size. The poor predictability of influenza outbreaks has been acknowledged to cause problems with power calculations for influenza studies (Beyer et al., 1996). The vagaries of actual circulating virus strains confound the problem. The study design will include planned recruitment of 120 subjects. Funding constraints will limit the sample size for lab testing to 25 individuals, at three time points. To maximize variability, participants with the greatest and lowest scores for positive trait affect on the PANAS will have blood drawn for cytokine testing. Blood will be drawn from 40 individuals to account for attrition. All sera will be frozen and stored, should additional testing be indicated.

Design

This study will include a prospective design with a convenience sample drawn from groups of medically stable individuals aged 65 and older living in a faith based community to measure the impact of positive emotions on immune response to influenza. The design is based on the assumption that there is systematic variance in the dependent variable (immune response) related to the independent variable of positive emotions (Kerlinger & Lee, 2000). Participants within the same community will self select into the

sample based on self reported positive trait emotions. The study will be conducted in ongoing residential settings, where social situations and exposures to circulating viruses will occur naturally, with population samples drawn from a variety of naturally occurring living situations for the elderly. The proposed research is prospective, starting from measures of positive emotions, examining immune response to vaccination, and performing ongoing surveillance for incidence of influenza illness in the surrounding community. This prospective design will lend considerable strength to the study since it will resolve any ambiguity regarding the temporal sequencing of positive emotions and immune response (Polit & Hungler, 1983).

A quasi-experimental design, such as that used in the cold studies (Cohen et al., 2003; Cohen et al., 2006) is not possible, due to ethical concerns. Researchers would be apprehensive regarding inoculation of an elderly population sample with influenza and observing for development of influenza disease, given the high morbidity and mortality associated with influenza for the elderly, as well as the psychological consequences of an imposed quarantine period. In addition, it would be unlikely that such a design would be approved by the necessary IRB at this point in time.

This proposed study expands upon previous research because it includes in vivo measures of immune response, a variety of elderly living situations (assisted and independent living within the same community), the inclusion of immune measures that include cytokine levels, ongoing surveillance for development of influenza like illness, concurrent surveillance of incidence of influenza disease within the immediate geographic area, measurement of state and trait positive emotions, measures of state and

trait negative emotions, and measure of a complex emotional ability associated with positive emotions and building of personal resources (resiliency). This last measure is consistent with the broaden and build theory. The study as a whole, however, will use a PNI model, seeking to link behavioral variables (influenza vaccination and positive emotions), with immune responses and health outcomes (cytokine response and development of disease). The use of cytokine measures provide a potential mediating pathway for behavioral variables to impact health outcomes, consistent with the PNI model.

As recommended for PNI research (Robinson, Mathews, & Witek-Janusek, 2002), data will be collected on a variety of demographical and behavioral factors that may impact the complex neuro-endocrine-immune network that forms the basis of the PNI framework. Many of these behavioral factors are risk factors for respiratory disease. This lends validity to the use of the PNI framework for this study linking positive emotions and behavioral variables, immune response and health outcomes. In addition to name, age, gender, race, and level of independent living status within the community, data will be collected on, substance use, caffeine, smoking, obesity, sleep, exercise, medication, and health status. A variety of approaches for measurement and control are included in the PNI literature. Stress has been discussed extensively in the PNI literature on vaccine effectiveness (Burns et al., 2003; S. Cohen et al., 2001), as well as in the psychology literature reviewed. Recommendations for PNI studies also suggest adding a measure of more than one functional area to identify changes occurring within other areas (Robinson et al., 2002). For these reasons, a self reported measures of stress, provided

via the Perceived Stress Scale (Cohen, et al., 1983) will be included in the proposed research. To control for sleep, as a confounder for immune response, participants will be requested to complete the Pittsburgh Sleep Quality Index (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989).

In addition to data collection noted above, methodologies consistent with published research will be used. For example, consistent with recommendations for immune studies, serum samples will be batched and analyzed simultaneously in order to decrease interassay variability (Robinson, Mathews, & Witek-Janusek, 2002). Consistency in laboratory supplies, agents, personnel, and quality control has been shown to impact study results. These will be controlled through the use of a single laboratory, source of supplies and consistent lab technicians for the study.

All serum derived cytokines will be measured using quantitative sandwich enzyme immunoassay techniques (Quantikine kits, R & D Systems, Minneapolis, MN). The coefficient of variation ranges between 2.6 - 4.9% for the individually assessed cytokines. Budgetary considerations influenced the sample size for cytokine measurements (See Table 2. Budget for Cytokine Testing). Based on power studies previously reviewed, however, it was anticipated that a sample size of 50 for cytokine measurement would be sufficient. Plans included drawing serum from 40 participants in both the high and low positive emotion groups, anticipating attrition.

Table 2. Budget for Cytokine Testing
N = 125(42 samples/kit = 3 kits)

Number of Cytokines and Kits	Cost per Kit	Total Cost
3 cytokines x 3 kits = 9 kits	$475	$4,275
Distribution of Kits		
Collection Time	Sample Size	Total Tests per Collection
Pre Vaccination	25 high positive affect 25 low positive affect	50
Post Vaccination	25 high positive affect 25 low positive affect	50
During episodes of Influenza like illness	Estimated at 25	25

Research Procedures

Setting

The study will be carried out in an older adult community located on 84 acres within a major metropolitan suburb. The adult community is faith based, though affiliation with the faith is not a prerequisite for residence. The community includes 9 levels of care ranging from independent living in private homes through adult day care, and assisted living, to total care requirements associated with physical and cognitive deficits. It is worth noting that the community also provides day care services for personnel working within the assisted living components. An intergenerational child day care program is included in the services offered. Young children are reported to be at high risk for influenza and to shed influenza strains for a mean duration of 7.6 days (Centers for Disease Control and Prevention, 2009). Since transmission of influenza to the elderly is an ongoing concern, community surveillance for influenza disease will include laboratory reported confirmed cases in all individuals, including those less than

five years of age during the study period, from State Board of Health surveillance programs and hospital laboratory based surveillance in the community.

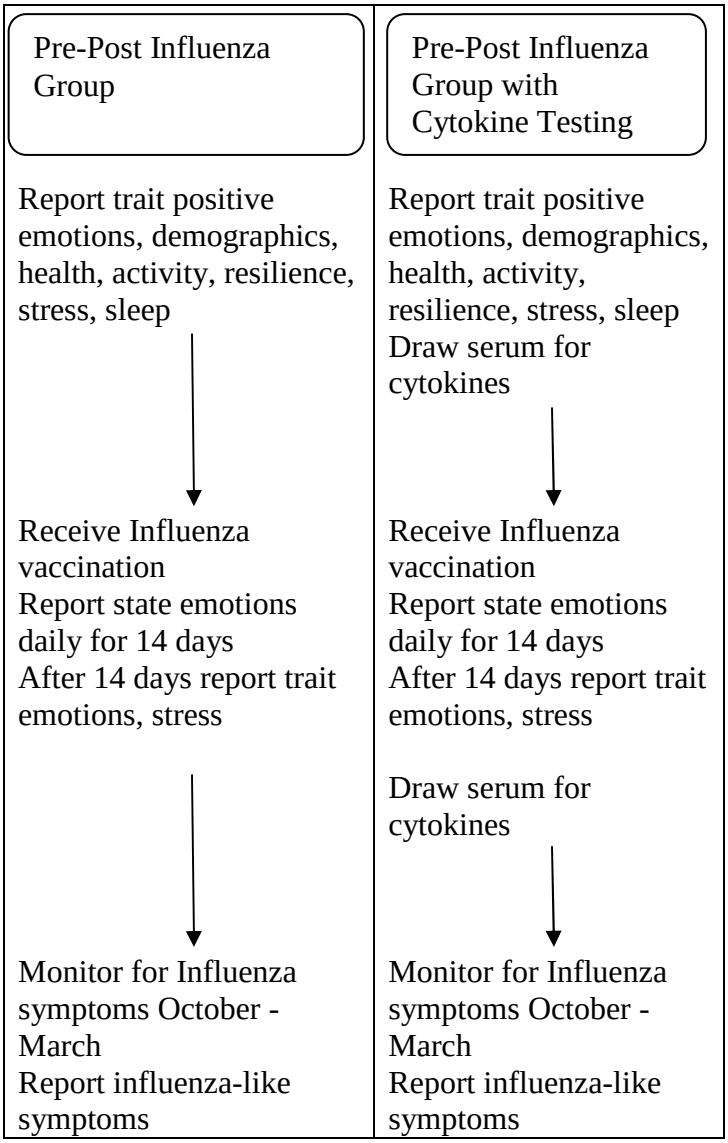
Sequence of Data Collection

Table 3 identifies Variables and Measurements, and Frequency of Measurement to be used in the proposed study. Figure 1 provides the study design and data collection sequence. An overview of the study is provided in Appendix A: Positive Emotions and Influenza Study Participant Instructions.

Table 3. Study Variables, Measurement and Frequency of Measurement

Variable	Measurement	Frequency of Measurement
Independent Variable – Positive Trait Emotions		
Trait positive Emotions	PANAS (Positive and Negative Affect Scale) with instructions for participants to identify how they generally felt.	Twice – Pre-vaccination and 2 weeks post vaccination
Dependant Variable – Immune Response		
Cytokine response	IL-4, IL-6, and IL-12	2-3 times: Pre-vaccination, 2 weeks post vaccination, and within 3-5 days of development of ILI
Th1 and Th2 response	IL-4: IL-12 ratio	For all cytokine measurements
Development of Influenza-like illness (ILI)	Participant report of respiratory or systemic symptoms of influenza.	Ongoing from vaccination (October) to March 31.
Potential Confounding Variables		
Demographic and behavioral variables	Health Assessment Survey	Once – After consent has been obtained at time of enrollment.
State positive emotions, state and trait negative emotions	PANAS with instructions for participants to fill out form for state (how they felt today) or trait (how they generally feel) based on desired measure.	State emotions to be recorded daily for two weeks following influenza vaccination, Trait emotions as above.
Adaptability	Ego-Resiliency Scale (ERS)	Once: Pre-vaccination at time of study enrollment.
Sleep	Pittsburgh Sleep Quality Index	2-3 times: Pre-vaccination, 2 weeks post vaccination, and within 3-5 days of development of ILI
Global Stress Appraisal	Perceived Stress Scale	2-3 times: Pre-vaccination, 2 weeks post vaccination, and within 3-5 days of development of ILI

Figure 1. Study design and data collection sequence.



The sequence of data collection will proceed as outlined below:

Stage one: Study enrollment: Occurs 6 weeks to 10 minutes prior to influenza vaccination.

1. Approvals to conduct the study are obtained from the Loyola University IRB and adult community corporate administration.
2. The study is announced via flyers and meetings held with residents of the adult community (Examples are provided in Appendix A).
3. An initial meeting with potential participants occurs.
    a. An explanation is provided that the study is being conducted to examine effect of positive emotions on immune response to influenza vaccination and disease.
    b. Exclusion criteria will include individuals who are not yet 65 years of age. Participants must agree to influenza vaccination and receive vaccination from usual health care provider or clinic during the study period. Participants will be medically stable. Individuals who have been hospitalized within the last month, and those who report signs of an active infection (as identified on health assessment survey) will be excluded. Immunocompromised patients, asthmatics, patients on immunosuppressive therapy, and patients with malignancies will be excluded from the study (examples of exclusions include: HIV or AIDS, post transplant patients, patients with autoimmune disorders or

malignancy, on chemotherapy, steroids, and other immunosuppressive therapies). Smokers will be excluded from the study.

c. Requirements for participation include sufficient cognitive ability to self-report emotional affect on the PANAS (Watson & Clark, 1994) and other measures, as well as follow through with daily PANAS reporting, and monitoring of self for respiratory symptoms. Participant orientation to person, place and date will be assessed when contact is made to obtain informed consent. Ability to read and reply to questionnaires will be assessed after consent is obtained. Elderly individuals who are not oriented, or do not have the mental capacity to complete questionnaires will be excluded from the study. Elderly individuals who have difficulty reading or writing, but have sufficient mental capacity to respond to items, as well as access to an individual capable of filling out the questionnaires will be eligible for participation if the support individual agrees to study training and parameters.

d. Participants must agree to receive influenza vaccine at a later date according to their own preference, physician's recommendation, or other criteria. The researcher will not provide vaccinations. Failure to receive influenza vaccination will exclude individuals from the study.

e. The researcher will obtain informed consent. The informed consent form is provided in Appendix B. Data is collected on demographics and other variables consistent with PNI studies (Robinson et al., 2002). This

information is obtained when the participants complete the Demographic Information Form and Health Assessment Survey (See Appendix C).

f. The participant will complete the PANAS (Watson & Clark, 1994) for trait emotions.

4. The researcher will request all participants to complete the remaining study questionnaires and mail the results via stamped, pre-addressed envelopes provided. These remaining questionnaires include: The Ego-Resiliency Scale (Block & Kremen, 1996), the Pittsburgh Sleep Quality Index (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989), and the Perceived Stress Scale (Cohen, et.al, 1983). These tools are provided in Appendix C.
5. After scoring the PANAS, the researcher will contact 40 individuals with high levels of positive trait emotions and 40 individuals with low levels of positive trait emotions. These individuals will have their temperatures taken with an electronic thermometer used in the ear canal and will have one 10 cc tube of blood drawn for cytokine testing (IL-4, IL-12, and IL-6). This will be done at a time and location convenient for the participant, within one week of completing the enrollment forms and prior to influenza vaccination.

Stage two: Participant receives influenza vaccination from health care provider or clinic.

6. The date of influenza vaccination is recorded by the participant or researcher on the data collection forms.
7. Following influenza vaccination, participants will record daily state emotions in the evening each day for two weeks using the PANAS (Watson & Clark, 1994).

8. Individuals who had blood drawn previously (See 5 above) will again be contacted by the researcher to arrange to have their temperature and a 10cc tube of blood taken for cytokine testing two weeks after receiving influenza vaccination.
9. After recording daily emotions for two weeks, all participants will again complete the PANAS (Watson & Clark, 1994) for trait emotions, the Perceived Stress Scale (Cohen, et.al, 1983), and the Pittsburgh Sleep Quality Index (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). All completed questionnaires will be mailed to the researcher in pre-addressed, stamped, envelopes.

Stage three: Monitoring for influenza like illness throughout the influenza season.

10. The participant will use the information sheet (See: Reporting Symptoms of Influenza Like Illness in Appendix C) to identify signs and symptoms of influenza. Participants will contact the research team member within 1-4 days of any development of signs or symptoms of influenza. This monitoring of signs and symptoms will continue through March.
11. If participants who previously had blood drawn develop signs and symptoms of influenza like illness, another 10 cc tube of blood will be drawn for cytokine testing within 3-5 days of symptom identification. These individuals will be asked to again complete the Perceived Stress Scale (Cohen, et.al, 1983), and the Pittsburgh Sleep Quality Index (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989).

12. Influenza levels within the community will be monitored by a research team member via monthly contact with the local health department and local hospitals.

Reminders and Incentives

Participants will be contacted by the researcher every one to two months by telephone, mail, or electronic mail, according to the participant's preferred method of contact. During these contacts the researcher will remind the participant to complete the study forms, receive influenza vaccination, or monitor and report signs and symptoms of influenza like illness, as appropriate for each stage of the study. At the time of enrollment, participants will be given a pen imprinted with the name of the study and the researcher's telephone number.

Measurements

The proposed research will include a variety of measurements for the independent variable (positive emotions) and the dependent variable (immune response). In addition, consistent with recommendations for conducting PNI research, information on demographics and a variety of baseline data will also be collected. Table 3 identifies variables, measurements to define the variables, and frequency of measurements to be performed. These are discussed below.

Psychological Measurements

Emotions

Positive state and trait emotions will be measured via participants' self report on the PANAS (Watson & Clark, 1994). Trait emotions will be measured before administration of influenza vaccination: This may be done any time from 6 weeks to 10

minutes prior to influenza vaccination. Participants will be asked to indicate on a 5 point scale, the degree to which they generally experience positive emotions such as happy, energetic, or pleased. Each of the seven positive affect scores will be included in the statistical analysis, as well as the mean scores for the 9 items. Though the aim of the study is to investigate positive emotions, data on negative emotions will also be collected and included in the analysis, based on recommendations from the psychology literature previously reviewed. Negative emotions will be measured for items such as sad, nervous, and angry. Since current affect has been shown to impact self-ratings for trait affect, data on self reports of trait affect will also be collected 2 weeks after influenza vaccination. Cronbach's α has been shown to equal .88 for positive affect, and .84 for negative affect on the PANAS (Zautra et al., 2005).

The PANAS will also be used to collect data on state emotions for 2 weeks following vaccination. Participants will be asked to record, at the end of each day, the degree to which they experienced positive and negative emotions as identified on the PANAS. This two week measurement of state emotions is based on studies which demonstrated that stress experienced within ten days to two weeks of immunization impacted immune response (Cohen et al., 2004; Cohen et al, 2006; Doyle, Gentile, & Cohen, 2005), to examine if this is a also a critical period for positive emotions.

Health Behaviors

Data will be collected on smoking, alcohol, caffeine intake, and physical activity (See Appendix C for Health Assessment Survey). Physical activity items were adapted from the Kaiser Physical Activity Survey and address 4 domains of physical activity;

household and care giving, occupational, sport and exercise, and active living habits (Ainsworth, Sternfeld, Richardson & Jackson, 2000). Use of prescription medication, supplements (vitamins, minerals, nutritionals, herbals, soy products, and naturopathic remedies) is also included in the Health Assessment Survey.

Resiliency

Several studies demonstrated the utility of positive emotions in building resiliency and the importance of resiliency in successful adjustment to life events (Cohn et al., 2009; Fredrickson et al., 2008; Ong et al., 2006; Zautra et al., 2005). Resiliency will be measured via participant self report on the Ego-Resiliency scale (ERS; Block & Kremen, 1996). The ERS measures adaptability and consists of 14 items which are self rated on a scale of 1 (does not apply at all) to 4 (applies very strongly). A sample item from the ERS is, “I like to take different paths to familiar places” (Block & Kremen, 1996). Participants will be asked to complete the ERS during the first stage of the study, after consent has been obtained. Cronbach’s α for the ERS was shown to equal .73 and .74 at two time points (Fredrickson et al., 2008).

Sleep

Research has linked sleep quality to immune response (Miller et al., 2004; Prather et al., 2007). Sleep will be measured in the proposed study using the Pittsburgh Sleep Quality Index (PSQI; Buysse et. al., 1989). The PSQI measures quality and patterns of sleep. Subjects are asked to rate their sleep over the past month. The PSQI differentiates "poor" from "good" sleep using 7 subscales: Subjective Sleep Quality, Sleep Latency, Sleep Duration, Habitual Sleep Efficiency, Sleep Disturbances, Use of Sleeping

Medication and Daytime Dysfunction. Scoring is based on a 0 to 3 scale, and a score of 3 reflects the negative extreme. A global sum of 5 or greater indicates a "poor" sleeper. Cronbach alpha is 0.83 for its 7 components.

Stress

A number of studies have demonstrated that stress adversely affects immune response to influenza vaccination (Miller et al., 2004; Pedersen, Zachariae, & Bovbjerg, 2009; Vedhara, Cox, Wilcock, Perks, Hunt, Anderson, et al., 1999). The Perceived Stress Scale (PSS;Cohen, Kamarck, & Memmelstein, 1983) is a 10 item scale that assesses the degree to which a person finds their lives as unpredictable, uncontrollable or overloaded (i.e., exceeding their adaptive capacities). The PSS is a measure of global stress appraisal as opposed to measurement of a specific event which evokes a stress response. Reliability has been shown to be 0.85 and Cronbach alphas range from 0.75-0.86. Stress will be measured before vaccination, 2 weeks after vaccination, and within 3-5 days of development of symptoms of influenza like illness.

Physiological Measurements

Cytokines

As discussed earlier, several cytokines have demonstrated significance for influenza vaccine effectiveness in studies of the elderly. Based on cytokine functions, it was determined that IL-4, IL-6, and IL-12 would be measured to evaluate immune response in the proposed study. IL- 6 is a proinflammatory cytokine, IL-4 is associated with a Th2 response, and IL-12 with a Th1 response. Immunosenessence in the elderly has been associated with a shift (McElhaney et al., 2006) from Th1 cytokines (such as IL-

12) to Th2 Cytokines (including IL-4). Serologic measurements of these cytokines will be done on a subset of individuals reporting high and low positive affect at 3 time points; prior to immunization, 2 weeks post immunization with influenza vaccine, and when symptoms consistent with influenza like illness are reported. Levels, as well as changes between time points will be compared.

Surveillance for influenza-like illness

Surveillance for influenza-like illness will be conducted via participant report of signs and symptoms consistent with CDC criteria (Centers for Disease Control and Prevention, 2009). Elderly participants and their care givers will be instructed to report any respiratory symptoms of abrupt onset such as cough, sore throat, or nasal congestion. They will also be instructed to report any systemic symptoms of influenza including abrupt onset of fatigue, body aches, headache, lethargy, feverishness or fever greater than 37.3°C. ILI will be defined as two respiratory symptoms, or one respiratory and one systemic system (McElhaney et al., 2006). When reviewing findings, reports of ILI will be correlated with levels of influenza activity in the community.

Definition of Variables

Definitions of variables are summarized below:

1. The independent variable is positive trait emotions.
    a. Positive emotions are defined as states consisting of pleasant dispositional characteristics such as happy, energetic and pleased. All positive emotions will be measured by self-report on the PANAS (Watson & Clark, 1994).

i. Trait positive emotions are positive emotions as defined above identified by the participant as those usually experienced.

ii. State positive emotions are positive emotions as defined above identified by the participant as those experienced that day.

b. Adaptability is as emotional construct defined as individuals' ability to equilibrate and re-equilibrate in response to their ever-changing being, and ever-changing world (Block & Kremen, 1996). Adaptability will be measured via self report on the Ego-Resiliency Scale (Block & Kremen, 1996).

2. The dependent variable is immune response to influenza

a. Development of influenza-like illness (ILI) will be defined as two respiratory symptoms (cough, sore throat, or nasal congestion), or one respiratory and one systemic system symptom (abrupt onset of fatigue, body aches, headache or lethargy, feverishness or fever greater than 37.3°C).

b. Cytokines levels identify proteins which influence the direction, magnitude and outcome of many effector mechanisms within the immune system (Coico & Sunshine, 2009). Serum levels of IL-4, IL-6, and IL-12 will be used to evaluate cytokine response in this study.

i. IL-4 is a Th2 cytokine that affects Th2 cell differentiation, B cell activation, and a IgE switch.

ii. IL-6 is a proinflammatory cytokine that increases during acute illness.

iii. IL-12 is a Th1 cytokine that activates natural killer cells (Coico & Sunshine, 2009).

c. Th1 vs. Th2 response is defined as higher levels of IL-12 compared to IL-4 levels. A shift from Th1 cytokines (such as IL-12) to Th2 cytokines (including IL-4), has been associated with aging and decreased protection against influenza (McElhaney et al., 2006). The mean IL-4 to IL-12 ratio will also be computed.

Protection of Human Subjects

Participants will be provided with information and asked to sign an informed consent prior to enrollment in the study. An informed consent form, based on the Loyola University Medical Center template can be found in Appendix B. Informed Consent. This form includes the purpose of the research, risks and benefits associated with participation, assurance that participation is totally voluntary, the distinction between research and clinical care, the opportunity to ask questions, and alternatives to participation.

There are minimal risks associated with this study. There is some risk that the subjects may experience pain during the blood drawing procedure. The blood drawing procedure may also result in bruising at the sight. To minimize the risk of this occurring, blood will be drawn by a trained Registered Nurse or phlebotomy staff. These minimal risks are necessary in order to measure immune response based on serum samples. This

data will provide information to compare with positive emotions to evaluate the impact of positive emotions on immune response to influenza vaccination.

Data Analysis

All analyses will be performed using SPSS for windows, version 17.0 (SPSS, 2009). Data will be assessed for normality and, if it is not normal, the data will be log transformed. One-tailed T-tests will be performed to compare pre-and post-vaccination findings. Logistic regression for binary results will be performed using 2 different analysis; one for affect and one for assisted living situations. A 2 X 2 repeated measures ANOVA with interactions for each time period will be performed.

Timeline for Study

Assuming committee approvals and defense of the proposed research is accomplished in the spring of 2010, and Loyola University Medical Center IRB Approval can be obtained, the elderly community's corporate administrators will be contacted over the summer of 2010 for approval to conduct the study. Study announcements and pre-vaccination meetings need to occur in September, 2010, since most vaccination programs begin in early October. The 2 week post vaccination blood draw would therefore occur in late October, or early November, based on the date of vaccination. Surveillance for influenza will continue through March 31, 2011, when data analysis will begin. Preliminary data reports and draft reports of the research will be available in autumn, 2011.

Study Limitations

Participant compliance with completing requested daily reporting of positive emotions will be a concern. Also, participants may believe that providing self assessments that include more positive emotions is more desirable or correct. For these reasons, clear instructions and reminders from the researcher will be incorporated in the plan. Due to these higher positive emotions experienced among the elderly (Chipperfield, Perry, & Weiner, 2003; Isaacowitz, Wadlinger, Goren, & Wilson, 2006; Jopp & Rott, 2006; Subramanian, Kim, & Kawichi, 2005), it may be difficult to obtain a suitable population size for comparison. The study plan is to use the range of positive emotions demonstrated by participants to identify those with higher and lower positive emotions.

Internal validity of PANAS-X reports can be evaluated through comparison of reported trait and state emotions, since these findings should correlate. The development of ILI provides construct validity for the concept of immune response to vaccination, as well as cytokine levels.

One concern is the potential effect of medication on measured variables. For this reason data will be collected on prescribed medications.

Miller et al. (2004) have identified the 10 days following vaccination as a critical period for stress to negatively impact immune response to influenza vaccination. This study will examine positive emotions during this critical period. This provides the opportunity to examine positive emotions as a potential buffer against stress, as well as whether positive emotions during this same post vaccination period predict improved

immune response. There is also a possibility, however, that influenza vaccination will impact positive emotions through neuroendocrine and cytokine response (Miller et al., 2004)

Conducting the study in natural settings leads strength to the construct validity, but these settings also allow for numerous confounding variables that will not be measured. The experience of requiring assisted living services, for example, may negatively impact an individual's self rating of resiliency. Depending on the level of isolation for some participants, the community setting may represent an artificially controlled exposure to exogenous pathogens. An influenza outbreak in the community may be of sufficient challenge to overcome participant's usually protective immunities.

The vagaries of circulating influenza strains and the match between vaccine and circulating strains always present challenges to conducting influenza studies, and that will be the case with this research. In addition, there is considerable variation in participants' history of exposure to influenza which may skew the results. For these reasons, all data will be examined for normality.

The population of this faith based community consists largely of white upper middle class individuals. This raises questions about the generalizability of the findings to elderly individuals from other races and socioeconomic groups. Higher levels of spirituality within the community may impact findings and will limit generalizability. Results will need to be clearly attributed to the sample populations studied.

Despite these limitations, this research provides an opportunity to examine the impact of positive emotions on immune response to influenza vaccine in a population of

medically stable elderly individuals. The study plan provides the opportunity to examine, via a prospective design, immune variables associated with positive emotions, starting with pre-vaccination levels through surveillance for development of influenza like illness. Most importantly, by examining the impact of positive emotions, this proposed research provides an opportunity to expand knowledge regarding influenza response to influenza in the elderly.

Methodology Addendum

When data collection began a number of changes in methodology were necessary based on recruitment limitations, participant response, and cytokine choice. These changes also required that some tailoring of the hypotheses occur. These changes in methodology, as well as the methods used for cytokine measurement, are discussed at this time.

Recruitment

Participant recruitment began after approval had been obtained from both the medical center IRB and administration for the faith-based community for the elderly. In order to obtain pre-vaccination cytokine measures from participants who met the study criteria, it was necessary to recruit medically stable, older adults prior to their receiving annual influenza vaccination for the current flu season. When approvals were obtained in the early fall 2010, access to all resident populations within the faith-based elderly community prior to influenza vaccination was no longer feasible. Some resident groups were already in the process of obtaining influenza vaccination. In order to increase the pool of potential candidates for the study, recruitment was expanded to individuals

outside of the faith-based community and the age criteria was lowered from 65 to 55 years and older. Twenty-two participants were recruited. These 22 participants will subsequently be referred to as the pre-post vaccination group.

In addition to informed consent, the pre-post vaccination group completed a demographic information worksheet that included race/ethnic group, marital status, living situation (alone, with spouse, with roommate, independent, assisted), education, employment, occupation and total household income. A Health Assessment Survey was completed that included questions on weight, height, smoking, alcoholic and caffeinated beverage consumption, current health problems, medication, symptoms of infection and recent hospitalization. Participants completed the PANAS (Watson & Clark, 1994) for trait emotions, the Physical Activity Survey (Ainsworth, Sternfeld, Richardson, & Jackson, 1999) the Ego-Resiliency Scale (Block & Kremen, 1996), the Pittsburgh Sleep Quality Index (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989), and the Perceived Stress Scale (Cohen, et.al, 1983). These tools were completed prior to receiving influenza vaccination and are provided in Appendix C. Participants had serum drawn for cytokine testing prior to influenza vaccination. An oral body temperature was taken prior to phlebotomy.

Beginning the day after influenza vaccination, participants were asked to complete a daily PANAS for state emotions each evening for 14 days. Two weeks after influenza vaccination, another serum was drawn for cytokine testing. Individuals were asked to complete another PANAS for trait emotions, Pittsburgh Sleep Quality Index, and Perceived Stress Scale. Participants were provided information on signs and symptoms

of influenza-like illness and asked to contact the researcher if they experienced these signs and symptoms. During the course of the influenza season, participants were contacted and reminded to report symptoms to the researcher.

As the 2010-2011 influenza season progressed, the pool of eligible candidates decreased as more individuals obtained their influenza vaccination. A retrospective subgroup of individuals who had already received vaccinations, and who could still be tracked over the duration of the flu season for self reporting of influenza-like illness, was recruited. No serum was drawn for cytokine testing of this retrospective subgroup, since pre-vaccination cytokine measurements were not possible. These individuals did not report daily trait emotions for two weeks, nor did they complete a second PANAS for trait emotions, a repeat Pittsburgh Sleep Quality Index, or a second Perceived Stress Scale. Thirty three participants were enrolled in this group. A total of 18 participants were recruited from the faith based elderly community, enrolled in either the pre-post vaccination group or the retrospective subgroup.

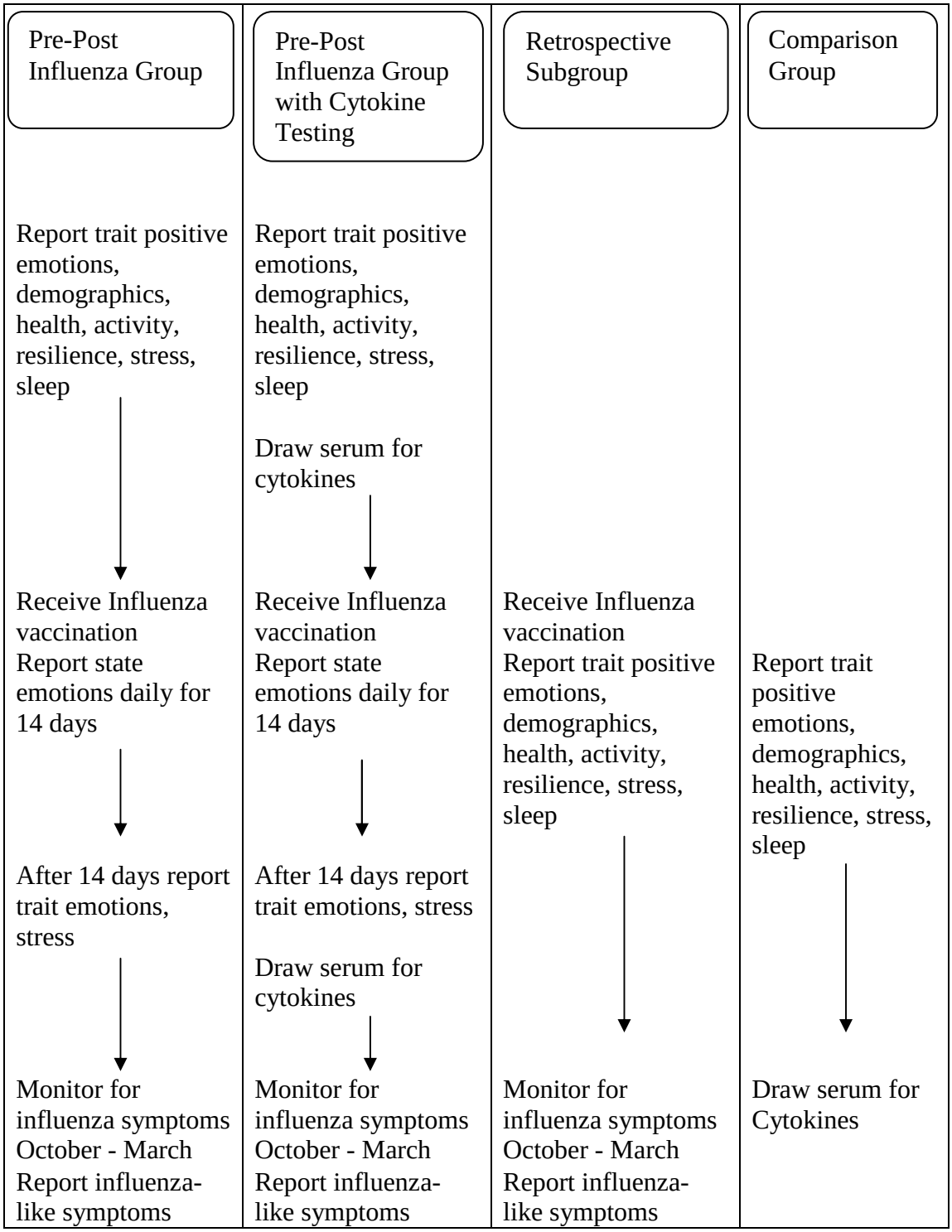
The original plan included providing participants with pens imprinted with the researcher's contact information. This was not done. The Reporting of Influenza Like Illness form including information on how to contact the researcher.

As the 2010-2011 influenza season drew to a close, the number of participants followed for development of influenza-like illness totaled 53. One participant was removed from the study because she did not meet the age criteria, and another participant requested to withdraw due to the lack of desire to complete the required paperwork.

In April 2011 the total sample size of 53 participants was reviewed by the researcher and dissertation committee. In order to allow for further evaluation, it was decided that a comparison group (Burns, 2005) would be recruited. As planned, the comparison group (N = 23) consisted of individuals who had not been vaccinated for influenza that season, and who were recruited from a university medical center affiliated fitness center in May 2011. These participants received $20 compensation for their time and effort. Oral body temperatures were taken and serum was drawn for cytokine testing at the time of recruitment. Members of the comparison group completed the PANAS for state emotions, the Demographic, Health, and Physical Activity Surveys, Pittsburgh Sleep Quality Index, Perceived Stress Scale, and Ego Resiliency Scale.

Informed consent was obtained at the time of recruitment for all participants. All changes in study parameters were approved by IRB prior to recruitment. The revised study design as a result of recruitment of the retrospective subgroup and comparison group is provided in Figure 2.

Figure 2. Revised Study Design and Data Collection Sequence for All Groups



Cytokine Measurement

Venous blood was collected in heparinized vacutainer tubes which were centrifuged at 2000RPM for 20 minutes at ~20° C. Serum was placed in aliquots and stored frozen at ≤ - 20 ° C until analyses were performed on all specimen.

While the original plan targeted IL-4, IL-6 and IL-12 to evaluate immune response, these cytokine measurements were deemed impractical after participant recruitment was completed. From the beginning phases of research planning, costs and test sensitivity, as well as previous findings and research design, factored into choice of cytokine measurement.

Over the course of the influenza season, only one participant reported development of symptoms compatible with influenza-like illness within time frames that allowed serum collection during the illness phase. After consideration of this development, the researcher and dissertation committee determined that measurement of IL-4 and IL-12 would not provide meaningful data in terms of immune response or differentiation of Th1 vs. Th2 type immune response. Factoring in this consideration, it was decided that IL-1β would be measured in collected serum, in addition to IL-6, as previously planned. Participant inability to contact the researcher upon onset of influenza symptoms also precluded investigation of any association between positive emotions and cytokine measurements during the initial period of influenza-like illness.

The role of IL-6, a pro-inflammatory cytokine, has been reviewed earlier. IL-1 is also a pro-inflammatory cytokine, stimulating the expression of genes associated with

acute and chronic inflammation. IL-1β action results in fever, lowered pain threshold, hypotension and vasodilatation (Paul, 2008).

Testing for IL-1β and IL-6 was performed using high sensitivity ELISA tests produced by R& D Systems, Minneapolis, MN. The Quantikine HS Human IL-1β immunoassay is a 6.5 hour solid phase ELISA designed to measure human IL-1 β levels in serum and plasma (Quantikine HS, Human IL-1 β/IL-1F2 Immunoassay). Briefly, as described in the package insert, this test employs the quantitative sandwich enzyme immunoassay technique. A monoclonal antibody specific for IL-1β was pre-coated onto a microplate. Standards and samples were pipetted into wells resulting in any IL-1β present to be bound by the immobilized antibody. Unbound substances were washed away and an enzyme-linked polyclonal antibody specific of IL-1β was added to the wells. Following a wash to remove any unbound antibody-enzyme reagents, a substrate solution was added. After an incubation period, an amplifier solution was added to the wells and color developed in proportion to the amount of IL-1β bound in the initial step. The color development was stopped and the intensity of the color was measured.

The Quantikine HS -Human IL-6 is a 5.5 hour solid phase ELISA which also employed quantitative sandwich enzyme immunoassay technique. As described in the package insert, a monoclonal antibody specific for IL-6 was pre-coated onto a microplate. Standards and samples were pipetted into wells and any IL-6 present was bound by the immobilized antibody. Unbound substances were washed away, and enzyme-linked polyclonal antibody specific for IL-6 was added. After washing to remove any unbound antibody-enzyme reagent, a substrate solution was added to the wells. After an

incubation period, an amplifier solution was added to the wells and color developed in proportion to the amount of IL-6 originally bound.

Revised Hypotheses

The study hypotheses needed to be retailored due to the revisions in methodology. Adjustments focused on age, the Th1 vs. Th 2 response, and the lack of cytokine measurements during the initial stages of influenza-like illness. The revised hypothesis eliminated analysis of a Th1 vs. Th2 response to influenza like vaccine since the cytokines measured, IL-1β and IL-6 would not differentiate a Th1 vs. Th2 type immune response. In addition, IL-1β was added to the hypothesis that higher positive emotions would result in lower levels of pro-inflammatory cytokines (as measured by IL-6 and IL-1β). Less specific hypothesis remained unchanged: Participants who reported higher trait emotions would demonstrate different cytokine responses; Positive trait emotions will affect cytokine measurement, resulting in differing cytokine profiles.

For clarity the revised hypotheses are provided:

1. Medically stable individuals aged 55 years and older who report higher trait positive emotions, will demonstrate lower incidence of influenza-like illness over the course of the influenza season (October through March) after receiving influenza immunization from clinics, healthcare providers or other vaccination sources.
2. Participants who self report higher positive trait emotions will demonstrate different cytokine responses:

a. Positive trait emotions will affect cytokine measurements, resulting in differing cytokine profiles.
b. Positive trait emotions will affect the cytokine response to respiratory viruses circulating within the community exhibited after receiving influenza vaccination.
c. Higher positive emotions will result in lower levels of pro-inflammatory cytokines (as measured by IL-6 and IL-1β).

CHAPTER FOUR

RESULTS

Characteristics of Study Sample

A total of 76 participants were enrolled. Consistent with PNI research, a number of control variables were assessed that might affect the relationship between positive emotions and immune response in older adults. All data was obtained via self-report, though computer generated medication lists were provided by a number of enrollees. Participant ages were between 55 and 96 years with a mean age of 70.4. Most participants (52) were female, representing 68.4% of participants. Most participants were Caucasion, with four African Americans enrolled which represented 5.3% of the sample. Five participants (6.7 %) reported they were single, 40 (53.3%) married, 6 (8 %) divorced or separated, and 24 (32 %) reported they were widowed. Thirty-three (44%) lived alone, 37 (49.3%) lived with their spouse, 5 (6.7%) lived with a roommate. Sixty- two individuals (83.8%) reported an independent living situation, while 12 (16.2%) of the 18 participants recruited from the faith-based elderly community reported residing within an assisted living situation. Twenty-three participants (30.7%) reported that they cared for a family member.

One individual (1.3%) reported education that terminated at the elementary school level. Seven (9.2%) reported some high school, and 14 individuals (18.4%) reported graduation from high school or vocational school. Thirteen (17.1%) had some

college, nine (11.8%) graduated from college, with 28 (36.8%) individuals reporting education at the level of graduate school and above. Four participants (5.3%) were unemployed, and 38 (50.7%) were retired. Based on reported employment status, one was a homemaker, two were students, and one participant worked at home. Five participants (6.7%) worked part time and 24 (32 %) worked full time. Total household income reported was less than $9,999 for one participant, $10,000 to $19,000 for four participants (5.3%), 20,000 to $29,000 for 15 participants (20%), $30,000 to $39,000 for six participants (8%), $40,000 to $49,000 for four participants (5.3%), and $50,000 or above for 44 (58.7%) of participants.

One participant smoked, and was not included in the group tracked for influenza-like illness. Forty-two (56%) drank alcoholic beverages. The mean number of caffeinated beverages consumed by participants over the previous three days was 5.4, with a range from 0 to 20. Nine participants (12%) reported cold symptoms within the week prior to enrollment, and one was hospitalized within the last 30 days for elective surgery. None were receiving hormone replacement therapy, corticosteroids, or chemotherapeutic agents. Body mass was calculated based on reported height and weight using the following formula: weight (lb) / [height (in)]^2 x 703. Body mass for participants ranged from 16.3 to 54.9, with a mean of 27.4 and a standard deviation of 5.9. The mean weight for the study sample was just above the BMI cut point of 25 for the overweight category (Division of Nutrition, Physical Activity, and Obesity, National Center for Chronic Disease Prevention & Health Promotion, 2011). Characteristics for all study participants are summarized in Table 4.

Table 4. Characteristics of Study Participants

N	76
Age [mean ± SD] (range)	70.4 ± 12 (55-96)
Gender	
Male	24 (31.6%)
Female	52 (68.4%)
Race	
White	72 (94.7%)
African-American	4 (5.3%)
Marital Status	
Single	5 (6.7%)
Married	40 (53.3%)
Divorced or Separated	6 (8%)
Widowed	24 (32%)
Living situation	
Lives Alone	33 (44%)
Lives with Spouse	37 (49.3%)
Lives with Roommate	5 (6.7%)
Independent or Assisted Living	
Independent	62 (83.8%)
Assisted	12 (16.2%)
Total Participants Recruited from Faith Based Elderly Community	18
Provide Care for a Family Member	23 (30.7%)
Education	
Elementary	1 (1.3%)
Some High School	7 (9.2%)
High School or Vocation School Graduate	14 (18.4%)
Some College	13 (17.1%)
College Graduate	9 (11.8%)
Graduate School and Above	28 (36.8%)
Employment	
Unemployed	4 (5.3%)
Retired	38 (50.7%)
Homemaker	1 (1.3%)
Student	2 (2.7%)
Employed Working at Home	1 (1.3%)
Working Part time	5 (6.7%)
Working Full time	24 (32%)
Total Household Income	
Less than $9,999	1 (1.3%)

$10,000 to $ 19,000	4 (5.3%)
$20,000, to $29,000	15 (20%)
$30,000 to $39,000	6 (8%)
$40,000 to $49,000	4 (5.3%)
$50,000 or above	44 (58.7%)
Current Smoker	1 (1.3%)
Currently Drink Alcoholic Beverages	42 (56%)
Number Caffeinated Beverages in Last 3 Days [mean ± SD] (range)	5.4 ± 4.3 (0- 20)
Infectious Symptoms in Past Week (cold symptoms)	9 (12 %)
Hospitalized in Last 30 Days	1 (1.3%)
Body Mass Index [mean, ± SD] (range)	27.36 ± 5.9 (16.3-54.9)

Differences in Variables Among Recruitment Groups

While recruitment from various elderly populations added to the generalizability of the study findings, the three separate recruitment groups introduced variability that could provide alternative explanations for relationships observed between positive emotions and immune response. These alternative explanations are important when interpreting findings. For this reason, a *t* test was performed to compare control variables among the recruitment groups.

Participants who had serum drawn for cytokine measurement were in the pre-post vaccination group and the comparison group. There were only two males in the pre-post vaccination group ($N = 21$) while the comparison group ($N = 23$) had 11. These two groups differed significantly in age ($p < .05$, two tailed). The mean age for the pre-post vaccination group was 73.5 (*SD* of 12.5), while the mean age for the comparison group was 66.7 (*SD* 6.49). An age difference between these two groups would be expected when recruitment procedures were considered: The pre-post vaccination group included residents from an elderly community as well as the general population, the comparison

group was recruited at a fitness center. In addition to gender, a number of other differences between the two groups emerged, consistent with their age differences. The younger comparison group had higher self reported Total Activity scores (M = 10.9, SD 1.8) compared to the pre-post vaccination group (M = 9.7, SD 1.7), this difference was significant, t (41) = -2.4, $p < .05$. They also had significantly higher incomes ($p < .05$) and were significantly more likely to be married ($p < .01$).

Participant Responses to Study Instruments

Study instruments have been previously reviewed. Positive trait emotions scores (Lively, Full of Pep, Energetic, Happy, Pleased, Cheerful, At Ease, Calm and Relaxed) from the PANAS, which was completed by all study participants, had high reliability, α = .9. Scores ranged from 0.9 to 4.0 with a mean of 2.6 and a SD of 0.7.

Consistent with several researchers in the area of positive emotions (Cohen et al., 2003; Cohen et al., 2006; Doyle, Gentile, & Cohen, 2006) positive emotion scores on the PANAS were separated into three subscales for analysis. Reliability for these subscales was high: Vigor (Lively, Full of Pep, Energetic), mean score 2.5, SD 0.8, α = .9; Well-Being (Happy, Pleased, Cheerful) mean score 2.9, SD 0.8, α = .9; Calm (At Ease, Calm and Relaxed), mean score 2.5, SD 0.9, α = .9.

Though the independent variable in this study was positive emotions, a number of researchers underscored the importance of measuring negative emotions, even when the variable of interest is positive emotions. Negative emotions scores on the PANAS (Sad, Depressed, Unhappy, On edge, Nervous, Tense, Hostile, Resentful and Angry) ranged from 0 to 3.00 with a mean of 0.5, and a standard deviation of 0.6. Negative emotion

scores had a small inverse relationship with age, $N = 76$, $r = -.08$, $p > .05$, and small positive relationships with log IL-6, $N = 38$, $r = .21$, $p > .05$, and IL-1β, $N = 39$, $r = .04$, $p > .05$. None of these was significant. Significance was demonstrated between negative emotion scores and scores for the Perceived Stress Scale, $N = 73$, $r = .40$, $p < .01$, Global Sleep on the PSQI, $N = 75$, $r = .50$, $p < .01$, and Total Activity score on the Physical Activity Survey, $N = 75$, $r = .22$, $p < .05$.

The Ego Resiliency Scale and Perceived Stress Scale were both used as planned in the study. Participant scores on the Ego Resiliency Scale had high reliability (M = 45.1, SD 6, α = .8). Scores on the Perceived Stress Scale, likewise demonstrated high reliability (M = 12.7, SD 5.2, α = .9).

The Pittsburgh Sleep Quality Index (PSQI) was used to self report sleep problems. Reliability for Global Sleep Scores from the Pittsburgh Sleep Quality Index was lower (M = 11.6, SD 2.5, α = .6), as were Total Activity Scores from the Physical Activity Survey (M = 9.9, SD 2, α = .5) which was used to self report physical activity related to home, work, sports, recreation and exercise. Field (2009) summarized justification for lower reliabilities seen with scales that measure a diversity of constructs. Scale reliabilities are lower when they have less unidimensionality, as seen in the Physical Activity Scale and PSQI which total various components of activity and sleep problems to respectively arrive at global measures. Mean score, standard deviation and reliability for all participants' responses on study instruments are summarized in Table 5.

Table 5. All Participants' Mean Score, Standard Deviation and Reliability for Study Instruments

Positive Emotions Score on PANAS	Mean 2.6, SD 0.7, α = .9
Vigor Subscale from PANAS	Mean 2.5, SD 0.8, α = .9
Wellbeing Subscale from PANAS	Mean 2.9, SD 0.8, α = .9
Calm Subscale from PANAS	Mean 2.5, SD 0.9, α = .9
Negative Emotions Score on PANAS	Mean .5, SD 0.6, α = .8
Ego Resiliency Scale	Mean 45.1, SD 6.0, α = .8
Perceived Stress Scale	Mean 12.7, SD 5.2, α = .9
Global Sleep Score from PSQI	Mean 11.6, SD 2.5, α = .6
Total Activity Score from Physical Activity Survey	Mean 9.9, SD 2.0, α = .5

Cytokine Results

Serum was drawn prior to influenza vaccination for 18 participants in the pre-post vaccination group. It was also drawn at the time of enrollment for 21 participants in the comparison group. Cytokine findings are summarized in Table 6 which provides cytokine results and Log_{10} transformed results for participants at study enrollment.

Oral temperatures were taken immediately prior to phlebotomy. All participants were afebrile, no oral temperatures exceeded 98.6 ° F.

The IL-6 results from serum drawn at enrollment (N = 39) ranged from 0.33 to 4.72. After plotting results, the 4.72 result was deemed to be an outlier and was eliminated. With this outlier eliminated, the maximum IL-6 result was 3.10. The mean IL-6 result for 38 participants was 1.15 with a *SD* of 0.70. For analysis, cytokine results were log10 transformed to better approximate a normal distribution. For IL-6 log10, results ranged from -0.48 to 0.49 with a mean result of -0.007 and a *SD* of 0.244.

The IL-1β results from 39 participants ranged from 0 to 0.18. IL-1β findings were log transformed to better approximate a normal distribution, but continued to demonstrate a strong positive skew ($z = 7.50$). The mean IL-1β result was 0.02 with a *SD* of 0.04. For IL-1 β log10, results ranged from 0 to 0.071 with a mean result of 0.007 and a *SD* of 0.017.

As previously noted, two groups had serum drawn for cytokine testing. The pre-post vaccination group that was recruited over the fall and winter 2010 had serum drawn prior to receiving annual influenza vaccination. The comparison group, recruited in May 2011 at a fitness center affiliated with an academic medical center, did not receive annual influenza vaccination for the 2010-2011 influenza season. Serum was drawn from this comparison group at the time of enrollment. IL-6 and IL-1β results for these two groups are presented at this time. The retrospective group did not have serum drawn.

IL- 6 results for 17 participants (outlier removed) in the pre-post vaccination group ranged from 0.33 to 3.10 with a mean result of 1.13 and a *SD* of 0.73. IL-6 $\log_{10}$ results for this group ranged from -0.483 to 0.492 with a mean result of -0.026 and a *SD* of 0.266. The IL-1 β results from this group included 18 measurements with a minimum level of 0 and a maximum of 0.11, a mean result of 0.01 and a *SD* of 0.03. For IL-1 β $\log_{10}$, results ranged from 0 to 0.047 with a mean result of 0.004 and a *SD* of 0.012.

For the comparison group, IL- 6 results for 21 participants ranged from 0.49 to 2.84 with a mean result of 1.18 and a *SD* of 0.70. IL-6 $\log_{10}$ results for this group ranged from -0.312 to 0.453 with a mean result of 0.009 and a *SD* of 0.230. The IL-1 β results from 21 participants in this group ranged from a minimum level of 0 to a

maximum of 0.18, a mean result of 0.02 and a *SD* of 0.05. For IL-1 β $\log_{10}$, results ranged from 0 to 0.071 with a mean result of 0.01 and a *SD* of 0.021. Cytokine data for all participants, as well as cytokine data separated out for the pre-post vaccination group and comparison group are presented in Table 6.

Table 6. Cytokine Results and Log_{10} Transformed Results at Study Enrollment

All Participants		[mean ± SD] (range)
N = 38	IL-6	1.15 ± 0.70 (0.33-3.10)
	IL-6 $\log_{10}$	-0.007 ± 0.244 (-0.483-0.492)
N = 39	IL-1 β	0.02 ± 0.04 (0-0.18)
	IL-1 β $\log_{10}$	0.007 ± 0.017 (0-0.071)
Pre-Post Vaccination Group		
N = 17	IL-6	1.13 ± 0.73 (0.33-3.10)
	IL-6 $\log_{10}$	-0.026 ± 0.266 (-0.483-0.492)
N = 18	IL-1 β	0.01 ± 0.03 (0-0.11)
	IL-1 β $\log_{10}$	0.004 ± 0.012 (0-0.047)
Comparison Group		
N = 21	IL-6	1.18 ± 0.70 (0.49-2.84)
	IL-6 $\log_{10}$	0.009 ± 0.23 (-0.312-0.453)
N = 21	IL-1 β	0.02 ± 0.05 (0-0.18)
	IL-1 β $\log_{10}$	0.01 ± 0.021 (0-0.071)

Relationships Among Study Variables

For this exploratory study on positive emotions and immune response to influenza in medically stable older adults, correlations between study variables were analyzed. There were a number of significant relationships between positive trait emotion scores and other variables reported by all participants ($N = 76$) at the time of study enrollment. Positive trait emotions were significantly related to age, $r = .21$, p (one tailed) $< .05$. These findings indicate older participants had higher scores for positive state emotions on the PANAS than younger participants. There was a large significant relationship

demonstrated between positive trait emotion scores and Ego Resiliency Scale scores , r = .49, p (one tailed) < .01. Participants that reported higher positive trait emotion scores on the PANAS also had higher scores on the Ego Resiliency Scale. There was a large significant inverse relationship between positive emotions scores and scores on the Perceived Stress Scale, r = -.54, p (one tailed) < .01, indicating participants who reported higher positive emotions scored lower on the Perceived Stress scale. A medium inverse relationship was demonstrated between positive trait emotion scores and Global Sleep Scores on the PSQI, r = -.25, p (one tailed) < .05, indicating individuals who reported higher trait emotions also reported fewer sleep problems.

There were significant relationships identified between log cytokine results and study variables. Log IL-6 results (N = 38) and age were highly correlated, r = .60, p (one tailed) < .01, indicating that older participants had higher log IL-6 levels. Log IL-6 levels were found to have a significant inverse relationship with Total Activity scores, r = -.44, p (one tailed) < .01, indicating that participants with higher log IL-6 levels reported less total activity. No significant relationship was demonstrated between IL-1B and other study variables, neither was there a significant relationship demonstrated between Log IL-6 and log IL-1B results (r = .01, p > .05).

Within this study of older adults with an age range of 55 to 96 years, there was a significant relationship between age and other variables, in addition to positive emotions and IL-6. There was a medium significant negative relationship demonstrated between age and Perceived Stress Scale scores, N = 73, r = -.36, p (one tailed) < .01, indicating older adults reported less stress. A large significant negative relationship was

demonstrated between age and Total Activity scores, $N = 75$, $r = -.73$, p (one tailed) < .01, indicating older adults reported less total activity.

There were also significant relationships demonstrated between other scale measurements. This includes scores on the Ego Resiliency Scale ($N = 74$) which had a medium significant negative relationship with scores on the Perceived Stress Scale, $r = -.29$, p (one tailed) < .01, indicating higher Ego Resiliency scores were associated with lower Perceived Stress scale scores. There was also a small to medium significant relationship between scores on the Ego Resiliency Scale and scores on the Total Activity Scale, $r = .29$, p (one tailed) < .01, indicating higher Ego Resiliency scores were associated with higher Total Activity scores.

Significant relationships between study variables are reported in Table 7. Data are included for all participants.

Table 7. Statistical Significance of Relationships Among Study Variables for all Participants

	Positive Emotion Scores	Log IL-6	Log IL-1β	Age	ERS Score	PSS Score	Global Sleep Score	Total Activity Score
Positive Emotion Scores	1	.18 ns	.16 ns	.21*	.49**	-.54**	-.25*	-.12ns
Age	.21*	.60**	-.02 ns	1	-.16 ns	-.36**	.05 ns	-.73**
ERS Score	.49**	.04 ns	.04 ns	-.16 ns	1	-.29**	-.08 ns	.25*
PSS Score	-.54**	-.19 ns	-.21 ns	-.36**	-.29**	1	.16 ns	.19 ns
Global Sleep Score	-.25*	.05 ns	-.03 ns	.05 ns	-.08 ns	.16 ns	1	.01 ns.
Total Activity Score	-.12 ns	-.44**	.14 ns	-.73**	.24*	.19 ns	.01 ns	1
Logged IL-6	.18 ns	1	.01 ns	.60**	.04 ns	-.19 ns	.05 ns	-.44**
Log IL-1β	.16 ns	.01 ns	1	-.02 ns	.04 ns	-.21 ns	-.03 ns	.14 ns
N	76	38	39	76	74	73	75	75

ns = not significant ($p > .05$), *$p < .05$, **$p < .01$

Non-parametric Variables

Testing for the independence of non-parametric variables was performed using chi-square testing to compare positive emotion scores and IL-6 log results with demographic and control variables. In order to examine these relationships using a chi-square statistic, positive trait emotion scores were dichotomized into 2 groups using a medium split. Similarly, IL-6 log results were divided into equal percentiles of the top and bottom 50% result levels using a medium split.

Chi-square testing was performed to test the relationships between positive emotions and marital status, widowhood, retirement, full or part-time employment, education at the college graduate level or above, income level, or caring for a child, family member, or significant other. While an attempt was made to examine assisted living status in relation to positive emotion scores, this was not possible, since one cell contained a count of less than 5, which violated the assumption for chi-square testing. Significant results were not found for full or part-time employment, education at the college graduate level or above, income level, or caring for a child, family member, or significant other.

Significant relationships were identified between positive emotions and being married, $\chi^2(1, N = 40) = 6.82$, $p < .05$, odds ratio = 0.50, with married participants demonstrating lower positive emotions than non-married participants; between positive emotions and being widowed, $\chi^2(1, N = 24) = 4.90$, $p < .05$, odds ratio = 1.67, with widowed participants reporting higher positive emotions than non-widowed participants; and between positive emotions and being retired, $\chi^2(1, N = 38) = 8.54$, $p < .005$, odds ratio = 1.50, with retired participants reporting higher positive emotions than non-retired participants.

When examining the relationships between categorical variables and cytokine results, chi-square analyses were only performed on log IL-6 results due to the granularity and skewed nature of the IL-1β results. Chi-square testing was performed between log IL-6 results and retirement, education at the college graduate level and above, household income over $49,000 annually, and providing care for a child, family

member or significant other. It was not possible to test the relationship between log IL-6 results and widowhood, full or part time employment status, and residence in an assisted living situation because cells for these variables contained counts of less than 5 violating the assumption for chi-square testing. Significance was not demonstrated for the relationship between log IL-6 results and annual household income over $49,000, or providing care for a child, family member or significant other. There was a significant relationship between log IL-6 results and being retired $\chi^2(1, N = 38) = 4.55$, $p < .05$, odds ratio = 2.17, with retired participants having higher IL-6 levels than non-retired participants. This seems to represent the finding that, based on the odds ratio, the odds of having higher log IL-6 levels if retired were 2.17. There was also a significant relationship between log IL-6 levels and reporting education at the college graduate level or above $\chi^2(1, N = 37) = 3.89$, $p < .05$, odds ratio = 0.6, with participants reporting education at the college graduate level or higher having lower IL-6 levels than participant with less education than a college degree. Based on the odds ratio, the odds of having higher log IL-6 results and education level at college graduate and above were 0.6. Participants who reported graduating from college or post-graduate education were likely to have lower log IL-6 levels.

Statistical Analysis of Cytokine Results

To test the hypothesis that higher trait positive emotions would result in lower levels of pro-inflammatory cytokines, hierarchical regression was performed. Positive emotion scores on the PANAS were the independent variable, with analyses performed using total positive emotion scores and scores from each subscale (Well-Being, Vigor,

and Calm), as independent variables. The regression analysis included age, activity, and gender as covariates, as well as the interactions of age & activity, age & gender, activity & gender, and age, activity, & gender as covariates. Regression analysis was performed for logged results of each of the two pro-inflammatory cytokines, log IL-6, and log IL-1β from serum drawn at the time of study enrollment.

None of the hierarchical regressions performed with log IL-6 results from serum drawn at study enrollment as the outcome variable was significant. The finding for which predictors had the highest contribution to the model was the Well-Being subscale scores predicting log IL-6 results with gender as a covariate, (b = .09, SE = .06, β =.27, t[1,36] = 1.63, p = .11). Even this model, with Well-Being subscale scores and gender as a covariate (t [36] = 1.63, p > .05) was not a significant predictor of log IL-6 results. Table 8 provides findings from the hierarchal regression with positive emotion scores, and each of the positive emotion subscale scores predicting log IL-6. In Table 8, data is provided for cytokine results drawn at study enrollment (N = 38) from the pre-post vaccination group and the comparison group.

Table 8. Results of Hierarchal Regression with Positive Emotions Scores as Independent Variable and Logged IL-6 Results as Dependant Variable with Age, Activity, and Gender as Covariates

	b	SE b	β	*t*(1,36)	*p*
Total Positive Emotion Score predicting log IL-6	-.07	.07	.18	1.08	.29
Well-being subscale predicting log IL-6	.07	.06	.21	1.31	.20
Vigor subscale predicting log IL-6	.03	.6	.08	.49	.63
Calm subscale predicting log IL-6	.05	.05	.15	.91	.37
Age covariate					
Total Positive Emotion Score predicting log IL-6	.00	.06	.00	.02	.98
Well-being subscale predicting log IL-6	.00	.05	.01	.08	.94

Vigor subscale predicting log IL-6	-.02	.05	-.05	-.33	.74
Calm subscale predicting log IL-6	.01	.04	.04	.30	.77
Activity covariate					
Total Positive Emotion Score predicting log IL-6	-.01	.07	-.02	-.14	.89
Well-being subscale predicting log IL-6	.00	.06	.01	.07	.95
Vigor subscale predicting log IL-6	-.01	.05	-.03	-.20	.84
Calm subscale predicting log IL-6	-.01	.05	-.03	-.19	.85
Gender covariate					
Total Positive Emotion Score predicting log IL-6	.09	.07	.22	1.33	.19
Well-being subscale predicting log IL-6	.09	.06	.27	1.63	.11
Vigor subscale predicting log IL-6	.03	.06	.10	.57	.57
Calm subscale predicting log IL-6	.06	.05	.19	1.14	.26
Age & activity covariates					
Total Positive Emotion Score predicting log IL-6	-.03	.06	-.06	-.42	.68
Well-being subscale predicting log IL-6	-.02	.05	-.05	-.35	.73
Vigor subscale predicting log IL-6	-.03	.05	-.09	-.61	.55
Calm subscale predicting log IL-6	-.00	.05	-.01	-.09	.93
Age & gender covariates					
Total Positive Emotion Score predicting log IL-6	.02	.06	.05	.39	.70
Well-being subscale predicting log IL-6	.03	.05	.07	.51	.61
Vigor subscale predicting log IL-6	-.01	.05	-.03	-.23	.82
Calm subscale predicting log IL-6	.03	.05	.09	.68	.50
Activity & gender covariates					
Total Positive Emotion Score predicting log IL-6	.01	.06	.02	.12	.91
Well-being subscale predicting log IL-6	.02	.06	.07	.41	.69
Vigor subscale predicting log IL-6	-.01	.05	-.02	-.12	.91
Calm subscale predicting log IL-6	.00	.05	.01	.03	.97
Age, activity, gender covariates					
Total Positive Emotion Score predicting log IL-6	-.01	.06	-.02	-.17	.87
Well-being subscale predicting log IL-6	-.00	.05	-.00	-.01	.99
Vigor subscale predicting log IL-6	-.02	.05	-.07	-.52	.60
Calm subscale predicting log IL-6	.01	.04	.02	.13	.89

Log IL-1β results from serum drawn at the time of study enrollment were also analyzed using hierarchical regression. Log IL-1β at study enrollment was the outcome variable with positive emotions scores and positive emotions subscales as the independent variables. Age, activity, and gender, as well as their interactions, were entered into the model as covariates. Calm subscale scores predicting log IL-1 β levels

approached significance at the .06 level when activity was added as a covariate. Adding covariates into the model did not increase the predictability to any substantial degree. Table 9 provides findings from this hierarchical with positive emotion scores, and each of the positive emotion subscale scores predicting logged IL-1β levels. Table 9 provides data for cytokine results drawn at study enrollment (N = 39) from the pre-post vaccination group and the comparison group.

Table 9. Results of Hierarchical Regression with Positive Emotions Scores as Independent Variable and Log IL-1β results as Dependant Variable, with Age, Activity, and Gender as Covariates

	b	*SE b*	β	*t*(1,36)	*p*
Total Positive Emotion Score predicting log IL-1β	.01	.01	.16	.98	.33
Well-being subscale predicting log IL-1β	.00	.00	.17	1.07	.29
Vigor subscale predicting log IL-1β	.00	.00	-.02	-.10	.92
Calm subscale predicting log IL-1β	.01	.00	.24	1.49	.14
Age covariate					
Total Positive Emotion Score predicting log IL-1β	.01	.01	.18	1.04	.31
Well-being subscale predicting log IL-1β	.01	.00	.20	1.17	.25
Vigor subscale predicting log IL-1β	.00	.00	-.02	-.09	.93
Calm subscale predicting log IL-1β	.01	.00	.26	1.55	.13
Activity covariate					
Total Positive Emotion Score predicting log IL-1β	.01	.01	.23	1.34	.19
Well-being subscale predicting log IL-1β	.01	.00	.27	1.50	.14
Vigor subscale predicting log IL-1β	.00	.00	-.01	-.06	.96
Calm subscale predicting log IL-1β	.01	.00	.34	1.96	.06
Gender covariate					
Total Positive Emotion Score predicting log IL-1β	.01	.01	.18	1.06	.30
Well-being subscale predicting log IL-1β	.01	.00	.20	1.17	.25
Vigor subscale predicting log IL-1β	.00	.00	-.02	-.09	.93
Calm subscale predicting log IL-1β	.01	.00	.26	1.58	.12
Age & activity covariates					
Total Positive Emotion Score predicting log IL-1β	.01	.01	.23	1.31	.20
Well-being subscale predicting log IL-1β	.01	.00	.26	1.44	.16
Vigor subscale predicting log IL-1β	.00	.00	-.01	-.06	.95
Calm subscale predicting log IL-1β	.01	.00	.34	1.95	.06

Age & gender covariates					
Total Positive Emotion Score predicting log IL-1β	.01	.01	.19	1.09	.28
Well-being subscale predicting log IL-1β	.01	.00	.22	1.24	.23
Vigor subscale predicting log IL-1β	.00	.00	-.01	-.08	.94
Calm subscale predicting log IL-1β	.01	.00	.27	1.61	.12
Activity & gender covariates					
Total Positive Emotion Score predicting log IL-1β	.01	.01	.24	1.31	.20
Well-being subscale predicting log IL-1β	.01	.00	.27	1.48	.15
Vigor subscale predicting log IL-1β	.00	.00	-.01	-.06	.95
Calm subscale predicting log IL-1β	.01	.00	.34	.19	.06
Age, activity, gender covariates					
Total Positive Emotion Score predicting log IL-1β	.01	.01	.23	1.28	.21
Well-being subscale predicting log IL-1β	.01	.01	.26	1.42	.17
Vigor subscale predicting log IL-1β	.00	.00	-.01	-.07	.95
Calm subscale predicting log IL-1β	.01	.00	.34	1.92	.06

Positive Emotions and Cytokines: Controlling for Age

Because of the strong correlation demonstrated between log IL-6 and age ($N = 76$, $r = .60$, $p < .001$) identified during the preliminary analysis, the data was re-examined to investigate the relationship between cytokines and positive emotions, this time controlling for age. After controlling for age, the hypothesized negative association between positive emotion scores and log IL-6 emerged. Trait positive emotion scores measured at study enrollment and log IL-6 results demonstrated a inverse relationship ($r = -.03$, $p > .05$), as did positive emotion subscale scores for vigor ($r = -.09$, $p > .05$), and well-being ($r = -.02$, $p > .05$). Participants who had higher positive trait emotion scores had lower levels of IL-6. These findings were also true for the trait positive emotion Well-Being and Vigor subscales. The effect size was small.

Positive Trait Emotions and Cytokine Profiles

To test the hypothesis that positive trait emotions would affect cytokine measurements, resulting in differing cytokine profiles, MANOVA testing was performed

with positive trait emotions scores reported at study enrollment as the predictor and log IL-6 and log IL-1β as the outcome variables. Significant findings were not identified for either log IL-6, F (18, 19) = 1.06, $p > .05$, or log IL-1β, F (18, 19) = 1.64, $p > .05$. Levene's test of equality of error variance was significant for log IL-1β, F (18, 19) = 6.53, $p < .001$, indicating there was shared variance for the dependant variable. The hypothesis was not supported.

Cytokine Levels Before and Fourteen Days After Influenza Vaccination

A one-way repeated-measures ANOVA was performed to compare cytokine results prior to influenza vaccination and two weeks after influenza vaccination in the pre-post vaccination group of participants. The results indicated that neither log IL-6, $F(1,4) = 1.36$, $p > .05$, nor log IL-1β levels, $F(1,4) = 3.31$, $p > .05$ were significantly different for serum drawn prior to influenza immunization and two weeks post influenza immunization. No differences were observed between cytokine results drawn at study enrollment and those drawn two weeks post vaccination. More specific immune testing, of hemagglutinin antibodies specific for influenza would have been needed to more fully evaluate response to influenza vaccination.

Measurements After Influenza Vaccination

Participants from the pre-post vaccination group ($N = 21$) reported state emotions daily for 14 days after influenza vaccination. They also underwent another phlebotomy for cytokine testing approximately 2 weeks after influenza vaccination. Most repeated measures in this group were highly correlated, lending construct reliability to the measures previously examined. There was a large significant correlation, for example,

between positive trait emotion scores obtained at study enrollment and two weeks post influenza vaccination ($N = 18$, $r = .5$, $p < .05$), as well as Perceived Stress Scale scores before and two weeks after vaccination ($N = 18$, $r = .5$, $p < .05$). Scores for positive trait emotions and Perceived Stress were highly correlated across both time points. There was a very large significant relationship between log IL-6 results across both time points ($N = 14$, $r = .9$, $p < .01$), indicating that log IL-6 levels from serum drawn prior to vaccination were highly correlated with those drawn two weeks after vaccination. This finding is in contrast to log IL-1β results. There was minimal correlation demonstrated between pre-vaccination log IL-1β results and log IL-1β levels two weeks post influenza vaccination ($N = 16$, $r = -.03$, $p > .05$).

To identify state emotions after influenza vaccination, participants were asked to record emotions they felt daily on the PANAS each evening for 14 days. Scores varied from a low of 2.2 on day 11 to a high of 2.9 on day 14. Mean daily positive emotion scores for each day after influenza vaccination reported by participants from the pre-post vaccination group were graphed and the results are attached below in Figure 3. The scores demonstrated two troughs, one on day five and one on day 11 followed by a rebound increase in mean positive state emotion scores. Data for these results are included in Table 9 which provides positive state emotion scores from the PANAS, and standard error of the mean for positive emotion scores each day after influenza vaccination reported by participants ($N = 13$ to 16) from the pre-post vaccination group.

Figure 3. Participants' Mean Daily State Positive Emotions Scores for Fourteen Days Following Influenza Vaccination

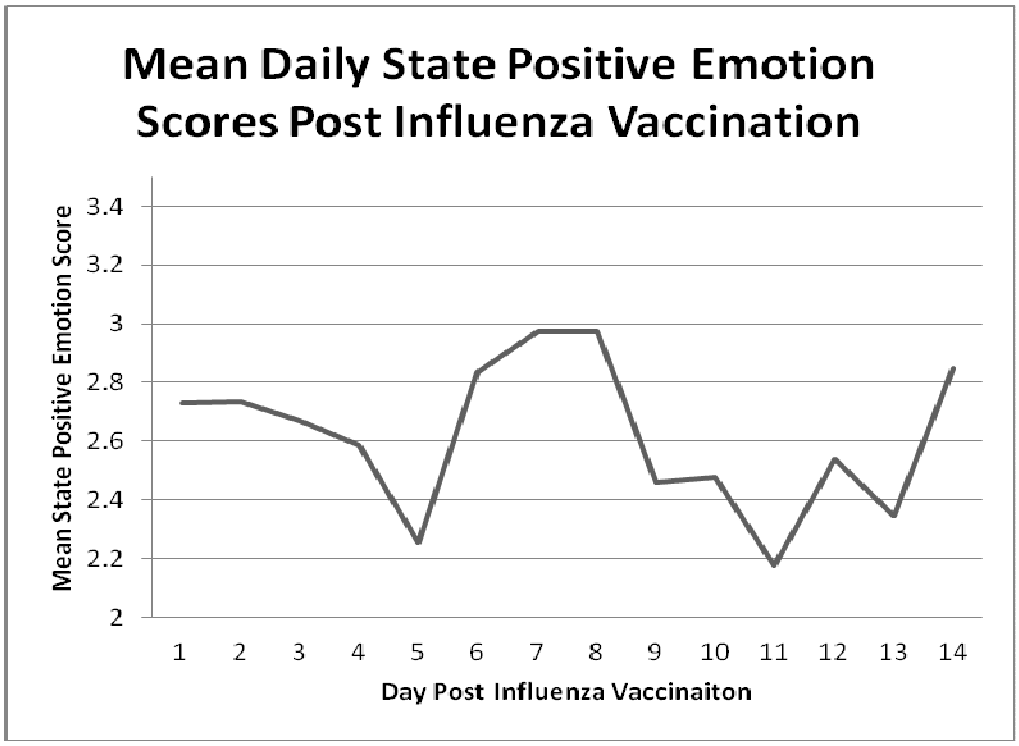


Table 10. Mean State Positive Emotion Score, Standard Error of the Mean, and Number of Participants who Reported Daily Emotions on PANAS for Fourteen Days After Influenza Vaccination

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
M State Positive Score														
	2.73	2.73	2.67	2.59	2.25	2.83	2.97	2.97	2.46	2.48	2.17	2.54	2.35	2.85
SE of the Mean														
	0.13	0.15	0.13	0.19	0.18	0.15	0.21	0.18	0.2	0.23	0.25	0.2	0.2	0.24
N	15	13	13	15	15	16	15	15	15	15	15	15	15	15

Influenza Results

Participants Who Reported Influenza-like Symptoms

Nine study participants reported symptoms consistent with influenza-like illness. These participants were included among the pre-post vaccination and retrospective subgroups, resulting in a total of 53 individuals followed for self-reporting of symptoms over the course of the influenza season. Six participants who reported symptoms were from the pre-post vaccination group and three were from the retrospective subgroup. The onset dates for reported symptoms occurred between January 3 and March 30, 2011.

Participants used the Reporting Symptoms of Influenza Like Illness form to respond via e-mail, telephone, or mail. Of the nine participants who reported symptoms consistent with influenza, five reported cough, five reported sore throat, eight reported nasal congestion, eight reported fatigue, seven reported headache, six reported lethargy/not wanting to do anything, and three reported feverishness, with all three of this last category reporting oral temperature greater than 99.1° F (37.3°C). None of the nine reported that they experienced body aches. All nine met the study criteria for influenza like illness defined as two respiratory symptoms, or one respiratory and one systemic symptom (Centers for Disease Control and Prevention, 2009; McElhaney, 2006). All reported influenza-like signs and symptoms while influenza activity was high to moderate based on national surveillance findings (Centers for Disease Control and Prevention May 27, 2011) and when the incidence of reported influenza B activity was higher (Chicago Department of Public Health, May 20, 2011).

While the age range for participants within these two groups ranged from 55 to 96, ages for participants who reported influenza-like symptoms demonstrated a much narrower range (58-62). The mean age for participants who reported influenza-like symptoms was 60, compared to a mean age of 72 for the group who did not report symptoms, this finding was significant, t (51) = 7.02, p = .000.

Of the nine participants who reported influenza-like symptoms, four were male and five were female, representing a greater proportion of males (56%) than the 53 member group from which the symptom reporters were drawn (24% males). All were white, with a household income greater than $50,000, married and living with their spouse in an independent living situation. None was from the faith-based elderly community. Seven were employed full time, one was unemployed, and one was a homemaker. Mean body mass index was slightly lower for participants who reported influenza-like symptoms (24.6) compared to those that did not (27.4), though this finding was not significant, $p > .05$. Alcoholic and caffeinated beverage selection was similar to other participants (66% drank alcohol, and consumed a mean number of five caffeinated drinks over the previous three days). Seven of them reported caring for a family member. Findings for individuals followed for influenza-like symptoms, comparing participants who reported symptoms with those that did not report symptoms are provided in Table 11.

Table 11. Demographic Information and Variables for Participants Followed for Reporting of Influenza-like Symptoms

Demographic/Variable	Participants that reported influenza-like symptoms (N = 9)		All participants followed for reporting of symptoms (N = 53)	
Gender (% male)	4 male, 5 female (44%)		13 male, 40 female (24%)	
Race	9 White		50 White, 2 African American	
Employment status (% Full-time)	1 unemployed, 1 homemaker, 7 Full-time (78%)		2 unemployed, 24 retired, 1 homemaker, 2 students, 2 part-time, 21 full-time (40%)	
Income	9 $50,000 and above		4 <20K, 15<30K, 4<40K, 24>5K	
Marital status	9 married		2 single, 25 married, 4 divorced or separated, 21 widowed	
Living situation	9 lived with spouse		Alone = 26, with spouse = 22, roommate =4	
Assisted living	No = 9		No = 39,Yes = 12	
Caring for child, spouse, family member or significant other (% Yes)	Yes = 7, No = 2 (78%)		Yes = 15, No = 37 (28%)	
	Reported Influenza-like Symptoms, N = 9		Did not Report Influenza-like Symptoms, N = 44	
	Mean	SD	Mean	SD
Age	60.00***	1.22	72.04	13.41
Body Mass Index	24.61	2.85	26.93	5.90
Positive Emotions Score	2.40	0.46	2.61	0.71
Vigor subscale score	2.41	0.68	2.39	0.85
Wellbeing subscale score	2.59	0.64	2.94	0.81
Calm subscale score	2.19*	.34	2.50	0.90
Perceived Stress Scale Score	16.67*	6.48	12.21	7.01
Total Activity Score	11.18**	1.23	9.50	2.02
Global Sleep Score	10.33**	0.71	11.58	2.43
Logged IL-6 at enrollment	-0.21*	0.22	-0.03	0.27
Logged IL-1β at enrollment	0.000	0.001	0.004	0.012

Multiple t tests performed on variables with no Bonferroni correction: *$p < .05$, ** $p < .005$, ***$p < .001$

Comparison of Group Means for Influenza Findings

A t test was performed to compare means of the independent variables for participants who reported symptoms consistent with influenza with those for participants who were followed for reporting of influenza-like symptoms but did not report symptoms. While participants who reported influenza-like symptoms had lower mean positive emotion scores (2.39) than those that did not (2.65), this result was not significant. Only the calm subscale score showed a significant difference (t (53) = 2.07, p = .045) between participants that reported influenza-like symptoms (M = 2.18, SE = 0.11) and those that did not (M = 2.57, SE = 0.15).

It should be noted that these determinations were made via t testing (2-tailed) to compare the means between the two groups. No Bonferroni or other correction was made to account for the multiple number of t tests performed. None the less, results of this t testing are provided to provide further information on findings beyond percentage scores for participants of this exploratory study on positive emotions and immune response to influenza.

The findings also support the study hypothesis that medically stable individuals aged 55 years and older who reported higher trait positive emotions, would demonstrate lower incidence of influenza-like illness over the course of the influenza season after receiving influenza immunization from clinics, healthcare providers or other vaccination sources. Significantly fewer participants who reported higher trait positive emotion scores on the calm subscale reported influenza-like symptoms.

It was anticipated that there would be significant differences in age between participants who reported influenza-like symptoms and those that did not. This was true (t [51] = 7.02, p = .000), but not in the direction anticipated by previous research. Individuals who reported influenza-like symptoms were significantly *younger* (M = 60, SE = 0.41) than those who did not report these symptoms (M = 74.5 , SE = 2.03).

Additionally, participants who reported influenza-like symptoms scored higher on the Perceived Stress Scale (M = 16.67, SE = 2.16) than those that did not report symptoms (M = 11.28, SE = 1.04). This finding was significant, t (50) = -2.17, p = .035. Participants who reported influenza-like symptoms also reported higher Total Activity Scores (M = 11.18, SE = 0.42) than those that did not report symptoms (M = 9.14, SE = 0.30). This finding was significant, t (50) = -2.95, p = .005. And participants who reported influenza-like symptoms reported lower Global Sleep Scores (indicating fewer sleep problems) on the PSQI (M = 10.33, SE = 0.24) than those that did not report symptoms (M = 11.84, SE = 0.39). This finding was significant, t (50) = 3.28, p = .002. Lastly, participants who reported influenza-like symptoms also had lower log IL-6 levels (M = -.21, SE = 0.09) from serum drawn at study enrollment, than those that did not report symptoms over the course of the influenza season (M = 0.08, SE = 0.07). This cytokine finding was significant, t (15) = 2.46, p = .026.

These t tests are reported to better demonstrate the relationship between the study variables of positive emotions and immune response to influenza. While the findings from these t tests have been reported as significant, they do not represent true statistical

significance. The small sample size was tested multiple times without the benefit of a Bonferroni or other correction.

Chi-Square: Calm Subscale and Symptom Reporting

To test the study hypothesis that participants who reported higher trait positive emotions would demonstrate lower incidence of influenza-like illness over the course of the influenza season, a chi-square analysis was performed with the upper and lower 50% of the Calm subscale scores from the PANAS as the independent variable and self-reporting of influenza-like symptoms over the course of the influenza season as the dependant variable. The Calm subscale included the following items; at ease, calm, and relaxed. There was a significant association between scores on the Calm subscale and reporting of influenza-like symptoms $x^2(1) = 23.11$, $p < .001$.

Logistic Regression for Influenza Findings

Logistical regression was performed to test the study hypothesis that medically stable individuals age 55 years and older with higher trait positive emotions would demonstrate lower incidence of influenza-like illness over the course of the influenza season after receiving influenza immunization from clinics, healthcare providers or other vaccination sources. The two outcome groups were participants who reported influenza like symptoms and those that did not. Logistic regression was used since the reporting of symptoms (dependant variable) was expected to have a non-linear distribution with the independent variable of positive emotion scores, as well as positive emotion subscale scores and identified covariates of age, activity, and gender. The *b* values are all negative, indicating that as positive emotions increased, reporting influenza-like

symptoms decreased, consistent with the study hypothesis. The results of these analyses were not significant. Findings are provided in Table 12.

Table 12. Results of Logistic Regression with Positive Emotions Scores as Independent Variable and Reporting Influenza-Like Symptoms as Dependant Variable, with Age, Activity, and Gender as Covariates

	b	*SE b*	Wald(1)	*p*	Exp (*B*)
Total Positive Emotion Score predicting symptom reporting	-.55	.51	1.15	.28	.58
Well-being subscale predicting symptom reporting	-.54	.43	1.55	.21	.59
Vigor subscale predicting symptom reporting	-.11	.43	.07	.80	.90
Calm subscale predicting symptom reporting	-.48	.41	1.37	.24	.62
Age covariate					
Total Positive Emotion Score predicting symptom reporting	-.22	.62	.13	.72	.80
Well-being subscale predicting symptom reporting	-.29	.52	.31	.58	.75
Vigor subscale predicting symptom reporting	-.20	.62	.11	.75	.82
Calm subscale predicting symptom reporting	-.04	.46	.01	.93	.96
Total activity score covariate					
Total Positive Emotion Score predicting symptom reporting	-.48	.56	.74	.39	.62
Well-being subscale predicting symptom reporting	-.42	.47	.80	.37	.66
Vigor subscale predicting symptom reporting	-.26	.49	.29	.59	.77
Calm subscale predicting symptom reporting	-.33	.45	.56	.46	.72
Gender covariate					
Total Positive Emotion Score predicting symptom reporting	-.48	.52	.85	.36	.62
Well-being subscale predicting symptom reporting	-.47	.44	1.14	.29	.63

Vigor subscale predicting symptom reporting	-.06	.44	.02	.90	.95
Calm subscale predicting symptom reporting	-.46	.41	1.23	.27	.63
Age & total activity score covariate					
Total Positive Emotion Score predicting symptom reporting	-.24	.62	.15	.70	.79
Well-being subscale predicting symptom reporting	-.33	.55	.37	.54	.72
Vigor subscale predicting symptom reporting	-.21	.62	.11	.74	.81
Calm subscale predicting symptom reporting	-.05	.46	.01	.92	.96
Age & gender covariate					
Total Positive Emotion Score predicting symptom reporting	-.09	.64	.02	.89	.91
Well-being subscale predicting symptom reporting	-.17	.55	.10	.75	.84
Vigor subscale predicting symptom reporting	-.01	.68	.00	.99	1.01
Calm subscale predicting symptom reporting	-.02	.47	.00	.96	.98
Total activity score & gender covariate					
Total Positive Emotion Score predicting symptom reporting	-.44	.58	.58	.45	.65
Well-being subscale predicting symptom reporting	-.38	.49	.61	.44	.68
Vigor subscale predicting symptom reporting	-.21	.50	.18	.67	.81
Calm subscale predicting symptom reporting	-.33	.45	.52	.47	.72
Age, total activity score, gender covariate					
Total Positive Emotion Score predicting symptom reporting	-.11	.65	.03	.87	.90
Well-being subscale predicting symptom reporting	-.21	.58	.14	.71	.81
Vigor subscale predicting symptom reporting	-.01	.69	.00	.99	1.01
Calm subscale predicting symptom reporting	-.03	.47	.00	.95	.97

Emotional Complexity

Emotional complexity has been identified as the ability to experience a range of both positive and negative emotions. Psychological researchers maintain this ability becomes manifest under stress and has been linked to emotional intelligence and resilience (Ong et al., 2006; Zautra et al., 2001). A variety of methods have been used to identify the co-existence of positive and negative emotions, including the use of ratios (Zelenski, J.M. 2000; Hay & Diehl, 2011).

PANAS trait emotion scores measured at enrollment were converted to a ratio of total negative emotion scores (sum of scores for sad, depressed, unhappy, on edge, nervous, tense, hostile, resentful, and angry divided by nine) to total positive emotion scores (sum of scores for lively, full of pep, energetic, happy, pleased, cheerful, at ease, calm and relaxed divided by nine). The ratio of negative to positive emotions had a range of 0 to 1.80 with a mean ratio of 0.23, *SD* of 0.31 for 76 participants. The mode for this measure was zero, with emotional complexity ratios of zero for seventeen participants. Scores had a significant positive skew ($z = 8.89$, $p < .001$).

There was a small inverse nonsignificant relationship between emotional complexity ratio and age, $N = 76$, $r = -.10$, $p > .05$. A significant relationship was identified between this emotional complexity ratio and scores on the Perceived Stress Scale ($N = 73$, $r = .45$, one-tailed, $p < .01$), with higher perceived stress scores being associated with higher emotional complexity ratios. There was a negative significant correlation between the emotional complexity ratio and participant scores on the Ego Resiliency scale ($N=74$, $r = -.21$, one-tailed, $p < .05$), with higher emotional complexity

ratios being associated with lower Ego Resiliency scale scores. MANOVA testing did not yield significant findings between the emotional complexity ratio and Ego Resiliency scale scores, $F(21,50) = 1.65$, $p > .05$, or Perceived Stress Scale scores, $F(21,50) = 1.42$, $p > .05$. After controlling for age however, MANOVA testing did yield significant results for the emotional complexity ratio and Perceived Stress scale scores, F (20, 50) = 1.96, $p = .051$, though not for the Ego Resiliency Scale scores F (20, 50) = 1.56, $p > .05$.

Positive Emotion Scores, Cytokines, and Activity

The small negative association demonstrated between Positive Trait Emotions and Total Activity scores ($N = 74$, r = -.12, $p > .05$) for all study participants was surprising given that positive emotions are generally shown to be associated with physical activity (Scully et al., 1998; Markowitz & Arent, 2010). To investigate these variables further, Total Activity scores and the relationship between these scores and Positive Trait Emotion scores were examined within the comparison group, who were recruited from a university medical center affiliated- fitness center.

As reported earlier the comparison group were significantly younger and had higher Total Activity scores when compared to the pre-post vaccination group, the other recruitment group that had serum collected for cytokine measurement. The comparison group ($N = 23$) demonstrated higher Total Activity scores ($M = 10.9$, SD 1.8), than Total Activity scores for the pre-post vaccination and retrospective groups ($N = 52$, $M = 9.5$, SD 2). The difference in Total Activity scores between the comparison group and the pre-post vaccination and retrospective groups was significant, t (73) = 2.945, p (two-tailed) = < .01). When the relationship between Positive Trait Emotions and Total

Activity scores for the comparison group was examined, a large significant negative relationship was identified ($N = 23$, $r = -.683$, $p < .01$). Individuals with lower activity scores in the comparison group reported significantly higher positive trait emotions. This contrasted sharply from the small negative relationship demonstrated between Total Activity scores and positive trait emotion scores for all study participants ($r = -.121$, $p > .05$). This change suggested that group membership in the comparison group moderated the relationship between positive emotions and Total Activity score.

Planned contrast tests indicated the comparison group differed significantly from the pre-post vaccination group and the retrospective group on total activity score, F (2, 72) = 3.142, $p < .05$. The differences between the comparison group and the pre-post vaccination group and the retrospective group is larger than the differences between the pre-post vaccination group and the retrospective group with each other.

Additional analysis of Positive Emotion Scores and cytokine results for all participants, independent of the above considerations for group membership was performed to examine the impact of Activity Level. Total Activity scores were divided into tertiles. MANOVA testing was performed to determine the relationship between activity level, positive emotions, and log cytokine results. There was a significant effect of activity level on positive emotion scores, F (2,32) = 3.96, $p < .05$, with the highest level of Total Activity scores being associated with lower Positive Trait Emotion scores, and activity level and IL-6, F (2,32) = 3.38, $p < .05$, with the highest level of Total Activity scores being associated with lower log IL-6 measurements. The relationship between Activity Score level and IL-1β was not significant, F (2,32) = 1.33, $p > .05$. Activity

level was shown to be a significant variable impacting the independent study variable of positive emotions, as well as the dependent study variable of log IL-6 results. Based on these findings, it was concluded that high activity levels were significant in the relationship between IL-6 and positive emotions for study participants.

CHAPTER FIVE

DISCUSSION

There were two conceptual models used for this research. They were the broaden-and-build theory from the field of positive psychology, and psychoneuroimmunology. These models were chosen because they fit the research problem exploring the relationship between positive emotions and immune response to influenza among medically stable adults, 55 years of age and older. The broaden-and-build theory provided a basis to examine the construct of positive emotions as a resource these older adults could build upon to increase their ability to combat threats such as the development of infection. Psychoneuroimmunology (PNI) provided insight into the mechanisms for how psycho-behavioral factors and physiological processes interact to impact immune response and health outcomes such as the development of influenza-like illness. In reviewing research on cytokines, sickness behavior, and immunity, Dantzer and Kelley (2007) observed that it was simplistic to consider the array of psycho-behavioral reactions to cytokines as isolated stimulus response mechanisms to insure survival from disease. Rather, examination of the role of pro-inflammatory cytokines involves communication systems between the immune and central nervous system. Because the goal of systemic pro-inflammatory response is to promote homeostasis, an understanding of the nature of these responses leads to a better understanding of the biology at all levels of organization for the organisms under review. Instead of

organisms, medically stable older adults going about life in everyday settings throughout the course of the 2010-2011 influenza season were studied. PNI provided an excellent basis for deconstructing the relationships between a number of behavioral and physiological mechanisms used by these older adults to ensure successful functioning in everyday life.

Relationships between Positive Emotions and Other Study Variables

Data was collected on a large number of participant variables in addition to trait positive emotions. The interaction between psychobehavioral factors and the neuro-endocrine-immune system forms the basis for PNI studies. The multi-directional nature of these interactions requires that study designs include control of these factors for meaningful interpretation of the results. The research described in this paper examined these variables as they occurred naturally in a group of older adults. An advantage of this type of research is to further illuminate the relationships between variables of interest in real life situations. While control of these variables would have been inconsistent with the goal of conducting this research in real life settings, it became even more important to measure these variables and examine their relationships.

Participants in this study of positive emotions and immune response to influenza were asked to record emotional experiences on the PANAS later in the day, at approximately the same time each day. This is consistent with studies that indicated individuals experience more positive emotions between noon and early evening. This recording of daily emotions is a strength of this study. State and trait emotions were highly correlated.

A significant relationship was identified between positive trait emotion scores on the PANAS and age for the 76 participants within this study, $r = .21$, p (one-tailed) $< .05$. This is consistent with findings from numerous studies within psychology and PNI. Positive emotions have been seen to increase with age in a number of studies (Chipperfield, Perry, & Weiner, 2003; Isascowitz & Smith, 2003; Ong, Mroczek,& Riffen, 2011). In evaluating this relationship, it is important to remember that participants for this study ranged in age from 55 to 96, with a average age of 70 years old. Within this forty-one year range of older adults, those at the elder end of the age spectrum reported significantly greater trait positive emotions than their younger study counterparts. The effect size for the correlation between reported positive trait emotions scores and age, among the age range of adults recruited for this study was small ($r = .21$).

While the general age pattern is that older adults are happier compared to young adults, some studies that focus exclusively on older populations have failed to report a significant association between age and positive affect (Steptoe, 2011; Isaacowitz & Smith, 2003). The relationship between positive emotions and age seen among the participants in this study is consistent with that reported in large nationally representative survey and life table estimates (Yang, 2008). It should also be noted that the sample for this study included individuals living within elderly communities and in assisted living situations, while the national studies surveys were drawn exclusively from adults residing in the general community (Smith et al., 2006). This study adds to the current state of knowledge regarding positive emotions among older adults in that participants were

recruited from a variety of living situations including an elderly community with residents in a variety of independent and assisted living situations.

Participants in this study had higher household incomes and more education. Fifty-nine percent of respondents reported incomes of $50,000 or above, which was slightly higher than the median Midwest household income of $48,877. Forty-nine percent of participants reported education at the Bachelor's degree level and above compared to national levels of 31.5% for this level of education for individuals aged 55 and older (U.S. Census Bureau, 2011). Research has demonstrated that higher income and education is associated with greater positive emotions (Steptoe et al., 2011; Bishop, Martin & Poon, 2006). In addition to being associated with higher positive emotions, the educational and financial benefits enjoyed by participants in this study afforded them greater access to healthcare and other support systems. Participants recruited from the elderly faith-based community were ensured that basic needs were met and physical, social, as well as medical support was available. Other recruits demonstrated utilization of healthcare resources via obtaining influenza vaccination or enrollment within a university medical center-affiliated fitness center.

There was not a significant gender difference in reported positive trait emotions for participants in this study. Because gender was shown to significantly impact positive emotions in other studies (Yang, 2008; Ross & Mirowsky, 2008), it was used as covariate in the regression analyses used in this research study. Gender was added later in the regression models used. It was not shown to significantly impact the relationships

between reported positive emotions and log IL-6 levels, or the relationship between positive emotions and self report of influenza-like symptoms in this study.

There was a significant negative association between stress scores reported on the Perceived Stress Scale, and reported positive trait emotion scores, $N = 73$, $r = -.54$, p (one-tailed) < .01, as well as a significant negative association between reported stress scores and age, $N = 73$, $r = -.36$, p (one-tailed) < .01. Participants who scored lower on the perceived stress scale scored higher on trait positive emotions on the PANAS. Participants who scored lower on the perceived stress scale were older. Both relationships are consistent with findings in the literature in which stress is shown to negatively impact positive emotions and older individuals experience less stress (Hay & Diehl, 2011; Ross & Mirowsky, 2008). The negative relationship between age and stress demonstrated in this study was large. While some researchers attribute the perception of lower stress among elderly individuals to age, maturity and experience (Ross et al., 2004) others cite a calmer lifestyle and greater control of the environment as possible explanations (Chipperfield, Perry & Weiner, 2003).

The PSQI was chosen as a study instrument to measure sleep, because of the reported relationship between sleep and immune functioning (Miller et al., 2004; Prather et al.,2007). The nearly midsize negative correlation between Global Sleep Scores reported on the PSQI and reported positive emotions, $N = 75$, $r = -.25$, p (one-tailed) < .05, indicated that participants with higher positive emotion scores had lower Global Sleep scores on the PSQI. This finding would be anticipated given that higher scores on the PSQI are due to greater reported sleep problems, which would be expected to have a

negative impact on positive emotions. Steptoe, Dockray and Wardle (2009) reviewed findings in which positive emotions were associated with fewer problems sleeping, independently of age. These findings were replicated for in the current study for medically stable older adults. Research has identified sleep as a mediator between stress and antibody response to influenza vaccination (Miller et al., 2004), underscoring the importance of this variable in interpreting results within this study. Mediation analysis was not possible due to the limited sample size.

Participants who were retired were more likely to report significantly higher trait positive emotions, $\chi^2(1, N = 73) = 8.54, p < .005$. While it is consistent with preconceived notions of working adults who can look forward to happy retirement, these notions are not consistent with published research. Steptoe et al. (2011) did not find that positive affect correlated with employment status after controlling for age and gender. Accordingly, for participants in this study, the association between increased age and retirement status was hypothesized to be a likely explanation for the association between positive emotion scores and retirement status. Additional analysis showed this not to be the case. Positive emotion scores were still significantly related to retirement status after controlling for age, $r = .22$, p (one-tailed) $< .05$. In addition, retirement was not a privilege reserved exclusively for older participants. A number of participants in this study reported retirement status despite being under 60 years of age.

Controlling for age did eliminate the significant relationship originally demonstrated between positive emotion scores and having lost one's spouse. Age, already demonstrated to be associated with higher positive emotions, would be impacting

the scores reported by widows and widowers, who were likely to be older. The relationship between positive emotion scores and age would account for the relationship demonstrated between positive emotions and status as a widow or widower. Statistical analyses showed this to be true. While the original relationship between positive emotions scores and status as a widow and widower was significant, when controlled for age, this relationship was no longer significant.

The negative relationship between positive emotion scores and married status also requires further examination. Social support and social interactions have been shown to be significant predictors for happiness in a number of studies (Bishop, Martin & Poon, 2006; Kurland, et al., 2006; Waldinger & Schulz, 2010). Consistent with these findings, it would be expected that being married would provide a measure of social support and would result in greater reported positive emotions. Waldinger and Schulz (2010) qualified the importance of relational satisfaction in marriage, rather than marital status, as the predictor for greater reports of happiness. They found time spent with others and happiness was moderated by marital satisfaction, and they reported that the variability in subjective well-being explained by marital status alone is modest. Because participants in the current study were not asked to report satisfaction in marriage, there was no measure of marital satisfaction to use as a predictor. In addition, marital status for participants in this study had a large significant negative relationship with age, $r = -.65$, p (one-tailed) $< .001$, indicating that married participants tended to be younger. This supports the conclusion that it was lower age associated with married status, rather than

marital status alone, which was driving the relationship identified. Married participants were younger, and younger participants reported lower positive emotion scores.

Resilience and Positive Emotion Scores

The large positive relationship between positive emotion scores and scores on the Ego Resiliency Scale (r = .49, p (one-tailed) < .01) provided support for the broaden-and-build theory of positive emotions. Resilience is defined as flexibility in response to changing situations, and the ability to bounce back from negative experiences (Block & Kremen, 1996). Resilience would provide a personal resource to be drawn upon when coping with life's difficulties. The large association between positive emotion scores and ego resiliency scores is consistent with the broaden-and-build theory that positive emotions build personal resources which individuals can use to successfully meet the challenges of everyday life. Steptoe et al. (2009) reviewed findings related to the association of positive affect with resilience factors, though none of these studies focused on older adult populations. The large correlation demonstrated between positive emotion and Ego Resiliency Scale scores (r = .489, p < .01) for the current study supported the broaden- and-build theory of positive emotions and demonstrated this relationship among a group of individuals aged 55-96. It is important to recognize the limits of the relationship demonstrated in this study. While a relationship between positive emotion scores and resiliency was demonstrated, a cause-effect relationship was not. Though the correlation efficient was large (r = .49), it does not provide information regarding the direction of causality between these two variables.

Emotional Complexity Ratio

Positive and negative emotion scores were converted to a ratio to examine the co-existence of negative and positive emotions. The ability to experience and differentiate between simultaneously occurring positive and negative emotions has been identified as an adaptive mechanism for coping with stress and an indication of emotional intelligence (Ong et al.,2006). The highly skewed nature of scores for this ratio with a mode of zero within the population for this study, is consistent with research demonstrating that individuals report higher positive emotions, and positive and negative emotions are relatively independent (Zelenski & Larsen, 2000).

Findings in this study were not consistent with previous research demonstrating that emotional complexity increases with age (Paquet, Kergoat & Dube, 2005; Ready, Carvalho, & Weinberger, 2008). There was a small inverse nonsignificant relationship between emotional complexity ratio and age, $N = 76$, $r = -.10$, $p > .05$. The discrepancy between study findings and previous research may be accounted for when age ranges are considered. Older Subjects may have had a higher emotional complexity ratio than young adults examined in previous studies, but there was an inverse relationship between emotional complexity and age within the 55 to 96 age range within this study.

A significant relationship was identified between the emotional complexity ratio and stress which was consistent with the Dynamic Model of Affect (Ong et al., 2006; Zautra, Johnson & Davis, 2005; Zautra et al., 2001), indicating that co-existing negative and positive affect emerges with stress. This lends further support to the broaden-and-build theory of positive emotions. It also underscores the complexity of the relationships

demonstrated among the variables examined within this study of positive emotions and immune response. An alternative explanation for the relationship between emotional complexity and stress is the association between stress and negative affect demonstrated for participants within this study.

Influenza Findings

2010-11 Influenza Vaccine Composition

Trivalent influenza vaccine for the 2010-11 influenza season included A/California/7/2009 (H1N1)-like, A/Perth/16/2009 (H3N2)-like, and B/Brisbane/60/2008-like antigens. The influenza A (H1N1) vaccine virus was obtained from the 2009 pandemic influenza A (H1N1) virus. In addition, Fluzone High-Dose manufactured by Sanofi Pasteur, which contained 60 mcg of hemagglutinin antigen for each vaccine strain was approved as an alternative to the standard dose trivalent vaccine for individuals 65 years of age and older (Centers for Disease Control and Prevention August 6, 2010).

No additional information on type of influenza vaccine received was available from study participants. While participants were queried regarding receipt of influenza vaccine for the 2010-11 Influenza season, they were not asked to specify if they received Fluzone High Dose or the standard trivalent vaccine.

Influenza Activity During 2010-2011 Influenza Season

Based on information provided by the Centers for Disease Control, influenza activity first began to increase in the southeastern United States during November 2010, with peak national activity seen in early February 2011. Nationally, the proportion of

specimen testing positive for influenza first exceeded 10% during the week ending November 27, 2010, peaked at 36% during the week ending February 5, 2011, and declined to < 10% during the week ending April 16, 2011. The geographic distribution of influenza activity was most extensive during the week ending February 26, 2011.

Influenza viruses identified during the 2010-2011 influenza season included 2009 H1N1 viruses, influenza A(H3N2) viruses and influenza B viruses, with influenza A(H3N2) viruses predominating. Based on laboratory-confirmed influenza-associated hospitalizations reported into the national surveillance system between October 1, 2010 and April 30, 2011, the cumulative hospitalization rate per 100,000 population was 22.5 among adults aged 50-64 years, and 65.0 among adults aged ≥ 65 years. Hospitalization rates were highest for individuals 65 years of age and older. In general, the CDC reported the percentages of outpatient visits for influenza-like illness were lower during the 2010-2011 season than the previous pandemic season (Centers for Disease Control and Prevention May 27, 2011; Centers for Disease Control and Prevention, 2010).

National surveillance findings on influenza incidence used for this study were supplemented with local board of health data for this study in which participants were primarily recruited from the City of Chicago and surrounding suburbs. The Chicago Board of Health reported the three strains of influenza occurring in nearly identical proportions based on PCR reporting from all specimens during the 2010-2011 Influenza season, with a higher proportion of Influenza B activity occurring later in the Flu season. When grouped by 10-year age intervals, the highest proportion of ICU admissions for Chicagoans with influenza were reported in patients in their 50's. Sixteen percent of ICU

admissions with influenza were at least 70 years old. Influenza activity in the City of Chicago spiked early in January before beginning to rise again in late January and peaking in February (City of Chicago Department of Public Health, March, 2011). Influenza activity remained high in the city of Chicago throughout March, finally starting to decrease in mid-March (Chicago Department of Public Health, May, 2011). Cases continued to occur at a decreasing rate through March, finally dwindling down to the single digits in May. Board of Health surveillance was discontinued at the end of May, 2011 (Chicago Department of Public Health, 2011). These findings from the Chicago Board of Health were supported by Infection Control Practitioners at Chicago area Hospitals: Spikes in influenza activity were seen in January, with peak activity occurring in February, and ongoing incidence throughout March, with final cessation in May, 2011 (Personal Communications, Chicago Area Hospital Infection Prevention and Control Staff, January-May, 2011).

Participant Reporting of Influenza-like Symptoms

There are an number of noteworthy findings for the nine individuals that reported development of influenza-like symptoms. That none of the symptom-reporters were residents of the faith-based community for the elderly is consistent with research that influenza vaccination is less effective for older adults residing in the general community and more effective for older individuals living in institutional settings (Goodwin, Viboud & Simonsen, 2006). The finding that older age was not a significant predictor of development of influenza-like illness after annual vaccination was inconsistent with the numerous studies that have shown that older individuals are at an increased risk for

influenza, even after receiving influenza vaccination (Mangtani et al., 2004; Jefferson, et al., 2005; Nichol et al., 2007). Upon reviewing circulating strains of influenza reported nationally and locally, and considering the narrow age range of individuals who reported influenza symptoms in conjunction with the period during which they reported these symptoms, it is likely that the reported symptoms were associated with viruses circulating within the identified time period, possibly influenza B or another respiratory pathogen, for which this limited age range of participants (58-62) had not developed adaptive immunity.

It was an important strength of this study design that cytokines and emotions could be measured prior to influenza vaccination, and these 53 individuals could be followed over the course of the influenza season for development of symptoms consistent with influenza. Development of an influenza screening form, consistent with established criteria (Centers for Disease Control and Prevention, 2009; McElhaney et al., 2006) provided a useful tool for symptom reporting via post, e-mail, or telephone. That nine individuals provided reports of influenza-like symptoms validates the use of the tool and methodology. The lack of reports from the faith-based community was validated by administrators within that community who verified that study participants did not develop influenza. An important component of the design was that the researcher kept in contact with study participants throughout the influenza season with periodic reminders to report any signs and symptoms. The study demonstrated the applicability of self-reporting influenza-like symptoms with the aid of a tool for participants to identify symptoms. Participant reports of influenza-like illness were evaluated in light of epidemiological

reports on influenza from national data bases and local board of health findings. This approach proved effective for assessing infectious disease outcomes for an elderly population living in a variety of independent and assisted living situations. Adding confirmatory testing regarding disease or immunity status would have lent further validity to the findings.

While use of a tool for participants to self-monitor and report influenza like-symptoms worked well, another aspect of the original study design was faulty. Only one community dwelling participant who developed influenza-like symptoms contacted the researcher so that phlebotomy could be arranged to measure cytokines during influenza-like illness. Other participants who reported influenza-like illness contacted the researcher two or more weeks post development of symptoms, with apologies that they were just too sick to make the effort earlier. While cytokine measurement during influenza-like illness would have provided valuable insight into immune functioning, researchers considering this design for future studies would have to take into account the limited ability of community dwelling individuals to contact a researcher while ill.

The goal of influenza vaccination, which is to prevent influenza, was met for all participants residing within the elderly faith-based community. None of them reported signs and symptoms consistent with influenza-like illness. The absence of reported influenza-like symptoms may also be associated with the lower stress scores reported by these participants. Lower reports of stress on the Perceived Stress Scale may have been due to having more of their basic needs met, by virtue of living within an elderly community with goals directed specifically at satisfying residents' physical, social, and

emotional needs, or it may be reflective of the older age of these residents. More research is need to address these specific questions.

All individuals who reported influenza like illness lived with their spouse, were white, with a household income greater than $50,000. Seven of the nine individuals worked full-time. While previously discussed studies cited the high costs of influenza due to hospitalization, the costs associated with lost work time is also an important consideration for employed influenza sufferers. These added costs, more often incurred for individuals under 65 years of age, are important public health considerations. Current national guidelines recommend influenza vaccination for all individuals over 6 months of age, addressing the need for individuals under 65 years of age to receive annual vaccination, though the cost for this preventive care must often covered by the private means (Centers for Disease Control and Prevention, 2009; Centers for Medicare & Medicaid Services, 2010).

Additional public health concerns regarding the costs incurred due to influenza-like illness, including costs associated with loss of work time and failure to meet care giving responsibilities, raised the question of what additional measures are available to prevent influenza for these younger-older adults. Findings from this study identify factors that can be considered to reduce risks for developing influenza when strains are circulating within the community. Worthwhile suggestions for nurses interested in providing patients with additional suggestions to prevent influenza, beyond the primary recommendation to receive annual vaccination might be to decrease stress, or increase activity to moderate levels. Consideration of high-dose Fluzone Influenza vaccination

may be worthwhile for individuals who would incur higher financial and personal costs due to time lost from ongoing responsibilities. Current national recommendations for high dose influenza vaccine are limited to individuals over 65 years of age.

The finding that seven of the nine individuals who reported influenza-like symptoms reported caring for a family member may be associated with the stress of this responsibility. Studies have found that providing care for a family member increases the risk of influenza due to the stress of the role (Segerstrom, Schipper & Greenberg, 2008). Research on care giving often focuses on the support required to meet the needs of a physically or mentally disabled parent or spouse. Based on anecdotal information offered by participants during study enrollment, care giving also included meeting the needs of an adolescent, child, or physically capable spouse. More research is needed to better identify risks and stresses associated with providing care for individuals who may not have disabilities, but are still dependant on others for physical, financial, and emotional support, and how these risks may be reduced.

Individuals who reported influenza-like symptoms had significantly lower levels of log IL-6 at enrollment when compared with levels for other individuals followed throughout the influenza season. This finding is not consistent with research which shows that elevated IL-6 increases the risk of developing disease (Carroll et al., 2011; Kruttgen & Rose-John, 2011; Glaser et al., 2003). It is, however, consistent with findings for all study participants demonstrating significantly higher IL-6 with increasing age ($r = .60$, p [one tailed] $< .01$). Higher IL-6 levels in older individuals is consistent with dysregulation of the aging immune system reported in the literature (Bernstein et

al.,1998; Keylock et al., 2007). Within this study the overriding factor of younger age, for individuals whose immune systems were susceptible to circulating strains of influenza virus between January 3 and March 30, 2011, would explain the lower IL-6 levels seen in individuals who reported influenza-like illness.

Similar interactions were seen for Total Activity scores which were higher in participants who reported influenza-like symptoms. Higher activity was shown to be associated with being younger for all participants, and individuals who reported influenza-like symptoms were younger. Adding to the association between younger age and activity level, were study findings for log IL-6, which demonstrated a significant inverse relationship with participant Total Activity Scores, $N = 37$, $r = -.44$, p (one-tailed) $< .01$, consistent with the role of IL-6 in impacting energy utilization (Janeway, Travers, Walport & Shlomchik, 2005). Lower IL-6 levels seen in younger participants who reported influenza-like illness would likely be associated with higher Total Activity scores measured at study enrollment, given the large negative relationship between total activity and age ($N = 75$, $r = -.73$, $p < .01$) demonstrated for all study participants.

Global Sleep scores on the PSQI were significantly lower for participants who reported influenza-like illness, meaning that these individuals reported fewer sleep disturbances upon enrollment. This finding may be attributable to the lower levels of IL-6 reported in these participants (Miller et al., 2004; Prather et al., 2007).

Higher scores on the PSS for individuals who reported influenza-like symptoms indicated these individuals experienced more stress which may have been associated with the responsibilities of work and care giving. Higher stress would put these individuals at

risk for higher IL-6 levels and development of disease (Costanzo et al., 2004). Within the framework of this study, these risks would be manifest in the development of influenza-like illness.

The aim of this study was to evaluate the relationship between positive emotions and health outcomes related to influenza-like illness for a group of medically stable older adults who had received influenza vaccination. The specific hypothesis was that medically stable individuals aged 55 and older who report higher trait positive emotions would demonstrate lower incidence of influenza-like illness over the course of the influenza season (October through March) after receiving influenza immunization from clinics, healthcare providers or other vaccination sources. A logistic regression for positive emotion scores on the PANAS (and positive emotion subscale scores for Vigor, Well-Being, and Calm) using reporting or non-reporting of influenza-like symptoms as the outcomes, and age, activity, and gender as covariates, as well as covariate interactions did not yield significant results. The covariates were chosen based on research that had demonstrated the significance of these variables. Numerous studies demonstrated that older individuals are at an increased risk for influenza, even after receiving influenza vaccination (Goodwin et al., 2006; Jefferson et al., 2005; Mangtani et al., 2004; Nichol et al., 2007). Numerous findings have also demonstrated that increased activity has been shown to impact the development of influenza in the elderly (Fondell et al., 2011; Gidron et al., 2005; Keylock et al., 2007; Schuler, Leblanc & Marzilli, 2003; Woods et al., 2009). Research demonstrating an association between gender and development of influenza is not as strong (Johnstone, Majumdar, Fox, & Marrie, 2008), though studies

have documented the increased risk of pneumonia as a result of influenza infection or other viral respiratory pathogens in males (El-Solh, Niederman & Drinka, 2010; Upshur & Goel, 2000). Another factor influencing the choice of gender as a covariate in the logistical regression was that males were more highly represented among the individuals who reported influenza-like symptoms (44%), than in the group that did not report symptoms (24%) within this study.

The negative direction of reported results for positive emotions were consistent with the hypothesis, indicating that as positive emotions increased, reporting influenza-like symptoms decreased. Positive emotions did not significantly predict reporting of influenza-like symptoms, however. The study was underpowered.

Consistent with the study hypothesis, participants who reported influenza-like symptoms had lower mean positive emotion scores, than those that did not (2.39 and 2.65 respectively). This result was not significant. Only the calm subscale score showed a significant difference ($N = 53$, $t = 2.07$, $p = .045$) between participants that reported influenza-like symptoms ($M = 2.2$, $SE = 0.11$) and those that did not ($M = 2.6$, $SE = 0.15$). This finding deviates slightly from that reported by Cohen et al. (2006) who experimentally exposed 193 quarantined individuals to Rhinovirus or Influenza A Virus. Cohen et al. found that individuals with higher positive emotions demonstrated fewer objective and subjective indications of upper respiratory symptoms. Of the three positive emotion subscales (Vigor, Well-Being, and Calm), the Calm subscale was the only one which did not demonstrate statistical significance in the Cohen et al. study, though scores on the Calm subscale were lower for individuals who developed upper respiratory

symptoms. There are numerous differences between the 2006 study by Cohen et al. and the research presently under discussion. One important difference is that participants in the Cohen et al. study ranged in age from 21 to 55 years of age, compared to participant age of 55 and above for this study. Scores on the calm subscale may be different for older individuals or this constellation of low arousal positive emotions may play a unique role in immune responses for older individuals. Further research is indicated in this area.

Cytokine Findings

Burns , Carroll, Ring & Drayson (2003) noted the importance of in vivo studies of immune function, citing problems associated with generalizing from in vitro to in vivo processes, and decrying the scant information afforded by isolated testing of a single aspect of a highly integrated, complex process such as the immune response. This study provided en vivo measures of immune function from serum drawn prior to and 2 weeks after influenza vaccination (the pre-post vaccination group), as well as a serum drawn at study enrollment for a comparison group of individuals that did not receive influenza vaccination.

Cytokine measures, drawn from participant serum, included IL-1 β and IL-6. Both are pro-inflammatory cytokines. The significance of a Th1 versus a Th2 response, noting the predisposition for a Th2 response seen in the immune systems of older adults when compared with younger adults (Segerstrom et al., 2008), was reviewed in this paper. A switch from Th1 to Th2 type response may contribute to the increased susceptibility to upper respiratory infections seen among older adults (Lutgendorf &

Constanzo, 2003). Analysis of a Th1 vs. Th2 response was not possible based on the Cytokines measured.

Hierarchical regression was performed for both cytokines, using total positive emotion scores on the PANAS and each of the positive emotion subscales as predictors for log results of each cytokine obtained from serum drawn at study enrollment. Age, activity and gender were entered as covariates, as well as interactions between these covariates. Published research formed the basis for the covariates used in the hierarchical regression. The positive association between cytokines and age is well documented (Bernstein et al.,1998; Glaser et al., 2003; Keylock et al., 2007; Lutgendorf & Costanzo, 2003; Segerstrom et al., 2008) and was also demonstrated in the large significant correlation between age and log IL-6 levels, $N = 38$, $r = .60$, p (one-tailed) $< .01$, in this study of individuals age 55-96. A number of studies document the relationship between activity and cytokines (Bernecker et al., 2011; Keylock et al., 2007; Woods et al., 2009), which was consistent with the large inverse relationship demonstrated by participants in this study for whom higher levels of physical activity were associated with lower levels of log IL-6, $N = 38$, $r = -.44$, p (one-tailed) $< .01$. There were no significant relationships demonstrated between cytokine levels and gender within this study. Gender was included as a covariate in the hierarchical regression for positive emotions, log Il-6 and log Il-1 β because of the relationship between female gender and lower cytokine levels documented in the literature (O'Connor et al., 2009; Prather, Marsland, Muldoon & Manuck, 2007; Steptoe, Dockray & Wardle, 2009).

The lack of significant findings from the hierarchical regression using trait positive emotion scores to predict log IL-6 results from serum drawn at study enrollment does not support the study hypothesis that higher positive emotions are associated with lower cytokine results. The slope for this regression was initially negative, in the direction proposed by the hypothesis, but reverted to a positive direction unless activity was entered as a covariate. It was possible that activity was moderating the relationship between IL-6 and positive emotions. This becomes an acceptable explanation when the complex interrelationship between IL-6, exercise, and positive emotions reported in various studies from sports medicine, PNI, and positive psychology are viewed as a whole. Positive emotions increase with low to moderate exercise, but decrease with strenuous exercise. IL-6 levels increase after strenuous exercise. IL-6 and positive emotions are inversely related. It is also worth pointing out that exercise was an important health strategy adopted by a number of study participants, and the importance of exercise as a health promotion strategy was likely to be even higher for enrollees at a university affiliated fitness center who chose not to receive annual influenza vaccination, as was the case for the comparison group. Analysis of mediating and moderating relationships between these variables was not possible given the small sample size for this study. The study was underpowered, especially given the interrelationship demonstrated between variables such as age, cytokine levels, positive emotions, activity, sleep, and stress.

The finding that log IL-6 results were significantly correlated with age is consistent with published research findings (Bernstein et al., 1998; Glaser et al., 2003;

Lutgendorf et al., 2001; Keylock et al., 2007). Higher levels of IL-6 are seen in older individuals.

An association between stress and IL-6 has been documented (Lutgendorf et al., 2001; 2004; Segerstrom, et al., 2008) with higher stress resulting in higher levels of IL-6. The relationship between stress and IL-6 demonstrated within the populations of adults age 55 and older within this study was not consistent with this previously published research. A small inverse relationship was found between log IL-6 levels and participant scores on the Perceived Stress Scale, $N = 35$, $r = -.19$, $p > .05$. Though the finding is not significant, the inverse relationship evidenced by study participants, given that research predicts a positive relationship, invites further investigation into the reason that increased stress was associated with lower cytokine levels for the participants in this study.

Some researchers have proposed that stress is lower for older adults (Ross & Mirowsky, 2008). Given the obvious challenges older adults encounter in meeting lives' responsibilities in the face of declining physical functioning, a more plausible explanation can be found in research demonstrating that stress is perceived differently by older adults (Kwag et al., 2011). Other researchers have suggested that older adults engage in active health promotion behaviors to cope with physical problems and lower the impact of emotional distress (Wrosch, Schulz & Heckhausen, 2002). This last explanation is consistent with actions exhibited by older adults within this study. They moved to an elderly community allowing them to better cope with increasing physical limitations, they received influenza vaccination providing protection against seasonal disease, they engaged in physical activity which would maintain health.

These health promotion activities do not, however, negate the reality of decreased immune functioning and cytokine dysregulation in later adulthood. Research has clearly demonstrated that levels of IL-6 increase with age, and that immune response to influenza vaccination is decreased in this population (Bernstein et al., 1998; Glaser et al., 2003). The health promotion activities may, however, be mitigating the well documented negative relationship between IL-6 and positive emotions (Steptoe et al., 2009). Just as the older adults within this study population demonstrated higher levels of positive emotions despite increasing levels of cytokines, it is possible they are using other strategies, such as physical activity, to cope with perceived stress.

Research has demonstrated an inverse relationship between IL-1β and activity (Prather et al., 2007). This relationship was not demonstrated in this study ($N = 38$, $r = .12$, $p > .05$). One explanation for the discrepancy was that the Physical Activity Survey was used to measured ongoing and recent activity levels, not activity at the moment of serum collection, which would be more reflective of the relationship between current levels of IL-1β and momentary activity levels.

The hypothesized relationship between positive emotions and IL-1β was not demonstrated. When findings were analyzed with hierarchical regression using trait positive emotions scores or positive emotion subscale scores as the predictor and log IL-1β as the outcome, results were not significant. Findings approached significance with calm subscale scores predicting log IL1 β results with activity as a covariate ($b = .01$, $SEb = .00$, $\beta = .34$, $t\ (1, 36) = 1.95$, $p = .06$. Once again, insufficient power may have contributed to findings.

The finding that higher education decreased the likelihood of higher log IL-6 levels from serum drawn at study enrollment, χ^2 (1, N =37) = 3.89, $p < .05$, odds ratio = 0.6, is easily overlooked among the complex relationship between variables in this study. Research supports the finding that socioeconomic status is an important variable when examining inflammatory markers (O'Connor et al., 2009). The advantages of higher education and income on physiological functioning underscores a limitation of the current study: Generalizability of findings to other socioeconomic levels.

The finding that IL-6 levels were likely to be higher for retired individuals, χ^2 (1, 38) = 8.54, $p < .005$,odds ratio = 1.67, is not consistent with other research which demonstrated no relationship between IL-6 and employment status after controlling for age and gender (Steptoe, Leigh & Kumari, 2011). This discrepancy invites further investigation. Additional information regarding time utilization, or the increases in physical activity since retirement might provide more insight.

Inconsistencies in the time of day during which serum was drawn may have impacted cytokine results. Serum was drawn over the course of the day, between 8:00 AM and 3:00 PM. The comparison group, for which recruitment sessions lasted into the early afternoon had more specimen collected later in the day. Other researchers controlled circadian variability by restricting the hours between which cytokine measurements were collected (Lutgendorf et al., 2001). There was also variability between recruitment groups in the time of year during which cytokines were drawn. The pre-post vaccination group has serum drawn in the fall. The comparison group had serum drawn in the spring. Seasonal variation may have affected cytokine levels. It is a

limitation of this study that collection times for cytokines were not more tightly controlled.

Measurements After Influenza Vaccination

The repeated measures taken pre-and post-vaccination were a strength of this study. Costs associated with repeat testing, as well as timing constraints which limited recruitment, resulted in a small sample size (N = 21) for this pre-post vaccination group. The number of participants with repeat cytokine testing was even smaller (N = 16), with 14 repeat tests obtained for IL-6 measurements, and 16 for IL1β.

While the number of participants pre-post vaccination was low, a number of interesting findings emerged from this aspect of the study. Participants were asked to record their daily state emotions for 14 days after receiving influenza vaccination and mean positive emotion scores were trended for the 16 participants who provided this data. Troughs in mean positive emotion scores were demonstrated on days 5 and 11 post influenza vaccination. Research provides a context to evaluate the relevancy of these findings. In addition to exploring trait emotions (how people usually feel), research on positive emotions also focused on the day-to-day momentary experiences of positive emotions (Hay et al., 2011; Steptoe et al., 2011). This line of inquiry included the role of daily emotional state as an important indicator of current and future well-being and health (Ong et al., 2010; Steptoe et al., 2011).

While ecological momentary assessment is regarded as a more precise measurement of daily experience, research using this methodology on 4,000 men and women aged 52-79 years of age indicated that experiences of positive emotions peaked

between noon and early evening (Steptoe et al., 2011). This provided some validation for the methodology used in the current study of positive emotions in which respondents were asked to record daily emotions later in the day.

Research linking positive effect, even over a single day, to increased survival (Steptoe et al., 2011), has important implications for the fluctuations in positive affect demonstrated by study participants over the fourteen days post influenza vaccination. If decreased daily positive emotions impact long term survival, additional research is warranted to demonstrate if the drops in daily emotions after receiving influenza vaccination seen for these participants are typical for older adults. The implication is not that these troughs in positive emotion levels represent a life threatening situation for these participants, but rather that the variance in state positive emotion experiences may provide information regarding immune response and the interaction between emotions, immunity, and disease. It is possible, for example, that the drops in positive emotions after immunization correspond to respective innate and adaptive immune responses to influenza vaccine. Decreases in positive emotion levels may also indicate periods of vulnerability during which individuals are more susceptible to respiratory diseases. One result could be the basis of the often-voiced rationale from individuals who say they fail to receive annual influenza vaccine because this immunization results in respiratory illness.

A noteworthy pattern emerged when mean daily positive emotion scores were trended over two weeks. Mean positive emotions scores dropped on days 5 and 11 post vaccination. Because participants were not queried regarding daily events, the reason for

this drop cannot be identified. One hypothesis that can be offered is that, given the negative correlation seen in this study and the literature between stress and positive emotions, drops in positive emotions were the result of a common shared experience. One experience shared among these participants was influenza vaccination which they received independently between October and December 2011. The findings that positive emotion scores decreased on day 5 and day 11 post vaccination may be due to the physiologic stress of mounting first an innate, then an adaptive immune response to influenza vaccination. This physiologic stress may have translated into a decrease in positive emotion scores recorded during the 2 week post vaccination period. More research is indicated to replicate this finding and more fully explore relationships between vaccination, immune response, and daily emotional state after influenza vaccination in the elderly.

Role of Physical Activity

Research has documented an association between positive emotions and physical activity (Pasco et al., 2011). Studies evaluating older adults supported the finding that physical activity increased positive emotions for this age group (Brown, Lui-Ambrose & Tate, 2008; Parker, Strath & Swartz, 2008). Closer scrutiny indicates the relationship between physical activity and positive emotions is more complex. While lower to moderate levels of physical activity have been shown to increase positive emotions, more demanding exercise regimens with higher intensity of activity were associated with decreasing levels of positive emotions (Ekkekakis, Parfitt & Petruzzello, 2011; Lee & Hung, 2012; Legrand & Thatcher, 2011; Scully et al., 1998). The small inverse

relationship between higher levels of activity and positive emotions reported by all participants on the Physical Activity Survey ($N = 75$, $r = -.12$, $p > .05$), demonstrated a significant increase in strength when examined for individuals in the comparison group of study participants who were recruited at a university medical center affiliated fitness center. Total Activity scores were significantly higher for the comparison group, t (73) = 2.945, p (two tailed) < .01, and there was a large significant inverse relationship between physical activity level and positive emotions, $N = 23$, $r = -.683$, $p < .01$. This group of participants with significantly higher total activity scores had significantly lower scores for trait positive emotions, the dependant variable for this study.

Cytokines, including IL-6 and IL-1, have been shown to increase after strenuous exercise (Bernecker et al., 2011; Olli-Pekka, et al., 2012; Stacey et al., 2010). Because participants completed a Physical Activity Survey that included questions on usual physical activity associated with work, home, recreation, and regular exercise, there is no indication of the temporal relationship between exercise and serum collection for participants. Some participants at the fitness center volunteered that they had already completed their workout sessions, and others had not yet started. It is a limitation of this study that the effect of recent exercise on cytokine levels could not be identified. Other researchers controlled for the effect of exercise on serum cytokine responses by asking subjects to refrain from exercise prior to serum being drawn for cytokines (Prather et al., 2007). Future studies should incorporate this strategy.

While activity level would be expected to be higher for the comparison group recruited at the fitness center, it should also be noted that other study participants

reported regular participation in running and exercise classes. Participants recruited from the faith-based elderly community reported regular participation in exercise sessions and walking, and even residents who used wheelchairs or carts for mobility reported that they did morning floor exercises upon waking each morning. While there was a large significant negative relationship demonstrated between age and Total Activity scores (r = -.73, $p < .01$), indicating that older participants had lower physical activity scores, regular exercise appeared to be incorporated into everyday life for a number of study participants.

Several studies documented the role of exercise in improving immune response after vaccination (Keylock et al., 2007; Romeo et al., 2010; Schuler, Leblanc & Marzilli, 2003; Woods et al., 2009). The role of physical activity in reducing the incidence of respiratory infection, and its importance as a strategy for preventing these infections among older adults, is well documented (Fondell et al., 2011; Gidron et al., 2005; Nieman, Hensen, Austin & Sha, 2011). These findings underscore the importance of activity in immune response, the dependant variable for this study.

Total activity scores demonstrated a significant inverse relationship with log IL-6 results (r = -.44, $p < .01$), but not with IL1-β (r = .14, $p >.05$) for study participants. As a whole, these findings are not consistent with an increase in cytokines following intense activity. Instead, the relationship demonstrated was consistent with lower to moderate activity associated with decreased cytokine levels. This would be consistent with decreased energy and sickness behavior associated with pro-inflammatory cytokines (Dantzer & Kelley, 2006).

Also, as previously noted, individuals who reported influenza-like symptoms had higher activity scores. One possible explanation for this was the increased activity level for the younger age group that reported influenza-like symptoms.

A relationship between highest activity levels and lower positive emotion scores, while moderate activity levels were associated with higher positive emotion scores was also demonstrated. The significant relationship identified between highest and lowest activity scores, the independent variable of positive emotions, F (2,32) = 3.96, p <.05, and the dependant variable of cytokine levels, F (2,32) = 3.38, p <.05, demonstrated the important role of activity in the relationships between variables in this study.

Calm Subscale: Active versus Passive Positive Emotions

The Circumplex Model (Larsen & Diener, 1992; Russell et al., 1980) in which emotions are characterized along the four dimensions of positive and negative valence, and high and low activation (or aroused and unaroused) would seem to have some applicability to the significant findings associated with the Calm subscale within this study. Similar concepts have been applied to older adults in whom the quality of emotions has been proposed to shift not only from negative to positive, but also from active to passive (Ross & Mirowsky, 2008). Ross and Mirowsky described the shift to more passive emotions as an outgrowth of decline occurring with older age. They maintained that the two underlying qualities of emotions with older adults are positive and passive, with contentment, calm, an ease being the most common emotions experienced by older adults.

Conclusions

Complexity of Variable Interactions

The complex role of physical activity with the independent study variable of positive emotions and the dependant variable of immune response underscores that the variables measured in this study have multi-factorial roles. The limited sample size did not allow for examination of moderator or mediator roles for variables such as age, or activity. Focus on stress as an independent variable for development of influenza was purposely avoided to allow for the exploration of variables such as positive emotions, cytokine levels, and activity. While the hypotheses for this study led to statistical analysis using cytokines as an outcome variable, research points to the role of cytokines as mediators (Doyle, Gentile & Coleman, 2006). The interrelationships demonstrated between variables in this study invited consideration of positive emotions as a mediator between stress and immune outcomes. While the sample size for this study was not sufficient for these explorations, future studies with larger samples sizes would allow for such analyses. Coe and Laudenslager (2007) summarized multiple levels of influence on the aging immune system and cite the importance of successful aging strategies to postpone biological processes responsible for physical decline seen later in life. The interactions between variables such as age, activity, cytokine levels, positive emotions, sleep, and stress invite further investigation of their role in successful aging and the choices older adults make to incorporate health promotion strategies into everyday life.

Participants in this study demonstrated a number of strategies to preserve health and prevent decline. Physical activity, influenza vaccination, enrollment at a hospital

affiliated fitness center, seeking out social engagement within a fitness center or elderly community, and regulation of emotional well-being are examples of such strategies. Health engagement control strategies have been demonstrated to be a mechanism to protect individuals from physical decline and preserve health (Wrosch et al., 2007). Study participants demonstrated ongoing application of health promotion strategies.

Immunity is an immensely complex system, with individualistic variety in functioning. Seeking to explore the impact of a significant psycho-behavioral variable such as positive emotions on aging immune systems in real life settings, while certainly meaningful, was also very complex given the multifaceted nature of significant variables and their interactions. The complexity of these interactions was demonstrated statistically in the shared variance among a number of study variables. When MANOVA testing was performed for reporting of influenza-like illness, scores on the Perceived Stress Scale and Total Activity, as well as IL-6 were shown to be significantly related to the independent variable. Shared variance was frequently identified during analyses (e.g. Significance of Levene's test of equality of error variance identified during MANOVA testing for positive emotion scores predicting IL1- β, F (18, 19) = 6.53, $p < .001$). This overlapping of effect may have been integral to the role and function of these variables in improving immune response, just as shared health promotions strategies and internal feedback about internal processes such as activity level, positive emotion, sleep, and cytokine levels were essential to the everyday functioning of the older adults in this study. These interrelationships demonstrate the usefulness of a PNI model as used in this study.

Limitations to the Study

The sample size for the study was not sufficient to complete regression analyses with the number of covariates identified, or for meditational or moderating analysis. In addition, challenges in recruiting study participants resulted in enrollment from a variety of settings that resulted in groups that differed in significant ways on key variables such as age and activity level. Combining these diverse groups added to the difficulty in finding significant differences and hypothesized results. These diverse groups did, however, provide valuable insights into how psycho behavioral and immune variables interact in real life settings.

Other limitations to the study included the lack of confirmatory testing regarding identification of influenza or other respiratory pathogens for participants that reported influenza-like symptoms. Serum for cytokine measures during the period in which participants were experiencing influenza-like illness were not drawn. Inconsistencies in the time of day serum was drawn for cytokine measurement did not account for diurnal rhythms and was a limitation. In addition, the pre-post vaccination group and the comparison group were tested during different times of the year, not accounting for possible seasonal variations in cytokine measurement. An additional limitation was the lack of control regarding recent exercise and serum drawing for cytokine measurement. Some Members from the fitness center were enrolled in the study and had blood drawn immediately after their exercise session, while some had completed these actions prior to exercising. Daily state positive emotions were measured for fourteen days after influenza vaccination, but participants were not queried as to daily events that may have occurred

during this period. While the Perceived Stress Scale was completed, there was no opportunity for participants to indentify the nature or source of stress. The major limitation, in addition to insufficient power, was relative homogenous sample of well-educated Caucasian middle class adults. In addition, all these older adults demonstrated ongoing use of health promotion strategies such as exercise, influenza vaccination or relocation to an elderly care community to ensure necessary support. This population limited the generalizability of the findings to lower social economic classes and individuals who fail to make positive choices regarding health promotion.

Findings for Study Hypotheses and Summary Findings

A brief summary of the specific study hypotheses and findings follow:

1. *Medically stable individuals aged 55 years and older who report higher trait positive emotions, will demonstrate lower incidence of influenza like illness over the course of the influenza season (October through March) after receiving influenza immunization from clinics, healthcare providers or other vaccination sources.*

Fifty-three individuals, who had received influenza vaccination, were followed over the course of the season for self-reporting influenza-like symptoms. Nine participants aged 58-62 reported symptoms consistent with influenza-like illness as identified on the Reporting Symptoms of Influenza Like Illness Form. Results of Logistical regression did not support the hypotheses, though slopes were in the predicted direction of higher positive trait emotions predicting less reporting of influenza symptoms. Participants who reported symptoms consistent with influenza had mean

lower positive trait emotion scores (2.4 vs. 2.6), but this finding was not significant. Support for the hypotheses was generated by *t* testing which demonstrated that participants that reported influenza-like symptoms also reported significantly lower positive emotions on the calm subscale, $t\ (53) = 2.07$, $p < .05$. Chi-square testing using the upper and lower 50% of the calm subscale scores from the PANAS as the independent variable and self reporting of influenza testing as the dependant variable also demonstrated a significant association, $\chi^2\ (1) = 23.11$, $p < .001$.

None of the participants that reported influenza-like symptoms were residents of the elderly community, supporting findings that influenza vaccination is most effective for elderly residents residing in group settings (Jefferson et al., 2005, Rivetti et al., 2009). The age for influenza-like symptom reporters ($M = 60$) was significantly lower than the mean age for the group followed for symptom development ($M = 72$), $t\ (51) = 7.02$, $p < .01$, which was inconsistent with research that older individuals are at highest risk for influenza (Magtani et al., 2004,; Jefferson, et al., 2005, Nichol et al., 2007). The restricted age range for individuals who reported symptoms, coupled with board of health data for circulating strains within the community for the period during which onset of symptoms were reported, is consistent with age cohort susceptibility to circulating influenza strain(s). In addition to age, other significant differences identified between participants who reported influenza-like symptoms and those that did not, included higher Total Activity scores $t\ (50) = -2.95$, $p < .005$, lower Global Sleep Scores on the PSQI, $t\ (50) = 3.28$, $p < .01$, lower scores on the Perceived Stress Scale, $t\ (50) = -2.17$, $p < .05$, and lower log IL-6 levels identified at study enrollment, $t\ (15) = 2.46$, $p < .05$. No

established national values are identified for these values on these scales among older adults. Daily trending of state positive emotion scores for two weeks post influenza vaccination demonstrated troughs on day 5 and 11, a finding which should be reexamined in a larger population.

2. *Participants who self report higher positive trait emotions will demonstrate different cytokine responses:*

    a. *Positive trait emotions will affect cytokine measurements, resulting in differing cytokine profiles.*

MANOVA testing did not yield significant results. Only when controlled for age, did a very small non-significant relationship in the predicted direction emerge (r = -.03, p > .05). The hypothesis was not supported.

    b. *Positive trait emotions will affect the cytokine response to respiratory viruses circulating within the community exhibited after receiving influenza vaccination.*

Reporting of influenza-like symptoms provided the outcome variable. There was only one cytokine level drawn while a participant was experiencing influenza-like symptoms, and no confirmatory influenza testing was performed. Results for reporting influenza-like illness are consistent with hypothesis 1 findings. Logistical regression did not support the hypothesis, though slopes were in the predicted direction of higher positive trait emotions predicting less influenza symptoms. Participants who reported influenza-like symptoms also reported significantly lower positive emotions on the calm subscale, t (53) = 2.07, p < .05. Chi-square testing for calm subscale scores and self

reporting of influenza- like symptoms yielded significant results, χ^2 (1) = 23.11, $p < .001$. The hypothesis was supported for reporting of trait positive emotions on the calm subscale of the PANAS.

c. *Higher positive emotions will result in lower levels of pro-inflammatory cytokines (as measured by IL-6 and IL-1β).*

Hierarchical regression analysis performed did not yield significant results. Calm trait subscale scores predicting log IL-1β levels approached significance with $p = .06$. Positive trait emotions on the Calm subscale of the PANAS were positively correlated with IL-6 at a level approaching significance. This near significant relationship is in contrast to findings reported by Prather et al., (2007) in which there was no relationship between IL-1β and mood, though Prather did not report on PANAS subscales. The sample size for the current study was inadequate for the analysis and number of covariates used.

Several findings relating to cytokine measurement emerged, relevant to evaluating an immune response within a PNI framework. IL-6 was highly correlated with age (N = 38, r = .6, p (one-tailed) < .01. There was a negative relationship between IL-6 and Total Activity scores (N = 38, r = -.44, p (one-tailed) < .01. Participants who reported influenza-like symptoms had lower levels of IL-6 identified at study enrollment, and this was attributed to the lower age of these symptom reporters. There was no correlation between IL-6 and IL-1β levels for individual participants, IL-6 and IL-1β levels were independent of each other. There was no difference between IL-6 and IL-1β levels detected prior to influenza vaccination and 2 week post vaccination.

A number of relationships between trait positive emotion scores and other study variables emerged. Positive emotion scores were highly correlated with age, $N = 76$, $r = .21$, p (one tailed) $< .05$ and negatively with Global Sleep Scores on the PSQI, $N = 75$, $r = -.25$, p (one tailed) $< .05$. A negative relationship was demonstrated between positive trait emotion scores and scores on the Perceived Stress Scale, $N = 73$, $r = -.54$, p (one tailed) $< .01$. The relationship between positive emotion scores and Ego Resiliency Scale scores, $N = 74$, $r = .49$, p (one tailed) $< .01$, supported the broaden-and-build theory of positive emotions (Fredrickson, 2004). When negative and positive trait emotion scores were converted to a ratio, there was a significant relationship between this ratio and perceived stress scale scores after controlling for age, F (20,50) = 1.96, $p = .05$, consistent with the Dynamic Model of Affect (Zautra et al., 2005). Scores for Ego Resiliency Scale and Total Activity demonstrated a medium positive relationship, $N = 75$, $r = .29$, p (one tailed) $< .01$. Scores on the Ego Resiliency Scale and the Perceived Stress scale were inversely related, $N = 74$, $r = -.29$, p (one tailed) $< .01$. Age and scores on the Perceived Stress Scale demonstrated a significant negative relationship, $N = 73$, $r = -.36$, p (one tailed) $< .01$, as did age and Total Activity scores, $N = 75$, $r = -.73$, p (one tailed) $< .01$. IL-6 and age had a large positive relationship, $N = 38$, $r = .6$, p (one tailed) $< .01$, while an large inverse relationship was demonstrated between IL-6 and Total Activity scores, $N = 37$, $r = -.44$, p (one tailed) $< .01$.

Odds ratios indicated married individuals were more likely to have lower positive emotions χ^2 (1, 40) = 6.82, $p < .05$, odds ratio = 0.50, but happiness within marriage was not measured. Odds ratios indicated individuals who were widowed were more likely to

have higher positive emotions, χ^2 (1, 24) = 4.90, p < .05,odds ratio = 1.67, but this relationship was no longer significant after controlling for age. Positive emotions increased for individuals who were retired χ^2 (1, 38) = 8.54, p < .005, odds ratio = 1.67, even after controlling for age.

There was a large positive relationship between IL-6 and age, N = 38, r = .6, p (one tailed) < .01, and a negative relationship between IL-6 and Total Activity scores, N = 37, r = -.44, p (one tailed) < .01. Odds ratios indicated individuals educated at the college graduate level and above were likely to have lower IL-6 levels, χ^2 (1, 37, = 3.89, p < .05,odds ratio = 0.6. Retired individuals were more likely to have higher IL-6 levels χ^2 (1, 38, = 4.55, p < .05, odds ratio = 2.17.

Positive Emotions, Cytokines, and Activity

A large significant negative relationship was demonstrated between age and Total Activity scores (r = -.73, p < .01), indicating that older participants had lower physical activity scores. A small inverse relationship between higher levels of activity and positive trait emotion scores reported by all participants on the Physical Activity Survey (N = 75, r = -.12, p > .05), was significantly higher for the comparison group recruited from a medical center-affiliated fitness center, t (73) = 2.945, p (two tailed) < .01, and there was a large significant inverse relationship between physical activity level and positive emotions for this group, N = 23, r = -.683, p < .01. When Total Activity Scores were divided into tertiles, MANOVA testing identified significant relationships between highest and lowest activity scores, and the independent study variable of positive emotions, F (2,32) = 3.96, p <.05, as well as the dependant study variable of IL-6 levels,

F (2,32) = 3.38, p <.05, underscoring the important role of activity in the relationships between variables in this study.

Post hoc Mediator Analysis for Positive Emotion Scores

A post hoc analysis for positive trait emotion scores mediating the relationship between Ego Resiliency and Perceived Stress Scale scores was significant, *Sobel* = 3.28, (*SE* = .09), *p* = .001. This mediator role offered a possible explanation as to "how" ego resiliency scores may decrease perceived stress scores, which is via positive trait emotions. Positive trait emotions may contribute to decreasing perceived stress directly, as well as indirectly via increased ego resiliency. Based on this model, an effect of resiliency is to access positive emotions that in turn reduce stress. This lends support to the role of positive trait emotions in coping with stress and building ego resiliency. Consistent with the broaden-and-build theory, positive emotions build resiliency. Individuals possessing greater ego resiliency mobilize positive emotions in response to stressful situations which decrease stress perception. This is a reiterative process with ever growing levels of ego resiliency and utilization of positive emotions to lower perceptions of stress.

The complexity of the relationships demonstrated, and the multi-purpose dimensions of several variables invite investigation of factors such as positive emotions, activity, sleep, and cytokines as mediators in immune response to influenza and other infections. Age, and possibly activity, should be examined as potential moderators between the previously identified variables. The sample size for this study was too small

to allow this type of analysis, but replication with a larger sample size would make it possible.

Additional research is needed to further identify the relationship, role and mechanism of positive emotions in improving health. Larger sample sizes were clearly needed to more thoroughly explore complex relationships such as those demonstrated between positive emotions, age, activity, cytokine levels, and disease reporting for older adults in this study. Exploration of these relationships in a more diverse population, with wider education and economic representation is also indicated. While replication of the study on a larger, more diverse sample provides an avenue for additional research, isolating one or more of the significant variables identified and exploring their role in immune response is an alternative.

Examining the role of positive emotions in immune response to seasonal influenza for older adults in real life settings provided the opportunity to more fully explore these complex interrelationships. Such findings have applicability to nursing's role in advising clients on health promotions strategies. These findings provide important insight into the ongoing and multiple interactions across physiological and psychological systems which may contribute to identifying those factors which make successful aging more likely.

APPENDIX A:

CONTENT OF STUDY FLIERS, ANNOUNCEMENTS, AND INSTRUCTIONS

Study Announcement

Working with professors and researchers from Loyola University's School of Nursing, I am conducting research on

Positive Emotions and Response to Influenza

If you are over 65 years of age and will receive influenza vaccination this year, you may be eligible.

Study participants will:

- Complete a number of questionnaires on health and emotions.

- Receive information on influenza like illness, asked to watch themselves for signs and symptoms and contact the researcher if they develop signs and symptoms.

Some participants will have a tube of blood drawn, and temperatures taken at three different times between October 2010 and March 2011.

Please contact me if you are interested in participating in this study.

Maryann Gierloff, RN, MS
Phone: (847) 934-1211

Study Announcement

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Some participants will have a tube of blood drawn and have their temperatures taken at three different times between October 2010 and March 2011.

A meeting will be held on_____at_____

Location_____

Please come to the meeting or contact me if you are interested in participating in this study.

Maryann Gierloff, RN, MS
Phone: (847) 934-1211)

Positive Emotions and Influenza Study Participant Instructions

Thank you for agreeing to take part in this study of positive emotions and influenza.

These are instructions for the three stages of the study. Packets for each stage of the study are printed on different colored paper. The researcher will contact you via e-mail or telephone, every one or two months over the course of the study, to remind you which stage of the study is occurring and what forms should be completed.

STAGE ONE – Before receiving influenza vaccination:

1. Complete the consent and study enrollment forms and return them to the researcher.

2. Complete additional forms (yellow pages labeled Stage One Forms) and mail them to the researcher in the postage paid envelope within the next week.

3. The researcher will contact some study participants to have blood drawn. One tube of blood will be drawn and this will be done at a time and location that is convenient for you. Your temperature will be also taken via the ear at this time.

STAGE TWO – Immediately after receiving influenza vaccination through your health care provider or from a Flu shot clinic:

1. Record the date of vaccination on the Stage Two Packet (pink pages).

2. Beginning the evening of your influenza vaccination, complete a PANAS form describing emotions you felt that day. You will complete PANAS forms for 14 days.

3. At the end of two weeks, complete the remaining forms in the Stage two package and mail all Stage Two materials to the researcher in the envelope provided.

4. The researcher will again contact participants who had blood drawn during Stage One. Another tube of blood will be drawn, approximately two weeks after influenza vaccination for these study participants. Temperatures will also be measured.

STAGE THREE – The remainder of the Influenza season: October through March 31:

1. Monitor yourself for signs and symptoms of influenza, using the Influenza Monitoring Form.

2. Contact the researcher (847-934-1211) if you have any of the signs and symptoms of influenza. Please call within 1-4 days of when you first experience symptoms.

3. If you previously had blood drawn, the researcher will once again arrange to have a tube of blood drawn within 3-5 days of the onset of your signs and symptoms.

APPENDIX B:

LOYOLA UNIVERSITY MEDICAL CENTER INFORMED CONSENT

LOYOLA UNIVERSITY MEDICAL CENTER
MAYWOOD, ILLINOIS
NEIHOFF SCHOOL OF NURSING
STRITCH SCHOOL OF MEDICINE

INFORMED CONSENT
(a copy of consent must be inserted in participant's file)

Participant's Name:_____

Project Title: Positive Emotions and immune response to influenza in medically stable elderly adults

The project will undergo rereview on or before_____

Patient Information

Principles Concerning Research: You are being asked to take part in a research project. It is important that you read and understand the principles that apply to all individuals who agree to participate in the research project described below:

1. Taking part in the research is entirely voluntary.

2. We do not know if you will personally benefit from taking part in the research but the knowledge obtained may help others.

3. You may withdraw from the study at any time without anyone objecting and without penalty or loss of any benefits to which you are otherwise entitled.

4. If during your participation in the research project, new information becomes available which would affect your being in the research project (such as better treatments or the side effects of the treatments), your doctor will discuss this new information with you and will help you make a decision about your continuing in the research.

The purpose of the research and how it is to be done and what your part in the research will be is described below. Also described are the risks, inconveniences, discomforts and other important information which you need to make a decision about whether or not you wish to participate. You are urged to discuss any question you have about this research with the staff members.

PURPOSE OF THE STUDY: Positive emotions have been shown to have a positive impact on health. The purpose of this study is to investigate how positive emotions affect

your body's immune response to influenza vaccination, as well as the possible development of influenza like illness during influenza season.

The primary aim of the study is to measure positive emotions, immune system regulators called cytokines, and the possible development of signs and symptoms of influenza like illness.

We will be asking 120 people to participate in this study. The information obtained from this study will be used to better understand how positive emotions affect immune responses to influenza vaccination and influenza which may be circulating in the community during flu season.

DISCRIPTION AND EXPLANATION OF PROCEDURES: You will be asked to fill out several questionnaires at the start of the study. You may also be asked to have your temperature taken and have a 10 cc tube of blood drawn, soon after enrollment, again 2 weeks of receiving influenza vaccination, and a third time if you develop signs and symptoms consistent with Influenza like illness.

Regardless of whether your blood is drawn or not, after you receive your annual influenza vaccination, you will be asked to rate your emotions each evening for 2 weeks. You will be asked to fill out more questionnaires, two weeks after influenza vaccination, and to mail all forms to the researcher in postage paid, preaddressed envelopes.

You will be provided a list of signs and symptoms consistent with influenza like illness and you will be asked to contact the study researcher if you experience these signs and symptoms. You will be asked to watch for these signs and symptoms for the duration of the influenza season, which lasts until March 31, 2011.

RISKS AND DISCOMFORTS: There are minimal risks associated with the study, as you will be asked to complete a questionnaire. There should be minimal discomfort from the needle stick during the blood drawing procedures.

REPRODUCTIVE AND SEXUAL ACTIVITY INFORMATION: Since this research does not include any reproductive or sexual activity information, none will be obtained.

BENEFITS: You will be given a pen with the researcher's telephone number on it to remind you to call if you experience signs and symptoms of influenza. There is no other benefit from participating in the study. The results from this study will be used to generate more information to improve recovery from infections.

ALTERNATIVE TREATMENTS: You do not have to participate in this study if you do not want to. Your decision about participation will not affect your care in any way. If

you are an employee of Loyola University or Lutheran Home, your decision about participation will not affect your evaluations, or career, or career opportunities in any way.

FINANCIAL INFORMATION: You will not be charged for any components of this study including questionnaire scoring, blood drawing procedure, or laboratory testing.

RESEARCH RELATED INJURY: There are no risks of research related injuries from this study.

INFORMATION COLLECTED AND WHAT WILL HAPPEN TO IT:

In order to meet the goals of the research study (see Purpose of Research section of this consent), we will collect information on you, your test results and whether you experience influenza like illness. The information will be collected by Maryann Gierloff, RN, MS, data administrators, and secretaries. Information about you will be provided to Loyola University of Chicago, the research sponsor, its data collection and study verification agencies and/or government regulatory agencies such as the Food and Drug Administration. In this way we will learn about the role of positive emotions in response to influenza vaccination, and influenza circulating within the community.

The information we will collect and send includes:

___ DEMOGRAPHIC INFORMATION (E.G., NAME, ADDRESS, PHONE NUMBER, MARITAL STATUS, EDUCATION).

____A HEALTH ASSESSMENT SURVEY WHICH INCLUDES INFORMATION ON HEIGHT AND WEIGHT, SMOKING, DRINKING, HEALTH PROBLEMS, MEDICATIONS, HABITS, AND ACTIVITIES.

____QUESTIONAIRES ABOUT YOUR EMOTIONS

____A QUESTIONAIRE WHICH MEASURES YOUR ABILITY TO ADJUST TO LIFE EVENTS

____A QUESTIONAIRE TO REPORT THE QUALTIY OF YOUR SLEEP

____A QUESTIONAIRE TO REPORT YOUR LEVEL OF STRESS

___BLOOD SAMPLES TO MEASURE CYTOKINE LEVELS FOR 80 PARTICIPANTS.

We will collect and provide this information about you at the time of your enrollment in the study, two weeks after influenza vaccination, and within 3-5 days of development of any signs and symptoms of influenza.

Once the information is disclosed outside of LUMC, it may no longer be protected by federal privacy laws.

It is possible that the sponsor of the study, research nurses, its data collection and/or study verification agencies, data administrators of staff of the Food and Drug Administration will come to LUMC and view the research records (see above for description of content). They may take notes or copy pages of the research records. This is done to verify the accuracy of the information LUMC is sending to them.

The results of this research study may be published in a journal for the purpose of advancing medical knowledge. You will not be identified by name or by any other identifying information in any publication or report about this research.

Consent for LUMC to use and disclose your medical information is required in order for you to participate in the study.

Withdrawal of Consent: Your consent to use and disclose your medical information for the purpose of this research study is completely voluntary. You can withdraw your consent for LUMC to use and disclose your information and your consent to participate in this study at any time without affecting your ability to receive care and treatment at Lutheran Home or Loyola University Medical center unrelated to the research study. Withdrawal means that all study procedures and follow-up will stop and we will not send any more information about you to the sponsor of this research or is designees. However, information already used and disclosed to the research sponsor prior to the time of your withdrawal from this study may continue to be used and disclosed by LUMC and the sponsor.

If you withdraw from the study we will ask that you sign the form attached to this consent and sent it to Maryann Gierloff, RN, MS, or give it to the study staff. Your withdrawal from the study will not have any effect on any actions by LUMC taken before the attached form is received by LUMC.

Your study investigator, the Institutional Review Board, the regulatory authorities or the study sponsor may terminate the study at any time with or without your consent.

CONSENT

I have fully explained to _____ the nature and purpose of the above described procedure and the risks that are involved in its performance. I have answered and will answer all questions to the best of my ability. I may be reached at _____

_____ _____
(Signature) Date

Maryann Gierloff, RN, MS, who is the principal investigator for this study, or her associates will be available to answer any questions you may have. Maryann Gierloff can be reached at 847-934-1211.

If you ever feel that you have been injured by participating in this study, or if you have any questions concerning your right as a research participant, you may contact Dr. Kennth Micetich, Chairman, Institutional Review board for the Protection of Human Subjects – Loyola Medical Center (708-216-4608).

Although you have the right to revoke this authorization except that such revocation will not apply to any uses and disclosures of your information that are described in the Loyola University Health System Notice of Privacy Practices or otherwise allowable under any Federal or State laws.

You will receive a signed copy of this informed consent document.

You have been fully informed of the above-described research program with its possible benefits and risks. Your signature below indicates that you are willing to participate in this research study and agree to the use and disclosure of information about you as describe above. You do not give up any of your legal rights by signing this consent document.

_____ Date: _____
(Signature: Patient/Legal Representative

_____Date: _____
(Signature: Witness)

REVOCATION OF AUTHORIZATION TO RELEASE PROTECTED HEALTH INFORMATION (PHI)

I, _____, hereby revoke my consent to participate in the Positive Emotions and Influenza study in conjunction with Loyola University Medical Center ("LUMC"). I also revoke my consent to release information I provided to LUMC that allowed LUMC to use and disclose my medical information to any sponsor as outlined on the consent form, which I signed on _____(insert date). I understand that this revocation does not apply to any action LUMC has taken reliance on the consent I signed earlier.

_____ _____

Patient Name or Personal Representative Date

Please return this form to:

Maryann Gierloff, RN, MS
1783 Kitson Circle
Inverness, Illinois 60067

Phone 847-935-1211

APPENDIX C:

DATA COLLECTION TOOLS

ID#_____

Demographic Information Form

Date of Birth _____/_____/_____
Month/day/year

1. **Name**_____

2. **Address**_____

3. **Phone Number**_____**Cell Phone**_____

4. **E-Mail**_____
You may be contacted by the study researcher once every month or two over the course of this study. How would you prefer to be contacted?_____

5. **Race/Ethnic Group**:

_____White
_____African American
_____Hispanic/Latina
_____Asian
_____American Indian/Alaska Native
_____Native Hawaiian or Other Pacific Islander
_____More Than One Race
_____Other

6. **Marital Status**: _____Single
_____Married
_____Divorced/Separated
_____Widowed

7. **Living Situation:** _____Lives Alone
_____Lives with Spouse
_____Lives with Roomate

8. **Independent or Assisted Living**
_____Independent
_____Assisted Living

9. **Education:** (Please circle the highest level of education completed in each category that applies to you)
Elementary/High School: 1 2 3 4 5 6 7 8 9 10 11 12
College: 1 2 3 4
Graduate School: 1 2 3 4 5 6 7 8
Vocational/Technical School: 1 2 3 4
Other (please specify)_____

10. **Current Employment:** (Please check all that apply to you)

_____Full time
_____Part time (Hours/week_____)
_____Employed and work at home
_____Homemaker
_____Unemployed
_____Student
_____Retired
_____Other

11. What is your usual occupation? _____

12. What is your total household income?

_____less than $9,999 _____$10,000to$19,000
_____$20,000 to $29,000 _____$30,000 to $39,000
_____$40,000 to $49,000 _____$50,000 or above

ID #_____

Health Assessment Survey

1. What is your current **weight**?_____pounds Current **height?____**feet**____**inches

2. Has your weight changed in the past month? ☐Yes ☐No
   ↓
   If YES
   Weight loss of ____pounds
   Weight gain of ____pounds

3. Do you currently smoke? ☐Yes ☐No

4. Have you recently stopped smoking? ☐Yes ☐No
   ↓
   If YES, when did you stop?____Month___Year

5. Do you drink alcoholic beverages? ☐Yes ☐No
   ↓
   If YES,
   How many alcoholic drinks do you have in a week **(including weekends)**?____
   (1 drink = 12 oz. Beer, 4 oz. wine, or 1 oz. hard liquor)
   How many **alcoholic drinks** did you have in the **last 3 days**? _____

6. Have you recently stopped drinking alcoholic beverages? □ Yes □ No
   ↓
   If YES, when did you stop?____Month_____Year

7. How many caffeinated beverages (coffee, tea, cola, Jolt, Mountain Dew) did you have in the last **3 days**?_____

8. In the past month, have you participated in any stress reduction program(s)?
   □ Yes □ No
   If YES, please describe the program_____

9. Please list all **current health problems**:

_____

_____

_____

12. Please list all **current prescription medications,** including hormones that you have taken in the last month. Please indicate the **time(s) taken** and the **dose(s)** for each medication. (**Use the back side of this form if needed**.)

Prescription Medication	**How many times per day?**	**Dosage**

13. Please list all **non-prescription medications,** including vitamins, minerals, enzymes, herbals, and naturopathic remedies as well as any other health-promoting supplements that you have taken in the last month**.** Please indicate the **time(s) taken** and the **dose(s)** for each substance listed: (**Use the back side of this form if needed**.)

Non Prescription Medications, such as Vitamins, Minerals, Supplements, Herbals	**How many times per day?**	**Dosage**

14. Have you experienced any of the following **symptoms or infections** in the past week? Please check all that apply:
□cold □flu □cough □wound □sore throat □tooth/gums infection

□ fever/chills □pneumonia □bladder/kidney infection □vaginal infection

□other_____

15. Have you been hospitalized within the last 30 days? □ Yes □ No

PHYSICAL ACTIVITY SURVEY

The following questions ask about the amount of physical activity you engage in. Questions refer to household and family care activities, occupational activities, daily routine activities, and activity related to sports and exercise.

SECTION I – HOUSEHOLD AND CAREGIVING ACTIVITIES

1. During the past month did you care for a child, family member, and/or significant other? □ No □ Yes
   If YES, please indicate the hours per week spent in caregiving _____hrs/week

2. During the past month how many hours per day do you spend preparing meals and/or cleaning up after meals? _____hrs/day

3. During the past month how many times have you done major cleaning, such as shampooing carpets, washing walls or windows, decorating or painting walls? _____times/month

4. During the past month how many times have you done routine cleaning, such as dusting, laundry, vacuuming, cleaning bathrooms, or changing linens? _____times/month

5. During the past month how many times have you gone grocery shopping and pushed a cart? _____times/month

6. During the past month how often have you done gardening or yard work, such as mowing the lawn, raking leaves, planting flowers? _____times/month

SECTION II- OCCUPATIONAL ACTIVITIES

7. Are you currently employed? □ No □ Yes
   If YES, what is your occupation?_____
   How many hours per week do you work? _____hrs/wk

IF you are currently working, how often do you do each of the following:

Activity	Never	Seldom	Sometimes	Often	Always
Sit					
Stand					
Walk					
Lift Heavy Loads					
Sweat from exertion					

SECTION III – ACTIVE LIVING HABITS – Consider the **past month** when you answer these questions.

9. How many minutes a day do you usually walk and/or bicycle to and from work, school or errands? ___minutes/day

10. How many hours per week do you watch television or sit at the computer at home? _____hours/week

11. How many times per week do you walk and/or bike for a stretch of at least 15 minutes at a time? _____times/wk

SECTION IV – PARTICIPATION IN SPORTS AND EXERCISE

12. In the past month how many times have you played sports or exercised?
____times/month ____hours of duration per session of sport or exercise

13. If you exercised in the past month, how many times did you "work up a sweat"? _____times/month

14. Name the sports or types of exercise you have engaged in during the past month.

_____

_____

15. How would you rate your level of physical activity over the past month?
___Same ___Slightly less ___Much less ___Slightly more ___Much more

16. In the past **3 days** how many times have you performed any activities that caused you to build up a sweat?_____

ID#_____ PANAS

Directions:

The table below lists a number of words that describe feelings and emotions. Read each item and then circle the appropriate number that best describes how you have felt **during the last day** (alternate wording for trait emotions: **how you generally feel**)

	Not at all accurate	**Somewhat accurate**	**Moderately accurate**	**Very Accurate**	**Extremely Accurate**
Lively	0	1	2	3	4
Full of Pep	0	1	2	3	4
Energetic	0	1	2	3	4
Happy	0	1	2	3	4
Pleased	0	1	2	3	4
Cheerful	0	1	2	3	4
At Ease	0	1	2	3	4
Calm	0	1	2	3	4
Relaxed	0	1	2	3	4
Sad	0	1	2	3	4
Depressed	0	1	2	3	4
Unhappy	0	1	2	3	4
On edge	0	1	2	3	4
Nervous	0	1	2	3	4
Tense	0	1	2	3	4
Hostile	0	1	2	3	4
Resentful	0	1	2	3	4
Angry	0	1	2	3	4

ID#_____

Ego-Resiliency Scale

Instructions: Please rate how strongly each statement applies to you by placing a check next to the appropriate number.

1. I am generous with my friends.
__1=does not apply__ 2=applies slightly__3=applies somewhat__4=applies very strongly

2. I quickly get over and recover from being startled.
__1=does not apply__ 2=applies slightly__3=applies somewhat__4=applies very strongly

3. I enjoy dealing with new and unusual situations.
__1=does not apply__ 2=applies slightly__3=applies somewhat__4=applies very strongly

4. I usually succeed in making a favorable impression on people.
__1=does not apply__ 2=applies slightly__3=applies somewhat__4=applies very strongly

5. I enjoy trying new foods I have never tasted before.
__1=does not apply__ 2=applies slightly__3=applies somewhat__4=applies very strongly

6. I am regarded as a very energetic person.
__1=does not apply__ 2=applies slightly__3=applies somewhat__4=applies very strongly

7. I like to take different paths to a familiar place.
__1=does not apply__ 2=applies slightly__3=applies somewhat__4=applies very strongly

8. I am more curious than most people.
__1=does not apply__ 2=applies slightly__3=applies somewhat__4=applies very strongly

9. Most of the people I meet are likable.
__1=does not apply__ 2=applies slightly__3=applies somewhat__4=applies very strongly

10. I usually think carefully about something before acting.
__1=does not apply__ 2=applies slightly__3=applies somewhat__4=applies very strongly

11. I like to do new and different things.
__1=does not apply__ 2=applies slightly__3=applies somewhat__4=applies very strongly

12. My daily life is full of things that keep me interested.
__1=does not apply__ 2=applies slightly__3=applies somewhat__4=applies very strongly

13. I would be willing to describe myself as a pretty "strong" personality.
__1=does not apply__ 2=applies slightly__3=applies somewhat__4=applies very strongly

14. I get over my anger at someone reasonably quickly.
__1=does not apply__ 2=applies slightly__3=applies somewhat__4=applies very strongly

ID#_____

PITTSBURGH SLEEP QUALITY INDEX (PSQI)

Instructions:

The following questions relate to your usual sleep habits during the past month ONLY. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

1. **During the past month, when have you usually gone to bed at night**?
   USUAL BED TIME_____

2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?
   NUMBER OF MINUTES_____

3. During the past month, when have you usually gotten up in the morning?
   USUAL GETTING UP TIME_____

4. During the past month, how many hours of *actual sleep* did you get at night? (This may be different than the number of hours you spend in bed.)
   HOURS OF SLEEP PER NIGHT_____

For each of the remaining questions, check the one best response. Please answer ***all*** questions.

5. During the past month, how often have you had trouble sleeping because you……..

(a) cannot get to sleep within 30 minutes

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

(b) Wake up in the middle of the night or early morning

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

(c) Have to get up to use the bathroom.

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

(d) Cannot breathe comfortably.

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

(e) Cough or snore loudly.

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

(f) Feel too cold.

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

(g) Feel too hot.

Not during the Past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

(h) Had bad dreams.

Not during the Past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

(i) Have pain.

Not during the Past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

(j) Other reason(s), please describe_____

_____

How often during the past month have you had trouble sleeping because of this?

Not during the Past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

6. During the past month, how would you rate your sleep quality overall?

Very good _____
Fairly good _____
Fairly bad _____
Very bad _____

7. During the past month, how often have you taken medicine (Prescribed or "over the counter") to help you sleep?

Not during the Past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

Not during the Past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

No problem at all _____
Only a very slight problem _____
Somewhat of a problem _____
A very big problem _____

10. Do you have a bed partner or share a room?

No bed partner or do not share a room _____
Partner/ flatmate in other room _____
Partner in same room, but not same bed _____
Partner in same bed _____

11. If you have a bed partner or share a room, ask him/her how often in the past month you have had……

(a) Loud snoring.

Not during the Less than Once or Three or more

Past month_____ once a week_____ twice a week_____ times a week_____

(b) Long pauses between breaths while asleep.

Not during the Less than Once or Three or more
Past month_____ once a week_____ twice a week_____ times a week_____

(c) Legs twitching or jerking while you sleep.

Not during the Less than Once or Three or more
Past month_____ once a week_____ twice a week_____ times a week_____

(d) Episodes of disorientation or confusion during sleep.

Not during the Less than Once or Three or more
Past month_____ once a week_____ twice a week_____ times a week_____

(e) **Other restlessness while you sleep: please describe_____**

_____

Not during the Less than Once or Three or more
Past month_____ once a week_____ twice a week_____ times a week_____

[Buysse DJ, Reynolds CF, Monk TH, Berman SR, DJ Kupfer (1989) The Pittsburgh Sleep Quality Index: A New Instrument for Psychiatric Practice and Research, **Psychiatry Research, 28**: 193-213].

ID#_____

Perceived Stress Scale

Instructions: The questions in this scale ask you about your feeling and thoughts during the last month. In each case, please indicate with a check how often you felt or thought a certain way.

1. In the last month, how often have you been upset because of something that happened unexpectedly?
___0=never ___1=almost never ___2=sometimes ___3=fairly often ___4=very often

2. In the last month, how often have you felt that you were unable to control the important things in your life?
___0=never ___1=almost never ___2=sometimes ___3=fairly often ___4=very often

3. In the last month, how often have you felt nervous and "stressed"?
___0=never ___1=almost never ___2=sometimes ___3=fairly often ___4=very often

4. In the last month, how often have you felt confident about your ability to handle your personal problems?
___0=never ___1=almost never ___2=sometimes ___3=fairly often ___4=very often

5. In the last month, how often have you felt that things were going your way?
___0=never ___1=almost never ___2=sometimes ___3=fairly often ___4=very often

6. In the last month, how often have you found that you could not cope with all the things that you had to do?
___0=never ___1=almost never ___2=sometimes ___3=fairly often ___4=very often

7. In the last month, how often have you been able to control irritations in your life?
___0=never ___1=almost never ___2=sometimes ___3=fairly often ___4=very often

8. In the last month, how often have you felt that you were on top of things?
___0=never ___1=almost never ___2=sometimes ___3=fairly often ___4=very often

9. In the last month, how often have you been angered because of things that were outside of your control?
___0=never ___1=almost never ___2=sometimes ___3=fairly often ___4=very often

10. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?
___0=never ___1=almost never ___2=sometimes ___3=fairly often ___4=very often

Reporting Symptoms of Influenza Like Illness

Dear Study Participant,

After you receive your influenza vaccination, and throughout the influenza season, please telephone the Study Researcher (847-934-1211) within 1-4 days if you experience an abrupt onset of any of the symptoms on the list below:

Report sudden unexpected beginning of any of the following symptoms:	**Date symptom first identified**
Cough	
Sore throat	
Nasal Congestion/Stuffy Nose	
Fatigue/Feeling Tired	
Body aches	
Headache	
Lethargy/Not wanting to do anything	
Feverishness/Feeling hot	
Oral temperature greater than 99.1° F	

Please monitor yourself for these symptoms for the duration of the influenza season, until March 31, 2011. When you call in to report symptoms, please provide your name, spelling your first and last name, and give your phone number.

Thank you.

Maryann Gierloff, RN, MS

Telephone: (847) 934-1211

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VITA

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