Alcohol Consumption, Frailty, and the Mediating Role of C-Reactive Protein in Older Adults

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ALCOHOL CONSUMPTION, FRAILTY AND THE MEDIATING ROLE OF C-REACTIVE PROTEIN IN OLDER ADULTS

by

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ABSTRACT

Frailty is a well-established indicator of late-life decline and is accompanied by higher rates of comorbidity and disability. Meanwhile, an estimated 41% of adults over the age of 65 report consuming alcohol – an identified health risk and protective factor depending on dosage. Given that the demographic group of older Americans is projected to double by the year 2050, identification of frailty risk and protective factors is imperative. The goals of this thesis are to (1) identify how varying levels of alcohol consumption relate to frailty, and (2) elucidate a possible mechanism that accounts for the relationship between alcohol consumption and frailty. A sample of stroke-free participants over the age of 65 was identified from the Health and Retirement Study. Study 1 utilized stepwise logistic regression models to identify predictors of prevalent frailty at baseline (2000), and of incident frailty 4, 8, and 12 years later. For both males and females, significant predictors of frailty at all years included age, depressive symptomatology, and medical burden score. In addition, BMI was a significant predictor of frailty for females at all years. With respect to alcohol use, results revealed that drinking 1-7 drinks per week had a protective effect for females at baseline (OR=0.50) and 12 years later (OR=0.75); however, no such protective effects were found for males. Given that extant research has identified CRP as a mediator between the relationship of moderate alcohol use and cardiovascular health benefits, Study 2 used a cross-sectional sample from the 2008 wave to examine the potential mediating role of CRP between moderate alcohol use and reduced frailty risk. Results from structural equation modeling support the hypothesized model that moderate alcohol is associated with less frailty, and that this relationship is partially mediated by CRP levels. Overall findings suggest that moderate alcohol use confers health benefits for females by

reducing frailty risk and that CRP is one mechanism by which alcohol use may confer protective effects for frailty. These results provide a starting place in an effort to better understand the protective effects of moderate alcohol use and can assist in improving prevention and treatment efforts for older adults by preventing or prolonging the onset of age-related diseases. Future research should further examine the relationship between alcohol use and frailty and determine if CRP mediates the relationship between moderate alcohol use and other beneficial health outcomes.

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CHAPTER 1: INTRODUCTION

Currently, there is an estimated 44.7 million adults over the age of 65 years living the United States (U.S. Census Bureau Population Division, 2014). The older adult population is projected to reach 88.5 million by 2050 to comprise 20% of the total U.S. population (Shrestha & Heisler, 2011). This burgeoning older adult population warrants the attention of health care providers, mental health professionals, and researchers, as older adults are at a unique risk for a variety of health problems, not the least of which is frailty. Frailty is well-established indicator of late life decline and has been broadly conceptualized as the multisystemic dysregulation of homeostatic mechanisms (Fried et al., 2001). Frailty is marked by increased dependency on others, high rates of health care utilization, and increased risk for death (Clegg & Young, 2011). These risks increase the potential financial and resource liability placed on them, their family and caregivers, and society. Therefore, it would be of benefit to identify protective factors that may serve to buffer older adults against the variety of health risks associated with their age group.

One recognized protective factor for a range of adverse health outcomes is moderate alcohol use (Ferreira & Weems, 2008b). Alcohol consumption is a normative and common behavior among adults, and recent estimates suggest 41% of adults 65 years and older report consuming alcohol (Substance Abuse and Mental Health Services Administration, 2014). The most notably cited benefit of moderate alcohol use is cardiovascular disease risk reduction (Corrao, Bagnardi, Zambon, & La Vecchia, 2004a; Corrao, Rubbiati, Bagnardi, Zambon, & Poikolainen, 2000; Ellison, 2002; Gunzerath, Faden, Zakhari, & Warren, 2004). Other cited benefits include decreased levels of stress and depression, and cognitive benefits (Goldberg,

Soleas, & Levesque, 1999). Further, moderate alcohol use has been identified as a protective factor against frailty, with odds ratios ranging from 0.69-0.87 (Woods et al., 2005). Interestingly, past work suggests, but has not clearly identified, specific mechanisms of action by which moderate alcohol use may confer this protective effect.

One hypothesized biological mechanism by which moderate alcohol use confers protective health effects is the regulation of C-reactive protein (CRP). C-Reactive protein is an inflammatory cytokine synthesized by the liver and found in blood plasma (Du Clos & Mold, 2004). It is a valid marker of inflammation such that when there is any tissue damage, which causes inflammation, CRP levels in blood plasma rise. Thus, reduced CRP levels are associated with better health outcomes, as cited in the cardiovascular health literature (Ridker, 2003). C-reactive protein has been linked to both alcohol consumption and frailty. Moderate alcohol use has been associated with decreased levels of CRP compared to abstinence and heavy alcohol use (Albert, 2003; Volpato et al., 2004). In addition, moderately elevated CRP levels predict incident frailty (Puts, Visser, Twisk, Deeg, & Lips, 2005). This synthesis suggests CRP as one possible mechanism by which moderate alcohol use may protect against frailty.

Goals of this thesis are to examine the relationship between moderate alcohol use and frailty (Study 1), and to examine whether CRP, one candidate mechanism, mediates this hypothesized relationship (Study 2). Results of this thesis may inform alcohol use guidelines for older adults, facilitate integration of disparate aspects of the health literature with respect to aging, and establish a theoretical framework for the study of health benefits related to moderate drinking among older adults.

CHAPTER 2: THE RELATIONSHIP BETWEEN ALCOHOL CONSUMPTION AND FRAILTY IN OLDER ADULTS

Introduction

Frailty is accompanied by higher rates of comorbidity, disability, and risk for hospitalization (Fried et al., 2001), and frailty onset marks a critical turning point in the healthcare of older adults. An extensive literature has emerged on prognostic implications of frailty, though comparably less is known about risk factors for frailty, and even less about protective factors. Meanwhile, recent estimates suggest approximately 41% of adults over the age of 65 report consuming alcohol (Substance Abuse and Mental Health Services Administration, 2014). In addition, Blazer and Wu (2009) found that 13% of older men and 8% of older women are at risk for well-documented health risks conferred by heavy drinking (Blazer & Wu, 2009; Moore, 2003). Though heavy alcohol use confers well-documented health risks, moderate alcohol use has been identified as a protective factor for some health outcomes (Goldberg et al., 1999; Lang, Wallace, Huppert, & Melzer, 2007a; Mukamal, Cushman, Mittleman, Tracy, & Siscovick, 2004; Thun et al., 1997). Other findings suggest it may protect against frailty onset for women (Woods et al., 2005), though more research is needed to investigate the generalizability of this finding to men, and over longer periods of time. With the demographic group of older Americans projected to double by the year 2050 (Shrestha & Heisler, 2011), identification of frailty risk and protective factors is matter of significant social and medical importance. The goals of this study are to identify how alcohol use, a normative and common behavior, relates to frailty, a common and disabling syndrome, in older adults.

Alcohol Use – A Risk and Protective Factor

Excessive alcohol use confers significant health risks for older adults (Ferreira & Weems, 2008b). Excessive alcohol use can lead to cycles of abuse; withdrawal; impairment including impaired driving, interpersonal problems, financial problems, and health problems; and death (Centers for Disease Control and Prevention, 2014), and age-related changes place older adults at unique risk for these adverse consequences (Heuberger, 2009; National Institute on Alcohol Abuse and Alcoholism, 1998; Sorocco & Ferrell, 2006). Alcohol is comprised of water-soluble molecules that distribute throughout the body once consumed. Generally as people age, the amount of body water decreases and the amount of body fat increases. Thus, when older adults consume alcohol, they may experience higher concentrations of blood alcohol volume because there is less water space for alcohol to distribute (Durfour, 1999). In addition, older adults are more likely to use polypharmacy, which puts them at greater risk for adverse alcohol-medication interactions (Sorocco & Ferrell, 2006). Older adults also are more likely to experience age-related falls and cognitive impairment which makes them more susceptible to the effects of alcohol (Sorocco & Ferrell, 2006). Studies also demonstrate that excessive alcohol use among older adults is positively associated with depression and anxiety symptomatology (Kirchner et al., 2007a).

Simultaneously, substantial studies also have demonstrated that moderate alcohol use is associated with health benefits (Goldberg et al., 1999; Lang, Wallace, et al., 2007a; Mukamal et al., 2004; Thun et al., 1997). What constitutes “moderate” alcohol use among older adults, however, has been difficult to define (Durfour, 1999), and may be characterized by quantity, frequency, blood alcohol concentration (BAC) levels, consequences of use and/or some

combination of these variables. Despite these potential confounds, several different strategies for characterizing moderate alcohol have been suggested. The Dietary Guidelines for Americans 2010, for instance, characterizes moderate alcohol use as no more than 1 drink per day for women and no more than 2 drinks per day for men (U.S. Department of Agriculture & U.S. Department of Health and Human Services, 2010). The NIAAA drinking guidelines for healthy, older adults not taking medications is no more than 7 drinks per week (National Institute on Alcohol Abuse and Alcoholism, 1998). Similarly, a study examining hazardous levels of alcohol consumption among disability-free older adults found no differences in the functioning and mortality among those who abstained and those who consumed up to two alcoholic drinks per day (Lang, Guralnik, Wallace, & Melzer, 2007).

Moderate alcohol use has been an identified protective factor for better health in adults (Goldberg et al., 1999; Kirchner et al., 2007a; Lang, Wallace, et al., 2007a; Mukamal et al., 2004; Thun et al., 1997). In a prospective study on alcohol consumption and mortality utilizing a sample size of over 400,000 participants, Thun et al. (1997) found that those who consumed 1-2 drinks daily had lower mortality rates than those who did not consume any alcohol. Commonly cited benefits of moderate alcohol include cardiovascular health and reduced risk of coronary heart disease (Corrao et al., 2004a; Corrao et al., 2000; Ellison, 2002; Gunzerath et al., 2004). A meta-analysis by Corrao et al. (2000) depicts the relationship between alcohol use and the risk of coronary heart disease as a J-shaped curve, suggesting moderate alcohol use decreases the risk of coronary heart disease but heavy use confers no benefit in this regard.

In addition to the quantity of consumption, alcohol's effect on aging also appears to vary by gender. Employing a large epidemiological data set, Dufouil, Ducimetiere, and Alperovitch (1997) found a positive linear association between average alcohol consumption up to 4 drinks

per day and overall cognitive functioning for women, but not for men. Similarly, McGuire, Ajani, and Ford (2007) reported that moderate alcohol use was protective with respect to cognitive functioning for women, but not for men over the age of 70. Lastly, findings by Balsa, Homer, Fleming, and French (2008) suggest that light to moderate alcohol use by women over the age of 65 may have beneficial health effects; no such effect was found for men. These intriguing findings underscore the importance of examining gender differences in the relationship between alcohol use and late-life decline.

Frailty

Frailty, broadly conceptualized as the multisystemic dysregulation of homeostatic mechanisms (Fried et al., 2001), is well-established indicator of late-life decline. Frailty is marked by increased dependency on others, loss of independence, high rates of health care utilization, and increased risk for death (Clegg & Young, 2011). Frailty has been associated with diverse aspects of late-life decline, including increases in orthostatic hypertension (Wee Lock, Barrett, Hossain, Kelley-Gagnon, & Lipsitz, 1997), vascular disease (Alonso-Bouzon et al., 2014), falls (Fried et al., 2001), heart rate variability (Varadhan et al., 2009b), and inflammation and markers of blood clotting (Walston et al., 2002).

Numerous frailty conceptualizations and measures variably emphasize physical, cognitive, psychological, and even social relationship aspects of the syndrome (Rockwood, 2005). Mitnitski, Song, and Rockwood (2004), for example, utilize a deficit accumulation approach to assess frailty by integrating many components associated with declines seen in aging; however, it is "less likely to yield a specific biological marker of frailty," (Mitnitski, Song & Rockwood, 2004, p. 634). By contrast, Fried and colleagues (2001) have operationalized

frailty as a phenotype, using prior research to identify its core components. According to their definition, frailty is defined as having three or more of the following conditions: unintentional weight loss, weakness, exhaustion, slow walking speed and low physical activity. In using a phenotypic conceptualization, Fried and colleagues (2001) distinguish frailty from high comorbidity and disability both conceptually and empirically. This strategy has been replicated across several frailty indices, including the Paulson-Lichtenberg Frailty Index (PLFI; Paulson & Lichtenberg, In Press), which will be used in the proposed research.

Frailty is positively associated with aging, being female, being African-American, lower education and income, and poorer health (Fried et al., 2001; Paulson & Lichtenberg, In Press; Woods et al., 2005). In addition, heavy drinking, cigarette smoking, physical inactivity, depression, social isolation, fair or poor perceived health, and prevalence of chronic conditions have been identified as prospective predictors of frailty in older adults (Strawbridge, Shema, Balfour, Higby, & Kaplan, 1998; Woods et al., 2005). Further, Woods and colleagues (2005) found a small but significant reduction in frailty risk (OR=.87) for older women who reported consuming <1 drink per week, and a larger protective effect (OR= .69) for older women who reported consuming between 1 and 14 drinks per week. Those who reported consuming more than 14 drinks per week, however, were found to have similar frailty risk to those who reported abstaining from alcohol altogether (Woods et al., 2005). Despite the study's female-only sample and three-year follow-up, these findings suggest alcohol use as one potential determinant of frailty among older adults.

The primary goal of this study is to examine the relationship between level of alcohol use and frailty, a variable characterizing late-life decline, in a demographically representative, longitudinal survey of Americans over the age of 65. It is hypothesized that, by comparison to

older adults who are either abstinent or heavy consumers of alcohol, those older adults who report moderate alcohol use will experience lower frailty prevalence cross-sectionally, and lower incidence of new cases of frailty over 4, 8 and 12 years. In addition, it is hypothesized that the protective effect of moderate alcohol use will be more robust for females than for males.

Method

Participants

The present study utilized data collected through the HRS. The HRS is a longitudinal, cohort study on health, retirement, and aging conducted by the University of Michigan with support from the National Institute of Aging. The first wave of data collection occurred in 1992 with adults over the age of 50 years living in the United States. Data has been and is collected biennially, and currently, the sample consists of over 30,000 adults. The method of data collection includes interviews, surveys, and links to personal records; this provides a wealth of information about each participant including their physical health, mental health, disability status, employment status, and housing situation. Further information on HRS survey design and data collection methods can be found in previously published reports (Hauser & Willis, 2004; Heeringa & Conner, 1995; Sonnega et al., 2014b).

The proposed research used HRS data from years 2000 (baseline), 2004, 2008 and 2012, as these are the years is when complete frailty data for participants are reported and available. Data used in these analyses incorporated both the direct data released from the HRS committee, and cleaned HRS data released by the RAND Center for the Study of Aging (RAND HRS). At baseline (2000), 11,762 people were surveyed with a response rate of 85.4% (*Health and Retirement Study: Sample Sizes and Response Rates*, 2011). Longitudinal data is available at 2-

year intervals through 2012, and typical inter-wave attrition is around 20%, the vast majority of which reflects death or incapacity. Participants had to be at least 65-years-old at the study's baseline year (2000) to be included in the study. Participants with a history of stroke were excluded, as individuals who have experienced a stroke are more likely to experience subsequent depression (Bour et al., 2009a), impairment in cognitive functioning (Tatemichi et al., 1994), and motor impairment (as cited in Langhome, Coupar, & Pollock, 2009). Further, participants who had missing data on the variables of interest at baseline also were excluded from the study.

Measures

Demographic Variables. Data on the following demographic variables were collected through interviewing participants either via telephone or face-to-face.

Age/Gender/Race. Data provided by the HRS includes participant age at each wave, and identified gender and race. Gender was determined based on participants' reports. Race was determined by asking participants first whether or not they considered themselves to be Hispanic of Latino. Then, participants were asked, "What race do you consider yourself to be: White, Black or African-American, American Indian, Alaska Native, Asian, Native Hawaiian, Pacific Islander, or something else?" If participants identified more than one race, they were asked to specify which race they considered themselves to be primarily. If race was missing and participants had identified to be Hispanic or Latino, their race was set to "White/Caucasian." While efforts were made during participant enrollment to oversample minority elders, the number of participants not identified as White/Caucasian remained small comparatively. Therefore, all races other than White/Caucasian were collapsed into one category defined as "Other."

Education. Participants' level of education is provided by the HRS data set in number of years. Participants' level of education was assessed by asking them, "What is the highest grade of school or year of college you completed?" Participants who reported 12 or fewer years of school were asked about receiving a High School degree. Participants who reported 13 or more years of school were asked if they received a college degree, with the assumption being that they had completed high school either through receiving a high school diploma or through obtaining their General Education Development (GED) diploma. If participants reported obtaining a college degree, they were asked, "What is the highest degree you have earned?"

Socio-economic status (SES). SES was assessed via total wealth (excluding secondary home) and total income. Total Wealth was calculated by the sum of all wealth components (i.e., combined value of: primary home; real estate, excluding primary home; vehicles; businesses; individual retirement account (IRA) and Keogh accounts; stocks and mutual funds; checking, savings and money market accounts; certificates of deposit (CDs), government and saving bonds, and treasury bills; bonds; and all other savings) less the sum of all debt (i.e., sum of first and second mortgages, home loans, and debt). Total Income for the last calendar year was calculated by summing the participant and spouse's earnings, pensions and annuities, Supplemental Security Income and Social Security Disability, Social Security retirement, unemployment and workers compensation, other government transfers, household capital income and other income.

Alcohol Use. Alcohol use was measured by the average number of reported drinks per week. In the HRS data set, alcohol use was measured by first asking participants, "Do you ever drink any alcoholic beverages, such as beer, wine, or liquor?" If participants responded "yes" to the initial question, they were asked two follow-up questions to assess the frequency and intensity of their consumption. The first follow-up question asked participants to report the

number of days per week on average that they consumed an alcoholic drink with respect to the last three months. Participants whose response was at least one drink per week or greater were then asked how many drinks they consumed on days they drink with respect to the past three months. Average number of drinks per week was calculated by multiplying the number of drinks per day by the number of drinking days per week.

Outcome Variables

***Frailty*.** Frailty was measured using the Paulson-Lichtenberg Frailty Index (PLFI; Paulson & Lichtenberg, In Press), which is based on Fried and colleagues' (2001) conceptualization of frailty as a phenotype. The frailty index includes five symptom criteria: wasting, weakness, slowness, fatigue or exhaustion, and falls. The wasting criterion was met if the participant reported a loss of 10% body weight over a 2-year period. The weakness criterion was met if the participant responded yes to "Because of health problems, do you have difficulty with lifting or carrying weights over 10 pounds, like a heavy bag of groceries?" The slowness criterion was met if participants responded affirmatively to "Because of a health problem, do you have any difficulty with getting up from a chai after sitting for long periods?" The fatigue or exhaustion criterion was met if the participant endorsed yes to "Since we last talked with you [in the last wave], have you had any of the following persistent or troublesome problems: […] severe fatigue or exhaustion?" Lastly, the falls criterion was met if the participant answered yes to "Have you fallen in the past two years?" Each affirmative response received a score of 1, and a score of 3 or more indicated that the participant is frail. The PLFI has been used successively in previous studies measuring frailty (Paulson & Lichtenberg, 2012). No PLFI indicators were drawn from the depression measure utilized below.

Control Variables

***Medical Burden*.** Medical burden was assessed via disease count method, with the presence of each disease adding a score of 1. Hence, higher scores indicate a higher degree of medical burden. The following diseases were accounted for in determining the medical burden score: hypertension, diabetes, cardiac disease, arthritis, pulmonary disorder, and cancer. Medical burden scores were not calculated for participants with more than one missing value on the variables used to assess medical burden, excluding one participant.

***Body Mass Index (BMI)*.** The HRS data set provides a calculated body mass index for each participant. To calculate BMI, weight in pounds was converted to kilograms and height in feet and inches was converted to meters. Then, weight was divided by the square of the height to obtain BMI in kg/m2. At each wave beginning in 1996, weight was collected again and this new weight, along with the original height, was utilized to calculate BMI at that wave.

***Depression (CES-D Score)*.** Depression was assessed using participants' scores on an abridged, 8-item version of the Center for Epidemiological Studies Depression (CES-D) measure (Radloff, 1977). Participants answered "yes" or "no" to each item-statement with respect to how they were feeling "much of the time" in the past week. Six of the statements were worded negatively ("felt depressed, felt that everything he/she did was an effort, sleep was restless, could not get going, felt lonely, and felt sad") and two of the statements were worded positively ("enjoyed life and was happy"). Scores range on a scale from 0-8, with higher scores suggesting higher levels of depression.

***Partner Status*.** Partner status was assessed by asking the participant their marital status (i.e., "married," "married, spouse absent," "partnered," "separated," "divorced," "separated/divorced," "widowed," and "never married"). Participants who reported being

"married" or "partnered" were identified as being "partnered" indicating that they are currently cohabitating with a partner regardless of their marital status (i.e., "partnered").

Statistical Methods

The effect of moderate alcohol use on prevalent and incident frailty was determined using four stepwise logistic regression models. The first logistic regression model examined the relationship between alcohol consumption and *prevalent* frailty using all available cross-sectional data at the 2000 wave. The next three logistic regression models examined the relationship between alcohol consumption in 2000 and future *incident* frailty in 2004, 2008, and 2012 (i.e., new cases of frailty in the 2004, 2008, and 2012 waves among respondents who were surveyed at 2004, 2008 or 2012 and were not frail in 2000). Alcohol was dummy coded using three dummy coded variables: "Drinks 1-7" represents participants who reported consuming an average of 1-7 drinks per week; "Drinks 8-14" represents participants who reported consuming an average of 8-14 drinks per week; and "Drink ≥15" represents participants who reported consuming an average of greater than or equal to15 drinks per week. All three groups were then compared to those participants who reported consuming 0 drinks per week (see *Table 1.1*). HRS participants who met the age criteria, denied history of stroke, and had complete data in 2000 were used to identify the prevalence of frailty at baseline. Participants who were identified as frail in 2000 were then excluded when predicting the incidence of new frailty cases in the following years: 2004, 2008, and 2012. Due to the large-scale values in SES variable as compared to the other variables, all SES values were transformed by dividing them by 100,000. Lastly, results were split by gender due to the gender differences seen in late-life decline.

Results

Complete data was available for 8,184 participants at the 2000 wave. Of the 8,184 participants, 286 males and 902 females were frail (prevalence=14.52%) and were excluded from the next three regression models that predicted incidence of frailty at the 2004, 2008, and 2012 waves. Due to increasing attrition over time, the three incident frailty analyses were completed using different sample sizes: in 2004, 5,862 participants were included; in 2008, 4,554 participants were included; and in 2012, 3,246 participants were included. As displayed in *Table 1.2*, the baseline sample (2000 wave) had a mean age of 74.31 years (*SD*=7.00), mean education of 11.90 years (*SD*=3.34), and was predominately white (85.70%). The sample also reported consuming a mean of 1.77 drinks per week on average (*SD*=5.04), a mean CES-D score of 1.55 (*SD*=1.86), and a mean medical burden score of 1.85 (*SD*=1.17). The changes in the demographic characteristics of the sample over time are a result of the people who attrited being older and less educated, and having more depressive symptomatology, a higher medical burden score, and lower SES.

Results of the first step-wise logistic regression cross-sectionally describing prevalent frailty in 2000 for males are displayed in *Table 1.3*. At the 2000 wave, 286 males (8.56% of males) were identified as frail. The first step included the following predictors: age, race, partner status, years of education, CES-D, medical burden score, BMI, and SES. The step 1 model was significant ($\chi^2[8]=417.74$, $p<0.001$). The model explained 26.6% (Nagelkerke R^2) of the variance in frailty and classified 91.8% of cases correctly. Significant correlates of prevalent frailty in step one included age ($\beta=0.04$, Wald=13.56, $p<0.001$, *Exp(β)*=1.04), SES ($\beta=-0.05$, Wald=5.46, $p=0.02$, *Exp(β)*=0.96), CES-D score ($\beta=0.46$, Wald=187.65, $p<0.001$, *Exp(β)*=1.58),

BMI (β=-0.05, Wald=7.25, p=0.01, *Exp(β)*=0.96), and medical burden score (β=0.58, Wald=98.79, p<0.001, *Exp(β)*=1.79). The addition of the drinking variable in the second step did not account for significantly more variance in the model, though the overall model remained significant (χ^2[11]=418.83, p<0.001). Hence, the significant correlates of prevalent frailty in the second step remained the same.

Results of the second step-wise logistic regression prospectively predicting incident frailty for males in 2004 are displayed in *Table 1.4.* At the 2004 wave, 254 males (10.30% of males) were identified as frail. Age, race, partner status, years of education, CES-D, medical burden score, BMI, and SES were included in the first step. The step 1 model was significant (χ^2[8]=145.47, p<0.001). The model explained 11.8% (Nagelkerke R^2) of the variance in frailty and classified 89.6% of cases correctly. Significant predictors of 2004 incident frailty in step one included age (β=0.09, Wald=61.37, p<0.001, *Exp(β)*=1.09), CES-D score (β=0.17, Wald=16.30, p<0.001, *Exp(β)*=1.18), and medical burden score (β=0.38, Wald=38.84, p<0.001, *Exp(β)*=1.47). In addition, BMI (β=0.03, Wald=3.56, p=0.06, *Exp(β)*=1.03) was approaching significance. The addition of the drinking variable in the second step did not account for significantly more variance in the model, though the overall model remained significant (χ^2[11]=150.74, p<0.001). In the second step, significant predictors of 2004 incident frailty remained the same with BMI no longer approaching significance.

Results of the third step-wise logistic regression prospectively predicting incident frailty for males in 2008 are displayed in *Table 1.5*. At the 2008 wave, 266 males (14.49% of males) were identified as frail. Age, race, partner status, years of education, CES-D, medical burden score, BMI, and SES were included in the first step. The step 1 model was significant (χ^2[8]=121.70, p<0.001). The model explained 11.4% (Nagelkerke R^2) of the variance in frailty

and classified 85.4% of cases correctly. Significant predictors of 2008 incident frailty in step one included age (β=0.09, Wald=58.95, p<0.001, *Exp(β)*=1.10), CES-D score (β=0.15, Wald=12.04, p=0.001, *Exp(β)*=1.16), and medical burden score (β=0.29, Wald=21.80, p<0.001, *Exp(β)*=1.33); years of education approached significance (β=-0.04, Wald=3.61, p=0.06, *Exp(β)*=0.96). The addition of the drinking variable in the second step did not account for significantly more variance in the model, though the overall model remained significant (χ^2[11]=123.47, p<0.001). Thus, significant predictors of 2008 incident frailty in the second step remained the same as those in the first step with years of education no longer approaching significance.

Results of the fourth and final step-wise logistic regression prospectively predicting incident frailty for males in 2012 are displayed in *Table 1.6.* At the 2012 wave, 251 males (19.55% of males) were identified as frail. Age, race, partner status, years of education, CES-D, medical burden score, BMI, and SES were included in the first step. The step 1 model was significant (χ^2[8]=92.85, p<0.001). The model explained 11.1% (Nagelkerke R^2) of the variance in frailty and classified 80.1% of cases correctly. Significant predictors of 2012 incident frailty in step one included age (β=0.09, Wald=33.82, p<0.001, *Exp(β)*=1.10), CES-D score (β=0.13, Wald=5.87, p=0.02, *Exp(β)*=1.13), and medical burden score (β=0.40, Wald=34.74, p<0.001, *Exp(β)*=1.50). The addition of the drinking variable in the second step did not account for significantly more variance in the model, though the overall model remained significant (χ^2[11]=98.02, p<0.001). Thus, significant predictors of 2012 incident frailty in the second step remained the same as those in the first step.

For females, results of the first pair of step-wise logistic regressions cross-sectionally describing prevalent frailty in 2000 are displayed in *Table 1.7.* At the 2000 wave, 902 females

(18.63% of females) were identified as frail. The first step included the following predictors: age, race, partner status, years of education, CES-D, medical burden score, BMI, and SES. The step 1 model was significant (χ^2[8]=779.85, p<0.001). The model explained 24.1% (Nagelkerke R^2) of the variance in frailty and classified 82.4% of cases correctly. Significant correlates of prevalent frailty in step one included age (β=0.06, Wald=91.03, p<0.001, *Exp(β)*=1.06), CES-D score (β=0.30, Wald=246.92, p<0.001, *Exp(β)*=1.36), BMI (β=0.02, Wald=7.07, p=0.01, *Exp(β)*=1.02), and medical burden score (β=0.52, Wald=193.82, p<0.001, *Exp(β)*=1.67). The addition of the drinking variable in the second step substantially improved the model (χ^2[3]=23.54, p<0.001). The model now explained 24.8% (Nagelkerke R^2) of the variance in frailty and classified 82.2% of cases correctly. In the second step, all of the significant correlates of prevalent frailty in the first step remained, and in addition, included Drinks 1-7 (β=-0.70, Wald=20.68, p<0.001, *Exp(β)*=0.50).

Results of the second step-wise logistic regression prospectively predicting incident frailty for females in 2004 are displayed in *Table 1.8*. At the 2004 wave, 570 females (16.78% of females) were identified as frail. The first step included the following predictors: age, race, partner status, years of education, CES-D, medical burden score, BMI, and SES. The step 1 model was significant (χ^2[8]=258.70, p<0.001). The model explained 12.3% (Nagelkerke R^2) of the variance in frailty and classified 83.0% of cases correctly. Significant predictors of 2004 incident frailty in the first step included age (β=0.07, Wald=81.49, p<0.001, *Exp(β)*=1.07), CES-D score (β=0.15, Wald=36.97, p<0.001, *Exp(β)*=1.16), BMI (β=0.05, Wald=22.80, p<0.001, *Exp(β)*=1.05), and medical burden score (β=0.35, Wald=63.20, p<0.001, *Exp(β)*=1.42). The addition of the drinking variable in the second step did not account for significantly more

variance in the model, though the overall model remained significant (χ^2[11]=263.13, p<0.001). In the second step, significant predictors of 2004 incident frailty remained the same.

Results of the third step-wise logistic regressions prospectively predicting incident frailty for women in 2008 are displayed in *Table 1.9*. At the 2008 wave, 595 females (21.89 % of females) were identified as frail. Age, race, partner status, years of education, CES-D, medical burden score, BMI, and SES were included in the first step. The step 1 model was significant (χ^2[8]=178.99, p<0.001). The model explained 9.8% (Nagelkerke R^2) of the variance in frailty and classified 77.7% of cases correctly. Significant predictors of 2008 incident frailty in the first step included age (β=0.07, Wald=68.54, p<0.001, *Exp(β)*=1.07), CES-D score (β=0.10, Wald=13.29, p<0.001, *Exp(β)*=1.10), BMI (β=0.03, Wald=8.30, p<0.01, *Exp(β)*=1.03), and medical burden score (β=0.30, Wald=43.17, p<0.001, *Exp(β)*=1.35). The addition of the drinking variable in the second step did not account for significantly more variance in the model, though the overall model remained significant (χ^2[11]=181.03, p<0.001). Thus, significant predictors of 2008 incident frailty in the second step remained the same as those in the first step.

Results of the fourth and final step-wise logistic regressions prospectively predicting incident frailty for women in 2012 are displayed in *Table 1.10*. At the 2012 wave, 527 females (26.86% of females) were identified as frail. Age, race, partner status, years of education, CES-D, medical burden score, BMI, and SES were included in the first step. The step 1 model was significant (χ^2[8]=132.30, p<0.001). The model explained 9.5% (Nagelkerke R^2) of the variance in frailty and classified 73.3% of cases correctly. Significant predictors of 2012 incident frailty in the first step included age (β=0.08, Wald=57.63, p<0.001, *Exp(β)*=1.08), CES-D score (β=0.12, Wald=16.27, p<0.001, *Exp(β)*=1.13), BMI (β=0.04, Wald=14.24, p<0.001, *Exp(β)*=1.04), and medical burden score (β=0.20, Wald=15.50, p<0.001, *Exp(β)*=1.23). The

addition of the drinking variable in step two substantially improved the model (χ^2[3]=7.69, p=0.05). The model now explained 10.0% (Nagelkerke R^2) of the variance in frailty and classified 73.2% of cases correctly. Significant predictors of 2012 incident frailty included those significant in step one and Drinks 1-7 (β=-0.29, Wald=3.84, p=0.05, $Exp(\beta)$=0.75).

Post-hoc logistic regression models were run excluding BMI as a control variable to eliminate effects of the potential confound BMI has with the baseline wasting frailty indicator. No substantive variation occurred in the results and thus, the variable was included.

Discussion

Primary findings reveal that consuming 1 to 7 alcoholic beverages per day confers a protective effect against frailty for older women, but not for older men. Specifically, after controlling for age, race, education, SES, partner status, BMI, medical burden, and CES-D scores, results were that prevalent frailty was reduced by 50 percent and incident frailty 12 years later was reduced by 25% for women who consumed 1-7 alcoholic beverages per week at baseline. No protective effects for moderate alcohol use for women were detected over shorter periods of 4 and 8 years, however, and this is not surprising. One possible reason protective effects among non-frail respondents could not be identified is because frailty symptoms emerge over time (Xue, 2011).

Also consistent with past findings (Fried et al., 2001; Strawbridge et al., 1998; Woods et al., 2005), older age, greater medical burden, and more depressive symptomatology consistently predicted frailty for both older men and women. These findings are suggestive of the debate on depression and frailty as separate constructs in the extant literature. Though depression and frailty may share risk factors, symptoms and consequences (Lohman, Dumenci, & Mezuk,

2015), conventional disease models have distinguished between the two constructs. Other work, also based on a subsample of women over age 80 drawn from the Health and Retirement Study (Paulson & Lichtenberg, 2013), found that depression longitudinally predicted frailty, and yet, frailty is not a longitudinal predictor of depression. The current finding that depression is a robust predictor of incident frailty for both older men and women partially supports a longitudinal relationship between these variables. Future research should further examine this interesting relationship.

A secondary finding of this study is that higher BMI scores consistently predicted greater frailty risk for older women, but not older men. This gender discrepant finding is consistent with previous findings that suggest frailty is associated with being overweight among females (Woods et al., 2005), but not among males (Cawthon, Marshall, Y., et al., 2007). This finding is believed to reflect the effects of significant disease burden and mobility deficits faced by older adults with obesity.

Our finding that moderate alcohol use did not yield a protective effect for older men is consistent with prior research (Balsa et al., 2008). It is interesting that our findings did not support prior research linking excessive alcohol use to worsened health outcomes (i.e., frailty). This null effect may be attributed to having relatively few participants who reported consuming more than 15 drinks per week and the consequent reduction of statistical power. It also may be attributed to a survival effect whereby only the most resilient heavy users of alcohol would be represented in this sample of older adults. This null finding may also reflect measurement error inherent to subjective data. Future research should seek to identify underlying mechanisms contributing to these relationships among older adults.

The primary limitation of this study is the reliance on subjective rather than objective alcohol use data. While this method is subject to measurement error, it is consistent with the vast majority of alcohol research due to the difficulties in obtaining objective measures (e.g., blood alcohol concentration). In addition, medical burden also was obtained via self-report confirming or denying the presence of physical diseases. While use of self-report medical data is likely to produce some measurement error, this method is common in population-based samples, and prior research has shown adequate concordance between self-report and objective medical data (Bush, Miller, Goldsen, & Hale, 1989).

The findings of this study extend our knowledge of the relationship between alcohol use and frailty, an indicator of late-life decline. Compared to prior studies, this study examines that relationship using a larger, more representative sample over a 12-year period. With the rapidly growing population of older adults, and thereby, prevalence of alcohol use among older adults, it is important to identify how alcohol use affects the aging process; these findings can be utilized to provide further empirically-supported drinking guidelines for older adults. Results from this study support current definitions of moderate drinking as one drink per day for women (National Institute on Alcohol Abuse and Alcoholism, 1998; U.S. Department of Agriculture & U.S. Department of Health and Human Services, 2010). In combination with research examining harmful drinking in the elderly, these findings may also be useful in both the assessment of alcohol abuse among the older adults and the development of primary interventions targeting healthy aging. Knowing how alcohol consumption relates to critical indicators of late-life decline such as frailty allows clinical healthcare personnel to provide more informed guidelines and recommendations to their patients. Additionally, these findings augment prevention research for older adults and will hopefully lead to a more sophisticated model of healthy aging.

Future research should seek to identify the mechanism by which alcohol consumption and frailty relate, specifically the protective effects of moderate use. Various mechanisms have been proposed to account for the protective effect of moderate alcohol use, ranging from biological basis (e.g., raises in HDL cholesterol which reduces risk of myocardial infarction (Thornton, Symes, & Heaton, 1983)) to lifestyle and behaviors associated with those who consume alcohol in moderation, such as regular socialization or other lifestyle factors (Maraldi et al., 2009).

CHAPTER 3: THE MEDIATING ROLE OF C-REACTIVE PROTEIN BETWEEN ALCOHOL CONSUMPTION AND FRAILTY IN OLDER ADULTS

Introduction

Frailty is a well-established indicator of late-life decline marked by loss of independence, high rates of health care utilization, and increased risk for death (Clegg & Young, 2011). In addition, substantial evidence has associated frailty with aging (Fried et al., 2001; Mello, Engstrom, & Alves, 2014; Paulson & Lichtenberg, In Press; Woods et al., 2005). The population of older adults in the United States is projected to double and comprise 20% of the total U.S. population by 2050 (Shrestha & Heisler, 2011). Given this, it is imperative for healthcare professionals and researchers to identify protective factors that may serve to insulate older adults from the variety of health risks associated with their age group, including frailty. Emerging alcohol research has identified health benefits related to moderate alcohol use, with cardiovascular benefits being most prominent (Corrao, Bagnardi, Zambon, & La Vecchia, 2004b). Research also suggests older adults who consume 1-2 drinks per day are at less risk for becoming frail (Cawthon, Marshall, Michael, et al., 2007; Strawbridge et al., 1998; Woods et al., 2005). The mechanism by which moderate alcohol use confers health benefits, however, remains less explored.

Alcohol Use – A Risk and Protective Factor

Emerging research suggests a complex relationship between alcohol consumption and health among older adults; more specifically, excessive alcohol use is most often associated with health risks, while moderate alcohol use has been associated health benefits (Ferreira & Weems,

2008a, 2008b; St John, Snow, & Tyas, 2010). Consequences of excessive alcohol use include cycles of abuse, withdrawal, interpersonal problems, financial problems, health problems, and death (Centers for Disease Control and Prevention, 2014). Studies also demonstrate that excessive alcohol use in older adults is positively associated with depression and anxiety symptomatology (Kirchner et al., 2007b). In contrast, moderate alcohol use has been identified as a protective factor for better health in adults (Goldberg et al., 1999; Kirchner et al., 2007b; Lang, Wallace, Huppert, & Melzer, 2007b; Mukamal et al., 2004; Thun et al., 1997). Cardiovascular benefits are the most notably discussed health benefits associated with moderate alcohol use, with studies consistently demonstrating that moderate alcohol use reduces the risks of coronary heart disease (Corrao et al., 2004b; Corrao et al., 2000; Ellison, 2002; Gunzerath et al., 2004). Further, meta-analysis by Corrao and colleagues (2000) illustrates the relationship between alcohol consumption and the cardiovascular risk as a J-shaped curve, suggesting moderate alcohol use decreases the risk of coronary heart disease.

What constitutes "moderate" alcohol use, however, has been difficult to define (Durfour, 1999), especially for older adults who experience age-related physiological changes that can lead to a decreased tolerance to alcohol (Heuberger, 2009) and make them more susceptible to the effects of alcohol, including cognitive impairment (Sorocco & Ferrell, 2006). Currently, the Dietary Guidelines for Americans 2010 characterizes moderate alcohol use as no more than 1 drink per day for women and no more than 2 drinks per day for men (U.S. Department of Agriculture & U.S. Department of Health and Human Services, 2010).

Frailty

Fried and colleagues (2001) have broadly conceptualized frailty, a facet of late-life decline, as the multisystemic dysregulation of homeostatic mechanisms. They operationalized frailty as a phenotype characterized by three or more of the following conditions: weakness, low physical activity, unintentional weight loss, exhaustion, and slow walking speed (Fried et al., 2001). Fried and colleagues (2001) distinguished phenotypic frailty from disability and high comorbidity, both conceptually and empirically. This approach has been replicated across several frailty indices, including the Paulson-Lichtenberg Frailty Index (PLFI; Paulson & Lichtenberg, In Press), which was used in conducting this research.

Frailty been associated with varying aspects of late-life decline, including vascular disease (Alonso-Bouzon et al., 2014), heart rate variability (Varadhan et al., 2009a), orthostatic hypertension (Wee Lock et al., 1997), and inflammation and markers of blood clotting (Walston et al., 2002). Frailty also positively correlates with aging, being African American, being female, poorer health, and lower education and income (Fried et al., 2001; Paulson & Lichtenberg, In Press; Woods et al., 2005). Additionally, research has identified physical inactivity, heavy drinking, cigarette smoking, social isolation, depression, and prevalence of chronic conditions as prospective predictors of frailty in older adults (Strawbridge et al., 1998; Woods et al., 2005).

By contrast to heavy drinking, moderate alcohol use has been identified as a protective factor against frailty (Shah & Paulson, 2015; Woods et al., 2005). Specifically, older women who reported consuming <1 drink per week had a small but significant reduction in frailty risk (OR=.87), and older women who reported consuming between 1 and 14 drinks per week had a

larger reduction in frailty risk (OR=.69). Those who reported abstaining from alcohol altogether, however, were found to have similar frailty risk as those who reported drinking >14 drinks per week (Woods et al., 2005). Similar results were found in a longer, 12-year longitudinal study examining the relationship between alcohol use and frailty among older adults in the United States (Shah & Paulson, 2015). In this study, women who consumed 1-7 alcoholic beverages per week at baseline were significantly less likely to be identified as frail compared to abstainers (OR=.50). Women who drank 1-7 alcoholic beverages per week and were not frail at baseline were less likely to become frail 12 years later (OR=.75) (Shah & Paulson, 2015). Despite broad findings suggesting that moderate alcohol use confers health benefits, including reduction in frailty risk, the mechanisms by which moderate use leads to health benefits remains poorly understood. One possible candidate mechanism is C-reactive protein.

C-Reactive Protein

C-reactive protein is an inflammatory cytokine and is positively associated with the onset and course of many diseases associated with aging, including cardiovascular disease, type 2 diabetes, arthritis and osteoporosis (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002). C-reactive protein is an annular, pentraxin protein, synthesized by the liver, and found in blood plasma (Du Clos & Mold, 2004). C-reactive protein is regarded as a valid marker of inflammation such that when there is any tissue damage, which causes inflammation, CRP levels in blood plasma rise. There are very few pathologies, besides liver failure, and drugs that reduce CRP values (Hirschfield & Pepys, 2003).

C-reactive protein has been associated with both frailty and alcohol consumption. Inflammatory processes increase the production of inflammatory cytokines, which attributes to

developing sarcopenia (i.e., the degeneration of skeletal muscle mass). Sarcopenia then leads to decreased muscle strength and slow walking speed, both of which are indicators of frailty (Ershler, 2007). Using the Longitudinal Aging Study Amsterdam (LASA), Puts et al. (2005) found that moderately elevated CRP levels predicted incident frailty using a deficit accumulation model of frailty.

With respect to alcohol use, lower CRP levels were associated with moderate alcohol consumption (defined as 5-7 drinks weekly) as compared to no alcohol use, even after controlling for variables such as smoking, diabetes, cholesterol and sex (Albert, 2003). Other studies examining this relationship across a wider distribution of alcohol use has identified a J-shaped association between weekly alcohol use and levels of CRP has been shown in a study among older adults between the ages of 70 and 79 years, suggesting those who consumed 1-7 drinks had the lowest levels of CRP compared to those who either abstained or drank more than 7 drinks per week (Volpato et al., 2004). Similarly, Suarez and colleagues (2013) found that moderate alcohol consumption lowered CRP values among adults ages 18-65, but this relationship was moderated by depressive symptomatology and was only significant among male participants. Further experimental and retrospective longitudinal studies, using samples of adults with mean ages 56 and 43 respectively, also demonstrated that moderate alcohol consumption significantly decreased CRP levels (Sierksma, 2002; Stewart, Mainous, & Gilbert, 2002). It is unknown whether this pattern is similar for older adults. These findings in conjunction with past research suggesting CRP predicts cardiovascular risk (Ridker, 2003) suggests that CRP may be one plausible mechanism by which moderate alcohol use reduces frailty risk.

Proposed Research

The primary goals of this study are to: (A) investigate the relationship between moderate alcohol use and frailty in a demographically-representative sample of Americans over the age of 65; and (B) elucidate a possible biological mechanism by which this relationship functions. It is hypothesized that participants who report consuming moderate alcohol (1-14 drinks weekly) will be less frail than participants who report abstaining from alcohol altogether. In addition, it is hypothesized that C-reactive protein will mediate this relationship, as characterized by a significant indirect relationship from moderate alcohol use to frailty through CRP.

Methods

Participants

The present study utilized data collected through the Health and Retirement Study (HRS). The HRS is a National Institute of Aging-supported, prospective, cohort study on health, retirement, and aging conducted by the University of Michigan. The first wave of data collection occurred in 1992 and data has been and is collected biennially. The sample currently consists of over 37,000 adults, ages 50 and older and living in the United States. Data collection methods include interviews, surveys, and links to personal records, which provides abundant information about each participant including their physical and mental health, disability status, employment status, and housing situation. Further information on HRS survey design and data collection methods can be found in previously published reports (Hauser & Willis, 2004; Heeringa & Conner, 1995; Sonnega et al., 2014a).

This study uses HRS data from the 2008 wave of data collection as that is when all three major variables of interest, alcohol use, frailty and CRP levels, are reported and available for

participants. Data used in these analyses incorporate both the direct data released from the HRS committee, and cleaned HRS data released by the RAND Center for the Study of Aging (RAND HRS). Longitudinal data is available at 2-year intervals through 2012. The average inter-wave attrition rate is around 20%, the vast majority of which reflects death or incapacity.

The current HRS data set used includes 37,319 participants. After excluding participants below the age of 65 at the 2008 wave, the sample size reduced to 11,349 participants. Then, remaining participants who reported experiencing a stroke also were excluded, as individuals who have experienced a stroke are more likely to experience subsequent depression (Bour et al., 2009b), impairment in cognitive functioning (Tatemichi et al., 1994), and motor impairment (as cited in Langhome et al., 2009). This exclusion narrowed the sample size to 10,162 participants. Next, remaining participants who had more than one missing value on the variables used to assess medical burden were excluded as this leads to an inadequate assessment of medical burden. Of the remaining 10,159 participants in the sample, participants with missing CRP values at the 2008 wave (n= 6,450) or CRP values above 10µg/mL (n=337) were excluded as CRP values exceeding 10µg/mL suggest a possibility of an acute phase response (Ridker, 2003). This CRP-related exclusion reduced the sample to 3,372 participants. Subsequently, heavy drinkers (i.e., those consuming more than 14 drinks per week) in the remaining sample were excluded from this study, and alcohol use was dichotomized as abstinent (0 drinks per week) and moderate (1-14 drinks per week). This method, supported by past research, allowed us to better elucidate the mechanism by which moderate alcohol has a protective effect by comparing moderate drinkers to non-drinkers. Of the remaining 3,256 participants in the sample, 27 participants missing values on the BMI variable were excluded, leaving a final sample of 3,229 participants (see *Figure 2.1*).

Measures

Alcohol Use. Alcohol use was assessed by calculating the average number of reported drinks per week. In the HRS data set, alcohol use was measured by first asking participants, "Do you ever drink any alcoholic beverages, such as beer, wine, or liquor?" If participants responded "yes" to the initial question, they were asked two follow-up questions to assess the frequency and intensity of their consumption. The first follow-up question asked participants to report the number of days per week on average that they consume an alcoholic drink with respect to the last three months. Participants whose response was at least one drink per week or greater, were then asked how many drinks they consume on days they drink with respect to the past three months. Average number of drinks per week was calculated by multiplying the number of drinks per day by the number of drinking days per week.

C-Reactive Protein. C-reactive protein was collected through an enzyme-linked immunosorbent assay (ELISA) using dried blood spot (DBS) (Crimmins et al., 2013). ELISA is a test that uses antibodies to detect the presence and amount of a protein, typically indicated by a color change once the antibody binds to the protein. The minimum CRP level required for detection is 0.035μg/mL. CRP data for 2008 was collected by DBS assays done at the University of Vermont. Imprecision was measured as the coefficient of variation (i.e., ratio of standard deviation to the mean), and indicates the reliability and validity of the measurement method. The within-assay imprecision is 8.1%, and between-assay imprecision is 11.0% (Crimmins et al., 2013).

Outcome Variable

Frailty. Frailty was measured using the Paulson-Lichtenberg Frailty Index (PLFI; Paulson & Lichtenberg, In Press), which is based on Fried and colleagues' (2001) conceptualization of frailty as a phenotype. The frailty index includes five symptom criteria: wasting, weakness, slowness, fatigue or exhaustion, and falls. The wasting criterion was met if the participant reported a loss of 10% body weight over a 2-year period. The weakness criterion was met if the participant responded yes to "Because of health problems, do you have difficulty with lifting or carrying weights over 10 pounds, like a heavy bag of groceries?" The slowness criterion was met if participants responded affirmatively to, "Because of a health problem, do you have any difficulty with getting up from a chair after sitting for long periods?" The fatigue or exhaustion criterion was met if the participant endorsed yes to "Since we last talked with you [in the last wave], have you had any of the following persistent or troublesome problems: […] severe fatigue or exhaustion?" Lastly, the falls criterion was met if the participant answered yes, "Have you fallen in the past two years?" Each affirmative response will receive a score of 1, and a score of 3 or more will indicate that the participant is frail. The PLFI has been used in previous studies measuring frailty (Paulson & Lichtenberg, 2012). No PLFI indicators were drawn from the depression measure utilized below.

Control Variables

Demographic Variables. Participants' identified gender and age at each wave is included in the data provided by the HRS. Data on these demographic variables were collected through interviewing participants either via telephone or face-to-face.

Medical Burden. Medical burden was assessed via disease count method, with the presence of each disease adding a score of 1. Hence, higher scores indicate a higher degree of

medical burden. The following diseases will be counted for in determining the medical burden: hypertension, diabetes, cardiac disease, arthritis, pulmonary disorder, and cancer. Medical burden was controlled for as these diseases increase levels of stress and inflammation, which thereby increase levels of CRP (Kiecolt-Glaser et al., 2002).

Body Mass Index (BMI). The HRS data set provides a calculated body mass index for each participant. The BMI calculation was based on the participant's height assessed in 1996 or at study intake, and their weight assessed in 2008.

Depression. Depression was assessed using participants' scores on an abridged, 8-item version of the Center for Epidemiological Studies Depression (CES-D) measure (Radloff, 1977). Participants answered "yes" or "no" to each item-statement with respect to how they were feeling "much of the time" in the past week. Six of the statements were worded negatively ("felt depressed, felt that everything he/she did was an effort, sleep was restless, could not get going, felt lonely, and felt sad") and two of the statements were worded positively ("enjoyed life and was happy"). Scores range on a scale from 0-8, with higher scores suggesting higher levels of depression.

Statistical Methods

A univariate comparison of drinkers and nondrinkers was completed using parametric and non-parametric methods, as appropriate to the specific problem. Structural equation modeling, specifically a path analysis using a mediation analysis adapted from Baron and Kenny (1986), was used to determine the overall relationship between alcohol use, C-reactive protein, and frailty (*Figure 2-2*). Path analysis is an extension of regression and allows for more complex modeling. This method is favored when testing multiple hypothesized relationships, as

traditional statistical methods would increase the Type 1 error rate (Hancock, 2003). First, a direct relationship between alcohol consumption and frailty was estimated. Then CRP was included in the model as a mediator. Control variables included age, gender, medical burden, BMI and CES-D score. Mediation of this relationship was identified based on a significant indirect relationship from alcohol to frailty through CRP. Data were prepared in SPSS and the structural equation model analysis was performed utilizing *Mplus* software program (Muthen & Muthen, 2012).

Results

The final sample consisted of 3,229 participants. As displayed in *Table 2.1*, the sample was predominantly female (60.0%), largely White/Caucasian (85.2%), and had a mean age of 74.50 years (*SD*=6.92), and a mean education of 12.30 years (*SD*=3.19). The sample reported a mean CES-D score of 1.26 (*SD*=1.80) and a mean medical burden score of 2.18 (*SD*=1.23). In addition, the mean BMI in the sample was 27.59kg/m^2 (*SD*=5.40) and mean CRP level was 2.56µg/mL (*SD*=2.21). Approximately 70% of participants included in this study reported being abstinent from alcohol, and *Table 2.1* provides separate sample characteristics for non-drinkers (n=2,289) and moderate drinkers (n=940). As expected, moderate drinkers differed significantly compared to non-drinkers. Specifically, compared to non-drinkers, moderate drinkers were more likely to be White ($\chi^2_{(df=1)}$=47.10, p<0.001), male($\chi^2_{(df=1)}$=79.24, p<0.001), and partnered ($\chi^2_{(df=1)}$=55.95, p<0.001). In addition, moderate drinkers reported lower BMI values (U=990,059.50, p<0.001), lower medical burden scores (U=926,420.00, p<0.001), and less depressive symptomatology (U=861,352.00, p<0.001) as compared to non-drinkers. Further, compared to non-drinkers, moderate drinkers were younger (U=1,016,484.00, p=0.014), more

educated (U=774,317.00, p<0.001), of higher SES (U=668,201.50, p<0.001), and less frail (U=831,567.50, p<0.001). Lastly, moderate drinkers had lower CRP values overall less depressive symptomatology (U=987,221.50, p<0.001) compared to non-drinkers.

The primary hypothesis that CRP would mediate the relationship between moderate alcohol use and frailty was examined using a path analysis (*Figure 2.2*). Overall, results suggest that the hypothesized model fit the data very well (RMSEA=0.064; Comparative Fit Index (CFI)=0.932; $\chi^2_{(df=7)}$=100.95, p<0.001). All pathways in the model were statistically significant, and thus, further support the hypothesized relationship between the variables. Specifically, moderate drinking was significantly associated with lower levels of CRP (β=-0.043, SE=0.017, p=0.012), and less frailty (β=-0.040, SE=0.016, p=0.012). Higher CRP values were significantly associated with more frailty (β=0.049, SE=0.016, p=0.002). The indirect pathway from alcohol to frailty through CRP also was statistically significant (β=-0.002, SE=0.001, p=0.050).

In addition to the primary variables of interest, all control variables used in the model also had statistically significant pathways. Specifically, moderate alcohol use was associated with being male (β=-0.140, SE=0.017, p<0.001) and reporting greater depressive symptomatology (β=-0.141, SE=0.017, p<0.001); higher CRP values were associated with both, higher medical burden scores (β=0.036, SE=0.018, p=0.042) and greater BMI values (β=0.235, SE=0.017, p<0.001); and frailty was associated with being female (β=0.144, SE=0.016, p<0.001) and older (β=0.120, SE=0.016, p<0.001), and having greater depressive symptomatology (β=0.323, SE=0.015, p<0.001) and greater medical burden (β=0.225, SE=0.016, p<0.001). Overall, the model accounted for 25.6% (p<0.001) of the variability in frailty.

Discussion

Primary findings from this study support the hypothesized model. Moderate alcohol use was associated with fewer frailty symptoms and lower CRP values. CRP was directionally and positively associated with frailty. The significant indirect relationship from moderate alcohol use to frailty suggests that CRP is one mechanism by which alcohol use may confer protective effects for frailty. Results further demonstrate that gender and CES-D score significantly predicted alcohol use. As hypothesized, gender, CES-D score, age and medical burden significantly predicted frailty, and medical burden and BMI significantly predicted CRP.

The current findings support relationships between individual variables alcohol and CRP (Albert, 2003), and CRP and frailty (Puts et al., 2005) that have been reported in past research. This is the first study to our knowledge to integrate these elements in such a way as to identify direct and indirect effects of moderate alcohol use on frailty. Emergence of integrated medical delivery emphasizes process models of disease, particularly for geriatric syndromes such as frailty. Current findings build on past work by suggesting a process model that elucidates one mechanism of the well-established preventative effects of moderate alcohol use. The small magnitude of this finding reflects numerous factors, not the least of which is that alcohol use is just one of many determinants of frailty status. As such, moderate alcohol use predicts only a small portion of the overall variability in frailty, and of that, only part is related to CRP. Nonetheless, these results establish a starting place for efforts to better understand the protective effects of moderate alcohol use. While further research must precede application of these findings to clinical intervention, these findings do raise a number of interesting questions about the mechanisms of moderate alcohol use. As mentioned, one proposed hypothesis is that alcohol

may attenuate IL-6 production, which would subsequently reduce CRP production (Albert, 2003).

In addition, further investigation should explore other mechanisms that account for the unexplained variance between alcohol use and frailty. Based on their findings, Maraldi et al. (2009) suggest that the relationship between moderate alcohol use and decreased risk of functional decline is weakened when lifestyle factors are taken into account. This suggests that those who consume alcohol in moderation may employ behaviors, such as regular socialization and physical activity, that account for the reduction in frailty risk (Maraldi et al., 2009). For instance, research suggests that routine moderate alcohol use reduces stress (Sayette, 1999) while other findings suggest that psychosocial stress is positively associated with CRP levels (Johnson, Abbasi, & Master, 2013). Hence, moderate alcohol use may decrease stress levels, thereby reducing CRP, and conferring health benefits. This hypothesis is further supported by a systematic review conducted by Johnson and colleagues (2013) who report that most studies demonstrate a significant negative relationship between chronic psychosocial stress and health outcomes, mediated through inflammation as measured by CRP levels (Johnson et al., 2013). These hypotheses remain important lines of inquiry. Future work also should consider the role of genetic and biological factors in the relationship between alcohol use and frailty. For example, Mukamal and colleagues (2004) found that Apolipoprotein-E (ApoE), mapped on chromosome 19, moderates the relationship between CRP and alcohol use.

Results from this study corroborate the extant research identifying CRP as one mechanism of action to account for the health benefits associated with moderate alcohol use. Specifically, moderate alcohol use and lower CRP values have been associated with cardiovascular benefits (Albert, 2003). Indeed, treatments involving inflammation reduction,

including use of Aspirin and prescribed exercise, offer demonstrated benefits with respect to cardiovascular health. Future research also should examine mechanisms by which moderate alcohol use beneficially relates to other health outcomes. For example, several studies also have documented the potential cognitive benefits associated with moderate alcohol use (Goldberg et al., 1999; Lang, Wallace, et al., 2007b; Panza et al., 2012), and future research might examine the potential mediating role of CRP.

Limitations of this study include the reliance on subjective rather than objective data. While this method to collect alcohol use data is subject to measurement error, it is congruent with the majority of extant alcohol research due to the difficulties in obtaining objective measures (e.g., blood alcohol concentration). Self-report also was used to obtain medical burden scores by confirming or denying the presence of physical diseases. Despite flaws that may be associated with self-report, this method is common in population-based samples, and prior research has shown adequate agreement between self-report and objective medical data (Bush et al., 1989).

APPENDIX A: TABLES

Table 1.1 *Frequency of Frailty*

2000 Prevalence		Males		Females	
2000 Drinks/Week	***n***	**# Frail**	**% Frail**	**# Frail**	**% Frail**
0	6,124	218	3.56	828	13.52
1-7	1,500	43	2.87	57	3.80
8-14	400	18	4.50	13	3.25
≥15	160	7	4.38	4	2.50

2004 Incidence		Males		Females	
2000 Drinks/Week	***n***	**# Frail**	**% Frail**	**# Frail**	**% Frail**
0	4,234	185	4.37	483	11.41
1-7	1,196	46	3.85	71	5.94
8-14	306	13	4.25	10	3.27
≥15	126	10	7.94	6	4.76

2008 Incidence		Males		Females	
2000 Drinks/Week	***n***	**# Frail**	**% Frail**	**# Frail**	**% Frail**
0	3,245	176	5.42	479	14.76
1-7	964	57	5.91	94	9.75
8-14	254	23	9.06	19	7.48
≥15	91	10	10.99	3	3.30

2012 Incidence		Males		Females	
2000 Drinks/Week	***n***	**# Frail**	**% Frail**	**# Frail**	**% Frail**
0	2,272	158	6.95	427	18.79
1-7	713	52	7.29	76	10.66
8-14	189	26	13.76	18	9.52
≥15	72	15	20.83	6	8.33

Table 1.2 *Sample Characteristics at Prevalence (2000) and Incidence (2004, 2008, 2012) Years*

	revalence (2000) ***n*** **=8,184**	**Incidence (2004)** ***n*** **=5,862**	**Incidence (2008)** ***n*** **=4,554**	**Incidence (2012)** ***n*** **=3,246**
Variable	***M(SD)***	***M(SD)***	***M(SD)***	***M(SD)***
Age	74.31 (7.00)	73.24 (6.35)	72.17 (5.70)	71.07 (4.98)
Education (years)	11.90 (3.34)	12.13 (3.24)	12.23 (3.21)	12.44 (3.10)
2000 CES-D	1.55 (1.86)	1.30 (1.70)	1.22 (1.64)	1.16 (1.60)
2000 Medical Burden	1.85 (1.17)	1.71 (1.15)	1.64 (1.10)	1.57 (1.07)
2000 BMI	26.37 (4.90)	26.52 (4.66)	26.71 (4.56)	26.85 (4.48)
2000 SES (in 100,000s)	3.87 (7.05)	4.29 (7.55)	4.55 (8.01)	4.77 (8.25)
2000 Drinks/Week	1.77 (5.04)	1.92 (5.28)	1.93 (5.09)	2.05 (5.51)
	Percentage of Sample			
Gender				
Male	40.80	42.10	40.30	39.60
Female	59.20	57.90	59.70	60.40
Race				
White	85.70	86.60	86.50	86.70
Other	14.30	13.40	13.50	13.30
Partnered	58.00	62.50	65.30	68.10
2000 % Frail	14.50	0.00	0.00	0.00
2004 % Frail	N/A	5.20	0.00	0.00
2008 % Frail	N/A	N/A	4.00	0.00
2012 % Frail	N/A	N/A	N/A	3.20

Table 1.3 *Results of Logistic Regression Predicting Frailty in 2000 for Males (n=3,342)*

	Step 1					Step 2				
	B	***SE***	***Wald***	***Exp(B)***	**95% CI**	***B***	***SE***	***Wald***	***Exp(B)***	**95% CI**
Age	0.04	0.01	13.59***	1.04	1.02-1.06	0.04	0.01	12.86***	1.04	1.02-1.06
Education (years)	-0.02	0.02	1.52	0.98	0.94-1.02	-0.02	0.02	1.15	0.98	0.94-1.02
Race	0.18	0.19	0.86	1.19	0.82-1.73	0.16	0.19	0.74	1.18	0.81-1.71
Partnered	0.29	0.16	3.20	1.33	0.97-1.82	0.28	0.16	3.06	1.32	0.97-1.81
2000 CES-D	0.46	0.03	187.65***	1.58	1.48-1.69	0.46	0.03	185.56***	1.58	1.48-1.69
2000 SES	-0.05	0.02	5.46*	0.96	0.92-0.99	-0.04	0.02	5.13*	0.96	0.92-0.99
2000 BMI	-0.05	0.02	7.25**	0.96	0.93-0.99	-0.05	0.02	7.45**	0.96	0.92-0.99
2000 Medical Burden	0.58	0.06	98.79***	1.79	1.59-2.00	0.57	0.06	95.70***	1.77	1.58-1.99
Drinks 1-7						-0.15	0.19	0.64	0.86	0.59-1.25
Drinks 8-14						-0.11	0.28	0.14	0.90	0.52-1.55
Drinks ≥ 15						-0.30	0.43	0.48	0.74	0.32-1.73
Constant	-6.05	1.08	31.16			-5.93	1.09	29.59		

***$p \leq 0.001$
**$p \leq 0.01$
*$p \leq 0.05$

Table 1.4 *Results of Logistic Regression Predicting Frailty in 2004 for Males (n=2,465)*

	Step 1					Step 2				
	B	***SE***	***Wald***	***Exp(B)***	**95% CI**	***B***	***SE***	***Wald***	***Exp(B)***	**95% CI**
Age	0.09	0.01	61.37***	1.09	1.07-1.11	0.09	0.01	60.09***	1.09	1.07-1.11
Education (years)	-0.02	0.02	0.52	0.99	0.95-1.03	-0.01	0.02	0.14	0.99	0.95-1.03
Race	-0.07	0.22	0.10	0.93	0.61-1.43	-0.08	0.22	0.15	0.92	0.60-1.41
Partnered	0.26	0.18	2.25	1.30	0.92-1.83	0.24	0.18	1.90	1.27	0.90-1.80
2000 CES-D	0.17	0.04	16.30***	1.18	1.09-1.28	0.16	0.04	15.69***	1.18	1.09-1.28
2000 SES	-0.02	0.01	2.20	0.98	0.96-1.01	-0.02	0.01	1.66	0.98	0.96-1.01
2000 BMI	0.03	0.02	3.56†	1.03	1.00-1.07	0.03	0.02	3.26	1.03	1.00-1.07
2000 Medical Burden	0.38	0.06	38.84***	1.47	1.30-1.66	0.38	0.06	37.07***	1.46	1.29-1.64
Drinks 1-7						-0.33	0.18	3.27	0.72	0.50-1.03
Drinks 8-14						-0.45	0.31	2.16	0.64	0.35-1.16
Drinks ≥ 15						0.09	0.36	0.07	1.10	0.55-2.20
Constant	-10.27	1.19	74.15			-10.14	1.20	71.62		

***$p \leq 0.001$
**$p \leq 0.01$
*$p \leq 0.05$
†$p \leq 0.06$

Table 1.5 *Results of Logistic Regression Predicting Frailty in 2008 for Males (n=1,836)*

	Step 1					Step 2				
	B	***SE***	***Wald***	***Exp(B)***	**95% CI**	***B***	***SE***	***Wald***	***Exp(B)***	**95% CI**
Age	0.09	0.01	58.95***	1.10	1.07-1.13	0.10	0.01	59.42***	1.10	1.07-1.13
Education (years)	-0.04	0.02	3.61†	0.96	0.92-1.00	-0.04	0.02	3.21	0.96	0.93-1.00
Race	0.03	0.22	0.02	1.03	0.97-1.01	0.02	0.22	0.01	1.02	0.67-1.57
Partnered	-0.07	0.18	0.16	0.93	0.66-1.32	-0.07	0.18	0.16	0.93	0.65-1.32
2000 CES-D	0.15	0.04	12.04***	1.16	1.07-1.27	0.15	0.04	11.83***	1.16	1.07-1.26
2000 SES	-0.01	0.01	0.62	0.99	0.97-1.01	-0.01	0.01	0.50	0.99	0.97-1.01
2000 BMI	0.00	0.02	0.00	1.00	0.97-1.04	0.00	0.02	0.00	1.00	0.97-1.04
2000 Medical Burden	0.29	0.06	21.80***	1.33	1.18-1.51	0.29	0.06	21.54***	1.33	1.18-1.50
Drinks 1-7						-0.19	0.17	1.17	0.83	0.59-1.16
Drinks 8-14						0.06	0.25	0.05	1.06	0.65-1.73
Drinks ≥ 15						0.18	0.37	0.24	1.12	0.58-2.45
Constant	-8.84	1.24	51.32			-8.89	1.24	51.20		

*** $p \leq 0.001$
** $p \leq 0.01$
* $p \leq 0.05$
† $p \leq 0.06$

Table 1.6 *Results of Logistic Regression Predicting Frailty in 2012 for Males (n=1,284)*

	Step 1					Step 2				
	B	***SE***	***Wald***	***Exp(B)***	**95% CI**	***B***	***SE***	***Wald***	***Exp(B)***	**95% CI**
Age	0.09	0.02	33.82***	1.10	1.06-1.13	0.09	0.02	34.52***	1.10	1.06-1.13
Education (years)	-0.03	0.02	1.70	0.97	0.93-1.02	-0.03	0.02	1.58	0.97	0.93-1.02
Race	-0.14	0.24	0.33	0.87	0.55-1.39	-0.12	0.24	0.24	0.89	0.56-1.42
Partnered	0.22	0.22	1.08	1.25	0.82-1.91	0.24	0.22	1.25	1.28	0.83-1.95
2000 CES-D	0.13	0.05	5.87*	1.13	1.02-1.26	0.12	0.05	5.49*	1.13	1.02-1.25
2000 SES	-0.01	0.01	1.05	0.99	0.97-1.01	-0.01	0.01	0.83	0.99	0.97-1.01
2000 BMI	0.03	0.02	3.04	1.03	1.00-1.07	0.03	0.02	2.94	1.03	1.00-1.07
2000 Medical Burden	0.40	0.07	34.74***	1.49	1.31-1.71	0.40	0.07	34.99***	1.50	1.31-1.71
Drinks 1-7						-0.22	0.19	1.43	0.80	0.56-1.15
Drinks 8-14						0.14	0.25	0.30	1.15	0.70-1.87
Drinks ≥ 15						0.55	0.33	2.67	1.73	0.90-3.32
Constant	-9.28	1.46	40.43			-9.41	1.47	41.01		

*** $p \leq 0.001$
** $p \leq 0.01$
* $p \leq 0.05$

Table 1.7 *Results of Logistic Regression Predicting Frailty in 2000 for Females (n=4,842)*

	Step 1					Step 2				
	B	***SE***	***Wald***	***Exp(B)***	**95% CI**	***B***	***SE***	***Wald***	***Exp(B)***	**95% CI**
Age	0.06	0.01	91.03***	1.06	1.05-1.07	0.06	0.01	86.14***	1.06	1.05-1.07
Education (years)	0.00	0.01	0.08	1.00	0.97-1.02	0.00	0.01	0.08	1.00	0.98-1.03
Race	0.00	0.11	0.00	1.00	0.80-1.24	-0.02	0.11	0.03	0.98	0.97-1.01
Partnered	-0.01	0.09	0.01	0.99	0.82-1.19	0.00	0.09	0.00	1.00	0.83-1.19
2000 CES-D	0.30	0.02	246.92***	1.36	1.30-1.41	0.30	0.02	241.81***	1.35	1.30-1.41
2000 SES	-0.02	0.01	2.26	0.98	0.96-1.01	-0.01	0.01	1.18	0.99	0.97-1.01
2000 BMI	0.02	0.01	7.07**	1.02	1.01-1.04	0.02	0.01	5.26*	1.02	1.00-1.03
2000 Medical Burden	0.52	0.04	193.82***	1.67	1.56-1.80	0.51	0.04	185.99***	1.66	1.54-1.78
Drinks 1-7						-0.70	0.15	20.68***	0.50	0.37-0.67
Drinks 8-14						-0.25	0.32	0.62	0.78	0.42-1.45
Drinks ≥ 15						-0.10	0.58	0.03	0.91	0.29-2.82
Constant	-8.00	0.63	160.23			-7.80	0.63	151.60		

***$p \leq 0.001$
**$p \leq 0.01$
*$p \leq 0.05$

Table 1.8 *Results of Logistic Regression Predicting Frailty in 2004 for Females (n=3,397)*

	Step 1					Step 2				
	B	***SE***	***Wald***	***Exp(B)***	**95% CI**	***B***	***SE***	***Wald***	***Exp(B)***	**95% CI**
Age	0.07	0.01	81.49***	1.07	1.06-1.09	0.07	0.01	80.81***	1.07	1.06-1.09
Education (years)	-0.01	0.02	0.36	0.99	0.96-1.02	-0.01	0.02	0.25	0.99	0.96-1.03
Race	-0.02	0.14	0.02	0.98	0.75-1.29	-0.02	0.14	0.03	0.98	0.74-1.28
Partnered	0.03	0.10	0.07	1.03	0.84-1.26	0.03	0.11	0.08	1.03	0.84-1.26
2000 CES-D	0.15	0.03	36.97***	1.16	1.12-1.22	0.15	0.03	35.65***	1.16	1.10-1.22
2000 SES	-0.01	0.01	0.38	0.99	0.98-1.01	-0.01	0.01	0.26	1.00	0.98-1.01
2000 BMI	0.05	0.01	22.80***	1.05	1.03-1.07	0.04	0.01	21.70***	1.05	1.03-1.07
2000 Medical Burden	0.35	0.04	63.20***	1.42	1.30-1.55	0.35	0.04	63.24***	1.42	1.30-1.55
Drinks 1-7						-0.17	0.15	1.40	0.84	0.63-1.12
Drinks 8-14						-0.19	0.35	0.29	0.83	0.42-1.64
Drinks ≥ 15						0.84	0.49	2.91	2.31	0.88-6.04
Constant	-8.75	0.78	125.69			-8.71	0.78	123.52		

***$p \leq 0.001$
**$p \leq 0.01$
* $p \leq 0.05$

Table 1.9 *Results of Logistic Regression Predicting Frailty in 2008 for Females (n=2,718)*

	Step 1					Step 2				
	B	***SE***	***Wald***	***Exp(B)***	**95% CI**	***B***	***SE***	***Wald***	***Exp(B)***	**95% CI**
Age	0.07	0.01	68.54***	1.07	1.05-1.09	0.07	0.01	68.94***	1.07	1.05-1.09
Education (years)	-0.02	0.02	1.25	0.98	0.95-1.01	-0.02	0.02	1.31	0.98	0.95-1.01
Race	-0.12	0.14	0.75	0.89	0.67-1.17	-0.12	0.14	0.75	0.89	0.67-1.17
Partnered	-0.17	0.10	2.83	0.84	0.69-1.03	-0.18	0.10	3.01	0.84	0.69-1.02
2000 CES-D	0.10	0.03	13.29***	1.10	1.05-1.16	0.10	0.03	13.75***	1.11	1.05-1.16
2000 SES	0.01	0.01	0.72	1.01	0.99-1.02	0.01	0.01	0.61	1.01	0.99-1.02
2000 BMI	0.03	0.01	8.30**	1.03	1.01-1.05	0.03	0.01	8.60**	1.03	1.01-1.05
2000 Medical Burden	0.30	0.05	43.17***	1.35	1.23-1.47	0.30	0.05	42.66***	1.35	1.23-1.47
Drinks 1-7						-0.01	0.13	0.00	0.99	0.76-1.29
Drinks 8-14						0.39	0.28	1.98	1.48	0.86-2.56
Drinks ≥ 15						-0.21	0.64	0.11	0.81	0.23-2.84
Constant	-7.28	0.79	84.03			-7.32	0.80	84.27		

*** $p \leq 0.001$
** $p \leq 0.01$
* $p \leq 0.05$

Table 1.10 *Results of Logistic Regression Predicting Frailty in 2012 for Females (n=1,962)*

	Step 1					Step 2				
	B	***SE***	***Wald***	***Exp(B)***	**95% CI**	***B***	***SE***	***Wald***	***Exp(B)***	**95% CI**
Age	0.08	0.01	57.63***	1.08	1.06-1.10	0.08	0.01	57.73***	1.08	1.06-1.10
Education (years)	-0.04	0.02	3.55†	0.97	0.93-1.00	-0.03	0.02	3.04	0.97	0.93-1.00
Race	-0.08	0.16	0.28	0.92	0.68-1.25	-0.10	0.16	0.42	0.90	0.67-1.23
Partnered	0.03	0.11	0.05	1.03	0.82-1.28	0.02	0.11	0.03	1.02	0.82-1.27
2000 CES-D	0.12	0.03	16.27***	1.13	1.07-1.20	0.12	0.03	16.16***	1.13	1.07-1.20
2000 SES	0.01	0.01	0.67	1.01	0.99-1.02	0.01	0.01	0.80	1.01	0.99-1.02
2000 BMI	0.04	0.01	14.24***	1.04	1.02-1.07	0.04	0.01	13.44***	1.04	1.02-1.07
2000 Medical Burden	0.20	0.05	15.50***	1.23	1.11-1.36	0.21	0.05	15.68***	1.23	1.11-1.36
Drinks 1-7						-0.29	0.15	3.84*	0.75	0.56-1.00
Drinks 8-14						0.39	0.30	1.73	1.48	0.83-2.66
Drinks ≥ 15						0.59	0.54	1.23	1.81	0.63-5.19
Constant	-7.75	0.93	68.98			-7.72	0.94	68.04		

*** $p \leq 0.001$
** $p \leq 0.01$
* $p \leq 0.05$
† $p \leq 0.06$

Table 2.1 *2008 Sample Characteristics*

	Total (n=3229)	Non-Drinkers (0 Drinks/Wk) (n=2289)	Moderate Drinker (1-14 Drinks/Wk) (n=940)
Variable	**M(SD)**	**M(SD)**	**M(SD)**
Age *	74.50(6.92)	74.74(7.09)	73.92(6.46)
BMI	27.59(5.40)	27.88(5.70)	26.90(4.53)
CES-D	1.26(1.80)	1.44(1.90)	0.81(1.42)
Medical Burden	2.18(1.23)	2.27(1.25)	1.96(1.16)
CRP	2.56(2.21)	2.66(2.25)	2.34(2.08)
SES (in hundred thousands)	5.69(12.29)	4.17(10.96)	9.37(14.39)
Education (years)	12.30(3.19)	11.85(3.26)	13.40(2.74)
Frailty	1.25(1.19)	1.36(1.23)	0.97(1.05)
		Percentage of Sample	
Gender			
Male	40.0	35.1	52.0
Female	60.0	64.9	48.0
Partnered	60.8	56.7	70.9
Race			
White	85.2	82.5	91.9
Other	14.8	17.5	8.1

Note: All values were significantly different by $p<0.001$ except for age (*) which was significant different by $p<0.01$.

APPENDIX B: FIGURES

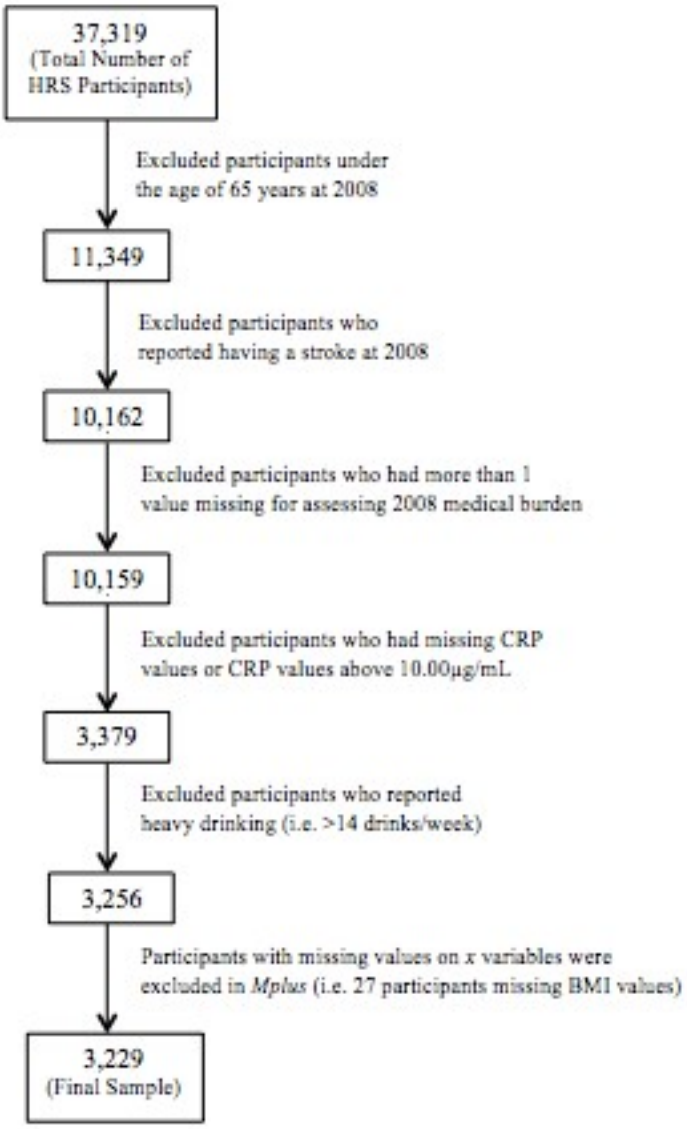

Figure 2.1 *Sample selection*

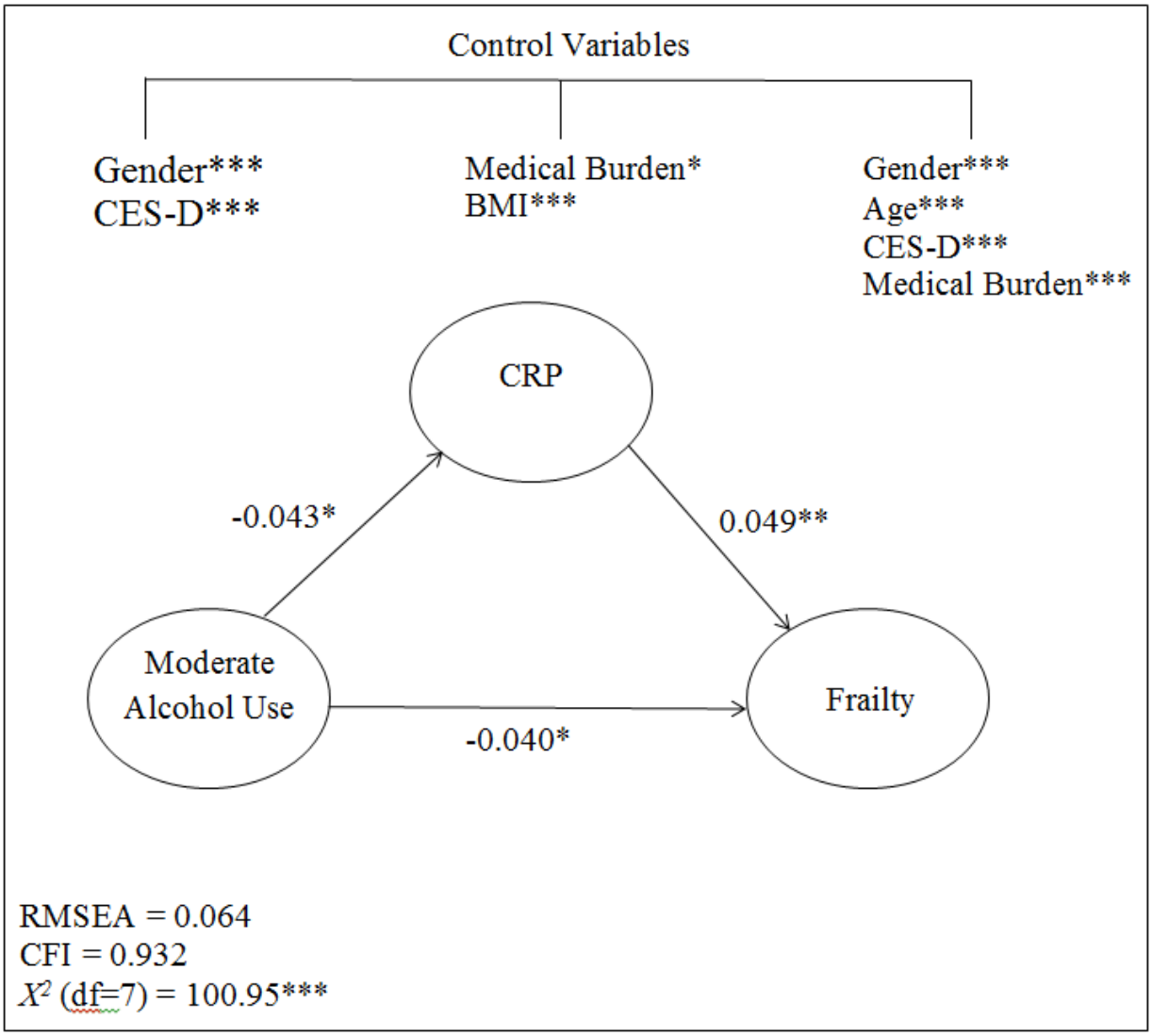

Figure 2.2 *Structural model depicting the relationship between moderate alcohol use, C-reactive protein and frailty.*

*$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$; CES-D=Center for Epidemiological Studies-Depression Scale; BMI=Body Mass Index; CRP=C-reactive protein

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