

Frailty, Inflammation, and Psychological Well-being in Older Adults

By

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Abstract

Background:

Frailty has been conceptualized as a state of enhanced vulnerability to the stressors older adults encounter in their daily lives, which results in an increased risk for poor health outcomes. Although estimating the prevalence of frailty has been complicated by the lack of a universally accepted measure of frailty, estimated prevalence rates have been approximately 6% of all those age 65 years and older, 18% of those age 75 to 84, and 36% of those age 85 and older, indicating the prevalence of frailty increases with age. Frail individuals are at increased risk for mortality, hospitalization, falls, worsening disability, nursing home admission, post-operative complications, and fractures compared to non-frail individuals. Overall, the literature suggests frail older adults are a vulnerable group of individuals whose poor health status is reflected in their physical health, physiological processes, and psychological health. However, these factors have been examined in relative isolation, which does not reflect the complex interplay of biopsychosocial factors involved in the health of older adults.

To address this complex interplay, a biopsychosocial approach to the study of frailty was undertaken. This study was guided by a framework that was a combination of Kang's Bio-Behavioral Conceptual Framework and Ryff's Theory of Psychological Well-being. According to Kang's Framework, health is affected by individual, environmental, behavioral, psychosocial, and biological domains, with the biological domain acting as a mediator of the relationship between each domain and the health outcome of interest. Ryff's Theory of Psychological Well-being states that well-being in older adults, comprised of both eudaimonic well-being and hedonic well-being, protects individuals from disease or disability by promoting more effective and efficient biological functioning, for instance, by preventing or dampening the inflammatory

response to stressors and impeding the development of chronic inflammation. Guided by Kang's Framework and Ryff's Theory, this study examined the relationships among frailty, inflammation, and psychological well-being in community-dwelling older adults. The specific aims were: (1) describe the biopsychosocial profiles of individuals classified as non-frail, pre-frail, and frail; (2) examine the influence of psychological well-being, sociodemographic, and health characteristics and changes in psychological well-being over time on frailty; and (3) examine the role of inflammatory proteins as mediators of the relationship between psychological well-being and frailty.

Methods:

A secondary data analysis was completed using data from 239 community-dwelling older adults who had participated in the National Survey of Midlife Development in the United States (MIDUS). MIDUS was a longitudinal study of patterns, predictors, and consequences of mid-life development on physical health, psychological well-being, and social responsibility in a nationally representative sample of community-dwelling adults between 25 and 74 years of age. Two waves of data collection have occurred, ten years apart. Data from participants who were 65 years of age or older at the time of the second wave of data collection (Time 2) and who had participated in the first wave of data collection (baseline) were used in this study. Frailty was measured at Time 2 based on Fried and colleagues' frailty phenotype measure. Fried's frailty measure is derived from a physiologic dysregulation theory of frailty which posits that chronic inflammation, with its degrading effects on bone and muscle mass, causes frailty, which can then be identified via five physical characteristics: unintentional weight loss, exhaustion, weakness, slowness, and low levels of physical activity. It is one of the most widely used measures in the frailty literature and has shown predictive validity in several studies. Inflammation was

measured with serum samples of inter-leukin-6 (IL-6) and C-reactive protein (CRP) at Time 2; two of the most commonly used inflammatory biomarkers in frailty and aging research.

Psychological well-being was measured at baseline and Time 2 using Ryff's Psychological Well-Being scale, which captures eudaimonic well-being, and scales measuring Positive Affect, Negative Affect, and Life Satisfaction, which capture hedonic well-being. Sociodemographic and health characteristics were measured at baseline and Time 2.

Results:

At baseline, the mean age of participants was 62.7 ($SD = 5.5$) years and ranged from 53 to 74 years. Women made up the majority of participants ($n = 130$, 54.4%). The majority of participants self-identified as Caucasian ($n = 225$, 94.1%), and the remaining participants identified themselves as African-American ($n = 6$, 2.5%), Other ($n = 3$, 1.3%), or chose not to respond or data regarding their race was missing ($n = 5$, 2.1%). The mean number of illnesses was 3.7 ($SD = 2.3$) and the mean number of medications was 0.9 ($SD = 1.1$). At Time 2, the mean age of participants was 71.8 ($SD = 5.4$) years and ranged from 65 to 84 years. The mean number of illnesses was 2.6 ($SD = 2.7$) and the mean number of medications was 1.6 ($SD = 1.4$).

At Time 2, 124 participants were classified as non-frail, 101 as pre-frail, and 11 as frail. Group comparisons on baseline sociodemographic and health variables revealed that frail participants were significantly older than non-frail and reported significantly more illnesses than pre-frail and non-frail participants. At Time 2 frail participants were significantly older than non-frail and reported poorer self-rated physical health than pre-frail and non-frail participants, and both pre-frail and frail participants reported significantly lower self-rated mental/emotional health than non-frail participants. Psychological well-being did not differ by group at baseline (controlling for age and number of illnesses) or Time 2 (controlling for age, perceived physical

health and perceived emotional health). Pre-frail and frail participants had significantly higher levels of CRP than non-frail participants, controlling for Time 2 group differences on sociodemographic and health variables (age, perceived physical health and perceived mental/emotional health) and use of anti-inflammatory medications (anti-hypertensives, anti-depressants, and corticosteroids).

Changes in psychological well-being over time were examined using repeated measures analysis of covariance, controlling for baseline group differences (age and number of illnesses). There was a significant increase in life satisfaction over time, but no significant group-by-time interactions. As a result of these findings, only baseline measures of Ryff's Psychological Well-being and affect were included in the subsequent analyses, while both baseline and Time 2 life satisfaction measures were included to capture change in that measure.

Two probit models, a eudaimonic model and hedonic model, were tested with frailty group as the dependent variable (i.e., non-frail, pre-frail, and frail). These models were unsuccessful due to non-convergence. A second approach was taken by utilizing the number of frailty characteristics (i.e., unintentional weight loss, exhaustion, weakness, slowness, and low levels of physical activity) as the dependent variable. Two zero-inflated Poisson regression models, a eudaimonic and hedonic model, were run given the large number of participants with zero frailty characteristics. These models examined the direct effects of psychological well-being, baseline age, baseline number of illness, and Time 2 inflammation on number of frailty characteristics. In addition, dummy-coded variables for sex, anti-depressives, corticosteroids, and anti-hypertensives were entered as covariates in the model to control for their effects on inflammation. Indirect effects between psychological well-being and frailty through inflammation were estimated to determine whether inflammation mediated these relationships.

In the eudaimonic model, the direct effects of baseline age, number of illnesses and eudaimonic well-being were not significant. The covariates for anti-hypertensives and corticosteroids were significant, indicating that taking anti-hypertensives was associated with more frailty characteristics and not taking corticosteroids was associated with having more frailty characteristics. The direct effects of inflammation on frailty characteristics were both significant, indicating higher levels of both IL-6 and CRP were associated with a higher number of frailty characteristics. The indirect effects of baseline eudaimonic well-being on number of frailty characteristics through IL-6 and CRP were not significant.

In the hedonic model, the direct effects of baseline age, number of illnesses, positive affect, negative affect, and life satisfaction, and Time 2 life satisfaction on number of frailty criteria were not significant. The covariates, anti-hypertensives and corticosteroids, were again significant. The direct effects of inflammation on frailty characteristics were both significant with higher levels of IL-6 and CRP being associated with a higher number of frailty characteristics. The indirect effects of the hedonic well-being variables on number of frailty characteristics through IL-6 and CRP were not significant.

Conclusions and Implications:

This study has contributed to the science of frailty in several ways. First, the relationship between psychological well-being and frailty has been examined in only a handful of previous studies. The examination of the biological mechanism underlying this relationship has not been examined in any study. Although evidence for the mediating role of inflammation between psychological well-being and frailty was not observed, future studies with larger samples of frail individuals are indicated. The fact that, regardless of frailty status, these older individuals reported high levels of both eudaimonic and hedonic well-being over 10 years is noteworthy.

Such findings suggest psychological well-being was either stable or resilient when faced with physical health challenges such as frailty. Second, while the frailty groups differed in terms of age and number of illnesses at baseline as expected, the group differences at Time 2 were related to perceptions of health rather than objective health measures such as number of illnesses or medications. Such findings suggest that perceptions of health among the frailty groups may be a fruitful area for further investigations. Future studies should examine how psychological well-being fluctuates over time and in relation to adverse events as well as how perceptions of health are related to well-being and inflammation. In addition, future work should examine strategies that promote and maintain psychological well-being and consider how those strategies may be incorporated into the care of frail older adults.

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Chapter One: Introduction

Frailty in old age has been conceptualized as a state of enhanced vulnerability to the stressors older adults encounter in their daily lives, which results in an increased risk for poor health outcomes (Buchner & Wager, 1992; Fried et al., 2001; Rockwood et al., 1994). When health outcomes are compared between the frail and non-frail, frail older adults are at significantly greater risk for worsening disability, falls, fractures, hospitalizations, post-operative complications, nursing home admission, and early mortality (Davis, Rockwood, Mitnitski, & Rockwood, 2011; Ensrud et al., 2007; Fried et al., 2001; Gallucci, Ongaro, Amici, & Regini, 2009; Garonzik-Wang et al., 2012; Graham et al., 2009; Klein, Klein, Knudtson, & Lee, 2005; Leung, Tsai, & Sands, 2011; Makary et al., 2010). Although estimating the prevalence of frailty has been complicated by the lack of a universally accepted measure of frailty, estimated prevalence rates have been approximately 6% of all individuals 65 year of age or older, 18% of individuals age 75 to 84, and 36 % of individuals age 85 and older (Fried et al., 2001; Rockwood et al., 2004). This trend indicates that the prevalence of frailty increases with age.

Frailty has also been associated with certain sociodemographic and health characteristics. Frail individuals are likely to be older, female, a racial/ethnic minority, and have lower levels of income and education (Alvarado, Zunzunequi, Béland, & Bamvita, 2007; Ávila-Funes et al., 2008; Cawthon et al., 2007; Cesari et al., 2006; Chen, Wu, Chen, & Lue, 2010; Espinoza, Jung, Hazuda, 2010; Szanton, Seplaki, Thorpe, Allen, & Fried, 2010). Multiple indicators of poor physical health status have been observed in frail older adults, including higher levels of morbidity and disability (Ensrud et al., 2009; Fried et al., 2001; Strawbridge, Shema, Balfour, Higby, & Kaplan, 1998; Woods et al., 2005). It has been proposed that poor physical health is the result of chronic inflammation. Frail older adults have been shown to have significantly

higher levels of inflammatory biomarkers such as inter-leukin 6 (IL-6) and C-reactive protein (CRP) when compared to non-frail older adults (Boxer, Dauser, Walsh, Hager, & Kenny, 2008; Leng, Xue, Tian, Walston, & Fried, 2007; Leng et al., 2011; Qu, Yang, Walston, Fedarko, Leng, 2009; Schmaltz et al., 2005; Walston et al., 2002).

In addition to poor physical health, frail older adults also appear to experience poor psychological health. Depression, anxiety, and elevated levels of negative affect have been associated with frailty (Barzilay et al., 2007; Chen et al., 2010; Ottenbacher et al., 2009). Frail older adults have exhibited lower levels of positive affect, health-related quality of life, life satisfaction, and psychological well-being when compared to non-frail older adults (Andrew, Fisk, & Rockwood, 2012; Bilotta et al., 2011; Frieswijk, Buunk, Steverink, & Slaets, 2004; Kirby, Coleman, & Daley, 2004; Masel, Graham, Reistetter, Markides, & Ottenbacher, 2011). Overall, the literature suggests frail older adults are a vulnerable group of individuals whose poor health status is reflected in their physical health, physiological processes, and psychological health. However, these characteristics have been examined in relative isolation, which does not reflect the complex interplay of biopsychosocial factors involved in the health of older adults.

Kang's Biobehavioral Conceptual Framework and Ryff's Theory of Psychological Well-Being (PWB) together provide a guide for examining the relationships among frailty, inflammation, and psychological well-being in older adults (Kang, Rice, Park, Turner-Henson, & Downs, 2010; Ryff, 1982, 1989). According to Kang's Framework, health is affected by factors within individual, environmental, behavioral, psychosocial, and biological domains. The biological domain acts as a mediator between the other domains and health. Ryff's Theory of Psychological Well-Being states that well-being in older adults is comprised of both eudaimonic well-being (autonomy, environmental mastery, purpose in life, positive relationship with others,

personal growth, and self-acceptance) and hedonic well-being (positive affect, negative affect, and life satisfaction). High levels of both types of well-being protect individuals from disease or disability by their effect on biological functioning. High levels of psychological well-being are purported to promote more effective and efficient biological functioning through a variety of ways including preventing or dampening the inflammatory response to stressors, which may impede the development of chronic inflammation over a period of time (Ryff et al., 2004).

Guided by Kang's Framework and Ryff's Theory, it was hypothesized that frail individuals would have different (more negative) biopsychosocial profiles than non-frail individuals. It was further hypothesized that psychological well-being would predict frailty over time, but that inflammatory processes would mediate the relationships between psychological well-being and frailty. To test these hypotheses, a secondary analysis of longitudinal data from 239 older adults (≥ 65 years of age) was completed. The specific aims were:

1. Describe the biopsychosocial profiles of individuals classified as non-frail, pre-frail, and frail.
2. Examine the influence of psychological well-being, sociodemographic, and health characteristics and changes in psychological well-being over time on frailty.
3. Examine the role of inflammatory biomarkers as mediators of the relationship between psychological well-being and frailty.

Chapter Two: Review of the Literature

In this chapter, the empirical literature on the relationship between frailty and sociodemographic characteristics, physical health and health outcomes, inflammation, and psychological health, will be reviewed and critiqued. Kang's Bio-Behavioral Conceptual Framework and Ryff's Theory of Psychological Well-Being will also be discussed as a way to conceptualize the relationships among frailty, inflammation, and psychological well-being in older adults.

Frailty in Older Adults

Over the past 20 years, researchers and clinicians have proposed several theories of frailty (Buchner & Wagner, 1992; Campbell & Buchner, 1997; Fried et al., 2001; Hamerman, 1999; Rockwood, Fox, Stolee, Robertson, & Beattie, 1994). These theories share a general conceptualization of frailty as a state of enhanced vulnerability to adverse health outcomes such as hospitalizations, falls, and infections. Beyond this general conceptualization, however, theories differ regarding causes and characteristics of frailty. Walston and Fried (1999) proposed physiologic dysregulations cause frailty by depleting an older adult's physiologic reserves, rendering the older adult unable to prevent or recover from stressors, such as a fall or an infection. According to this theory, physical vulnerabilities (specifically, unintentional weight loss, exhaustion, weakness, slow gait speed, and low physical activity levels) constitute frailty. Rockwood and colleagues (1994) proposed "deficits" in physical, psychological, and social domains (e.g., chronic disease, social isolation) cause frailty by out-numbering and overwhelming "assets" (e.g., high level of physical function, access to resources) that allow older adults to maintain independence in the community. According to this theory, not only do physical deficits constitute frailty, but social (e.g., living alone, never married) and psychological

(e.g., depression) deficits constitute frailty, as well (Rockwood, Andrew, & Mitnitski, 2007; Rockwood & Mitnitski, 2007). Several other theories have been proposed, and most are similar to either Walston and Fried's theory, with a focus on biological mechanisms, or Rockwood's theory, with a focus on deficits in the physical, social, and psychological domains (Buchner & Wagner, 1992; Gobbens, van Assen, Luijkx, Wijnen-Sponselee, & Schols, 2010; Raphael et al., 1995).

The lack of a guiding theory (and corresponding measure) of frailty has complicated attempts to advance the science. For example, some approaches include chronic conditions and difficulty with activities of daily living as characteristics of frailty itself, whereas others consider these to be correlates or causes of frailty (Fried et al., 2001; Gobbens, van Assen, Luijkx, Wijnen-Sponselee, & Schols, 2010; Rockwood et al., 1999; Song et al., 2010). The studies reviewed below used the second approach, meaning the variables examined were not included as part of the measure used to identify individuals as frail but were conceptualized as causes or correlates of frailty.

Frailty and Sociodemographic Characteristics

To better understand who is more likely to be frail among older adults, sociodemographic characteristics, specifically age, gender, race, ethnicity, and socioeconomic status, have been examined. Age has shown a consistent relationship to frailty; the older an individual, the more likely he or she is frail. Cross-sectional studies of large, nationally representative samples (N=923 to 8,100) in the United States (U.S.), Canada, Italy, France, Latin America, and Taiwan have found frail participants to be significantly older than non-frail participants (Alvarado et al., 2007; Ávila-Funes et al., 2008; Cawthon et al., 2007; Cesari et al., 2006; Chen et al., 2010; Ensrud et al., 2009; Fried et al., 2001; Rockwood et al., 2004; Song, Mitnitski, & Rockwood,

2010). Prospective cohort studies of large, national representative samples (N=1,152 to 40,657) in the U.S., Canada, and the Netherlands have reported an increase in the incidence of frailty as the sample ages (Gill, Gahbauer, Han, & Allore, 2011; Ostir, Ottenbacher, & Markides, 2004; Rockwood, Song, & Mitnitski, 2011; Woods et al., 2005; Puts, Visser, Twisk, Deeg, & Lips, 2005). These findings suggest a possible causal role for age in the development of frailty. However, not all participants became frail with age, indicating that other factors may influence the development of frailty.

In many of these studies, frailty and gender were also found to be related. In large cross-sectional studies in the U.S., Italy, France, and Latin America, women were more likely to be classified as frail than men (Alvarado et al., 2008; Ávila-Funes et al., 2008; Chen et al., 2010; Fried et al., 2001; Mitnitski et al., 2005; Song et al., 2010). In a longitudinal study of health and aging in Mexican Americans 65 years of age and older (N=1,558), women were 27% more likely than men to be considered frail at a seven-year follow-up assessment (Ostir et al., 2004). The reasons for this gender difference have not been examined extensively, but differences in physiologic processes, such as the hormonal changes accompanying menopause, or differences in health behaviors may play a role (Ershler & Keller, 2000). More longitudinal studies comparing the development and progression of frailty in men and women are needed to shed light on possible gender differences.

Frailty prevalence has been found to differ with regard to race, ethnicity, and socioeconomic status in cross-sectional studies. Hirsch and colleagues (2006) compared frailty prevalence rates between Caucasian (N=4,491) and African American (N=786) men and women across different age cohorts (i.e., 65 to 74 years of age, 75 to 85 years of age). In all cohorts, African Americans had significantly higher prevalence rates of frailty. In a sample of 5,993

community-dwelling men over 65 years of age, Cawthon and colleagues (2007) found a significantly higher proportion of African American (6.6%) and Asian American men (5.8%) were considered frail compared to Caucasian men (3.8%) and Hispanic men (2.4%), who had the lowest prevalence of frailty among these groups. In The San Antonio Longitudinal Study of Aging, Mexican American adults over the age of 65 (n=312) were more likely than European American adults over the age of 65 (n=285) to be frail at baseline, but this difference disappeared once income and a diagnosis of diabetes mellitus were entered as covariates (Espinoza et al., 2010). These findings contradict those from Cawthon and colleagues (2007) and suggest associations between race or ethnicity and frailty may be confounded with other sociodemographic characteristics, such as income, which may interact to increase one's risk for being considered frail.

Education and income have also been related to frailty. In a cross-sectional study of English men and women aged 65 and older (N=4,818), lower income and higher levels of neighborhood deprivation (i.e., low levels of employment, high crime rates) were significant predictors of frailty after controlling for age and gender (Lang et al., 2009). Another cross-sectional study of 727 women aged 65 and older from the Women's Health and Aging Study found lower levels of income and education were significant predictors of frailty, after controlling for race (Szanton et al., 2010). These studies provide preliminary evidence for increased risk for frailty among individuals with lower levels of education and income, but they do not explain how or why low levels of education and income are associated with frailty.

A major consideration when reviewing these studies on frailty is the possible confounded nature of the variables examined. For example, the association between gender and frailty could be confounded by age because, on average, women live longer than men and thus are more likely

to live long enough to become frail (Centers for Disease Control and Prevention, 2010). The relationship between frailty and race or ethnicity could be confounded by socioeconomic status. Some racial/ethnic groups are more likely to have lower levels of education and income, both of which are associated with fewer preventive health behaviors as well as less access to health services and resources (Hayward, Miles, Crimmins, & Yang, 2000; Pampel, Krueger, & Denny, 2010; U.S. Bureau of the Census, 2001). While many of the studies reviewed have controlled for possible confounding variables in analyses, such an approach limits understanding of possible causal roles these variables may play with regard to frailty. To better understand the relationships between sociodemographic characteristics and frailty, longitudinal studies in diverse samples are needed.

Frailty, Physical Health, and Health Outcomes

The research on the relationship between physical health and frailty has highlighted the discrepancies among theories regarding what characteristics constitute frailty. As mentioned previously, different theories include physical health characteristics such as, co-morbidities and disability, as characteristics defining frailty, whereas other theories propose these as correlates of frailty (Fried, Ferrucci, Darer, Williamson, & Anderson, 2004; Rockwood et al., 1999). In studies utilizing frailty measures that do *not* include number of chronic conditions or disability as characteristics that define frailty, frail individuals had significantly higher number of chronic conditions and higher levels of disability (i.e., difficulties with activities of daily living) than non-frail or individuals with lower frailty scores, depending on the frailty measure used (Ensrud et al., 2009; Fried et al., 2001; Strawbridge et al., 1998; Woods et al., 2005). The relationship between frailty and specific chronic conditions has received limited attention. However, Chang and colleagues (2011) observed a dose-response relationship between inflammatory diseases

(e.g., coronary artery disease, rheumatoid arthritis) and the risk of being classified as frail in a cross-sectional study of 620 community-dwelling women between 70 and 79 years of age.

Women with more inflammatory diseases were more likely to be considered frail. With the cross-sectional design of the study, it could not be determined whether inflammatory diseases caused frailty, but the findings suggested that inflammatory diseases might play a role in frailty, at least in women.

Self-rated health status, a measure of one's perception of their own health, has been found to be related to frailty in studies utilizing different frailty theories and measures. Individuals classified as frail have reported significantly lower self-rated health status than their non-frail counterparts or those with lower frailty scores, depending on the measure of frailty used (Ávila-Funes et al., 2008; Cawthorn et al., 2007; Ensrud et al., 2007; Ensrud et al., 2009; Fried et al., 2001; Ho, Williams, & Hardwick, 2002; Strawbridge et al., 1998; Woods et al., 2005). Findings from these cross-sectional studies indicate frail individuals are more likely to perceive their health as poor, but whether that perception contributes to the development or progression of frailty has not been clear. Only one study examined self-rated health longitudinally and found it to be one of several significant predictors, including age, race, and inflammation, of becoming frail over time (Barzilay et al., 2007).

Several studies have provided evidence for the increased risk of poor health outcomes in individuals who are frail. Analyses of longitudinal data from large prospective cohort studies such as the Canadian Study of Health and Aging (CSHA), the TRELONG Study (Italian), the Hispanic Established Populations for Epidemiologic Studies of the Elderly (PEESE), and others have found frail individuals experience earlier mortality than non-frail individuals, even after controlling co-morbidities and age (Davis et al., 2010; Gallucci, et al., 2009; Graham et al., 2009;

Klein et al., 2005). In the Study of Osteoporotic Fractures, an eight-year longitudinal study of community-dwelling women at least 65 years old, those classified as frail at baseline were more likely to experience falls, fractures, and earlier mortality than non-frail women (Ensrud et al., 2007). Four longitudinal studies of older adult patients undergoing surgery have found pre-operative classification as frail significantly increased the likelihood of experiencing post-operative complications, such as delirium, longer lengths of stay, discharge to skilled or assisted-living facility, and delayed graft function in kidney transplantations after controlling for age, gender, and co-morbidity status (Garonzik-Wang et al., 2012; Leung et al., 2011; Makary et al., 2010; Robinson, Daniel, Steigmann, & Moss, 2011). These studies provide support for the claim that frail individuals are a vulnerable group of older adults.

Frailty and Inflammation

One of the major theories of frailty posits that frailty is the result of the dysregulation of physiologic systems (Walston & Fried, 1999). The focus on physiologic dysregulation has resulted in research examining biomarkers in frail, older adults. These biomarkers provide information regarding which systems may be dysregulated and how the dysregulation of specific systems may lead to frail older adults' compromised physical health and increased vulnerability to experiencing poor health outcomes.

Of particular interest has been the examination of inflammation, which is thought to play a major role in aging processes. The research on inflammation and aging has been extensive, and reviews of both cross-sectional and longitudinal studies of older adults have shown a consistent relationship between aging and elevated levels of inflammatory biomarkers such as interleukin-6 (IL-6) and C-reactive protein (CRP) (Ershler & Keller, 2000; Franceschi et al., 2007). While results from these studies indicate an increase in inflammatory biomarkers in the majority of

older adults, the extent to which these biomarkers increase varies across individuals. The reasons for this inter-individual variability in inflammatory levels have not been entirely clarified, but higher inflammatory levels have been associated with low socioeconomic status, low levels of physical activity, and higher perceived stress in older adults (Colbert, et al., 2004; McDade, Lindau, & Wroblewski, 2010; Reuben, Judd-Hamilton, Harris, & Seeman, 2003).

The consequences of elevated inflammatory levels in older adults have also been studied extensively. Longitudinal studies have found older adults exhibiting higher inflammatory levels to be at much higher risk for disability and mortality as well as chronic diseases such as osteoporosis and coronary artery disease (Blake & Ridker, 2003; Cesari et al., 2003; Harris et al., 1999; Salanitro et al., 2012). Given the role of inflammation in the development of chronic diseases, disability, and mortality, it has been hypothesized that inflammation may also play a similar role in frailty (Ferrucci et al., 2002; Fulop et al., 2010; Walston, 2004).

To better understand the relationship between frailty and inflammation, specifically IL-6 and CRP, several cross-sectional studies have been conducted. These studies have, for the most part, utilized the Fried Frailty measure, which is derived from a physiologic dysregulation theory (Fried et al., 2001; Walston & Fried, 1999). The measure assesses individuals on five characteristics that are conceptualized as the physical manifestations of physiologic dysregulation: unintentional weight loss, exhaustion, weakness, slow gait speed, and low physical activity levels. Individuals are classified as non-frail if they exhibit none of these characteristics; pre-frail if they exhibit one or two; and frail if they exhibit three or more. Using this measure, cross-sectional studies of community-dwelling older adults have found those classified as frail to have significantly higher levels of IL-6 and CRP compared to non-frail individuals, even after adjusting for factors known to affect inflammation such as age, gender,

race, and chronic diseases (Boxer et al., 2008; Leng et al., 2002; Leng et al., 2007; Leng et al., 2011; Qu et al., 2009; Schmaltz et al., 2005; Walston et al., 2002). Sample sizes of these studies have ranged from very small (N=30) to very large (N=4,325), but results have been consistent. Cross-sectional studies utilizing different frailty measures, such as those based on physical function (e.g., timed get-up-and-go tests, self-reported difficulty with activities of daily living), or the Frailty Index, which calculates an individual's number of deficits (e.g., memory problems, living alone), have also found significantly higher levels of IL-6 and CRP in individuals classified as frail compared to individuals classified as non-frail (Hubbard, O'Mahony, Calver, & Woodhouse, 2009; Puts et al., 2005).

Given the cross-sectional design of these studies, it has not been possible to establish causality between frailty status and inflammation. Few longitudinal studies have examined the development and trajectory of frailty over time, and only one longitudinal study has examined the relationship between the development of frailty over time and inflammatory biomarkers. Barzilay and colleagues (2007) conducted a secondary data analysis of the Cardiovascular Health Study, a prospective cohort study of cardiovascular health in community-dwelling men and women 65 years of age and older. Longitudinal data from participants who at baseline were non-frail according to the Fried Frailty measure and who did *not* report congestive heart failure, diabetes, coronary heart disease, Parkinson disease, stroke, anti-depressant use, or a Mini-Mental State Examination score below 18 were analyzed to determine whether inflammation and/or insulin-resistance were associated with frailty classification at a nine-year follow-up assessment. Baseline characteristics found to be related to classification as pre-frail or frail nine years later were being older, female, African American, of lower socioeconomic status (i.e., low income), reporting lower self-rated health status, depressive symptoms, and higher levels of baseline IL-6,

CRP, and insulin resistance. Findings from this study suggested that inflammation, along with other biological, social, and psychological factors, play a role in the development of frailty.

Frailty and Psychological Health Characteristics

Although a large portion of the frailty literature has been dedicated to the study of physical health and physiological processes such as inflammation, psychological health in frail older adults has received more attention in recent years. A large body of research has provided evidence for relationships between numerous psychological characteristics such as psychological well-being and distress and health outcomes in older adults (Friedman & Ryff, 2012; Shankar, McMunn, Banks, & Steptoe, 2011; Steptoe, O'Donnell, Marmot, & Wardle, 2005). In general, higher levels of psychological distress are associated with poorer health in old age; while higher levels of psychological well-being are associated with better health in old age (Clarke & Currie, 2009; Wolitzky-Taylor, Castrioota, Lenze, Stanley, & Craske, 2010). Such findings have spurred an interest in examining how variables such as affect, anxiety, depression, psychological well-being, and life satisfaction or perceived quality of life may differ between non-frail and frail individuals.

Affect has been found to be significantly related to frailty, with negative affect increasing one's risk for being considered frail and positive affect decreasing one's risk (Ostir et al., 2004; Ottenbacher et al., 2009; Park-Lee, Fredman, Hochber, & Faulkner, 2009). In a longitudinal study of 1,558 initially non-frail Mexican American men and women 65 years of age and older, individuals with higher levels of positive affect at baseline were less likely to be classified as frail or pre-frail, according to the Fried Frailty measure, at the two, five, and seven year follow-up assessments (Ostir et al., 2004). In the same sample, Ottenbacher and colleagues (2009) found that individuals with higher negative affect levels at baseline were more likely to become frail at

a ten-year follow-up assessment. Park-Lee and colleagues (2009) found similar results regarding the protective role of positive affect in the development of frailty in a two-year long study of women over the age of 65 (N=954). Positive affect may have a protective role against the development of frailty, while negative affect may have a detrimental role. However, all three studies used items from the Center for Epidemiologic Studies Depression Scale (CES-D) to measure positive and negative affect as well as two items from the CES-D to classify individuals as frail. This approach may have inflated the relationships observed between affect and frailty, and raises questions as to whether such an association would be observed using more independent measures.

Frail individuals have also reported elevated levels of anxiety and depression. In a cross-sectional study of 112 community-dwelling older adults 65 years of age and older, participants were assigned frailty scores based on cognitive functioning, functional dependence, and medication use. Participants with higher frailty scores reported significantly higher levels of health anxiety, defined as concerns, fears, and preoccupations with one's physical health (Bourgault & Hadjistavropoulos, 2009). In three large, cross-sectional studies of community-dwelling older adults (N=548 to 2,238), individuals classified as frail according to the Fried Frailty measure reported higher depression and anxiety scores than non-frail individuals (Chang, et al., 2011; Chen et al., 2010; Ni Mhaolain et al., 2012). The association between frailty and depression appears consistent in cross-sectional studies. Depression has been predictive of frailty development in only one longitudinal study. Depressive symptoms, along with number of medications, a diagnosis of arthritis, and elevated inflammatory levels, were found to be a significant predictor of the development of frailty, as measured with the Fried Frailty measure, over a nine-year period in men and women over the age of 65 (Barzilay et al., 2007). However,

in these studies the CES-D was again used as part of the frailty measure and also as the measure of depressive symptoms, making the association between depressive symptoms and frailty unclear.

Other psychological factors examined in relation to frailty have included psychological well-being, life satisfaction, and health-related quality of life (HrQoL). In a cross-sectional survey study of 233 men and women living in retirement communities in the United Kingdom, participants were classified as frail if they reported difficulties with physical functioning (i.e., weakness in arms or legs), nutritive functioning (i.e., loss of appetite), cognitive functioning (i.e., difficulty paying attention), or sensory functioning (i.e., ability to read a newspaper, hearing over the phone) (Kirby, Coleman, & Daley, 2004). Frail individuals reported significantly lower levels of overall scores on Ryff's Psychological Well-Being Scale, which measures well-being in terms of self-acceptance, autonomy, positive relationships with others, environmental mastery, purpose in life and personal growth (Ryff, 1989). Andrew and colleagues (2012), observed a similar relationship in 5,703 Canadian men and women over the age of 70. Frailty was assessed using the Frailty Index, which is a sum of deficits (e.g., difficulties with activities of daily living, number of morbidities, and sensory problems). Higher levels of frailty (i.e., more deficits), were associated with lower overall scores on Ryff's Psychological Well-Being scale independent of age, gender, education, cognitive function, and depressive symptoms.

In a cross-sectional study study of 455 community-dwelling older adults in the Netherlands, frailty, as measured by problems in physical, cognitive, and psychosocial domains, was associated with lower levels of life satisfaction (Frieswijk, Buunk, Steverink, & Slaets, 2004). Health-related quality of life (HrQoL) was lower in frail older adults in cross-sectional studies in Japan, Italy, Taiwan, the Netherlands, and United States (Bilotta et al., 2011;

Kanauchi, Kubo, Kanauchi, & Saito, 2008; Lin et al., 2011; Masel, Graham, Reistetter, Markides, & Ottenbacher, 2011). A longitudinal study of 484 community dwelling adults age 75 years and older by Gobbens and colleagues (2012) found that frailty classification at baseline was a significant predictor of poorer HrQoL two years later. In these studies the measures of frailty were not consistent, but were similar in that they assessed individuals' problems with physical functioning (e.g., get up and go), social functioning (e.g., social isolation), and/or cognitive functioning (e.g., memory assessments). Overall, using different measures, frail older adults are consistently more likely to experience poorer psychological health than non-frail older adults.

In addition to the problems inherent in the utilization of different frailty measures, the studies on frailty and psychological health are limited in other ways. First, these studies have lacked clearly explicated theories or conceptual frameworks that include the mechanism or mechanisms by which psychological health and frailty are related. Second, the limited number of longitudinal studies inhibits the ability to examine the causal relationship between psychological health characteristics and frailty. While cross-sectional studies have shown frail older adults are more likely to have poor psychological health, whether poor psychological health contributes to the development of frailty is unclear.

Summary

The research on frailty is still in its early stages, but studies have shown consistent relationships between frailty and age, female gender, racial/ethnic minority status, lower socioeconomic status, poor physical health, poor health outcomes, high levels of inflammation, and poor psychological health. However, there are major limitations across the reviewed studies. First, the measures used to identify frailty have not been consistent across studies, making it

difficult to untangle the characteristics, correlates, and causes of frailty. Second, the small number of longitudinal studies has made establishing causality between these factors and frailty difficult. Third, these biopsychosocial factors (i.e., sociodemographic characteristics, physical health, inflammation, and psychological health) have been studied largely in isolation from each other, limiting the understanding of how the complex interplay of these factors are related to frailty. Fourth, studies examining the relationships between psychological characteristics and frailty have been largely atheoretical, limiting the ability to understand mechanisms that explain their relationships with frailty. Theoretically guided studies that take into account the complex interplay of sociodemographic, physical health, physiologic processes such as inflammation, and psychological health would deepen our understanding of frailty and identify targets for interventions aimed at preventing the development and/or progression of frailty.

Theoretical Framework

To address the lack of theoretically guided, multivariate studies of frailty, two models were used to develop the biopsychosocial approach utilized in this study. These two models were Kang's Bio-Behavioral Conceptual Framework and Ryff's Theory of Psychological Well-Being.

Kang's Bio-Behavioral Conceptual Framework

Kang and colleagues (2010) developed this bio-behavioral conceptual framework in response to the limited number of nurse researchers incorporating biological concepts into their studies of health outcomes. The authors argued that this framework enriched traditional psychosocial and behavioral nursing research studies by including biological mechanisms to explain how psychosocial and behavioral factors influence health. The model is shown in Figure 2.1 and consists of 6 inter-related domains: individual, environmental, behavioral, biological, psychosocial, and health outcomes. These domains were derived from three well-established

models utilized frequently in bio-behavioral research: Selye's (1974) physiological model of stress, Lazarus and Folkman's (1984) cognitive appraisal model of stress and coping, and McEwen's (1998, 2003) model of allostasis and allostatic load.

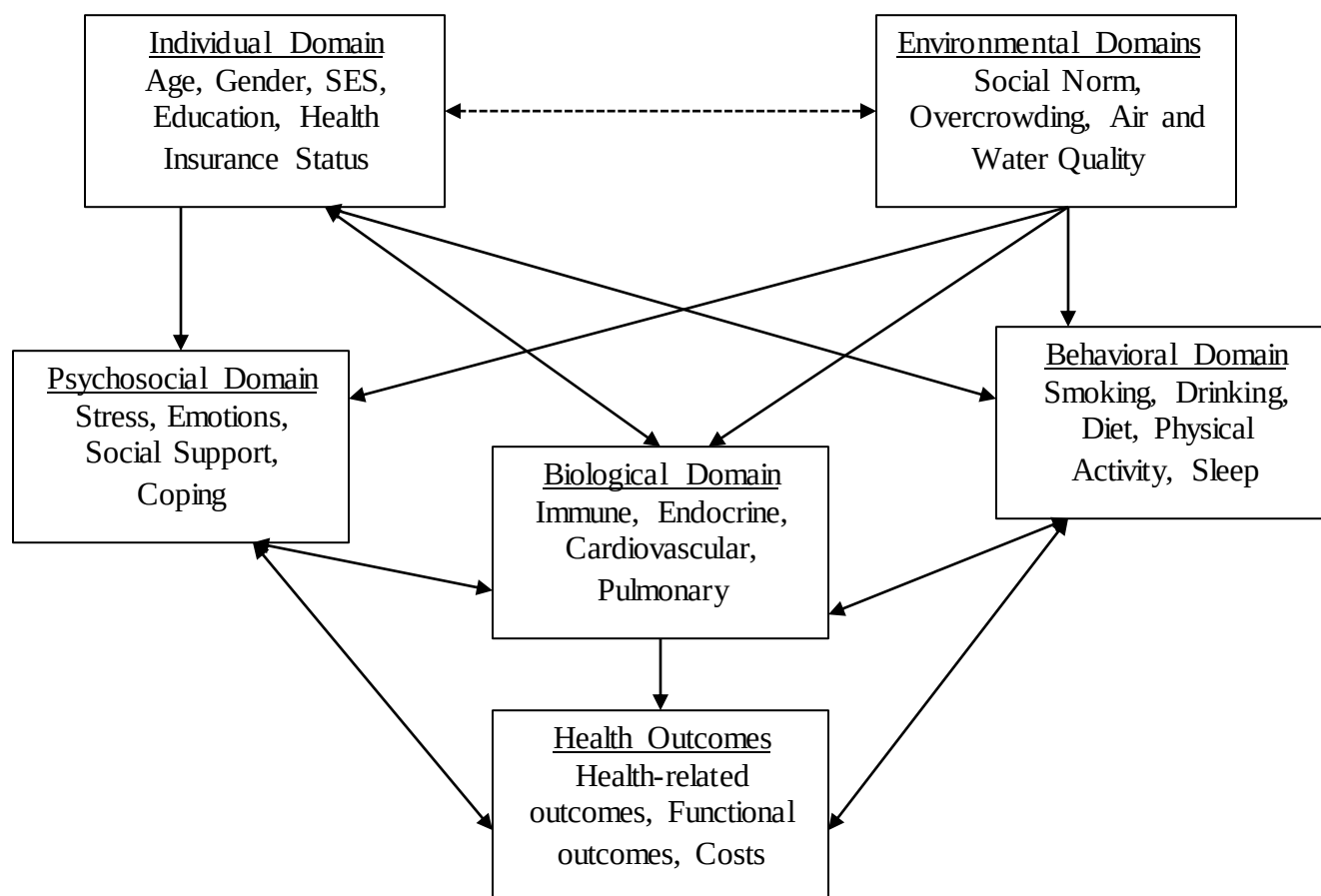


Figure 2.1 Kang's Bio-Behavioral Conceptual Framework

Bidirectional <----->
 Unidirectional ----->
 Correlated <====>

The individual domain consists of general sociodemographic characteristics as well as those that uniquely identify an individual such as his or her genetic make-up. The environmental domain consists of external factors that may influence health, such as pollution, and larger sociological factors, such as social norms and acculturation. The behavioral domain consists of activities individuals engage in that may affect their health, such as physical activity or smoking. The biological domain consists of biological markers of physiological systems such as IL-6 for the immune system and glycosylated hemoglobin for the endocrine system. The psychosocial domain consists of psychological factors including personality characteristics, perceptions of stress, and perceptions of social support. Finally, the health outcomes domain consists of the health outcome of interest, in the case of the current study, frailty in older adults.

These domains are related in different ways. The individual domain can influence the psychosocial domain; for example, lower socioeconomic status is associated with higher levels of chronic stress (Baum, Garofalo, & Yali, 1999). The environmental domain can influence the behavioral domain; for example, living in an unsafe neighborhood can limit one's ability to engage in outdoor physical activity. The individual and environmental domains are correlated; for example, individuals of lower socioeconomic status are more likely to live in areas of overcrowding or with poor air and water quality (Evans & Kantrowitz, 2002). Bi-directional relationships exist between the health outcome domain and the psychosocial and behavioral domains. For example, acute and chronic stress (psychosocial domain) and lack of physical activity (behavioral domain) are associated with increased risk for cardiovascular disease (Black & Garbutt, 2002). A diagnosis of cardiovascular disease may, in turn, increase stress (psychological domain) or may prompt behavioral changes such as engaging in more physical activity or improving eating habits (behavioral domain).

The biological domain plays a central role in this framework. The biological domain mediates the relationships between all other domains and health outcomes. Kang and colleagues (2010) illustrated this mediating role using the example of stress, inflammation, and atherosclerotic disease. Atherosclerotic disease is caused by the accumulation of lipids and other materials along the arterial wall. This accumulation stimulates a chronic inflammatory response in the arterial walls, which can be detected through elevated inflammatory markers such as CRP and IL-6. Acute stress activates the hypothalamic-pituitary-adrenal axis, leading to damage of the arterial wall and a subsequent elevation in inflammation in response to that damage. Chronic stress has been associated with a progression of this inflammatory response, which can then contribute to the development and progression of atherosclerotic disease (Black & Garbutt, 2002; Ellins et al., 2008; Everson-Rose & Lewis, 2005). This particular example focuses on the psychosocial, biological, and health domains, but the bio-behavioral literature provides numerous other examples of how behavioral (e.g., physical activity), environmental (e.g., pollution) and individual (e.g., socioeconomic status) characteristics can influence biological factors (e.g., inflammation) which then affect health outcomes (e.g., development of diabetes, asthma, cancer).

Kang and colleague's (2010) Framework was useful to the conceptualization of this study in two ways. First, the frailty literature has identified numerous correlates of frailty, and these correlates are consistent with several of the domains identified in Kang's Framework. Thus, the Framework served as a way to organize the variables of interest in the study. This was important because previous studies of frailty have, for the most part, examined these domains in isolation. Second, the framework specified the mediating role of biological factors in health. While a large portion of the frailty literature has been devoted to the examination of inflammation in frail older

adults, limited attention has been given to how these processes mediate the relationship between other characteristics, especially psychological characteristics, and frailty. As evidenced by the example of atherosclerotic disease, psychological characteristics can be an important factor in the development and progression of health outcomes and may point to potentially modifiable risk factors. Kang's Framework does not offer guidance with regard to which specific psychological characteristics would be related to both biological factors and frailty, thus indicating a need to incorporate a psychologically focused theory into the study framework, specifically, Ryff's Theory of Psychological Well-being.

Ryff's Theory of Psychological Well-Being

Ryff developed the theory of psychological well-being as way to understand well-being from a life-course perspective (Ryff, 1982). Ryff argued previous theories of successful aging lacked theoretical foundations and incorporated concepts of well-being (e.g., happiness) that were not specific to aging but applicable to adults in general, regardless of age (Ryff, 1982). In addition, the literature on psychology and aging had focused on negative psychological characteristics such as loneliness, while neglecting positive psychological characteristics such as autonomy (Ryff, 1989).

Drawing from theories in developmental and positive psychology, Ryff (1982) developed a theory of psychological well-being in older adults. According to this theory, well-being consists of six dimensions: self-acceptance, purpose in life, personal growth, positive relations with others, environmental mastery, and autonomy. Ryff considered the theory to be a conceptualization of eudaimonic well-being and compared it to other conceptualizations of well-being referred to as hedonic well-being. Eudaimonic well-being is described as the realization of one's personal potential and is typically operationalized using Ryff's Psychological Well-Being

scale, which measures the six dimensions described in the theory. Hedonic well-being is described as the pursuit of pleasure and happiness and is typically operationalized as affect and life satisfaction (Ryff, 1989; Ryff & Keyes, 1995). Both types of well-being have shown associations with age and health, indicating the examination of both types is necessary to gain a comprehensive understanding of how well-being and health are related in older adults.

In cross-sectional studies, older adults (65 years and older) have reported significantly higher levels of environmental mastery, autonomy, and self-acceptance compared to young adults (18 to 29 years old), while young adults have shown higher levels of purpose in life and personal growth (Ryff, 1989; Ryff, 1991; Ryff & Keyes, 1995). Life satisfaction, a measure of hedonic well-being, has been found to be stable or even increase with age in longitudinal studies (Bowling, Farquhar, Grundy, & Formby, 1993; Collins, Glei, & Goldman, 2009; Fujita & Diener, 2005; Koivumaa-Honkanen, Kaprio, Honkanen, Viinamäki, & Koskenvuo, 2005). Affect and age have shown a more complicated relationship. Some longitudinal studies show decreases in the intensity and frequency of positive affect, while others have shown stability in the intensity of positive affect in older adults (Henley & Davis, 1967; Smith & Baltes, 1993; Kurland, Gill, Patrick, Larson, & Phelan, 2006). Cross-sectional studies have found older adults tend to have lower levels of negative affect than younger adults, and longitudinal studies have shown these lower levels of negative affect are relatively stable over time (Ferring & Filipp, 1995; Kunzmann, Little, & Smith, 2000; Morzcek & Kolarz, 1998; Smith & Baltes, 1993; Shmotkin, 1990).

With regard to health, higher levels of eudaimonic and hedonic well-being have been found to incur a multitude of health benefits. In longitudinal studies of older adults, dimensions of eudaimonic well-being, such as purpose in life and positive relationships with others, have

been shown to have protective effects against early mortality, the development of Alzheimer's disease, and poor sleep quality (Boyle, Barnes, Buchman, & Bennett, 2009; Boyle, Buchman, Barnes, & Bennett, 2010; Phelan, Love, Ryff, Brown, & Heidrich, 2010). These effects were observed even after controlling for several sociodemographic (e.g., age, gender) and health characteristics (e.g., number of medical conditions, symptoms of depression). In a recent meta-analysis of 54 prospective observational studies of mortality in older adults, higher baseline levels of positive affect and life satisfaction, two measures of hedonic well-being, were found to be protective against mortality in samples of healthy older adults and samples of older adults with specific illnesses such as cancer or HIV/AIDs (Chida & Steptoe, 2008). In a review of the literature on positive affect and health, higher levels of positive affect were associated with lower levels of morbidity, fewer reported symptoms and better self-reported health status in adults (Pressman & Cohen, 2005). Higher levels of negative affect have been associated with reporting higher pain levels, more reported symptoms, and increasing levels of comorbidity (Cohen & Rodriguez, 1995; Friedman & Ryff, 2012; Robinson & Riley, 1999).

Both eudaimonic and hedonic well-being appear to play a role in health, but the mechanism by which these types of well-being influence health has only recently been explored. It has been hypothesized that higher levels of eudaimonic and hedonic well-being may enhance biological functioning, which in turn, may prevent the development of diseases or promote faster recovery from an illness or other adverse health events (Ryff, Singer, & Love, 2004). Of particular interest has been the relationship between eudaimonic and hedonic well-being and inflammation. Higher levels of eudaimonic and hedonic well-being are thought to prevent or dampen the inflammatory response to stressors, which may lessen the development of chronic inflammation over a period of time. To test this hypothesis, numerous studies have examined

associations between eudaimonic and hedonic well-being and inflammatory biomarkers. A cross-sectional study in 74 women between 61 and 90 years of age, found higher levels of positive relations with others was related to lower levels of IL-6, and higher levels of purpose in life and environmental mastery were related to lower levels of soluble IL-6 receptors (sIL-6r), which act to up-regulate the activity of IL-6 (Friedman et al., 2007). In a cross-sectional study of 998 adults between the ages of 35 and 86 (mean age = 58), participants with higher levels of purpose in life and positive relationship with others had lower levels of IL-6, and individuals with higher levels of positive affect had lower levels of CRP (Friedman & Ryff, 2012). In a cross-sectional study of 885 men and women between 30 and 54 years of age, higher levels of negative affect were associated with higher circulating levels of IL-6 and CRP after controlling for age, gender, race, and medical conditions (Marsland, Prather, Peterson, Cohen, & Manuck, 2008). A review of cross-sectional and longitudinal studies concluded that positive affect is associated with lower levels of inflammation, particularly IL-6 and CRP (Dockray & Steptoe, 2010). Evidence for the beneficial effect of eudaimonic and hedonic well-being on biological function indicates biological processes may be a mechanism by which well-being affects health outcomes.

Frailty has been related to both eudaimonic and hedonic well-being (Andrew et al. 2012; Kirby et al., 2004; Ostir et al., 2004; Ottenbacher et al., 2009; Park-Lee et al., 2009). However, no study has examined biological mechanisms, such as inflammation, as a way to understand how these psychological characteristics may be related to frailty. Using Kang's Framework and Ryff's Theory, plus the empirical evidence supporting the relationship between psychological well-being and inflammation, a conceptual framework was developed for this study (See Figure 2.2). According to this framework, both eudaimonic and hedonic well-being (collectively called psychological well-being) have a direct effect on inflammation and indirect effects on frailty

through their effect on inflammation. Higher levels of psychological well-being are related to lower levels of inflammation and less frailty. Higher levels of inflammation are related to frailty, and inflammation mediates the relationship between psychological well-being and frailty. This relationship does not happen in isolation, but occurs above and beyond the influence of sociodemographic and health characteristics associated with psychological well-being, inflammation, and frailty.

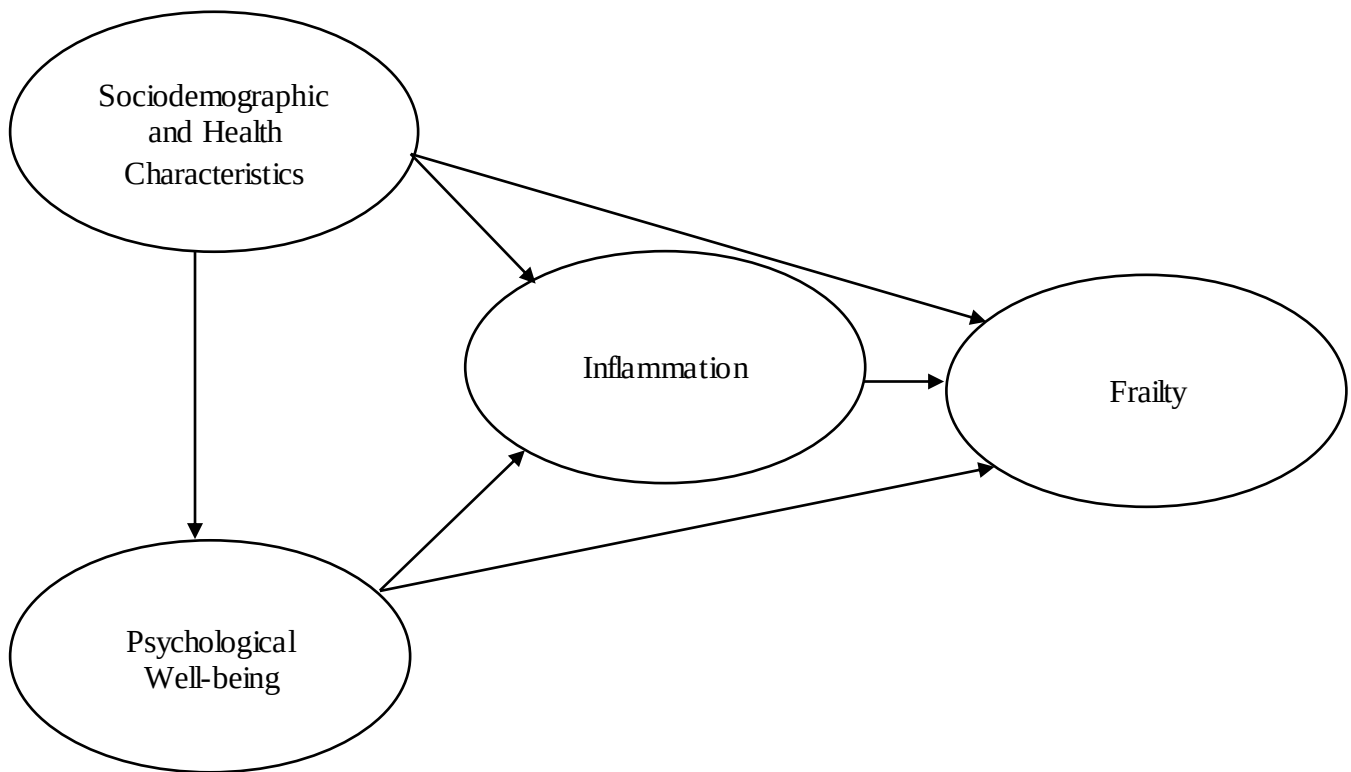


Figure 2.2 Diagram of Conceptual Model

Specific Aims and Hypotheses

Based on this model, the specific aims of this study were:

Specific Aim 1. Describe the biopsychosocial profiles of individuals classified as non-frail, pre-frail, and frail.

Specific Aim 2. Examine the influence of psychological well-being, sociodemographic, and health characteristics and changes in psychological well-being over time on frailty.

Specific Aim 3. Examine the role of inflammatory biomarkers as a mediator of the relationship between psychological well-being and frailty.

The major hypotheses guiding this study were:

- 1) Individuals who are older, female, with more chronic conditions, more medications, poorer self-rated physical and emotional health, and lower levels of psychological well-being will be more likely to be frail compared to non-frail and pre-frail individuals.
- 2) The relationship between psychological well-being and frailty is mediated by the inflammatory biomarkers, IL-6 and CRP.

Chapter Three: Methods

In this chapter, the design, sample, procedure, and instruments will be described.

Study Design

This study was a secondary analysis of data from the National Survey of Midlife Development in the United States (MIDUS), a longitudinal study of patterns, predictors, and consequences of mid-life development on physical health, psychological well-being, and social responsibility in a nationally representative sample of community-dwelling adults between 25 and 74 years of age (Brim, Ryff, & Kessler, 2004). The first wave of data collection, MIDUS I, (hereafter referred to as baseline), occurred between 1995 and 1996 and consisted of both a telephone interview and mailed self-administered questionnaire (SAQ) the participants returned after completion. Respondents provided data regarding their physical health (e.g., history of cancer and other disease diagnoses, current medications), mental health (e.g., depression), health behaviors (e.g., frequency and intensity of physical activity, smoking and drinking habits), and sociodemographic characteristics (e.g., age, income, education).

The second wave of data collection, MIDUS II (hereafter referred to as Time 2), occurred between 2004 and 2009, was a longitudinal follow-up to the MIDUS I study, and consisted of five research projects. For this study, data from Project 1 and Project 4 were used for Time 2 data. Project 1 was a follow-up of the psychosocial, sociodemographic, and health data collected in MIDUS I, and Project 4 consisted of a comprehensive biomarker and physical assessment on a sub-sample of individuals who had participated in MIDUS I and MIDUS II Project 1 (Institute of Aging, 2011). Participants aged 65 years and older at the time of their participation in MIDUS II Project 4 were included in this study (see Figure 3.1).

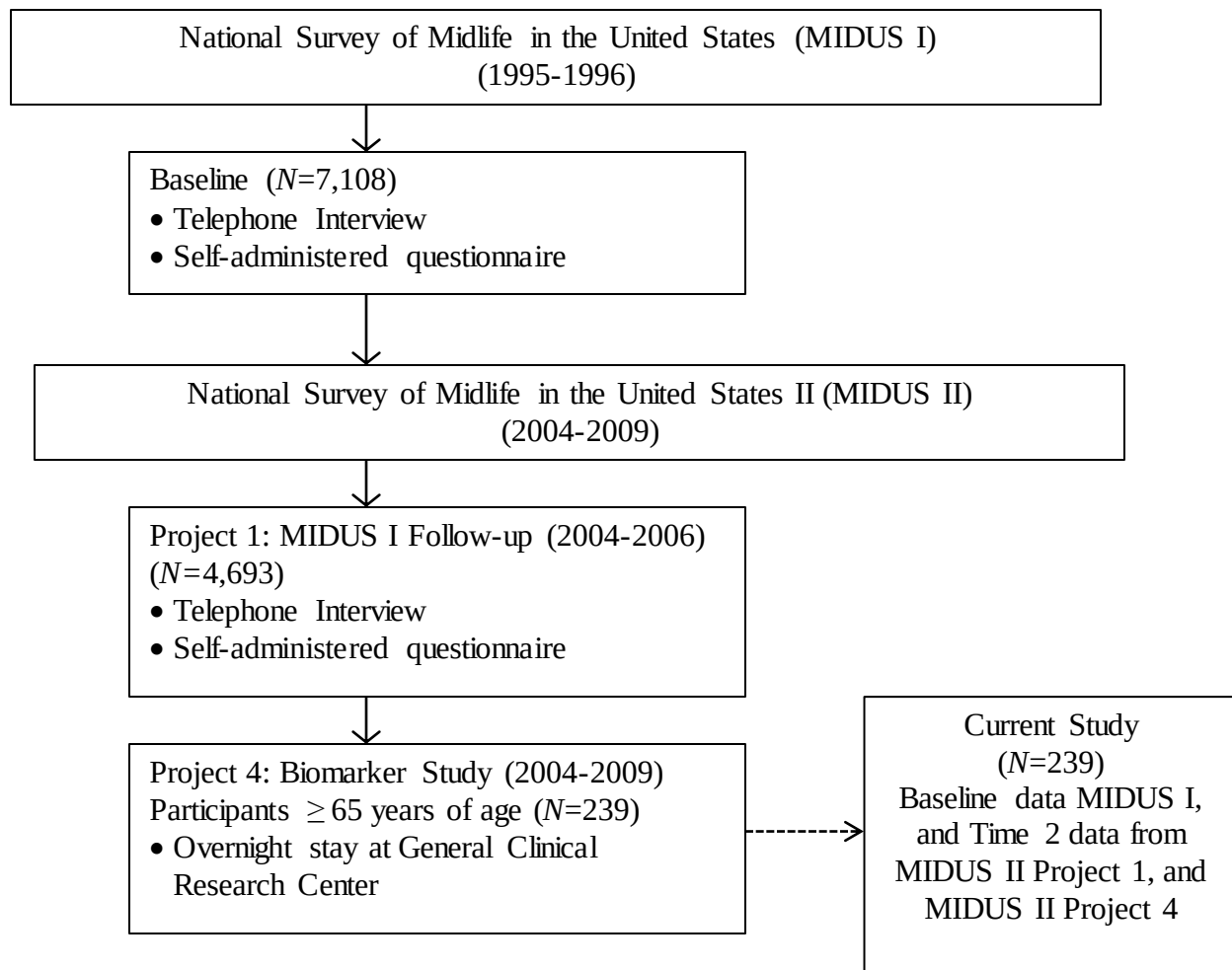


Figure 3.1 Flow Diagram of Data Sources for Current Study

MIDUS I and II Samples and Procedure

MIDUS I (Baseline)

Baseline data were collected from 7,108 participants who were in one of four subsamples: a national random-digit-dial sample (RDD) (n=3,487), oversamples from five metropolitan areas in the United States (n=757), siblings of individuals from the RDD sample (n=950), and a national sample of RDD twin pairs (n=1,914). For MIDUS I, the main RDD sample was selected from working telephone banks. Oversampling of older adults and males was achieved by varying the probability of carrying out the interview as a joint function of the age and gender of the randomly selected respondent. Oversampling of five metropolitan areas was

carried out in the same manner. Potential subjects were contacted via telephone, provided a brief summary of the study, and if the potential participant expressed interest, eligibility screening was completed. Eligibility criteria for MIDUS I included the following: (1) age 25 to 74; (2) living in a non-institutionalized setting with a working telephone; (3) ability to speak English; (4) having sufficient health (cognitive and physical) to complete a 45-minute telephone interview and a SAQ; and (5) having sufficient literacy to complete a SAQ. If the participant was found to be eligible, verbal consent was obtained prior to the telephone interview. After completion of the telephone interview, participants were then mailed the SAQ containing additional questions regarding physical health, psychosocial well-being, and sociodemographic characteristics. Telephone interviews were conducted on 7,108 individuals who met the eligibility criteria and 6,329 (89% of those who completed a telephone interview) completed and returned the SAQ.

MIDUS II (Time 2)

The overall purpose of MIDUS II was to investigate the long-term consequences of behavioral and psychosocial factors for health and illness.

Project 1. For MIDUS II Project 1, attempts to contact individuals from MIDUS I were made, and if contact was achieved individuals were again provided a description of the study, interest was assessed, and verbal consent was obtained prior to starting the telephone interview. After the completion of the telephone interview, participants were mailed the SAQ and asked to complete and return it via postal mail. The data collected via the telephone interview and the SAQ were largely repeated baseline assessments with additional questions in selected areas (e.g., cognitive functioning, optimism and coping, stressful life events, and caregiving). A total of 4,963 individuals (approximately 75% of MIDUS I participants, adjusting for mortality) completed the telephone interview, and 4,032 individuals (approximately 81% of those who

completed the telephone interview) completed and returned the SAQ. Retention rates between MIDUS I and MIDUS II were highest among Caucasians, females, and married individuals with more education and better health status (Radler & Ryff, 2010).

Project 4. Participants who had participated in MIDUS I and MIDUS II Project 1 and lived in designated regions located close to the General Clinical Research Centers affiliated with MIDUS were recruited for participation in Project 4 (Dienberg Love et al., 2010). The purpose of Project 4 was to support the overall purpose of MIDUS II through the assessment of a variety of biological indicators of physiology and health. Eligible individuals were mailed a letter and descriptive brochure providing information about the purposes of Project 4 and what was involved in study participation. Follow-up phone calls were made and the individual's interest in participating in Project 4 was assessed. For those interested, travel arrangements were made, and all travel expenses were paid for by the study. Eligible participants were assigned to one of the three Project 4 data collection sites (UCLA/Site 1, University of Wisconsin (UW)/Site 2, or Georgetown University/Site 3) based on the region (West Coast, Midwest, East Coast, respectively) in which they lived. For older adults or those uncomfortable traveling alone, companions were allowed to accompany them to the research center. Upon arrival, participants provided written consent for participation.

Participants stayed overnight at the General Clinical Research Center, usually arriving in the afternoon of Day 1 and leaving about noon on Day 2 (Dienberg Love et al., 2010). Upon arrival on Day 1, a complete medical history, bone density scan, and physical assessment were completed, and a 12-hour urine specimen collection was started. On Day 2, a fasting blood sample was collected and participants completed cognitive and physiological response assessments. Data on cognitive and physiological response assessments were not used in this

study. At the end of these assessments, participants were provided a report of their blood pressure, body-mass index, and other health information and also received \$200 for their participation in the study. Reports of their cholesterol, hemoglobin A1c, and bone density were mailed to them approximately one to two months later.

Protection of Human Subjects

The research proposals for MIDUS I and MIDUS II were reviewed and approved by the Institutional Review Boards at each of the participating university, including the University of Wisconsin-Madison. In both MIDUS I and MIDUS II Project 1, verbal consent was obtained from participants before the telephone interview and written consent was obtained in the returned self-administered questionnaires. For MIDUS II Project 4, written consent was obtained upon arrival for the overnight stay at the General Clinical Research Center. For this secondary data analysis, an IRB exemption was obtained from the University of Wisconsin-Madison Social and Behavioral Sciences Institutional Review Board (see Appendix B) because this is a publicly available data set.

In the original MIDUS studies, all data collection forms were coded by subject number only, and the master list pairing numbers with names was stored in a separate locked location and in a password-protected computer file. These efforts were meant to protect participants' privacy. All data used for this study were obtained through the Inter-University Consortium for Political and Social Research (ICPSR) website (<http://www.icpsr.umich.edu/icpsrweb/ICPSR/>), which houses the publicly available and de-identified data from MIDUS I and MIDUS II.

Sample

The sample for this study included men and women (N = 239) who were 65 years of age or older at the time of their participation in MIDUS II Project 4. A power analysis was completed

to determine the necessary sample size needed to test the relationships among frailty, inflammation, psychological well-being, and sociodemographic and health characteristics using structural equation modeling. Given the limited examination of psychological well-being and its relationship to frailty, the effect size of 0.20 was chosen to detect a small effect. The statistical program MPlus (Muthén, & Muthén, 1998) was used, and a sample size of 239, with an estimated effect size of 0.20, $\alpha < .05$, resulted in power of 0.83 (Cohen, 1988).

Instruments

Only the MIDUS measures pertinent to this study are described in this section (see Table 3.2). Demographic information was gathered during the telephone and self-administered questionnaires in MIDUS I and MIDUS II Project 1. Demographic data used in this study included: age, gender, race, years of education, retirement status, and pre-tax household income. These variables were chosen because they are commonly used to describe older adults samples and many of them have been found to be related to frailty in older adults (Fried et al., 2001; Hirsch et al., 2006; Ostir et al., 2004; Ottenbacher et al., 2009; Puts et al., 2005; Szanton et al., 2009).

Frailty

Fried Frailty Phenotype. Frailty classification was determined using MIDUS II Project 4 data (Time 2), and the process for determining classification was based on the Fried Frailty Phenotype measure developed by Fried and colleagues (2001). This measure is based on Walston and Fried's (1999) theory of frailty, which posits that physiologic dysregulation, particularly chronic inflammation, is an underlying cause of frailty. It is one of the most widely used frailty measures, has consistently been related to elevated inflammatory levels in older adults, and has shown predictive validity by predicting poor health outcomes in frail, older adults including

hospitalization, falls, and post-operative complications (Ensrud et al., 2007; Fried et al., 2001; Leng et al., 2002; Leng et al., 2005; Leung et al., 2011; Puts et al., 2005; Walston et al., 2002).

The Fried measure assesses individuals on five characteristics:

1. Shrinking (weight loss and sarcopenia) – Fried and colleagues proposed two approaches for measuring this characteristic. The first is participant's answer to the question, "In the last year have you lost more than 10 pounds unintentionally (i.e., not due to dieting or exercise)?" Individuals who respond "Yes" to this question are categorized as having this characteristic. The second option is the calculation of percent weight loss over a 12-month time frame using the following equation: $(\text{weight in previous year} - \text{current measured weight}) / (\text{weight in previous year}) = K$. If $K \geq 0.05$ and the subject did not report that he/she was trying to lose weight, he/she is considered to have this characteristic.
2. Poor endurance/Exhaustion – This characteristic is assessed using two items from the CES-D Depression Scale asking "How often in the last week did you feel this way?" Response options are (a) "I felt that everything I did was an effort"; (b) "I could not get going." Response options are 0 ("rarely or none of the time (<1 day)"), 1 ("some or a little of the time (1-2 days)"), 2 ("a moderate amount of the time (3-4 days)"), or 3 ("most of the time"). Responses "2" or "3" to either of the questions are categorized as having the exhaustion characteristic.
3. Weakness – This characteristic is assessed with measures of grip strength, and cutoffs for grip strength are stratified by gender and body mass index (BMI) quartiles. For specific cutoffs, see Table 3.1.

4. Slowness – This characteristic is assessed with time taken to walk 15 feet at the participant's usual pace. Cutoffs for slowness are stratified by gender and height. For specific cutoffs see Table 3.1.
5. Low activity – This characteristic is assessed with the short version of the Minnesota Leisure Time Activity questionnaire about walking, chores (moderately strenuous), mowing the lawn, raking, and other activities (Taylor et al., 1978). The number of kilocalories expended per week is calculated using a standardized algorithm, and cutoff scores are stratified by gender.

Items for these 5 characteristics are coded as either 1 (has the characteristic) or 0 (does not have the characteristic), and the number of characteristics exhibited is summed. Participants are classified as follows: sum of 0 = non-frail, sum of 1 or 2 = pre-frail, and sum greater than or equal to 3 = frail.

MIDUS Frailty Measure. For this study, the frailty measure was created from variables either identical or similar to the variables used in the Fried measure (see Table 3.1).

1. Shrinking - This characteristics was assessed by calculating percent weight loss in participant between MIDUS II Project 1 and MIDUS II Project 4. The average span of time between participation in the two projects was approximately 24 months, so the time frame for the calculation of this variable is different from the Fried measure. To take into consideration whether not individual may have been trying to lose weight between the two times, individuals who lost more than 5% of their body weight but reported in Project 1 that they had lost weight in the past 12 months through diet and exercise were not categorized as having this characteristic. This approach was an attempt to take into account those individuals who had recently been

- engaged in weight loss behaviors (i.e., diet and exercise) that may have been a reason or the reason for any weight loss that took place between Projects 1 and 4. For this study, individuals who lost 5% or more of their body weight and did not report recent engagement in weight loss behaviors were considered to have this characteristic. Individuals who experienced a weight loss of less than 5% of their body weight, lost no weight, or gained weight were classified as not having this characteristic.
2. Exhaustion - The same two items from the CES-D Depression scale were used to assess individuals on the exhaustion characteristic. However, in the Fried version, the response options are numbered 0 to 3 while in the MIDUS version, the response options were numbered from 1 to 4. The text attached to the corresponding numbers was the same between the Fried and MIDUS measures. For MIDUS participants, responses of “3” or “4” to either of the questions were categorized as having this characteristic.
 3. Weakness - Weakness was assessed in the same manner as the Fried measure by using a dynamometer, a tool to measure grip strength. In MIDUS II Project 4, participants performed three trials on each hand and, per usual practice in physical therapy studies, the average of the three trials on the dominant hand was used (personal communication, Dr. Mary Sesto, September 29, 2011).
 4. Slowness - As in the Fried measure, slowness was assessed using gait speed, but the MIDUS assessment utilized a 50 feet walking distance, not the 15 feet walking distance utilized in the Fried measure. To place the Fried and the MIDUS frailty measures on the same metric, feet per second was calculated for the MIDUS participants, and the cutoff criteria provided by the Fried measure was converted into

feet per second as well. The newly calculated Fried cutoff points were utilized to categorize individuals as to whether or not they had this characteristic.

5. Low activity levels – A measure of kilocalories expended per week is not available within the MIDUS II Project 4 database, however, there is a self-report measure of engaging in regular exercise. The item asked participants, “Do you engage in at least 20 minutes of physical activity at least 3 times per week?” Response options were 1 (“Yes”), 2 (“No”), 8 (“Refused”), 7 (“Unsure”), or 9 (“Inappropriate”). Participants who reported, “Yes”, “Refused”, “Unsure” or “Inappropriate” were classified as not having this characteristic, and participants reporting “No” were classified as having this characteristic. To establish the equivalency of using this cutoff criteria with the Fried criteria, the estimated weekly kilocalories expended while engaging in 20 minutes of easy walking three times a week was calculated according to energy expenditure levels established by Ashworth and colleagues (2005) *and* using the algorithm established in the Minnesota Leisure Physical Activity Questionnaire, which was used by Fried and colleagues (Taylor et al., 1978). These two approaches yielded approximately the same estimated weekly kilocalories expended (107 and 109 respectively) and lend support to the equivalency between the Fried and MIDUS measures of this characteristic.

The number of frailty characteristics exhibited was summed for each participant, and participants were classified using the Fried measure approach with 0 characteristics = non-frail, 1-2 characteristics = pre-frail, and 3 or more characteristics = frail.

Inflammatory Biomarkers

Inflammatory biomarkers were measured at MIDUS II Project 4 (Time 2) by assaying serum samples for IL-6 and C-reactive protein levels (CRP). Quantikine® high-sensitivity enzyme linked immunosorbent assay (ELISA) kits were used to measure the serum levels of IL-6 (R&D Systems, Minneapolis, MN). The laboratory intra-assay coefficient of variance was 4.09% and the inter-assay coefficient of variance was 13% for IL-6. CRP was measured using the BNII nephelometer from Dade Behring utilizing a particle enhanced immunonephelometric assay (Dade Behring Inc., Deerfield, IL). The laboratory intra-assay coefficient of variance was 2.3 - 4.4%, and the inter-assay coefficient of variance was 2.1-5.7%. These inflammatory biomarkers were chosen based on previous studies linking each to frailty and psychological well-being (Ryff et al., 2004; Friedman et al., 2007; Leng et al., 2007; Puts et al., 2005).

Psychological Well-Being

Eudaimonic well-being was measured using Ryff's Psychological Well-Being Scale (Ryff, 1995) at baseline and Time 2. The six dimensions of PWB (self-acceptance, purpose in life, personal growth, positive relations with others, environmental mastery, and autonomy) were measured at both times. Example items include "Some people wander aimlessly through life, but I am not one of them" (Purpose in Life), "I have confidence in my own opinions, even if they are different from the way most other people think" (Autonomy), and "In general, I feel I am in charge of the situation in which I live" (Environmental Mastery). Responses options ranged from 1 ("strongly agree") to 7 ("strongly disagree"), and positive items were reverse coded so higher scale scores reflected higher levels of PWB. In Ryff's original formulation of the PWB Scale, each subscale contained 20 items, and subsequent studies included 14 items for each subscale (Ryff, 1989; Ryff & Essex, 1992). The sub-scales of the 20-items per sub-scale version were

found to have Chronbach's alpha reliability values ranging from 0.86 to 0.93 and six-week, test-retest reliability correlations ranging from 0.80 to 0.88. For the 14-items per sub-scale version, the Chronbach's alpha reliability estimates ranged from 0.83 to 0.91 and were found to have significant correlations with the parent 20-item subscales ($r = 0.97-0.98$) (Ryff, 1989; Ryff & Essex, 1992).

Each subscale contained only three items in an effort to reduce participant burden given the large number of questions they were being asked via the telephone interview and the self-administered questionnaire. As a result of the reduction in the number of items per subscale, the Chronbach's alpha coefficients for these subscales ranged from 0.36 (Purpose in Life) to 0.56 (Self-Acceptance). At Time 2, the number of items for each subscale was increased to seven with three of those items carried over from baseline. While these 7-item subscales have higher reliability estimates, they could not be utilized to examine changes over time; only the 3 item subscales could be utilized. The reliabilities for the 3-item subscales at Time 2 ranged from 0.32 (Purpose in Life) to 0.66 (Self-Acceptance). The three-item subscales have been shown to be significantly correlated to their 7-item parent subscales but, given these low reliabilities, another approach was devised (Ryff & Keyes, 1995). Dr. Ryff (personal communication) suggested calculating a composite measure of PWB by summing the items for each of the sub-scales and creating an average overall composite score of PWB. Using this approach, the possible range for this average composite score was 3 to 21. The Chronbach's alphas were much improved: 0.76 at baseline and 0.77 at Time 2.

Hedonic well-being was measured using the Positive and Negative Affect Scale and the Life Satisfaction Scale (measured at baseline and Time 2). Affect and life satisfaction have shown relationships with frailty in previous studies, and positive and negative affect have been

related to inflammation in older adults (Frieswijk, Buunk, Steverink, & Slaets, 2004; Ostir et al., 2004; Ottenbacher et al., 2009). The Positive and Negative Affect Scale contained two sub-scales, one for positive affect and one for negative affect. The question stem, “During the past 30 days, how much of the time did you feel...?” was followed by 12 terms (six per sub-scale) such as “cheerful” or “in good spirits” for positive affect and “nervous” or “hopeless” for negative affect. Responses options were 1 (“all of the time”), 2 (“Most of the time”), 3 (Some of the time”), 4 (“A little of the time”) or 5 (“none of the time”). Items were reverse coded when necessary so that higher sub-scale scores reflected higher levels of positive or negative affect. Scale scores were obtained by calculating the mean across each sub-scale with the possible range for the sub-scale score being 1 to 5. The Chronbach’s alpha coefficients for these scales were 0.80 for the Positive Affect Scale and 0.83 for Negative Affect Scale at baseline and 0.89 for Positive Affect Scale and 0.77 for the Negative Affect Scale at Time 2. Life satisfaction was assessed with the Life Satisfaction Scale, constructed from five items assessing life overall, work, health, and family (i.e., relationship with spouse/partner and relationship with children). Each question asked, “On a scale of 0 to 10 where 0 means the worst and 10 means the best, how would you rate your ____ these days?” The average of these five items was used to calculate the scale score for life satisfaction for a possible score range of 0 to 10. Previous studies using this scale have found it to be valid and reliable (Fleeson, 2004; Prenda & Lachman, 2001). For this scale, the Chronbach’s alpha coefficients were 0.75 at baseline and 0.70 at Time 2.

Health Measures

Four measures were used to assess health in the participants: self-rated physical health, self-rated mental/emotional health, number of illnesses, and number of medications.

Self-rated Physical Health and Self-rated Mental/Emotional Health. Self-rated physical health and self-rated mental/emotional health were two separate measures. Self-rated physical health was assessed at baseline by asking participants, “In general, would you say your PHYSICAL HEALTH is...” and the following response options were provided: “Poor”, “Fair”, “Good”, “Very Good”, or “Excellent”. The next question participants were asked was, “What about your MENTAL OR EMOTIONAL HEALTH?” The same response options as self-rated physical health were provided. The response options were coded 1 thru 5 with higher scores representing better self-rated physical or mental/emotional health. At Time 2, the same questions were asked, but the response options were reversed and the responses were reverse coded to facilitate comparisons with baseline responses. Self-rated physical health and self-rated mental/emotional health were chosen because both have been found to be a significant predictor of morbidity and mortality in older adults (Pietz & Petersen, 2007; Wang & Satariano, 2007). Frail individuals reported lower levels of self-reported health in general, so both questions were included to capture individual’s perceptions of their overall health (Ávila-Funes et al., 2008; Cawthorn et al., 2007; Ensrud et al., 2009; Fried et al., 2001; Woods et al., 2005).

Number of illnesses. Participants completed a self-report checklist of 29 illnesses common in adults including hypertension, diabetes, asthma, and chronic sleep problems. Participants replied “Yes” or “No” to whether or not they had experienced each illness in the past 12 months. The total number of illnesses was summed. An additional item, “swallowing problems” was added at Time 2, but this item was not included in the calculation of the number of illnesses in this study to allow for the examination of change in number of illnesses over time.

Medications. Participants completed a self-report checklist of 11 medications including medications for hypertension, diabetes, high cholesterol, and arthritis at baseline and Time 2.

Participants responded “Yes” or “No” to whether they had a prescription for that type of medication and if they had taken that type of medication in the past 30 days. An additional item, “pain medications” was added at Time 2, but this item was not included in the calculation of the number of medications so as to allow for the examination of change in number of medications over time. In addition, the use of specific medications known to have anti-inflammatory effects was measured. At Time 2, participants reported whether or not they were currently taking corticosteroids or medications for depression or hypertension. Participants responded either “Yes” or “No” to each medication.

Table 3.1

The Fried Frailty Characteristics and the MIDUS Frailty Characteristics

Fried Frailty Measure	MIDUS Frailty Measure
<i>Unintentional Weight Loss</i>	<i>Unintentional Weight Loss</i>
(Weight in previous year – current measured weight) / (weight in previous year) = K.	(MIDUS II Project 1 weight – MIDUS II Project 4 weight) / (MIDUS II Project 1 weight) = K.
If $K \geq 0.05$ and the participant does not report trying to lose weight = meets criterion	If $K \geq 0.05$ the participant did not report trying to lose weight = meets criterion
<i>Exhaustion</i>	<i>Exhaustion</i>
CES-D Items: “How often in the past week...”	CES-D Items: “How often in the past week...”
(a) I felt that everything I did was an effort	(a) I felt that everything I did was an effort
(b) I couldn’t get going	(b) I couldn’t get going
Responses:	Responses:
0 = “rarely or none of the time (<1 day)”	1 = “rarely or none of the time”
1 = “some of a little of the time (1 – 2 days)”	2 = “some of a little of the time”
2 = “a moderate amount of time (3 – 4 days)”	3 = “a moderate amount of time”
3 = “most of time”	4 = “most of time”
Responses of 2 or 3 = meets criterion	Responses of 3 or 4 = meets criterion

Table 3.1 (continued)

The Fried Frailty Characteristics and the MIDUS Frailty Characteristics

Fried Frailty Measure		MIDUS Frailty Measure	
Weakness		Weakness	
Grip Strength: lowest 20% by gender and BMI		Grip Strength: lowest 20% by gender and BMI	
Gender/Height	Meets criterion if	Gender/Height	Meets criterion if
<i>Men</i>		<i>Men</i>	
BMI ≤ 24	≤ 29 kg/force	BMI ≤ 24	≤ 29 kg/force
BMI 24.1 – 26	≤ 30 kg/force	BMI 24.1 – 26	≤ 30 kg/force
BMI 26.1 – 28	≤ 30 kg/force	BMI 26.1 – 28	≤ 30 kg/force
BMI > 28	≤ 32 kg/force	BMI > 28	≤ 32 kg/force
<i>Women</i>		<i>Women</i>	
BMI ≤ 23	≤ 17 kg/force	BMI ≤ 23	≤ 17 kg/force
BMI 23.1 – 26	≤ 17.3 kg/force	BMI 23.1 – 26	≤ 17.3 kg/force
BMI 26.1 – 29	≤ 18 kg/force	BMI 26.1 – 29	≤ 18 kg/force
BMI > 29	≤ 21 kg/force	BMI > 29	≤ 21 kg/force
Slowness		Slowness	
Walking time for 15 feet: slowest 20%		Feet/second for a 50 feet distance	
		Converted Fried cut – offs to feet/sec	
		15 feet / 7 seconds = 2.1 feet per second	
		15 feet / 6 seconds = 2.5 feet per second	
Gender/Height	Meets criterion if	Gender/Height	Meets criterion if
<i>Men</i>		<i>Men</i>	
≤ 173 cm	≥ 7 seconds	≤ 173 cm	≥ 2.1 ft./second
> 173 cm	≥ 6 seconds	> 173 cm	≥ 2.5 ft./second
<i>Women</i>		<i>Women</i>	
≤ 159 cm	≥ 7 seconds	≤ 159 cm	≥ 2.1 ft./second
> 159 cm	≥ 6 seconds	> 159 cm	≥ 2.5 ft./second

Table 3.1 (continued)

The Fried Frailty Characteristics and the MIDUS Frailty Characteristics

Fried Frailty Measure	MIDUS Frailty Measure
<i>Low Physical Activity</i>	Low Physical Activity
Kilocalories expended per week: lowest 20%	“Do you engage in at least 20 minutes of
Males < 383 Kcals/week = meets criterion	physical activity at least 3 times per week?”
Females < 270 Kcals/week = meets criterion	Participants reporting “No” = meets criterion

The number of characteristics across all 5 was summed. Participants were classified as:

0 characteristics = Non-Frail

1 to 2 Criteria = Pre – Frail

3 or more Criteria = Frail

Table 3.2

Study Variables and Time of Measurement

Variable	Time 1	Time 2
Frailty Classification		X
Inflammatory Biomarkers		
• Interleukin-6 (IL-6)		X
• C-Reactive Protein (CRP)		X
Psychological Well-Being		
• Eudaimonic Well-being	X	X
○ Ryff's Psychological Well-being Scale		
• Hedonic Well-Being	X	X
○ Positive Affect Scale		
○ Negative Affect Scale		
○ Life Satisfaction Scale		
Health	X	X
• Self-reported physical health status		
• Self-reported mental/emotional health status		
• Number of illnesses		
• Number of Medications		
Anti-inflammatory Medications		X
• Corticosteroids		
• Anti-depressives		
• Anti-hypertensives		
Sociodemographic		
• Age, gender, education, income, marital status, race, retirement status	X	X

Chapter Four: Data Analysis and Results

This chapter describes the data analyses conducted for this study and the results. First, the preliminary data analyses are described. Second, the sociodemographic, health, and psychological well-being characteristics of the sample at baseline and Time 2 are presented. Third, the data analyses conducted and results for each specific aim are presented.

Preliminary Data Analysis

All of the variables were reviewed for missing values, outliers, and fit between the distributions and the assumptions of multivariate analysis such as normality, linearity, and homoscedasticity. Descriptive statistics were computed to assess the distribution of the variables, and all values were found to be within the expected range. The means and standard deviations for all variables were found to be plausible. Six variables were found to have asymmetric, as well as very peaked distributions (i.e., kurtosis): positive affect at baseline (MIDUS I) (skewness = -1.43, kurtosis = 3.11) and Time 2 (skewness = -0.41, kurtosis = 0.83), negative affect at baseline (skewness = 2.10, kurtosis = 6.07) and Time 2 (skewness = 2.68, kurtosis = 11.06), serum IL-6 at Time 2 (skewness = 3.17, kurtosis = 12.34), and serum CRP at Time 2 (skewness = 6.59, kurtosis = 55.89). The values for the positive and negative affect variables were transformed using Box-Cox transformations resulting in improvements in both their skewness and kurtosis values. Analyses using the transformed affect variables were compared to those using the original data and no differences in significance of parameter estimates were found. Results are reported using the original values of the positive and negative affect variables.

The values for IL-6 and CRP variables were log-transformed resulting in improvements in the skewness of the variables. For descriptive statistics, untransformed values of IL-6 and CRP are reported, but all other analyses with IL-6 and CRP utilized the log-transformed version of

these variables. In addition, a total of 76 individuals in the current study were a part of a twin sub-sample. To determine whether the genetic overlap of these individuals may have influenced parameter estimates, a random 38 of these participants were removed, and analyses re-ran. Using the adjusted sample did not result in any differences in the significance of parameter estimates. Therefore, results from the full sample are reported.

For missing data on items used to calculate scale scores (e.g., Ryff's Psychological Well-Being), MIDUS researchers utilized either mean imputation or the scale score was calculated using the items for which data was provided so long as the participants provided data on a minimum number of items on that specific scale. For Ryff's Psychological Well-Being measure, mean imputed values were calculated for those participants who provided data on at least one of the three items. The imputed value was then included in the calculation of the overall mean. For the Positive Affect, Negative Affect and the Life Satisfaction measures, the scale score was calculated if respondents provided a valid response to at least one item. Missing data resulted in loss of participants' data as follows: for Ryff's Psychological Well-Being, 7 participants at baseline and 2 at Time 2; for Positive Affect, 6 at baseline and 4 at time 2; for Negative Affect, 5 at baseline and 3 at Time 2; for Life Satisfaction, 5 at baseline and 1 at Time 2.

Description of the Sample

Baseline Demographic characteristics

The baseline demographic characteristics of all participants are described in Table 4.1. The mean age of participants at baseline was 62.7 ($SD=5.5$) years and ranged from 53 to 74 years. Women made up the majority of participants ($n=130$, 54.4%). This was a highly educated sample; only 7.8% did not graduate from high school, and 40.3% were college graduates. Approximately half of the participants (47.7%) reported an annual household income of more

than \$50,000. The majority of participants self-identified as Caucasian ($n=225$, 94.1%), and the remaining participants identified themselves as African-American ($n=6$, 2.5%), Other ($n=3$, 1.3%), or chose not to respond or data regarding their race was missing ($n=5$, 2.1%). The majority of participants were married ($n=185$, 77.4%) and were not retired ($n=143$, 59.8%).

Table 4.1

Baseline Demographic Characteristics (N=239)

Variables	<i>M</i>	<i>SD</i>	<i>Range</i>	<i>n</i>	%
Age (years)	62.7	(5.5)	53-74		
53 – 59*				90	37.7
60 – 69				110	46.0
≥ 70				39	16.3
Gender (Female)				130	54.4
Highest Level of Education					
Some Grade School to GED				19	7.9
High School Graduate				57	23.8
Some College				66	27.6
College Graduate				44	18.5
Graduate or Professional School				52	21.8
Missing				1	0.4
Income					
Less than \$20,000				28	11.7
Between \$20,000 and \$50,000				86	36.0
More than \$50,000				114	47.7
Missing				11	4.6
Race/Ethnicity					
Caucasian				225	94.1
African American				6	2.5
Other				3	1.3
Missing				5	2.1
Marital Status					
Married				185	77.4
Separated or Divorced				30	12.6
Widowed				19	7.9
Never Married				5	2.1
Retired				143	59.8

Note. *One participant was 53 years old at the time of their participation at baseline, but 65 at the time of the participation at Time 2.

The Time 2 descriptive statistics for age, income, marital status, and retirement status are shown in table 4.2. The mean age at Time 2 was 71.8 ($SD = 5.4$) years and ranged from 65 to

84 years. The number of participants with incomes less than \$20,000 increased from baseline, as did the number of participants who were retired and who were widowed.

Table 4.2

Time 2 Demographic Characteristics (N=239)

Variables	<i>M</i>	<i>SD</i>	<i>Range</i>	<i>n</i>	%
Age (years)	71.8	(5.4)	65-84		
65-70				122	51.0
71-79				86	36.0
≥ 80				31	13.0
Income					
Less than \$20,000				56	23.4
Between \$20,000 and \$50,000				86	36.0
More than \$50,000				90	37.7
Missing				7	2.9
Marital Status					
Married				163	68.2
Separated or Divorced				32	13.4
Widowed				38	15.9
Never Married				5	2.1
Missing				1	0.4
Retired				178	74.5

Health characteristics

Descriptive statistics regarding participants' self-rated physical health, self-rated mental/emotional health, number of illnesses, and number of medications at baseline and Time 2 are shown in Table 4.3. At baseline and Time 2, the average values of self-reported physical and mental/emotional health variables indicated participants perceived their physical health to be "Good" or "Very good" and their mental or emotional health to be "Very good".

Table 4.3

Baseline and Time 2 Descriptive Statistics for Health Variables (N=239)

	<u>Baseline</u>		<u>Time 2</u>	
	<u>M</u>	<u>(SD)</u>	<u>M</u>	<u>(SD)</u>
Self-rated physical health	3.7	(0.9)	3.7	(1.0)
Self-rated mental health	3.9	(0.9)	4.0	(1.0)
Number of Illnesses	2.5	(2.3)	2.6	(2.7)
Number of Medications	0.9	(1.1)	1.6	(1.4)

The mean number of illnesses was similar at baseline and Time 2. Descriptive statistics regarding specific illnesses reported by participants are shown in Table 4.4. At baseline, the five most commonly reported illnesses were bone or joint disease, sciatica/lumbago/recurrent backache, high blood pressure, recurring stomach trouble, and hay fever. At Time 2, the five most commonly reported illnesses were bone or joint disease, high blood pressure, sciatica/lumbago/recurrent backache, urinary or bladder problems, and recurring stomach problems.

Table 4.4

Frequency and Percentage of Illnesses Reported at Baseline and Time 2 (N=239)

	<u>Baseline</u>		<u>Time 2</u>	
	<u>n</u>	<u>%</u>	<u>n</u>	<u>%</u>
Bone/joint disease	78	32.6	90	37.7
Sciatica, lumbago, recurrent backache	56	23.4	44	18.4
High blood pressure	50	20.9	90	37.7
Recurring stomach trouble	42	17.6	36	15.1
Hay fever	37	15.5	21	8.8
Urinary or bladder problems	35	14.6	51	21.3
Persistent foot trouble	35	14.6	29	12.1
Emotional disorder	33	13.8	21	8.8
Persistent skin trouble	30	12.6	25	10.5
Asthma/bronchitis/emphysema	24	10.0	29	12.1
Chronic sleeping problems	24	10.0	25	10.5
Piles or hemorrhoids	22	9.2	18	7.5
Thyroid disease	19	7.9	27	11.3
Migraine headaches	19	7.9	10	4.2
Hernia or rupture	11	4.6	7	2.9
Persistent trouble with your teeth	11	4.6	9	3.8
Being constipated	10	4.2	18	7.5
Other lung problems	9	3.8	8	3.3
Trouble with gums or mouth	7	2.9	2	0.8
Diabetes or high blood sugar	7	2.9	30	12.6
Gall bladder trouble	6	2.5	7	2.9
Ulcer	6	2.5	1	0.4
Neurological disorders	3	1.3	6	2.5
Stroke	2	0.8	2	0.8
Alcohol or drug problems	2	0.8	2	0.8
Autoimmune disorders	2	0.8	5	2.1
Varicose veins requiring treatment	1	0.4	2	0.8
Tuberculosis	0	0.0	2	0.8
AIDs or HIV infection	0	0.0	1	0.4

Repeated measures (baseline, Time 2) analyses of variance were performed for the four health variables separately: self-rated physical health, self-rated mental/emotional health, number of illnesses, and number of medications. The results from these analyses are shown in Table 4.5. Time was significant only for number of medications, which increased from baseline to Time 2.

Table 4.5

Results of Repeated Measures Analysis of Variance for Health Measures

Effect	<i>n</i>	<i>MS</i>	<i>df</i>	<i>F</i>	<i>p</i>
Self-rated Physical Health	239	0.01	1	0.02	0.90
Self-rated Mental/Emotional Health	239	0.10	1	0.19	0.66
# of Illnesses	234	1.34	1	0.41	0.52
# of Medications	229	81.33	1	88.23	0.001**

Note. ** $p < 0.01$

Psychological Well-Being

Descriptive statistics for the eudaimonic (Ryff's Psychological Well-Being) and hedonic (affect and life satisfaction) dimensions of psychological well-being are shown in Table 4.6. At baseline and Time 2, participants reported low levels of negative affect and high levels of positive affect, life satisfaction, and psychological well-being.

Table 4.6

*Baseline and Time 2 Descriptive Statistics for**Psychological Well-Being (N=239)*

	<u>Baseline</u>		<u>Time 2</u>	
	<u>M</u>	<u>(SD)</u>	<u>M</u>	<u>(SD)</u>
Eudaimonic Well-Being				
Ryff's PWB	17.3	(2.0)	17.4	(2.1)
Hedonic Well-Being				
Positive Affect	3.6	(0.6)	3.7	(0.6)
Negative Affect	1.3	(0.5)	1.7	(0.4)
Life Satisfaction	8.3	(1.1)	8.3	(1.0)

Repeated measures (baseline, Time 2) analyses of variance were conducted for each psychological well-being variable separately (Ryff's PWB, affect, and life satisfaction). The results for this analysis are shown in Table 4.7. Only positive affect changed significantly over time and increased. Overall, the participants reported good physical and mental/emotional health and high levels of psychological well-being at baseline and Time 2. In addition, little change was noted over the 10 years between baseline and Time 2.

Table 4.7

Results for Repeated Measures Analysis of Variance for Psychological Well-Being Variables

Effect	<i>n</i>	<i>df</i>	<i>MS</i>	<i>F</i>	<i>p</i>
Ryff's PWB Scale	230	1	1.32	0.87	0.35
Positive Affect	229	1	0.97	5.13	0.02*
Negative Affect	232	1	0.02	0.13	0.72
Life Satisfaction	233	1	0.55	1.12	0.29

Note. * $p < .05$

Inflammation

Descriptive statistics for the inflammatory biomarkers IL-6 and CRP are shown in Table 4.8. Eight participants with CRP levels greater than 10 $\mu\text{g/ml}$ were excluded from these calculations because these levels are indicative of an acute infection and may be unrepresentative of an individual's normal inflammatory levels. In addition, three individuals were missing values for these two measures. The mean value for CRP was lower than observed in the National Health and Nutrition Examination Survey for older adults between 70 and 79 years of age, for which the mean value was 5.7 ($SD=10.5$) (Woloshin & Schwartz, 2005). However, the mean value for IL-6 was somewhat higher than reported in previous studies of participants of similar age (Schaap et al., 2006; Szanton, Allen, Seplaki, Bandeen-Roche, & Fried, 2009; Tiainen, Hurme, Hervonen, Luukaala, & Jylhä, 2010). The "normal" range for IL-6 has not yet been determined, but IL-6 is typically less than 1 pg/ml in young adults and can increase to more than 2.5 mg/ml in older adults (Ferrucci et al., 2005).

Table 4.8

Time 2 Descriptive Statistics for Serum IL-6 and Serum CRP (N=228)

	<u>M</u>	<u>SD</u>
Serum IL-6 (pg/ml)	3.1	3.3
Serum CRP ($\mu\text{g/ml}$)	2.9	5.8

Baseline bivariate correlations among the sociodemographic, health, and psychological well-being variables are shown in table 4.9. Pearson-product moment and Spearman Rank-order correlations were calculated. The Pearson and the Spearman coefficients did not differ by more than 0.10 for any of the correlations, so the Pearson correlations are reported. Older age was

associated with lower negative affect, higher positive affect, and higher life satisfaction. Female gender was associated with more illnesses and medications and higher levels of negative affect. Greater number of illnesses and medications were associated with lower scores on Ryff's Psychological Well-being scale, lower positive affect and life satisfaction, and higher levels of negative affect. Higher self-rated physical and emotional/mental health were associated with higher levels of Ryff's PWB scale, positive affect and life satisfaction, and lower levels of negative affect.

Time 2 bi-variate correlations among the Time 2 sociodemographic, health, psychological well-being, and inflammation biomarkers are shown in table 4.10. These correlations excluded those 8 individuals who had CRP levels greater than 10 $\mu\text{g/ml}$. In general, the associations were similar to those observed at baseline with a few exceptions. Older age was now associated with lower self-rated physical and mental/emotional health, and being female was associated with higher levels of eudaimonic well-being (Ryff's PWB scale). Higher levels of CRP were associated with older age, being female, lower self-rated physical health, more illnesses, more medications, lower levels Ryff's PWB scale, and higher levels of negative affect. Higher levels of IL-6 were related to taking more medications and higher levels of CRP.

Table 4.9

Baseline bi-variate correlations among sociodemographic, health, and psychological well-being variables (N=239)

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. Age	1													
2. Gender ^a	-0.17**	1												
3. Education ^b	0.01	-0.08	1											
4. Race ^c	0.16*	-0.05	0.01	1										
5. Marital Status ^d	0.10	-0.27**	-0.01	0.05	1									
6. Retirement Status ^e	0.44**	-0.26*	0.07	0.12	0.08	1								
7. Income	-0.30**	-0.04	0.26**	-0.05	0.23**	-0.20**	1							
8. Physical health ^f	0.01	0.05	0.05	0.03	0.10	-0.06	0.22**	1						
9. Mental/Emotional health ^g	-0.07	-0.03	0.10	-0.09	0.13*	-0.08	0.24**	0.52**	1					
10. Number of Illnesses	-0.05	0.19**	0.03	0.05	-0.06	0.01	-0.11	-0.37**	-0.36**	1				
11. Number of Medications	-0.03	0.23**	0.02	-0.01	-0.09	0.02	-0.00	-0.28**	-0.13*	0.50**	1			
12. Ryff's PWB ^h	0.06	-0.01	0.15*	-0.01	0.12	0.04	0.13*	0.20**	0.32**	-0.15*	-0.06	1		
13. Negative Affect	-0.13*	0.18**	-0.09	0.05	-0.15*	-0.10	-0.14*	-0.24**	-0.43**	0.42**	0.39**	-0.36**	1	
14. Positive Affect	0.16*	-0.04	-0.01	-0.01	0.04	0.03	0.02	0.27**	0.48**	-0.41**	-0.24**	0.42**	-0.59**	1
15. Life Satisfaction	0.14*	-0.09	-0.64	-0.03	0.17*	0.14*	0.09	0.42**	0.44**	-0.43**	-0.30**	0.44**	-0.55**	0.613**

Note. ** $p < 0.01$, * $p < 0.05$ ^a Gender: Female = 1, Male = 0. ^b Education: High School or Less = 0, At least some College = 1. ^c Race = Non-Caucasian = 0, Caucasian = 1. ^d Marital status: married = 1, Unmarried = 0. ^e Retirement: Retired = 1, Not retired = 0. ^f Self-Rated Physical. ^g Self-rated mental/emotional health. ^h Ryff's Psychological Well-being Scale calculated by averaging the sum of the 6 subscales.

Table 4.10

Time 2 Bi-variate correlations among sociodemographic, health, psychological well-being, and inflammatory biomarkers (N=228)

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1. Age	1														
2. Gender ^a	-0.16*	1													
3. Race ^b	0.12	0.11	1												
4. Marital Status ^c	-0.02	-0.01	0.07	1											
5. Retirement Status ^d	0.23*	0.24**	0.11	0.12	1										
6. Income	-0.19**	-0.20**	0.03	0.27**	-0.21**	1									
7. Physical health ^e	-0.21**	-0.17**	0.08	0.05	-0.04	0.11	1								
8. Mental/Emotional health ^f	-0.103	-0.09	0.04	0.04	-0.04	0.15*	0.49**	1							
9. Number of Illnesses	0.06	0.10	0.03	-0.07	0.02	-0.03	-0.29**	-0.12	1						
10. Number of Medications	0.13*	0.13	-0.01	0.02	0.14*	0.00	-0.37**	-0.08	0.53**	1					
11. Ryff's PWB ^g	-0.05	-0.05	0.01	0.002	0.03	0.10	0.33**	0.37**	-0.16*	-0.18**	1				
12. Negative Affect	-0.08	-0.02	0.06	-0.02	0.01	-0.09	-0.21**	-0.34**	0.26*	0.27**	-0.38**	1			
13. Positive Affect	0.09	0.05	-0.10	0.07	0.02	-0.07	0.28**	0.39**	-0.17**	-0.09	0.51**	-0.57**	1		
14. Life Satisfaction	-0.08	-0.06	0.03	0.23**	0.08	0.10	0.52**	0.33**	-0.29**	-0.31**	0.50**	-0.41**	0.52**	1	
15. Serum IL-6 (log)	0.06	0.045	0.01	0.05	0.02	0.04	-0.08	-0.04	0.08	0.16*	0.04	0.09	0.02	-0.01	1
16. Serum CRP (log)	0.28**	0.29**	0.03	0.01	0.08	-0.08	-0.15*	-0.06	0.28**	0.15*	-0.16*	0.16*	-0.00	-0.13	0.40**

Note. ** $p < 0.01$, * $p < 0.05$ ^a Gender: Female = 1, Male = 0. ^b Race = Non-Caucasian = 0, Caucasian = 1. ^c Marital status: married = 1, Unmarried = 0. ^d Retirement: Retired = 1, Not retired = 0. ^e Self-Rated Physical ^f Self-rated mental/emotional health. ^g Ryff's Psychological Well-being Scale calculated by averaging the sum of the 6 subscales.

Results related to Study Aims

Specific Aim 1 Results

The first specific aim of this study was to describe the baseline and Time 2 bio-psychosocial profiles of non-frail, pre-frail, and frail individuals. To describe these profiles, participants were first classified into frailty groups using data from Time 2 and according to the classification system described in detail in the measurement section in Chapter Three. A total of 124 participants were classified as non-frail, 101 participants were classified as pre-frail, and 11 participants were classified as frail. There were 3 participants who were missing data on one or more of the five frailty characteristics and could therefore not be classified. The frequency and percentage of participants with each characteristic are shown in Table 4.11. The frailty characteristic most frequently exhibited by participants was low activity level.

Table 4.11

Frequency and Percentage of Participants Who had Each Characteristic (N=236)

Frailty Characteristic	<i>n</i>	%
Low Activity Level	59	24.7
Weakness	42	17.6
Poor Endurance / Exhaustion	22	9.2
Weight Loss	20	8.4
Slowness	19	7.9

Table 4.12 describes the frequency and percentage of participants by number of characteristics met. In the sample, 95% had two or fewer characteristics.

Table 4.12

Frequency and Percentage of Participants by Number of Characteristics (N=236)

# of Frailty Characteristics	<i>n</i>	%
0	124	53.2
1	78	32.6
2	23	9.6
3	8	3.4
4	2	0.8
5	1	0.4

The baseline and Time 2 bio-psychosocial profiles for the frailty groups were described and analyzed for group differences. Given the small number of participants in the frail category ($n=11$) and the problems encountered with estimating confidence intervals using small samples, bootstrapping was utilized in these analyses. In bootstrapping, data are repeatedly resampled with replacement (i.e., the sampled case is entered back into the sampling pool before the next sampling) and a sampling distribution of the statistics of interest is estimated (Efron & Tibishirani, 1986; Mooney & Duval, 1993). This estimated sampling distribution is then utilized to calculate the confidence intervals of the statistic, instead of the assumed sampling distribution used in traditional inferential statistics (Mooney & Duval, 1993). In this study, bootstrapping was set to 1,000 samples and sampling with replacement was used. If a significant main effect was observed, Tukey post-hoc comparisons were conducted, and the bootstrapped 95% confidence intervals were used to identify which groups were significantly different from each other.

At baseline, the three groups were compared on sociodemographic and health variables using analysis of variance (ANOVA) for continuous variables (separately for each variable: age, income, self-rated physical health, self-rated mental/emotional health, number of illness, number

of medications) and chi-square analyses for dichotomous variables (i.e., gender, education, marital status, retirement status, and race).

The results of the chi-square analyses are shown in Table 4.13. No significant group differences were observed for gender, education, marital status, retirement status, or race.

Table 4.13

Chi-Square Analysis for Sociodemographic Characteristics by Frailty Group

Characteristic	Frailty Classification			<i>n</i>	χ^2	<i>p</i>
	Non-frail	Pre-frail	Frail			
Gender ^a				236	0.60	0.74
Male	53	47	5			
Female	71	52	5			
Education ^b				235	0.32	0.85
H.S. or less	38	34	3			
At least some college	85	65	7			
Marital Status ^c				236	1.31	0.52
Married	94	101	10			
Not Married	30	23	1			
Retirement Status ^d				236	4.33	0.12
Retired	48	43	7			
Not Retired	66	50	2			
Race/Ethnicity ^e				231	0.84	0.66
Caucasian	117	95	10			
Non-Caucasian	4	5	0			

Note. ^a Gender: Female = 1, Male = 0. ^b Education: High School of Less = 0, At least some College = 1. ^c Marital status: married = 1, Unmarried = 0. ^d Retirement: Retired = 1, Not retired = 0. ^e Race = Non-Caucasian = 0, Caucasian = 1. ** $p < 0.01$, * $p < 0.05$

The results from the ANOVA analyses are shown in Table 4.14. At baseline, there were significant main effects of frailty group on age, self-rated physical health, and number of illnesses. Tukey post-hoc comparisons indicated that frail participants were significantly older than non-frail participants, and frail participants had significantly more illnesses than both non-frail and pre-frail participants. The Tukey post-hoc comparisons did not reveal any significant pair-wise comparisons for self-rated physical health.

Table 4.14

Baseline Sociodemographic and Health Characteristics by Frailty Group

Characteristic	Frailty Classification			<i>n</i>	<i>df</i>	<i>MS</i>	<i>F</i>	<i>p</i>
	Non-frail	Pre-frail	Frail					
Age	61.89 _a (4.74)	62.99 _{ab} (5.92)	66.99 _b (6.66)	233	2	142.17	5.01	0.007**
Income (thousands)	78 (61)	63 (50)	43 (39)	225	2	9.21	2.97	0.054
Self-rated Physical Health	3.79 (0.95)	3.58 (0.85)	3.11 (1.20)	236	2	2.88	3.38	0.036*
Self-rated Mental/Emotional Health	4.00 (0.92)	3.95 (0.86)	3.50 (0.71)	236	2	1.46	1.74	0.178
# of Illnesses	2.23 _a (2.23)	2.53 _a (2.146)	5.00 _b (3.56)	231	2	36.48	7.14	0.001**
# of Medications	0.88 (0.98)	0.93 (1.10)	1.80 (1.10)	236	2	3.29	2.79	0.064

Note. ** $p < 0.01$ * $p < .05$. Standard deviations appear in the parentheses below means. Means with differing subscripts within rows are significantly different based on bootstrapped 95% confidence intervals using Tukey's post-hoc paired comparisons.

At Time 2, the three groups were compared with separate ANOVAs for age, income, self-rated physical health, self-rated mental/emotional health, number of illness, and number of medications). The results are shown in Table 4.15. There were main effects of frailty group on

age, self-rated physical health, and self-rated mental/emotional health. Tukey post-hoc comparisons indicated that frail participants were significantly older than non-frail participants. For self-rated physical health, frail participants reported significantly lower levels than pre-frail and non-frail participants. For self-rated mental/emotional health, pre-frail and frail participants had significantly lower levels than non-frail participants.

Table 4.15

Time 2 Sociodemographic and Health Characteristics by Frailty Group

Characteristic	Frailty Classification			<i>n</i>	<i>df</i>	<i>MS</i>	<i>F</i>	<i>p</i>
	Non-frail	Pre-frail	Frail					
Age	71.23 _a (4.83)	72.23 _a (5.75)	75.80 _b (6.94)	236	2	137.50	4.89	0.008**
Income (thousands)	53 (45)	51 (46)	34 (28)	229	2	1.70	0.84	0.43
Self-rated Physical Health	3.71 _a (0.88)	3.63 _a (0.96)	3.10 _b (1.10)	236	2	3.55	4.22	0.016*
Self-rated Mental / Emotional Health	4.07 _a (0.92)	3.78 _b (0.94)	3.60 _b (0.97)	236	2	3.92	5.07	0.007**
# of Illnesses	2.23 (1.91)	2.73 (2.42)	3.70 (2.45)	236	2	7.95	1.08	0.34
# of Medications	1.46 (1.21)	1.74 (1.52)	1.82 (1.40)	227	2	2.37	1.29	0.28

Note. ** $p < 0.01$ * $p < 0.05$. Standard deviations appear in the parentheses below means. Means with differing subscripts within rows are significantly different based on bootstrapped 95% confidence intervals using Tukey's post-hoc paired comparisons.

For psychological well-being (Ryff's PWB, positive affect, negative affect, and life satisfaction) baseline ANCOVAs were conducted separately for each measure by frailty group with age and number of illnesses as the covariates. These covariates were chosen because they were significantly different among frailty groups in the previous analyses. Results from these

ANCOVAs are shown in Table 4.16. There were no significant group differences on any of the psychological well-being variables.

Table 4.16

Baseline Psychological Well-being by Frailty Group

Characteristic	Frailty Classification			<i>n</i>	<i>df</i>	<i>MS</i>	<i>F</i>	<i>p</i>
	Non-Frail	Pre-Frail	Frail					
Ryff's PWB Scale	17.39 (1.97)	17.35 (2.06)	16.82 (1.78)	229	2	0.60	0.15	0.86
Positive Affect	3.60 (0.64)	3.57 (0.68)	3.62 (0.80)	230	2	0.31	0.88	0.42
Negative Affect	1.30 (0.44)	1.36 (0.47)	1.52 (0.64)	231	2	0.06	0.36	0.70
Life Satisfaction	8.33 (8.28)	8.30 (1.02)	7.40 (1.26)	231	2	1.30	1.27	0.28

Note. Covariates were age and number of chronic conditions.

At Time 2, ANCOVAs were conducted separately for each psychological well-being measure (Ryff's PWB, positive affect, negative affect, and life satisfaction) by frailty group. Age, self-rated physical health and self-rated mental/emotional health were entered as covariates because they were significantly different across the groups at Time 2. The results for this analysis are shown in Table 4.17. There were no main effects for group on any of the psychological well-being variables.

Table 4.17

Time 2 Psychological Well-being by Frailty Group

Characteristic	Frailty Classification			<i>n</i>	<i>df</i>	<i>MS</i>	<i>F</i>	<i>p</i>
	Non-frail	Pre-frail	Frail					
Ryff's PWB Scale	17.59 (2.06)	17.39 (1.98)	15.83 (1.78)	235	2	5.35	1.52	0.22
Positive Affect	3.71 (0.56)	3.64 (0.67)	3.62 (0.58)	233	2	0.17	0.16	0.85
Negative Affect	1.26 (0.35)	1.36 (0.41)	1.52 (0.66)	234	2	0.05	0.99	0.37
Life Satisfaction	8.42 (0.98)	8.34 (1.02)	7.27 (1.35)	236	2	2.09	2.70	0.07

Note. Covariates were age, self-reported emotional/mental health, and self-reported physical health.

Inflammatory biomarkers (IL-6 and CRP) were only measured at Time 2. Participants whose untransformed CRP levels were greater than 10 µg/ml (n=8) were excluded from these analyses given that such elevated levels are considered indicative of acute infection. ANCOVAs were tested separately for each biomarker by frailty group. Age, self-reported physical health status, self-reported mental/emotional health status and whether or not individuals had taken anti-depressants, anti-hypertensive medications, or corticosteroids in the past 30 days were used covariates. Age, self-reported physical health status, and self-reported mental/emotional health status were chosen as covariates given their observed group differences at Time 2. The three medication variables were included because they are known to have effects of serum IL-6 and CRP levels (Fliser, Buchholz, & Haller, 2004; Kenis & Maes, 2002; Silversti et al., 2003). The three medication variables were dummy coded as "0" if the participant had not taken the medication or "1" if the participant reported taking that specific medication in the past 30 days.

The results from these analyses are shown in Table 4.18. There was a significant main effect for frailty group for serum CRP. Tukey post-hoc pairwise comparisons indicated pre-frail and frail individuals had significantly higher levels of CRP than non-frail. No significant group differences were observed for IL-6 serum levels. However, the p value was 0.052, so it may have been the small number of frail individuals limited to the ability to detect significant group difference on IL-6 even though bootstrapping was utilized.

Table 4.18

Time 2 Inflammatory Biomarkers by Frailty Group

Biomarker	Frailty Classification			<i>n</i>	<i>MS</i>	<i>df</i>	<i>F</i>	<i>p</i>
	Non-frail <i>M</i> (SD)	Pre-frail <i>M</i> (SD)	Frail <i>M</i> (SD)					
Serum CRP (log)	0.07 (0.97) _a	0.41 (0.92) _b	1.08 (0.89) _b	225	6.76	2	7.81	0.001**
Serum IL-6 (log)	0.77 (0.56)	0.99 (0.56)	1.41 (0.64)	225	1.22	2	2.99	0.052

Note. ** $p < 0.01$ Serum samples of CRP and IL-6 were missing for 3 participants and 8 participants with CRP levels greater than 10 µg/ml were not included in these analyses. Age, self-reported physical health, self-reported mental/emotional, corticosteroid, antihypertensive, and anti-depressive medications were covariates.

Specific Aims 2 and 3

The second aim of this study was to examine the influence of baseline sociodemographic, health, and psychological well-being variables, and change in psychological well-being over time on Time 2 frailty group classification. The third aim of this study was to examine the role of inflammatory biomarkers as a mediator of the relationship between psychological well-being and frailty group. Figure 4.1 illustrates the conceptual framework guiding these specific aims.

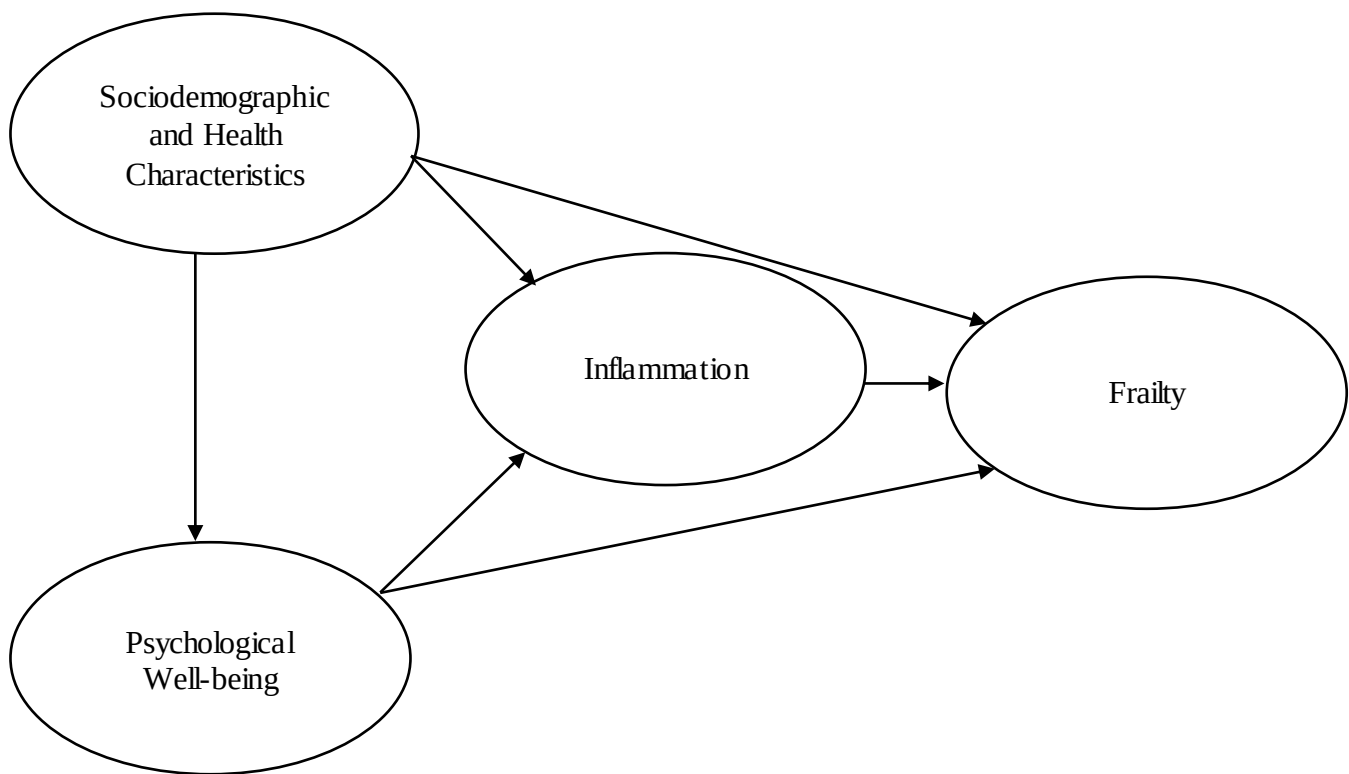


Figure 4.1 Conceptual Framework

For Specific Aim 2, whether psychological well-being variables changed over time was examined first using a 3 (group) by 2 (Time) ANCOVA for each psychological well-being variable separately. The covariates for this analysis were those found to be significantly different between the groups at baseline: age and number of illnesses. Results for this analysis are shown in Table 4.19. The main effects for group were not significant. There was a significant main effect for time for life satisfaction, but not for any of the other psychological well-being measures. None of the group-by-time interactions was significant. Given that there were no significant changes over time for Ryff's Psychological Well-Being, positive affect, or negative affect, the Time 2 measures of these variables were not included in the subsequent analyses for Aims 2 and 3.

Table 4.19

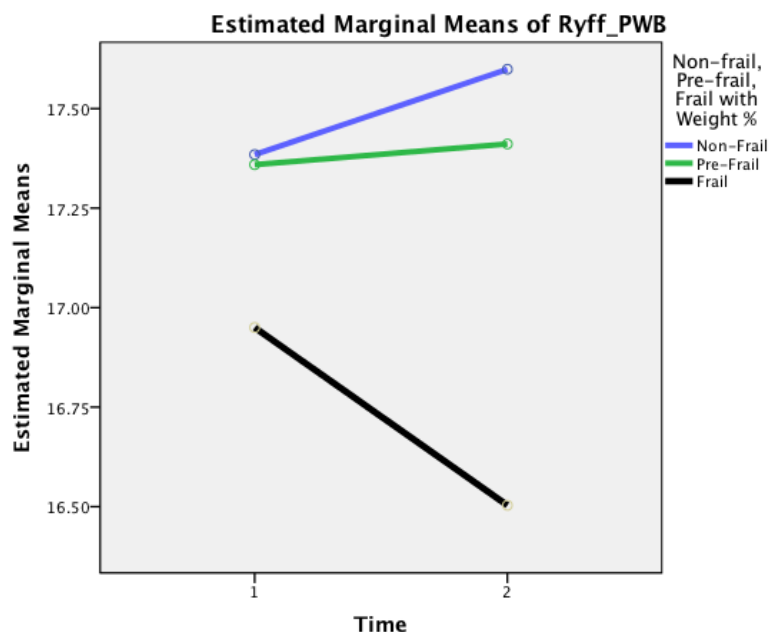
Repeated Measures Analysis of Covariance for Psychological Well-being

Source	<i>n</i>	<i>df</i>	<i>F</i>	η^2	<i>p</i>
Group					
Ryff's PWB	228	2	0.799	0.007	0.451
Positive Affect	227	2	0.546	0.005	0.580
Negative Affect	229	2	1.186	0.010	0.307
Life Satisfaction	231	2	2.023	0.018	0.135
Time					
Ryff's PWB	228	1	3.40	0.015	0.07
Positive Affect	227	1	0.491	0.002	0.484
Negative Affect	229	1	0.000	0.000	0.993
Life Satisfaction	231	1	8.530	0.036	0.004*
Time x Group					
Ryff's PWB	228	2	0.731	0.007	0.482
Positive Affect	227	2	0.827	0.007	0.439
Negative Affect	229	2	0.588	0.005	0.556
Life Satisfaction	231	2	0.087	0.001	0.971

Note. * $p < 0.01$ Covariates were baseline age and number of illnesses.

Profile plots of the estimated marginal means from these analyses are shown in Figures 4.2 thru 4.5. In Figure 4.2, psychological well-being shows an increasing trend for non-frail and pre-frail participants and a decreasing trend for frail participants. In Figure 4.3, positive affect shows an increasing trend for non-frail and pre-frail participants and a decreasing trend for frail

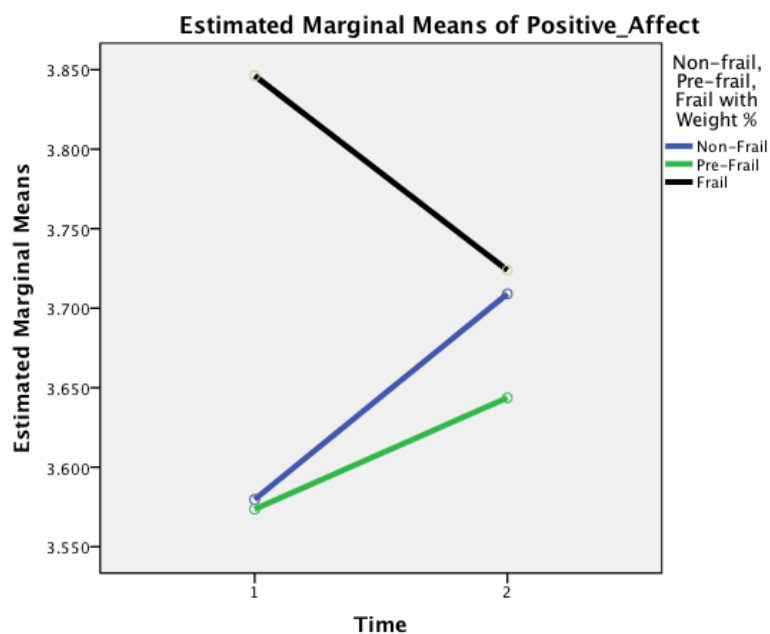
participants. In Figure 4.4, negative affect shows a decreasing trend for non-frail participants, a stable trend for pre-frail participants, and an increasing trend for frail participants. In Figure 4.5 life satisfaction shows an increasing trend for non-frail and pre-frail and decreasing trend for frail participants.



Covariates appearing in the model are evaluated at the following values: M1 age computed by subtracting Date of Birth from M1 interview date = 62.48, Sum of chronic conditions = 2.50

Figure 4.2 Profile plot for Estimated Marginal Means for Repeated Measures Analysis of Covariance for Ryff's PWB.

Note. Covariates were baseline age and number of illnesses.



Covariates appearing in the model are evaluated at the following values: M1 age computed by subtracting Date of Birth from M1 interview date = 62.55, Sum of chronic conditions = 2.51

Figure 4.2 Profile plot for Estimated Marginal Means for Repeated Measures Analysis of Covariance for Positive Affect.

Note. Covariates were baseline age and number of illnesses.

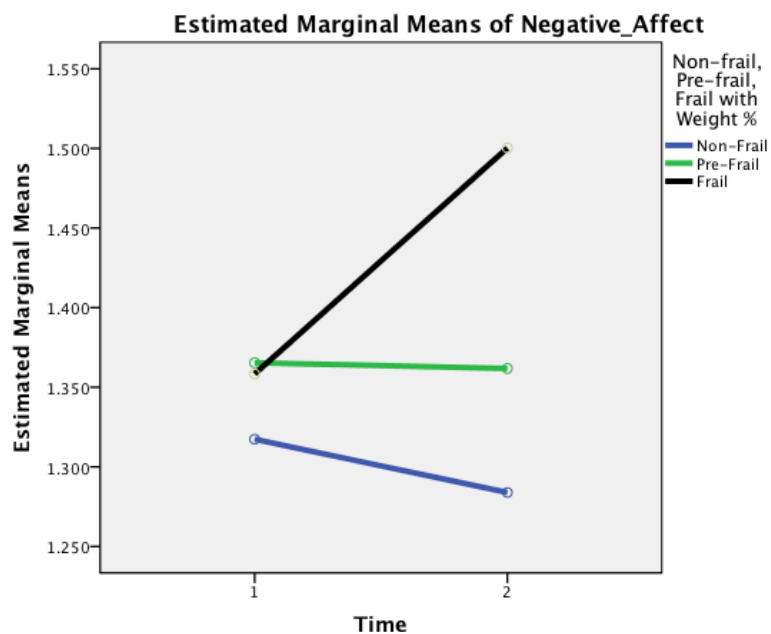
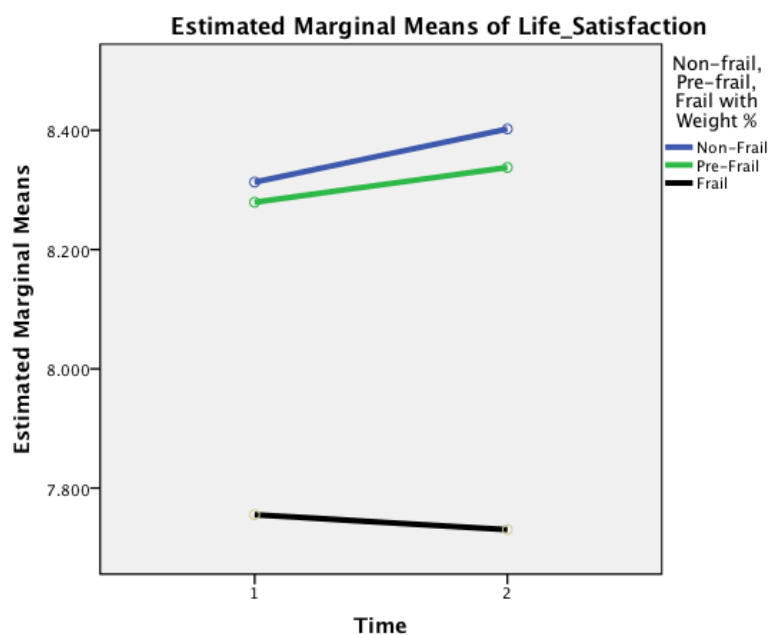


Figure 4.3 Profile plot for Estimated Marginal Means for Repeated Measures Analysis of Covariance for Negative Affect.

Note. Covariates were baseline age and number of illnesses.



Covariates appearing in the model are evaluated at the following values: M1 age computed by subtracting Date of Birth from M1 interview date = 62.53, Sum of chronic conditions = 2.49

Figure 4.5 Profile plot for Estimated Marginal Means for Repeated Measures Analysis of Covariance for Life Satisfaction

Note. Covariates were baseline age and number of illnesses.

An attempt was made to address specific aims two and three by testing two probit models with frailty group (i.e., non-frail, pre-frail, and frail) as the dependent variable using the statistical program Mplus 6.0 (Muthén & Muthén, Los Angeles, CA). This approach also utilized Composite Indicator Structure Equation Modeling, which incorporates measurement error of the composite psychological well-being variables (i.e., Ryff's PWB, positive affect, negative affect, and life satisfaction) into the model and improves the accuracy of parameter estimates (Bandalos, 2002). Measurement error was calculated with the following equation: $[(1 - \text{Chronbach's } \alpha) \times (\text{variance of the composite variable})]$, and the composite variable was then set to equal this value within the model.

The original eudaimonic model is shown in Figure 4.6. For specific aim 2, the direct effects (i.e., the bolded lines) of baseline age, number of illnesses, and Ryff's Psychological Well-Being measure on frailty group were examined. Age and number of illnesses were selected because those variables were found to be significantly different across groups in previous analyses (see Specific Aim 1). For specific Aim 3, the mediating role of the inflammatory biomarkers, IL-6 and CRP, was examined by estimating the indirect effects (i.e., the dashed lines in the figure) of baseline Ryff's Psychological Well-Being on frailty group through IL-6 and CRP. The covariates of sex, anti-depressive, corticosteroid, and anti-hypertensive medications were added given their known effects on inflammation. Indirect effects were calculated by first estimating the direct effects between the mediating variable and the independent variable and between the mediating variable and the dependent variable. The product of these two direct paths was then calculated to estimate the indirect effect (MacKinnon, 2008). For example, to calculate the indirect effect of baseline Ryff's Psychological Well-Being on number of frailty characteristics through IL-6, the direct effect between Ryff's Psychological Well-Being and IL-6

is estimated, the direct effect between number of frailty characteristics and IL-6 is estimated, and then the coefficients of those two effects are multiplied.

The original hedonic model is shown in Figures 4.7 and 4.8. The model is shown in two figures for clarity. For specific aim 2, the direct effects (i.e., the bolded lines) of baseline age, number of illnesses, baseline life satisfaction, negative affect, positive affect, and Time 2 life satisfaction on frailty group were examined. Age and number of illnesses were selected because those variables were found to be significantly different across groups in previous analyses (see Specific Aim 1). For specific Aim 3, the mediating roles of the inflammatory biomarkers, IL-6 and CRP, were examined by estimating the indirect effects (i.e., the dashed lines in the figure) of baseline life satisfaction, positive affect, and negative affect and Time 2 life satisfaction on frailty group through IL-6 and CRP. The covariates of sex, anti-depressive, corticosteroid, and anti-hypertensive medications were added as covariates given their known effects on inflammation.

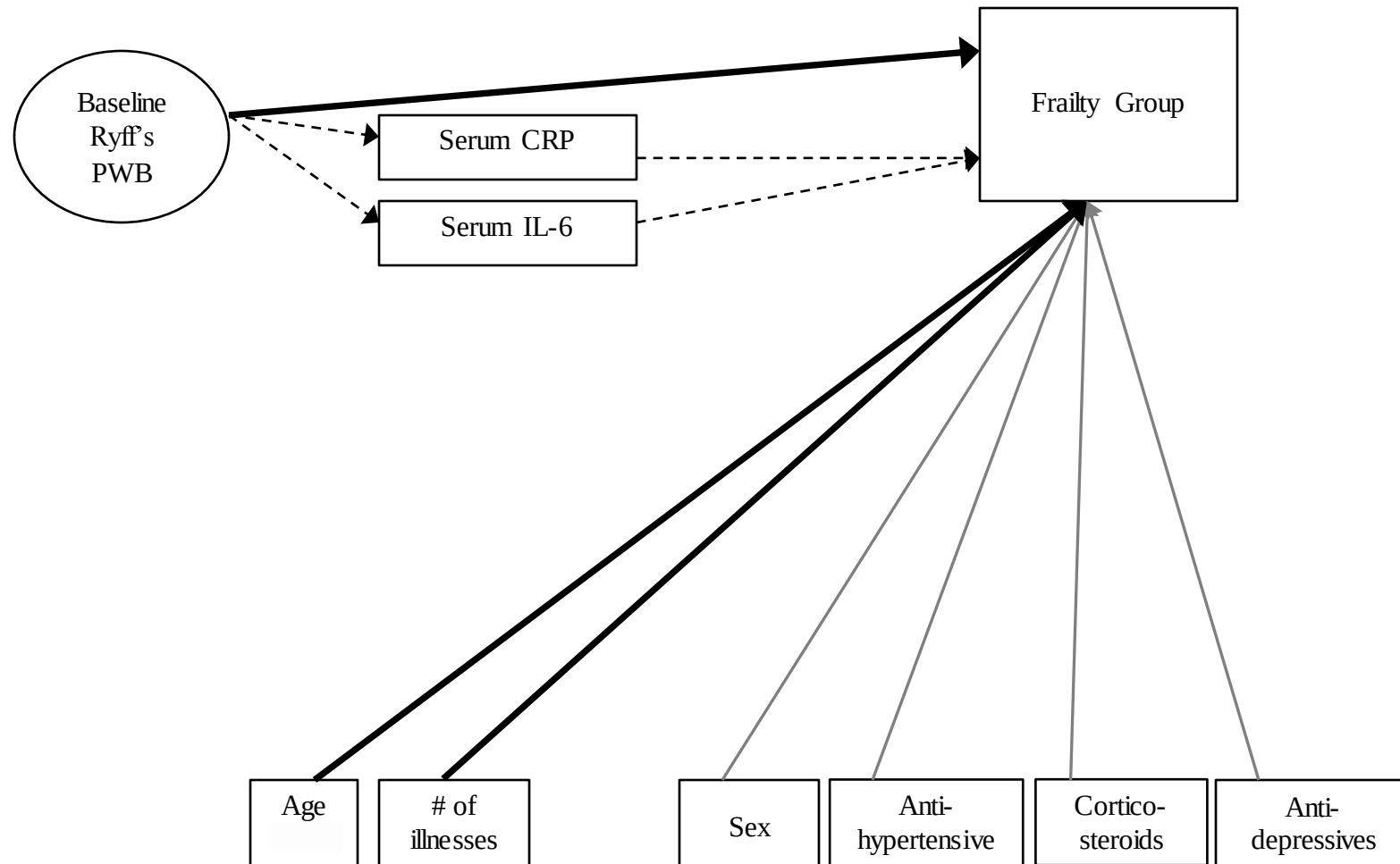
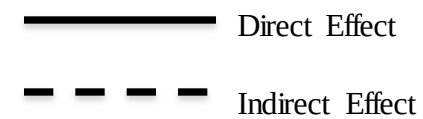


Figure 4.6 Original Eudaimonic Model



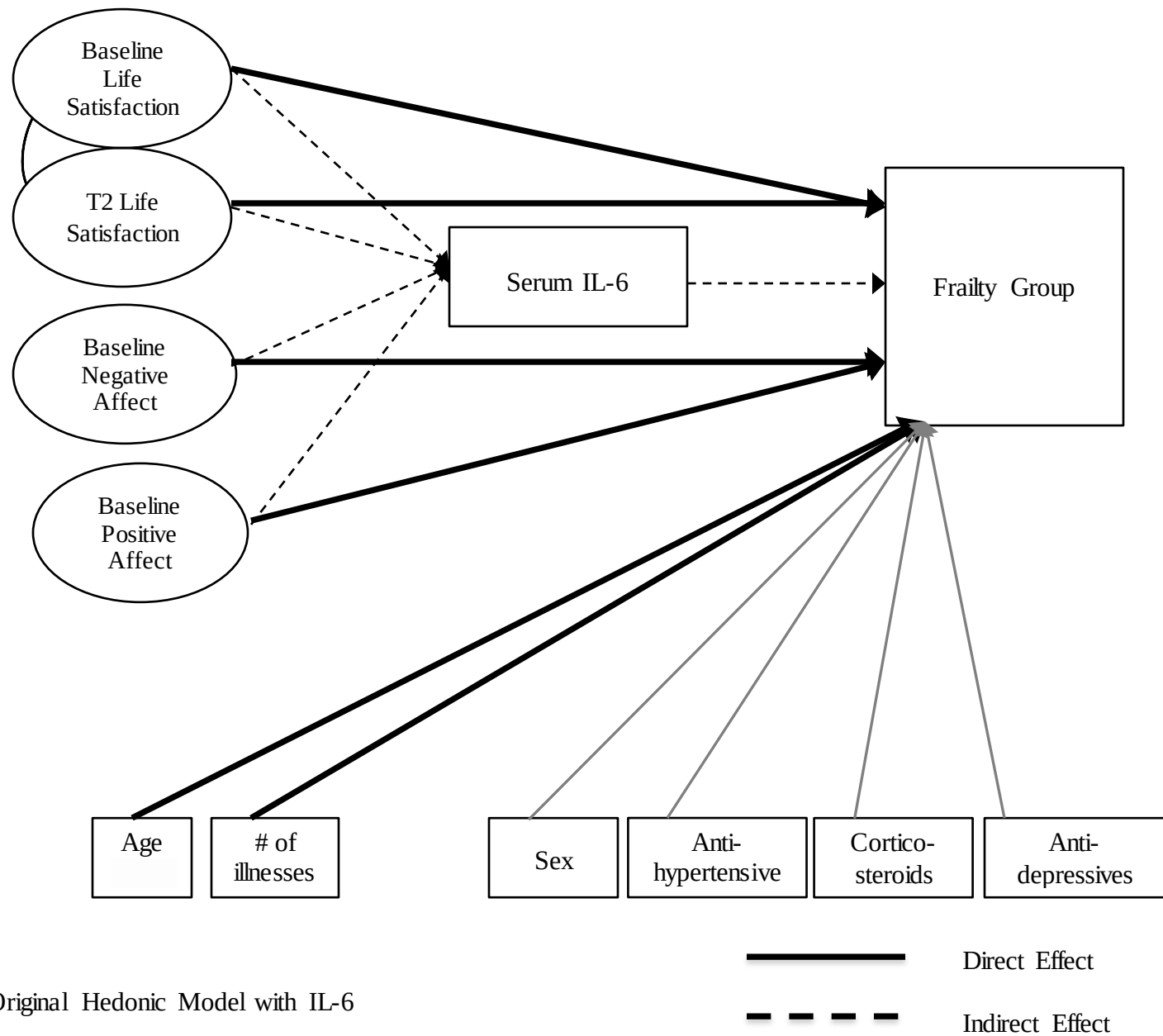


Figure 4.7 Original Hedonic Model with IL-6

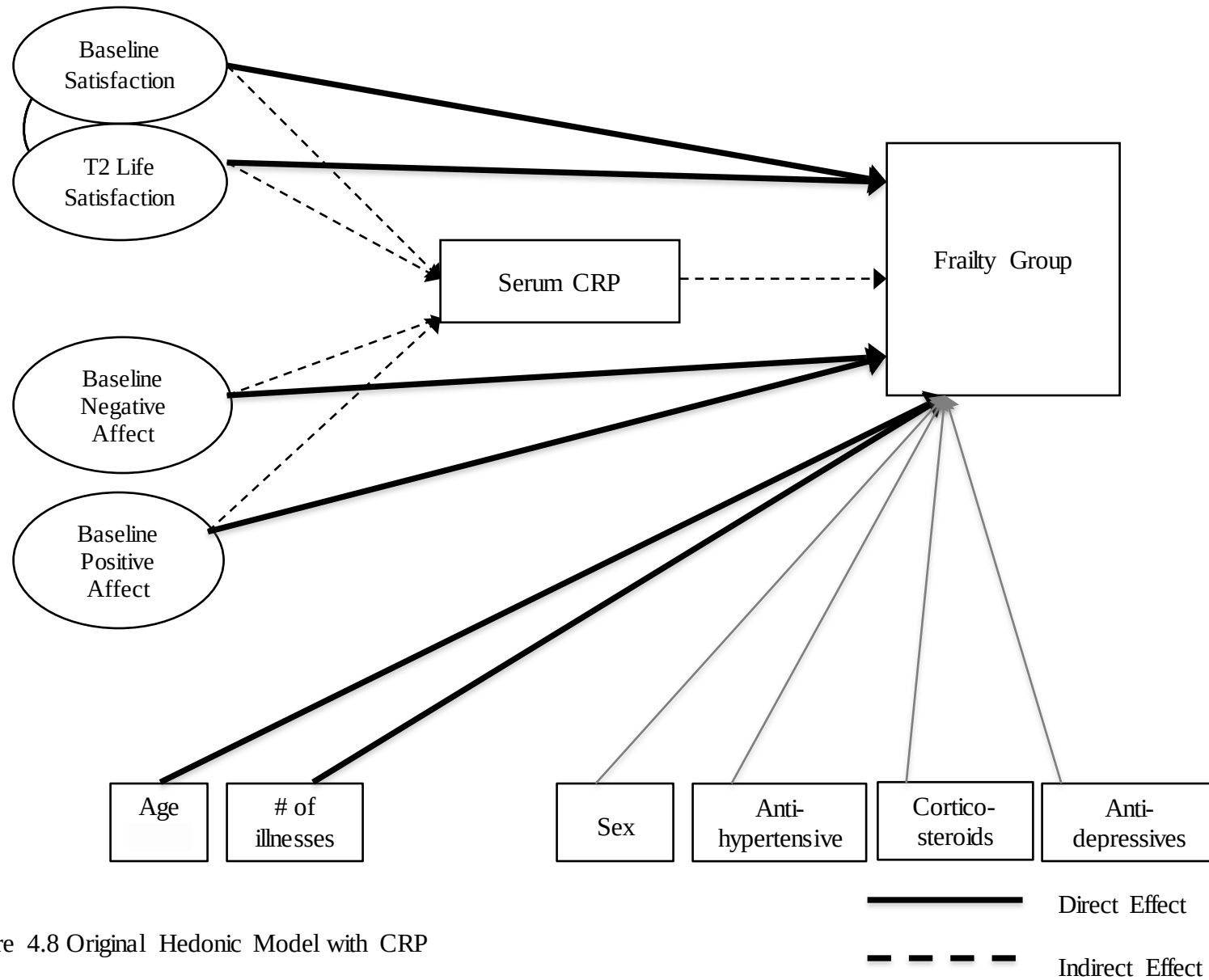


Figure 4.8 Original Hedonic Model with CRP

The analyses of these models were unsuccessful due to non-convergence. Without convergence, parameter estimates are not calculated, and the model cannot be examined.

A second approach was then used in which the number of frailty characteristics (0 to 5) was the dependent variable. That is, the dependent measure was changed from a nominal to an ordinal measure. This approach was conceptually consistent with the original approach given that as the number of frailty characteristics increase, the frailty classification changes. As shown in Figure 4.9, the distribution of the number of frailty characteristics followed a Poisson distribution: it was truncated at 0 and positively skewed (Allison, 1999). In addition, a large proportion of the observations were clustered around the 0 value indicating the distribution was “zero-inflated”. Such a distribution violates the statistical assumptions of ordinary least squares regression and must be analyzed using another approach, specifically zero-inflated Poisson regression or zero-inflated negative binomial regression (Allison, 1999; Hutchinson & Holtman, 2005). Poisson regression assumes the dependent variable follows a Poisson distribution and exhibits equidispersion, equality of the mean and the variance. Negative binomial regression assumes a Poisson distribution, but does not make any assumptions regarding dispersion. Mplus provides a dispersion parameter estimate for count variables such as the dependent variable used in this study. The parameter estimate was 0.114 with a two-tailed p-value of 0.461, indicating equidispersion was present and zero-inflated Poisson regression could be utilized.

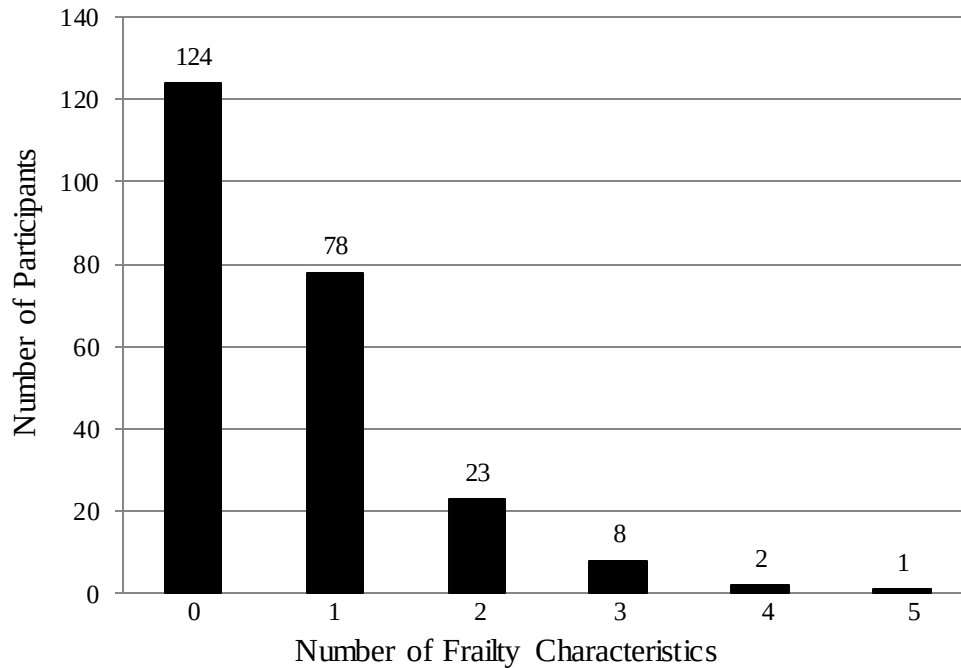


Figure 4.9 Distribution of Number of Frailty Characteristics.

In zero-inflated Poisson regression, two models are estimated. The inflated model estimates specified parameters using logistic regression with the “non-zero” categories (i.e., those with 1 to 5 frailty characteristics) as the reference category and the “zero” category (i.e., 0 frailty characteristics) as the comparison category. The parameter estimates from the inflated model are then utilized in the Poisson model to correct for the overrepresentation of zero counts in the distribution and to improve the model’s parameter estimates (Hutchinson & Holt, 2005). The Poisson model then uses the natural log of the outcome variable in the analysis, and coefficients can be interpreted by calculating the change in the outcome count expected with each unit increase in the independent variable (Allison, 1999). This can be calculated with the following equation ($100 \times [e^{\mathbf{B}} - 1]$) where e is the constant 2.718 and $\mathbf{B}$ is the regression coefficient.

In the current study, the reference category included participants who had 1 to 5 frailty characteristics, and participants who had 0 frailty characteristics were the comparison category in the inflated model. Age, number of illnesses, and the two inflammatory biomarkers were chosen as covariates for the inflated model. Figure 4.10 shows the operationalized eudaimonic well-being Poisson portion of the model. The direct paths for Ryff's Psychological Well-being, age, and number of illnesses were examined for Specific Aim 2. Two indirect paths were examined for Specific Aim 3: baseline Ryff's PWB on number of frailty characteristics through IL-6 and baseline Ryff's PWB on number of frailty characteristics through CRP.

Figure 4.11 shows the operationalized hedonic well-being Poisson portion of the model with the mediating variable, serum CRP as an example. Both variables were estimated within the same model, but only one is shown for the sake of clarity given the number of paths to be estimated. The direct paths of baseline and Time 2 life satisfaction, baseline positive affect, baseline negative affect, age and number of illnesses were examined for Specific Aim 2. Eight indirect paths were examined for Specific Aim 3 (4 for each biomarker): baseline and Time 2 life satisfaction on number of frailty characteristics through IL-6 and through CRP; and baseline positive affect and baseline negative affect through IL-6 and through CRP on number of frailty characteristics.

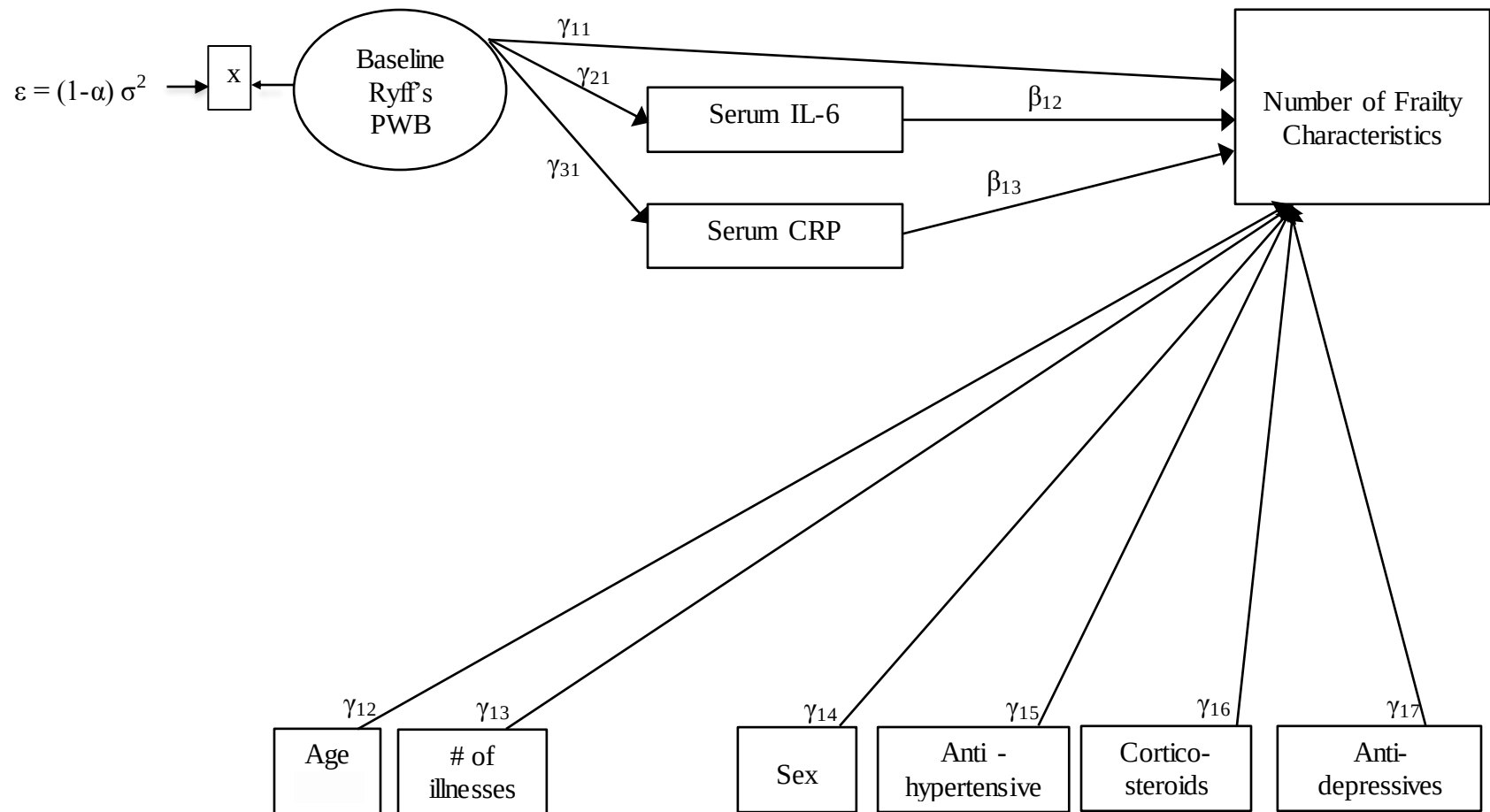


Figure 4.10 Operationalized Eudaimonic Model

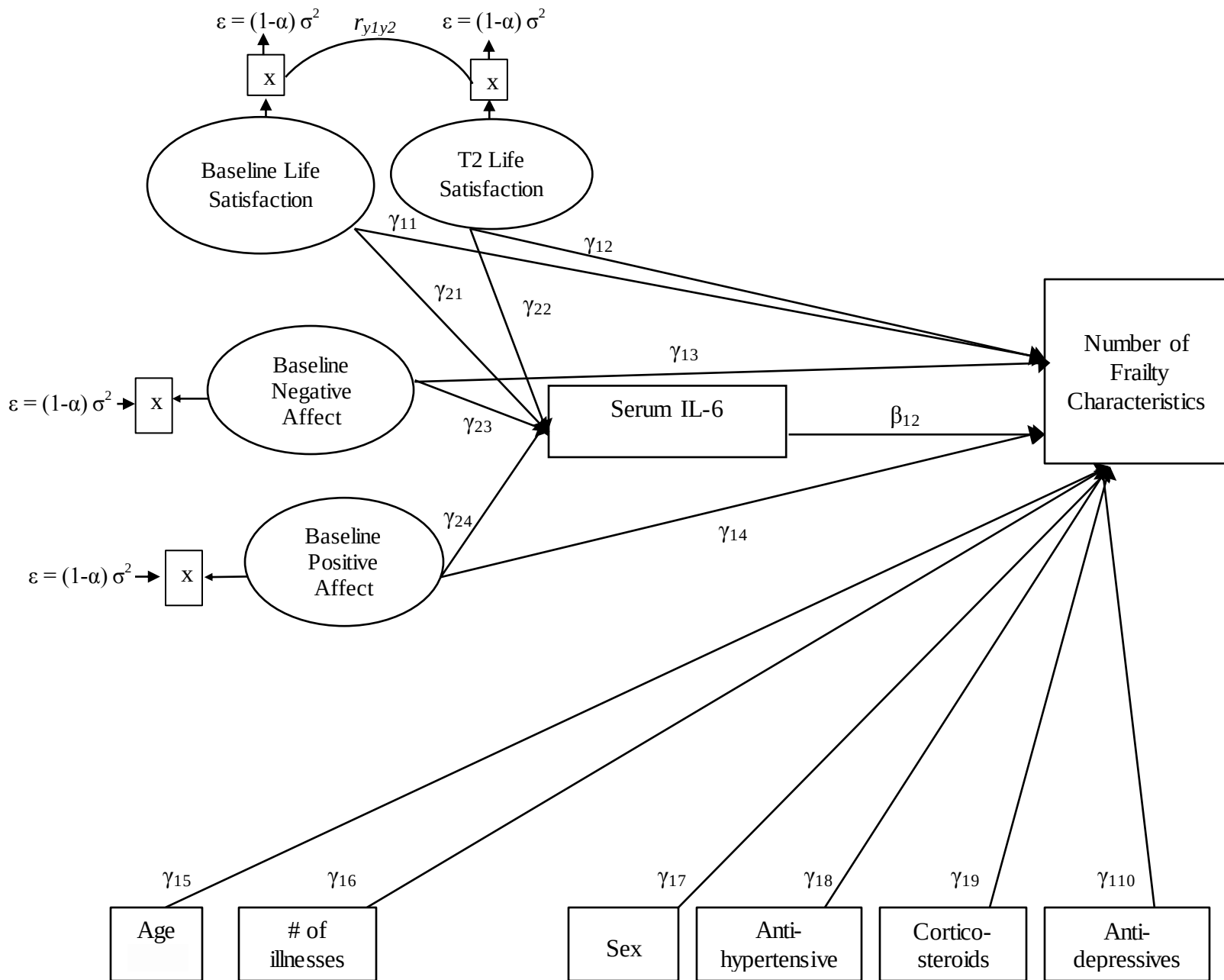


Figure 4.11 Operationalized Hedonic Model with IL-6

In both the eudaimonic and hedonic Models, 16 participants were excluded from the analyses due to missing data. These participants were compared to participants who were included in the sample on key variables using boot-strapped t-tests and chi-square analyses. Results from these analyses are shown in tables 4.20 and 4.21, respectively. There were no significant differences between those excluded and those included in the zero-inflated Poisson regression models.

Table 4.20

Comparison of Participants Excluded and Participants Included in Zero-Inflated Poisson Models

	Included (n=223)		Excluded (n=16)	
	<u>M</u>	<u>(SD)</u>	<u>M</u>	<u>(SD)</u>
<i>Baseline</i>				
Age	62.5	(5.4)	64.1	(6.8)
Income (thousands)	71	(55)	76	(75)
Self-rated physical health	3.7	(0.9)	3.6	(0.9)
Self-rated emotional health	3.9	(0.9)	4.4	(0.9)
Number of Illnesses	2.4	(2.3)	3.5	(2.3)
Number of Medications	0.9	(1.1)	1.1	(1.1)
Negative Affect	1.3	(0.5)	1.3	(0.4)
Positive Affect	3.6	(0.6)	3.8	(0.9)
Life Satisfaction	8.3	(1.1)	8.4	(1.1)
Ryff's PWB	17.3	(2.0)	18.1	(1.8)
<i>Time 2</i>				
Age	71.8	(5.3)	74.2	(5.7)
Income (thousands)	51	(45)	50	(46)
Self-rated physical health	3.9	(0.9)	3.8	(1.1)
Self-rate emotional health	3.6	(0.9)	3.4	(1.0)
Number of Illnesses	2.4	(2.2)	2.8	(1.9)
Number of Medications	1.7	(1.6)	2.3	(1.8)
Negative Affect	1.3	(0.4)	1.3	(0.3)
Positive Affect	3.7	(0.6)	3.7	(0.6)
Life Satisfaction	8.4	(1.0)	8.0	(1.4)
Ryff's PWB	17.5	(2.0)	16.6	(3.2)

Table 4.21

Comparison of Participants Excluded and Participants Included in Zero-Inflated Poisson Models

Characteristic	Included (n=223)	Excluded (n=16)	χ^2	<i>p</i>
Baseline Gender ^a			0.02	0.88
Male	102	7		
Female	121	9		
Baseline Education ^b			0.38	0.54
High School or Less	72	4		
At least some college	150	12		
Baseline Marital Status ^c			0.99	0.32
Married	171	14		
Not Married	52	2		
Baseline Retirement Status ^d			0.05	0.82
Retired	90	6		
Not Retired	133	10		
Baseline Race/Ethnicity ^e			0.50	0.48
Caucasian	214	12		
Non-Caucasian	9	0		
Time 2 Marital Status ^c			1.30	0.26
Married	150	13		
Not Married	72	3		
Time 2 Retirement Status ^d			1.46	0.23
Retired	168	10		
Not Retired	53	6		

Note. ^a Gender: Female = 1, Male = 0. ^b Education: High School of Less = 0, At least some College = 1. ^c Marital status: married = 1, Unmarried = 0. ^d Retirement: Retired = 1, Not retired = 0. ^e Race = Non-Caucasian = 0, Caucasian = 1. ** $p < 0.01$, * $p < 0.05$

Specific Aim 2 Results. The direct path coefficients for the eudaimonic and hedonic models are shown in tables 4.22 and 4.23, respectively. In Table 4.22, the results for Specific Aim 2 are the path coefficients for baseline Ryff's PWB, baseline age, and baseline number of illnesses underneath the "*Poisson Portion*" heading. For the eudaimonic model, none of the direct paths were significant. In Table 4.23, the results for Specific Aim 2 are the path coefficients for baseline life satisfaction, Time 2 life satisfaction, baseline positive affect, baseline negative affect, baseline age, and baseline number of illnesses underneath the "*Poisson Portion*" heading. For the hedonic model, none of the direct paths were significant.

Table 4.22

Path Coefficients, Standard Errors, and 95% Confidence Intervals for Eudaimonic Model (N =223)

	Path Coefficient	Unstandardized Estimate	Standardized Standard Error	95% CI	Standardized Estimate
<i>Inflate Portion</i>					
Non-frail on					
Age		0.016	0.087	(-0.159, 0.181)	0.011
# of Illnesses		-3.076	0.047	(-1.025, -0.841)	-0.933**
IL-6		1.267	0.110	(-0.107, 0.326)	0.109
CRP		1.910	0.076	(0.095, 0.394)	0.244**
<i>Poisson Portion</i>					
# Frailty Characteristics on					
Baseline Ryff's PWB	γ_{11}	-0.050	0.137	(-0.422, 0.115)	-0.153
Age	γ_{12}	0.016	0.144	(-0.130, 0.433)	0.152
# of Illnesses	γ_{13}	0.014	0.150	(-0.236, 0.353)	0.059
Sex	γ_{14}	-0.080	0.147	(-0.359, 0.218)	-0.071
Anti-hypertensives	γ_{15}	0.551	0.131	(0.227, 0.741)	0.484**
Corticosteroids	γ_{16}	-0.572	0.139	(-0.629, 0.083)	-0.356*
Anti-depressives	γ_{17}	0.183	0.138	(-0.172, 0.369)	0.099
IL-6	β_{12}	0.300	0.158	(0.040, 0.660)	0.350*
CRP	β_{13}	0.363	0.109	(0.413, 0.839)	0.626**
IL-6 on					
Baseline PWB	γ_{21}	-0.010	0.087	(-0.199, 0.144)	-0.027
CRP on					
Baseline PWB	γ_{31}	-0.031	0.076	(-0.206, 0.094)	-0.056

Note. ** $p < .01$, * $p < .05$. A total of 16 participants were excluded from analyses: 3 were missing data on the dependent variable (i.e., number of frailty characteristics), 3 were missing data on the CRP and IL-6 measures, 8 had CRP levels greater than 10 $\mu\text{g/ml}$, and 2 were missing data on Baseline Ryff's PWB measure.

Table 4.23

Path Coefficients, Standard Errors, and 95% Confidence Intervals for Hedonic Model (N =223)

	Path Coefficient	Unstandardized Estimate	Standardized Standard Error	95% CI	Standardized Estimate
<i>Inflate Portion</i>					
Non-frail on					
Age		0.019	0.090	(-0.163, 0.190)	0.013
# of Illnesses		-3.124	0.051	(-1.032, -0.831)	-0.931**
IL-6		1.387	0.115	(-0.107, 0.343)	0.118
CRP		1.900	0.080	(0.081, 0.397)	0.239**
<i>Poisson Portion</i>					
# Frailty Characteristics on					
Baseline LS	γ_{11}	-0.440	0.605	(-1.931, 0.442)	-0.745
Time 2 LS	γ_{12}	0.177	0.387	(-0.540, 0.975)	0.218
Baseline NA	γ_{13}	0.326	0.325	(-0.449, 0.824)	0.188
Baseline PA	γ_{14}	0.607	0.393	(-0.190, 1.351)	0.580
Age	γ_{15}	0.018	0.134	(-0.099, 0.425)	0.163
# of Illnesses	γ_{16}	-0.002	0.148	(-0.299, 0.283)	-0.008
Sex	γ_{17}	-0.143	0.131	(-0.376, 0.139)	-0.119
Anti-hypertensives	γ_{18}	0.536	0.127	(0.193, 0.692)	0.443**
Corticosteroids	γ_{19}	-0.491	0.137	(-0.556, -0.018)	-0.287*
Anti-depressives	γ_{110}	0.166	0.127	(-0.166, 0.334)	0.084
IL-6	β_{12}	0.280	0.156	(0.001, 0.611)	0.306*
CRP	β_{13}	0.305	0.161	(0.178, 0.811)	0.495**
Baseline LS with T2 LS	r_{y1y2}	0.590	0.066	(0.305, 0.875)	0.789**

Table 4.23 (continued)

	Path Coefficient	Unstandardized Estimate	Standardized Standard Error	95% CI	Standardized Estimate
IL-6 on					
Baseline LS	γ_{21}	-0.542	1.061	(-2.919, 1.241)	-0.839
Time 2 LS	γ_{22}	0.272	0.648	(-0.964, 1.575)	0.306
Baseline NA	γ_{23}	-0.770	0.309	(-1.011, 0.199)	-0.405
Time 1 PA	γ_{24}	0.208	0.486	(-0.771, 1.134)	-0.181
CRP on					
Baseline LS	γ_{31}	-1.166	1.066	(-3.286, 0.856)	-1.219
Time 2 LS	γ_{32}	0.826	0.648	(-0.636, 1.886)	0.627
Baseline NA	γ_{33}	-0.333	0.305	(-0.717, 0.480)	-0.118
Baseline PA	γ_{34}	1.008	0.525	(-0.435, 1.625)	0.595

Note. ** $p < .01$, * $p < .05$. A total of 16 participants were excluded from analyses: 3 were missing data on the dependent variable (i.e., number of frailty characteristics), 3 were missing data on the CRP and IL-6 measures, 8 had CRP levels greater than 10 $\mu\text{g/ml}$, 1 was missing data on Baseline PA, and 1 was missing data on Time 2 Life Satisfaction.

Specific Aim 3 Results. The indirect paths were calculated using the direct path coefficients of each psychological well-being variable (Ryff's PWB, life satisfaction, affect) to the inflammatory biomarkers and the direct path coefficients from the biomarkers to the number of frailty characteristics. For the eudaimonic model, these direct effects are shown in Table 4.22. There were significant direct effects for the covariates, corticosteroids ($\gamma_{16} = -0.356, p < 0.011$) and anti-hypertensives ($\gamma_{15} = 0.484, p < 0.000$). These effects indicated the greater the number of frailty characteristics, the less likely the participant was taking corticosteroid medications and the more likely they were taking anti-hypertensive medications. There were no significant direct effects of baseline Ryff's PWB on IL-6 or CRP. However, there were significant direct effects of IL-6 ($\beta_{12} = 0.350, p = 0.027$) and CRP ($\beta_{13} = 0.626, p < 0.000$) on number of frailty characteristics. For each unit increase in IL-6, the percent increase in the expected number of frailty characteristics was 47.7%, holding all other variables in the model constant. With each unit increase in CRP, the percent increase in the expected number of frailty characteristics was 87.0% after holding all other variables in the model constant. These findings indicated that higher levels of IL-6 and CRP were predictors of a greater number of frailty characteristics. The indirect effects of baseline Ryff's psychological well-being on number of frailty characteristics through IL-6 and CRP are shown in Table 4.24. These indirect effects were tested for significance using the Sobel test, which compares the strength of the indirect effect to the null hypothesis that the effect is equal to zero (Sobel, 1982; Preacher & Hayes, 2004). None of the indirect effects were significant.

For the hedonic model, the direct effects are shown in Table 4.23. There were significant direct effects for the covariates, corticosteroids ($\gamma_{19} = -0.287, p = 0.036$) and anti-hypertensives ($\gamma_{18} = 0.443, p = 0.001$). These effects indicated the greater the number of frailty characteristics,

the less likely the participants was taking corticosteroid medications and the more likely they were taking anti-hypertensive medications. There were no significant direct effects of hedonic well-being on IL-6 or CRP. However, there were significant direct effects of IL-6 ($\beta_{12} = 0.306$, $p = 0.049$) and CRP ($\beta_{13} = 0.495$, $p = 0.002$) on number of frailty characteristics. With each unit increase in IL-6, the percent increase in the expected number of frailty characteristics was 35.8%, holding all other variables in the model constant. With a unit increase in CRP, the percent increase in the expected number of frailty characteristics is 64.0%, holding all other variables in the model constant. The indirect effects of the hedonic measures on number of frailty characteristics through serum IL-6 and serum CRP are shown in table 4.25. These effects were also tested for significance using the Sobel test, and none were significant.

Table 4.24

Indirect Effects for Eudaimonic Model (N =223)

	Path Coefficient	Indirect Estimate	Standard Error	Sobel Test Value	95% CI
Indirect Effect					
Baseline PWB via IL-6	$\gamma_{11}\beta_{12}$	-0.003	-0.009	-0.300	(-0.023, 0.017)
Baseline PWB via CRP	$\gamma_{11}\beta_{13}$	-0.011	0.016	-0.712	(-0.042, 0.020)

Table 4.25

Indirect Effects for Hedonic Model (N =223)

	Path Coefficient	Indirect Estimate	Standard Error	Sobel Test Value	95% CI
Indirect Effect					
Baseline LS via IL-6	$\gamma_{11}\beta_{12}$	-0.112	0.164	-0.686	(-0.435, 0.210)
Time 2 LS via IL-6	$\gamma_{12}\beta_{12}$	0.057	0.127	0.445	(-0.193, 0.306)
Baseline NA via IL-6	$\gamma_{13}\beta_{12}$	-0.160	0.170	-0.943	(-0.493, 0.172)
Baseline PA via IL-6	$\gamma_{14}\beta_{12}$	0.043	0.121	0.358	(-0.194, 0.280)
Baseline LS via CRP	$\gamma_{11}\beta_{13}$	-0.356	0.339	-1.050	(-1.019, 0.308)
Time 2 LS via CRP	$\gamma_{12}\beta_{13}$	0.252	0.278	0.907	(-0.292, 0.796)
Baseline PA via CRP	$\gamma_{14}\beta_{13}$	0.307	0.297	1.033	(-0.276, 0.891)
Baseline NA via CRP	$\gamma_{13}\beta_{13}$	-0.102	0.267	-0.380	(-0.645, 0.422)

Summary of Findings

Overall, these analyses indicated somewhat different biopsychosocial profiles for non-frail, pre-frail and frail individuals. At baseline, participants classified as frail were older and reported more illnesses but did not differ in other domains. At Time 2, participants classified as frail were older and reported lower physical health and mental/emotional health and had higher levels of CRP. Over time, psychological well-being was stable except for an increase in life satisfaction. Baseline characteristics did not predict number of frailty characteristics at Time 2. Both inflammatory biomarkers were significant predictor of frailty classification in that higher levels of both inflammatory biomarkers were predicted having a greater number of frailty characteristics. The hypothesized role of inflammation as a mediator of the relationship between psychological well-being and frailty was not supported.

Chapter Five: Discussion

The purpose of this study was to examine the relationships among frailty, inflammation, and psychological well-being using longitudinal data from a sample of 239 community-dwelling older adults. While the literature on frailty has been extensive, covering several areas including physical health, physiological processes (i.e., inflammation), and psychological health, these areas have largely been studied isolation from one another. In addition, studies examining psychological health and frailty have been largely cross-sectional and atheoretical. To address these gaps in the literature, this longitudinal study utilized a conceptual framework to (a) describe frailty comprehensively; (b) address the relationships among individual, psychological, and biological domains and their relation to frailty; and (c) explore a mechanism by which these domains influence frailty.

This study has made a number of important contributions to the study of frailty. With the incorporation of a conceptual framework, the use of longitudinal data, and the examination of inflammation as a mediator, this study and its findings provide empirical, theoretical, and methodological contributions to the science of frailty. Each of these will be described in turn.

Empirical Contributions

In this nationally representative sample, very few individuals were classified as frail ($n=11$) at Time 2, and the remainder of the sample was almost equally split between the non-frail ($n=124$) and pre-frail individuals ($n=101$). One reason for such a small number of frail individuals may be the younger age and overall physical and psychological health of the MIDUS participants. The average age of the sample at both baseline and Time 2 was lower than in previous studies of frailty, as were the average number of illnesses. Because previous studies have shown that the prevalence of frailty increases with age and that frail individuals exhibit higher levels of morbidity, the low number of frail individuals in this sample was not surprising.

A third wave of data collection, MIDUS 3, is currently underway, and, the average age of participants in this study will be approximately 83 years if they participate in this third assessment. One would expect a greater number of the participants would be identified as frail, and participants would also be more likely to report a greater number of illnesses than at Time 2. Re-examination of the frailty groups at this third time point may reveal group differences that were not observed at baseline or Time 2.

Another possible reason for the small number of frail individuals was the use of the modified Fried frailty measure. In the current study, we were not able to calculate the number of kilocalories expended per week by participants as in the original Fried frailty measure. This modified version may have affected frailty classification, but the equivalency of our modified physical activity criterion to the criterion used in Fried's measure was established. Therefore, the likelihood of the modified version resulting in incorrect classification was low.

The frail individuals in this study were generally similar to the non-frail and pre-frail individuals. However, frail individuals were significantly older than the non-frail at both baseline and Time 2, replicating findings from both cross-sectional and longitudinal studies on frailty (Alvarado et al., 2007; Ávila-Funes et al., 2008; Cawthon et al., 2007; Cesari et al., 2006; Chen et al., 2010; Ensrud et al., 2009; Fried et al., 2001; Gill et al., 2011; Ostir et al., 2004; Puts et al., 2005; Rockwood et al., 2004; Rockwood et al., 2011; Song et al., 2010; Woods et al., 2005). The lack of group differences on other sociodemographic characteristics (e.g., gender, income, education, race, or ethnicity) may be due to the homogeneity of the sample and the overall positive bias (i.e., high levels of income and education) on these measures.

With regard to health characteristics, frail participants had more illnesses than both non-frail and pre-frail participants at baseline. This finding is consistent with previous studies using the Fried Frailty measure indicating frail individuals typically exhibit higher levels of morbidity

(Avila-Funes et al., 2008; Fried et al., 2001; Walston et al., 2002; Woods et al., 2005). However, at Time 2, ten years later, the groups no longer differed on number of illnesses. This finding highlights the importance of the distinction between frailty and morbidity. In the original study testing the validity of the Fried frailty measure, nine common chronic conditions (myocardial infarction, angina, congestive heart failure, claudication, arthritis, cancer, diabetes, hypertension, and chronic obstructive pulmonary disease) were assessed to determine participants' morbidity status. Of the individuals classified as frail, 26.6% did not report having any of these conditions and of the individuals with two or more of these conditions, only 11.6% were classified as frail (Fried et al., 2001). Fried's findings indicated that while frailty and morbidity are related, being frail does not necessarily mean the individual experiences morbidity and morbidity does not necessarily mean the individual is frail. It has been suggested that other characteristics of chronic illnesses, such as severity or duration, may be more informative in trying to understand how frailty and morbidity are related (Weiss, 2011). Such measures were not available in this study. More longitudinal studies are needed to further clarify how specific morbidities, as well as morbidity severity and duration, may be related to frailty.

It is also intriguing that although at Time 2 the three frailty groups did not differ on more "objective" measures of health (i.e., number of illnesses, number of medications), both pre-frail and frail participants perceived their mental/emotional health to be poorer than did non-frail participants. Also, frail participants perceived their physical health less positively than did the other groups. In gerontological research, a common finding is that older persons perceive their physical and emotional health as better than objective measures indicate (Banerjee, Perry, Tran, & Arafat, 2010; Foley, Ancoli-Israel, Britz, & Walsh, 2004). Why frail individuals report this more negative perception is an important question since perceived health is predictive of both morbidity and mortality (Pietz & Petersen, 2007; Wang & Satariano, 2007). Similar differences

in perceived physical health have been found in other studies of frailty, but studies have not examined perceived mental/emotional health (Ávila-Funes et al., 2008; Barzilay et al., 2007; Cawthorn et al., 2007; Ensrud et al., 2007; Ensrud et al., 2009; Fried et al., 2001; Ho et al., 2002; Strawbridge et al., 1998; Woods et al., 2005). Perceptions of these two areas of health may have different implications for frailty in terms of their effects on engaging in health behaviors, how an individual copes with changes in health status (i.e., becoming frail), and an individual's psychological well-being.

For the inflammatory biomarkers, frail individuals had higher levels of CRP and, although not statistically significant ($p = .052$), the mean level of IL-6 for the frail group was the highest among the three groups. Levels of CRP greater than 2.5 $\mu\text{g/ml}$ have been associated with increased risk for sarcopenia, disability, osteoporosis, and cardiovascular disease (Bourdel-Marhcasson, Laksir, & Puget 2010; Glack, Rifai, Buring, & Ridker, 2003). The mean levels of CRP across groups in this study were lower than those reported in previous studies, but the mean CRP level for the frailty group ($M=3.98$, $SD=2.5$) exceeded the 2.5 $\mu\text{g/ml}$ value indicative of poor health outcomes (Bourdel-Marhcasson et al., 2010). In young adults, IL-6 is typically less than 1 pg/ml , but can increase with age to more than 2.5 pg/ml in older adults (Ferrucci et al., 2005). The mean levels of IL-6 trended in the expected direction with frail individuals having the highest levels ($M=5.10$, $SD=4.5$) and non-frail the lowest levels ($M=1.62$ $SD=1.4$), but only the frailty group exceed the 2.5 pg/ml level cited by Ferrucci and colleagues (2005).

While IL-6 and CRP are linked physiologically in that IL-6 stimulates the production of CRP in the liver during the inflammatory response, both biomarkers are affected by a variety of other factors including exercise, alcohol, and hormone replacement therapy (Ablij & Meinders, 2002; Bermudez, Rifai, Buring, Manson, & Ridker, 2002). It was not possible to examine all these factors within this relatively small sample, but future studies should further examine how

these factors are related differently to IL-6 and CRP in frail individuals, especially in younger samples where chronic inflammation may be in its earlier stages and more amenable to intervention.

Regardless of frailty classification at Time 2, participants reported high levels of psychological well-being at both baseline and Time 2 with no significant differences observed among the three groups. Previous studies have found frail individuals to have significantly lower levels of psychological well-being, but those studies utilized different frailty measures, utilized measures of psychological well-being that may have overlapped with the frailty measure, or the samples were older and exhibited poorer physical health (Andrew et al., 2012; Kirby et al., 2004; Ostir et al., 2004; Ottenbacher et al., 2009). These differences between studies make it difficult to determine why the frail individuals in this study did not report lower levels of psychological well-being. In studies using different frailty measures, cognitive functioning, ability to complete activities of daily living, and sensory problems were included as part of the frailty measure (Andrew et al., 2012; Kirby et al., 2004). Problems in those areas may be related to psychological well-being, but those problems are not captured by the Fried Frailty measure, which focuses on the physical presentation of frailty. In addition, psychological well-being is generally higher in groups with higher levels of education and income, and the sample in this study was relatively advantaged in these areas, which may explain the lack of association between frailty and psychological well-being (Marmot, Ryff, Bumpass, Shipley, & Marks, 1997; Ryff, Magee, Kling, & Wing, 1999).

The longitudinal data on the psychological well-being measures allowed for the examination of changes in psychological well-being over time, something most previous studies have not been able to examine. Only life satisfaction changed significantly over time, with non-frail and pre-frail participants increasing in their life satisfaction scores, while frail individuals

decreased (although the interaction was not statistically significant). Psychological well-being thus appeared to be stable or resilient over the ten year period, regardless of frailty classification. However, it should be noted that psychological well-being was assessed at only two time points, so only linear changes could be detected and whether fluctuations occurred or were related to frailty or inflammation could not be determined. Second, while there were no significant differences across the groups on psychological well-being variables, trends (Figures 4.2 thru 4.5) indicated frail individuals were experiencing a downward trajectory with regard to psychological well-being. While more research is needed to better understand these trajectories, if these trajectories are supported there are implications for future intervention research. The inclusion of psychological well-being assessments maybe beneficial in identifying potential declines in psychological well-being and interventions promoting activities that may benefit psychological well-being could be tested.

The models of eudaimonic and hedonic well-being predicting inflammation and frailty were not supported. The high levels of psychological well-being may be a reason for these findings. For eudaimonic well-being, the use of a composite psychological well-being score did not allow for the examination of how the six dimensions of eudaimonic well-being were related to inflammation or frailty. In previous studies, purpose in life and positive relationships with others have been consistently related to better health outcomes and lower inflammation and could be investigated in future studies of frailty (Boyle et al., 2009, Friedman et al., 2007; Phelan et al., 2010). For hedonic well-being, the measures used for affect captured trait affect, which has been shown to be predictive of several positive health outcomes (e.g., longer life span, few chronic conditions) and associated with lower inflammatory levels (Pressman & Cohen, 2005; Steptoe, Dockary, & Wardle, 2009). Why affect was not related to either frailty or inflammation may have been because of the high levels of positive affect, low levels of negative affect, and

lack of variability observed in these measures. For life satisfaction, even though a statistically significant change was observed over time for this measure, that change may not have been large enough to have an effect on inflammatory biomarkers or frailty.

Inflammation was related to frailty in that higher levels of both IL-6 and CRP were associated with a great number of frailty characteristics. These findings are consistent with Walston and Fried's (1999) theory of frailty and with empirical findings within the frailty literature. However, the mediating role of inflammation between psychological well-being and frailty was not supported. Reasons for this may have been related to the high levels of psychological well-being in this sample, the measures of psychological well-being utilized, or because the theory needs refinement in the case of frailty. However, given the empirical literature on psychological well-being, inflammation, and health outcomes, the lack of findings in this study is most likely due to the sample and measures used. Studies with a greater number of frail individuals and with a greater variability in psychological well-being are needed to re-examine these models.

Theoretical Contributions

Previous studies on frailty have been largely atheoretical, particularly those examining psychological health and frailty. To address this issue, a theoretical approach to the study of frailty was attempted in two ways. First, Kang and colleagues' (2010) Bio-behavioral Conceptual Framework was used as a way to organize the inclusion of variables from the individual, psychological, and biological domains in this study on frailty. In addition, the framework specified the biological domain as a mediator of the effects of other domains on frailty. However, Kang's framework does not specify the factors within each domain whose effects on health outcomes may be mediated by factors within the biological domain. Further, research examining the relationships between psychosocial factors and frailty is limited.

Therefore, a second theory was utilized to guide the incorporation of psychological factors into the study in order to explore of the relationships among the individual, psychological and biological domains and frailty.

To further develop the conceptualization of how psychological factors may be related to frailty and the mechanism underlying that relationship, Ryff's Theory of Psychological Well-being was incorporated into the conceptual framework. According to Ryff, psychological well-being is comprised of eudaimonic and hedonic well-being, both of which have been found to incur positive effects on health outcomes (Boyle et al., 2009; Boyle et al., 2010; Chida & Steptoe, 2008; Phelan et al., 2010; Pressman & Cohen, 2005). These positive effects are hypothesized to be the result of higher levels of well-being promoting better physiological functioning (Ryff et al., 2004; Steptoe, Demakakos, de Oliveira, & Wardle, 2012). Although these hypothesized effects have been supported in studies of non-frail individuals, they had not been examined in frail individuals.

By combining Kang's framework and Ryff's theory, this study provided a new perspective on the study of frailty by bringing together areas of frailty research that had, in the past, been studied in relative isolation. In particular, this approach illustrated how psychological factors, such as psychological well-being, may be related to frailty via biological factors such as inflammation. Such an approach may be a model for the examination of how other psychological factors are related to biological factors within the context of frailty. By expanding the focus of frailty research to include the examination of multiple domains simultaneously, the potential to better understand the role of these domains in the development and progression of frailty is greatly enhanced.

Methodological Contributions

The methodological contributions of this study include the use of the number of frailty characteristics instead of frailty categories as a way to conceptualize frailty and the incorporation of measurement error into the data analyses. Due to small number of individuals in the frail category and the issues this created during data analysis, the number of frailty characteristics was used as the dependent variable in the eudaimonic and hedonic models. Such an approach may be beneficial to use in samples of younger older adults where the number of individuals classified as frail may be relatively small. Studying frailty in younger older adults is particularly important so the process of when and how frailty develops can be examined. Utilizing the number of frailty characteristics may be a worthwhile approach and allow for a better understanding of what factors are related to higher levels of frailty in younger older adults, who are usually not well represented in the frailty literature.

The incorporation of measurement error into the data analyses is also an important methodological contribution to note. The incorporation of measurement error aided in increasing the robustness of the coefficients estimated in the zero-inflated Poisson regression models. This is particularly important in this study given the psychometric issues with Ryff's Psychological Well-Being Scale that were discussed in Chapter 3. Using the shortened version of Ryff's PWB measure (i.e., 3 items per subscale), Andrew and colleagues (2012) found that frailty was associated with lower levels of personal growth, environmental mastery, positive relationships with others, self-acceptance, and overall psychological well-being. However, the psychometric problems associated with this measure (i.e., the low Cronbach's alphas for the 3-item subscales) were not acknowledged or taken into account in the study's analyses. This brings into question the reliability of those findings and whether the associations observed may have been influenced by error in the PWB measure. Given the difficulty inherent in the measurement of psychological

constructs, it is important that robust statistical approaches are incorporated into studies examining their relationships to frailty.

Implications for Research

The first major implication for future research is to examine these relationships in a sample with a larger number of frail individuals. Even with the statistical approaches employed, such a small number of frail individuals may have inhibited the ability to detect group differences. Future studies should examine the relationships between all six dimensions of eudaimonic well-being, inflammation, and frailty. Examination of these dimensions of eudaimonic well-being may point to differential relationships with biological functioning, which may then be related to frailty. In addition, studies examining psychological well-being over shorter periods of time and with more time points may allow for examination of fluctuations of psychological well-being related to acute stressors and non-linear changes over time. With the third wave of MIDUS (MIDUS 3) currently underway, it will be possible to examine psychological well-being at a third time point, as well as inflammation and frailty status. With three assessment points, whether the trajectories of psychological well-being observed in this study are supported could be examined, as could non-linear changes. Whether such changes are related to inflammation and frailty and what other factors may affect changes in psychological well-being (i.e., life events, coping strategies) may point to future areas for research and possible interventions. With a second assessment of frailty, changes in frailty classification could also be examined and causal relationships tested. While this study included community-dwelling older adults, the examination of the conceptual model in other groups of frail older adults, (e.g., those living in assisted living facilities) may result in different findings pertaining to psychological well-being and inflammation. Given that frail individuals are at increased risk for poor health outcomes, examining psychological well-being and inflammation after an adverse event, such as

a hospitalization, would be important. Hospitalizations are stressful events that could precipitate inflammatory responses and whether higher levels of psychological well-being might confer protection against a negative physiological response is an important hypothesis to test. Stressful events, such as hospitalization or other care transitions, may be a particularly important time for interventions aimed at decreasing inflammation and/or improving psychological well-being.

Qualitative research may also be beneficial in terms of examining how frail individuals manage to maintain or recover high levels of psychological well-being. Qualitative studies have examined the day-to-day experiences of frail older adults living at home and have provided insight into how these individuals manage stressors, such as falls or problems preparing food for themselves (Nicholson et al., 2012; Porter, 2007; Porter, Matsuda, & Lindbloom, 2010). Studies examining what it means to be “well” to frail individuals and how to maintain or protect that well-being would particularly meaningful. In addition, qualitative studies examining well-being after an adverse event could complement quantitative studies examining psychological well-being and inflammation by gaining insight into how frail individuals experience the event and how they manage recovery from such an event. Finally, qualitative research may provide insight into this study’s finding regarding the discrepancies across groups on self-reported physical and emotional/mental health. Describing what factors play into how frail, pre-frail, and non-frail individuals perceive their physical and emotional health would help to identify components of physical and mental/emotional health that are important to these individuals.

Implications for Practice

This study’s findings are very preliminary, but a practice implication related to findings about inflammation and frailty can be suggested. Inflammation was higher in frail individuals. These findings are consistent with previous research and provide support for initiating anti-inflammatory interventions to promote health in pre-frail and frail individuals. Interventions

related to physical activity may be particularly effective in attempting to decrease inflammation and improve the physical characteristics that constitute frailty, such as weakness and slowness.

Strengths and limitations

There are several strengths to this study. First, MIDUS is a nationally representative sample of the United States. Second, the study included longitudinal data on psychological well-being measures allowing for the examination of how psychological well-being changed over time and whether such a change was related to frailty. Previous studies examining psychological health and frailty have largely been cross-sectional. This study provided evidence for high levels of psychological well-being in non-frail, pre-frail, and frail individuals over ten years. Third, this study was guided by a conceptual framework derived from Kang's Bio-behavioral Framework and Ryff's Theory of Psychological Well-being. Previous studies of psychological health and frailty have not been theoretically guided. In addition, the utilization of this framework brought together different domains of frailty research (i.e., physical health, physiological processes, and psychological health) that had previously been examined in isolation from one another. While the hypotheses were not supported, the study findings lay the groundwork for further examinations of frailty, inflammation, and psychological well-being over time in a larger and more diverse sample. Fourth, this study incorporated measurement error into the estimation of model parameters. Such approaches to ensuring robust parameter estimation have not been utilized before in the frailty literature and contribute to the reliability of this study's findings. Fifth, the frailty measure used in this study was almost identical to the Fried measure, which allowed for the comparison of this study's findings with the majority of the research on frailty.

While the current study had many strengths, certain limitations must be acknowledged. First, because this study was a secondary data analysis, there were limitations with regard to the study design and to the measures available for analysis. Data for frailty classification were only

available at Time 2, and therefore causal relationships among many of the sociodemographic and health characteristics, psychological well-being, inflammation, and frailty could not be determined. Second, due to poor reliability coefficients for the six subscales of Ryff's Psychological Well-being scale at baseline, a composite scale score had to be used. Such an approach did not allow for the examination of how sub-scales were related to frailty and/or inflammation over time. Third, the small number of frail individuals ($n=11$) may have limited our ability to detect significant group differences, even though statistical procedures (i.e., bootstrapping) were utilized in an attempt to compensate for such a small group. Fourth, several of the measures used in the study were self-report measures. Responses to questions regarding one's psychological well-being may have been subject to social desirability bias and questions about health may have been subject to problems related to recall, for example, when asked about illnesses in the past year or medication use.

Conclusions

This study has contributed to the science on frailty in several ways. First, the relationship between psychological well-being and frailty had only been examined in a handful of previous studies, and the examination of the biological mechanism underlying this relationship had not been examined in any study. While evidence for the mediating role of inflammation between psychological well-being and frailty was not observed, future studies with large samples of frail individuals are indicated to confirm these findings. The fact that, regardless of frailty status, individuals reported high levels of both eudaimonic and hedonic well-being over 10 years is noteworthy. Such findings suggest individuals' psychological well-being is stable or resilient when it comes to physical health challenges. Future work should examine strategies that promote and maintain psychological well-being and how those strategies may be incorporated into the care of frail older adults.

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Appendix A Inter-University Consortium of University for Political and Social Research Terms of Use for Rachel A. Roiland

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- If the confidentiality of human subjects has been violated, the case may be reported to the Federal Office for Human Research Protections. This may result in an investigation of the user's institution, which can result in institution-wide sanctions including the suspension of all research grants.
- A court may award the payment of damages to any individual(s)/organization(s) harmed by the breach of the agreement.

Definitions

authorized user

A faculty member, staff member, or student at a member institution

ICPSR

Inter-university Consortium for Political and Social Research

member institution

An institutional member of ICPSR

Official/Designated Representative

An individual appointed to represent a university's interests in ICPSR. This individual is also charged with providing user support to campus users.

promise of confidentiality

A promise to a respondent or research participant that the information the respondent provides will not be disseminated without the permission of the respondent; that the fact that the respondent participated in the study will not be disclosed; and that disseminated information will include no linkages to the identity of the respondent. Such a promise encompasses traditional notions of both confidentiality and anonymity. Names and other

identifying information regarding respondents, proxies, or other persons on whom the respondent or proxy provides information, are presumed to be confidential.

research subject

A person or organization observed for purposes of research. Also called a respondent. A respondent is generally a survey respondent or informant, experimental or observational subject, focus group participant, or any other person providing information to a study or on whose behalf a proxy provides information.

Appendix B Notice of Action University of Wisconsin–Madison Institutional Review Board-Exemption Status for Current Study

**Notice of Action
University of Wisconsin–Madison
Institutional Review Board (IRB)**

Principal Investigator: Susan M Heidrich, Ph.D.
Department: Nursing, School of
Point of Contact: Rachel A Roiland
Protocol Title: Frailty, Inflammation, and Psychological-Well Being in Older Adults
Protocol Number: SE-2011-0342
IRB: Social & Behavioral Sciences IRB (Contact: Lil Larson, 263-2320)
Committee Action: Qualifies as Exempt from IRB Review as of: **May 25, 2011**

Special Notes or Instructions: This protocol was determined to be exempt per 45 CFR, 46.101 b (4) as research involving the study of data that are publicly available. The study proposes to do analysis of the National Survey of Midlife Development in the United States (MIDUS) to examine how inflammatory biomarkers and psychosocial well-being are related to frailty and to each other in older adults. Risk is considered minimal.

INVESTIGATOR RESPONSIBILITIES:

Annual review is not required for this protocol since it was determined to be exempt. However, any changes to the protocol, including but not limited to changes in procedures, subject population or recruitment of subjects, must be reviewed by the IRB before the changes are incorporated to insure they do not change the exempt status of the protocol.

Any new information that would affect potential risks to subjects or any adverse reactions must be reported immediately to the IRB contact listed above.