Spring 2017

# Multimorbidity and Mortality Risk: The Effect of Depressive Symptom Trajectories among Middle-Aged and older adults

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# Multimorbidity and Mortality Risk: The Effect of Depressive Symptom Trajectories Among Middle-Aged and Older Adults

by

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Bachelor of Science
University of South Carolina, 2015

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Submitted in Partial Fulfillment of the Requirements

For the Degree of Master of Science in Public Health in

Epidemiology

The Norman J. Arnold School of Public Health

University of South Carolina

2017

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## DEDICATION

I dedicate this thesis to my parents, David and Terri O'Shields. Since I was a child they have always stressed the importance of following your dreams. Without their love and support I would not have been able to follow my dreams. Thank you Mom and Dad for showing me how to work hard while staying true to who you are. You both have been the best role models and I never taken for granted all you have done, and continue to do, for Maggie and myself. I love you!

## ACKNOWLEDGEMENTS

Without the help of my committee members this thesis would not have been possible. I want to thank my chair, Dr. Kellee White, for her encouragement and endless support through this tiring thesis process. When I did not see an end in sight she kept me focused, and it was much appreciated.

I would also like to thank my readers, Dr. Anwar Merchant, and Dr. Alexander McLain. Their support and comments throughout this thesis journey were both helpful and encouraging.

I would also like to thank Colby Niven for always allowing me to vent about my thesis struggles while continuing to support me day after day. Even when I did not believe in myself anymore he always did, and I will never be able to thank him enough.

Finally, I would like to thank my amazing cohort. Bryn, Jourdyn, Susannah, Samantha, Kerry, Marilyn, Tsion, and Danielle, as our time together comes to an end I want to thank you all for being tremendous cheerleaders throughout these past two years. You all have made these past two years unforgettable; so thank you.

# ABSTRACT

**Introduction**

Multimorbidity, commonly defined as having two or more chronic conditions, is a major burden in middle-aged and older adults, causing increased risks for hospitalizations, medical care costs, and even death. One condition with severe adverse effects in the older population is depression. Depression has been shown to increase ones social isolation while compounding self-management, eventually increasing ones chance for mortality. Multimorbidity coupled with depression has been shown to increase the risk for mortality; however, these results are typically based on a one-time depression evaluation. The main objective of this study is to examine if depressive symptom trajectories modifies the effect multimorbidity has on all-cause and cause-specific (cancer and cardiovascular disease) mortality.

**Methods**

Data obtained from the Health and Retirement Study (HRS) was used for this study. A multimorbidity variable was created using data from the 2004 wave of the HRS. Three distinct depressive symptom trajectories were created using the biennial waves from 1998, 2000, 2002, and 2004 (persistently low, persistently moderate, and persistently high). Deaths were analyzed and categorized from the 2006, 2008, 2010, 2012, and 2014 datasets. Confounders were analyzed in 2004 and were included based on their

presence in similar studies. There were a total of 13005 individuals aged 50 and older who fit the criteria for this study. Separate Cox proportional hazards models were created and ran to examine the association depressive symptom trajectories have on modifying the effect multimorbidity has on all-cause and cancer mortality. Fine and Gray models were created and ran to examine the association depressive symptom trajectories have on modifying the effect multimorbidity has on cardiovascular disease (CVD) mortality.

**Results**

From the final study population, 58.5% had persistently low depression symptoms, 24.9% had persistently moderate depression symptoms, and 16.6% had persistently high depression symptoms. We found depressive symptom trajectories to significantly modify the association between multimorbidity and cardiovascular mortality, specifically among individuals who had three or more chronic conditions. The greatest risk of cardiovascular death was among individuals who had three or more chronic conditions and had persistently high depressive symptom trajectories (HR: 1.85; 95% CI: 1.22, 2.79). Depressive symptom trajectories did not significantly modify the association between multimorbidity and all-cause or cancer mortality.

**Conclusion**

The findings from this study found that depressive symptom trajectories did not modify the risk of all-cause or cancer-mortality in multimorbid individuals. Depressive symptom trajectories did modify the association between multimorbidity and cardiovascular

mortality. Findings from this study partially suggest that depressive symptom trajectories may help to further stratify people who are at a higher risk for CVD mortality. More studies need to be conducted to see if depressive symptom trajectories modify the risk of death in all-cause and cancer-mortality when taking into account the combination of diseases and the severity of the illness. Managing individuals with persistent depressive symptoms and comorbid diseases should be explored to see if properly managing these illnesses could mitigate the mortality effects seen.

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## LIST OF ABBREVIATIONS

BDI ..... Beck Depression Inventory

BMI ..... Body Mass Index

CDC ..... Centers for Disease Control and Prevention

CES-D ..... Center for Epidemiologic Studies Depression Scale

CI ..... Confidence Interval

COPD ..... Chronic Obstructive Pulmonary Disease

CRP ..... C-Reactive Protein

CVD ..... Cardiovascular Disease

GDS ..... Geriatric Depression Scale

GED ..... General Educational Development

HPA ..... Hypothalamic-Pituitary-Adrenal

HRS ..... Health and Retirement Study

HS ..... High School

ICD-9-CM ..... International Classification of Diseases, Ninth Revision, Clinical Modification

IL-6 ..... Interleuken-6

LIPA ..... Light Intensity Physical Activity

MET ..... Metabolic Equivalent of Task

MIPA ..... Moderate Intensity Physical Activity

SD ..... Standard Deviation

VIPA ..... Vigorous Intensity Physical Activity

# CHAPTER 1

# INTRODUCTION

Middle-aged and older adults represent a sizable proportion of the U.S. population with complex health care needs including higher utilization of health care services, polypharmacy, frequent hospitalizations, and multimorbidity (Bodenheimer & Berry-Millet, 2009). The prevalence of multimorbidity, the presence of two or more conditions, ranges between 55% and 98% for middle-aged and older adults (Strauss et al., 2014; Ward, 2010). High levels of multimorbidity are associated with an increased risk of hospitalizations, deterioration of physical and cognitive health, higher medical care expenditures, and death (Moran et al., 2015; Quiñones et al., 2011; Violan et al., 2014). Despite an accumulation of research examining multimorbidity and mortality, the epidemiology and clinical course of multimorbidity remains poorly understood.

Depression is fairly common among middle-aged and older adults with multiple chronic conditions (Rote, Chen, & Markides, 2015; Sinnige et al., 2013). Depression may lead to increased social isolation, compound self-management by preventing one from being adherent to medication and behavioral lifestyles (i.e., physical activity), and activate the hypothalamic-pituitary-adrenal axis (HPA) which is associated with adverse health outcomes (i.e., cardiovascular disease programming) (Barth, Schumacher, & Herrmann-Lingen, 2004; van Dooren et al., 2013; Pinquart & Duberstein, 2010; Xiong &

Zhang, 2013). The combination of multimorbidity and depression may lead to a heightened vulnerability for death (Mezuk & Gallo, 2013). Several prior studies have identified depression as a significant risk factor for all-cause mortality, cardiovascular, cancer, and diabetic mortality (Barth, Schumacher, & Herrmann-Lingen, 2004; van Dooren et al., 2013; Pinquart & Duberstein, 2010). ] However, the few studies reporting a significant association between multimorbidity, depression, and mortality, examined depression only at a single point in time. Depressive symptoms are dynamic (Gilsanz et al., 2015). The course of depressive symptoms may vary over time, with fluctuating severity or the remitting and relapsing nature of symptoms (Musliner et al., 2016). Increasingly, longitudinal patterns of depressive symptoms (i.e. trajectories) are studied in older adults (Andreescu et al., 2008; Byers et al., 2012; Hsu, 2012; Hybels et al., 2016; Kuchibhatla et al., 2012; Kuo et al., 2011; Liang et al., 2011; Montagnier et al., 2014;). However, little is known about the potential heterogeneity in the relationship between multimorbidity and mortality by depression symptom trajectories.

Targeted and treating long-term depression among middle-aged and older adults may provide an opportunity to reduce all-cause and cause-specific mortality. However, our understanding of these mechanisms is limited and a more detailed study of the relationship between multimorbidity, depressive symptoms trajectories, and mortality is warranted. The overall objective of this study was to assess the longitudinal association between multimorbidity and depressive trajectories on all-cause mortality among a multi-ethnic community-dwelling sample of middle aged and older adults from 1998-

2014, using data from the Health and Retirement Study (HRS). The following question was explored:

Question 1: Do depressive symptom trajectories modify the association between multimorbidity status and all-cause and cause-specific (cardiovascular and cancer) mortality?

Hypothesis 1: It is hypothesized that high-risk depressive symptom trajectories will be associated with an increased risk of all-cause mortality in comparison to low-risk depressive symptom trajectories.

Hypothesis 2: It is hypothesized that high-risk depressive symptom trajectories will be associated with cardiovascular and cancer mortality in comparison to low-risk depressive symptom trajectories.

# CHAPTER 2

# LITERATURE REVIEW

## Multimorbidity

Multimorbidity is popularly defined as the co-existence of two or more chronic conditions (Barnett et al., 2012; Fortin et al., 2004; Salive, 2013; Uijen & Lisdonk, 2008; Van den Akker et al., 1998). The number of chronic conditions a person is diagnosed with has been shown to increase with age (Barnett et al., 2012; Glynn et al., 2011; Salive, 2013). Current multimorbidity prevalence is estimated to range from 65-98% in older adult populations, those aged 65 and older (Glynn et al., 2011). In the United States it is estimated that 81 million Americans will have more than two chronic conditions by 2020 (Fortin et al., 2005).

Multimorbidity has been shown to be associated with a wide variety of adverse health events including a decline in functional status, quality of life, and increasing health care costs and utilization (Glynn et al., 2011; Marengoni et al., 2011; Salive, 2013). Studies from several different countries have found an increased risk of functional decline or disability in regards to increasing numbers of chronic diseases (Bayliss et al., 2004; Kadam & Croft, 2007; Loza et al., 2009; Marengoni et al., 2009; Marengoni et al., 2011). For both longitudinal and cross-sectional studies participants' functional status was ascertained by asking about necessary activities of daily living

including questions regarding bathing, walking, dressing, eating, and using the toilet (Bayliss et al., 2004; Kadam & Croft, 2007; Loza et al., 2009; Marengoni et al., 2009). Some have hypothesized the clinical course, severity, and treatment type of these conditions could affect the rate of decline in older adults (Bayliss et al., 2004; Marengoni et al., 2009).

Multimorbidity has also been shown to have negative effects on quality of life. The current literature shows an inverse association regarding the number of chronic conditions one has and their quality of life (Byles et al., 2005; Chen, Baumgardner, & Rice, 2007; Loza et al., 2009; Walker, 2007). Quality of life commonly incorporates a person's perceived physical, mental, and social well-being over time (Chen, Baumgardner, & Rice, 2007). A person's perceived health status and quality of life has been documented to predict all-cause mortality, disease-specific morbidity, and functional decline; therefore causing room for concern when dealing with patients who have multiple chronic conditions (Bayliss, Ellis, & Steiner, 2007). An individual's self-management, self-care, and lack of a support system could hasten the decline of their perceived quality of life (Bayliss, Ellis, & Steiner, 2007).

Health care costs and utilization is another consequence to having multiple chronic conditions. The number of chronic conditions one has is strongly associated with increased healthcare costs, number of medications, and hospital admissions (Condelius et al., 2008; Glynn et al., 2011; Laux et al., 2008; Marengoni et al., 2011; Schneider, O'Donnell, & Dean, 2009; Wolff, Starfield, & Anderson, 2002). A large study looking at

Medicare recipients showed two thirds of the beneficiaries had multiple chronic conditions yet accounted for 95% of the Medicare expenditures (Wolff, Starfield, & Anderson, 2002). This spike in healthcare costs, medication prescriptions, and admissions could be due to the complexity of care one receives as the number of conditions increases (Schneider, O'Donnell, & Dean, 2009). Those who have multiple diagnoses potentially receive contradictory advice from multiple physicians and receive redundant services providing a challenge in managing these multiple ailments (Schneider, O'Donnell, & Dean, 2009). These adverse health events associated with multimorbidity highlight the burden those with multiple chronic conditions face. Additionally, physicians have the problem of treating multiple conditions where one medication could improve one chronic illness while worsening another.

In addition to having studies highlighting the consequences associated with multimorbidity there is also well-documented literature on common chronic disease conditions that are found together in individuals. One study recently conducted looked at common dyads and triads of multiple chronic conditions across varying age groups and found there were distinct clusters of conditions (Ward & Schiller, 2013). The two most common dyads in both men and women aged 65 and older were ever having hypertension and arthritis and ever having diabetes and hypertension (Ward & Schiller, 2013). In regards to the most common triads in men and women aged 65 and older ever having arthritis, diabetes, and hypertension was the highest followed by ever having arthritis, cancer, and hypertension (Ward & Schiller, 2013). While diabetes and hypertension were found to be highly clustered with other diseases, depression was

found to be the most commonly clustered ailment in a similar study (Sinnige et al., 2013). Similarly this study also concluded hypertension, diabetes, and coronary artery disease had a high prevalence of clustering among one another (Sinnige et al., 2013). Finally, another study looked at patients who had Alzheimer's disease and found congestive heart failure, chronic obstructive pulmonary disease, diabetes, and cancer were all clustered together (Vogeli et al., 2007). While these results show high rates of hypertension and diabetes there are also stark differences. This gives room for more research to be conducted in comorbid clustering but does give evidence to support the high amounts of multimorbidity in populations.

**Multimorbidity and Mortality in Older Adults**

Increased healthcare costs, disability, and quality of life are all adverse health effects of multimorbidity, however, the increased risk of mortality is also well documented and of major concern. Many studies have shown that an increase in multiple chronic conditions increases one's risk of mortality, especially in older populations (Gijsen et al., 2001; Loprinzi, Addoh, & Joyner, 2016; Marengoni et al., 2011; Menotti et al., 2001; St John et al., 2014). The studies that examined the association multimorbidity had on mortality were in a variety of locations and had varying follow up times; however, the point remained that the presence of multimorbidity significantly increased one's risk of mortality (Gijsen et al., 2001; Loprinzi, Addoh, & Joyner, 2016; Marengoni et al., 2011; Menotti et al., 2001; St John et al., 2014).

**Measuring Multimorbidity**

While the literature is robust in the consequences multimorbidity is associated with the measurement and classification of multimorbidity is not as well documented. Multimorbidity is commonly measured through a simple disease count in individuals or through weighted indices (Charleson Index, Elixhauser) that assess the burden of morbidity over a broad range of conditions (Diederichs, Berger, & Bartels, 2011; Huntley et al., 2012; Kadam & Croft, 2007). These popular methods come with their own advantages and disadvantages. A basic disease count is the most common way to measure multimorbidity and involves summing the number of conditions one has from either self-reported, physician-reported, or medically recorded data (Huntley et al., 2012). While data on disease counts and types of diseases is typically readily available it is hard to compare between studies due to the varying number of conditions included for analysis (Huntley et al., 2012). In recent systematic reviews the number of conditions studied ranged from 4 to 102 different conditions (Diederichs, Berger, & Bartels, 2011; Fortin et al., 2012; Harrison et al., 2014). Additionally, most disease counts are based on summing up all chronic conditions but chronicity is seldom defined (Huntley et al., 2012). Even among the multimorbidity literature there is a wide range of how investigators group the number of conditions one has for analysis. For example, some authors categorize multimorbidity as a binary outcome, no multimorbidity vs multimorbidity (Bähler et al., 2015; Landi et al., 2010; Sharkey, 2003). However, others classify multimorbidity according to varying disease counts; ranging from low multimorbidity status (2-3 conditions) to high (6+ conditions) or to other

predetermined, relevant disease count groups (Fung et al., 2008; Glynn et al., 2011; Kadam & Croft, 2007; Menotti et al., 2001; St John et al., 2014). This heterogeneity in disease count classification reinforces the limitation in using disease count data. This study aims to capture specific populations who are at a higher risk of mortality based on the number of chronic conditions they have.

Another common way to measure multimorbidity is through weighted indices (Diederichs, Berger, & Bartels, 2011; Huntley et al., 2012). While there have been several indices created to measure multimorbidity the "Charlson Index" is the most frequently used (Diederichs, Berger, & Bartels, 2011). This index was created to use in longitudinal studies to allow investigators to classify comorbid conditions in evaluating prognoses, specifically mortality (Charlson et al., 1987; Diederichs, Berger, & Bartels, 2011; Huntley et al., 2012; Needham et al., 2005). This index provides a means for investigators to assess the number of chronic conditions and their severity by looking at the number of diseases a patient has multiplied by the relative mortality risk weight (Charlson et al., 1987 Diederichs, Berger, & Bartels, 2011). For example, congestive heart failure receives a mortality risk weight of one, whereas a metastatic solid tumor receives a mortality risk weight of six (Needham et al., 2005). Since the time the Charlson Index was first created there have been multiple versions created, differing in the number of disease categories (Huntley et al., 2012). Since this measure has been around for 30 years it has since been validated in an array of settings (Huntley et al., 2012). Another advantage to using this index is it can be calculated from readily available data (Huntley et al., 2012). However, in a recent systematic review it was

found that simpler methods, such as disease counts, were just as predictive in mortality and other healthcare outcomes (Huntley et al., 2012).

These two primary ways of classifying and measuring multimorbidity do an adequate job at examining the association multimorbidity has on health outcomes, however, more research is warranted to see if there are valid disease cut-points to be used as well as the number of comorbid conditions to be included in the analysis.

**Depression in Older Adults**

The World Health Organization defined depression as a common mental disorder which can be characterized by sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, feelings of tiredness, and poor concentration (Depression). Major depressive disorder estimates vary for older adults, aged 65 and older, with estimates ranging from 1-5% to 15-19% (Cahoon, 2012; Fiske, Wetherell, & Gatz, 2009). However, the risks of a major depressive disorder have been shown to increase with age; as older adults 75 and older have estimates between 5-9% (Rodda, Walker, & Carter, 2011). While the estimates for major depressive disorder vary there is a consensus of a higher prevalence of older adults who experience clinically significant depressive symptoms, ranging from 5-37% (Fiske, Wetherell, & Gatz, 2009; Rodda, Walker, & Carter, 2011). Additionally, these approximations were amplified when looking at older adults who resided in long-term care facilities with a range of having major depressive disorder or experiencing clinically relevant depressive symptoms to be between 14-44% (Cahoon, 2012; Jones, Marcantonio, & Rabinowitz,

2003; Teresi et al., 2001; Thakur & Blazer, 2008). However, these results could be heightened by older adults who are undiagnosed or untreated (Barbour & Blumenthal, 2005; Barg et al., 2006; Rodda, Walker, & Carter, 2011). Depression recognition and management is of utmost importance as the presence of depression increases ones risk for morbidity, suicide, disability, and healthcare utilization while decreasing ones physical, mental, and social functioning (Barbour & Blumenthal, 2005; Cahoon, 2012; Fiske, Wetherell, & Gatz, 2009; Rodda, Walker, & Carter, 2011). A recent meta-analysiss showed depression to be clustered with eight other diseases including hypertension, arthritis, diabetes mellitus, chronic obstructive pulmonary disease (COPD)/asthma, stroke, cancer, heart failure, and heart disease (Sinnige et al., 2013).

**Depression and Mortality**

Research has shown that depression and depressive symptoms can significantly increase the risk of all-cause mortality for both men and women in older populations (Cuijpers & Smit, 2002; Mykletun et al., 2009; Saz et al., 2001). One study even controlled for a variety of behavioral and lifestyle risk factors that could mediate in the association, however, they still saw mortality to be significantly increased by depression by 37% (Mykletun et al., 2009).

According to the Centers for Disease Control and Prevention (CDC) cardiovascular disease is the leading cause of death for both men and women, where one in four deaths is from this disease (Heart Disease Facts, 2015). Cardiovascular disease already has a high mortality rate but research has shown that depression

increases this mortality rate (Barefoot et al., 1996; Barth, Schumacher, & Herrmann-Lingen, 2004; Frasure-Smith et al., 2009; Schulz et al., 2000). The range of mortality was between 24-84%, with this showing an increase risk in mortality (Barefoot et al., 1996; Barth, Schumacher, & Herrmann-Lingen, 2004; Frasure-Smith et al., 2009; Schulz et al., 2000). Depression was also shown to elevate mortality risk in patients who had suffered a myocardial infarction (Lespérance et al., 2002; Van Melle et al., 2004). Although the mechanism for why depression and cardiovascular disease heighten one's risk for mortality there have been several plausible mechanisms proposed. One proposed mechanism is the lifestyle which is commonly associated with depressed patients: cigarette smokers, inactive, and hypertensive (Carney et al., 2002; Joynt, Whellan, & O'Connor, 2003). These risk factors are known to increase one's chances of being diagnosed with cardiovascular disease. For example the relative risk of cardiovascular mortality associated with smoking an additional pack of cigarettes a day increases by 39% (Joynt, Whellan, & O'Connor, 2003). An additional lifestyle factor hypothesized to increase cardiovascular mortality risk is the act of noncompliance that is commonly seen in depressed individuals (Carney et al., 2002; Joynt, Whellan, & O'Connor, 2003; Wang et al., 2002). Wang and colleagues conducted a study looking at antihypertensive medication use and found depressed individuals were more likely to be non-adherent compared to their non-depressed counterparts (Wang et al., 2002). This lack of compliance could play a significant role in cardiovascular mortality. There have also been several proposed physiologic mechanisms examining the association between depressive symptom trajectories and cardiovascular mortality.

Cancer is the second leading cause of death in the United States and will affect approximately 39% of men and women in their lifetime (Cancer Stat Facts: Cancer of any Site, n.d.; Leading Causes of Death, 2017). Many studies and meta-analyses have documented that depression significantly increased one's cancer mortality risk (Giese-Davis et al., 2010; Pinquart & Duberstein, 2010; Satin, Linden, & Phillips, 2009). In fact one randomized controlled trial found that decreased depression symptoms was associated with better survival compared to those with higher depression symptoms (Giese-Davis et al., 2010). A meta-analysis showed cancer patients who experienced depressed symptoms to have a 25% increased risk of mortality when looking at grouped relative risks (Satin, Linden, & Phillips, 2009). Depression was also found to accelerate disease progression in depressed cancer patients compared to non-depressed patients; potentially being one of the reasons depressed individuals have increased mortality rates (Sephton et al., 2009). They also found a stronger association of 39% in patients who had a mild or major depressive diagnosis (Satin, Linden, & Phillips, 2009). Additionally, depression is seen in cancer patients at higher rates compared to the general population, with oropharyngeal, pancreatic, breast, and lung cancers seeing higher rates of depression compared to other cancer types (Massie, 2002; Satin, Linden, & Phillips, 2009). One proposed mechanism is the dysregulation of cortisol levels which typically follow a circadian rhythm (Sephton et al., 2009; Spiegel & Giese-Davis, 2003; Weinrib et al., 2010). Typically, negative feedback should be present during night hours, however, in depressed individuals it has been shown not to be as active, causing the cortisol levels to be abnormal (Sephton et al., 2009; Weinrib et al., 2010). This abnormal

cortisol level has been shown to increase mortality risk and decrease functional disability (Sephton et al., 2009; Weinrib et al., 2010).

Although depression is a debilitating disease on its own, it has also been shown to be associated with a wide variety of morbidities and increased mortality rates. Therefore, it is imperative to find ways to combat depression's negative effects so individuals are not losing precious time.

**Depressive Symptom Trajectories**

In studies where depression is involved there are two common ways of measuring depression and its associated symptoms: a single baseline measurement or trajectories of symptoms over a specified period of time. Popularly, depression status is ascertained through a validated questionnaire where participants are commonly asked how often they experience certain depressive symptoms (Rao & Cohen, 2004). The Center for Epidemiologic Studies Depression Scale (CES-D), Geriatric Depression Scale (GDS), and Beck Depression Inventory (BDI) are common tools used to determine depression status and symptoms in study subjects (Krebber et al., 2014; Rao & Cohen, 2004; Shafer, 2006). By summing the responses to the questions provided the analyst can classify the participant based on predetermined cut-points for major, mild, some depressive symptoms, and no depression. These depression scales have shown to have both a sensitivity and specificity between 70-85%, strengthening the use of these measures in studies (Rao & Cohen, 2004). By only using one single measurement of depression, researchers are only able to gather information on a snapshot into the

participants' mental state. A single depression measurement does not allow researchers to examine changes in depression status over time which could be an important factor in describing the association at hand (Sin, Yaffe, & Whooley, 2015). Additionally, single depression measurement does not capture intra-individual variability in symptoms which may have clinical importance as older adults experience different depression symptoms over time (Kaup et al., 2016). Finally, a single baseline measurement could underestimate the risk of depression. For example, someone could live with persistently high depression yet when they were surveyed their mood was positive; thus not accurately presenting their true symptoms.

Utilizing depressive symptom trajectories is becoming more robust in the literature (Gunn et al., 2013; Liang et al., 2011). Depression trajectories allow the investigator the see temporal changes of depression symptoms which could reflect the natural history of depression in the study population (Andreescu et al., 2008; Kuchibhatla et al., 2012; Rote, Chen, & Markides, 2015). Additionally, depression trajectories could be used to identify risk factors and certain outcomes associated with varying trajectories (Hsu, 2012; Musliner et al., 2016). Depressive symptom trajectories provide a more precise estimate over time and therefore allow for the identification of high risk groups (Kaup et al., 2016). To create depression trajectories researchers utilize the same tools (CES-D, GDS, BDI) used when only looking at baseline measurements of depression (Andreescu et al., 2008; Hsu, 2012; Kuchibhatla et al., 2012; Rote, Chen, & Markides, 2015). However, instead of collecting depression status at a single point in time trajectory methods systematically gather depression status periodically for a

specified period of time. After collecting this information latent growth curve analyses can be performed to identify the varying trajectories (Byers et al., 2012; Liang et al., 2013; Rote, Chen, & Markides, 2015). Although the use of depression trajectories has many advantages it still has several limitations. One limitation is the trajectories are dependent on the frequency of data collection involving depression status, and since collection typically occurs annually or biannually there are still potential gaps left in understanding the natural history (Rote, Chen, & Markides, 2015). Depression status is typically determined through self-report, not a clinical diagnosis, and this self-reporting could skew the trajectories slightly (Andreescu et al., 2008; Kuchibhatla et al., 2012). However, the advantages of this method outweigh the limitations and should therefore be used in research when looking at depression influences. The use of depressive symptom trajectories can be more informative than a traditional, single measurement, as depressive symptom trajectories can identify high risk groups. Upon identification of high risk groups depression management programs can be targeted to treat these individuals.

**Depression Management among Multimorbid Individuals**

Individuals who have depression coupled with multiple chronic conditions have been shown to have more adverse health outcomes and increased mortality rates. However, could depression management mitigate some of these negative outcomes? Four randomized controlled trials found that depression management could reduce adversary effects in multimorbid individuals, including a decrease in mortality rate

(Bogner & de Vries, 2008; Gallo et al., 2016; Harrison et al., 2012; Katon et al., 2010). Management programs included individual and group sessions aimed at educating the individual on depression, chronic conditions, and healthy lifestyle factors (diet, exercise), as well as collaborating with a medical team to come up with the best medication regimen with ample follow-up time to provide information on the individual's progress and adherence to the program (Bogner & de Vries, 2008; Gallo et al., 2016; Harrison et al., 2012; Katon et al., 2010). In the trials listed significant reductions were seen in depressive symptoms, blood pressure readings, cholesterol levels, mortality rates, and increased quality of life, and well-being (Bogner & de Vries, 2008; Gallo et al., 2016; Harrison et al., 2012; Katon et al., 2010). The results from these randomized controlled trials show promising benefits in reducing adverse outcomes depression can have on chronic diseases.

# CHAPTER 3

# METHODS

**Data Source:**

The data is from the Health and Retirement Study which is a longitudinal biennial survey of a nationally representative sample of U.S. adults aged 50 and older that collects detailed information on physical health and functioning, cognition, disability, socioeconomic factors, and health care expenditures. The Health and Retirement study was sponsored by the National Institute of Aging and was conducted by the Institute of for Social Research at the University of Michigan (Sonnega et al., 2014). Data collection began in 1992 and is ongoing. The response rate was 81.4% in 1992 and was between 85% and 90% in the following waves (Heeringa & Connor, 1995; Juster & Suzeman, 1995, Sonnega et al., 2014). Detailed information concerning the sample design, recruitment, response rates, and measurement validation are discussed extensively elsewhere (Heeringa & Connor, 1995; Juster & Suzeman, 1995, Sonnega et al., 2014). HRS provides sampling weights for the data sets and there is an oversampling of African Americans and Hispanics, at about twice the rate of White respondents (Sonnega et al., 2014).

**Study Population**

This study used data from the Health and Retirement Study (HRS), primarily utilizing the biennial waves from the years 1998, 2000, 2002, 2004, 2006, 2008, 2010, 2012, and 2014. The RAND files were utilized which are a cleaned and processed version with consistent variable names (St Clair et al., 2002). Individuals were excluded if they were younger than 50 years old or had missing information regarding the depression symptom trajectories. Individuals who did not provide information on all eight chronic disease statuses were also excluded from the analysis. 192 individuals were excluded from the analysis because they were younger than 50. Additionally, 88 individuals were excluded from the analysis because they did not provide responses on all of the eight chronic diseases in question. After the exclusions of the 280 participants, the final analytic study population was 13005.

**Measurement of Variables**

**Exposure Variable**

Multimorbidity was the main exposure for this study. Multimorbidity was operationalized based on the self-report of eight chronic conditions. Chronic disease status was collected based on self-report and ascertained by asking respondents, "Has a doctor ever told you that you have high blood pressure or hypertension". Eight chronic conditions were used for analysis: high blood pressure, diabetes mellitus, cancer (excluding cancer of the skin), lung disease, heart disease, stroke, psychiatric problems, and arthritis. The total number of conditions was summed across all participants who

indicated yes to a condition, giving a maximum score of eight chronic conditions. Similar to prior studies, the number of chronic conditions was categorized as: 0, 1, 2, and 3+ (Menotti et al., 2001; Wong et al., 2008). When analyzing cancer, diabetes, and cardiovascular mortality the groupings were 1, 2, and 3+ to account for the small sample sizes in the groups.

**Outcome Variable**

All-cause mortality was the main outcome of interest for this study. Deaths occurring from 2006-2014 were assessed and included in the analysis. Updates on vital status were recorded at each biennial wave. If a death was reported, an exit interview was conducted with the spouse or closest relative of the deceased to ascertain timing, medical expenditures, and cause of death (Sonnega et al., 2014). Secondary outcomes included cause-specific mortality outcomes: cardiovascular diseases, cancer, and diabetes mellitus. All mortality outcomes will be assessed 2006-2014.

Cardiovascular and circulatory diseases were grouped using previously validated administrative claims-based algorithms of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for chronic rheumatic heart diseases (393-398), hypertensive diseases (401-405), ischemic heart diseases (410-414), diseases of pulmonary circulation (415-417), other forms of heart disease (420-429), cerebrovascular diseases (430-438), diseases of the arteries, arterioles, and capillaries (440-448), and diseases of veins and lymphatics, and other diseases of the circulatory system (451-459) (American Medical Association, 2004).

Cancer was also be grouped using previously validated administrative claims-based algorithms of ICD-9-CM codes for malignant neoplasms of lip, oral cavity, and pharynx (140-149), malignant neoplasms of digestive organs and peritoneum (150-159), malignant neoplasms of respiratory and intrathoracic organs (160-165), malignant neoplasms of bone, connective tissue, skin, and breast (170-175), Kaposi's Sarcoma (176), malignant neoplasms of genitourinary organs (179-189), malignant neoplasms of other and unspecified sites (190-199), and malignant neoplasms of lymphatic and hematopoietic tissue (200-208) (American Medical Association, 2004).

As of 2010 these exit interviews, conducted by the Health and Retirement Study, had been conducted for 93% of deceased participants (Sonnega et al., 2014). The death records were verified through linkage between HRS data and the National Death Index or the Social Security Death Index (Sonnega et al., 2014). The month and year of death are recorded by the HRS to assign mortality status.

**Effect Modifier**

Depressive symptom trajectories were created prior to this analysis in able to assess the hypothesis which suggested multimorbidity and all-cause mortality differed depending on course of depressive symptoms. The depressive symptom trajectories were created using HRS data from 1998-2004. The trajectories used in this analysis were created using the depressive symptoms which were measured using an 8-item version of the CES-D. HRS asked participants whether symptoms were experienced in the previous week (yes or no) to the following questions: felt depressed; felt that everything

I did was an effort; my sleep was restless; could not going; felt lonely; enjoyed life; felt sad; and was happy. Positive items were reverse coded. HRS created a variable for the summed depressive score for the participants. Reports of ≥3 symptoms were classified as having elevated depressive symptoms. This dichotomization of depressive symptoms threshold has been found to have high sensitivity and specificity and has been used in prior studies (Mondesir et al., 2015). All participants who were missing more than four items on the depressive scale were excluded from the analysis. The three trajectories that were used in this analysis are those among older adults with persistently high, persistently low depressive symptoms, persistently moderate depressive symptoms.

**Confounders**

In this analysis all confounders were assessed using the results from the 2004 wave of the Health and Retirement Study, prior to any mortality analysis. The confounders used in this analysis have been previously identified in studies, thus supporting them to be included in this study (Gallo et al., 2016, Lin et al., 2009, Loprinzi, Addoh, & Joyner, 2016, Marengoni et al., 2009).

Sex was analyzed and categorized as “male” and “female”.

Age, in years, was analyzed using an HRS created variable. This already created variable was collected and included in the analysis as a continuous variable.

Race and ethnicity was collected by asking two questions: “Do you consider yourself primarily White or Caucasian, Black or African American, American Indian, or

Asian, or something else" and "Do you consider yourself Hispanic or Latino". Three mutually exclusive categories were created to be used for this analysis: "Non-Hispanic White", "Non-Hispanic Black" and "Hispanic".

Educational status was analyzed using a RAND created variable. This variable was created by combining the years of schooling and highest degree earned in a more general way. The RAND created categories were "less than high school", "GED", "high school graduate", "some college", and "college and above". "High school graduate" included participants who reported 12 years of schooling exactly yet had no college degree. Those who were grouped into "some college" reported a response showing obtained a high school diploma or general educational development (GED) with more than 12 years of schooling. Respondents who reported earning a college degree, of Bachelor's status or higher, were grouped in the category of "college and above". For analysis three education categories were created: less than a high school diploma, high school diploma, and greater than a high school diploma.

Self-rated health was the participant's self-reported general health status. The possible answers to how a participant rated their general health status are: "excellent", "very good", "good", "fair", and "poor". For this analysis self-rated health was classified into two categories: fair-poor and good-excellent.

Body Mass Index (BMI) was analyzed using a RAND created variable. This RAND created variable took the respondent's height, in feet and inches, and converted it to meters. Likewise, the respondent's weight, in pounds, was converted to kilograms. To

calculate each participant's BMI the respondent's weight, now in kilograms, was divided by their height in meters squared. The RAND created BMI was a continuous variable and was analyzed as a continuous variable for this analysis.

Current smoking status was analyzed by asking participants if they currently smoked cigarettes. Respondents answered "yes" if they were a current smoker and "no" if they were not. For analysis these self-reported categories of "yes" and "no" will be utilized.

Physical activity was obtained by asking participants three questions regarding their vigorous, moderate, and mild levels of physical activity intensity. To ascertain vigorous intensity physical activity, participants were asked, "How often do you take part in sports or activities that are vigorous, such as running or jogging, swimming, cycling, aerobics, or gym workout, tennis, or digging with a spade or shovel". To gauge participants moderate intensity physical activity, participants were asked, "How often do you take part in sports or activities that are moderately energetic such as, gardening, cleaning the car, walking at a moderate pace, dancing, and floor or stretching exercises". Finally, light intensity physical activity was ascertained by asking participants, "How often do you take part in sports or activities that are mildly energetic, such as vacuuming, laundry, and home repairs". The response categories for each of the physical activity questions were "hardly ever or never", "1 to 3 times per month", "once per week", "greater than once per week", and "everyday". Individual responses to the questions were weighted by intensity using an average metabolic equivalent of task

(MET) calculation (Latham & Williams, 2015). Intensity responses were multiplied by their corresponding rates, 1.8 for vigorous, 1.4 for moderate, and 1.2 for light. The scores were then summed for all three intensity levels of physical activity, which produced a range from 0 to 17.6. The thresholds used to determine physical activity intensity were: sedentary group (< 2.0); light intensity physical activity (≥2.0 – 4.0); moderate physical activity (>4.0 – 8.0); and vigorous physical activity (≥8.0). These cut points were based upon established MET thresholds (Latham & Williams, 2015).

**Statistical Analysis**

Descriptive statistics were reported for all parametric study variables by multimorbidity grouping, with means and standard deviations calculated for continuous variables and frequencies and percentages computed for categorical variables. Variables that were nonparametric in nature were reported by multimorbidity grouping, with medians for continuous variables. Bivariate analyses were conducted to determine whether there were significant differences between multimorbidity classification and determined covariates.

The association between multimorbidity and all-cause mortality and cancer mortality were analyzed using Cox proportional hazards models. Cardiovascular mortality and diabetes mortality were analyzed using Fine and Gray models to account for any competing risks that could be present when analyzing these two causes of deaths. A competing risk is present when an individual is at risk for more than one mutually exclusive event, such as death from cardiovascular disease which will prevent

death from any other cause (diabetes) from occurring (Gondara, 2015). These competing risk models allowed for probabilities of death to be calculated even when there were competing risks present (Gondara, 2015). Prior to running any Cox proportional hazards models the proportionality assumption was tested to ensure this method was best in examining the association of interest. Depressive symptom trajectories were used to test the effect varying trajectories play on the three separate outcomes in question. Separate models were created for each of the outcomes of interest and included confounders based on prior studies concerning many of these variables as confounders in the association between multimorbidity and all-cause mortality (Landi et al., 2010, Loprinzi, Addoh, & Joyner, 2016, St John, Tyas, Menec, & Tate, 2014). Four models were generated to model all-cause and cause-specific mortality: Model 1 (Multimorbidity, survey year); Model 2 (Model 1 + age, sex, race, education); Model 3 (Model 2 + BMI, self-rated health, smoking status, physical activity level); and Model 4 (Model 3 + interaction term). A cross product term was included to account for each potential interaction in the model. Two sided p-values ≤.05 were considered statistically significant for all variables, including the interaction term.

Sampling weights were incorporated to account for the complex sampling design. All the data management functions and statistical analyses were performed using SAS version 9.4, Cary, NC, USA.

**Sensitivity Analysis**

A sensitivity analysis was performed to assess the distribution of the data looking at other chronic condition groupings, in comparison to the categorization proposed above. When analyzing the literature, there were several different ways to operationalize multimorbidity (Kleisiaris et al., 2016; Menotti et al., 2001; Villarreal et al., 2015; Wong et al., 2008). Appendix A. shows the distribution of chronic conditions in this population. This distribution coupled with the literature search helped determine the best way to operationalize multimorbidity.

# CHAPTER 4

# RESULTS

The distribution of multimorbidity is provided (Table 4.1). Nearly 33% of the study population was diagnosed with three or more chronic conditions. Additionally, 28% of the study population was diagnosed and living with 2 chronic conditions. Approximately 26% of the population had been diagnosed one chronic condition. Only 14% of the study population had not been diagnosed with one of the eight chronic conditions in question.

The distribution of socio-demographic and lifestyle factors by multimorbidity classification are listed in Table 4.2. The mean age for those individuals who had 0 chronic conditions was 66.1 years. As the number of conditions one was diagnosed with increased so did the average age. The average age of study participants who had been diagnosed with one chronic condition (68.3 years), two chronic conditions (70.1 years), and three or more chronic conditions (71.7 years) was significantly older than those with 0 chronic conditions (p-value <.0001 for all multimorbidity groupings). Individuals categorized as having 0 chronic conditions were more likely to be female (59.3%). The percentage of females was statistically higher in individuals who had one (62.3%, p-value .0293), and two chronic conditions (63.1, p-value .0057) compared to those with 0 chronic conditions. Individuals who had three or more chronic conditions saw an increase in the percentage of women; however, this difference was not statistically

significant when compared to individuals with 0 chronic conditions (61.9%, p-value .0504). Among individuals who had 0 chronic conditions more than four fifths were Whites (80.6%), less than one tenth were African American (9.0%), and one tenth were Hispanic (10.4%). However, the racial demographic significantly differed as the number of chronic conditions increased. The percentage of Whites decreased for individuals with two and three or more chronic conditions (79.7%, 78.2%), yet increased slightly in individuals with one chronic condition (81.6%). The percentage of Blacks increased for individuals with one, two, or three or more chronic conditions (11.0%, 13.5%, and 15.3% respectively). The Hispanic distribution decreased as the number of chronic conditions increased (7.4%, 6.7%, and 6.4% respectively). This change in the racial makeup was significantly different for all multimorbidity classifications. One chronic condition, two chronic conditions, and three or more conditions had a statistically significant racial distribution when compared to 0 chronic conditions (p-value .0002, p-value <.0001 and p-value <.0001, respectively). The majority of individuals who had only 0 chronic conditions had more than a high school diploma (49.8%) while one fifth of these individuals had less than a high school diploma (19.9%). As the number of chronic conditions increased so did the percentage of individuals who had less than a high school diploma. For individuals who had one chronic condition, over one fifth had not completed high school (20.9%), while 45.2% had more than a high school diploma. This was a significantly different breakdown of education compared to those with 0 chronic conditions (p-value .0060). Similarly, individuals who had two chronic conditions were more likely to have less than a high school diploma (24.8%), while approximately two

fifths had more than a high school diploma (40.1%). This breakdown was also significantly different from the breakdown of individuals with 0 chronic conditions (p-value <.0001). Approximately one third of the individuals who had three or more chronic conditions had less than a high school diploma (34.6%), while one third had more than a high school diploma (34.0%). This breakdown of educational attainment was significantly different from the educational attainment of individuals with 0 chronic conditions (p-value <.0001). More than four fifths (84.3%) of individuals who had 0 chronic conditions were non-smokers. Compared to individuals who had no chronic conditions, those with one chronic condition, saw a statistically significant increase in the percentage of non-smokers (87.0%, p-value .0075). Compared to individuals who had no chronic conditions, those with two (88.7, p-value <.0001) or three or more chronic conditions (87.4, p-value .0013), saw a statistically significant increase in the percentage of non-smokers. Over nine tenths (92.5%) of the individuals who had 0 chronic condition rated their health as good, very good, or excellent. However, as the number of chronic conditions increased the perception of ones' self-rated health decreased. Approximately 84.9% of individuals who had 1 chronic condition rated their health as good, very good, or excellent, this being significantly different from those individuals with 0 chronic conditions (p-value <.0001). Additionally, only about three fourths (74.9%) of individuals who had two chronic conditions rated their health as good, very good, or excellent; being statistically significant from those with 0-1 chronic conditions (p-value <.0001). Only 51.3% of individuals who had three or more chronic conditions rated their health as good, very good, or excellent. This was statistically

different than the percentage of self-rated health for individuals with 0 chronic conditions. Of the individuals who had 0 chronic conditions the majority engaged in vigorous physical activity (51.6%), approximately one third engaged in moderate intensity physical activity (36.4%), one tenth engaged in light intensity physical activity (9.7%), and 2.30% were sedentary. There were significant changes seen in physical activity levels as the number of chronic conditions increased to one, two, and three or more chronic conditions (p-value <.0001, p-value <.0001, p-value <.0001, respectively). Vigorous physical activity levels declined for those who had one, two, and three or more chronic conditions (44.6%, 35.1%, and 23.8%, respectively). Moderate intensity physical activity increased slightly among individuals who had one, two, and three or more chronic conditions (39.3%, 40.7%, and 38.8%, respectively). Light intensity physical activity saw increases in one, two, and three or more chronic conditions (11.3%, 16.9%, and 21.7%, respectively). Levels of sedentary behavior also increased for one, two, and three or more chronic conditions (4.9%, 7.3%, and 15.8%, respectively). Finally, the average BMI level for individuals with 0 chronic conditions was 25.7. BMI levels, for one, two, and three or more chronic conditions, saw significant increases (Averages: 26.6, 27.5, and 28.7; p-values: <.0001, respectively).

Figure 4.1 depicts the breakdown of all-cause, cardiovascular, and cancer, mortality by multimorbidity grouping. Approximately 5.3% of the individuals who died from cardiovascular disease had 0 chronic conditions. Individuals who had 1 chronic condition saw 178 deaths, or approximately 13.2% of the total number of cardiovascular deaths. This was statistically more deaths than those who had 0 chronic conditions (p-

value .0333). Similarly, individuals who had two chronic conditions saw about one fourth of the cardiovascular deaths (348 deaths, 25.8%). This was statistically more deaths than those with 0 chronic conditions (p-value <.0001). The greatest number of cardiovascular deaths occurred in individuals who had three or more chronic conditions (752 deaths, 55.74). This was statistically more deaths than those who had 0 chronic conditions (p-value <.0001). Around one tenth (8.3%) of the individuals who died from cancer had 0 chronic conditions. Individuals who had one chronic condition saw 196 cancer deaths, or 19.9% of the total number of cancer deaths. Although a greater number of deaths occurred, this was not statistically more deaths than those who had 0 chronic conditions (p-value .2646). There were 269 cancer deaths, or 27.3%, to occur in individuals who had two chronic conditions. This was statistically more cancer deaths compared to those who had 0 chronic conditions (p-value .0234). Individuals who had four or more chronic conditions and died from cancer had statistically more cases than those with 0 chronic conditions (439 cases, 44.5%; p-value .0003).

Figure 4.2 displays the distribution of depression status by the number of chronic conditions. There were significant changes seen in depression status as the number of chronic conditions increased from 0 chronic conditions to one, two, and three or more chronic conditions (p-value <.0001, p-value <.0001, p-value <.0001, respectively). 18.13% of those who had persistently low depression had 0 chronic conditions. Persistently low depression levels increased from those with 0 chronic conditions to those with one, two, and three or more chronic conditions (30.0%, 28.25%, and 23.7%, respectively). 10.6% of the individuals with persistently moderate depression symptoms

had 0 chronic conditions. Persistently moderate depression symptoms increased among individuals who had one, two, and three or more chronic conditions (21.8%, 28.9%, and 38.7%, respectively). Individuals who had 0 chronic conditions made up approximately 5.1% of the population with persistently high depression symptoms. Persistently high depression symptoms saw drastic increases in one, two, and three or more chronic conditions (15.2%, 25.3%, and 54.4%, respectively).

Figure 4.3 graphically presents the interaction between depression trajectories and multiple chronic conditions have on all-cause mortality. With 0 chronic conditions being the reference group, it is shown that having persistently low depression scores and one chronic condition has no increased risk for all-cause mortality (HR: 1.0; 95% CI: 0.8, 1.2). Having two or three or more chronic conditions coupled with persistently low depression symptoms showed a slight increase in all-cause mortality, however, these results did not reach statistical significance (HR: 1.0 and 1.17; 95% CI: 0.848, 1.210 and 0.980, 1.385, respectively). Having one or two chronic conditions coupled with persistently moderate depression symptoms led to a slight increase in all-cause mortality, however, these estimates did not reach statistical significance (HR: 1.146 and 1.186; 95% CI: 0.849, 1.548 and 0.895, 1.571, respectively). Similarly, having three or more chronic conditions with persistently moderate depression pointed towards an increased risk for all-cause, yet this did not reach statistical significance (HR: 1.287; 95% CI: 0.981, 1.687). Having persistently high depression with multiple chronic conditions did not show of an increased risk for all-cause mortality. Having one chronic condition with persistently high depression scores only showed of a slight increase in the risk of

mortality, but failed to reach significance (HR: 1.058; 95% CI: 0.692, 1.618). Two and three or more chronic conditions with persistently high depression both showed an increase in the estimate for all-cause mortality, but failed to reach statistical significance (HR: 1.152 and 1.287; 95% CI: 0.775, 1.712 and 0.879, 1.885, respectively).

Figure 4.4 shows the adjusted associations of the interaction between depression trajectories and having multiple chronic conditions on cancer mortality. With one being the reference group, it is shown that having two or three or more chronic conditions coupled with persistently low depression scores leads to a slight increase in cancer mortality (HR: 1.072 and 1.094, respectively). However, both of these failed to reach statistical significance (95% CI: 0.844, 1.361 and 0.868, 1.378, respectively). Contrary to the results seen in persistently low depression scores, persistently moderate depression scores led to a slight decrease in cancer mortality rates for both two and three or more chronic conditions (HR: 0.945 and 0.836, respectively). These results however failed to reach statistical significance (95% CI: 0.650, 1.375 and 0.592, 1.181, respectively). Similarly, persistently high depression symptoms showed a slight decrease in cancer mortality rates for both two and three or more chronic conditions (HR: 0.868 and 0.942, respectively). These results did not reach statistical significance (95% CI: 0.511, 1.472 and 0.591, 1.501, respectively).

Figure 4.5 shows the adjusted associations between the interaction between depression trajectories and multiple chronic conditions on cardiovascular mortality. Individuals who had two chronic conditions and persistently low depression symptoms

saw an increase in cardiovascular mortality, however, this failed to reach significance (HR: 1.230, 95% CI: 0.985, 1.537). Individuals who had three or more chronic conditions and had persistently low depression symptoms saw a statistically significant increase in cardiovascular mortality compared to those with only one chronic condition (HR: 1.486; 95% CI: 1.201, 1.839). Participants who had two chronic conditions and persistently moderate depression symptoms saw an increase in cardiovascular death, but lacked significance (HR: 1.416; 95% CI: 0.984, 2.038). Those with three or more chronic conditions and had persistently moderate depression symptoms saw a statistically significant increase in cardiovascular mortality compared to those who had one chronic condition (HR: 1.758, 95% CI: 1.260, 2.453). Similar to previous multiple chronic condition levels; individuals who had two chronic conditions with persistently high depression symptoms saw an increased risk for cardiovascular mortality, but failed to reach significance (HR: 1.223; 95% CI: 0.771, 1.940). Finally, individuals who had three or more chronic conditions and persistently high depression symptoms saw a statistically significant increase in cardiovascular mortality (HR: 1.847; 95% CI: 1.223, 2.789).

Table 4.1: Distribution of multimorbidity classification

| | N | % |
|---|---|---|
| **0 Chronic Conditions** | 1833 | 14.09 |
| **1 Chronic Condition** | 3319 | 25.52 |
| **2 Chronic Conditions** | 3623 | 27.86 |
| **3+ Chronic Conditions** | 4230 | 32.53 |
| **Total** | 13005 | 100.00 |

Table 4.2: Baseline Characteristics by Multimorbidity Grouping: HRS 2004

| | 0 Chronic Conditions | | 1 Chronic Condition | | | 2 Chronic Conditions | | | 3+ Chronic Conditions | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | %, SD | N | %, SD | P-Value[a] | N | %, SD | P-Value[b] | N | %, SD | P-Value[c] |
| **Age (mean, SD)** | 66.10 | 8.75 | 68.33 | 9.20 | **<.0001**[d] | 70.14 | 9.13 | **<.0001** | 71.69 | 9.24 | **<.0001** |
| **Gender** | | | | | **.0293** | | | **.0057** | | | .0504 |
| **Male** | 747 | 40.75 | 1250 | 37.66 | | 1337 | 36.90 | | 1611 | 38.09 | |
| **Female** | 1086 | 59.25 | 2069 | 62.34 | | 2286 | 63.10 | | 2619 | 61.91 | |
| **Race/Ethnicity** | | | | | **.0002** | | | **<.0001** | | | **<.0001** |
| **White** | 1438 | 80.961 | 2658 | 81.61 | | 2850 | 79.72 | | 3253 | 78.22 | |
| **Black** | 161 | 9.02 | 359 | 11.02 | | 484 | 13.54 | | 638 | 15.34 | |
| **Hispanic** | 185 | 10.37 | 240 | 7.37 | | 241 | 6.74 | | 268 | 6.44 | |
| **Education** | | | | | **.0060** | | | **<.0001** | | | **<.0001** |
| **Less than HS** | 365 | 19.91 | 695 | 20.94 | | 899 | 24.81 | | 1462 | 34.56 | |
| **High School** | 556 | 30.33 | 1123 | 33.84 | | 1271 | 35.08 | | 1331 | 31.47 | |
| **More than HS** | 912 | 49.75 | 1501 | 45.22 | | 1453 | 40.10 | | 1437 | 33.97 | |
| **Self-Rated Health** | | | | | **<.0001** | | | **<.0001** | | | **<.0001** |
| **Fair/Poor** | 137 | 7.47 | 502 | 15.13 | | 909 | 25.11 | | 2058 | 48.71 | |
| **Good/Excellent** | 1696 | 92.53 | 2816 | 84.87 | | 2711 | 74.89 | | 2167 | 51.29 | |
| **Physical Activity** | | | | | **<.0001** | | | **<.0001** | | | **<.0001** |
| **Sedentary** | 42 | 2.30 | 162 | 4.89 | | 263 | 7.27 | | 666 | 15.76 | |
| **LIPA** | 177 | 9.68 | 375 | 11.31 | | 613 | 16.93 | | 917 | 21.70 | |
| **MIPA** | 666 | 36.43 | 1301 | 39.25 | | 1472 | 40.66 | | 1638 | 38.76 | |
| **VIPA** | 943 | 51.59 | 1477 | 44.56 | | 1272 | 35.14 | | 1005 | 23.78 | |
| **BMI (mean, SD)** | 25.73 | 4.43 | 26.57 | 4.82 | **<.0001** | 27.52 | 5.36 | **<.0001** | 28.66 | 6.44 | **<.0001** |

[a] p-value represents the comparison of variables in individuals with one chronic condition and those who reported 0 chronic conditions
[b] p-value represents the comparison of variables in individuals with two chronic conditions and those who reported 0 chronic conditions
[c] p-value represents the comparison of variables in individuals with three or more chronic conditions and those who reported 0 chronic conditions
[d] bold font signifies a significant p-value

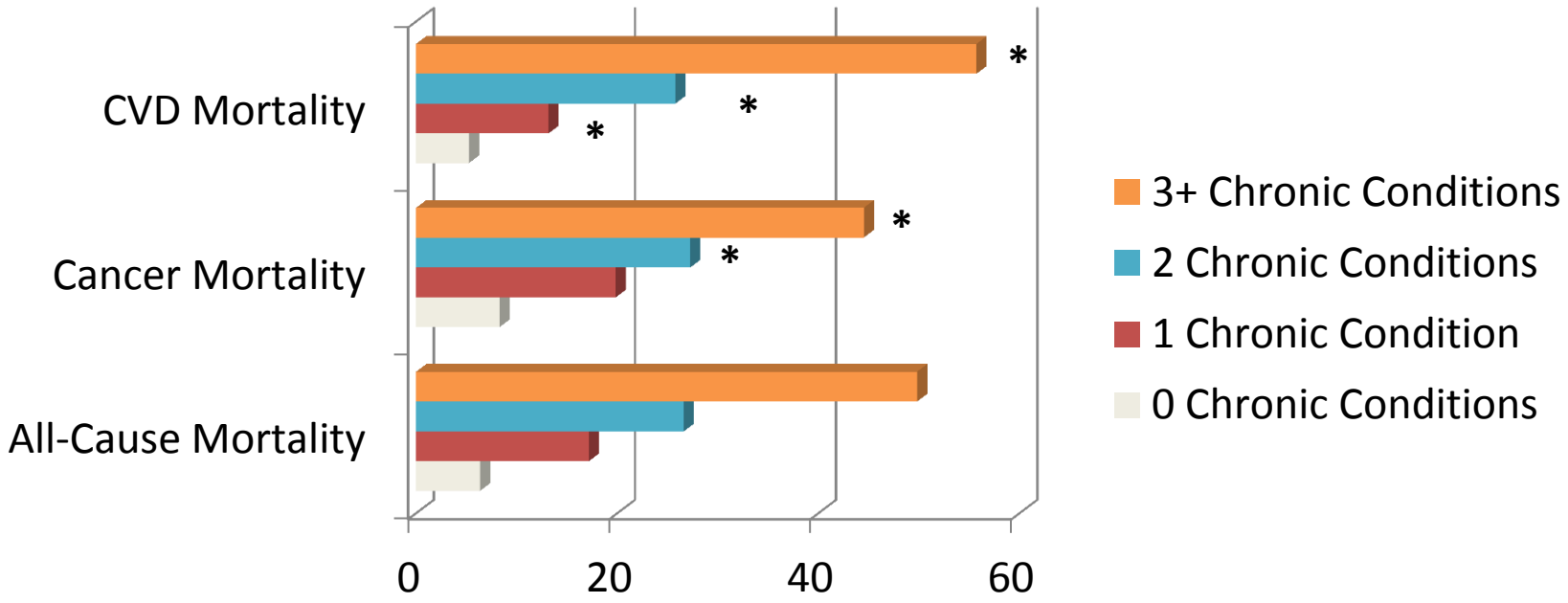




Figure 4.1: Number of Deaths from All-Cause, Cardiovascular Disease, and Cancer by Multimorbidity Grouping[a,b,c,d]

[a] p-value represents the comparison of variables between individuals who died and had one chronic condition and those who died and had 0 chronic conditions

[b] p-value represents the comparison of variables between individuals who died and had two chronic conditions and those who died and had 0 chronic conditions

[c] p-value represents the comparison of variables between individuals who died and had three or more chronic conditions and those who died and had 0 chronic conditions

[d] * signifies a significant p-value

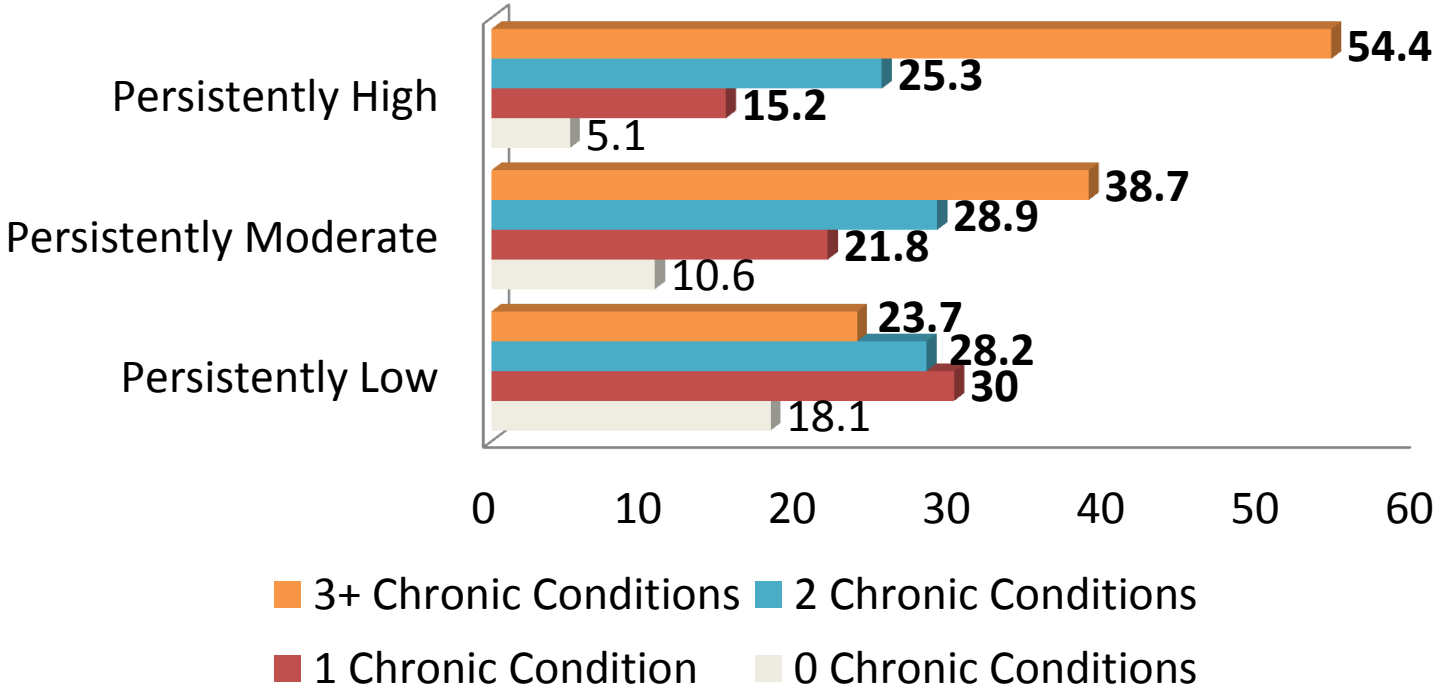


Figure 4.2: Depression Symptom Trajectories by Multimorbidity Classification

[a] p-value represents the comparison of variables in individuals with one chronic condition and those who reported 0 chronic conditions

[b] p-value represents the comparison of variables in individuals with two chronic conditions and those who reported 0 chronic conditions

[c] p-value represents the comparison of variables in individuals with three or more chronic conditions and those who reported 0 chronic conditions

[d] bold font signifies a significant p-value

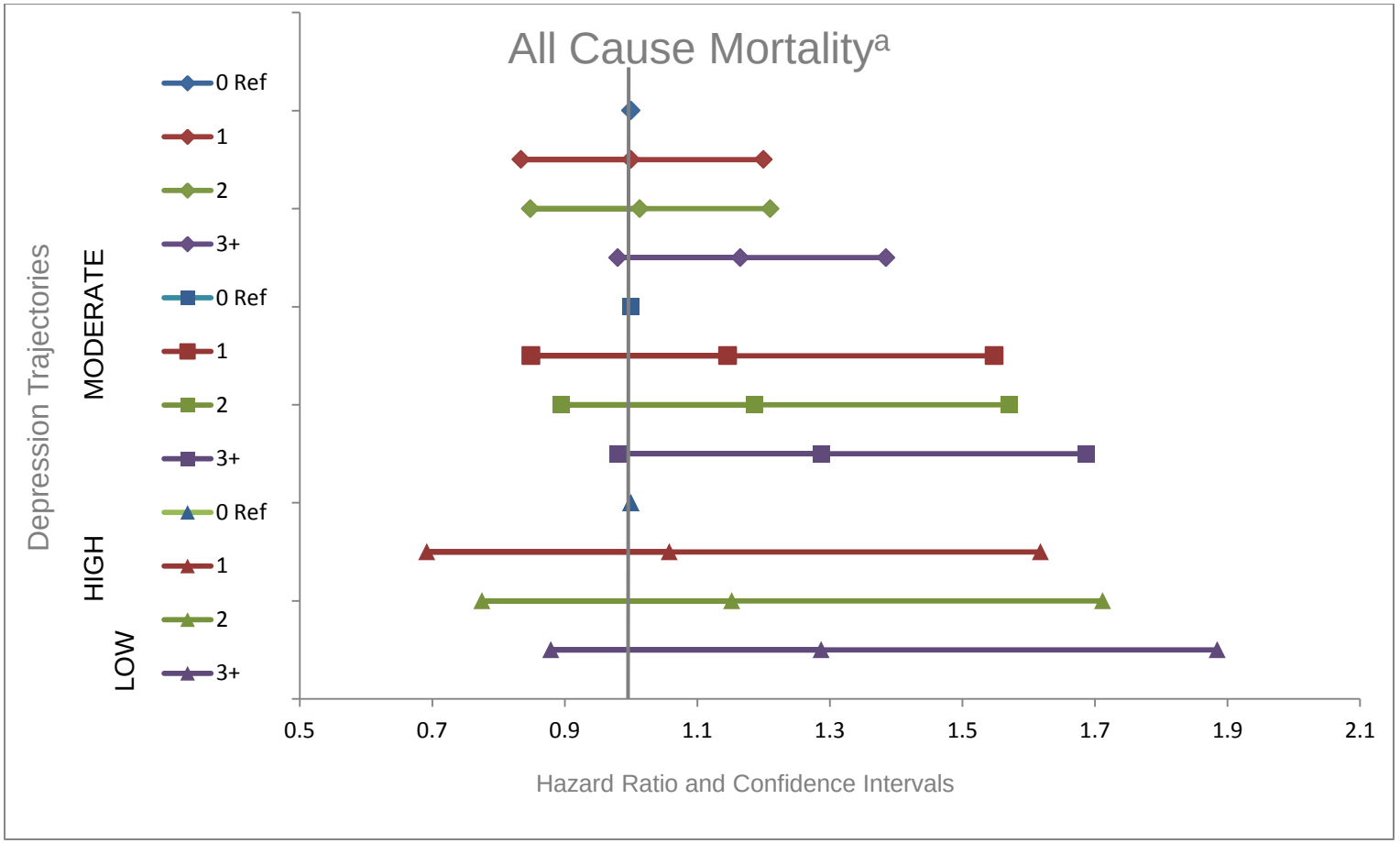


Figure 4.3: Interaction between Depressive Symptom Trajectories and Multimorbidity on All-Cause Mortality

[a]: Adjusted for age, race, education, gender, self-rated health, smoking status, physical activity, and BMI

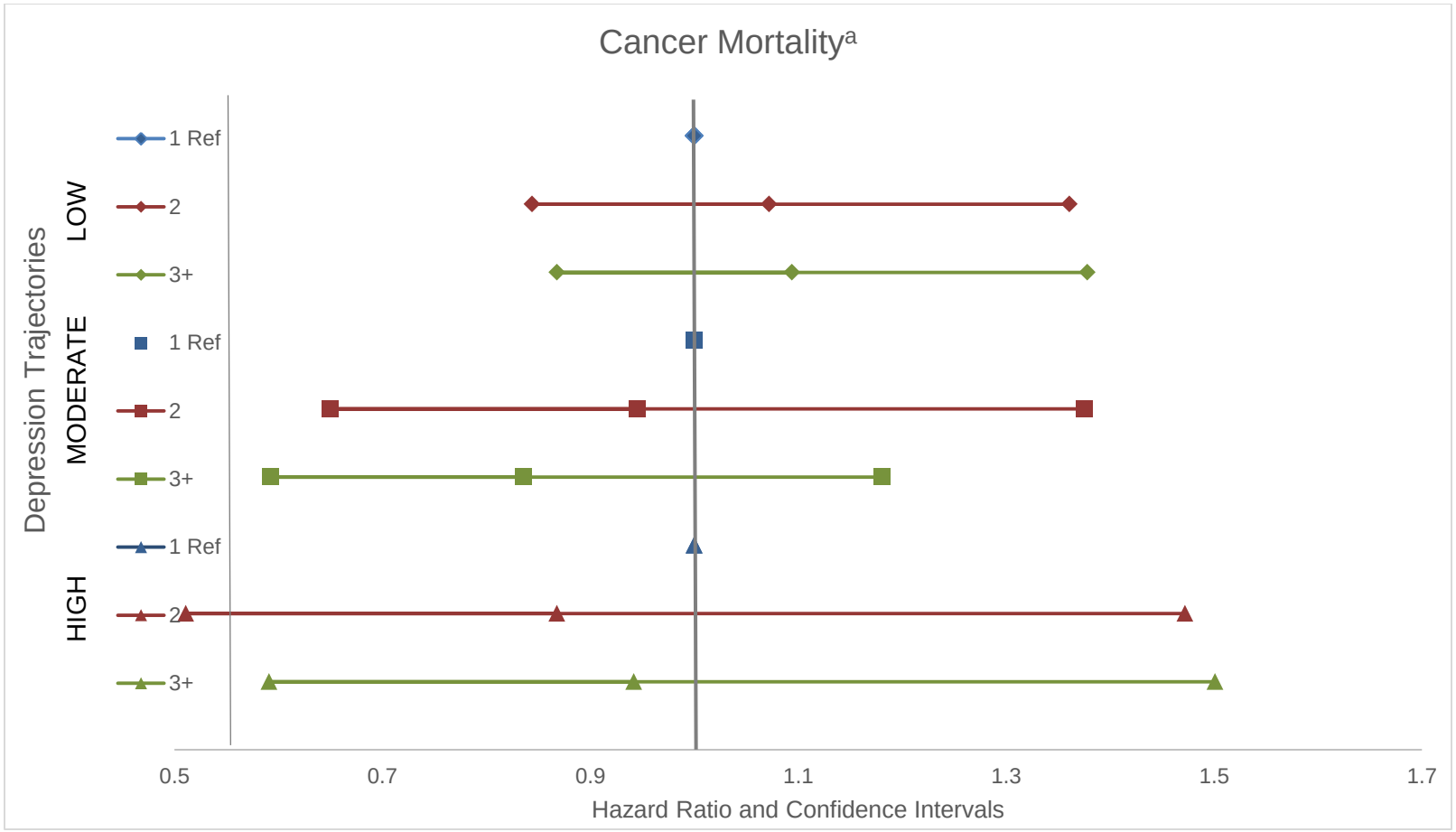


Figure 4.4: Interaction between Depressive Symptom Trajectories and Multimorbidity on Cancer Mortality

[a]: Adjusted for age, race, education, gender, self-rated health, smoking status, physical activity, and BMI

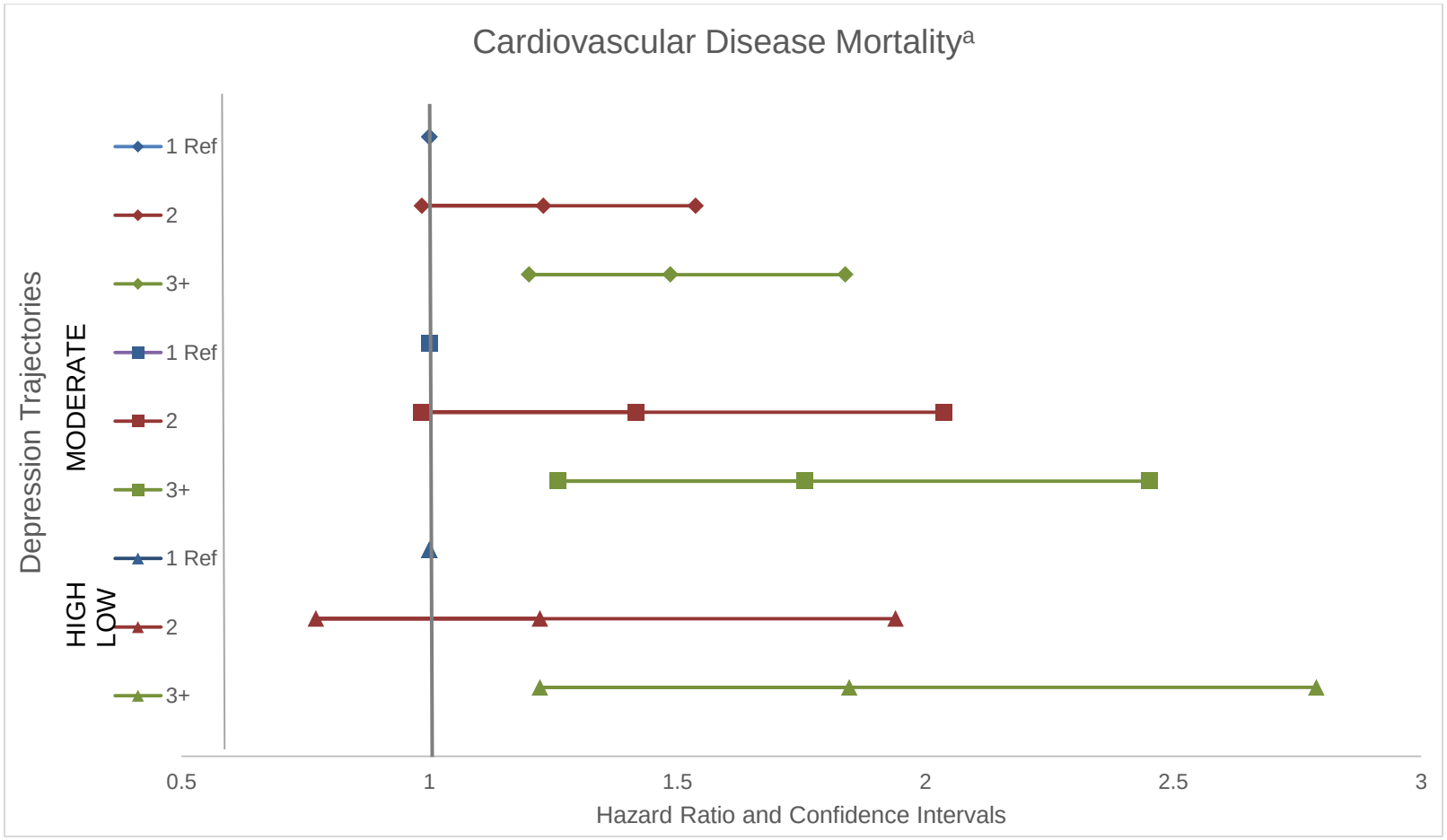


Figure 4.5: Interaction between Depressive Symptom Trajectories and Multimorbidity on CVD Mortality

[a]: Adjusted for age, gender, race, education, smoking status, self-rated health, physical activity, and BMI

CHAPTER 5

DISCUSSION

This study was conducted to examine the association depressive symptom trajectories coupled with multiple chronic conditions has on all-cause and cause-specific mortality. Our results indicated having persistent depressive symptoms, along with multiple chronic conditions, can cause an interaction, increasing one's risk for mortality, specifically cardiovascular mortality. Having three or more chronic conditions along with persistently high depressive symptoms showed the highest risk of cardiovascular death. This leads one to suggest that a dose-response association could be present; illustrated by the greater number of chronic conditions one has along with persistently higher depressive trajectory scores can lead to the greatest risk of death. Although a clear association was seen in cardiovascular mortality, the association between depressive symptom trajectories and multimorbidity on all-cause mortality was not as strong. Cancer mortality also lacked significance, yet the direction of association was opposite of that which was hypothesized.

**Depressive Symptom Trajectories and Multimorbidity on All-Cause Mortality**

Our results indicate the interaction between multimorbidity and persistent depressive symptoms is not significant in predicting all-cause mortality. Although the direction indicates a possible association between depressive symptom trajectories,

multimorbidity, and all-cause mortality risk, these results did not reach statistical significance. In a 2015 study conducted by Gallo and colleagues they analyzed depressed and non-depressed patients with medical comorbidity to see if depressed patients had an increased risk of all-cause mortality (Gallo et al., 2016). When looking at depressed patients receiving usual care practices only those with the highest comorbidity saw a significant increase in all-cause mortality, the lower levels of comorbidity did not reach statistical significance (Gallo et al., 2016). This result is similar to what we saw in our study, as the direction looked to be pointing to an association between depressive symptom trajectories and multimorbidity on all-cause mortality, yet did not quite reach statistical significance. The lack of significance here could be due to small sample sizes in some of the groups being analyzed. Since the study at present just looked at the number of conditions an individual has and not the combination of conditions one has, this could be a reason for the lack of significance found.

**Depressive Symptom Trajectories and Multimorbidity on Cancer Mortality**

The results from our study indicate the interaction between depression symptom trajectories and number of chronic conditions one has is not predictive for cancer mortality. The direction of association for the interaction between depressive symptom trajectories and multimorbidity on cancer mortality were slightly negative or null. Current literature has shown that depression can cause an increase in mortality, however, the role multimorbidity plays in this interaction is not as well understood (Giese-Davis et al., 2010; Pinquart & Duberstein, 2010; Satin, Linden, & Phillips, 2009). A

study aimed to analyze certain chronic conditions and depression (Gunn et al., 2012). This study found after adjusted analyses that depression symptoms was not significantly associated with cancer (Gunn et al., 2012). This leads one to hypothesize that depression and multimorbidity might not be the driving factor for cancer mortality. However, this study only looked at depression during a single measure, so having additional studies analyzing depression symptom trajectories is warranted. Other factors (treatment, stage, aggressiveness, type) could play a more decisive role in cancer mortality than the interaction between depression symptom trajectories and multimorbidity. In this current study we did not have information on stage, aggressiveness, or type of cancer, which all could play a more critical role in cancer mortality

**Depressive Symptom Trajectories and Multimorbidity on Cardiovascular Mortality**

The results from our study indicate the interaction between depressive symptom trajectories and number of chronic conditions is predictive in cardiovascular mortality. Regardless of persistent depression status, (low, moderate, high) individuals who had three or more chronic conditions saw an increased risk of cardiovascular mortality. However, those with persistently high depression symptom trajectories and three or more chronic conditions saw the greatest risk for cardiovascular mortality (HR: 1.847; 95% CI: 1.223-2.789). These results are consistent with previous literature that showed depression increased mortality risk in patients with cardiovascular disease (Barefoot et al., 1996; Barth, Schumacher, & Herrmann-Lingen, 2004; Frasure-Smith et al., 2009;

Penninx et al., 2001; Schulz et al., 2000). In a study among individuals who had cardiovascular disease and major depression the risk of mortality was 3.0 times that of non-depressed cardiovascular disease patients (Penninx et al., 2001). Our results rereinforce the importance of prioritizing cardiovascular disease and depression management, as the results are consistently pointing to an increased mortality risk. This study shows the potential stratifying cardiovascular multimorbid patients by persistent depression status can have in identifying high risk groups for targeted interventions.

**Strengths and Limitations**

This study has much strength, with one being the diverse, yet nationally representative study population. Even with an oversampling of African Americans and Hispanics the study population is still highly generalizable for the American population (Sonnega et al., 2014). Additionally, this study analyzed depression using trajectory methodology which allowed the investigators to see changes in depression symptoms over time, reflecting the natural history of the disease (Andreescu et al., 2008; Kuchibhatla et al., 2012; Rote, Chen, & Markides, 2015). This measurement method also allowed the investigator to identify risk factors and certain outcomes with these different trajectories (Hsu, 2012; Musliner et al., 2016). Analyzing how the interaction between depressive symptom trajectories and multimorbidity affects cause-specific mortality is a strength of this study. The literature on how depressive symptom trajectories and multimorbidity affect cause-specific outcomes is lacking. Our study is able to provide new light on how depressive symptom trajectories and multimorbidity

affects cancer and cardiovascular mortality. Future studies should be conducted to see if the associations seen here are replicated in varying populations. An additional strength is the methodology involved with dealing with competing risks. Since cardiovascular disease and diabetes are competing risks, due to the fact an individual is at risk for more than one mutually exclusive event, using a model that accounted for these risks made the results more reliable and valid (Gondara, 2015). Finally, this study had a clear temporal order shown, as the exposure status was collected prior to the outcome.

Although this study had several strengths it also possesses several limitations. Since this study used data from the HRS there is the possibility of recall bias; as some participants might recall past illnesses differently than others. For example, someone diagnosed with hypertension could potentially recall medical illnesses they have been diagnosed with differently than someone without hypertension. A large study was conducted in Canada comparing the agreement of self-report data to health administrative data on seven chronic conditions: myocardial infarction, asthma, diabetes, chronic lung disease, stroke, hypertension, and congestive heart failure (Muggah et al., 2013). The researchers found good to very good agreement when looking at diabetes and hypertension, moderate agreement for myocardial infarction and asthma, and poor agreement for stroke, congestive heart failure, and COPD (Muggah et al., 2013). In all cases the prevalence was higher in the health administrative data except when looking at myocardial infarction and stroke (Muggah et al., 2013). This shows that self-report data is a good tool at looking at some chronic conditions, yet it does lack strength in other chronic conditions. There is also a possibility of information

bias in this study. Depression has a negative stigma associated with it so individuals might not have accurately reported feeling sad or other depressive like qualities. Another limitation to this study is the lack of knowledge on disease severity and treatment information. We do not know if individuals were properly managing their illnesses, or if this would have affected our outcomes. Additionally, we did not adjust for pharmacological or non-pharmacological information on depression treatments. There was no available information on non-pharmacological treatment methods, and pharmacological methods were only available for a sub-sample of the population. Finally, covariates were not assessed as time-varying, so covariate status could have changed. Although we did not assess confounders as time varying it is believed their effect would be minimal as physical activity was one of our potential time varying confounders. Physical activity intensity has been shown to decrease with age, so we believe the effects potentially shown would have been minimal

**Conclusions**

It is well known and documented that having an increased number of chronic conditions increases your likelihood of mortality. However, the effects depression, coupled with having multiple chronic conditions, has on mortality is not as well understood. This study found that the interaction between depression and multiple chronic conditions can increase ones risk for cardiovascular and diabetes mortality. The majority of the study population has more than one chronic condition, consistent with the older American population, so it is imperative to properly manage and monitor these individuals to help reduce the risk of mortality. Although it has been reported that

depressed individuals are more likely to engage in poor management and lifestyle choices (lack of medication adherence, more likely to smoke, sedentary lifestyle) a randomized controlled trial reported the promising mortality benefits seen in depressed, multimorbid patients after receiving chronic disease management (Gallo et al., 2016). The mortality benefits seen in Gallo's study, coupled with the affects seen in this current study, highlight the importance chronic disease management could play in treating patients with depression and multiple chronic conditions. Additional management studies should be conducted to see if the effects are consistent when looking at cause-specific mortalities.

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## APPENDIX A-SENSITIVITY ANALYSIS

Table A.1: Distribution of the Number of Chronic Conditions

| # of Conditions | N | % |
|---|---|---|
| **0** | 1833 | 14.09 |
| **1** | 3319 | 25.52 |
| **2** | 3623 | 27.86 |
| **3** | 2374 | 18.25 |
| **4** | 1235 | 9.50 |
| **5** | 447 | 3.44 |
| **6** | 137 | 1.05 |
| **7** | 34 | 0.26 |
| **8** | 3 | 0.02 |
| **Totals** | 13005 | 100% |

Table A.2: Distribution of Chronic Conditions by Depression Trajectories

| Conditions | Low (N, %) | Moderate (N, %) | High (N, %) |
|---|---|---|---|
| **0** | 1378, 10.60 | 344, 2.65 | 111, 0.85 |
| **1** | 2284, 17.56 | 706, 5.43 | 329, 2.53 |
| **2** | 2140, 16.46 | 936, 7.20 | 547, 4.21 |
| **3** | 1193, 9.17 | 691, 5.31 | 490, 3.77 |
| **4** | 485, 3.73 | 378, 2.91 | 372, 2.86 |
| **5** | 103, 0.79 | 141, 1.08 | 203, 1.56 |
| **6** | 17, 0.13 | 40, 0.31 | 80, 0.62 |
| **7** | 2, 0.02 | 4, 0.03 | 28, 0.22 |
| **8** | 0, 0.00 | 0, 0.00 | 3, 0.02 |
| **Totals** | 7602, 58.45 | 3240, 24.91 | 2163, 16.63 |

Table A.3: Number of Chronic Conditions by Depression Status for All-Cause Mortality

| Conditions | No Death (N, %) | | | Death (N, %) | | |
|---|---|---|---|---|---|---|
| | Low | Moderate | High | Low | Moderate | High |
| **0** | 1211, 13.52 | 282, 3.15 | 83, 0.93 | 167, 4.12 | 62, 1.53 | 28, 0.69 |
| **1** | 1843, 20.58 | 545, 6.09 | 235, 2.62 | 441, 10.89 | 161, 3.98 | 94, 2.32 |
| **2** | 1576, 17.60 | 631, 7.05 | 338, 3.77 | 564, 13.93 | 305, 7.53 | 209, 5.16 |
| **3** | 752, 8.40 | 382, 4.27 | 276, 3.08 | 441, 10.89 | 309, 7.63 | 214, 5.28 |
| **4** | 245, 2.74 | 168, 1.88 | 167, 1.86 | 240, 5.93 | 210, 5.19 | 205, 5.06 |
| **5** | 40, 0.45 | 55, 0.61 | 67, 0.75 | 63, 1.56 | 86, 2.12 | 136, 3.36 |
| **6** | 6, 0.07 | 16, 0.18 | 25, 0.28 | 11, 0.27 | 24, 0.59 | 55, 1.36 |
| **7** | 1, 0.01 | 0, 0.00 | 11, 0.12 | 1, 0.02 | 4, 0.10 | 17, 0.42 |
| **8** | 0, 0.00 | 0, 0.00 | 0, 0.00 | 0, 0.00 | 0, 0.00 | 3, 0.07 |
| **Totals** | 2674, 63.36 | 2079, 23.22 | 1202, 13.42 | 1928, 47.60 | 1161, 28.67 | 961, 23.73 |

Table A.4: Number of Chronic Conditions by Depression Status for Cancer Mortality

| Conditions | No Death (N, %) | | | Death (N, %) | | |
|---|---|---|---|---|---|---|
| | Low | Moderate | High | Low | Moderate | High |
| **0** | 114, 3.72 | 41, 1.34 | 20, 0.65 | 53, 5.38 | 21, 2.13 | 8, 0.81 |
| **1** | 312, 10.19 | 115, 3.76 | 72, 2.35 | 128, 12.98 | 46, 4.67 | 22, 2.23 |
| **2** | 406, 13.26 | 231, 7.54 | 171, 5.58 | 157, 15.92 | 74, 7.51 | 38, 3.85 |
| **3** | 333, 10.88 | 243, 7.94 | 170, 5.55 | 108, 10.95 | 66, 6.69 | 44, 4.46 |
| **4** | 176, 5.75 | 172, 5.62 | 165, 5.39 | 64, 6.49 | 38, 3.85 | 40, 4.06 |
| **5** | 49, 1.60 | 66, 2.16 | 109, 3.56 | 14, 1.42 | 20, 2.03 | 27, 2.74 |
| **6** | 9, 0.29 | 19, 0.62 | 49, 1.60 | 2, 0.20 | 5, 0.51 | 6, 0.61 |
| **7** | 1, 0.03 | 3, 0.10 | 14, 0.46 | 0, 0.00 | 1, 0.10 | 3, 0.30 |
| **8** | 0, 0.00 | 0, 0.00 | 2, 0.07 | 0, 0.00 | 0, 0.00 | 1, 0.10 |
| **Totals** | 890, 29.07 | 1400, 45.72 | 772, 25.21 | 526, 53.35 | 271, 27.48 | 189, 19.17 |

Table A.5: Number of Chronic Conditions by Depression Status for CVD Mortality

| Conditions | No Death (N, %) | | | Death (N, %) | | |
|---|---|---|---|---|---|---|
| | Low | Moderate | High | Low | Moderate | High |
| **0** | 1328, 11.51 | 329, 2.85 | 103, 0.89 | 48, 3.56 | 15, 1.11 | 8, 0.59 |
| **1** | 2162, 18.75 | 666, 5.77 | 305, 2.64 | 117, 8.67 | 38, 2.82 | 23, 1.70 |
| **2** | 1943, 16.85 | 831, 7.21 | 476, 4.13 | 187, 13.86 | 100, 7.41 | 61, 4.52 |
| **3** | 1019, 8.84 | 573, 4.97 | 412, 3.57 | 159, 11.79 | 108, 8.01 | 70, 5.19 |
| **4** | 387, 3.36 | 282, 2.45 | 279, 2.42 | 83, 6.15 | 87, 6.45 | 85, 6.30 |
| **5** | 75, 0.65 | 94, 0.82 | 152, 1.32 | 26, 1.93 | 40, 2.97 | 42, 3.11 |
| **6** | 14, 0.12 | 28, 0.24 | 52, 0.45 | 3, 0.22 | 11, 0.82 | 24, 1.78 |
| **7** | 2, 0.02 | 3, 0.03 | 17, 0.15 | 0, 0.00 | 1, 0.07 | 11, 0.82 |
| **8** | 0, 0.00 | 0, 0.00 | 1, 0.01 | 0, 0.00 | 0, 0.00 | 2, 0.15 |
| **Totals** | 6930, 60.09 | 2806, 24.33 | 1797, 15.58 | 623, 46.18 | 400, 29.65 | 326, 24.17 |