8-2020

The Long-Term Multidimensional Impact of Persistent Multisite Pain on Physical and Psychological Disability, and Mortality in Community-Dwelling Older Adults

Saurja Thapa
University of Massachusetts Boston

THE LONG-TERM MULTIDIMENSIONAL IMPACT OF PERSISTENT MULTISITE PAIN ON PHYSICAL AND PSYCHOLOGICAL DISABILITY, AND MORTALITY IN COMMUNITY-DWELLING OLDER ADULTS

A Dissertation Presented

by

SAURJA THAPA

Submitted to the Office of Graduates Studies,
University of Massachusetts Boston,
in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

August 2020

Nursing PhD Program

THE LONG-TERM MULTIDIMENSIONAL IMPACT OF PERSISTENT MULTISITE PAIN ON PHYSICAL AND PSYCHOLOGICAL DISABILITY, AND MORTALITY IN COMMUNITY-DWELLING OLDER ADULTS

A Dissertation Presented

by

SAURJA THAPA

Approved as to style and content by:

Suzanne G. Leveille, Professor
Chairperson of Committee

Janice B. Foust, Associate Professor
Member

Ling Shi, Associate Professor
Member

Tongjian You, Associate Professor
Member

Priscilla Gazarian, Program Director
PhD in Nursing Program

Ann Gakumo, Chair
Department of Nursing

ABSTRACT

THE LONG-TERM MULTIDIMENSIONAL IMPACT OF PERSISTENT MULTISITE PAIN ON PHYSICAL AND PSYCHOLOGICAL DISABILITY, AND MORTALITY IN COMMUNITY-DWELLING OLDER ADULTS

August 2020

Saurja Thapa, B. S., Smt. Nagarathamma College of Nursing
M.A., University of Central Missouri
Ph.D., University of Massachusetts Boston

Directed by Professor Suzanne Leveille

Persistent multisite pain is highly prevalent, affecting 25-43% of community-dwelling older adults. Although existing evidence suggests that persistent multisite pain is associated with physical and psychological disability, studies use a cross-sectional assessment approach that overlooks pain duration or persistence. This study aimed to estimate the persistence of multisite pain and the proportion of incident multisite pain and examine the association between persistent multisite pain and physical (ADL and IADL) and psychological disability (depression and anxiety) at 18 months and six years. Also, the association between baseline persistent multisite pain and mortality was assessed.

Secondary data analysis of the MOBILIZE Boston Study (MBS) was performed using data from baseline, 18 months, and six years. Pain distribution assessed longitudinally at three-time points were categorized as no pain, single-site pain, incident multisite pain, and persistent multisite pain. Chi-square analysis, ANOVA tests, and several multivariable regression models were employed.

The prevalence of persistent multisite pain was 26% and 27%, and incident multisite pain was 10% and 18% at 18 months and six years, respectively. For individuals with incident multisite pain, the risk for ADL difficulty became evident only at six years, but individuals with persistent multisite pain consistently had a much higher risk for ADL difficulty at 18 months and six years. There is a substantial increase in the risk for a lot of IADL difficulty in individuals with incident or persistent multisite pain compared to individuals with no pain. Incident multisite pain was not associated with depression and anxiety at six years, while persistent multisite pain was associated with psychological disability at 18 months and six years. Essentially, persistent multisite pain is more debilitating than incident multisite pain. There was no association between persistent multisite pain and mortality at 12.4 years.

This study's findings contribute to geriatric pain research by revealing the disabling consequences of the persistence of multisite pain. Proper utilization of multisite pain measures and assessment of the functional capacity is crucial when evaluating elders with multisite pain. Importantly, clinicians need to be aware of depression and anxiety when treating the elderly with multisite pain.

ACKNOWLEDGMENTS

I want to express my utmost appreciation to Dr. Suzanne Leveille, my mentor, and my chair. I'm grateful for her relentless support and guidance throughout my Ph.D. journey. This journey would not have been possible without her constant motivation and encouragement. I'm extremely glad that our areas of interest matched, and I was very fortunate to have the opportunity to work with a great mentor and a renowned scientist.

I would also like to extend my sincere gratitude to my committee members Dr. Janice Foust, Dr. Tongjian You, and Dr. Ling Shi, for their valuable suggestions and crucial critiques. I sincerely want to acknowledge all the nursing faculty members for their great support. Truthfully, the support we get from our nursing faculty in UMB is unmatched elsewhere.

I am tremendously grateful to my beloved parents, Suresh Kumar and Sushila Thapa, brother Shashank Thapa and my extended family for their immense love, support and confidence. I am incredibly fortunate to have a beloved husband, Dr. Santosh Raj Poudel, who never stopped believing in me. This incredible journey would not have been feasible without his true love and support. I would also like to extend my thanks to my friends and colleagues for their immense love, care, and support- It has been an incredible journey.

Finally, thank you, Almighty God, for the strength, guidance, and courage.

TABLE OF CONTENTS

LIST OF TABLES

Table Page

Table Page

Table Page

Table Page

LIST OF FIGURES

Figure Page

Figure Page

CHAPTER I

INTRODUCTION

The world's population is aging. In the U.S., older adults currently account for 15% of the total population, which is projected to increase to more than 20 percent by 2030 (U.S. Census Bureau, 2014). Musculoskeletal pain is the most predominant form of pain causing dependency and incapacitation (Blyth & Noguchi, 2017; Briggs et al., 2016; Brown, Kirkpatrick, Swanson, & McKenzie, 2011). Over the years there has been a growing literature on geriatric pain and studies have mostly focused on single-site pain (e.g., knee pain, hip pain) (Farrokhi et al., 2016; Ledoux, Dubois, & Descarreaux, 2012; Thomas, Dunn, Mallen, & Peat, 2008; Weiner, Sakamoto, Perera, & Breuer, 2006). However, among older adults, persistent musculoskeletal joint pain co-occurring in more than one anatomical site is common (Croft, Dunn, & Von Korff, 2007; Croft, Jordan, & Jinks, 2005; Leveille et al., 1998; Stubbs, Schofield, Patchay, & Leveille, 2016). The existing evidence from the pain literature has indicated that the greater burden associated with musculoskeletal pain in older adults is related to multisite pain (Cecchi et al., 2009; Croft, Jordan, & Jinks, 2005; Ling et al., 2003; Morone et al., 2009; Peat et al., 2006). It is estimated that 25-43% of older adults have persistent multisite pain (Buchman et al., 2010; Croft et al., 2005; Patel, Guralnik, Dansie, & Turk, 2013). Also, persistent multisite pain may have a more significant impact on

physical and psychological health compared to single-site pain as studies have indicated that persistent multisite pain is associated with a greater risk for physical disability (Croft et al., 2005; Eggermont, Bean, Guralnik, & Leveille, 2009; Keenan, Tennant, Fear, Emery, & Conaghan, 2006; Leveille, Bean, Ngo, McMullen, & Guralnik, 2007; Leveille et al., 1998, 2001; Patel et al., 2013; Peat et al., 2006; Scudds & Robertson, 2000) and psychological disability (Denkinger et al., 2014; Eggermont, Penninx, Jones, & Leveille, 2012).

Despite being a highly prevalent disabling condition in older adults, multisite pain has relatively received less attention than single-site pain. Also, the available treatment that focuses on site-specific pain may have only a marginal effect on lessening disabilities in individuals with multisite pain unless the targeted treatment benefits other co-existing pain sites as well. Besides, present studies use a cross-sectional pain assessment method to understand persistent multisite pain, overlooking pain duration or persistence. Additionally, most practices are based on the evidence from studies conducted in the general or younger population, indicating a clear lack of studies in the older population. Likewise, the issues of persistent multisite pain and its consequences in the geriatric population are less well published. To the author's knowledge, this is a first population-based study to explore the relationship between longitudinally assessed persistent pain and ADL and IADL disability, depression, and anxiety at 18 months and six years in community-dwelling older adults. This study also examines the relationship between persistent pain and mortality in older adults. To date, no studies have investigated the relationship between incident multisite pain and physical and psychological disability in older adults.

In the following section of this chapter, background, significance, purpose statement, specific aims with hypotheses, and theoretical framework will be discussed in detail.

Background and Significance of the Problem

In the United States, over the years, there has been a steady increase in life expectancy. The current overall life expectancy for males is 78.6 years and 81.1 years for females (Asmundson & Katz, 2009). This rapid growth in life expectancy has led to a significant increase in the number of older adults in the United States (U.S). Currently, older adults account for 15 percent of the total population. With a continuous growth rate of 1.5 times the average rate, older adults will increase to 20 percent of the total population by 2030 (U.S. Census Bureau, 2014). The increased life expectancy carries the risk of chronic diseases, which leads to functional impairment and physical disabilities (Filho, Mambrini, Malta, Lima-Costa, & Peixoto, 2018; Fong, 2019). About 85% of elders live with at least one chronic health condition, and 60% have two chronic diseases (National Council of Aging, 2018). Chronic conditions such as musculoskeletal disorder (e.g., arthritis) is a major cause of persistent pain and, although non-fatal, has a significant impact on the physical and psychological disabilities in older adults (American Geriatric Society (AGS), 2002; Verbrugge, Lepkowski, & Konkol, 1991). Persistent pain of musculoskeletal origin is the common form of pain, affecting more than 50 percent of older adults living in the community (Briggs et al., 2016; Brown et al., 2011; Helme & Gibson, 2001; Tatsuya et al., 2017). Despite the higher prevalence, persistent musculoskeletal pain (MSP) is still a poorly understood risk factor for functional impairment in older adults.

Chronic health conditions are precursors for developing disabilities, and multiple comorbidities often increase the severity of disability in an individual (Colón-Emeric,

Whitson, Pavon, & Hoenig, 2013; Hung, Ross, Boockvar, & Siu, 2012; Verbrugge et al., 1991; Verbrugge & Patrick, 1995). Disability is a significant predictor of negative outcomes such as falls, hospitalization, nursing home admission, and mortality (Fong, Mitchell, & Koh, 2015; Gaugler, Duval, Anderson, & Kane, 2007; Leveille et al., 2009; Majer, Nusselder, Mackenbach, Klijs, & Van Baal, 2011; Mor, Wilcox, Rakowski, & Hiris, 1994). According to Aging Statistics, in the U.S, among older adults aged 65 and over, 29% had difficulty in one or more ADL, and 12% had difficulties only in instrumental activities of daily living (IADL) (Federal Interagency Forum on Aging-Related Statistics, 2016). The well-recognized Nagi model of disablement proposes that the disablement process begins as pathology and progresses to physical impairments and functional limitations, eventually leading to disability (Nagi, 1976; Verbrugge & Jette, 1994).

Several studies have investigated the relationship between pain and disability in older adults with few studies demonstrating a direct pain-disability relationship. For instance, Leveille and colleagues (2007) showed a direct relationship between pain and disability, as psychological symptoms and physical impairments did not mediate the relationship between musculoskeletal pain and severe mobility disability. Likewise, another study proposed the direct effect of pain on disability (Kahana, Kahana, Namazi, Kercher, & Stange, 1997). Additionally, musculoskeletal pain-related disability was seen even without any radiographic arthritic changes in older adults (Hochberg, Lawrence, Everett, & Cornoni-Huntley, 1989). Cross-sectional studies have shown that persistent multisite musculoskeletal pain is associated with a physical disability (Croft et al., 2005; Eggermont, Bean, et al., 2009; Keenan et al., 2006; Leveille et al., 2007, 1998, 2001; Patel et al., 2013; Peat et al., 2006; Scudds & Robertson, 2000) and longitudinal studies have indicated that persistent multisite

musculoskeletal pain predicts physical disability among older adults (Buchman et al., 2010; Eggermont et al., 2014; Leveille et al., 2001). Apart from physical disability, cross-sectional studies have also shown that persistent multisite pain is related to psychological distress such as depression and anxiety in elders (Denkinger et al., 2014; Eggermont, Bean, et al., 2009; Eggermont et al., 2012; Patel et al., 2013). However, these studies use a cross-sectional pain assessment approach which overlooks the actual persistence of pain. Additionally, mortality related to pain is not a well-established area; existing studies demonstrate conflicting results regarding mortality risk in the elders with musculoskeletal pain (Andersson, 2009; Docking et al., 2015; Jordan & Croft, 2010; Shega et al., 2013; B. H. Smith, Elliott, & Hannaford, 2003; D. Smith, Wilkie, Croft, & McBeth, 2018).

Furthermore, the increase in life expectancy and decrease in mortality has led to the development of morbidity related theories such as the theory of the expansion of morbidity (Gruenberg, 1977), the theory of compression of morbidity (F. J. Fries, 1980), and the theory of dynamic equilibrium (Manton, 1982). Over the years, several studies have tested these theories based on the ongoing trends of life expectancy, disability, and disability-free life expectancy (Cai & Lubitz, 2007; Crimmins, Hayward, Hagedorn, Saito, & Brouard, 2009; Crimmins, Zhang, & Saito, 2016; Manton, Gu, & Lowrimore, 2008). Some studies indicated an increase in total life expectancy accompanied by an increase in active life expectancy or disability-free life, congruent with the theory of the compression of morbidity (Cai & Lubitz, 2007; Crimmins et al., 2009). However, other studies have reported inconsistent findings. For instance, Freedman and Spillman (2016) reported that older black women were the most disadvantaged group because of the modest gain in the number of years of active life and no gain in the expected proportion of active life expectancy. Mainly, individuals with higher

education experienced the compression of morbidity, and the expansion of morbidity was observed among those with lower socioeconomic status (Crimmins & Saito, 2001). Basically, socio-demographic factors such as gender, race, and particularly income and education played a significant role in determining the increase in life expectancy, compression of morbidity, expansion of morbidity, and increased active life expectancy. Overall, there is a widening of the gender-race gap in disability-free life expectancy and an uneven increase in disabled life expectancy in the studies.

Musculoskeletal pain as single-site pain. Traditionally, epidemiological studies on musculoskeletal pain have extensively examined pain at specific body sites such as knee or hip (Ledoux et al., 2012; Thomas et al., 2008; Weiner et al., 2006). But the accumulated evidence from the literature has shown that the occurrence of musculoskeletal pain in one location is associated with a higher probability of having pain in another location (Croft et al., 2007; Leveille et al., 2007, 1998; Peat et al., 2006; Stubbs et al., 2016). Similar to other studies, in our previous study (Thapa, Shmerling, Bean, Cai, & Leveille, 2018), we found that consistently around 80 to 90% of those who reported pain in one joint or in the back area had multisite pain. Although isolated pain is related to poor health outcomes, pain frequently co-exists and hardly manifests as a single-site pain among elders (Croft et al., 2007; Leveille et al., 1998; Stubbs et al., 2016). Also, pain measures limited to assessing single sites such as knee or back fail to capture multisite pain, which may substantially impact the physical and psychological health in older adults.

Therefore, understanding the differences in risk for physical and psychological disability among individuals with persistent multisite pain compared to single-site pain, and no pain in a representative sample of community-dwelling older adults is crucial.

Musculoskeletal pain as widespread pain. Apart from site-specific studies, persistent musculoskeletal pain has also been analyzed as chronic widespread pain (CWP). As early as 1970, researchers placed considerable effort into developing a universal pain classification system, and a vast amount of work was laid into the representation of the pain sites in the human body (Loeser & Black, 1975). Because pain can present itself as a symptom or as a disease, and due to its complex nature, classifying pain, specifically persistent pain, has been problematic (Davies, Crombieb, & Macrae, 1998). The American College of Rheumatology (ACR) recognized the existence of pain in multiple locations on the body. It defined chronic widespread pain (CWP) as pain present for at least three months, on at least two contralateral quadrants, above and below the waist and the axial skeletal (Wolfe et al., 1990). This definition was initially created as the diagnostic standard for patients with fibromyalgia. In 1996, pain experts Macfarlane and colleagues stated that the ACR definition of CWP was too broad and failed to reflect the original concept of CWP and thus, proposed a more stringent definition called the Manchester definition of CWP [CWP(M)], which defined CWP(M) as pain lasting for at least three months, in at least two specific areas of two contralateral limbs and the axial skeleton (Macfarlane, Croft, Schollum, & Silman, 1996). The main difference between the two definitions is that Manchester CWP requires the pain to be present in at least two sections of two contralateral limbs and the axial skeleton, while ACR defines CWP as the pain located axially, above and below the waist, and on both sides of the body. The ACR definition is too inclusive and may not reflect the concept of truly diffuse and widespread pain. For example, pain in the right foot, left hand, and back pain satisfies the ACR definition of CWP, but this may not be a true CWP (Hunt, Silman, Benjamin, Mcbeth, & Macfarlane, 1999). The main argument here is that both the

definitions of CWP do not adequately explain persistent multisite pain in older adults. This was evident when Eggermont and colleagues reported that 14.7% of the participants had chronic widespread pain, and 25% had multisite pain but did not meet chronic widespread pain criteria (Eggermont, Bean, et al., 2009). Therefore, the populations overlooked in both clinical and population-based studies are those who do not satisfy the definitions of CWP but have persistent multisite pain.

Disabling burden of persistent multisite pain in older adults. Persistent musculoskeletal multisite pain is a highly prevalent condition, affecting 25-43% of the older adults residing in the community (Buchman et al., 2010; Croft et al., 2005; Patel et al., 2013; Thapa et al., 2018). Persistent musculoskeletal pain is typically a part of multisite pain problem as studies have consistently reported that single-site pain increases the risk for pain in other locations (Buchman et al., 2010; Croft et al., 2007; Leveille et al., 2007; Peat et al., 2006). Persistent musculoskeletal multisite pain is defined as pain present in the previous month that lasted for at least three months during the last year, in two or more anatomical sites. The pain areas include hands/wrists, shoulders, back, chest, hips, knees, and feet (Leveille et al., 2009; Thapa et al., 2018). In our previous study (Thapa et al., 2018), risk factors independently associated with persistent multisite pain, but not single-site pain, were mobility limitations, BMI, multiple comorbidity, depression, and anxiety. Also, persistent multisite pain shared similar risk factors and pathways to already established geriatric syndromes such as urinary incontinence, frailty, falls, and functional decline (Thapa et al., 2018). The burden can be measured in terms of the adverse outcomes associated with persistent multisite pain. An increasing number of cross-sectional studies investigating the relationship between pain and disability have demonstrated that persistent multisite pain is an

important factor contributing to mobility limitation and functional impairment in older adults (Croft et al., 2005; Eggermont, Bean, et al., 2009; Keenan et al., 2006; Leveille et al., 2007, 1998; Patel et al., 2013; Peat et al., 2006). Longitudinal studies have also indicated that individuals with a higher number of pain locations have a significantly greater likelihood of developing physical disability compared to individuals with single-site pain or no pain (Buchman et al., 2010; Eggermont et al., 2014; Leveille et al., 2001). Persistent multisite pain also has a greater effect on emotional and psychosocial status than single-site pain. Studies have consistently demonstrated that older adults with persistent multisite pain have the most significant risk for depression and anxiety (Denkinger et al., 2014; Eggermont, Bean, et al., 2009; Eggermont et al., 2012; Patel et al., 2013). Several other consequences associated with persistent multisite pain include increased fall risk (Leveille et al., 2009; Welsh, Clarson, Mallen, & McBeth, 2019), poor sleep quality (Q. Chen, Hayman, Shmerling, Bean, & Leveille, 2011), pain catastrophizing (Nawai, 2017), and decreased quality of life (Laslett et al., 2012). Additionally, studies showed that global pain severity ratings increased as the number of pain sites increased (Croft et al., 2005; Leveille et al., 1998; Peat et al., 2006). Besides, Fowler et al. (2013) also reported that multisite pain among obese older women was a significant mediator of the negative impact of obesity on physical function and disability.

Long term pain-related outcome such as mortality is not a well-studied area, particularly in the older population. No studies to date have examined the relationship between persistent multisite pain and mortality. Moreover, prior studies examining pain and mortality relationship have demonstrated inconsistent results (Andersson, 2009; Docking et al., 2015; Jordan & Croft, 2010; Shega et al., 2013; B. H. Smith et al., 2003; D. Smith, Wilkie, Croft, & McBeth, 2018). It is possible that the risk for mortality may be compounded

by a combination of factors including pain-related morbidity, age-related comorbidities, and other lifestyle factors such as physical inactivity and higher body mass index. Despite the higher prevalence, debilitating consequences, and qualifying as a geriatric syndrome (Thapa et al., 2018), persistent multisite pain has relatively received less attention than single-site pain. It is also not a well-studied pain characteristic among elders. Moreover, cross-sectional pain assessment approach fails to capture the persistence of pain.

It is hypothesized that older people with the persistence of multisite pain have greater physical and psychological disability. Also, older adults with persistent pain will be at an increased risk for early mortality compared to those with no pain. Hence, this study's findings will add to the body of science by examining the consequence of incident and persistence of multisite pain on physical and psychological disability in older adults. Health care providers should thoroughly assess elders for multisite pain because it may be a critical clinical indicator in recognizing elders at a higher risk for physical and psychological disability and mortality. Identifying and treating older individuals suffering from persistent multisite pain with targeted interventions may improve function and promote independence. This study further extends the literature by using a longitudinal method to assess pain and examine the consequences of persistence of multisite pain and incident multisite pain in relation to physical and psychological disability among community-dwelling older adults.

Statement of Purpose

The primary purpose of this study was to understand the multidimensional impact of persistent multisite pain on several aspects of physical and psychological health and mortality in a population of older adults residing in the community. This study determined the association between persistent multisite pain and two domains of physical disability: self-

care and independent living. Also, the association between persistent multisite pain and psychological disability, such as anxiety and depression, was examined. Additionally, the relationship between persistent multisite pain and mortality was studied.

Descriptive aim.

Specific aim #1. To estimate the persistence of multisite pain and the proportion of new onset of multisite pain at 18 months and six years in a population of older adults living in the community.

Analytic aims.

Specific aim #2. To examine the association between persistent multisite pain and the risk of developing physical disability in community-dwelling older adults.

Hypothesis #2. Older adults with persistent multisite pain are more likely to have a poorer physical function (ADL and IADL) at the 18-month and six-year follow-up compared to older adults with no pain.

Specific aim #3. To determine the association between persistent multisite pain and the risk of developing psychological disability in community-dwelling older adults.

Hypothesis #3a. Older adults with persistent multisite pain are more likely to report depression and anxiety at the 18-month and six-year follow-up than those with no pain.

Hypothesis #3b. Older adults with incident multisite pain are more likely to report depression and anxiety at the six-year follow-up than those with no pain.

Specific aim #4. To determine the association between persistent multisite pain and mortality at 12.4 years in older adults.

Hypothesis #4. Accounting for socioeconomic status, lifestyle factors, and comorbidities, older adults with persistent multisite pain have an increased risk of mortality than those with no pain.

Theoretical Framework

Aging is related to ubiquitous changes in the biological system, psychological system, and social functioning (Gibson, 2006). Historically, the theory of pain largely depended on the presumed linearity between biological or pathophysiological aspects of pain and pain report (Turk, Fillingim, Ohrbach, & Patel, 2016; Turk & Okifuji, 2002). However, with the introduction of gate control theory, Ronald Melzack and Patrick Wall have underscored the role of psychosocial factors in the pain experience (Melzack & Wall, 1965). Today, pain is recognized as a complex perceptual experience influenced not only by sensory, cognitive, biological, and emotional factors but also by behavioral responses, which may ease, exacerbate, or extend pain (Garland, 2013). Persistent pain, a biopsychosocial phenomenon, is the pain that persists for more than three to six months, which may or may not be associated with any distinct disease processes (American Geriatrics Society (AGS), 2009; Merskey & Bogduk, 1994). In contrast, acute pain is pain caused by a particular disease or injury and is generally related to skeletal muscle spasm, triggering the sympathetic nervous system. Besides, for acute pain, efforts are placed on treating the root cause of the pain, while persistent pain is typically managed but not cured (Grichnik & Ferrante, 1991). Although the unidimensional biomedical model focuses on the disease process, it lacks the understanding of health, function, and quality of life-related to pain (Gagliese, Gauthier, Narain, & Freedman, 2018; Turk & Flor, 1999; Turk & Okifuji, 2002). The multidimensional, biopsychosocial model integrates the biological, psychological, and sociocultural situation to

provide a comprehensive outlook for understanding an individual's experience and response to pain.

The biopsychosocial model proposed by George Engel in 1977, views illness as a complex interaction between biological, psychological, and social factors (Engel, 1977; Garland, 2013). The interaction of sensory, behavioral, cognitive-affective, and environmental factors leads to a complex experience of persistent pain (Keefe et al., 1996). Studies have underscored the disabling consequences of persistent pain on several aspects of an individual's functioning: physical, social, and emotional (Turk & Okifuji, 2002). In 2011, the National Academy of Medicine's landmark report, *Relieving Pain In America*, also emphasized using the biopsychosocial approach while managing patients with persistent pain (Institute of Medicine (IOM), 2011). More importantly, over the years, the biopsychosocial model has received a great deal of attention in conceptualization and treatment of persistent pain, and it is particularly dominant in the studies of chronic pain (Gatchel, Peng, Peters, Fuchs, & Turk, 2007; Turk et al., 2016).

King's system model. The King's conceptual model, developed by Imogene King in 1981, was founded on the basis that human beings are open systems, constantly exchanging energy and information with the environment (King, 1981). The three primary concepts are personal, interpersonal, and social systems. These multidimensional, open, and dynamic networks are interrelated and continuously interacting with one another (King, 1981). In a recently published dissertation, the King's conceptual model was applied to elucidate the biopsychosocial perspective in which older adults experienced pain and disability through personal systems, interpersonal systems, and social systems using the MOBILIZE Boston (MBS) dataset (Thakral, 2015). In this study, the longitudinal pain assessment method was

used to examine the multidimensional impact of the persistent multisite pain on physical and psychological disability compared to incident multisite pain, single-site pain, and no pain using the MBS I and II datasets. Also, the relationship between baseline persistent multisite pain and mortality was examined at 12.4 years. The three systems, personal systems, interpersonal systems, and social systems describe the physical and social environment in which individual functions and provide a biopsychosocial framework in which older adults experience persistent multisite pain and its related disability. Therefore, the King's Systems Model will provide a theoretical perspective and is the nursing conceptual framework selected to guide this study. Within the context of King's conceptual framework, the role of a nurse is to help the individuals maintain and reestablish health so that they can function in their socially defined roles (King, 1981).

King (1981) defines health as "the dynamic life experiences of a human being, which implies continuous adjustment to stressors in the internal and external environment through optimum use of one's resources to achieve maximum potential for daily living" (p.5). Within the perspective of King's system model, an individual is considered as personal systems that include the element specific to an individual, for example, perception (King, 1981). Perception is unique to an individual. It may affect how one interprets the aging process as well as the physiological and psychological understanding of pain and its experience. A qualitative study on 19 older adults, ages 67-92 with disabling hip and knee osteoarthritis, reported that regardless of the physical limitations related to pain, the perception and attitude determined the pain tolerance level and adherence to pain medication (Sale, Gignac, & Hawker, 2006). Aging is characterized by a rising susceptibility to chronic diseases due to age-related multisystem homeostatic dysregulation and the general senescence in multiple

organ systems (Divo, Martinez, & Mannino, 2014; Fabbri et al., 2015). Older adults with chronic conditions are at an increased risk of decreased functional decline than elders without such conditions (Fong, 2019). Multiple morbidities can often lead to the development of complex pain in older people. The pain experienced in the older age is unique and complicated, partly contributed by the age-related alterations in pharmacokinetics and pharmacodynamics such as distribution, metabolism, and elimination of several pain medications (Abdulla et al., 2013; American Geriatrics Society (AGS), 2009). This further translates to under-prescribing of the analgesics in elders (Bressler & Bahl, 2003; Institute of Medicine (IOM), 2011). Essentially, persistent pain in older adults is different biologically, psychologically, and therapeutically than in younger adults (Yezierski, 2012).

Additionally, the pain experience is complicated by both nociceptive (tissue damage or inflammation) and neuropathic pain (nerve damage) that frequently co-exists in elders (Reid, Eccleston, & Pillemer, 2015). Besides, experimental research on pain has indicated a modest and varying age-related decrease in pain sensitivity, particularly to mild noxious stimuli. The higher threshold to mild pain may be related to under-reporting of the pain perception, which eventually leads to tissue injury (Gibson, 2006; Institute of Medicine (IOM), 2011). Contrary to decreased sensitivity to mild pain, clinical and experimental studies involving older adults have also reported increased susceptibility to severe or persistent pain related to the extended impairment after the tissue injury, nerve injury, and inflammation, and decrease in the plasticity of the nociceptive system in the elderly (Gibson, 2006; Molton & Terrill, 2014). With the age-related decline in pain sensitivity to mild noxious stimuli, an older person's underreporting of pain symptoms may also be related to several other reasons. First of all, older adults tend to endure a higher pain threshold (Gibson,

2006; Institute of Medicine (IOM), 2011). Secondly, older adults may consider pain a natural part of aging (Kaye, Baluch, & Scott, 2010; Thielke, Sale, & Reid, 2012). Thirdly, due to perception and beliefs that pain and disability are related to aging, older adults may frequently downplay their symptoms, preventing them from seeking appropriate medical treatment (Miaskowski, 2000; Sofaer et al., 2005). Additionally, the age-related changes in the structure, function, and chemistry of the nervous system such as loss of brain volume, a decrease in the functioning of the endogenous pain modulatory mechanism, a significant decrease in the density of unmyelinated fibers may influence the pain perception in elders (Farrell, 2012; Molton & Terrill, 2014). However, due to the mixed finding, it is not possible to conclude if older adults have an increased or decreased sensitivity to pain.

Studies have estimated that the prevalence of persistent pain increases, decreases, and there is no difference in the pain prevalence with age (Donald & Foy, 2004; Jinks, Jordan, & Croft, 2002; Macfarlane et al., 2009; McCarthy, Bigal, Mindy, Derby, & Lipton, 2009; Patel et al., 2013; Thomas, Peat, Harris, Wilkie, & Croft, 2004). Older women are more likely to report multiple pain sites (Leveille, Zang, McMullen, Kelly-Hayes, & Felson, 2005) and have more significant disability than their male counterparts (Murtagh & Hubert, 2004).

The interpersonal systems are the communication and interaction between two or more individuals (King, 1981). Aging can affect an older individual's ability to engage and effectively communicate with care providers regarding their pain experiences and pain-related characteristics. Typical age-related changes are sensory deficits (e.g., vision, hearing) (Gopinath et al., 2012; Sloan, Ostermann, Brown, & Lee, 2005), which can unintentionally lead to miscommunication between older adults and care providers. The method of

communication used during a consultation is another factor in determining the effectiveness of any communication. For e.g., direct (face-to-face) versus indirect (telephone). Telephone consultation is found to be shorter, allows to present fewer problems, less data collection, and weaker counseling and rapport building between the health care provider and the patient compared to face-to-face consultation (McKinstry et al., 2010). The aging-associated changes and poor communication during the consultation may be barriers to successful communication and engagement between older individuals and healthcare providers, resulting in the insufficient evaluation and poor management of multisite pain. Therefore, pain is often underreported and undiagnosed, leading to more prolonged suffering among older people.

Social systems are complete interacting systems consisting of a large group with a common interest, such as the health care system (King, 1981). It is not uncommon for older adults to face difficulties while accessing the healthcare system for timely pain treatment and management. For example, lack of transportation, lack of insurance, poverty, poor communication, the complexity of the health care system, lack of family support, culture, and race/ethnicity (Horton & Johnson, 2010). Additionally, societal beliefs and expectations influence the pain experience in older people. The acceptance of pain as a natural part of aging and reluctance to pain treatment often complicates pain management in older people. Moreover, aging is mediated by factors such as attitudes and beliefs, including the cultural construction of aging (Lane & Smith, 2018). However, such is the societal belief and expectation rather than a medical reality (Sofaer et al., 2005).

King (1981) considers individuals as open systems, continuously interacting with their environment. Therefore, in this study, the constant interaction between personal,

interpersonal, and social systems offered a biopsychosocial framework in which an older person experiences persistent multisite pain and its physical and psychological consequences, as illustrated in figure 1. Persistent multisite pain, chronic health conditions, and disabilities are the stressors that affect the ability of an older person to maintain health and function in their roles. Multisite pain and its related comorbidities exist within the older person's internal environment. Persistent multisite pain was measured using a joint pain questionnaire (JPQ). A joint pain questionnaire was originally used in the Women's Health and Aging Study (Hochberg, Corti, Ferrucci, & Guralnik, 1995). A 13-item joint pain questionnaire assessed pain in hands and wrists, shoulders, back, chest, hips, knees, and feet. Diabetes Mellitus was measured using an algorithm that included laboratory results for a random glucose level (≥200 mg/dl), glycosylated hemoglobin (≥7%), self-reported diabetes mellitus, and use of anti-diabetic medications (Leveille et al., 2008). Lung disease was a self-reported physician-diagnosed chronic health condition. Heart disease was determined based on self-report of heart attack, congestive heart failure, angina pectoris, pacemaker, or cardiac arrhythmia (Rose, 1962). Physical disability exists in both the internal and external environments, which were regarded as having difficulty performing tasks related to self-care and independent living. Katz scale determined the level of difficulties in performing self-care activities such as bathing, dressing, transferring, using the toilet, and eating (Katz, Ford, Moskowitz, Jackson, & Jaffe, 1963). Lawton scale assessed the ability to perform independent living activities that included shopping, preparing meals, and household chores (Lawton & Brody, 1969). Psychological disability such as depression and anxiety occurred in internal and external environments assessed by CESD-R (Eaton, Muntaner, Smith, Tien, & Ybarra, 2004; Radloff, 1977) and Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983),

respectively. Depression and anxiety also elevate pro-inflammatory cytokines, which increase the pain experience (C. M. B. de Oliveira, Sakata, Issy, Gerola, & Salomão, 2011; Felger & Lotrich, 2013). Generally speaking, persistent pain is associated with poor health outcomes; however, it is essential to note that older adults who effectively adapt and manage their persistent pain may maintain their functional status and autonomy. Negative coping and inadequate pain management may contribute to physical disability and psychological distress. Although the existing evidence on the pain-mortality linkage is controversial, in our C-T-E model, we also posited that persistent multisite pain contributes to mortality in older adults (Figure 1). Proxy respondents, family contacts, and obituary searches were ascertained to identify deaths in the following 12.4 years.

Overall due to inconsistent findings, pain cannot be merely established as increased or decreased with age. More research is necessary to distinguish the physiological processes of pain perception among elders, and understand persistent multisite pain, a complex entity that is more common among older women. The present study highlighted the need for innovative models and supported using a system theory (i.e., King's System Model) to guide a study of persistent pain, a complicated pain experience in older adults. The original research MOBILIZE Boston Study used Saad Nagi's model as its conceptual framework to hypothesize disability in aging populations (Leveille et al., 2008). The Nagi Disablement Model, developed by Nagi, is well-established and provides an essential foundation for aging and disability (Nagi, 1976). Persistent multisite pain through the displacement process has the potential to influence an older person's holistic health. In this regard, Nagi-framework is parallel to King's conceptual system model because disability is the outcome of personal and environmental factors conceptualized in the broader biopsychosocial context (Thakral, 2015).

An application of King's model was constructed to predict the relationship between persistent multisite pain and physical and psychological disability and mortality in older people (per specific aims), as illustrated in Figure 1. A second model was developed in which we postulated that chronic health conditions (e.g., osteoarthritis) contribute to the development of persistent multisite pain in elders, which in turn leads to physical disability (ADL and IADL), psychological disability (depression and anxiety), and mortality. Additionally, both physical and psychological disability are regarded as the consequences of persistent multisite pain, postulated to stem from related processes, though not the same. Potential confounding factors include age, gender, race, education, health factors (BMI, physical activity, MMSE), chronic health conditions, and medications. Primarily, in Specific Aim 1, we examined the persistence and incidence of multisite pain. For Specific Aims #2 and #3, we hypothesized that physical disability (ADL and IADL disability) and psychological disability (depression and anxiety) are the two distinct consequences of persistent multisite pain. In Specific Aim #4, we postulated that elders with persistent multisite pain are at an increased risk of mortality (Figure 2).

CHAPTER II

LITERATURE REVIEW

This chapter will discuss a broad overview of current evidence on persistent multisite pain among the aging population. Also, the statistics to describe the shift in the U.S. aging demographics are presented to elucidate the growing older population. Besides, this literature review will primarily focus on the epidemiology and the consequences of persistent multisite pain on physical and psychological health and mortality in older adults. In this study, the term persistent multisite pain was defined as musculoskeletal pain in two or more (≥2) sites lasting three or more (≥3) months in the previous year and present in the past month. The pain sites include hands/wrists, shoulders, back, chest, hips, knees, and feet (Thapa et al., 2018). Older adults are adults aged 65 years and over. The definition of older adults is based on a range of characteristics such as chronological age, transformations in social roles, and functional abilities. In most developed countries, adults aged 60 or 65 are generally considered elderly. In the U.S., adults aged 65 years and over are eligible to receive Medicare benefits and viewed as older adults, reflecting the retirement age agreed by demographers, employers, and insurers (American Geriatrics Society (AGS), 2009). A literature search was conducted across different databases (CINAHL, Medline, and PubMed) by using a combination of the following search terms: chronic pain, persistent pain, multisite pain,

physical performance, physical function, depression, anxiety, older adults, mortality, and epidemiology.

Demographics and Changing Age Structure

Post-World War II marks a remarkable period in history for the rapid growth in childbirths. Baby-boomers are individuals born between the years 1946 and 1964 (Silva, 2016). In 2011, the first baby-boomer reached 65 years, and more baby boomers are turning 65 years and over, thus marking the beginning of population aging. The term population aging refers to an increase in the proportion of population aged 60 (or 65) years or above (U.S. Census Bureau, 2014). The baby-boomers generation has created a significant shift in the age distribution by changing the size and composition of the total population (U.S. Census Bureau, 2014). It is projected that between 2012-2050, there will be massive growth in the older population in the United States. The estimated prevalence of older adults was 43.1 million in 2012, which is expected to be 83.7 million by 2050 (U.S. Census Bureau, 2014). The steady growth in the health care sector has led to this continual increase in the overall life expectancy (Kochanek, Murphy, Xu, & Arias, 2017; U.S. Census Bureau, 2014). According to the National Center for Health Statistics, the overall life expectancy for the U.S. population in 2016 was 78.6 years. Gender-specific life expectancy for males and females was 78.6 and 81.1, respectively (Kochanek et al., 2017). Population reports have indicated that women's life expectancy has always surpassed men's life expectancy (U.S. Census Bureau, 2014). However, over the next several decades, it is estimated that there will be a rapid increase in men’s life expectancy. For instance, older women constituted 56.4% in 2012; but it is predicted that there will be a slight decrease to 55.1% by 2030, continuing to remain the same until 2050. The decline in older females and the increase in older males

population is more dramatic among those aged 85 years over the next several years, thus narrowing the life expectancy gap between women and men (U.S. Census Bureau, 2014).

Defining Pain

According to the International Association for the Study of Pain, pain is defined as "An unpleasant sensory and emotional experience associated with actual or potential tissue injury or described in terms of such damage" (Institute of Medicine (IOM), 2011). The terms "persistent pain" and "chronic pain" are substitutable but persistent pain is more explicit and is not related to negative outlooks by both providers and the elderly. Therefore, for this study, persistent pain is used. Persistent pain has been recognized as pain that lasts beyond the normal healing time, usually more than three to six months, which may or may not be associated with any distinct disease processes (American Geriatrics Society (AGS), 2009; Merskey & Bogduk, 1994). However, there is no consistency in the definition of persistent pain in the literature. The variations are mainly based on the duration as studies consider persistent pain as pain that lasts longer than one week to three months in the previous year and present in the previous month or weeks (Eggermont et al., 2014; Landi et al., 2009; Leveille et al., 2001; Patel et al., 2013; Scudds & Robertson, 2000). Persistent pain is typically managed but not cured, while for acute pain, efforts are placed on treating the chief cause of the pain (Grichnik & Ferrante, 1991).

Additionally, persistent pain may be a consequence of a systemic risk rather than a local disease process because studies have shown an association between pain and anatomical, chemical, and functional changes of the nervous system (Garland, 2013; Seifert & Maihöfner, 2011; Siddall, 2013). Also, findings from neuroplasticity research have considerably expanded our understanding of the neuroplastic transformations that occur

during pain chronification and pain-related complex interactions with mind and body. Neuroplasticity is the ability of the nervous system and brain to adjust and change according to the body and the surrounding environment throughout a person's lifetime (Siddall, 2013). Thus, the proposed pathophysiology behind the central sensitization is the maladaptive approach of neuroplasticity in individuals with pain, predisposing to a highly-sensitive brain and nervous system, which may lead to or aggravate persistent pain (Pelletier, Higgins, & Bourbonnais, 2015; Siddall, 2013). For the purpose of this study, existing studies on persistent musculoskeletal pain in ≥ 2 sites in older adults were included; however, studies based on cancer-related persistent pain were excluded.

An Overview: Musculoskeletal Pain in Older Adults

Persistent musculoskeletal pain is a common problem in older adults (Brown et al., 2011; Johannes, Le, Zhou, Johnston, & Dworkin, 2010; Patel et al., 2013). The prevalence of persistent pain is highest among older adults, affecting 50%-80% of community-dwelling older adults (Brown et al., 2011; Donald & Foy, 2004; Patel et al., 2013). Persistent pain is more common among older women than older men (Patel et al., 2013; Reyes-Gibby, Aday, & Cleeland, 2002). In a Swedish population of older adults, 63.5% of the women and 36.5% of the men had persistent pain (C. Larsson, Hansson, Sundquist, & Jakobsson, 2017). Likewise, in a Canadian study, among older women and older men, 59.3% and 48.4%, respectively reported having pain (Scudds & Østbye, 2001). The pain prevalence with age is inconsistent, as some studies report increasing pain prevalence with age (Donald & Foy, 2004; Jinks et al., 2002). Whereas others have reported a decrease in pain prevalence (Macfarlane et al., 2009; Thomas et al., 2004), and no difference in the pain prevalence with age (McCarthy et al., 2009; Patel et al., 2013). Due to these inconsistent findings, it is still

unclear whether pain prevalence increases, decreases, or remains constant with advancing age.

Education is inversely related to pain as fewer years of educational attainment was associated with higher pain prevalence (Blyth et al., 2001; Patel et al., 2013; Reyes-Gibby et al., 2002). Likewise, pain prevalence was significantly higher in older adults with a higher body mass index (BMI) (McCarthy et al., 2009). Using the data from the population-based InCHIANTI Study, an epidemiological survey conducted in Italy, Di Iorio et al. (2007) reported that older adults with persistent lower back pain had difficulty performing most of the instrumental activities of daily living compared to those with no back pain. Mood disorders are strongly associated with persistent pain (Eggermont et al., 2014; McCarthy et al., 2009; Patel et al., 2013).

Persistent musculoskeletal pain is a multisite pain problem in older people. Studies have indicated that persistent pain present in one location is associated with a higher likelihood of having pain in another location (Croft et al., 2005; Leveille et al., 1998; Peat et al., 2006; Stubbs et al., 2016). Also, persistent musculoskeletal multisite pain was associated with lower physical performance and earlier disability onset (Eggermont et al., 2014; Patel et al., 2013). Using the MOBILIZE dataset, recently, Thakral and colleagues (2019) examined the relationship between persistent pain quality and disability in older adults. In the study, pain quality was measured using the short version of the McGill Pain questionnaire with 20 pain quality descriptors, which were categorized as follows: sensory, cognitive/affective, and neuropathic. The study revealed that older adults with three persistent categories had a higher risk of developing new or worsening IADL difficulty (RR 2.69, 95%CI 1.34-7.79) and ADL (RR 5.83; 95% CI 1.32-25.85) compared to those with one persistent category after

controlling for potential risk factors and pain severity. Also, the elevated risk for ADL and IADL disability associated with persistent pain quality was higher in elders reporting pain qualities from different categories compared to those reporting pain qualities from a single category. Our study is unique from previous studies and the recent work conducted by Thakral and colleagues (2019), which investigated persistent pain quality and disability in older people. This current study uses a longitudinal pain assessment method to determine the effect of persistent multisite pain and incident multisite pain on physical disability (ADL and IADL), psychological disability (depression and anxiety) in older adults. Also, baseline persistent multisite pain and mortality at 12.4 years was examined.

Persistent Multisite Pain in Older Adults

Persistent musculoskeletal multisite pain is a highly prevalent condition in older adults (Buchman et al., 2010; Croft et al., 2005; Patel et al., 2013). Musculoskeletal pain is a part of the multisite pain problem because pain present in one location is associated with a higher likelihood of having pain in another location in older people (Croft et al., 2005; Leveille et al., 1998; Peat et al., 2006; Stubbs et al., 2016). Also, the probability of developing a new pain site is relatively higher in those with pain, and the risk increases significantly as the number of pain sites increases regardless of the pain location (Eggermont et al., 2014). Persistent multisite musculoskeletal pain is a unique condition as the pathway of persistent multisite pain is not defined by a discrete disease process. Also, persistent multisite pain in older adults shares similar risk factors and pathways to already established geriatric syndromes such as urinary incontinence, fall, frailty, and ADL disability (Thapa et al., 2018). From the National Health and Aging Trends Study (NHATS), a national population-based survey developed to study several aspects of functioning in U.S. older adults, Patel and

colleagues (2013) reported that 40% had persistent multisite pain. Similarly, the analysis of the MOBILIZE Boston Study (MBS), a population-based cohort study of older adults residing in the urban and suburban areas in Boston, was in line with the national NHATS data (40%) (Leveille et al., 2009; Thapa et al., 2018). Using the data from Rush Memory and Aging Project, a longitudinal study of 900 community-dwelling older adults, Buchman et al. (2010) found that 25% of the participants had multisite pain. Likewise, a study conducted in the U.K. found that 43% of older adults had multisite pain (Croft et al., 2005). In another study conducted in the U.K., older adults with persistent musculoskeletal pain enrolled from 10 community sites in the U.K. that included day centers, community activity clubs, and sheltered housing 59% had persistent multisite pain (Stubbs et al., 2016). There was a remarkably higher prevalence of persistent multisite pain compared to single-site pain in the studies. For instance, Buchman et al. (2010) reported that 14% had single-site pain, whereas 25% had multisite pain. According to the NHATS data, 40% had multisite pain, while 13% had single-site pain. In the MOBILIZE Boston Study, Leveille et al. (2009) reported that the prevalence of persistent multisite pain and single-site pain was 40% and 24%, respectively. In another study, among those with persistent musculoskeletal pain, 59% had multisite pain compared to 41% with single-site pain (Stubbs et al., 2016). The variation in the prevalence estimates can be attributed to study design, case definitions, duration of pain, and the method of data collection. For example, in the MOBILIZE Boston Study, a population-based cohort study, participants were observed for a specific time. On the contrary, Stubbs's study collected data only once, and the participants were research volunteers and were not randomly selected. Thus, the results are prone to volunteer bias and can only be generalizable to research volunteers and not to the overall older population (Stubbs et al., 2016).

Gender differences in the prevalence of multisite pain were observed as several studies reported that older women experienced a higher burden of multisite pain than older men (Buchman et al., 2010; Eggermont, Bean, et al., 2009; Keenan et al., 2006). Scudds & Robertson (2000) reported that 66.5% of women had multisite pain compared to 56.1% of men. Using the Framingham Heart Study dataset, a population-based cohort study of adults ≥70 years, Leveille and colleagues (2005) indicated that the likelihood for widespread pain was three times higher in older women compared to men even after for adjusting for known potential confounders (OR 2.99; 95%CI 1.76-5.10). In the same study, the prevalence of multisite pain among women and men was 19.9% and 17.1%, respectively (Leveille et al., 2005). Also, Peat et al. (2006) endorsed that pain in multiple areas was more common in women than in men. Additionally, Croft et al. (2005) reported that proportionally more women had multisite pain than single-site pain. Likewise, in a sample of community-living older disabled women, Leveille et al. (1998) found that 87% of those with persistent severe foot pain had multisite pain (≥2). Similar results were observed in non-disabled community-dwelling older adults (Leveille et al., 2009). In a nationally representative sample of older adults in the United States (U.S.), Patel and colleagues (2013) also demonstrated that among women multisite pain was more prevalent than single-site pain. Essentially, older women are at a higher risk for multisite pain.

The number of pain locations was not associated with age (Buchman et al., 2010; Eggermont, Bean, et al., 2009; Leveille et al., 2009; Patel et al., 2013), similar to the finding from other epidemiological studies where older age was not related to pain. According to the MBS data, the higher prevalence of multisite pain was associated with higher years of education (Eggermont, Bean, et al., 2009; Leveille et al., 2009). This finding contrasts with

the data from Rush Memory and Aging Project, where the number of pain locations was inversely related to education. The discrepancy in the results may be associated with the overall higher proportion of college graduates in the MOBILIZE sample. The other risk factor associated with multisite pain was body mass index. A higher body mass index (BMI) was significantly associated with an increased number of pain sites (Eggermont, Bean, et al., 2009; Leveille et al., 2009; Pan et al., 2017). For instance, obese older adults reported more sites of pain compared to overweight and normal weight (Fowler-Brown et al., 2013). Besides, multisite pain was a significant mediator of the negative impact of obesity on physical function and disability among obese older women (Fowler-Brown et al., 2013).

Furthermore, Leveille and colleagues (2009) revealed that individuals with multisite pain had a greater risk for falls (adj. RR 1.53; 95%CI 1.17-1.99) compared to individuals with single-site pain (adj. RR 1.11; 95% CI 0.84-1.48) and no pain. A recently conducted review by Welsh and colleagues (2019) included 22 and 18 studies for systematic review and meta-analysis, respectively, and demonstrated that multisite pain was associated with an increased risk for falls in older adults. Other poor outcomes associated with persistent multisite pain include sleep impairment (Q. Chen et al., 2011), and higher pain catastrophizing score (Nawai, 2017). Furthermore, ratings of global pain severity increase as the number of pain sites increases (Croft et al., 2005; Leveille et al., 1998; Peat et al., 2006).

Persistent multisite pain increases the risk for depression (Denkinger et al., 2014; Eggermont, Bean, et al., 2009; Patel et al., 2013). Compared to those with single-site pain and no pain, an increased number of pain sites was related to more depressive symptoms (Eggermont et al., 2012; Mänty, Thinggaard, Christensen, & Avlund, 2014). For instance, 12% of older individuals with persistent multisite pain had depressive symptoms compared to

5.7% with single-site pain and 5% with no pain (Eggermont, Bean, et al., 2009). Persistent multisite pain was also associated with an increased risk for the onset of mobility disability (Eggermont et al., 2014). Basically, there is a general consistency among several studies and within various pain syndromes that mobility problems and physical disability are more significant in older individuals with persistent multisite pain compared to those with no pain (Croft et al., 2005; Leveille et al., 2007, 2001; Mottram, Peat, Thomas, Wilkie, & Croft, 2008; Peat et al., 2006). Several cross-sectional studies have demonstrated an association between persistent multisite pain and physical disability in older adults (Croft et al., 2005; Eggermont, Bean, et al., 2009; Keenan et al., 2006; Leveille et al., 2007, 1998, 2001; Patel et al., 2013; Peat et al., 2006; Scudds & Robertson, 2000). Longitudinal studies have shown that persistent multisite pain is associated with physical disability, predicts the incident disability, and progression of disability (Buchman et al., 2010; Eggermont et al., 2014; Leveille et al., 2001; Shah et al., 2011). However, these studies use cross-sectional pain assessment approach, which disregards the duration or persistence of pain.

Physical Disability in Older Adults

Physical disability in older adults is associated with adverse health outcomes, including increased fall risk, health care utilization, hospitalization, nursing home admission, poor quality of life, and early mortality (Fong et al., 2015; Forjaz et al., 2015; Fried & Guralnik, 1997; Gaugler et al., 2007; Guralnik, Fried, & Salive, 1996; Guralnik et al., 1994; Leveille et al., 2007; Majer et al., 2011; Mor et al., 1994; Wu et al., 2016). According to Aging Statistics, among older adults enrolled in Medicare, 29% had difficulty performing one or more self-care activities (ADL). About 12% had difficulty performing only tasks

related to instrumental activities of daily living (IADL) (Federal Interagency Forum on Aging-Related Statistics, 2016).

Physical disability is a significant outcome associated with aging that affects every day functioning and limits an older person's ability to live independently in the community (Manini, 2011; Ostir et al., 1999). Age is a strong factor associated with physical disabilities (Dong, Chang, & Simon, 2014). The effect of age on mobility limitation was demonstrated by Mottram et al. (2008) as increasing age was related to a continual increase in walking difficulty, thus, indicating a clear relationship between age and mobility. Aging is also associated with gradual physical impairment causing loss of adaptive response to stressful stimuli (T. Hadjistavropoulos et al., 2007). Moreover, a functional decline can be insidious in onset and is associated with a significant caregiver burden (Beaton, Mcevoy, & Grimmer, 2015; Blyth & Noguchi, 2017).

Obesity and physical inactivity and are other risk factors associated with disability (Duchowny, Clarke, & Peterson, 2018; J. F. Fries, 1996; McGrath, Robinson-Lane, Peterson, Bailey, & Vincent, 2018; Samper-Ternent & Al Snih, 2012). Other factors associated with disability include poor muscle mass strength and chronic health conditions (Manini, 2011). Muscle strength in older people is strongly related to functional limitations and physical disability (Duchowny et al., 2018; McGrath et al., 2018). Physical disability can also be an outcome of frailty (Vermeulen et al. 2011). Older women are at a greater risk of functional decline than older men (Federal Interagency Forum on Aging-Related Statistics, 2016). Disability is a significant risk factor for mortality as studies have found that elders with disabilities are at a higher risk of dying than non-disabled elders (Majer et al., 2011; Wu et al., 2016). The collective effect of chronic diseases and the physiological changes associated

with aging leads to physical disability in elders (Fong, 2019; Fried & Guralnik, 1997; Landi et al., 2010). Common chronic conditions (e.g., diabetes, heart disease, arthritis) contribute to functional decline in older adults (Fong, 2019). Pain is an important risk factor for functional decline and activity limitations in older adults. On performing the analysis of the Asset and Health Dynamics Among the Oldest Old (AHEAD) data, a longitudinal population-based household survey showed that 20% of the older adults had significant pain-related activity limitations (Reyes-Gibby et al., 2002). Studies also showed that musculoskeletal pain is an independent risk factor for functional decline in elders and the risk increases substantially for those with pain in two or more sites (Eggermont et al., 2014; Patel et al., 2013). Thus, disability is both a risk factor for poor health consequences and an adverse health outcome in older adults. Physical disability can be measured using both self-report questionnaires and performance-based measures in older adults. The well-established Katz ADL and Lawton's IADL self-report measures assess the abilities of an older individual to perform self-care tasks (ADLs) and complex tasks of independent living (IADLs) (Guralnik et al., 1994). A combined measure of self-reported ADL and IADL limitations measures an older person's functional capability to live independently (Fuller-Thomson, Yu, Nuru-Jeter, Guralnik, & Minkler, 2009; Guralnik et al., 1994).

Furthermore, over the past few years, constant growth in the health care sector has led to a continual increase in life expectancy, with an average of 78.6 years for men and 81.1 years for women (Kochanek et al., 2017; U.S. Census Bureau, 2014). The overall rise in life expectancy and decline in mortality over the years has led scientists to develop theories that posit disabled and disability-free years an individual might expect to live due to the improved medical technologies and lifestyle changes. The three significant theories are as follows:

theory of the expansion of morbidity, the theory of compression of morbidity, and the theory of dynamic equilibrium. Gruenberg (1977) proposed the expansion of morbidity theory- the increase in life span would be related to living an increased number of years with chronic illness. Also, the advancement in medical technologies and a decrease in mortality from fatal diseases together will lead to an increase in longevity, but disease and disability will become more common during the later stage of life. Fries (1980) held a favorable view of aging. The theory of compression of morbidity was based on the assumption that rectangularization of the survival curve will continue leading to compression of morbidity. Also, a delay in the onset of chronic disease at the very end of a fixed natural life span is estimated, such that disability is postponed to older ages before death. By compressing the morbidity to a later stage, older adults would be living a longer active life expectancy. Active life expectancy is living free of disability or dependent state (Katz, 1983). Manton (1982) proposed the dynamic equilibrium, which predicted the decrease in mortality would be related to increases in disability; however, the level of severity of the disability will decrease. Furthermore, several studies have tested these theories to estimate the ongoing trends of increasing life expectancy, disability, and disability-free life expectancy (Cai & Lubitz, 2007; Crimmins et al., 2009, 2016; Manton et al., 2008). On analyzing two longitudinal surveys of the U.S. community-dwelling population, Crimmins and colleagues (2009) reported that from 1984 to 2000, adults aged 70 and over adults experienced a significant increase in disability-free life expectancy along with total life expectancy. However, no change in mortality was observed for both IADL disabled and non-disabled older adults. On the other hand, Cai & Lubitz (2007) evaluated the Medicare Current Beneficiary Survey from 1992-2003 and found an increase in total life expectancy and active life expectancy for both men and women but

noticed a decline in life expectancy for those with a severe disability. The increase in life expectancy was seen for all subgroups of populations. However, some groups have gained more life expectancy than others. Freedman et al. (2016) analyzed the datasets that comprised of 1982 and 2004 National Long-Term Survey and the 2011 National Health and Aging Trends Study and reported a growing female disadvantage in the U.S. population. The analysis indicated that older women had a small increase in life expectancy, accompanied by an even smaller delay in disability. Conversely, for older men, the prevalence of disability has decreased, and the life expectancy had increased. Also, older men experienced a longer active life expectancy as the functional limitation was postponed to older ages. Therefore, older women, despite their longer lives, do not live more active years compared to their male counterparts.

On using the National Health Interview Survey to identify the disability-free life expectancy trends from 1970 to 2010, Crimmins et al. (2016) revealed a decrease in disability in older adults compared to younger adults. This shift was similar for both men and women over the entire analysis. However, for the oldest age group (≥85 years), only women experienced marked improvement in terms of disability. Among adults age 65 and over, an increase in disability-free life was higher compared to the increase in disabled life, thus, demonstrating some level of compression of morbidity at age 65 years.

Also, there is a widening of the gender-race gap as there is an uneven increase in disabled life expectancy between the groups. Black men had the highest increase (1.2 years), and the white male had the smallest increase (0.6 years). Among women, white and black had 1.1yrs and 0.7yrs increase in disabled life expectancy, respectively (Solé-Auró, Beltrán-Sánchez, & Crimmins, 2014). Also, Freedman and Spillman (2016) reported that older black

women were the most disadvantaged group because of the modest gain in the number of years of active life and no gain in the expected proportion of active life expectancy compared to other groups. In general, over the past two decades, white men have experienced an increase in disability-free life expectancy, and both black men and women are the most disadvantaged group because they tend to live a longer disabled life.

Socioeconomic status (SES), mainly education, is a significant contributor to overall morbidity and mortality. In general, studies showed that individuals with higher education or income tend to live a considerable proportion of their lives healthy, disability-free, and experience lesser adverse health outcomes than those with fewer years of education and lower socioeconomic status. The educational differences relating to total life expectancy were more significant among men than women (Crimmins & Saito, 2001). Also, black women are the most disadvantaged group. Interestingly, blacks with the highest education have longer total expected lives and expected healthy lives than whites with the same education level. Basically, higher education has led to compression of morbidity, and the expansion of morbidity has been noted with a lower socioeconomic status. In short, socioeconomic status (SES) plays a substantial role in determining the morbidity and mortality (Crimmins & Saito, 2001).

Furthermore, an increase in active life expectancy accompanied by an increase in total life expectancy in accordance with the theory of the compression of morbidity and dynamic equilibrium was evident in some studies (Cai & Lubitz, 2007; Crimmins et al., 2016; Freedman et al., 2016; Manton et al., 2008) and particularly among the White population (Crimmins et al., 2016; Freedman et al., 2016). Therefore, these findings have demonstrated significant disparities based on race, gender, and socio-economic status.

Primarily, over the years, white older men have benefitted the most for a variety of reasons, which includes an increase in life expectancy, compression of morbidity, decrease disabled life, an increase in active life expectancy, and adopting a home-based setting from long term care. There was an increase in life expectancy for the black older adults with a modest delay in experiencing disability and fewer years of disability-free life. Even though the percentage of active life expectancy has slightly increased, it is way behind their white counterparts.

In the next section, persistent multisite pain and physical disability relationship using the self-reported measures will be discussed in detail.

Relationship Between Persistent Multisite Pain and Physical Disability

The growing evidence highlights the debilitating impact of persistent multisite pain on physical disability in the aging population. Cross-sectional studies have demonstrated an association between persistent multisite musculoskeletal pain and physical disability in older adults (Croft et al., 2005; Eggermont, Bean, et al., 2009; Keenan et al., 2006; Leveille et al., 2007, 1998, 2001; Patel et al., 2013; Peat et al., 2006; Scudds & Robertson, 2000) and longitudinal studies have shown that persistent multisite pain is associated with a physical disability and it also predicts the progression of disability in elders (Buchman et al., 2010; Eggermont et al., 2014; Leveille et al., 2001; Shah et al., 2011). Several studies have indicated a higher disability risk in elders with multisite pain than those with no pain. Scudds & Robertson (2000) conducted a cross-sectional study in a sample of community-dwelling elders and used Stanford Health Assessment Questionnaire (HAQ), which included activities from eight different functional categories, such as dressing, grooming, rising, eating, gripping, etc. In the study, individuals having more pain sites were more likely to have physical disability. For instance, the number of pain sites increased the risk for physical

disability by 14% (OR 1.14; 95% CI 1.06-1.22) for each one-unit increase in the number of pain locations on the body diagram. In a prospective cohort study of the very old and frail elderly population with a mean age of 84.3 years, Landi and colleagues (2009) reported that the risk of incident disability was 2.34 times higher for individuals with multisite pain (unadj. OR 2.34; 95% CI 1.11-4.94) compared to single-site pain (unadj OR1.04; CI 0.27-4.02) and no daily pain during the two-year follow-up. Using the data from Rush Memory and Aging Project, a longitudinal study of non-disabled elders residing in the community, even after controlling for age, sex, and education, the odds of developing ADL and IADL disability increased by 20% (HR 1.20, 95% CI 1.09-1.31) and 10% (HR 1.10, 95% CI 1.01- 1.20) respectively for every additional pain site at a 5.6 years follow-up (Buchman et al., 2010).

Using the Women's Health and Aging Study (WHAS) data, a prospective population-based cohort study of 1002 community-dwelling older disabled women, Leveille et al. (2001) reported that older disabled women with widespread pain at baseline had an almost three-fold increased risk for having a lot of difficulty with ADLs (OR 2.77; CI 1.45-5.29) and walking 2 to 3 blocks (OR 2.58; CI 1.35-4.91) and an almost 4-fold increase in difficulty for lifting 10 lbs. (OR 3.60; CI 1.69.-7.66) compared to women with no pain or mild pain. At the 3-year follow-up, among women with no severe difficulty performing or inability to perform tasks at baseline, those with widespread pain were almost twice as likely to develop a lot of difficulty in performing ADLs, walking, and lifting 10 lbs. Similarly, another study indicated that individuals with persistent multisite pain had a higher risk of developing disability than individuals with single-site pain and no pain at the 18-month follow-up (Eggermont et al., 2014). Using the MOBILIZE dataset, Eggermont et al. (2014) reported that elders with multisite pain had more than the three-fold increased risk for ADL disability (RR 3.63; 95%

CI 1.78-7.41) and two-fold increased risk for IADL disability (RR 2.14; 95% CI 1.37-3.34) compared to those with no pain. However, the relationship between single-site pain and physical disability was not statistically significant. In a sample of nonagenarians, older individuals with multisite pain were at an increased risk of developing severe disability (Mänty et al., 2014).

Furthermore, findings from several studies revealed a graded effect, meaning every additional painful area was associated with increased site-specific disability and site-specific pain severity (Croft et al., 2005; Leveille et al., 1998; Peat et al., 2006; Keenan et al., 2006, Patel et al., 2013; Scudds & Robertson, 2000). Persistent multisite pain has a robust effect on physical disability. It is possible to argue that multisite pain could be a more crucial clinical marker than single-site pain.

However, there were variations across these studies in terms of the definition of persistent pain, mainly the duration of pain, as studies consider persistent pain as pain that lasts anywhere from more than one week to more than three months (Eggermont et al., 2014; Landi et al., 2009; Leveille et al., 2001; Patel et al., 2013). There were also differences in the physical function measures utilized in the studies. For example, physical function was measured by Western Ontario and McMaster Universities Arthritis Index (WOMAC), Stanford Health Assessment Questionnaire (HAQ), Katz ADL, Lawton's IADL, Duke Older Americans ADL. This indicates that there is a lack of consistency in the use of instruments across the studies. Also, the method of data collection varied across the studies (survey, telephone interview, face-to-face interview), along with the study populations, follow-up period, method of analysis, adjustment for confounding factors, and the definition of

multisite pain. Besides, the studies use a cross-sectional pain assessment approach which overlooks the persistence of pain.

Moreover, it is worth pointing out that in the study, Eggermont et al. (2014) used the MOBILIZE Boston Study dataset (MBS) to understand the pain-disability linkage which was limited to understanding the effects of chronic pain on the development of disability, using the baseline and 18-month follow-up dataset. However, in the current study, we used the six-year follow-up data, which is now available from the MOBILIZE Boston Study along with the baseline and the18-month follow-up. The longitudinal assessment of pain and data from three-time points, baseline, 18-month, and six-year was used to examine the longitudinal effect of pain on physical and psychological disability at the 18 month and 6-year follow-up. We also determined the differences in the risk for ADL and IADL disability, depression, and anxiety among those with persistence of multisite pain compared to those with incident multisite pain, single-site pain, and no pain. Hence, this is the first population-based study to use a longitudinally assessed pain and examine the impact of persistence of multisite pain on physical disability in community-dwelling older adults at the 18month and 6-year follow-up.

Physical health and mental health are inter-related. Therefore, this study examined both the physical and psychological consequences of persistent pain in community-dwelling older adults. In the next section, the relationship between persistent multisite pain and depression and anxiety will be discussed.

Relationship Between Persistent Multisite Pain and Psychological Disability

Depression. Because of the devastating consequences, understanding late-life depression is important. It is also highly prevalent in the older population (Djernes, 2006; Luppa et al., 2012; van't Veer-Tazelaar et al., 2008). Depression affects 13% of young-old

adults (65-74 years) and 19% of old-old adults (>85 years) (Federal Interagency Forum on Aging-Related Statistics, 2016). Depression significantly increases the risk of physical disability, poor quality of life, morbidity, and mortality (Blazer, 2003; Chapman & Perry, 2008; DaSilva, Geenen, & Jacobs, 2018; Djernes, 2006; Hamer, Bates, & Mishra, 2011; Rodda, Walker, & Carter, 2011).

The association between age and depression is unclear as previous epidemiologic studies that examined the trends of age-related depression revealed inconsistent conclusions. For instance, Solhaug and colleagues (2012) conducted a prospective cohort study and reported that the prevalence of depression increased with age. On using the data from PIKO (Preventive Intervention Frail Elderly) study that used health surveys to collect data from 2850 community-dwelling older adults aged ≥75 years, Van't Veer-Tazelaar et al. (2008) reported that the depression prevalence increased with age. Luppa and colleagues (2012) conducted a systematic review and meta-analysis of 24 studies on adults >75 years and concluded that the depression is common in the latest life and increases significantly in the oldest-old group (>85years). Other studies demonstrated a decrease in the prevalence of depression with the increasing age (Hasin, Goodwin, Stinson, & Grant, 2005; Rubio et al., 2011). These discrepancies are likely attributable to the methodological reasons such as variability in sample characteristics, utilization of different diagnostic approaches to identify depression (self-reported versus structured interview-based diagnosis), study design, and confounding variables.

Depression in older age is relatively different than at a younger age. Compared to younger adults, depressed older adults are more likely to present somatic symptoms, cognitive changes, loss of interest in activities, and are less likely to exhibit affective

symptoms (Fiske, Wetherell, & Gatz, 2009). Also, increasing age is related to decreased recovery from depression (Solhaug et al., 2012). Additionally, the relapse rates for depression are higher in older adults compared to middle or younger adults. Besides, remission rates of depression are somewhat different in late life than midlife (Mitchell & Subramaniam, 2005). Moreover, depressed older adults who attempt suicide are at a higher risk of completing suicide than depressed younger adults (Manthorpe & Iliffe, 2010). Essentially, depression in older adults has different presentation and requirements than younger adults (Gallo, Anthony, & Muthen, 1994; Rodda et al., 2011).

The manifestation of depression in older adults is related to biological factors (e.g., genetic), psychological factors (e.g., personality), and social influences (e.g., social support) (Laird, Krause, Funes, & Lavretsky, 2019). Women, in general, have a higher prevalence of depression than men, well into late life. Studies demonstrate that older women are at an increased risk for depression compared to older men (Denkinger et al., 2014; Djernes, 2006; Eggermont et al., 2012; Hasin et al., 2005; Haynie, Berg, Johansson, Gatz, & Zarit, 2001). Luppa and colleagues (2012) examined the gender-specific prevalence of depression in the later stage of life (>75 years). In the study, the prevalence estimates of major depression for older women ranged between 4.0%-10.3% compared to 2.8%-6.9% for older men.

Socioeconomic characteristics such as low income and fewer years of education are significant risk factors for depression (Fiske et al., 2009; Rubio et al., 2011). Other factors associated with depression were being unmarried and living alone (Djernes, 2006; Schulman, Gairola, Kuder, & McCulloch, 2002). Social isolation increased the risk of depression while having supportive social networks decreased the depression risk (Djernes, 2006; Schulman et al., 2002). Genetics is a stronger risk factor for depression in the early lifespan than during

the older age (Fiske et al., 2009; Kendler, Gatz, Gardner, & Pedersen, 2006). Among the elderly, non-genetic biological risk factors play a significant role in the manifestation of depression, partly because age-related changes make depression more common during the later stage of life (Fiske et al., 2009).

Depression is both an outcome and a risk factor for several chronic health conditions (Krishnan et al., 2002). Depression is highly associated with other disease conditions such as heart disease, cancer, musculoskeletal disorder, and cerebrovascular disease (Eggermont et al., 2012; Krishnan et al., 2002; National Institute of Mental Health, 2016; Valvanne, Juva, & Erkinjuntti, 1996). Also, cognitive impairment and dementia were commonly observed among depressed older adults (Djernes, 2006; Fiske et al., 2009). Additionally, Eggermont et al. (2012) reported that depressive symptoms were significantly related to reduced cognitive function, indicated by the lower Mini-Mental Status Exam (MMSE) score. Similarly, Valvanne et al. (1996) reported that the risk of major depression was significantly higher in those with dementia (OR=4.9;95%CI 2.2-11.2).

Furthermore, depression increases the risk of physical disability (Cole & Dendukuri, 2003; Djernes, 2006; Yang & George, 2005). Using the MOBILIZE Boston study dataset, Eggermont and colleagues (2012) pointed out that older adults with an increased number of depressive symptoms were more likely to have slower gait speed and poorer balance. Age and disease-related functional impairment may also lead to the development of depressive symptoms in elderly (Yang & George, 2005). Depression and disability are interrelated and can have a reciprocal effect (Y. Lee & Park, 2008; Lenze et al., 2001, 2005). They share a bidirectional relationship and are a significant risk factor for one another. Depression and persistent pain are highly prevalent comorbid conditions, existing simultaneously in the older

adults (Herr & Mobily, 1992; Onubogu, 2014; Tsai, Tak, Moore, & Palencia, 2003; Zis et al., 2017). It is estimated that 13% of the older population experience both pain and depression concurrently (Zis et al., 2017). The persistent subclinical neuroinflammation is the common pathogenic factor between persistent pain and depression (Zis et al., 2017). Studies indicate that elders with an increased number of pain sites have higher depressive symptoms compared to individuals with single-site pain and no pain (Eggermont et al., 2012; Mänty et al., 2014). For instance, among those with persistent multisite pain, 12% had depressive symptoms compared to 5.7% of those with single-site pain and 5% of those with no pain (Eggermont, Bean, et al., 2009). Likewise, in another study, Denkinger and colleagues (2014) indicated that multisite pain was strongly associated with depression even when adjusted for age and sex (OR1.20; 95%CI 1.11-1.31) compared to those with no pain.

Additionally, studies have demonstrated an interacting effect of gender on the pain and depression linkage among older people. For example, Onder and colleagues (2006) found that as the number of pain sites increased, the relationship between pain and depression became further distinct, but was evident only among women. Similarly, Leveille et al. (2005) revealed that a higher number of pain-sites was associated with greater depressive symptoms. However, this association was significant only for women and not for men. Therefore, the findings signify that older women with multisite pain are at an increased risk for depression compared to their male counterparts. Besides, pain also has an adverse impact on psychiatric treatment outcomes, often leading to treatment resistance (Gerrits et al., 2012).

Because both pain and depression share similar pathophysiological pathways, they cannot be regarded as two separate dimensions. Treatment should be focused on both the

conditions to improve pain, depression, and function in elders. Depression also increases the risk of mortality in older people (DaSilva et al., 2018; Penninx, Geerlings, & Deeg, 1999). In a recent study, DaSilva et al. (2018) concluded that depression played a strong mediating role in the pain-mortality linkage. Despite the higher prevalence and its devastating consequences, the relationship between persistent multisite pain and depression is not a well-studied area, particularly in the older population. Our study is among the first population-based studies to use a longitudinal pain assessment method and examine the relationship between persistence of multisite pain and depression in community-dwelling older adults. Considering the older population's existing and predicted growth, addressing the issues related to mental health is essential to improve function and reduce the mortality risk.

Anxiety. Anxiety disorders are the most common mental health problem (Bryant et al., 2013) and highly prevalent in the elderly population (Boehlen et al., 2020; Canuto et al., 2018; Koychev & Ebmeier, 2016; Mehta et al., 2003; Porensky et al., 2009). Epidemiological studies on community samples showed a discrepancy in the prevalence of anxiety in the older population. For instance, a study conducted in France reported that 14% of older adults had an anxiety disorder (Ritchie et al., 2004). In a study from Germany, 6.6% fulfilled the criteria for anxiety disorder (Heun, Papassotiropoulos, & Ptok, 2000). Mehta et al. (2003) conducted a study in the U.S. using the data from the Health Aging and Body Composition (Health ABC) study, a population-based cohort study that consisted of more than 3,000 community-dwelling older adults aged 70-79 years, and reported that 15% of older adults had symptoms of anxiety. On reviewing 19 studies for a systematic review, Bryant and colleagues (2008) revealed that anxiety symptoms are relatively higher than an anxiety disorder. The anxiety disorder ranged from 1.2% to 15%, and the anxiety symptoms ranged from 15% to 52%

among community-residing older adults (Bryant, Jackson, & Ames, 2008). The wide variation in the prevalence estimate within these studies can be attributed to the definition of anxiety symptom and anxiety disorder, different countries, sampling technique, assessment instrument, and differences in the age cutoffs applied in the studies.

Studies indicate that the prevalence of anxiety symptoms is almost twice as common as depressive symptoms in older adults (Bryant et al., 2008; Reynolds, Pietrzak, El-Gabalawy, Mackenzie, & Sareen, 2015). To study the chronology of depressive and anxiety disorders, King-Kallimanis (2009) used the data from the National Comorbidity Study-Replication, a nationally representative sample of 9282 Americans comprising adults aged 18 years and older. Separate analyses were conducted based on the age-group. In the study, anxiety disorder preceded depressive disorder in older people. For example, 77.6% (52) of older adults experienced anxiety disorder prior to depression compared to 7.5% (5) of older adults who reported that depressive disorder preceded anxiety disorder, and 14.9% (10) of older individuals reported that both anxiety and depression existed at the same time (King-Kallimanis et al., 2009). Also, on examining the prevalence and correlation of anxiety symptoms in the absence of depression using the Hopkins Symptom Checklist in adults between 70 -79 years, Mehta et al. (2003) found that anxiety symptoms were present in 43% of older adults without depression and 15% of those with depression. Despite anxiety disorder preceding depressive disorder, anxiety in older adults often goes undiagnosed and is typically detected in conjunction with depression (Koychev & Ebmeier, 2016). Anxiety disorders are classified as generalized anxiety disorder (GAD), panic disorder, and different phobia-related disorders. Among the anxiety disorders, GAD is considered the commonest in older adults which is described by excessive, uncontrollable worrying of health, finance, and

relationship which lasts for more than six months period (Bryant et al., 2008; Koychev & Ebmeier, 2016; Porensky et al., 2009; Stein & Sareen, 2015). Anxiety-related symptoms can also impair the outcomes of the antidepressant treatment and contribute to the recurrence of depression in elders (Flint, 2005). Moreover, the literature demonstrated the co-occurrence of anxiety and depression as depressed older people concurrently report anxiety-related symptoms or anxiety disorders (Flint, 2005; King-Kallimanis et al., 2009; Lenze, Mulsant, Shear, Houck, & Reynolds, 2006).

In terms of gender, older women are more likely to experience anxiety than older men (Boehlen et al., 2020; Grenier et al., 2019; Wolitzky-Taylor, Castriotta, Lenze, Stanley, & Craske, 2010). In a population-based cohort study, Mehta et al. (2003) found that the likelihood of having anxiety symptoms among white women was 70% greater than white men (OR 1.7; 95%CI 1.2-2.2). Black women had 30% greater odds of having anxiety symptoms than white men (OR 1.3; 95% 95%CI 0.9-1.8). However, the likelihood of having anxiety symptoms was similar for black and white men (OR 1.0; CI 0.6-1.4). Thus, findings indicate that older women, primarily white older women, are at a higher risk of developing anxiety. Sociodemographic factors such as lower education and being single, divorced or separated also increased the risk for anxiety disorder in older people (Wolitzky-Taylor et al., 2010).

Other risk factors associated with anxiety were disease conditions such as migraine, arthritis, back pain, peptic ulcer disease, hyperthyroidism, asthma, irritable bowel, rheumatoid arthritis, diabetes, coronary heart disease, and chronic obstructive pulmonary disease (Culpepper, 2009). In a general population study, McWilliams, Goodwin, & Cox (2004) analyzed a nationally representative sample of 3032 adults aged between 25 to 74

years and reported that anxiety disorders such as GAD and panic attacks were more common in individuals with arthritis, migraine, or back pain compared to those without any of these painful conditions. Likewise, individuals with an anxiety disorder are at an increased risk of having musculoskeletal pain, gastrointestinal pain, and cardiorespiratory pain compared to those without anxiety disorders (De Heer et al., 2014). Several other risk factors associated with anxiety included multimorbidity, stressful life events, adverse experience in childhood, poor health, and physical disability (Wolitzky-Taylor et al., 2010). Additionally, Clifford and colleagues (2015) identified similar predisposing factors but added lifestyle factors such as smoking and alcoholism and lack of social support to the list of risk factors for anxiety in older adults.

Anxiety in older adults is associated with adverse health outcomes such as physical disability and poor quality of life. In a cross-sectional study, 164 older adults with a diagnosis of GAD based on the Structural Clinical Interview for DSM-IV Axis I Disorders (SCID), and 42 older adults with no lifetime history of psychiatric disorder were recruited from primary care and mental health setting. In the study, compared to the non-anxious participants, older adults with GAD were more disabled, had decreased quality of life, and increased healthcare utilization (Porensky et al., 2009). In another cross-sectional study which was conducted on the general population, De Heer et al. (2014) used the data from Netherlands Study of Depression and Anxiety (NESDA) and reported that having anxiety disorder was strongly associated with musculoskeletal pain (OR 2.29; 95%CI- 1.49-3.51) compared to those with no depressive symptoms and/or anxiety disorder when adjusted for age, gender, education, partner status, use of antidepressant, psychotropic drugs, chronic conditions, and the number of depressive episodes (De Heer et al., 2014). Moreover,

comorbid depression and anxiety increased the odds of having musculoskeletal pain by 3.88 (95%CI 2.33-6.47) (De Heer et al., 2014).

Pain literature has primarily focused on the pain-depression relationship than pain-anxiety linkage, specifically among older people. On extensive review, only one cross-sectional study from Brazil has examined the pain-anxiety relationship in the elderly population (Santos, Cendoroglo, & Santos, 2017). In the study, 41 older adults with a mean age of 85.7 years were included, and persistent pain was significantly correlated with the anxiety trait (r=31.5%; p=0.048). Due to lack of studies in older adults, the evidence on pain-anxiety relationship is based mainly on the general population (Gerrits et al., 2012; McWilliams, Cox, & Enns, 2003; McWilliams et al., 2004), primary care setting (Olfson & Gameroff, 2007), community, general practice, and mental health care setting (De Heer et al., 2014). Asmundson & Katz (2009) reviewed the co-occurrence of anxiety disorder and persistent pain from eight studies and reported that 20% to 70% of patients with panic disorder had persistent pain. McWilliams et al. (2004) used the Midlife Development in the United States Survey (MIDUS), a nationally representative sample of adults 25-74 years. In the study, the associations between the painful conditions such as back pain and arthritis and the anxiety disorders (GAD and panic attack) were significantly higher than individuals with painful conditions and depression. In another study, Gerrits et al. (2012) used the Netherlands Study of Depression and Anxiety (NESDA) data, an 8-year cohort study consisting of 1209 participants. In the study, individuals with joint pain, a higher number of pain sites, and persistent pain were associated with a poorer course of an anxiety disorder at the 2-year follow-up. Anxiety disorder also increased the odds of highly disabling and severely limiting pain (OR4.84; 95%CI 2.22-10.57) compared to those with no depressive and/or anxiety

disorder when adjusted for potential confounding factors (De Heer et al., 2014). Additionally, Sareen et al. (2005) reported that anxiety disorders such as PTSD (OR 2.52; 95%CI 1.67-8.81) and panic attacks (OR 2.00; 95%CI 1.22-3.28) were significantly associated with any bone and joint disease even after adjusting for age, gender, socioeconomic status, and mental disorder.

Likewise, Olfson &Gameroff (2007) found that patients with anxiety (GAD) had significantly higher levels of pain interference ratings than patients without anxiety (GAD). Besides, persistent severe pain was significantly related to having chronic depression, anxiety disorder, or both depression and anxiety disorder (Gerrits et al., 2012). In terms of healthcare expenditure, patients with anxiety disorder and pain have increased healthcare costs than those without anxiety disorders (Olfson & Gameroff, 2007). Besides, the presence of both depression and anxiety with persistent pain is also associated with higher healthcare utilization and medical services (Gerrits et al., 2012). However, a major drawback of these studies is that findings cannot be generalized to the older population.

Diagnosing and managing anxiety in older adults can be challenging due to the coexistence of depressive disorder. The above findings have clearly demonstrated a co-occurring and interrelated linkage between persistent pain and anxiety (Asmundson & Katz, 2009; Grachev, Fredrickson, & Apkarian, 2002; H. D. Hadjistavropoulos & Lachapelle, 2000). The shared underlying pathophysiology may be the reason for a strong association between pain and anxiety. Pain may trigger anxiety, which, in turn, makes an individual more sensitive towards pain, leading to the persistence of pain experience (Vlaeyen & Linton, 2000). Moreover, anxiety disorders share similar pathophysiological pathways as pain, facilitating the central modulation of the pain response in several areas of the brain (De Heer

et al., 2014). These different regions in the brain perform a vital role in the processing of negative affect and chronic pain. The amygdala along with insular cortex plays an essential part in the pathophysiology of anxiety by coordinating the automatic threat response, integrating the emotions from sensory features, context, and learning via cortical and subcortical inputs as well as through their connections with other areas of the brain (Holzschneider & Mulert, 2011). Along with the hypothalamus, different regions of the brain, such as periaqueductal gray (PAG) and anterior cingulate cortex (ACC), are involved in anxiety (Burston et al., 2019; Damsa, Kosel, & Moussally, 2009; Grachev et al., 2002).

Furthermore, both periaqueductal gray (PAG) and anterior cingulate cortex (ACC) are found to be activated in individuals with osteoarthritis (Burston et al., 2019). Also, anxiety induces stress hormones and elevates the production of pro-inflammatory cytokines (Maes et al., 1998), which may increase the pain experience (De Heer et al., 2014; C. M. B. de Oliveira et al., 2011). Basically, anxiety disorders and persistent pain share similar underlying behavioral and cognitive processes, as observed by increased alertness towards any threat and avoidance of physical exertion (Asmundson & Katz, 2009).

It is possible to conclude that anxiety symptoms and disorders, independent of depression, are common in individuals with pain. Yet, the coexisting nature of pain-anxiety is not explored, specifically in older adults. Due to the lack of studies among older adults, studies from the general population were included to generate evidence on the pain-anxiety linkage; however, it cannot be generalized to older adults. Despite being treatable, anxiety disorders are often underrecognized and undertreated and are mostly detected while treating depression in older people (Grenier et al., 2019; Koychev & Ebmeier, 2016). Anxiety may

act as a precursor for depression in older adults; therefore, better screening and early treatment can help in preventing depression.

More research is needed to untangle the pain-anxiety relationship in older adults. Our study will add to the body of knowledge and address the gap by studying the pain and anxiety linkage in elders. This is the first population-based study to demonstrate the relationship between longitudinally assessed pain and psychological disability in a population of community-dwelling older adults at the 18-month and six-year follow-up.

Relationship Between Persistent Multisite Pain and Mortality

In recent years there has been a growing interest among researchers in understanding the pain-mortality relationship. Epidemiological studies assessing the mortality risk in older people with pain have demonstrated conflicting results (Docking et al., 2015; Jordan & Croft, 2010; Kåreholt & Brattberg, 1998; Shega et al., 2013; D. Smith, Wilkie, Croft, & McBeth, 2018; D. Smith, Wilkie, Croft, Parmar, & McBeth, 2018). On analyzing the longest and largest population-based prospective cohort study on adults >75 , Docking et al. (2015) revealed that elders with disabling back pain had an increased risk of mortality compared to those with no back pain (HR1.4; 95% CI 1.1-1.8). The association remained significant even after adjusting for sociodemographic characteristics (HR1.5; 95% CI 1.2-1.9). However, on further adjustment for potential disease conditions the relationship remained of borderline significance (HR1.3; 95% CI 0.99-1.7).

In a cohort study consisting of participants ≥ 50 years, identified from general practices, contributed to the General Practice Research Database (GPRD), Jordan & Croft (2010) investigated mortality rates in the year following consultation for musculoskeletal problems. In the study, participants with one recorded consultation for a musculoskeletal

problem in the year 1996, with no history of musculoskeletal consultation two years prior to their first consultation, were enrolled. The risk of dying in the first year follow-up was higher for individuals with hip pain (HR2.36; 95% CI 1.99-2.77), back pain (HR2.07; 95% CI 1.87-2.28), and shoulder pain (HR1.42; 95% CI 1.17-1.71) compared to individuals with no record of musculoskeletal consultation at any time during the calendar years 1994-1996, after adjusting for age and sex. The likelihood of dying in the ten-year follow-up for individuals with hip pain was 1.32 (HR1.32; 95% CI 1.22-1.43), and back pain was 1.17 (HR1.17; 95% CI 1.12-1.22). In another study consisting of Swedish nationally representative samples of adults aged >53 years, pain in the back, hip, and shoulders was not associated with mortality. However, pain in the chest and extremities was associated with mortality (Kåreholt & Brattberg, 1998).

In a recent study, D. Smith, Wilkie, Croft, and McBeth (2018) used the English Longitudinal Study of Ageing (ELSA) and the North Staffordshire Osteoarthritis Project (NorStOP), both population-based cohort studies of adults ≥ 50 years. In the study, there was no association between mortality and widespread pain based on the ACR criteria (MRR 1.07; 95%CI 0.92-1.23) or widespread pain that did not meet the ACR criteria (MRR 1.06; 95%CI 0.94-1.19). However, pain interference was associated with an increased risk of mortality. For instance, the mortality rate ratio (MRR) for participants who were often troubled with pain increased by 29% (MRR 1.29; 95%CI 1.12-1.49). For those reporting quite a bit of pain interference, the mortality risk increased by 38% (MRR 1.38 95% CI 1.20-1.59), and extreme pain interference had an 88% increased risk for mortality (MRR 1.88; 95%CI 1.54-2.29). Conversely, using the Canadian Study of Health and Aging (CSHA) data, Shega et al. (2013)

reported that older people with moderate or severe pain were had a lower mortality risk compared to those with no or very mild pain (HR 0.85; 95%CI 0.75-0.96).

From the English Longitudinal Study of Ageing (ELSA) and the North Staffordshire Osteoarthritis Project (NorStOP), population-based cohort studies of adults >50 years, D. Smith, Wilkie, Croft, Parmar, et al. (2018) revealed that the pain-mortality relationship was strongly mediated by physical function and lifestyle factors. For instance, functional limitation increased the mortality risk by 31% (HR1.31; CI 1.20-1.39), and symptoms that prevented walking quarter of a mile elevated the mortality risk by 45% (HR1.45; CI 1.35-1.58). The mortality risk was increased by 32% and 14% for those who reported poor self-rated health (HR1.32; CI1.23-1.41) and physical inactivity (HR1.14; CI 1.10-1.20).

Gender differences were observed in the studies. Older women with disabling back pain had a higher risk of premature mortality (HR 1.4; 95%CI1.1-1.9) than older women with no back pain when adjusted for sociodemographic characteristics. However, no statistically significant association was found for men (HR1.0; 95%CI0.5-1.9) (Docking et al., 2015). Shega et al. (2013) reported that over the five years, the likelihood of dying was lower for older women with pain than older women without any pain (HR0.40; 95%CI 0.33-0.47). However, the pain-mortality relationship was not significant in men (HR1.00; 95%CI 0.84-1.19).

Due to fewer studies on pain-mortality linkage among the elderly population, studies from the general population were included to better understand the pain-mortality relationship. In the next section, the pain-mortality relationship in the general population is discussed.

Pain-mortality relationship is controversial among the general population. Findings from systematic review and meta-analysis have also revealed some heterogeneity in the pain-mortality linkage (Macfarlane, Barnish, & Jones, 2017; D. Smith, Wilkie, Uthman, Jordan, & McBeth, 2014). In a systematic review and meta-analysis, D. Smith et al. (2014) included ten studies and concluded that the relationship was between chronic pain and mortality was modest but non-significant. In a recent meta-analysis, Macfarlane et al. (2017) studied six observational studies and reported that chronic widespread pain was associated with excess mortality. In the same study, Macfarlane et al. (2017) also conducted a separate study using the data from U.K. Biobank, which consisted of 7130 individuals with chronic widespread pain and 281718 individuals with no chronic pain and revealed that individuals with chronic widespread pain experienced higher mortality risk compared to those with no chronic pain. However, on adjusting for lifestyle factors the excess mortality risk was reduced. Andersson (2009) conducted a study in a Swedish population of adults aged 25-74 years and reported that the persistent widespread pain was not significantly associated with mortality for the older age group (age 65-74 years). However, for the younger age group (age 26-64 years), the mortality risk was more than twice for individuals with widespread pain than those with no pain (adj.HR2.65, 95% CI: 1.45-4.84). Likewise, Ashberg et al. (2016) found no association between mortality and persistent musculoskeletal pain. Besides, widespread pain may be a marker of an underlying disease (Andersson, 2009; Macfarlane, McBeth, & Silman, Alan, 2001; McBeth, Silman, & Macfarlane, 2003; McBeth et al., 2009)

Several general population studies have indicated that lifestyle factors mediate the pain-mortality relationship. Andersson (2009) reported that individuals with widespread chronic pain had an increased risk for mortality (HR 1.95; CI: 1.26-3.03) compared to those

without any chronic pain. However, on adjusting for lifestyle factors such as smoking, physical activity, BMI, stress, and insomnia, the relationship no longer remained significant (HR 1.09; CI: 0.62-1.90). In the study, the excess mortality risk was significantly explained by health behaviors such as current smoking (HR1.55; 95% CI1.02-2.36) and low physical activity (HR1.66; 95% CI: 1.14-2.42). Likewise, Macfarlane et al. (2017) demonstrated that adjusting for lifestyle factors substantially decreased the excessive risk noted in individuals with chronic widespread pain. Harmful lifestyle factors such as high BMI, low physical activity, smoking, and poor diet quality mediated the relationship between pain and mortality. It is evident that lifestyle factors and health conditions play a critical role in determining the pain and mortality relationship.

Also, musculoskeletal pain may be associated with increased mortality risk, but this relationship is still ambiguous. The variations in the findings across these studies may be attributed to inconsistent definitions of pain, differences in the study population, sampling frame, adjustment of confounding variables, follow-up duration, and data analysis methods. These studies conducted on the general population, in which older individuals are sampled in the proportion that they appear in that particular population, may not be very insightful in understanding the pain-mortality relationship in older adults. Clearly, studies on persistent pain and mortality in the older population are inadequate, and more studies are needed to elucidate pain-mortality linkage in older population. Therefore, we intend to test the hypothesis that older people with multisite pain are at increased mortality risk compared to those with no pain. Ours is the first population-based study to examine persistent multisite pain and mortality relationship in community-dwelling older adults at 12.4 years.

Pathway underlying pain-mortality relationship in older adults. Although the underlying mechanism linking pain with mortality is not fully understood. It is possible that chronic conditions (e.g., osteoarthritis) may contribute to persistent musculoskeletal multisite pain, which in turn could lead to disability in older adults (Buchman et al., 2010; Eggermont et al., 2014; Shah et al., 2011). Physical disability may mediate the pain-mortality relationship in older adults (Wu et al., 2016). A second possible explanation is a persistent pain as a significant barrier to physical activity (Koltyn, 2002; Taylor, 2014). Older people with persistent pain may be less physically active because of fear of falling or reinjury (Griffin, Harmon, & Kennedy, 2012; C. Larsson, Ekvall Hansson, Sundquist, & Jakobsson, 2016; Martin, Hadjistavropoulos, & McCreary, 2005; Stubbs et al., 2013). Several studies have demonstrated a lower level of physical activity in elders with persistent pain than those with no pain (Herbolsheimer et al., 2016; Holden, Nicholls, Young, Hay, & Foster, 2015; Kaplan, Huguet, Newsom, & McFarland, 2003; A. Larsson et al., 2015). Reduced physical activity is often explained by the fear-avoidance model of pain (Leeuw et al., 2007; Vlaeyen & Linton, 2000). Limiting physical activity leads to a cycle of restriction, decreased participation in social events, and reduced physical capability (Mackichan, Adamson, & Gooberman-Hill, 2013). Physical inactivity contributes to physical deconditioning and functional decline, leading to impaired physical performance and disability (Manini & Pahor, 2009). Functional disability, in turn, predicts mortality in elders (Majer et al., 2011; Wu et al., 2016). The third explanation is that older people with pain tend to restrict their joint movement as a result of reflex inhibition of skeletal muscles, which leads to muscle weakness (Young, 1993). Together with impaired muscle strength, decreased physical disability, and negative lifestyle factors may increase the mortality risk in elders with pain.

CHAPTER III

STUDY DESIGN AND METHODS

This chapter aims to 1) describe the data source, research design, and study participants 2) explain the methods of data collection 3) explain the statistical analysis approach applied in the study.

Research Methodology

Data source. The MOBILIZE Boston Study (MBS), which stands for Maintenance of Balance, Independent Living, Intellect, and Zest, was funded by the National Institute of Aging (NIA). MBS is a population-based prospective cohort study of older adults living in the Boston area that focused on novel risk factors for falls. Baseline assessments took place from 2005-2008. Data were collected at the three-time points; baseline, 18-month, and at six-year follow-up.

Research design. The study estimated the prevalence and incidence of new and persistent multisite pain. The longitudinal pain assessment method was used to generate the pain distribution variable categorized as incident multisite pain, persistent multisite pain, single-site pain, and no pain at 18-months and 6-year follow-up. The study examined the association between persistent multisite pain and physical disability and psychological

disability. Also, the relationship between baseline persistent multisite pain and mortality was examined at 12.4 and 9.8 years.

Study participants. This study is an analysis of the MOBILIZE Boston study. In MBS I, a total of 765 community-dwelling participants were enrolled using door-to-door population-based recruitment approach, from 2005-2008. Participants who were 70 years and over and lived in the urban and suburban area within a 5-mile radius of the study center at Hebrew Senior Life in Boston, were randomly selected for recruitment using town lists. A detailed description on the design, recruitment and methods was published previously elsewhere (Leveille et al., 2008). The inclusion criteria were age 70 years or over; having the ability to understand and speak in English; planning to be in the area for two years; having the ability to walk 20 feet without any personal assistive device. Individuals were excluded from the study if they had a diagnosis of terminal disease, severe hearing or vision impairment, or moderate or severe cognitive impairment determined by the Mini-Mental Status Examination score less than 18 (MMSE <18). Eligible spouses or domestic partners aged 65 and older were also allowed to join the study. The participants provided informed consent before the start of the baseline assessment. The extensive baseline assessment was conducted in two parts; an in-home interview followed up by a clinical assessment within three weeks. The time required for the completion of each portion of the assessment was three hours. The original assessment was repeated at 18 months and six years from baseline. The Institutional Review Board of Hebrew Senior Life and collaborating institutions approved the MBS study.

For this secondary data analysis, the MOBILIZE Boston Study I, which included baseline and the 18-month follow-up, and the MBS II, a 6thyear follow-up wave, which

occurred between 2011-2015, were used. Of 765 participants enrolled at baseline, 681 (89%) continued the study at 18 months. Among participants who discontinued the study, 21(2.7%) died, and 63 (8%) dropped out of the study for several reasons: 22 participants had an advancing illness, and 17 participants had personal and family-related issues and study duration. Thirteen participants were lost to follow-up, and eleven participants were withdrawn by the investigator due to inability to perform the assessment.

Of the 765 older adults from the MOBILIZE Boston Study I, only 532 remained available for the MBS II study at the start of the six-year follow-up. The reasons for MBS II unavailability were as follows: inability to reach or failure to follow-up (n=16), death (n=34), refusal to participate (n=25), and ineligibility (n=103). Ineligibility was mainly related to severe health problems (n=46), relocation to another area (n=38), admission to the nursing home (n=10), a new diagnosis of advanced dementia (n=7), a new diagnosis of terminal illness (n=1) and deafness or blindness (n=1). Only 354 participants completed the 2-part follow-up assessment (MBS II) at the Hebrew Rehabilitation Center in Boston. The assessment included a one-hour telephone health interview followed by a three-hour clinic assessment within approximately two weeks. Conducting epidemiologic studies in older populations is challenging, expensive, and time-consuming. Yet, it is necessary to conduct studies on the elderly population to uncover the potential risk factors and the outcomes associated with the disease. It will allow generalizing the research findings on the elderly, who are the largest and ever-growing portion of the population (Leveille et al., 2009; Samelson et al., 2008).

Measures

The variables of interest were selected and reconstructed from the original dataset. Longitudinally assessed pain distribution was categorized as no pain, single-site pain, incident multisite pain, and persistent multisite pain. Potential confounding variables included sociodemographic, health characteristics, chronic health conditions, and medications. The outcome variables were physical disability (ADL, IADL), psychological disability (depression, anxiety), and mortality.

Outcome variables.

Physical disability. The disability status was assessed using Activities of Daily Living (ADLs) and Instrumental Activities of Daily Living (IADLs) measures. Activities of Daily Living (ADLs) disability is having difficulty in performing self-care tasks, and Instrumental Activities of Daily Living (IADLs) disability is difficulty in performing independent living tasks.

Self-care. Katz Index of Independence in Activities of Daily Living assesses the functional status in older adults by evaluating daily activities such as bathing, dressing, transferring, using the toilet, and eating (Katz et al., 1963). It assesses the ability of an individual to care for oneself and maintain independence on an everyday basis. Having difficulty in performing a basic daily activity is considered as a disability. Participants responded by identifying the difficulty in performing each ADL activity with one of the following options: no difficulty, a little difficulty, some difficulty, a lot of difficulties, or inability to perform the ADL activity. We combined the responses to these questions to categorize ADL as three-level variables (no difficulty in performing daily activities, little or some difficulty, and a lot of difficulty or inability to perform the ADL activities). The Katz

ADL was initially developed in the 1950s and ever since has been widely used to assess functional status in community-dwelling older adults (Buchman et al., 2010; Eggermont et al., 2014; Murabito et al., 2008). Several studies have found that ADL disability predicts adverse outcomes such as hospitalization, institutionalization, and mortality (Fong et al., 2015; S. J. Lee, Lindquist, Segal, & Covinsky, 2006; Majer et al., 2011; Mor et al., 1994). A meta-analysis included 12 longitudinal studies that consisted of community-based samples of older adults reported that having three or more dependencies in activities of daily living (ADL) was the strongest predictor of institutionalizations (Gaugler et al., 2007). From the National Health and Nutrition Examination Survey (NHANES), a nationwide population-based dataset Wu and colleagues (2016) reported that disability is associated with all-cause mortality in older adults. Thus, these studies are a few examples of the ADL assessment's predictive validity, even though there is no formal reliability and validity information.

Furthermore, studies have compared self-reported disabilities to physical performance measures and found a correlation (Guralnik et al., 1994; Sherman & Reuben, 1998; Studenski et al., 2003). For instance, Guralnik et al. (1994) compared performance-based measures of lower extremity functioning with self-reported ADL disabilities in predicting mortality and institutionalization. They found a strong association between the self-reported difficulty to perform ADL tasks and performance-based functional status in older adults. The studies also highlight the use of self-report ADL disability in conjunction with physical performance measure as they complement one another and add to the information in understanding an older person's functional status (Guralnik et al., 1994; Studenski et al., 2003).

Independent living. Lawton's Instrumental Activities of Daily Living (IADL) assesses the complex skills of independent living required in a community-setting (Lawton & Brody,

1969). These tasks are more difficult and complicated than performing basic ADL tasks. IADL disability was classified as difficulty performing any of these tasks: shopping, preparing meals, and light and heavy housework. Participants' response options included no difficulty, a little difficulty, some difficulty, a lot of difficulties, or inability to perform each of the activities. Similar to ADL difficulty, we collapsed the responses to these questions to classify IADL difficulty as a three-level variable. We categorized IADL difficulty as no difficulty, a little or some difficulty, and a lot of difficulties or inability to perform the IADL tasks. The assessment of functional status is essential, and Lawton's IADL provides information on community-dwelling older adults' functional capacity, thus estimating the ability of older adults to adapt to their surroundings independently (Lawton & Brody, 1969). The ability to perform IADL tasks is lost prior to ADL tasks; therefore, assessing the ability to carry out IADL tasks may detect a subtle physical and cognitive decline in older adults (Coyne, 2019). In a retrospective study, Cromwell, Eagar, and Poulos (2003) examined the Lawton's scale's ability to identify patients with cognitive impairment in a sample of 1905 community-residing older adults without dementia. In the study, a statistically significant association was found between three IADL items (telephone use, self-medicating, and managing finances) and cognitive impairment, thus confirming the predictive validity of the IADL assessment. Besides, the original study (Lawton & Brody, 1969) tested the validity and examined the correlation between Lawton IADL and three other scales that measures the functional abilities and determined a satisfactory level of interrater reliability and construct validity. The interrater reliability determined in the study in a sample of 12 participants was 0.85, and the reproducibility coefficient was 0.96 for men and 0.93 for women (n=97 and n=168, respectively).

Psychological disability.

Depression. Depression symptomatology was measured based on the modification of the 20-item Hopkins Revision of the Center for Epidemiologic Studies Depression Scale (CESD-R) (Eaton et al., 2004; Radloff, 1977). The diagnostic algorithm following DSM-IV was applied to categorize minor or major depression. The CES-D is a self-report measure. Participants with minor or major depression had symptoms of either anhedonia or dysphoria. Individuals with major depression had to fulfill five out of nine symptom clusters (dysphoria, anhedonia, appetite disturbance, sleep disturbance, trouble thinking, guilt, tiredness, psychomotor retardation, or suicidal ideation). In comparison, those with minor depression reported having two out of nine symptom clusters. Duration criteria included having symptom clusters almost every day for two weeks in the past month. In this study, depression was defined as the presence of minor or major depression and categorized as a dichotomous variable, "0" = no depression, and "1" =depression. Studies have used CESD to understand depressive symptoms in relation to falls, chronic pain, cognition, and disability among the community-living older adults (Brewster, Peterson, Roker, Ellis, & Edwards, 2017; Eggermont et al., 2012). CESD demonstrates strong psychometric properties and is a valid and reliable measure to assess depression in older adults (Berkman et al., 1986; Irwin, Artin, & Oxman, 1999).

Anxiety. Anxiety symptoms were assessed to understand the psychological condition of older adults. The Hospital Anxiety and Depression Scale (HADS) is a two-dimension, self-rating scale used to measure psychological problems in non-psychiatric patients (Zigmond & Snaith, 1983). The HADS initially developed by Zigmond and Snaith (1983) is a simple yet reliable instrument that detects the level of psychological distress in an

individual. Although the instrument was developed to assess the mood disorder in the hospital setting, many studies have used and confirmed its validity for use in community settings (Snaith, 2003). The HADS scale consists of two subscales, anxiety and depression, and it comprises of 14 items, of which seven items are related to anxiety, used in the MOBILIZE Boston Study, and the other seven items relate to depression. The anxiety-related items are as follows; "I feel tense or wound up," "I get a sort of frightened feeling as if something bad is about to happen," "Worrying thoughts go through my mind," "I can sit at ease and feel relaxed," "I get a sort of frightened feeling like butterflies in the stomach," "I feel restless and have to be on the move," and "I get sudden feelings of panic." Each item in the questionnaire is scored from 0-3, and the respondent rates each item on a 4-point scale that ranges from 0 (absence) to 3 (strongly present).

In our study, we used HADS as both continuous and binary variables. The presence of anxiety symptoms was measured as HADS scores ≥ eight and classified as a binary variable, which was coded as "0" = no anxiety and "1" = anxiety. Overall, the psychometric properties of the HADS scale are considered to be satisfactory by several studies. For example, a study by Helvik et al. (2011) supported the psychometric properties of HADS in a sample of hospitalized patients who were 65 and older. The reliability for HADS-A determined by Cronbach's alpha was 0.78. Also, Djukanovic et al. (2017) conducted a psychometric evaluation study and confirmed HADS as a valid measure in the adults aged 65-80 years. Furthermore, a literature review on the validity of the Hospital Anxiety and Depression Scale by Bjelland (2002) also supported the overall psychometric properties of HADS. The Cronbach's alpha for HADS-A ranged between 0.68 to 0.9. Additionally, the sensitivity and specificity of 0.80 for HADS-A was close to that of the General Health

Questionnaire (GHQ). The anxiety scale detects symptom severity and cases of anxiety disorders in the general population and an older population (Bjelland et al., 2002).

Mortality. Deaths were assessed up to 12.4 years, and the date of death of study participants was ascertained through proxy respondents, family contacts, and obituary searches. There was extensive ascertainment of mortality until 06/06/2015 (9.8 years) and less complete ascertainment until 12.4 years. Subsequently, we compared the regression results between persistent multisite pain and mortality at 12.4 years and 9.8 years.

Predictor variables.

Persistent multisite pain. Persistent musculoskeletal pain was measured using a Joint Pain Questionnaire (JPQ). The 13-item joint pain questionnaire assessed the pain in hands and wrists, shoulders, back, chest, hips, knees, and feet. The JPQ was originally used in the Women's Health and Aging Study (Hochberg et al., 1995). In order to match the American Pain Society's definition of chronic pain, the duration was changed to pain lasting three or more months instead of one month in the previous year (Hochberg et al., 1995). Persistent multisite pain was defined as pain present in the previous month and pain that lasted for ≥ 3 months in the previous year in ≥ 2 anatomical sites (Leveille et al., 2009; Thapa et al., 2018).

Pain categories at the 18-month and six-year follow-up were constructed based on pain status at baseline and the 18 month/six-year follow-up. Pain distribution assessed longitudinally was categorized as a four-level variable at the 18-month and six-year follow-up; (1) No pain, single-site pain, and multisite pain at baseline → no pain at 18 months/6 years (No pain); (2) No pain, single-site pain, and multisite pain at baseline → single-site pain at 18 months/6 years (Single-site pain); (3) No pain or single-site pain at baseline→ multisite pain at 18 months/6 years (Incident multisite pain); (4) Multisite pain at baseline

→multisite pain at 18 months/6 years (Persistent multisite pain). No pain was the reference group. Multisite pain at baseline that persisted as multisite pain at 18 months or six years was categorized as persistent multisite pain, also referred to as the persistence of multisite pain as pain measures were longitudinally assessed.

Covariates. Sociodemographic characteristics information was collected at the baseline home visit in the MBS I and MBSII assessment, which included age, gender, race, and years of education. Body mass index (BMI) was calculated from measured height and weight (weight(kg)/height $(cm)^2$). Physical Activity Scale for the Elderly (PASE), a self-administered physical activity questionnaire consisting of 10 items, included walking, sports, recreational activities, exercises, housework, and yard work in the past week. The scores grouped into tertiles (0-66,66-123, >123) corresponded to sedentary, light activity, and moderate to vigorous activity (Washburn, Smith, Jette, & Janney, 1993). Based on the metabolic equivalents (METS), the quantity of time spent in each activity (h/wk) is multiplied by the item weight for each activity. The weighted sum of the ten reported activities is considered as the total PASE score (Washburn et al., 1993). Mobility in walking was calculated as the number of blocks walked per week (i.e., 12 city blocks=1 mile). The number of blocks walked was categorized into 4-groups (0-3, 4-12, 13-60, >60 blocks/week). Cognitive status assessed using mini-mental status examination (MMSE) score that ranged between 0-30 and a cut-off value of <24 was regarded as having a cognitive impairment (Folstein, Folstein, & McHugh, 1975). Diabetes Mellitus was measured using an algorithm that included laboratory results for a random glucose level (≥200 mg/dl), glycosylated hemoglobin (≥7%), self-reported diabetes mellitus, and use of anti-diabetic medications (Leveille et al., 2008). Lung disease was a self-reported physician-diagnosed chronic health

condition. The presence of heart disease was determined based on self-report of heart attack, congestive heart failure, angina pectoris, pacemaker, or cardiac arrhythmia (Rose, 1962).

Medications. The containers of both prescription and over-the-counter medications that the participant had used in the last two weeks were examined during the home visit. The research nurse recorded the name, route, strength, and frequency of each medication, which were subsequently coded by applying the Iowa Drug Information System ingredient codes (IDIS). Analgesic drugs were categorized into opioid, non-opioid, and aspirin, except for the daily dose of 325 mg or less of aspirin used for cardiac protection (Leveille et al., 2008). The analgesic medication was coded as a dichotomous variable, "Yes" or "No" depending on the use or no use of any analgesics. Psychiatric drugs were also coded as a binary variable, "0" and "1" based on the intake or no intake of any psychiatric medications. This study was performed following the University of Massachusetts Boston IRB approval.

Statistical Analysis

In the statistical analysis, firstly, a univariate analysis was performed to assess the variables individually for mean, standard deviation, frequency, percentage, and missing data at baseline, 18 months, and at six years. Baseline sociodemographic and health characteristics were exhibited according to pain distribution using descriptive statistics, mainly frequency distributions and percentages.

Descriptive aim.

Specific aim #1. To estimate the persistence of multisite pain and the proportion of new onset of multisite pain at 18 months and six years in a population of older adults living in the community.

Univariate analysis. The frequency distribution, percentages, and missingness of the pain distribution variable classified as no pain, single-site pain, and multisite pain (≥2 sites) at baseline, 18 months, and six years was checked using the STATA software.

Bivariate analysis. Using the Chi-square analysis, the pain distribution variable at baseline was cross tabulated with the pain distribution variable at 18 months. There were missing data on one participant at baseline. Pain distribution assessed longitudinally was categorized as a four-level variable at 18 months: no pain, single-site pain, incident multisite pain, and persistent multisite pain The primary predictor variable was constructed based on the following: (1) No pain, single-site pain, and multisite pain at baseline → no pain at 18-month follow-up (No pain); (2) No pain, single-site pain, and multisite pain at baseline → single-site pain at 18-month follow-up (Single-site pain); (3) No pain or single-site pain at baseline→ multisite pain at 18-month follow-up (Incident multisite pain); (4) Multisite pain at baseline →multisite pain at 18-month follow-up (Persistent multisite pain). No pain was the reference group. Likewise, the pain distribution variable at baseline was cross-tabulated with the pain distribution variable at the six-year follow-up. All the participants at six years had complete information on pain distribution. Chi-square analysis was performed to assess the change in pain distribution from baseline to the six-year follow-up. Pain distribution assessed longitudinally was categorized as a four-level variable: (1) No pain, single-site pain, and multisite pain at baseline → no pain at six-year follow-up (No pain); (2) No pain, single-site pain, and multisite pain at baseline → single-site pain at six-year follow-up (Single-site pain); (3) No pain or single-site pain at baseline→ multisite pain at six-year follow-up (Incident multisite pain); (4) Multisite pain at baseline →multisite pain at six-year follow-up (Persistent multisite pain). No pain was the reference group.

Analytic aims.

Specific aim #2. To examine the associations between persistent multisite pain and the risk of developing physical disability in community-dwelling older adults.

Hypothesis #2. Older adults with persistent multisite pain are more likely to have poorer physical function (ADL and IADL) at the 18-month and six-year follow-up compared to older adults with no pain.

Univariate analysis. The frequency distribution, percentage, and missingness of ADL, and IADL at 18-months and 6-years, along with potential confounding factors such as sociodemographic characteristics (age, gender, race, education), health characteristics (BMI, MMSE, and physical activity), chronic health conditions (heart disease, diabetes mellitus, lung disease, depression, anxiety), and medications such as psychiatric drugs and analgesics at baseline were assessed using Stata software.

Bivariate analysis. The pain distribution variable was cross tabulated with Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) at 18 months and six years using the Chi-square analysis.

Multivariate analysis. Physical disability, as the dependent variable, had two domains-Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL). Activities of daily living (ADL), a three-level dependent variable was categorized as no difficulty, little or some difficulty, and a lot of difficulty or inability to perform one or more ADL task. A series of multinomial logistic regression models were performed to determine the multivariable-adjusted relationship between pain distribution and ADL disability at 18-months. The full model was adjusted for sociodemographic characteristics (age, gender, race, education), health characteristics (BMI, MMSE, and physical activity),

chronic health conditions (heart disease, diabetes mellitus, lung disease, depression, anxiety), and medications such as psychiatric drugs and analgesics. Similarly, a sequence of Multinomial logistic regression models adjusted for potential covariates determined the association between pain distribution and ADL disability categories at six years. Instrumental activities of daily living (IADL) as a three-level variable was classified as no difficulty, little or some difficulty, and a lot of difficulty or unable to perform one or more IADL task. The multivariable adjustment determined the association between pain distribution and IADL disability at 18-months and six years.

The relationship between persistent multisite pain and physical disability (ADL and IADL) were examined using a Multinomial logistic regression analysis at 18 months and six years. Relative Risk Ratios (RRR) and 95% CI calculated from Multinomial logistic regression determined the risk of physical disability among individuals with persistent multisite pain than those with no pain.

Specific aim #3. To determine the association between persistent multisite pain and the risk of developing psychological disability in community-dwelling older adults.

*Hypothesis #3a**.** Older adults with persistent multisite pain are more likely to report depression and anxiety at the 18-month and six-year follow-up than those with no pain.*

*Hypothesis #3b**.** Older adults with incident multisite pain are more likely to report depression and anxiety at the six-year follow-up than those with no pain.*

*Univariate analysis**.*** The frequency distribution, percentage, mean, standard deviation and missingness of depression and anxiety at 18 months and six years were assessed using Stata software.

Bivariate analysis. A Chi-square test was performed to examine the relationship between depression and pain distribution at 18 months and six years. Chi-square test and ANOVA test were also used to assess the association between anxiety as a binary and continuous outcome variable and pain distribution at 18-month and six-year follow-up.

Multivariate analysis. Logistic regression modeling determined the relationship between depression and pain distribution at 18 months and six years (Hypothesis #3a and #3b). The potential covariates were sequentially added beginning with age, gender, race, and education (Model 2), additionally adjusted BMI, physical activity, and cognitive status (Model 3), additionally adjusted for chronic health conditions (heart disease, diabetes mellitus, lung disease, and IADL) (Model 4), and finally adjusted for medications such as psychiatric drugs and analgesics (Model 5). The same multivariable analysis was repeated to estimate the association between multivariable adjustment risk factors and depression at six years. The odds ratio (OR) and 95% confidence intervals (CI) calculated from logistic regression determined the risk of depression among those with persistent multisite and incidence multisite pain than those with no pain at the 18-month and 6-year follow-up.

Logistic regression models were performed to examine the relationship between pain distribution and anxiety as a binary variable. Generalized linear regression modeling was used for anxiety as a continuous variable at the 18-month and six-year follow-up (Hypothesis #3a and #3b). Anxiety was the dependent variable, and pain distribution (persistent multisite pain, incident multisite pain, single-site pain, and no pain) was the predictor variable. Potential risk factors such as age, gender, race, and education were added (Model 2). The models were additionally adjusted for health characteristics such as BMI, physical activity, and cognitive status measured using MMSE (Model 3), and chronic health conditions (heart

disease, diabetes mellitus, lung disease, and IADL) (Model 4). The final model was additionally adjusted for analgesics and psychiatric drugs (Model 5) at 18-months. Similarly, the multivariable adjustment determined the association between pain distribution and anxiety at six years and the final model was adjusted for potential confounders such as age, gender, race, education, BMI, MMSE, physical activity, heart disease, diabetes mellitus, lung disease, IADL, psychiatric drug, and analgesic. Beta and standard errors (SE) calculated from the generalized linear regression model for anxiety as a continuous dependent variable. Odds ratios (OR) and 95% confidence intervals (CI) calculated from logistic regression determined the likelihood of anxiety among individuals with persistent multisite pain and incidence multisite pain than those with no pain.

Specific aim #4. To determine the association between persistent multisite pain and mortality at 12.4 years in older adults.

Hypothesis #4. Accounting for socioeconomic status, lifestyle factors, and comorbidities, older adults with persistent multisite pain have an increased risk of mortality compared to those with no pain.

Survival analysis was performed to understand the pain-mortality linkage. The event of interest was death related to persistent pain in this study. Cox proportional hazards regression modeling examined the relationship between baseline persistent multisite pain and mortality. There was less extensive ascertainment until 12.4 years. but extensive ascertainment until 06/06/2015 (9.8 years). Therefore, two separate analyses were performed to compare the regression results at 9.8 years and 12.4 years of follow-up. The starting point for the analyses was the baseline date of entry. In the first analysis, two-steps were involved. In the first step, participants with persistent multisite pain at baseline who survived to the end

of the study, or dropped out, or lost to follow-up before the end of the observation period were coded as "0". In the second step, participants who died during the 12.4 years were coded as "1". Time-to-event was generated by using the most recent death date; in this case, it was 1/27/2018 (12.4 yrs) minus the baseline interview dates for participants who experienced death.

Next, extensive ascertainment of death, 06/06/2015 (9.8 years), was selected as the censoring date. In this second analysis, participants contributed person-time beginning at baseline until 6/06/2015. At first, the event was coded as "0" if individuals with persistent multisite pain at baseline survived to the end of the study, or dropped out, or were lost to follow-up before the end of the observation period. In the second step, the event was coded as "1" if participants died during the 9.8 years of follow-up. Time-to-event was generated by using the date of death minus the baseline interview date in the study, for those who experienced death by 6/6/2015. The hazard ratio and 95% confidence interval (CI) calculated from Cox proportional hazards regression modeling calculated the risk of dying among those with baseline persistent multisite compared to those with no pain. In the unadjusted model 1, the overall effect of persistent multisite pain on mortality in older adults was examined. Potential risk factors were sequentially added to the several models. Total six multivariable models were performed: unadjusted model (model 1), adjusted for sociodemographic (model 2), additionally adjusted for health characteristics (model 3), additionally adjusted for health factors (model 4), further adjusted for chronic conditions (model 5), and finally adjusted for ADL disability (model 6). The statistical significance level was p-value <0.05. Analyses were performed using Stata software, version 14 (StataCorp LLC, College Station, TX, USA).

CHAPTER IV

RESULTS

Study Participants (18-Month Follow-Up)

Of 765 participants enrolled at baseline, 681 (89%) continued the study at 18 months. Among participants who discontinued the study, 21(2.7%) died, and 63 (8%) dropped out of the study for several reasons: 22 participants withdrew due to advancing illness, and 17 participants did not continue due to personal and family-related issues and the study duration. Investigator withdrawal and lost to follow-up were 11 and 13 participants, respectively. Participants who dropped out of the study at 18 months walked fewer blocks per week, had a diagnosis of diabetes, lower BMI, and scored lower on the Mini-Mental State Examination (MMSE) than participants who completed the study. No differences were observed according to pain category (Table 1).

Study Participants (Six-Year Follow-Up)

Out of 765 participants at baseline, only 354 remained in the study while 411 died or dropped out of the study by the six-year follow-up assessment. At the six-year follow-up, participants who died or dropped out of the study had fewer years of education and a diagnosis of heart disease and diabetes. Participants who dropped out had significantly greater ADL and IADL disability, walked fewer blocks per week and scored lower on the

MMSE test for cognitive impairment, and were more likely to use psychiatric drugs than participants who stayed in the study. Besides, there were no differences according to pain category (Table 2).

Baseline Characteristics

At baseline, the average age of the 765 study members was 78 years (SD =5.4; range 64-97 years). The majority were Caucasian (78%), almost two-thirds were female (64%) and college graduates (66%) (Table 3). In terms of health conditions, 42% of the participants had heart disease, 20% had diabetes, and 16% had lung disease. About one-quarter and one-fifth reported using analgesics daily and psychiatric drugs, respectively. Majority of the participants were overweight, and about 30% walked four miles or more every week. The prevalence of little or some ADL and IADL difficulty was 15% and 19%, respectively. About 8% of the study participants reported having a lot of ADL difficulty or inability to perform one or more ADL activities. In comparison, 21% reported having a lot of IADL difficulty or inability to perform one or more IADL tasks (Table 4, Figure 3). Depression and anxiety were reported by 7% and 10% of the study participants (Table 4, Figure 4).

The prevalence of sociodemographic and health characteristics of the participants at 18-month and six-year follow-ups are shown in Table 3. There was an increase in the prevalence of ADL disability at the 18-month and at six-year follow-up. For instance, 8% reported a lot of ADL difficulty or inability to perform ADL tasks at baseline compared to 10% and 16% at 18 months and six years, respectively (Table 4, Figure 3). The prevalence of IADL disability was 22% at 18 months and 16% at six years. Prevalence of depression was 9% at 18 months and 7% at six years, and anxiety at the 18-month and 6-year follow-up was 5% and 4%, respectively (Table 4, Figure 4).

In the next section, results will be presented in detail according to the specific aim and hypothesis. We studied a multidimensional impact of persistent multisite pain in community-dwelling older adults. Specifically, we first examined the onset and persistence of multisite pain. Next, we investigated the relationship between persistent multisite pain and physical and psychological disability at the 18-month and six-year follow-up. Finally, we examined the impact of baseline persistent multisite pain on mortality at 12.4 years.

Specific Aim # 1

To estimate the persistence of multisite pain and the proportion of new onset of multisite pain at 18 months and six years in a population of older adults living in the community.

Of the 681 participants, however only 633 (83%) reported information on pain. One person had missing data with respect to the pain distribution variable; therefore, this study was mainly limited to 632 cohort members at the 18-month follow-up.

18-month follow-up. Table 5 displays the prevalence of longitudinally assessed pain distribution from baseline to 18 months. Out of the 632 participants, about one-quarter (26%) had persistent multisite pain, and a similar proportion (28%) had single-site pain. About 10% of the participants had incident multisite pain at the18-month follow-up whereas 36% of the participants did not have any pain (Figure 5). Baseline sociodemographic and health characteristics according to longitudinally assessed pain distribution at 18-month follow-up are presented in Table 6. Age was not related to pain distribution, but there was a significant association between gender and pain distribution. Precisely, more older women than older men had pain. For instance, of those reporting persistent multisite pain, 77% were women compared to 23% of men (Table 6). Out of those with incident multisite pain and single-site

pain, 61% and 63% were women, respectively. Individuals with persistent multisite were more likely to have lung disease compared to individuals without any pain (25% and 10%, respectively). A greater proportion of participants with persistent multisite pain were more likely to use daily analgesics compared to participants with no pain (42% and 10%, respectively). No association was observed with education. Likewise, health factors such as BMI, cognitive function measured using Mini-Mental Status Examination (MMSE<24), and physical activity were not associated with pain distribution. Similarly, the presence of heart disease, diabetes, and the use of psychiatric drugs were also not associated with pain distribution at 18 months (Table 6).

Six-year follow-up. Of the 765 older adults enrolled in the MBSI study, 354 (46%) cohort members completed the MBSII study between 2011- 2015. Table 5 presents the prevalence of longitudinally assessed pain distribution from baseline to six years. Out of the 354 participants at the six-year follow-up, 27% had persistent multisite pain while 18% had incident multisite pain. About one-quarter (23%) had single-site pain, and 32% had no pain (Figure 5). Basically, persistent multisite pain stayed the same but incident multisite pain increased over time from 10% at 18 months to 18% at 6 years. Out of the 354 participants, 70% with multisite pain at baseline continued to have persistent multisite pain at the end of the six-year follow-up. Table 7 displays the baseline characteristics according to longitudinally assessed pain distribution at six years. Baseline factors significantly associated with pain distribution at the six-year follow-up were gender, lung disease, and the use of daily analgesics. The majority of participants with persistent multisite were women than men (78% and 22%, respectively). Of those with persistent multisite pain, 22% had lung disease compared to 17% of participants with no pain. Participants with persistent multisite pain

were more likely to use daily analgesics compared to participants with no pain (39% and 15%, respectively). Additional analysis showed 46% (354) were present at all three assessments.

Specific Aim #2

To examine the associations between persistent multisite pain and the risk of developing physical disability in community-dwelling older adults.

Hypothesis #2. Older adults with persistent multisite pain are more likely to have a poorer physical function (ADL and IADL) at the 18-month and six-year follow-up compared to older adults with no pain.

Pain Distribution and ADL Disability

18-month follow-up. The results of Chi-Square tests demonstrated that ADL difficulty was significantly associated with pain distribution at 18 months (p-value <0.001) (Table 8). Among participants with persistent multisite pain, 23% reported a lot or inability to perform ADL tasks compared to 5% of those with incident multisite pain, 7% of those with single-site pain, and 3% of those with no pain (Figure 6).

The relationship between persistent pain and physical disability in community-dwelling older adults at 18 months was examined using multinominal logistic regression analysis, as shown in Table 10. Physical disability, as the dependent variable, had two domains: ADL and IADL. The final multivariable model included 599 study participants. After adjusting for sociodemographic characteristics (age, gender, race, education), health characteristics (BMI, MMSE, and physical activity), chronic health conditions (heart disease, diabetes mellitus, lung disease, depression, and anxiety), and medications (psychiatric drugs and analgesics), it was found that persistent multisite pain was significantly associated with

a higher likelihood of having little or some ADL difficulty (RRR 2.41; 95% CI 1.26- 4.61) and a lot of ADL difficulty (RRR 7.26; 95% CI 2.55-20.71) than those with no pain at 18 months. Null effects were found for incident multisite pain as a predictor of little or some ADL difficulty and also, for a lot of ADL difficulty or inability to perform ADL activity. Also, there was no significant relationship between single-site pain and ADL difficulty at the 18-month follow-up.

Six-year follow-up. According to the results of Chi-Square tests, the longitudinally assessed pain distribution was significantly associated with ADL difficulty at the six-year follow-up (p-value<0.0001) (Table 9). Out of 97 study participants with persistent pain at six-year follow-up, 28% reported having a lot of ADL difficulty or being unable to perform one or more ADL tasks, compared to 17% of participants with incident multisite pain, 15% of those with single-site pain and 4% of participants with no pain (Figure 9).

The relationship between pain distribution and ADL disability at six-year follow-up was examined using Multinominal logistic regression, as presented in Table 11. After controlling for potential confounders, 344 participants were included in the final model. The multivariable adjustment for sociodemographic characteristics, BMI, cognitive status and physical activity, heart disease, diabetes mellitus, lung disease, depression, anxiety, and medications such as psychiatric drugs and analgesics, individuals with persistent multisite pain had a higher likelihood of little or some ADL difficulty (RRR 5.03; 95% CI 1.87-13.55) and a lot of ADL difficulty or inability (RRR 10.62; 95% CI 3.23-34.97) than those with no pain at six-year follow-up. Participants with incident multisite pain had 4.6 times increased risk of a lot of ADL difficulty (RRR 4.67; 95% CI 1.31-16.70) than those with no pain at six years.

Basically, for the incident multisite pain group, the risk became evident over time (six years), but the persistent multisite pain group consistently had a higher risk for ADL difficulty both at 18 months and six years.

Pain Distribution and IADL Disability

18-month follow-up. According to Chi-Square tests, difficulty with the instrumental activity of daily living (IADL) was significantly associated with pain characteristics at 18-months (p-value<0.001) (Table 8). The prevalence of highest level of IADL difficulty was observed among individuals with persistent multisite pain with 45% of them having a lot or inability to perform IADL tasks compared to 21% of participants with incident multisite pain, 15% of those endorsing single-site pain, and 11% of participants without any pain (Figure 7).

Multinominal logistic regression analysis was used to examine the association between pain distribution and IADL difficulty among community-dwelling older adults (Table 12). The final model consisted of 599 participants. After multivariable adjustment, participants who had persistent multisite pain at the 18-month follow-up experienced the greatest risk for little or some IADL difficulty (RRR 4.0; 95% CI 2.11-7.59), and a lot of difficulty or inability to perform one or more IADL tasks (RRR 7.33; 95% CI 3.76-14.27) compared to those with no pain at 18 months. Individuals with single-site pain and incident multisite pain also had a higher risk for little or some IADL difficulty (RRR 1.83; 95% CI 1.04-3.20) (RRR 2.28; 95% CI 1.05-4.92), respectively. However, single-site pain and incident multisite pain were not significantly associated with a lot of IADL difficulty at 18 months.

Six-year follow-up. There were similar risks associated with IADL disability and pain distribution at six years (p-value <0.001) (Table 9). A greater proportion of participants

with persistent multisite pain were more likely to have a lot of IADL difficulty or unable to perform IADL tasks compared to those with no pain (34% and 4%, respectively) (Figure 10).

The association between pain distribution and IADL disability at the six-year follow-up was investigated, as shown in Table 13. Multinominal logistic regression was used to examine this relationship, and 342 participants represented in the final model. After multivariable adjustment, individuals with persistent multisite pain had almost a three-fold increased risk of little or some IADL difficulty (RRR 2.96; 95% CI 1.10-8.01) and 18-fold increased risk of a lot of IADL difficulty (RRR 18.10; 95% CI: 5.36- 61.12) compared to those with no pain. Individuals with incident multisite pain also had a higher likelihood of little or some IADL difficulty (RRR 4.06; 95% CI 1.49- 11.10) and a lot of IADL difficulty (RRR 4.97; 95% CI 1.29- 19.21) compared to those with no pain. Due to the significant overlap of the confidence intervals, we cannot confidently conclude that there was a substantial difference in the risk for IADL disability between incident and persistent multisite pain at six years. No significant association was found between single-site pain and IADL disability at six years.

Mainly, persistent multisite pain was a strong predictor of both ADL and IADL disability. Therefore, these findings indicate that individuals with persistent multisite pain have the most significant burden of physical disability. As predicted, older adults with persistent multisite pain had poorer physical health (ADL and IADL) at the 18-month and the six-year follow-up compared to older adults with no pain. Thus, hypothesis 1 was supported as older adults with persistent multisite pain experience a higher level of physical disability compared to those with no pain.

In summary, the risk for physical disability (ADL and IADL) was highest among individuals with persistent multisite pain and lowest among individuals with no pain in the 18-month and six-year follow-up period.

Specific Aim #3

To determine the association between persistent multisite pain and the risk of developing psychological disability in community-dwelling older adults.

Hypothesis #3a. Older adults with persistent multisite pain are more likely to report depression and anxiety at the 18-month and six-year follow-up than those with no pain.

Hypothesis #3b. Older adults with incident multisite pain are more likely to report depression and anxiety at the six-year follow-up than those with no pain.

Pain Distribution and Depression

18-month follow-up. Chi-square tests demonstrated that depression was significantly associated with pain distribution at the 18-month follow-up (p-value <0.001) (Table 8). A greater proportion of participants with persistent multisite pain were more likely to have depression compared to participants with no pain (19% and 3%) (Figure 8).

The hypothesis was tested by examining the association between pain distribution and depression derived from the logistic regression analysis. Depression as the dependent variable was binary and categorized as "1" for individuals with depression and "0" for individuals with no depression. Longitudinally assessed pain distribution was classified as no pain, single-site pain, incident multisite pain, and persistent multisite pain with no pain as the reference category. Several potential confounders were included in the model to determine the independent association between depression and pain distribution (Table 14). Model 1 was adjusted for age, gender, education, and race. Model 2 was additionally adjusted for

BMI, physical activity, and cognitive status measured using MMSE. Next, Model 3 was additionally adjusted for chronic health conditions such as heart disease, diabetes mellitus, lung disease and IADL. The final Model 5, which included 611 study participants, was additionally adjusted for analgesics and psychiatric drugs. After adjusting for all the covariates, individuals with persistent multisite pain were 6.6 times more likely to have depression compared to those without pain (OR 6.59; 95% CI: 2.56-16.94), which was also the only statistically significant association (Table 14). No meaningful relationship was found between incident multisite pain and depression for both adjusted and unadjusted models. Similarly, there was no significant relationship between single-site pain and depression.

Six-year follow-up. The relationship between depression and pain distribution was statistically significant at the six-year follow-up (p-value=0.011) (Table 9). Depression was most prevalent in individuals with persistent multisite pain. About 14% of those with persistent multisite pain had depression compared to 5% of participants with incident multisite pain and single-site pain and 4% of those with no pain (Figure 11).

The relationship between pain distribution and depression at six years was examined using logistic regression, as shown in Table 15. The final model consisted of 327 participants after adjusting for sociodemographic (Model 3), health characteristics (Model 4), chronic health conditions (Model 5), and medications such as psychiatric drugs and analgesics (Model 6). Multisite pain was independently associated with an increased likelihood of depression (OR 4.56;95%CI:1.10-18.98). Besides, we did not find an association between depression and incident multisite pain and single-site pain for either the crude or adjusted models.

Hence, persistent multisite pain was found to be a statistically significant predictor of depression both at the 18-month and 6-year follow-up.

Pain Distribution and Anxiety

18-month follow-up. According to the ANOVA and Chi-Square tests, anxiety was associated with pain distribution at the18-month follow-up (p-value <0.0001 and 0.034, respectively) (Table 8). The prevalence of anxiety was about four times higher in participants with persistent multisite pain compared to participants with no pain (8.43 vs. 2.18) (Figure 8).

The relationship between pain distribution and anxiety was examined using both logistic regression and linear regression at the18-month follow-up. Anxiety as the binary dependent variable was categorized as "1" for those with anxiety score ≥ 8 and "0" for those with an anxiety score < 8. Logistic regression was used to examine this relationship, and 611 participants represented in the final model. After multivariable adjustment, individuals with persistent multisite pain had 4.3 times increased likelihood for anxiety (OR 4.34; CI 1.32-14.26) than those with no pain. Generalized linear regression was used to investigate the relationship between anxiety as a continuous variable and pain distribution. In the final model, after adjustment for potential confounders such as age, gender, race, education, BMI, MMSE, physical activity, heart disease, diabetes mellitus, lung disease, IADL, psychiatric drug, and analgesic, presence of persistent multisite pain was strongly associated with anxiety score (p-value<0.0001) (Table 16),

Six-year follow-up. Using the ANOVA test, anxiety was associated with pain distribution at the 6-year follow-up (p-value=0.01). However, according to Chi-Square test, anxiety was not associated with pain distribution at the 6-year follow-up period (p-

value=0.636) (Table 9, Figure 11). Anxiety and pain distribution at six years was examined using logistic regression and generalized linear regression. The final model included 325 participants. For anxiety as a binary outcome, logistic regression was used to examine the association between pain distribution and anxiety. There was no association between incident multisite pain and anxiety symptoms at six years (adj. OR 2.12; 95% CI 0.31-14.41). Similarly, there was no relationship between persistent multisite pain and anxiety symptoms for both crude (OR 2.40; 95% CI 0.58-9.85) and adjusted model (adj. OR1.71; 95% CI 0.28-10.33) (Table 17). Furthermore, we also performed generalized linear regression to investigate the relationship between anxiety as a continuous outcome variable and pain distribution at the 6-year follow-up. In the final model, after adjusting for sociodemographic, health characteristics, chronic health conditions, and medications, an association was observed between the presence of persistent multisite pain and anxiety score at the six-year follow-up (p-value=0.009). In other words, participants with persistent multisite pain had higher scores on the anxiety scale compared to those with no pain. No association was found between incident multisite pain and anxiety symptoms (B=0.08; p-value=0.205). As predicted, persistent multisite pain was found to be associated with anxiety at 18 months and six years. However, there was no association between incident multisite pain and anxiety at the six-year follow-up.

Hence, hypothesis 3a was supported because older adults with persistent multisite pain were more likely to have depression and anxiety symptoms at both follow-up periods compared to those with no pain. Hypothesis 3b, on the contrary, was rejected because we did not find an association between incident multisite pain and anxiety, and depression at the six-year follow-up.

Specific Aim #4

To determine the association between persistent multisite pain and mortality at 12.4 years in older adults.

Hypothesis #4. Accounting for socioeconomic status, lifestyle factors, and comorbidities, older adults with persistent multisite pain have an increased risk of mortality than those with no pain.

Pain and Mortality

The hazard ratio obtained from Cox proportional hazards regression modeling was used to examine the relationship between baseline persistent multisite pain and mortality. The analysis was conducted in two steps. For the first step of the analysis, the event was coded as "0" if participants with persistent multisite pain at baseline survived to the end of the study or dropped out or lost to follow-up before the end of the observation period. In the second step, event coded as "1" if participants died during 12.4 years. Of the 765 participants at baseline, a total of 144 participants had died by 12.4 years, an estimated 19% mortality. The average follow-up time was ten years (SD= 2.72), ranging between 0.19-12.4 years. The total death rate per 100 person-years was 1.86, and the total person-years of follow-up was 7725. The mortality rates per 100 person-years for no pain, single-site pain, and multisite pain were 1.64, 1.81, and 2.07, respectively. Also, the mortality rate per 100 person-years for men was 2.03, while 1.77 for women (Table 30, 31). We did not find an association between persistent multisite pain and mortality for both crude and adjusted models (adj. HR: 0.96; 95% CI 0.62-1.49) (Table 18).

Additional analysis was conducted based on other pain characteristics such as pain severity and pain interference. Pain severity and pain interference were used as continuous independent variables. After examining the relationship between pain severity and mortality adjusted for confounders, we did not find an increased mortality risk related to pain severity in the unadjusted and adjusted models (adj. HR 1.01; 95% CI 0.92- 1.10) (Table 19). On further investigating the relationship between pain interference and mortality, as shown in Table 20, we did not find that pain interference predicted mortality (adj. HR 0.94; 95% CI 0.86-1.03).

Furthermore, there was less complete ascertainment until 12.4 years, but extensive ascertainment was performed until 06/06/2015 (9.8 years). Therefore, another set of analyses were performed to compare the regression results between 12.4 years and 9.8 years. For the second analysis, 06/06/2015 (9.8 years) was selected as the censoring date. Out of the 765 participants at baseline, a total of 126 (16.5%) participants had died before 9.8 years. The average follow-up time was 7.9 years (SD=1.87), ranging between 0.19-9.75 years. The total death rate per 100 person-years was 2.07, and the total person-years of follow-up was 6062. The mortality rate per 100 person-years was highest for the persistent multisite pain group (2.38). The mortality rate per 100 person-years was 2.11 for the single-site pain group and 1.69 for the no pain group. Also, the mortality rate per 100 person-years for men and women was 2.27 and 1.97, respectively (Table 30, 31). There was no excess mortality risk related to persistent multisite pain in the unadjusted or adjusted models (adj. HR1.04; 95%. CI 0.65-1.67) (Table 21). Also, we did not find an association between pain severity and mortality using the most rigorous mortality ascertainment (adj. HR1.02; 95% CI 0.93-1.12) (Table 22).

Besides, pain interference did not predict mortality (adj. HR 0.96; 95% CI 0.87-1.05) (Table 23).

Overall, baseline persistent multisite pain, pain severity, and pain interference, did not predict mortality at 9.8 years and 12.4 years. Thus, hypothesis 4 was rejected because older adults with persistent multisite pain in this study have no increased risk of mortality than those with no pain.

Stratified analysis by gender. We further conducted a stratified analysis according to gender to examine the association between pain characteristics (number of pain sites, pain severity, and pain interference) and mortality at 9.8 years and 12.4 years. For both men and women, we did not find an association between persistent multisite pain and mortality (Table 24 and Table 27) and between pain interferences and mortality (Table 26 and Table 29) at 12.4 years and at 9.8 years. However, only among women at 12.4 years follow-up, pain severity predicted mortality in the unadjusted model (HR 1.11; 95% CI 1.01-1.22, p-value=0.024) (Table 25). No other significant associations were observed between pain characteristics and mortality at 12.4 years. Similarly, among women, at 9.8 years, there was an increased mortality risk related to pain severity in the unadjusted model (HR 1.14; 95% CI 1.04- 1.26, p-value=0.006) and the relationship persisted when the model was adjusted for sociodemographic characteristics such as age, gender, race, and education (HR 1.11; 95% CI 1.01-1.22, p-value=0.037) (Table 28). However, with further adjustments for possible confounders, the relationship was no longer significant.

CHAPTER V

DISCUSSION

In this study, we first examined the prevalence of persistent multisite pain and incident multisite pain at an 18-month and six-year follow-up. We then investigated the association between persistent multisite pain and physical disability during the 18-month and six-year follow-up. Next, we examined the relationship between the persistent multisite pain and psychological disability at 18 months and six years. Lastly, we studied whether persistent multisite pain at baseline is associated with excess mortality in older adults during the 12.4 years. The results revealed that the persistence of multisite pain is an independent predictor of ADL and IADL disability, depression, and anxiety in this population of community-dwelling older adults at the 18-month and 6-year follow-up. However, there was no association between persistent multisite pain and mortality during the 12.4 years. In the original study, MOBILIZE Boston Study (MBS), the researchers used the Nagi Model of Disablement (Verbrugge & Jette, 1994) as the study framework to study the pain experience and its functional consequences. In this study, we applied the systems model and focused on the interaction between personal, interpersonal, and social systems to explain the complex experience of persistent pain and its consequences. This study supported the use of the King Systems model to guide the study of persistent multisite pain and its effect on community-

dwelling older adults. Essentially, Chapter 5 presents the study's significant findings and compares and contrasts the results with previous work in a similar area. To the best of the author's knowledge, our study is among the first population-based cohort study to examine the impact of the persistence of multisite pain measured overtime on the physical and psychological disabilities and mortality in community-dwelling older adults. The following section of this chapter presents the study findings, implications, strengths, limitations, and the conclusion.

Study Findings

At the 18-month follow-up, the prevalence of persistent multisite pain was 26%, and 10% had incident multisite pain at this assessment wave. At the six-year follow-up, 27% of the study cohort had multisite pain that persisted from earlier study waves, and 18% had incident multisite pain. The total prevalence of persistent multisite pain was 36% and 45% at 18-month and 6-year follow-up, respectively. These prevalence estimates for multisite pain in the older population are similar to previous studies conducted in the U.S., U.K., and Japan population, where multisite pain prevalence ranges between 25-43% (Buchman et al., 2010; Croft et al., 2005; Murata et al., 2019; Patel et al., 2013; Stubbs et al., 2016). According to the National Health and Aging Trends Study (NHATS), a nationally representative sample of older adults in the United States, Patel and colleagues found that 40% of the participants had persistent multisite pain (Patel et al., 2013). Similarly, Buchman et al. (2010) used the data from Rush Memory and Aging Project, a longitudinal study of 900 non-disabled community-dwelling elders, and found that 25% of the participants had multisite pain. Croft et al. (2005) used the cross-sectional survey approach in adults aged 50 years, registered with three general practices in North Staffordshire, U.K., and reported that 43% had persistent multisite

pain. In another cross-sectional study conducted in the U.K, Stubbs and colleagues found that 59% of older adults recruited at senior centers in England had multisite pain (Stubbs et al., 2016). Also, a recent observational study conducted in Japan studied 267 community-dwelling older adults with the mean age of 75.3 years, recruited from community clubs. In the study, 30.3% had persistent multisite pain (Murata et al., 2019). However, in the two studies (Murata et al., 2019; Stubbs et al., 2016), the participants were not randomly selected. They were research volunteers making the results prone to volunteer bias, and findings are only generalizable to research volunteers and not to the overall older population. On the contrary, the study participants in the MOBILIZE Boston Study were recruited door-to-door based on a random city/town list of older adults living within a 5-mile radius of the Institute for Aging Research in Boston, and the participants were observed over a period of time.

Hypothesis #2. Older adults with persistent multisite pain are more likely to have a poorer physical function (ADL and IADL) at the 18-month and six-year follow-up compared to older adults with no pain.

As hypothesized, we found that persistent multisite pain was an independent predictor of ADL and IADL disability in this population of community-dwelling older adults.
Our study found that the risk of ADL disability was highest among those with persistent multisite at the 18-month and six-year assessment. Also, participants with persistent multisite pain had the most significant risk of IADL disability at the 18-month and six-year assessment. Our findings are in line with previous cross-sectional and longitudinal studies investigating the relationship between persistent multisite pain and physical disability. For instance, in a cohort study consisting of 900 non-disabled community-dwelling older adults, each additional painful site was associated with a 20% increased risk for ADL disability

(H.R.: 1.20, 95%CI 1.11-1.31) and 10% increased risk for IADL disability (H.R.: 1.10, 95%CI 1.01-1.20) adjusted for potential confounding factors in the average follow-up of 5.6 years (Buchman et al., 2010). From the Women's Health and Aging Study (WHAS), a prospective population-based cohort study of 1002 community-dwelling older disabled women, Leveille and colleagues reported that women with widespread pain were 1.7 times more likely to have little or some difficulty (OR 1.65, 95% CI 1.02-2.67) and 2.8 times more likely to have a lot of difficulties (OR: 2.77; 95% CI 1.45-5.29) with ADL tasks than those with no pain or mild pain at one site (Leveille et al., 2001). Moreover, among women without severe difficulty with performing ADL or inability to perform each of the ADL tasks at baseline, having widespread pain almost doubled the risk for progression to severe difficulty in performing ADLs tasks, compared to women with no pain or mild pain, after adjusted for confounders during the 3-year follow-up period. In an observational study conducted in Denmark, Manty and colleagues (2014) included 1177 nonagenarians sample, aged 92 and 93 years based on the nationwide Danish 1905 cohort study, and participants were traced through the Danish Civil Registration System. The study found that multisite pain increased the risk of developing severe disability during the 2-year follow-up period but did not predict the onset of overall disability. It is worth noting that the study participants in the Manty study were limited to the oldest old group; thus, the findings may only be generalized to the oldest-old adults. In another prospective cohort study consisting of a total of 204 participants who were very old and frail, the mean age of 84.3 years living in the community in central Italy, individuals with multisite pain were twice as likely to develop disability compared to those without pain at a two-year follow-up (Landi et al., 2009).

In a cross-sectional study of 885 community-residing Canadian older population, Scudds & Robertson (2000) reported that the number of pain sites was significantly associated with physical disability with a 14% increase in the odds ratio for each additional pain site, with a mean of 5.8 pain sites (OR:1.14; 95% CI 1.06-1.22). Additionally, Butera and colleagues recently reviewed 17 studies on multisite pain and its impact on physical and psychosocial function in older adults and concluded that multisite pain might be associated with increased risk for disability (Butera, Roff, Buford, & Cruz-Almeida, 2019).

Several studies have indicated a direct effect of pain on physical disability. From an analysis of the Women's Health and Aging Study (WHAS) data, Leveille and colleagues demonstrated a direct relationship between pain and disability without evidence that psychological symptoms or measures of functional limitations and physical performance mediated the relationship between musculoskeletal pain and severe mobility disability (Leveille et al., 2007). The participants in the Women's Health and Aging Study (WHAS) were older disabled women (≥65years) living in the community. On the contrary, the MOBILIZE Boston Study participants were recruited from the general population of older men and women living in the community. In a nationally representative sample using the National Health and Nutrition Examination Survey (NHANES), Hochberg and colleagues (1989) reported that there was musculoskeletal pain-related disability without any radiographic arthritic changes in older adults.

Despite studies demonstrating the strong pain-disability linkage, the mechanisms underlying the association between pain and functioning are poorly understood. Decreased physical activity and impaired physical function frequently found in older adults with persistent pain are a possible explanation for pain-disability linkage. Persistent pain acts as a

significant barrier to physical activity (Koltyn, 2002; Taylor, 2014). As shown in a previous study of the MOBILIZE Boston cohort, most often older adults with persistent multisite pain are less likely to engage in physical activity than individuals with single-site pain and no pain (Eggermont, Milberg, Lipsitz, Scherder, & Leveille, 2009). Several studies have repeatedly found a lower level of physical activity in elders with persistent pain than those with no pain (Herbolsheimer et al., 2016; Kaplan et al., 2003; C. Larsson et al., 2016). Underutilization of analgesics can also lead to reduced physical activity in elders (Kaplan et al., 2003). Mainly, inactivity contributes to physical deconditioning, which increases the risk of impaired physical performance and elevates the risk of disability in older adults (Manini & Pahor, 2009). Physical inactivity also leads to dynapenia or reduced muscle strength, a strong predictor of disability, morbidity, and mortality in older adults (Manini, 2011; Newman et al., 2006). Neuromuscular impairments associated with a mobility disability are muscle strength, power, speed of movement, range of motion (ROM), asymmetry, and trunk extensor muscle endurance (Bean et al., 2013; Hicks et al., 2012). Muscle weakness is also related to functional limitations and physical disability (Duchowny et al., 2018; McGrath et al., 2018). Persistent pain contributes to neuromuscular impairments in older adults (Ishak, Zahari, & Justine, 2017; Makris et al., 2016). For example, trunk extensor muscle endurance (TEE), leg strength, and rapid leg coordination were significantly lower in older individuals with back pain than those without back pain (Makris et al., 2016). Also, elders with chronic low back pain have poor back and abdominal muscle strength than those without chronic low back pain (Ishak et al., 2017). Besides, muscle impairments and decreased physical function are outcomes of other chronic conditions that often co-exist with pain and aging (Whitson et al., 2010). Therefore, it is possible that the combined effect of lower physical activity,

neuromuscular impairments, chronic conditions, and aging puts an older person with persistent multisite pain at an increased risk for poor physical performance and physical disability.

In summary, multisite pain, a disabling condition affecting a large portion of the older population, is a crucial under-recognized risk factor leading to physical disability in older adults. Further research is necessary to understand multisite pain and disability linkage. Future studies are also needed to develop interventions to prevent physical disability in elders with persistent multisite pain.

Hypothesis #3a. Older adults with persistent multisite pain are more likely to report depression and anxiety at the 18-month and six-year follow-up than those with no pain.

Hypothesis #3b. Older adults with incident multisite pain are more likely to report depression and anxiety at the six-year follow-up than those with no pain.

In our study, depression was highly prevalent among individuals with persistent multisite pain at the 18-month and six-year follow-up. Consistent with our stated hypotheses, the study signifies that the persistence of multisite pain is a strong predictor for depression in older adults. The finding is in line with a previous population-based cohort study among community-dwelling older adults with the mean age of 76 years conducted in Germany. In the study, multisite pain was strongly associated with depression, adjusted for age and sex (OR 1.20; 95%CI 1.11-1.31) (Denkinger et al., 2014). In the same cohort, using the MOBILIZE Boston dataset, Eggermont et al. (2012) independently examined the two types of depressive symptoms, Somatic CESDR domain, and Cognitive CESDR domain in relation to pain. The study found that both Cognitive and Somatic CESDR domains were associated with persistent multisite pain (p-value<0.001). In another study, Manty et al. (2014) found a

relationship between depression and persistent multisite pain. A possible explanation is that chronic musculoskeletal pain, more specifically multisite pain, is associated with a lower level of physical activity in older individuals (Murata et al., 2019; Stubbs, Patchay, Soundy, & Schofield, 2014), and lower level of physical activity is associated with depression in older people (L. D. S. S. C. B. de Oliveira, Souza, Rodrigues, Fett, & Piva, 2019).

Another possible explanation is that the physical disability caused by pain can cause social isolation, increasing the risk for depression (Jang, Haley, Small, & Mortimer, 2002). Also, the age and disease-related functional decline may contribute to the development of depressive symptoms in older people (Yang & George, 2005). Pain and depression are comorbid conditions in older people, and neuroinflammation plays a vital role in the development of depression and persistent pain. The sharing of different regions of the brain, such as the amygdala and hypothalamus and common pathophysiological mechanism may also explain the co-occurrence of depression and pain in the elderly population (Zis et al., 2017). Moreover, the current evidence indicates that there is substantial overlap among pain and depression-induced neuroplasticity modifications and neurobiological mechanism modifications. These intersections are central to the manifestation and development of chronic pain-induced depression (Sheng, Liu, Wang, Cui, & Zhang, 2017). Pain also has a deleterious impact on psychopathology and psychiatric treatment outcomes, with pain often leading to treatment resistance (Gerrits et al., 2012). Therefore, treating pain without considering depression or vice-versa may not generate expected outcomes as both pain and depression are interactive and cannot be regarded as two separate dimensions. To improve pain and depression, the Stepped Care for Affective Disorders and Musculoskeletal Pain (SCAMP) trial, a 12-month randomized control trial, enrolled adult patients with the mean

age of 55.5 years with musculoskeletal pain in the lower back, hip or knee and with and without depression (Kroenke et al., 2007, 2009). At the end of the two-year follow-up, the trial revealed that among adults with comorbid pain and depression, the use of optimized antidepressant therapy in combination with pain self-management led to significant improvement in pain reduction and depression severity (Kroenke et al., 2009). However, the SCAMP trial was not focused on elders; therefore, similar studies should be conducted on older adults in the future. Research on the overlapping neuroplastic changes caused by pain and depression is warranted to recognize and intervene in pain-related depression in older adults. Combining pharmacological, non-pharmacological, and behavioral components in the treatment of elders suffering from comorbid pain and depression may help reduce pain, depression, and improve function. However, the relationship between persistent multisite pain and depression is not well investigated in older adults.

In our study, we also found that participants with the persistence of multisite pain were more likely to report anxiety at the 18-month and six-year follow-up compared to those without pain. This is congruent with previous study findings in terms of a significant association between persistent multisite pain and anxiety. For example, a population-based cohort study conducted in older adults reported that multisite pain was strongly associated with anxiety even when controlled for potential confounding factors (Denkinger et al., 2014). In another cross-sectional study conducted in Brazil, a significant association was found between persistent pain and anxiety in older adults (Santos et al., 2017). The study findings are in line with previous studies investigating the linkage of pain-anxiety in the general population (Asmundson & Katz, 2009; Gerrits et al., 2012; McWilliams et al., 2004).

A plausible explanation may be related to sharing underlying behavioral and cognitive processes by both anxiety and chronic pain. These include elevated somatic attention, hypervigilance, avoidance behavior, attentional bias, hyperstimulation, decreased gastrointestinal activity, and physiological arousal (e.g., increased heart and respiratory rate, elevated blood pressure, increased muscular tension, and high blood flow to skeletal muscle) (Asmundson, Coons, Taylor, & Katz, 2002; Asmundson & Katz, 2009; Burston et al., 2019; Vlaeyen & Linton, 2000; Woo, 2010). A recently conducted study on a general population showed that having higher anxiety scores but not depression was significantly associated with greater pain sensitivity in participants with knee osteoarthritis (Burston et al., 2019). Overall, little is known about the correlates between persistent multisite pain and anxiety in the older population. The occurrence of anxiety is independent of depression, yet the pain literature has not explored the co-existing pain-anxiety relationship, particularly among the elderly. Diagnosing and managing anxiety in older adults can be challenging due to the co-existence of depressive disorder. Future studies are needed in understanding the multisite pain and anxiety linkage, independent of depression

Furthermore, there is some degree of overlap between the three conditions: depression, anxiety, and pain. Both depression and anxiety share the same pathophysiological pathways as pain and facilitate the central modulation of the pain response in the several regions of the brain such as the hypothalamus, periaqueductal gray, and amygdala (De Heer et al., 2014; C. M. B. de Oliveira et al., 2011; Meerwijk, Ford, & Weiss, 2013). Also, depression and anxiety stimulate stress and increase the level of pro-inflammatory cytokines (Felger & Lotrich, 2013; Maes et al., 1998). This response could elevate the pain experience (C. M. B. de Oliveira et al., 2011). Besides, the co-occurrence nature of pain-anxiety-

depression complicates the process of diagnosing and treating anxiety/depression in elders with persistent pain. Even when affective disorder and persistent pain are accurately diagnosed, the efficacy of the treatment for anxiety or depression may be less effective for individuals with persistent pain (Holmes, Christelis, & Arnold, 2012).

Considering the co-existing nature of pain and affective disorders in general, surprisingly, our hypothesis 3b was not supported as there was no association between incident multisite pain, and depression and anxiety at the six-year follow-up. In this study, we defined incident multisite pain as having no pain or single-site pain at baseline, which developed into multisite pain at 18-month or six-year follow-up. On the other hand, persistent multisite pain at baseline that persisted as multisite pain at 18-months or six years was considered persistent multisite pain, also referred to as persistence of multisite pain as pain measures were longitudinally assessed. Although we expected that incident multisite pain would be associated with psychological disability at the six-year follow-up, we did not find a significant association between incident multisite pain and anxiety and depression at six-year follow-up. On the contrary, the persistence of multisite pain was an independent risk factor for depression and anxiety at 18-month and six-year follow-up.

In terms of physical disability, among individuals with incident multisite pain, the risk for ADL difficulty became evident only at six years, but individuals with persistent multisite pain consistently had a much higher risk for ADL difficulty at 18 months and, they continued to have a higher risk at six years. For instance, at six years, participants with incident multisite pain had a relative risk of 4.67 (95% CI: 1.31-16.70) for a lot of ADL difficulty, whereas participants with persistent multisite pain had a relative risk of 10.62 (95% CI: 3.23-34.97) for a lot of ADL difficulty than those with no pain. Regarding IADL

difficulty at 6-years, the relative risk for a lot of IADL difficulty for individuals with incident multisite was 4.97 (95% CI 1.29-19.21) and the relative risk for a lot of IADL difficulty for those with persistent multisite pain was 18.10 (95% CI 5.36-61.12). Hence, there is a substantial increase in the risk of having a lot of IADL difficulty for individuals with incident or persistent multisite pain compared to individuals with no pain. However, due to the substantial overlap in the confidence interval, we cannot conclude the risk for ADL/IADL difficulty between the incident and persistent multisite pain group at 6 years was substantially different. These findings reveal that it is not incident multisite pain, but the persistence of multisite pain that act as a significant predictor of physical and psychological disability in older adults. Basically, persistent multisite pain is more debilitating than incident multisite pain. Using the longitudinal approach is important because it allows the assessment of the persistence of pain, which is more meaningful in the older population. It helps to better understand the persistence of pain and its impact on older adults' physical and physiological disability. The longitudinal method also allowed to generate persistence of pain, as studies, in general, evaluate persistent pain in a single cross-sectional assessment. The drawback of the single assessment is that it overlooks the duration or persistence of pain determined as persistent pain.

Moreover, by applying the longitudinal method, we were able to show the significant difference in the risks among participants with persistent multisite pain compared to those with incident multisite pain, single-site pain, and no pain. By assessing pain persistence, we could more accurately identify a population with greater vulnerability in terms of physical and psychological disability in older adults. The underlying mechanism is unclear, but it is plausible that the persistence of pain may cause neuroplastic changes in the brain and spinal

cord, altering an individual's perception and response towards pain. These neuroplastic changes related to the persistence of pain may modify the pain experience in older adults, making the pain difficult to treat and often accompanied by mood disorders like depression and anxiety, as observed in our study. The evidence from current research also indicates that the poorly treated persistent pain can lead to sensitization (Holmes et al., 2012). Because the literature is scant and limited, especially in older adults, we underscore the need for more research to untangle the pain-anxiety-depression relationship. The findings from our study will help develop targeted interventions and establish techniques to delay or prevent mood disorder in older people with the persistence of multisite pain. Clinicians should be aware to routinely screen and monitor for depression and anxiety in the presence of persistent multisite pain in elders. It may be that older people with depression or anxiety and pain are a unique group and require different treatment than individuals that do not have pain accompanying depression or anxiety (De Heer et al., 2014). Future studies should also investigate the role of other psychological factors such as pain catastrophizing and self-efficacy in relation to the persistence of pain, which may contribute to variability in pain-related experiences in older adults.

Hypothesis #4. Accounting for socioeconomic status, lifestyle factors, and comorbidities, older adults with persistent multisite pain have an increased risk of mortality than those with no pain.

Our study results showed no relationship between baseline persistent multisite pain and mortality in older adults at 9.8 years and 12.4 years. This study addresses the significant but controversial issue of the pain-mortality relationship in the elderly population. Although the lack of a significant association between pain and mortality in our study is consistent with

several studies listed in a recently conducted meta-analysis by Macfarlane et al. (2017). Our study's findings contrast to the results from some studies (Andersson, 2004; Docking et al., 2015; Jordan & Croft, 2010; D. Smith, Wilkie, Croft, & McBeth, 2018) but are consistent with several other studies. Macfarlane et al. (2007) did not find an association between multiple joint pain and increased mortality risk in a population-based prospective study from Finland. Similarly, in a large prospective cohort study conducted in Norway, there was no significant association between individuals with chronic musculoskeletal complaints or chronic widespread musculoskeletal complaints and mortality (Asberg et al., 2016). Likewise, in a Swedish population of adults aged 25-74 years, Andersson (2009) on examining the pain and mortality relationship for the older age group (≥65yrs) reported that both regional pain and widespread pain was not significantly related to mortality. Additionally, Smith et al. (2014) reviewed ten observational studies for systematic review and meta-analysis and revealed a modest but not significant relationship between persistent pain and excess mortality.

However, in one study by Kareholt & Brarrberg (1998), pain in the extremities was associated with mortality; but the pain in back, hips, and shoulder was not associated with death. In the study, individuals with severe pain in the extremities had a 34% higher mortality risk than those without pain in the extremities. Similarly, pain in the lower extremities is predictive of greater disability in older adults (knee and foot) (J. Chen, Devine, Dick, Dhaliwal, & Prince, 2003; Croft et al., 2005; Leveille et al., 1998). Also, pain in the lower extremities (e.g., knee pain) accompanied by pain in another site is related to greater physical and psychological disability (Croft et al., 2005). Chronic widespread pain is defined as pain present for at least three months, on at least two contralateral quadrants, above and

below the waist and the axial skeletal (Wolfe et al., 1990). Because chronic widespread pain includes pain in the extremities and pain in the extremities can be more disabling in older adults, this may further explain the possibility of an increase in mortality among those with chronic widespread pain, as explained by Macfarlane et al. (2007). Moreover, it is well-established that disability is associated with increased mortality risk in older adults (Wu et al., 2016).

In our study, the mortality rates were highest in the persistent multisite pain group, followed by the single-site pain group and then the no pain group at 9.8 and 12.4 years. The increased mortality rates in participants with pain compared to those with no pain is consistent with the findings from the National Health and Nutrition Examination Survey (NHANES) data, which had a total of 15,311 adults aged 20 years and older. The study was neither restricted to older adults nor musculoskeletal pain (Patel & Turk, 2015). In contrast, the MOBILIZE cohort included older adults (≥65years) with persistent musculoskeletal pain in hands, shoulders, hip, knee, foot, and adults aged ≥65 years.

We further conducted gender stratified analysis and found a significant association between pain severity and mortality in the unadjusted model at 9.8 years and 12.4 years, only among women. Overall, we did not find the effect of gender on the pain-mortality relationship, which contrasts with previous studies showing that pain and mortality relationships varied by sex. For instance, in population-based prospective cohort studies of older adults with the mean age of 83 years, older women had 40% increased risk of mortality associated with disabling back pain (adj. HR 1.4; 95% CI 1.1-1.9) while no significant relationship was observed for older men (adj.HR 1.0; 95% CI: 0.5-1.9) compared to participants with no pain (Docking et al., 2015). On conducting secondary data analysis using

the Canadian Study of Health and Aging (CSHA) dataset, a nationally representative observational study of adults aged ≥65 years, Shega et al. (2013) reported that the likelihood of dying was lower for older women with pain than older women without pain (HR: 0.40; 95%CI 0.33-0.47). However, the pain-mortality relationship was not significant for older men (HR 1.00, 95%CI 0.84-1.19) over the five years. Due to the mixed evidence on the effect of gender on the pain-mortality relationship, future studies should examine the pain-mortality relationship stratified by gender and to confirm if older women with pain are at increased, decreased, or at no risk of excess mortality. The lack of a significant association between pain and mortality in our study is surprising. This finding may also be related to the higher years of education and a higher level of physical activity seen in the MOBILIZE Boston Study population compared to the average older population. Hence, pain-mortality association should be studied further in other populations.

Besides, persistent multisite predicts the progression of disability and is strongly associated with physical disability (Croft et al., 2005; Leveille et al., 1998, 2001; Peat et al., 2006). Physical disability is a strong predictor of mortality in the older population (Majer et al., 2011; Wu et al., 2016). This significant finding was observed in our study as physical disability (ADL) was associated with mortality, even when adjusted for sociodemographic, health factors, chronic health conditions, and medications. Therefore, one suggested explanation may be that persistent multisite pain contributes to physical disability, which in turn may lead to early mortality.

Furthermore, the accumulating evidence from recent studies also indicates that lifestyle factors (e.g., physical activity), depression, and functional limitation strongly mediate the pain and mortality linkage (Andersson, 2009; DaSilva et al., 2018; Macfarlane et

al., 2017; D. Smith, Wilkie, Croft, Parmar, et al., 2018). Thus, the pain-mortality relationship may not be a direct pathway. Older individuals with chronic musculoskeletal pain may be less physically active than those without pain (Stubbs et al., 2013). A recent study demonstrated that the number of chronic musculoskeletal pain sites was associated with lower physical activity, even after controlling for confounders such as age, gender, obesity, and depressive symptoms (Murata et al., 2019). Physical inactivity is also significantly associated with depression in elders (Lampinen, Heikkinen, & Ruoppila, 2000; Overdorf, Kollia, Makarec, & Alleva Szeles, 2016). Moreover, both aging and pain are related to functional limitations (Covinsky, Lindquist, Dunlop, & Yelin, 2009), and persistent multisite pain is associated with physical disability in elders (Croft et al., 2005; Leveille et al., 1998). Additionally, persistent multisite pain increases the risk for depression (Denkinger et al., 2014; Eggermont, Bean, et al., 2009; Eggermont et al., 2012; Leveille et al., 2005; Mänty et al., 2014). Hence, depression and physical disability are closely related and have a reciprocal effect on one another (Y. Lee & Park, 2008; Lenze et al., 2001, 2005). It is well-established that both depression and physical disability are associated with excess mortality risk in elders (DaSilva et al., 2018; Majer et al., 2011; Penninx et al., 1999; Wu et al., 2016). This demonstrates that the pain-mortality relationship may not be a straightforward one as expected.

Another possible explanation is that persistent pain is a significant barrier to physical activity (Koltyn, 2002; Taylor, 2014). Older people with persistent pain have lower physical activity levels than those with no pain (Kaplan et al., 2003; C. Larsson et al., 2016). The decreased level of physical activity is often explained by the fear-avoidance model of pain, which views avoidance of activity as a result of fear of injury or movement, resulting in

disability and suffering (Leeuw et al., 2007; Vlaeyen & Linton, 2000). Limiting physical activity leads to a cycle of restriction, decreased participation in social activities, impaired physical performance, and disability (Mackichan et al., 2013; Manini & Pahor, 2009). Physical inactivity is strongly related to morbidity and mortality in older adults (Booth, Roberts, & Laye, 2012; Llamas-Velasco et al., 2016). A sedentary lifestyle increases the risk of weight problems such as overweight and obesity (Jakicic & Davis, 2011), and obesity is already a huge problem affecting 35% of the older population (Ogden, Carroll, Kit, & Flegal, 2013). Obesity is also associated with few, if not all, leading causes of death, including diabetes, heart disease, hypertension, cancer, arthritis, and functional limitations (Samper-Ternent & Al Snih, 2012). Persistent multisite pain is also significantly associated with a higher body mass index (Leveille et al., 2009; Pan et al., 2017). These major chronic conditions are responsible for functional decline in older adults (Fong, 2019). Obesity in older people is related to decreased physical activity and impaired physical function in community-residing older adults (Riebe et al., 2009). Physical inactivity and obesity are regarded as significant risk factors for disability (J. F. Fries, 1996; Samper-Ternent & Al Snih, 2012). Disability plays a vital role in mortality as disabled older people are at risk of dying than non-disabled (Majer et al., 2011; Wu et al., 2016).

Given that the common factors such as the higher body mass index and physical inactivity are significantly associated with persistent multisite pain and excess mortality in older adults, it is reasonable to surmise that persistent multisite pain would be an essential predictor to mortality. Overall, it appears that functional disability is a strong predictor of mortality among community-dwelling older adults. Therefore, it is crucial to improve function by targeting older people with reduced functional abilities, which may reduce the

risk of excess mortality in older adults in an ever-growing aging population. By applying a biopsychosocial approach and involving a multidisciplinary team while treating elders with persistent multisite pain may alleviate pain and improve both physical and psychological disabilities among older people.

This current study's results extend the previous literature by including longitudinally assessed persistent pain, measures of physical disability, and both the measures of psychological disability, depression, and anxiety in a representative sample of community-dwelling older adults and consequently showing that persistence of multisite pain, is a significant predictor of physical and psychological disability. The study adds new insights into the shortcomings of a single cross-sectional assessment of persistent pain, which disregards the duration of persistent pain. Using the longitudinal pain assessment approach we found a marked difference in the risk for ADL and IADL disability, depression, and anxiety in individuals with persistence of multisite pain compared to individuals with incident multisite pain, single-site pain, and no pain.

Implications for Nursing

The findings from this study have several implications for research and clinical practice. The observed strong relationship between persistent multisite pain and physical and psychological disability among community-dwelling older adults in both the short and long-term emphasizes the severe and disabling effect of persistent multisite pain on older people. It is essential that clinicians routinely count and assess the number of painful sites. Using multisite pain measures to identify the number of pain sites during the pain assessment and knowing the functional ability is crucial for evaluating older adults with multisite pain. The increased risk of physical and psychological disability at 18 months and six years suggests

that persistent multisite pain is a significant risk factor for ADL, IADL disability, depression, and anxiety in older adults. The underlying causes of persistent multisite pain should be identified and targeted. Using the longitudinal approach allowed the assessment of the persistence of pain, which is more meaningful in older adults' populations. As elders with the persistence of multisite pain more likely to experience depression/anxiety, clinicians need to be aware of depression and anxiety when older patients report the persistence of pain in multiple locations. Diagnosing and treating anxiety/depression in patients with persistent multisite pain can be challenging due to the bidirectional relationship. However, routinely screening and monitoring for any psychological distress may help identify depression/anxiety in older adults with multisite pain. Using a biopsychosocial approach and involving a multidisciplinary team while treating an older individual with potential multisite pain is critical for adopting optimal strategies that will help to optimize function and psychological health in an aging population. Pain and depression are comorbid conditions; one influencing the reaction of another. For instance, pain negatively affects the response of depression to treatment and vice-versa. Thus, older adults with depression and pain are a unique group and require different treatment than individuals that do not have pain accompanying depression or anxiety. A Stepped Care for Affective Disorders and Musculoskeletal Pain (SCAMP) study, a 12-month randomized controlled trial, enrolled adult patients with the mean age of 55.5 years with musculoskeletal pain in the lower back, hip or knee and with and without depression (Kroenke et al., 2007, 2009). The trial consisted 12 weeks of antidepressant therapy (phase 1), that was followed by a six-week session of pain self-management program (PSM) provided over 12 additional weeks by using a blend of medication and behavioral intervention (phase 2), and a 6-month continuation phase which was mainly monitoring of

symptoms and treatment reinforcement (phase 3). The study enrolled 250 primary care patients with clinically significant depression and musculoskeletal pain (lower back, hip, knee) and 250 non-depressed patients with the same pain criteria. A nurse care manager delivered the program under the supervision of a physician specialist. The SCAMP findings revealed that antidepressants combined with pain self-management programs successfully reduced depression severity and improved response and remission rates in the patients. Also, there was a moderate decrease in pain severity and pain-related disability (Kroenke et al., 2007, 2009). However, there was no specific information on pain and disability in the depressed older people. The ultimate goal is to reduce the overall burden and improve function in elders living with comorbid persistent multisite pain and depression. Therefore, older adults may also benefit from similar programs that incorporate behavioral and medication components into the program with the primary focus on elders.

Persistent multisite pain strongly contributes to physical disability in elders. Therefore, the assessment of functional status is a critical component in the evaluation of an older person in a clinical setting. Developing individually tailored programs and interventions and implementing optimal strategies to reduce the burden of multisite pain and delay or prevent functional impairment and physical disability is necessary, which may, in the long run, prevent the likelihood of early mortality. Nurses should promote the regular use of analgesics to maximize pain relief. Encouraging the use of both pharmacological and non-pharmacological approaches that are complementary or alternative strategies can augment pain relief. Physical therapy, cognitive-behavioral therapy, and many other therapies offer an alternative or complementary approach to persistent pain (American Geriatrics Society (AGS), 2009). Also encouraging the elders to keep a pain diary or daily log may allow them

to track the different treatment modalities that are impacting the older adults' pain and function (Kaye et al., 2010).

Lifestyle factors such as physical activity and body mass index (BMI) is widely recognized to influence physical and mental health in individuals with pain. Because there is strong scientific evidence suggesting that physical activity is beneficial to prevent physical and psychological disabilities, nurses should motivate older adults to remain physically active, to help manage their pain, depression/anxiety, and function. Nurses can encourage the use of an accelerometer or a daily log or a tracking device to allow older people to track their daily steps or exercise, which will promote self-management. Older adults should be encouraged to follow the recommended level of physical activity every week, consisting of at least 150 minutes of moderate-intensity aerobic exercise per week and muscle-strengthening activities that involve major muscle groups at least twice or more per week. Physical activity such as walking, gardening, dancing, hiking, swimming, improves mood, function, and lowers the rate of all-cause mortality in older adults (WHO, 2019). Other exercise programs, such as yoga and tai chi, are useful in treating pain (Bonura & Tenenbaum, 2014; Hall et al., 2017; You et al., 2018). Also, a few non-pharmacological approaches, such as relaxation techniques, CBT, and hypnotherapy, may help treat pain and depression/anxiety in elders (American Geriatric Society (AGS), 2009).

Among older adults, pain self-management can be unique and complex. Therefore, individual factors and disease-related factors should be considered while planning and developing pain self-management programs specifically for the geriatric population. The self-management programs should include core-skills developed by Lorig and Holman (2003). The features that distinguish self-management programs from traditional patient

education are that it uses the self-efficacy theory based on patient-centered problems and identified five core self-management skills: problem-solving, decision making, resource utilization, the formation of a patient-provider partnership, and action planning (Lorig & Holman, 2003). Applying these core-skills in the self-management program may serve as an effective strategy for managing persistent multisite pain in older adults. Moreover, Albert Bandura (2004) underscored the importance of monitoring health behavior and circumstances in which it occurs and using proximal goals to help change one's behavior.

The self-management model also emphasizes different process components, such as self-monitoring. Generally, in studies related to pain self-management, the process of engagement is not well-understood. In patients with chronic diseases, the engagement process is vital because it helps to form an active partnership with health care providers which promotes collaboration and evaluation of treatment options, a better understanding of their chronic condition, and self-monitoring of symptoms and health conditions (Carman et al., 2013; Gruman et al., 2010). Measuring the process of engagement is crucial because they are explicit, specific, uncomplicated, and provides substantial evidence by isolating what approach is working and what needs to be changed (Rubin, Pronovost, & Diette, 2001). Therefore, the engagement process can be measured using a diary or a daily log, which can provide valuable information to understand the engagement process during self-management. Because the engagement process helps build confidence in managing and controlling pain, nurses should promote and encourage older adults to engage in daily logging habits.

Although there is a strong theoretical foundation for self-monitoring in behavioral change interventions (Burke, Wang, & Sevick, 2011), behavioral intervention programs often do not include self-monitoring mechanisms to their plan. Future intervention programs may

incorporate the five-core skills of self-management, including self-monitoring, to reduce the burden of physical and psychological disability among elders with persistent multisite pain. Exercise programs can be designed and implemented depending on the age group: young-old, middle-old, and very old adults. Organizing varied exercise opportunities or giving incentives in the form of financial reimbursement for exercising may promote the elder's physical activity. Also, considering the unique factors associated with physical activity behavior among older men and women when designing intervention programs for older adults may generate effective results. More public policies need to be developed to promote physical activity in older adults (e.g., cycling, walking).

Over the last three decades, self-management programs have shown to be effective in managing and reducing pain. However, there is a dire need for a comprehensive instrument to measure persistent pain self-management (PPSM), especially in older adults. The instrument can be based on the social cognitive theory and self-efficacy as the theoretical framework, and both theories explain the principles of self-management. The instrument can be developed based on the most recent definition of persistent pain self-management proposed by Stewart et al. (2014), "A multidimensional process occurring when an older adult perceives the need to self-manage pain and is willing and able to do so with support from others. It involves an older adult with persistent pain being an active individual in their treatment, engaged in the personal development of skills, and aware of their responses to symptoms. The older adult initiates, participates, and develops their methods of symptom control by using pain management techniques that lead to improvements in the physical, psychological, and social health domains" (p. 220).

Furthermore, in our previous study (Thapa et al., 2018), we found the risk factors for persistent multisite pain were relatively similar to other recognized geriatric syndromes such as falls, frailty, functional decline, and urinary incontinence. In the study, we concluded that persistent multisite pain qualifies as a distinct geriatric syndrome. In this current study, we further revealed that persistent multisite pain is strongly associated with physical and psychological disability in older adults. The evidence from this study directs towards developing targeted intervention and prevention strategies for older adults with persistent multisite pain. Therefore, future intervention studies should incorporate pain management approaches in older adults with mood problems to prevent the functional consequences of pain. Individually tailored interventions and programs should focus on pain management by incorporating pharmacological and non-pharmacological approaches to reduce disability in older adults. Thus, persistent multisite pain as a geriatric syndrome may be an important clinical marker for recognizing older adults who are at an increased risk of functional loss. Our study results have important translational implications since the findings indicate that public health policy should promote lifestyle modifications and interventions that may alleviate pain and lessen the burden of a wide range of disabilities in a growing aging population.

Strength and Limitations

The MOBILIZE Boston Study (MBS), a prospective population-based cohort study was supported by the National Institute of Aging. The MBS collected comprehensive data on several aspects of functional measures, psychological disability, pain, comorbidities, and mortality in the community-dwelling older adults. MOBILIZE study used a representative sample of the older community-dwelling population in the Boston area. Most importantly,

the use of door-to-door population-based-approach recruitment instead of a more limited clinical sample allows generalizing our study finding to English-speaking older adults living in the urban and suburban communities without moderate to severe cognitive impairment. Besides, the collection of data at baseline, 18-month, and 6-year follow-up allowed us to capture the significant disabling consequences of persistent multisite pain on physical and psychological domains in both the short and long term. As highlighted earlier, the study findings are generalizable to community-dwelling older adults. Also, applying the longitudinal method to assess pain's persistence allowed the consideration of the length or persistence of pain. Using the longitudinal approach, we were able to study the persistence of pain because persistent pain in a single cross-sectional assessment overlooks the duration or the actual persistence of pain. To date, no studies have examined the impact of the incident multisite site on physical and psychological disability. This is the first study to use the longitudinal assessment of persistent pain, to assess the persistence of pain and to reveal the differences in the risk associated with ADL and IADL disabilities, depression, and anxiety among those with the persistence of multisite pain compared to those with incident multisite pain. Also, our study is the first to investigate the relationship between persistent multisite pain and psychological distress and mortality in the aging population.

We also did an additional analysis using the 9.8 years data because there was extensive ascertainment data on mortality until 06/06/2015. The results confirmed the findings from the 12.4 years data. We additionally performed a gender stratified analysis using 9.8 years and 12.4 years data to investigate if there is a gender effect on the pain-mortality relationship in older adults.

Our study has several limitations. First, participants enrolled in the MBS were representative of the overall demographic profile of elders living in the Boston area, on comparing with data from the 2000 U.S. Census; however, participants in the MBS study have a relatively higher education level. This unique characteristic of this study population may have limited the ability to detect the effect of pain on mortality. Second, MBS excluded participants who were unable to walk 20 feet without personal assistance; thus, older adults with disability at baseline or those who developed disability during the follow-up were less likely to participate in the 6-year follow-up. Third, the pain assessment was restricted to persistent pain present in the musculoskeletal regions that included pain in hands and wrists, shoulders, chest, back, hips, knees, and feet which are regarded as most usual sites of pain contributing to disability in older adults (Eggermont et al., 2014). Other pain sites such as the abdomen and head were not included because depending upon previous research, musculoskeletal pain is a significant cause of disability in older adults. Also, abdominal pain and headache pain, have a lower prevalence in older adults but could be studied in subsequent studies for their impact on physical and psychological disability. Fourth, although we adjusted for several important comorbidities that may confound the pain-mortality linkage, the list is not exhaustive.

Conclusion

This study sought to test the hypothesis that persistent multisite pain is associated with physical and psychological disability and mortality in community-dwelling older adults using the population-based longitudinal dataset. The King's System model is the conceptual framework used to guide the study. It offers a biopsychosocial perspective in which older adults experience pain and disability through personal systems, interpersonal systems, and

social systems. We used a longitudinal approach to generate persistence of multisite pain because persistent pain in a single cross-sectional assessment overlooks the duration or persistence of pain. This is the first population-based cohort study to examine the impact of the persistence of multisite pain measured overtime on the physical and psychological disabilities and mortality in community-dwelling older adults. Our study is also a first to understand the influence of incident multisite pain on physical and mental disability. Older adults with the persistence of multisite pain are at a higher risk of ADL and IADL disability. Also, the persistence of multisite pain predicts depression and anxiety at the18-month and six-year follow-up. Nonetheless, persistent multisite pain at baseline is not associated with mortality in older adults at 9.8 years and 12.4 years. Because persistent multisite is a common problem in older adults, pain assessment and treatment need to be improved using multidimensional approaches. Utilization of multisite pain measures and understanding the functional capability is crucial when evaluating older adults with multisite pain. Importantly, healthcare providers also need to be aware of depression and anxiety when older patients report multisite pain in their body. Applying a biopsychosocial approach while treating an older individual with multisite pain may optimize physical and psychological health, indirectly influencing elders' mortality. Although previous studies have examined the relationship between multisite pain and disabilities. The findings of this current study extend the previous literature by including longitudinal assessed persistent pain and using two significant measures of psychological disability in a representative sample of community-dwelling older adults and, consequently, showing that persistence of multisite pain, is a significant predictor of physical and psychological disability. Using the longitudinal assessment of persistent pain, we assessed the persistence of multisite pain and found a

marked difference in the risk for ADL and IADL disabilities, depression, and anxiety compared to those individuals with no pain. Assessing the persistence of multisite pain is a novel approach in identifying elders who are at an increased risk for physical and psychological disability. Primarily, this study contributes to the evolving field of geriatric pain research by demonstrating the disabling consequences of the persistence of multisite pain. Future studies need to develop individually tailored interventions to prevent functional loss in older adults with persistent multisite pain.

Table 1.
Socio-Demographic and Health Characteristics of Participants Who Completed the Follow-Up Assessment Compared to Participants Who Died or Dropped Out at 18 Months

Characteristics	Completed 18-month follow-up N= 680 n (%)	Died/Dropped out N= 84 n (%)	p-value*
Age groups (yrs.)			0.202
<75	212 (31.13)	22 (26.19)	
75-79	221 (32.45)	23(27.38)	
≥80	248 (36.42)	39(46.43)	
Gender			0.683
Male	244 (35.83)	32(38.10)	
Female	437(64.17)	52(61.90)	
Education			0.085
≤High School	227 (33.38)	36 (42.86)	
College graduate	453(66.62)	48 (57.14)	
Race			0.876
White	526 (77.35)	67(79.76)	
Black	111 (16.32)	12(14.29)	
Other	43(6.32)	5(5.95)	
BMI[a]			**0.053**
<25kg/m2	190 (28.44)	32(40.51)	
Overweight 25.0-29.9kg/m2	288(43.11)	32(40.51)	
Obese >30kg/m2	190(28.44)	15 (18.99)	
Physical Activity[b]			0.065
Sedentary activity	216(31.95)	35(43.21)	
Light activity	226(33.43)	27 (33.33)	
Moderate to vigorous activity	234(34.62)	19(23.46)	
[c]Blocks walked (per week)			**0.009**
0 - 3 blocks/week	135(20.67)	29(35.37)	
4-12 blocks/week	158(24.20)	22(26.83)	
13-60 blocks/week	215(32.92)	17(20.73)	
>60 blocks/week	145(22.21)	14(17.07)	
[d]Heart Disease			0.351
Yes	280 (41.12)	39(46.43)	
No	401(58.88)	45(53.57)	
[e]Diabetes Mellitus			**0.018**
Yes	128(18.80)	25(29.76)	
No	553(81.20)	59(70.24)	
Lung disease			0.157
Yes	105(15.42)	18(21.43)	
No	576 (84.58)	66(78.57)	
Analgesics			0.141
Yes	163(23.94)	26(31.33)	
No	518(76.06)	57(68.67)	
Psychiatric drugs			0.416
Yes	138(20.26)	20(24.10)	
No	543(79.74)	63(75.90)	
[f]MMSE Mean (SD)	27.18(2.56)	26.08 (3.21)	**0.003**
Pain category			0.932

No pain	245(36.03)	29 (34.52)	
Single-site pain	166(24.41)	20 (23.81)	
Multisite pain	269(39.56)	35 (41.67)	
ADL			0.249
No difficulty	532(78.12)	60(71.43)	
Little or some difficulty	100(14.68)	14(16.67)	
A lot of difficulty or inability	49(7.20)	10(11.90)	
IADL			0.282
No difficulty	411 (60.44)	44(52.38)	
Little or some difficulty	126 (18.53)	21(25.00)	
A lot of difficulty or inability	143 (21.03)	19(22.62)	
Depression			0.411
Yes	48(7.05)	8(9.52)	
No	633(92.95)	76(90.48)	
Anxiety			0.159
Yes	66(9.78)	12(14.81)	
No	609(90.22)	69(85.19)	
Anxiety Score (SD)	3.63(2.93)	4.04(2.90)	0.2371

[a]Body mass index (BMI) calculated as weight in kilograms divided by height in meters squared.
[b]Physical activity measured using the Physical Activity Scale for the Elderly score (PASE).
[c]Blocks walked per week; 0-3 blocks/week, 4-12 blocks/week, 13-60 blocks/week, >60 blocks/week
[d] Self-reported heart disease included conditions: heart attack, congestive heart failure, angina, pacemaker, or cardiac arrhythmia. [e]Diabetes mellitus was defined from algorithm of self-report of disease, use of diabetes related medications, random glucose level and hemoglobin A1C.
[f]Daily analgesics defined as use of one or more analgesic medications at least daily in the last 2 weeks.
[g]Psychiatric drug defined as any use versus no use of a psychiatric medication in the previous 2 weeks.
[h]Mini Mental State Examination (MMSE) assessed cognitive impairment (<24) used as a continuous variable.
*****Chi-square analysis, for all categorical variables and ANOVA test for continuous variables (MMSE and anxiety), d.f.=(r-1) (c-1).

Table 2.
Socio-Demographic and Health Characteristics of Participants Who Attended the 6-Year Follow-Up Assessment Compared to Participants Who Died or Dropped Out at the 6-Year Follow-Up

Characteristics	Completed 6-year follow-up N= 354	Died/Dropped out N= 411 |	p-value*
Age groups (yrs.)			0.719
<75	107 (30.23)	127 (30.90)	
75-79	118 (33.33)	126 (30.66)	
>=80	129 (36.44)	158 (38.44)	
Gender			0.310
Male	121 (34.18)	155 (37.71)	
Female	233 (65.82)	256 (62.29)	
Education			**<0.001**
<=High School	91 (25.78)	172 (41.85)	
College graduate	262 (74.22)	239 (58.15)	
Race			0.378
White	282(79.89)	311(75.67)	
Black	51(14.45)	72(17.52)	
Other	20 (5.67)	28(6.81)	
BMI[a]			0.774
<25kg/m2	108(30.95)	114(28.64)	
25.0-29.9kg/m2	148(42.41)	172(43.22)	
>30kg/m2	93(26.65)	112(28.14)	
Physical Activity[b]			0.556
Sedentary activity	110(31.34)	141(34.73)	
Light activity	118 (33.62)	135(33.25)	
Moderate to vigorous activity	123(35.04)	130(32.02)	
[c]Blocks walked (per week)			**<0.001**
Less than 1 mile	53(15.41)	111(28.39)	
Upto 1mile/week	79 (22.97)	101(25.83)	
Upto 5 miles/week	122(35.47)	110(28.13)	
More than 5 miles	90(26.16)	69(17.65)	
[d]Heart Disease			**0.045**
Yes	134(37.85)	185(45.01)	
No	220(62.15)	226(54.99)	
[e]Diabetes Mellitus			**<0.001**
Yes	50(14.12)	103(25.06)	
No	304(85.88)	308(74.94)	
Lung disease			0.118
Yes	49(13.84)	74(18.00)	
No	305(86.16)	337(82.00)	
[f]Daily Analgesics			0.548
Yes	84 (23.73)	105 (25.61)	
No	270(76.27)	305 (74.39)	
[g]Psychiatric drugs			0.045
Yes	62(17.51)	96(23.41)	
No	292(82.49)	314(76.59)	

[f]MMSE Mean (SD)	27.69(2.37)	26.52(2.77)	**<0.0001**
Pain category			0.717
No pain	125 (35.31)	149 (36.34)	
Single-site pain	91(25.71)	95 (23.17)	
Multisite pain	138(38.98)	166 (40.49)	
ADL			**0.007**
No difficulty	292(82.49)	300(72.99)	
Little or some difficulty	42 (11.86)	72 (17.52)	
A lot of difficulty or inability	20 (5.65)	39 (9.49)	
IADL			**0.001**
No difficulty	235 (66.38)	220 (53.66)	
Little or some difficulty	63 (17.80)	84 (20.49)	
A lot of difficulty or inability	56 (15.82)	106 (25.85)	
Depression			0.799
Yes	25(7.06)	31(7.54)	
No	329(92.94)	380(92.46)	
Anxiety			0.136
Yes	30(8.55)	48(11.85)	
No	321(91.45)	357(88.15)	
Anxiety Score (SD)	3.46(2.80)	3.86(3.03)	0.0607

[a]Body mass index (BMI) calculated as weight in kilograms divided by height in meters squared.
[b]Physical activity measured using the Physical Activity Scale for the Elderly score (PASE).
[c]Blocks walked per week; 0-3 blocks/week, 4-12 blocks/week, 13-60 blocks/week, >60 blocks/week.
[d] Self-reported heart disease included conditions: heart attack, congestive heart failure, angina, pacemaker, or cardiac arrhythmia. [e]Diabetes mellitus was defined from algorithm of self-report of disease, use of diabetes related medications, random glucose level and hemoglobin A1C.
[f]Daily analgesics defined as use of one or more analgesic medications at least daily in the last 2 weeks.
[g]Psychiatric drug defined as any use versus no use of a psychiatric medication in the previous 2 weeks.
[h]Mini Mental State Examination (MMSE) assessed cognitive impairment (<24) used as a continuous variable.
*****Chi-square analysis, for all categorical variables and ANOVA test for continuous variables (MMSE and anxiety), d.f.=(r-1) (c-1).

Table 3.
Demographic and Health Characteristics at Baseline, 18 Months, and 6 Years from MOBILIZE Boston Study (I and II)

Characteristics	Baseline Total=765, N (%)	18 months Total=681, N (%)	6 years Total=354, N (%)
Age groups (yrs.)			
<75	234 (30.59)	212 (31.13)	107 (30.23)
75-79	244 (31.90)	221 (32.45)	118 (33.33)
≥80	287 (37.52)	248 (36.42)	129 (36.44)
Gender			
Male	276 (36.08)	244 (35.83)	121 (34.18)
Female	489 (63.92)	437 (64.17)	233 (65.82)
Education			
≤High School	263 (34.42)	227 (33.39)	91 (25.78)
College graduate	501 (65.58)	453 (66.62)	262 (74.22)
Race			
White	593 (77.62)	526 (77.35)	283 (79.94)
Black	123 (16.10)	111 (16.32)	51 (14.41)
Other	48 (6.28)	43 (6.32)	20 (5.65)
BMI[a]			
<25kg/m2	222 (29.72)	175 (28.18)	136 (39.42)
25.0-29.9kg/m2	320 (42.84)	254 (40.90)	136 (39.42)
>30kg/m2	205 (27.44)	192 (30.92)	73 (21.16)
Physical Activity[b]			
Sedentary activity	251 (33.16)	202 (31.86)	-
Light activity	253 (33.42)	240 (37.85)	-
Moderate to vigorous activity	253 (33.42)	192 (30.28)	-
[c]Blocks walked (per week)			
No walking	8 (1.09)	12(1.90)	9 (2.57)
<1 mile	300 (40.87)	230(36.33)	164 (46.86)
1-3.9 miles	205(27.93)	187 (29.54)	112 (32.00)
≥4 miles	221(30.11)	204 (32.23)	65 (18.57)
[d]Heart Disease			
Yes	319 (41.70)	289 (42.44)	155 (45.19)
No	446 (58.30)	392 (57.56)	188 (54.81)
[e]Diabetes Mellitus			
Yes	153 (20.00)	114 (16.74)	48(13.56)
No	612 (80.00)	567 (83.26)	306(86.44)
Lung disease			
Yes	123 (16.08)	77 (11.31)	54 (15.25)
No	642(83.92)	604 (88.69)	300 (84.75)
[f]Analgesics			
Yes	189 (24.74)	-	84 (23.73)
No	575 (75.26)	-	270 (76.27)
[g]Psychiatric drugs			
Yes	158 (20.68)	-	62 (17.51)
No	606 (79.32)	-	292 (82.49)

[h]MMSE Mean (SD)	27.06 (2.66)	26.91 (2.75)	25.30 (3.93)

[a]Body mass index (BMI) calculated as weight in kilograms divided by height in meters squared.
[b]Physical activity measured using the Physical Activity Scale for the Elderly score (PASE).
[c]Blocks walked per week; 0-3 blocks/week, 4-12 blocks/week, 13-60 blocks/week, >60 blocks/week.
[d] Self-reported heart disease included conditions: heart attack, congestive heart failure, angina, pacemaker, or cardiac arrhythmia. [e]Diabetes mellitus was defined from algorithm of self-report of disease, use of diabetes related medications, random glucose level and hemoglobin A1C.
[f]Daily analgesics defined as use of one or more analgesic medications at least daily in the last 2 weeks.
[g]Psychiatric drug defined as any use versus no use of a psychiatric medication in the previous 2 weeks,
[h]Mini Mental State Examination (MMSE) assessed cognitive impairment (<24) used as a continuous variable.

Table 4.
Prevalence of ADL, IADL, Depression, and Anxiety at Baseline, 18 Months, and 6 Years from MOBILIZE Boston Study (I and II)

Outcome	Baseline Total=765, N (%)	18 months Total=681, N (%)	6 years Total=354, N (%)
Physical disability			
[a]ADL			
No difficulty	592 (77.39)	474 (75.24)	246 (69.49)
Little or some difficulty	114 (14.90)	96 (15.24)	53 (14.97)
A lot of difficulty or inability	59 (7.71)	60 (9.52)	55 (15.54)
[b]IADL			
No difficulty	455 (59.55)	357 (56.76)	249 (70.74)
Little or some difficulty	147 (19.24)	131 (20.83)	48 (13.64)
A lot of difficulty or inability	162 (21.20)	141 (22.42)	55 (15.62)
Psychological disability			
[c]Depression			
Yes	56 (7.32)	55 (8.68)	25 (7.06)
No	709 (92.68)	579 (91.32)	329 (92.94
[d]Anxiety			
Yes	78 (10.32)	32 (5.05)	15 (4.26)
No	678 (89.68)	602 (94.95)	337 (95.74)
[e]Anxiety Score (SD)	3.67 (2.9)	2.66 (2.54)	2.30 (2.36)

[a]ADL difficulty, defined as the level of difficulty in one or more of activities: bathing, dressing, transferring, using the toilet, and eating (Katz et al., 1963). ADL difficulty is the 3-level dependent variable
[b]IADL difficulty, the level of difficulty in one or more of activities: shopping, preparing meals, and light and heavy housework (Lawton & Brody, 1969). IADL difficulty is the 3-level dependent variable.
[c]Depression defined as presence of minor or major depression, categorized as a dichotomous dependent variable. Depression assessed with Eaton method, modification of the Center for Epidemiologic Studies Depression Scale (CESD-R) (Eaton et al., 2004; Radloff, 1977).
[d e]The Hospital Anxiety and Depression Scale (HADS) measure anxiety symptoms with HADS scores >=8 was classified as a binary variable (Zigmond & Snaith, 1983).
[e]Anxiety symptoms as a continuous dependent variable.

Table 5.
Prevalence of Longitudinally Assessed Pain Distribution from Baseline to 18 Months, and 6 Years

Characteristics	18 months Total=632, N (%)	6 years Total=354, N (%)
Pain distribution		
No pain[a]	229 (36.23)	112 (31.64)
Single site pain[b]	175 (27.69)	82 (23.16)
Incident multisite pain[c]	62 (9.81)	63 (17.80)
Persistent multisite pain[d]	166 (26.27)	97(27.40)

Pain distribution assessed longitudinally was categorized as a four-level variable at 18-month and 6-year follow-up. (1) [a]No pain, single site pain, and multisite pain at baseline → no pain at 18-month follow-up (No pain); (2) [b]No pain, single-site pain, and multisite pain at baseline → single-site pain at 18-month follow-up (Single-site pain); (3) [c]No pain or single site pain at baseline→ multisite pain at 18-month follow-up (Incident multisite pain); (4) [d]Multisite pain at baseline →multisite pain at 18-month follow-up (Persistence of multisite pain). No pain was the reference group. Pain categories at 6-years was determined based on pain status at baseline and 6-year follow-up.

Table 6.
Baseline Characteristics According to Longitudinally Assessed Pain Distribution in an Older Population at 18 Months (N=632)

Characteristics	Total N=632	No pain[a] N (%) Total=229	Single site pain[b] N (%) Total=175	Incident multisite pain[c] N (%) Total= 62	Persistent multisite pain[d] N (%) Total =166	p-value*
Age (yrs.)						0.107
<75	200 (31.65)	74 (32.31)	54 (30.86)	25 (40.32)	47 (28.31)	
75-79	208 (32.91)	69 (30.13)	58 (33.14)	26(41.94)	55 (33.13)	
≥80	224 (35.44)	86 (37.55)	63 (36.00)	11(17.74)	64 (38.55)	
Gender						**0.001**
Male	226 (35.76)	98 (42.79)	65 (37.14)	24 (38.71)	39 (23.49)	
Female	406 (64.24)	131 (57.21)	110 (62.86)	38 (61.29)	127 (76.51)	
Education						0.087
≤High school graduate	203(32.17)	66 (28.82)	50 (28.74)	21 (33.87)	66 (39.76)	
College graduate	428 (67.83)	163 (71.18)	124 (71.26)	41(66.13)	100 (60.24)	
Race						0.729
White	489 (77.50)	176 (76.86)	138 (78.86)	50 (80.65)	125 (75.76)	
Black	101 (16.01)	39 (17.03)	26 (14.86)	6 (9.68)	30 (18.18)	
Other	41 (6.50)	14 (6.11)	11 (6.29)	6 (9.68)	10 (6.06)	
BMI[e]						0.164
< 25.0kg/m2	181 (29.24)	71 (31.42)	58 (33.92)	14 (23.33)	38 (23.46)	
25.0-29.9kg/m2	262 (42.33)	101 (44.69)	64 (37.43)	28 (46.67)	69 (42.59)	
≥30.0kg/m2	176 (28.43)	54 (23.89)	49 (28.65)	18 (30.00)	55 (33.95)	
Physical Activity[f]						0.315
Sedentary	194 (30.94)	68 (29.69)	47 (27.17)	17 (27.42)	62 (38.04)	
Light activity	213 (33.97)	74 (32.31)	63 (36.42)	25 (40.32)	51 (31.29)	
Moderate to vigorous activity	220 (35.09)	87 (37.99)	63 (36.42)	20 (32.26)	50 (30.67)	
Heart Disease[g]						0.061
Yes	265 (41.93)	80 (34.93)	81 (46.29)	27 (43.55)	77 (46.39)	
No	367 (58.07)	149 (65.07)	94 (53.71)	35 (56.45)	89 (53.61)	
Diabetes[h]						0.595
Yes	115 (18.20)	38 (16.59)	30 (17.14)	11 (17.74)	36 (21.69)	
No	517 (81.80)	191 (83.41)	145 (82.86)	51 (82.26)	130 (78.31)	
Lung disease						**<0.001**
Yes	92 (14.56)	23 (10.04)	16 (9.14)	12 (19.35)	41 (24.70)	
No	540 (85.44)	206 (89.96)	159(90.86)	50 (80.65)	125(75.30)	
Daily analgesics[i]						**<0.001**
Yes	150 (23.73)	24 (10.48)	38 (21.71)	19 (30.65)	69 (41.57)	

No	482 (76.27)	205 (89.52)	137 (78.29)	43 (69.35)	97 (58.43)	
Psychiatric drugs[j]						0.058
Yes	127 (20.09)	33(14.41)	42 (24.00)	13 (20.97)	39 (23.49)	
No	505 (79.91)	196 (85.59)	133 (76.00)	49 (79.03)	127 (76.51)	
MMSE (<24) Mean (SD)[k]	27.24(2.51)	27.39(2.35)	27.43 (2.41)	27.31(2.62)	26.81(2.75)	

Pain distribution assessed longitudinally was categorized as a four-level variable. (1) [a]No pain, single site pain, and multisite pain at baseline → no pain at 18-month follow-up (No pain); (2) [b]No pain, single-site pain, and multisite pain at baseline → single-site pain at 18-month follow-up (Single-site pain); (3) [c]No pain or single site pain at baseline→ multisite pain at 18-month follow-up (Incident multisite pain); (4) [d]Multisite pain at baseline →multisite pain at 18-month follow-up (Persistence of multisite pain). No pain was the reference group. [e]Body mass index is calculated as weight in kilograms divided by height in meters squared. [f]Physical activity measured using the Physical Activity Scale for the Elderly score (PASE). [g] Self-reported heart disease included conditions: heart attack, congestive heart failure, angina, pacemaker, or cardiac arrhythmia. [h]Diabetes mellitus was defined from algorithm of self-report of disease, use of diabetes related medications, random glucose level and hemoglobin A1C. [i]Daily analgesics defined as use of one or more analgesic medications at least daily in the last 2 weeks.

[j]Psychiatric drug defined as any use versus no use of a psychiatric medication in the previous 2 weeks, [k]Mini Mental State Examination (MMSE) assessed cognitive impairment (<24) used as a continuous variable.

*Chi-square test for all categorical variables and ANOVA test for continuous variable, d.f.= (r-1) (c-1).

Table 7.
Baseline Characteristics According to Longitudinally Assessed Pain Distribution in an Older Population at 6 Years (N=354)

Characteristics	Total N=354	No pain[a] N (%) Total=112	Single site pain[b] N (%) Total=82	Incident multisite pain[c] N (%) Total= 63	Persistent multisite pain[d] N (%) Total =97	p-value[*]
Age (yrs.)						0.711
<75	107 (30.23)	38 (33.93)	25 (30.49)	14 (22.22)	30 (30.93)	
75-79	118 (33.33)	36 (32.14)	25 (30.49)	22 (34.92)	35 (36.08)	
80-85	129 (36.44)	38 (33.93)	32 (39.02)	27 (42.86)	32 (32.99)	
Gender						**0.010**
Male	121 (34.18)	46 (41.07)	27 (32.93)	27 (42.86)	21 (21.65)	
Female	233 (65.82)	66 (58.93)	55 (67.07)	36 (57.14)	76 (78.35)	
Education						0.105
≤High school graduate	91 (25.78)	25 (22.52)	19 (23.17)	13 (20.63)	34 (35.05)	
College graduate	262 (74.22)	86 (77.48)	63 (76.83)	50 (79.37)	63 (64.95)	
Race						0.341
White	282 (79.89)	92 (82.14)	67 (81.71)	49 (77.78)	74 (77.08)	
Black	51 (14.45)	11 (9.82)	14 (17.07)	10 (15.87)	16 (16.67)	
Other	20 (5.67)	9 (8.04)	1 (1.22)	4 (6.35)	6 (6.25)	
BMI[e]						0.916
< 25.0kg/m2	108 (30.95)	38 (34.23)	23 (28.75)	19 (30.65)	28 (29.17)	
25.0-29.9kg/m2	148 (42.41)	48 (43.24)	34 (42.50)	27 (43.55)	39 (40.62)	
≥30.0kg/m2	93 (26.65)	25 (22.52)	23 (28.75)	16 (25.81)	29 (30.21)	
Physical Activity[f]						0.609
Sedentary	110 (31.07)	32 (28.57)	29 (35.80)	19 (30.65)	30 (31.25)	
Light activity	118 (33.33)	38 (33.93)	28 (34.57)	25 (40.32)	27 (28.12)	
Moderate to vigorous activity	126 (35.59)	42 (37.50)	24 (29.63)	18 (29.03)	39 (40.62)	
Heart Disease[g]						0.654
Yes	134 (37.85)	37 (33.04)	33 (40.24)	25 (39.68)	39 (40.21)	
No	220 (62.15)	75 (66.96)	49 (59.76)	38 (60.32)	58 (59.79)	
Diabetes[h]						
Yes	50 (14.12)	10 (8.93)	12 (14.63)	15 (23.81)	13 (13.40)	0.060
No	304 (85.88)	102(91.07)	70 (85.37)	48 (76.19)	84 (86.60)	
Lung disease						**0.005**
Yes	49 (13.84)	19 (16.96)	5 (6.10)	4 (6.35)	21 (21.65)	
No	305 (86.16)	93 (83.04)	77 (93.90)	59 (93.65)	76 (78.35)	
[i]Daily Analgesics						**<0.001**
Yes	84 (23.73)	17 (15.18)	18 (21.95)	11 (17.46)	38 (39.18)	
No	270 (76.27)	95 (84.82)	64 (78.05)	52 (82.54)	59 (60.82)	
[j]Psychiatric drugs						0.170
Yes	62 (17.51)	15 (13.39)	11 (13.41)	14 (22.22)	22 (22.68)	

No	292 (82.49)	97 (86.61)	71 (86.59)	49 (77.78)	75 (77.32)	
[k]MMSE<24 Mean (SD)	27.69 (2.37)	28.01 (2.19)	27.79 (2.18)	27.41(2.42)	27.42 (2.67)	0.142

Pain distribution assessed longitudinally was categorized as a four-level variable. (1) [a]No pain, single site pain, and multisite pain at baseline → no pain at 18-month follow-up (No pain); (2) [b]No pain, single-site pain, and multisite pain at baseline → single-site pain at 18-month follow-up (Single-site pain); (3) [c]No pain or single site pain at baseline→ multisite pain at 18 months follow-up (Incident multisite pain); (4) [d]Multisite pain at baseline →multisite pain at 18-month follow-up (Persistence of multisite pain). No pain was the reference group. [e]Body mass index is calculated as weight in kilograms divided by height in meters squared [f]Physical activity measured using the Physical Activity Scale for the Elderly score (PASE). [g] Self-reported heart disease included conditions: heart attack, congestive heart failure, angina, pacemaker, or cardiac arrhythmia. [h]Diabetes mellitus was defined from algorithm of self-report of disease, use of diabetes related medications, random glucose level and hemoglobin A1C. [i]Daily analgesics defined as use of one or more analgesic medications at least daily in the last 2 weeks.

[j]Psychiatric drug defined as any use versus no use of a psychiatric medication in the previous 2 weeks, [k]Mini Mental State Examination (MMSE) assessed cognitive impairment (<24) used as a continuous variable.

*Chi-square test for all categorical variables and ANOVA test for continuous variable, d.f.= (r-1) (c-1).

Table 8.
Prevalence of ADL and IADL Difficulty, Depression, and Anxiety According to Longitudinally Assessed Pain Distribution in an Older Population at the 6-Year Follow-Up (N=632)

Characteristics	Total N=632	No pain N (%) Total=229	Single site N (%) Total=175	Incident multisite pain N (%) Total= 62	Persistent multisite pain N (%) Total=166	p-value*
[a]ADL (N=628)						
No difficulty	474(75.48)	192(84.96)	133(76.44)	55(88.71)	94(56.63)	**<0.001**
Little or some difficulty	94(14.97)	27(11.95)	29(16.67)	4(6.45)	34(20.48)	
A lot of difficulty or inability	60 (9.55)	7(3.10)	12 (6.90)	3(4.84)	38 (22.89)	
[b]IADL(N=628)						**<0.001**
No difficulty	357(56.85)	167(73.57)	108(61.71)	33(54.10)	49(29.70)	
Little or some difficulty	130(20.70)	34(14.98)	40(22.86)	15(24.59)	41(24.85)	
A lot of difficulty or inability	141(22.45)	26(11.45)	27(15.43)	13(21.31)	75(45.45)	
[c]Depression (N=632)						**<0.001**
Yes	54(8.54)	7(3.06)	12(6.86)	4(6.45)	31(18.67)	
No	578(91.46)	222(96.94)	163(93.14)	58(93.55)	135(81.33)	
Anxiety						
Yes	31(4.91)	5(2.18)	10(5.71)	2(3.23)	14(8.43)	**0.034**
No	610(95.09)	224(97.82)	165(94.29)	60(96.77)	152(91.57)	
[d]Anxiety Score (SD)	2.66 (2.54)	1.77(2.13)	3.0(2.70)	3.0(2.53)	3.40(2.53)	**<0.0001**

[a]ADL difficulty, defined as the level of difficulty in one or more of activities: bathing, dressing, transferring, using the toilet, and eating (Katz et al., 1963). ADL difficulty is the 3-level dependent variable
[b]IADL difficulty, the level of difficulty in one or more of activities: shopping, preparing meals, and light and heavy housework (Lawton & Brody, 1969). IADL difficulty is the 3-level dependent variable.
[c]Depression defined as presence of minor or major depression, categorized as a dichotomous dependent variable. Depression assessed with Eaton method, modification of the Center for Epidemiologic Studies Depression Scale (CESD-R) (Eaton et al., 2004; Radloff, 1977). [d]The Hospital Anxiety and Depression Scale (HADS) measure anxiety symptoms as a continuous dependent variable (Zigmond & Snaith, 1983).
*Chi square test was performed to examine the relationship between categorical outcome variables (ADL, IADL, depression, and anxiety) and pain characteristics. ANOVA test was used to assess the association between anxiety as a continuous outcome variable and pain distribution, d.f.= (r-1) (c-1).

Table 9.
Prevalence of ADL and IADL Difficulty, Depression, and Anxiety According to Longitudinally Assessed Pain Distribution in an Older Population at the 6-Year Follow-Up (N=354)

Characteristics	Total N=354	No pain N (%) Total=112	Single site N (%) Total=82	Incident multisite pain N (%) Total= 63	Persistent multisite pain N (%) Total =97	p-value*
[a]ADL						**<0.001**
No difficulty	246 (69.49)	99(88.39)	60 (73.17)	40(63.49)	47(48.45)	
Little or some difficulty	53 (14.97)	8(7.14)	10(12.20)	12(19.05)	23(23.71)	
A lot of difficulty or inability	55 (15.54)	5(4.46)	12(14.63)	11(17.46)	27(27.84)	
[b]IADL						**<0.001**
No difficulty	249(70.74)	97(88.18)	64(78.05)	41(65.08)	47(48.45)	
Little or some difficulty	48(13.64)	9(8.18)	8(9.76)	14(22.22)	17(17.53)	
A lot of difficulty or inability	55(15.62)	4(3.64)	10(12.20)	8(12.70)	33(34.02)	
[c]Depression						**0.011**
Yes	25(7.06)	4(3.57)	4(4.88)	3(4.76)	14(14.43)	
No	329(92.94)	108(96.43)	78(95.12)	60(95.24)	83(85.57)	
Anxiety						0.636
Yes	15(4.26)	3(2.68)	3(3.66)	3(4.92)	6 (6.19)	
No	337 (95.74)	109(97.32)	79(96.34)	58(95.08)	91(93.81)	
[d]Anxiety Score (SD)	2.30(2.36)	1.65(1.89)	2.30(2.42)	2.33(2.36)	3.04 (2.59)	**0.01**

[a]ADL difficulty, defined as the level of difficulty in one or more of activities: bathing, dressing, transferring, using the toilet, and eating (Katz et al., 1963). ADL difficulty is the 3-level dependent variable.
[b]IADL difficulty, the level of difficulty in one or more of activities: shopping, preparing meals, and light and heavy housework (Lawton & Brody, 1969). IADL difficulty is the 3-level dependent variable.
[c]Depression defined as presence of minor or major depression, categorized as a dichotomous dependent variable. Depression assessed with Eaton method, modification of the Center for Epidemiologic Studies Depression Scale (CESD-R) (Eaton et al., 2004; Radloff, 1977). [d]The Hospital Anxiety and Depression Scale (HADS) measure anxiety symptoms and is a continuous dependent variable (Zigmond & Snaith, 1983).
[*]Chi square test was performed to examine the relationship between categorical outcome variables (ADL, IADL depression, anxiety) and pain characteristics. ANOVA test was used to assess the association between a continuous outcome variable (anxiety) and pain distribution, d.f.= (r-1) (c-1).

Table 10.
Relationship Between Persistent Multisite Pain and ADL Difficulty Among Community-Dwelling Older Adults, at the 18-Month Follow-Up

	Little or some ADL Difficulty vs No difficulty[1]	p-value	A lot ADL Difficulty vs No difficulty[1]	p-value
	RRR (95%CI)[2]		RRR (95%CI)[2]	
Predictor[3]				
Model I[a] (N=628)				
Single-site pain	1.55 (0.88- 2.74)	0.131	2.47 (0.949- 6.450)	0.064
Incident multisite pain	0.52 (0.17-1.54)	0.237	1.50 (0.374- 5.978)	0.569
Persistent multisite pain	2.57 (1.47- 4.51)	**0.001**	11.09 (4.772-25.762)	**<0.0001**
Model II[b] (N=626)				
Single-site pain	1.57 (0.88- 2.81)	0.130	2.55 (0.96- 6.74)	0.060
Incident multisite pain	0.65 (0.21-1.96)	0.441	2.10(0.51- 8.65)	0.303
Persistent multisite pain	2.72 (1.51- 4.89)	**0.001**	11.15(4.67- 26.63)	**<0.0001**
Model III[c] (N=608)				
Single-site pain	1.52 (0.83-2.77)	0.171	2.54 (0.87- 7.41)	0.088
Incident multisite pain	0.66 (0.21- 2.00)	0.458	2.16 (0.48- 9.63)	0.313
Persistent multisite pain	2.67 (1.48- 4.84)	**0.001**	9.82 (3.75- 25.76)	**<0.0001**
Model IV[d] (N=599)				
Single-site pain	1.47 (0.80-2.70)	0.213	2.66 (0.90-7.86)	0.078
Incident multisite pain	0.63 (0.20-1.93)	0.413	1.58 (0.34-7.48)	0.561
Persistent multisite pain	2.54 (1.36-4.72)	**0.003**	7.92 (2.89-21.67)	**<0.0001**
Model V[e](N=599)				
Single-site pain	1.43 (0.78- 2.65)	0.251	2.49 (0.83- 7.50)	0.105
Incident multisite pain	0.61 (0.20-1.88)	0.385	1.48 (0.31- 7.10)	0.625
Persistent multisite pain	2.41 (1.26-4.61)	**0.008**	7.26 (2.55-20.71)	**<0.0001**

[1]ADL difficulty, defined as the level of difficulty in one or more of activities: bathing, dressing, transferring, using the toilet, and eating (Katz et al., 1963).
[2]Relative risk ratios and 95% confidence intervals (CI) calculated from multi-nominal logistic regression where ADL difficulty is the 3-level dependent variable.
[3]Joint pain questionnaire (JPQ), a 13-item joint pain questionnaire assessed persistent musculoskeletal pain Study (Hochberg et al., 1995). Pain distribution assessed longitudinally was categorized as a four-level variable. (1) [a]No pain, single site pain, and multisite pain at baseline → no pain at 18-month follow-up (No pain); (2) [b]No pain, single-site pain, and multisite pain at baseline → single-site pain at 18-month follow-up (Single-site pain); (3) [c]No pain or single site pain at baseline→ multisite pain at 18-month follow-up (Incident multisite pain); (4) [d]Multisite pain at baseline →multisite pain at 18-month follow-up (Persistence of multisite pain). No pain was the reference group.
[a]Model I included ADL difficulty as dependent variable and pain characteristics. **[b]Model II** additionally adjusted for sociodemographic: age, gender, race, and education. **[c]Model III** additionally adjusted for health characteristics: BMI, MMSE, and physical activity. **[d]Model IV** additionally adjusted for chronic conditions: heart disease, diabetes mellitus, lung disease, depression, and anxiety. **[e]Model V** additionally adjusted for medications: psychiatric drug and analgesic.

Table 11.
Relationship Between Persistent Multisite Pain and ADL Difficulty Among 354 Community-Dwelling Older Adults, at the 6-Year Follow-Up

	Little or Some ADL Difficulty vs No ADL difficulty[1]	p-value	A lot ADL Difficulty vs No ADL difficulty[1]	p-value
	RRR (95% CI)[2]		RRR (95% CI)[2]	
Predictor[3]				
Model I[a] (N= 354)				
Single-site pain	2.06 (0.77- 5.51)	0.149	3.96(1.33-11.80)	**0.013**
Incident multisite pain	3.71(1.41- 9.76)	**0.008**	5.44(1.78-16.67)	**0.003**
Persistent multisite pain	6.06(2.52- 14.54)	**<0.0001**	11.37(4.12- 31.40)	**<0.0001**
Model II[b] (N=354)				
Single-site pain	2.07(0.77- 5.54)	0.147	4.01(1.32-12.22)	**0.014**
Incident multisite pain	3.83(1.45- 10.12)	**0.007**	6.80(2.15-21.51)	**0.001**
Persistent multisite pain	6.15(2.55-14.80)	**<0.0001**	13.05(4.60-37.04)	**<0.0001**
Model III[c] (N=352)				
Single-site pain	2.01(.73- 5.53)	0.178	3.85 (1.23-12.07)	**0.021**
Incident multisite pain	3.32 (1.21- 9.08)	**0.020**	6.06(1.84-19.96)	**0.003**
Persistent multisite pain	7.08 (2.82-17.74)	**<0.0001**	13.15 (4.45-38.85)	**<0.0001**
Model IV[d] (N= 347)				
Single-site pain	2.00 (0.72-5.58)	0.183	3.67 (1.13- 11.92)	**0.030**
Incident multisite pain	3.38 (1.22 - 9.38)	**0.019**	6.33 (1.86- 21.61)	**0.003**
Persistent multisite pain	6.62 (2.61- 16.78)	**<0.0001**	14.23 (4.58- 44.18)	**<0.0001**
Model V[e] (N= 344)				
Single-site pain	2.04 (0.70-5.95)	0.189	2.68 (0.79- 9.03)	0.112
Incident multisite pain	3.28 (1.13-9.53)	**0.029**	4.58 (1.30- 16.11)	**0.018**
Persistent multisite pain	5.57(2.13-14.62)	**<0.0001**	11.80 (3.68- 37.84)	**<0.0001**
Model VI[f] (N=344)				
Single-site pain	2.09 (0.70-6.22)	0.187	2.67 (0.78- 9.11)	0.116
Incident multisite pain	3.02 (1.01- 9.04)	**0.048**	4.67 (1.31- 16.70)	**0.018**
Persistent multisite pain	5.03 (1.87- 13.55)	**0.001**	10.62 (3.23- 34.97)	**<0.0001**

[1]ADL difficulty, defined as the level of difficulty in one or more of activities: bathing, dressing, transferring, using the toilet, and eating (Katz et al., 1963).
[2]Relative risk ratios and 95% confidence intervals (CI) calculated from multi-nominal logistic regression where ADL difficulty is the 3-level dependent variable
[3]Joint pain questionnaire (JPQ), assessed persistent musculoskeletal pain(Hochberg et al., 1995). Pain distribution assessed longitudinally was categorized as a four-level variable. (1) [a]No pain, single site pain, and multisite pain at baseline → no pain at 18-month follow-up (No pain); (2) [b]No pain, single-site pain, and multisite pain at baseline → single-site pain at 18-month follow-up (Single-site pain); (3) [c]No pain or single site pain at baseline→ multisite pain at 18-month follow-up (Incident multisite pain); (4) [d]Multisite pain at baseline →multisite pain at 18-month follow-up (Persistence of multisite pain). No pain was the reference group.
[a]**Model I** included ADL difficulty as dependent variable and pain characteristics [b]**Model II** additionally adjusted for time variable. [c]**Model III** additionally adjusted for sociodemographic: age, gender, race, and education. [d]**Model IV** additionally adjusted for health characteristics: BMI, MMSE, and physical activity. [e]**Model V** additionally adjusted for chronic conditions: heart disease, diabetes mellitus, lung disease, depression, and anxiety. [f]**Model VI** additionally adjusted for medications: psychiatric drug and analgesic.

Table 12.
Relationship Between Persistent Multisite Pain and IADL Difficulty Among Community-Dwelling Older Adults, at 18 Months

	A little or some IADL Difficulty vs No IADL difficulty[1]	p-value	A lot IADL Difficulty vs No IADL difficulty[1]	p-value
	RRR (95% CI)[2]		RRR (95% CI)[2]	
Predictor[3]				
Model I[a] (N=628)				
Single-site pain	1.82 (1.08- 3.05)	**0.023**	1.61 (0.89- 2.90)	0.116
Incident multisite pain	2.23 (1.09- 4.56)	**0.027**	2.53 (1.18- 5.43)	**0.017**
Persistent multisite pain	4.11(2.36- 7.16)	**<0.0001**	9.83 (5.68- 17.01)	**<0.0001**
Model II[b] (N=626)				
Single-site pain	1.83 (1.08-3.10)	**0.025**	1.66 (0.91-3.05)	0.099
Incident multisite pain	2.73 (1.31-5.69)	**0.008**	3.56 (1.61- 7.89)	**0.002**
Persistent multisite pain	4.30 (2.42- 7.64)	**<0.0001**	10.68 (5.60-19.02)	**<0.0001**
Model III[c] (N=608)				
Single-site pain	1.91 (1.11- 3.29)	**0.020**	1.65 (0.87- 3.11)	0.123
Incident multisite pain	2.60 (1.23- 5.51)	**0.012**	2.67 (1.14-6.29)	**0.024**
Persistent multisite pain	4.53 (2.51-8.16)	**<0.0001**	9.45 (5.14- 17.37)	**<0.0001**
Model IV[d] (N=599)				
Single-site pain	1.90(1.09- 3.31)	**0.023**	1.57 (0.83- 3.00)	0.169
Incident multisite pain	2.41(1.12- 5.17)	**0.024**	2.45 (1.02- 5.88)	**0.045**
Persistent multisite pain	4.39(2.36- 8.14)	**<0.0001**	7.95 (4.19- 15.10)	**<0.0001**
Model V[e] (N=599)				
Single-site pain	1.83 (1.04- 3.20)	**0.035**	1.51 (0.78- 2.90)	0.219
Incident multisite pain	2.28 (1.05- 4.92)	**0.036**	2.32 (0.95- 5.62)	0.063
Persistent multisite pain	4.00 (2.11-7.59)	**<0.0001**	7.33 (3.76-14.27)	**<0.0001**

[1]IADL difficulty, defined as the level of difficulty in one or more of activities: shopping, preparing meals, and light and heavy housework (Lawton & Brody, 1969).
[2]Relative risk ratios and 95% confidence intervals (CI) calculated from multi-nominal logistic regression where IADL difficulty is the 3-level dependent variable
[3]Pain distribution assessed longitudinally was categorized as a four-level variable. (1) [a]No pain, single site pain, and multisite pain at baseline → no pain at 18-month follow-up (No pain); (2) [b]No pain, single-site pain, and multisite pain at baseline → single-site pain at 18-month follow-up (Single-site pain); (3) [c]No pain or single site pain at baseline→ multisite pain at 18-month follow-up (Incident multisite pain); (4) [d]Multisite pain at baseline →multisite pain at 18-month follow-up (Persistence of multisite pain). No pain was the reference group.
[a]Model I included IADL difficulty as dependent variable and pain characteristics. **[b]Model II** additionally adjusted for sociodemographic: age, gender, race, and education. **[c]Model III** additionally adjusted for health characteristics: BMI, MMSE, and physical activity. **[d]Model IV** additionally adjusted for chronic conditions: heart disease, diabetes mellitus, lung disease, depression, and anxiety. **[e]Model V** additionally adjusted for medications: psychiatric drug and analgesic.

Table 13.
Relationship Between Persistent Multisite Pain and IADL Difficulty Among 354 Community-Dwelling Older Adults, at 6 Years

	Little or Some IADL Difficulty vs. No IADL difficulty[1]	p-value	A lot IADL Difficulty vs No IADL difficulty[1]	p-value
	RRR (95% CI)[2]		RRR (95% CI)[2]	
Predictor[3]				
Model I[a] (n=352)				
Single-site pain	1.35 (0.49- 3.67)	0.560	3.79 (1.14 - 12.60)	**0.030**
Incident multisite pain	3.68 (1.48- 9.18)	**0.005**	4.73 (1.35- 16.59)	**0.015**
Persistent multisite pain	3.90 (1.62- 9.40)	**0.002**	17.03(5.79- 50.87)	**<0.0001**
Model II[b] (n=352)				
Single-site pain	1.32 (0.48- 3.63)	0.589	3.72(1.11- 12.44)	**0.033**
Incident multisite pain	4.10 (1.62- 10.37)	**0.003**	5.27(1.49- 18.66)	**0.010**
Persistent multisite pain	4.09 (1.68- 9.95)	**0.002**	17.85 (5.92- 53.79)	**<0.0001**
Model III[c] (n=350)				
Single-site pain	1.18 (0.43- 3.28)	0.749	3.82 (1.12- 13.05)	**0.033**
Incident multisite pain	3.82 (1.46- 9.96)	**0.006**	5.15 (1.43- 18.59)	**0.012**
Persistent multisite pain	3.58 (1.42- 9.00)	**0.007**	20.56 (6.59- 64.07)	**<0.0001**
Model IV[d] (n=345)				
Single-site pain	1.13 (0.40-3.17)	0.832	3.36 (0.95-11.85)	0.060
Incident multisite pain	3.69 (1.39- 9.75)	**0.009**	5.17 (1.40- 19.05)	**0.014**
Persistent multisite pain	3.19 (1.24- 8.22)	**0.014**	22.62 (7.06- 72.45)	**<0.0001**
Model V[e] (n=342)				
Single-site pain	1.23 (0.43-3.50)	0.703	2.58 (0.70- 9.58)	0.156
Incident multisite pain	4.05(1.48- 11.03)	**0.006**	4.93 (1.29- 18.94)	**0.020**
Persistent multisite pain	3.06 (1.15- 8.14)	**0.025**	19.84 (5.93- 66.42)	**<0.0001**
Model VI[f] (n=342)				
Single-site pain	1.21 (0.42- 3.48)	0.723	2.50 (0.67- 9.31)	0.170
Incident multisite pain	4.06 (1.49- 11.10)	**0.006**	4.97(1.29- 19.21)	**0.020**
Persistent multisite pain	2.96 (1.10-8.01)	**0.032**	18.10 (5.36-61.12)	**<0.0001**

[1]IADL difficulty, defined as the level of difficulty in one or more of activities: shopping, preparing meals, and light and heavy housework (Lawton & Brody, 1969).
[2]Relative risk ratios and 95% confidence intervals (CI) calculated from multi-nominal logistic regression where IADL difficulty is the 3-level dependent variable
[3]Pain distribution assessed longitudinally was categorized as a four-level variable. (1) [a]No pain, single site pain, and multisite pain at baseline → no pain at 18-month follow-up (No pain); (2) [b]No pain, single-site pain, and multisite pain at baseline → single-site pain at 18-month follow-up (Single-site pain); (3) [c]No pain or single site pain at baseline→ multisite pain at 18-month follow-up (Incident multisite pain); (4) [d]Multisite pain at baseline →multisite pain at 18-month follow-up (Persistence of multisite pain).No pain was the reference group. **[a]Model I** included instrumental activities of daily living (IADL) as dependent variable and pain characteristics. **[b]Model II** additionally adjusted for time variable. **[c]Model III** additionally adjusted for sociodemographic: age, gender, race, and education. **[d]Model IV** additionally adjusted for health characteristics: BMI, MMSE, and physical activity. **[e]Model V** additionally adjusted for chronic conditions: heart disease, diabetes mellitus, lung disease, depression, and anxiety. **[f]Model VI** additionally adjusted for medications: psychiatric drug and analgesic.

Table 14.
Relationship Between Persistent Multisite Pain and Depression Among Community-Dwelling Older Adults, at 18 Months

	Depression[1]	p-value
	OR (95% CI)[2]	
Predictor[3]		
Model I[a] (N= 632)		
Single-site pain	2.33 (0.90-6.06)	0.081
Incident multisite pain	2.19 (0.62-7.73)	0.224
Persistent multisite pain	7.28 (3.12-16.10)	**<0.0001**
Model II[b] (N= 630)		
Single-site pain	2.37 (0.91- 6.19)	0.079
Incident multisite pain	2.30 (0.64- 8.29)	0.203
Persistent multisite pain	6.69 (2.81- 15.90)	**<0.0001**
Model III[c] (N= 612)		
Single-site pain	2.41 (0.91 - 6.37)	0.076
Incident multisite pain	1.63 (0.40 - 6.72)	0.498
Persistent multisite pain	7.02 (2.91-16.91)	**<0.0001**
Model IV[d] (N= 611)		
Single-site pain	2.34 (0.88- 6.24)	0.090
Incident multisite pain	1.55 (0.37- 6.49)	0.546
Persistent multisite pain	5.80 (2.33- 14.44)	**<0.0001**
Model V[e] (N=611)		
Single-site pain	2.22(0.81- 6.04)	0.120
Incident multisite pain	1.64 (0.38- 7.13)	0.509
Persistent multisite pain	6.59 (2.56-16.94)	**<0.0001**

[1]Depression defined as presence of minor or major depression was categorized as a dichotomous variable. Depression was assessed using the Center for Epidemiologic Studies Depression Scale (CESD-R) (Eaton et al., 2004; Radloff, 1977).
[2]Odds ratios and 95% confidence intervals (CI) calculated from logistic regression.
[3]Pain distribution assessed longitudinally was categorized as a four-level variable. (1) [a]No pain, single site pain, and multisite pain at baseline → no pain at 18-month follow-up (No pain); (2) [b]No pain, single-site pain, and multisite pain at baseline → single-site pain at 18-month follow-up (Single-site pain); (3) [c]No pain or single site pain at baseline→ multisite pain at 18-month follow-up (Incident multisite pain); (4) [d]Multisite pain at baseline →multisite pain at 18-month follow-up (Persistence of multisite pain).No pain was the reference group. **[a]Model I** included depression as the dependent variable and pain characteristics. **[b]Model II** additionally adjusted for sociodemographic: age, gender, race, and education. **[c]Model III** additionally adjusted for health characteristics: BMI, MMSE, and physical activity. **[d]Model IV** additionally adjusted for heart disease, diabetes mellitus, lung disease and IADL. **[e]Model V** additionally adjusted for medications: psychiatric drug and analgesic.

Table 15.
Relationship Between Persistent Multisite Pain and Depression Among Community-Dwelling Older Adults, at 6 Years

	Depression[1]	p-value
	OR (95% CI)[2]	
Predictor[3]		
Model I[a] (N= 354)		
Single-site pain	1.38(0.34 -5.71)	0.652
Incident multisite pain	1.35 (0.29- 6.23)	0.701
Persistent multisite pain	4.55(1.45-14.35)	**0.010**
Model II[b] (N= 354)		
Single-site pain	1.36 (0.33- 5.62)	0.673
Incident multisite pain	1.45(0.31- 6.74)	0.635
Persistent multisite pain	4.60(1.45- 14.58)	**0.009**
Model III[c] (N= 353)		
Single-site pain	1.36(0.32- 5.75)	0.673
Incident multisite pain	1.16 (0.241- 5.54)	0.856
Persistent multisite pain	5.51(1.66-18.24)	**0.005**
Model IV[d](N=340)		
Single-site pain	0.99(0.21- 4.74)	0.992
Incident multisite pain	0.97 (0.18- 5.12)	0.967
Persistent multisite pain	6.49 (1.83- 23.07)	**0.004**
Model V[e] (N= 327)		
Single-site pain	0.90 (0.18-4.40)	0.892
Incident multisite pain	0.81(0.15- 4.46)	0.807
Persistent multisite pain	4.75 (1.15-19.57)	**0.031**
Model VI[f] (N= 327)		
Single-site pain	1.00 (0.20-4.95)	0.995
Incident multisite pain	0.74 (0.13-4.23)	0.735
Persistent multisite pain	4.56 (1.10-18.98)	**0.037**

[1]Depression defined as presence of minor or major depression was categorized as a dichotomous variable. Depression was assessed using the Center for Epidemiologic Studies Depression Scale (CESD-R) (Eaton et al., 2004; Radloff, 1977).
[2]Odds ratios and 95% confidence intervals (CI) calculated from logistic regression.
[3]Pain distribution assessed longitudinally was categorized as a four-level variable. (1) [a]No pain, single site pain, and multisite pain at baseline → no pain at 18-month follow-up (No pain); (2) [b]No pain, single-site pain, and multisite pain at baseline → single-site pain at 18-month follow-up (Single-site pain); (3) [c]No pain or single site pain at baseline→ multisite pain at 18-month follow-up (Incident multisite pain); (4) [d]Multisite pain at baseline →multisite pain at 18-month follow-up (Persistence of multisite pain).No pain was the reference group
[a]**Model I** included depression as dependent variable and pain characteristics. [b]**Model II** additionally adjusted for time variable. [c]**Model III** additionally adjusted for sociodemographic: age, gender, race, and education. [d]**Model IV** additionally adjusted for health characteristics: BMI, MMSE and physical activity – blocks walked. [e]**Model V** additionally adjusted for chronic conditions: heart disease, diabetes mellitus, lung disease, IADL. [f]**Model VI** additionally adjusted for medications: psychiatric drug and analgesic.

Table 16.
Relationship Between Persistent Multisite Pain and Anxiety Among Community-Dwelling Older Adults, at the 18 Months

	Anxiety[1,2]		Anxiety Score[1,3]		
	Odds ratio (95% CI)[2]	p-value	Beta[3]	Standard Error[3]	p-value
Predictor[4]					
Model I[a] (N=632)					
Single-site pain	2.72 (0 .91-8.09)	0.073	0.21	0.24	**<0.0001**
Incident multisite pain	1.49 (0.28- 7.89)	0.637	0.14	0.35	**0.001**
Persistent multisite pain	4.13 (1.46- 11.69)	**0.008**	0.28	0.25	**<0.0001**
Model II[b] (N=630)					
Single-site pain	2.59 (0.86-7.79)	0.089	0.21	0.25	**<0.0001**
Incident multisite pain	1.24 (0.23-6.64)	0.804	0.13	0.35	**0.001**
Persistent multisite pain	3.63(1.27- 10.42)	**0.016**	0.27	0.25	**<0.0001**
Model III[c] (N=612)					
Single-site pain	2.77 (0.91-8.40)	0.072	0.21	0.24	**<0.0001**
Incident multisite pain	0.65 (0.07-5.78)	0.696	0.11	0.35	**0.008**
Persistent multisite pain	4.19(1.44-12.18)	**0.009**	0.28	0.25	**<0.0001**
Model IV[d] (N= 611)					
Single-site pain	2.61(0.85- 8.05)	0.094	0.20	0.25	**<0.0001**
Incident multisite pain	0.65(0.07-5.98)	0.704	0 .11	0.35	**0.013**
Persistent multisite pain	4.12(1.34-12.72)	**0.014**	0.27	0.26	**<0.0001**
Model V[e] (N= 611)					
Single-site pain	2.08 (0.64- 6.78)	0.224	0.19	0.24	**<0.0001**
Incident multisite pain	0.53 (0.05-5.32)	0.589	0.11	0.34	**0.006**
Persistent multisite pain	4.34 (1.32-14.26)	**0.016**	0.28	0.26	**<0.0001**

[1] The Hospital Anxiety and Depression Scale (HADS) was used to measure anxiety (Zigmond & Snaith, 1983).
[2]Odds ratios and 95% confidence intervals (CI) calculated from logistic regression where anxiety is a binary dependent variable. HADS scores >=8
[3]Beta and standard errors calculated from generalized linear regression model where anxiety is a continuous dependent variable
[4]Pain distribution assessed longitudinally was categorized as a four-level variable. (1) [a]No pain, single site pain, and multisite pain at baseline → no pain at 18-month follow-up (No pain); (2) [b]No pain, single-site pain, and multisite pain at baseline → single-site pain at 18-month follow-up (Single-site pain); (3) [c]No pain or single site pain at baseline→ multisite pain at 18-month follow-up (Incident multisite pain); (4) [d]Multisite pain at baseline →multisite pain at 18-month follow-up (Persistence of multisite pain). No pain was the reference group
[a]**Model I** included anxiety as dependent variable and pain characteristics. [b]**Model II** adjusted for sociodemographic: age, gender, race, and education. [c]**Model III** additionally adjusted for health characteristics: BMI, MMSE, and physical activity. [d]**Model IV** additionally adjusted for heart disease, diabetes mellitus, lung disease and IADL. [e]**Model V** additionally adjusted for medications: psychiatric drug and analgesic.

Table 17.
Relationship Between Persistent Multisite Pain and Anxiety Among Community-Dwelling Older Adults, at the 6 Years

	Anxiety[1,2]		Anxiety Score[1,3]		
	Odds Ratio (95% CI)[2]	p-value	Beta[3]	Standard Error[3]	p-value
Predictor[4]					
Model I[a] (N=352)					
Single-site pain	1.38 (0.27-7.02)	0.698	0.12	0.33	0.052
Incident multisite pain	1.88(0.37-9.61)	0.449	0.11	0.37	0.066
Persistent multisite pain	2.40 (0.58-9.85)	0.226	0.26	0.32	**<0.0001**
Model II[b] (N= 352)					
Single-site pain	1.38 (0.27-7.02)	0.698	0.12	0.34	0.051
Incident multisite pain	1.87(0.37-9.61	0.451	0.11	0.37	0.072
Persistent multisite pain	2.40(0.58-9.85)	0.226	0.26	0.32	**<0.0001**
Model III[c] (N=351)					
Single-site pain	1.32 (0.25- 6.87).	0.743	0.11	0.34	0.079
Incident multisite pain	1.91 (0.36- 10.24)	0.448	0.11	0.37	0.072
Persistent multisite pain	2.28 (0.54- 9.64)	0.263	0.24	0.32	**<0.0001**
Model IV[d] (N=338)					
Single-site pain	1.18 (0.21-6.49)	0.853	0.09	0.34	0.148
Incident multisite pain	1.60 (0.29-8.88)	0.594	0.08	0.39	0.190
Persistent multisite pain	1.93 (0.43-8.72)	0.391	0.22	0.34	**0.001**
Model V[e] (N=325)					
Single-site pain	1.79(0.26-12.15)	0.553	0.11	0.36	0.078
Incident multisite pain	1.97(0.31-12.61)	0.473	0.09	0.40	0.163
Persistent multisite pain	1.54(0.28-8.40)	0.615	0.18	0.37	**0.010**
Model VI[f] (N=325)					
Single-site pain	2.14 (0.28-16.15)	0.460	0.12	0.36	0.058
Incident multisite pain	2.12 (0.31-14.41)	0.441	0.08	0.39	0.205
Persistent multisite pain	1.71 (0.28-10.33)	0.560	0.18	0.37	**0.009**

[1] The Hospital Anxiety and Depression Scale (HADS) was used to measure anxiety (Zigmond & Snaith, 1983)
[2]Odds ratios and 95% confidence intervals (CI) calculated from logistic regression where anxiety is a binary dependent variable. HADS scores >=8
[3]Beta and standard errors calculated from generalized linear regression model where anxiety is a continuous dependent variable
[4]Pain distribution assessed longitudinally was categorized as a four-level variable. (1) [a]No pain, single site pain, and multisite pain at baseline → no pain at 18-month follow-up (No pain); (2) [b]No pain, single-site pain, and multisite pain at baseline → single-site pain at 18-month follow-up (Single-site pain); (3) [c]No pain or single site pain at baseline→ multisite pain at 18-month follow-up (Incident multisite pain); (4) [d]Multisite pain at baseline →multisite pain at 18-month follow-up (Persistence of multisite pain). No pain was the reference group
[a]Model I included anxiety as dependent variable and pain characteristics. **[b]Model II** additionally adjusted for time variable. **[c]Model III** additionally adjusted for sociodemographic: age, gender, race, and education. **[d]Model IV** additionally adjusted for health characteristics: BMI, MMSE, and physical activity. **[e]Model V** additionally adjusted for chronic conditions: heart disease, diabetes mellitus, lung disease, IADL. **[f]Model VI** additionally adjusted for medications: psychiatric drug and analgesic.

Table 18.
Relationship Between Persistent Multisite Pain and Mortality Among Community-Dwelling Older Adults, at 12.4 Years (Total Observation =765, Deaths= 144)

	Mortality	
Predictor[2]	HR (95%CI)[1]	p-value
Model I[a] (N=764)		
Single-site pain	1.10(0.71- 1.71)	0.678
Persistent multisite pain	1.26(0.86- 1.85)	0.227
Model II[b] (N=762)		
Single-site pain	1.12 (0.72- 1.74)	0.628
Persistent multisite pain	1.16(0.78-1.71)	0.468
Model III[c] (N=744)		
Single-site pain	1.18(0.75- 1.85)	0.473
Persistent multisite pain	1.19(0.80-1.77)	0.400
Model IV[d] (N=744)		
Single-site pain	1.12(0.71- 1.76)	0.635
Persistent multisite pain	1.07(0.71-1.62)	0.742
Model V[e] (N=744)		
Single-site pain	1.12(0.71-1.77)	0.627
Persistent multisite pain	1.08(0.71- 1.65)	0.725
Model VI[f] (N=744)		
Single-site pain	1.09(0.69-1.73)	0.702
Persistent multisite pain	0.96(0.62-1.49)	0.851

[1]Hazard ratios and 95% confidence intervals (CI) calculated from Cox proportional hazard regression modeling
[2] A 13-item joint pain questionnaire (JPQ) assessed persistent musculoskeletal pain (Hochberg et al., 1995), at baseline. Persistent pain was categorized as a three-level independent variable. Time to death (yrs.) was the outcome variable. No pain was the reference group. Baseline persistent multisite pain as the predictor variable. [a]**Model I** without adjustments. [b]**Model II** adjusted for age, gender, race, and education. [c]**Model III** additionally adjusted for BMI, PASE, and MMSE. [d]**Model IV** additionally adjusted for heart disease, diabetes mellitus, lung disease, and depression. [e]**Model V** additionally adjusted for psychiatric drug and analgesics. [f]**Model VI** additionally adjusted for ADL.

Table 19.
Relationship Between Pain Severity at Baseline and Mortality Among Community-Dwelling Older Adults at 12.4 Years (Total Observation=765, Deaths=144)

	Mortality	
Predictor[2]	HR (95% CI)[1]	p-value
Model I[a] (N=762)		
Pain severity	1.04 (0.97- 1.12)	0.271
Model II[b] (N=760)		
Pain severity	1.02 (0.95- 1.11)	0.536
Model III[c] (N= 742)		
Pain severity	1.03 (0.95- 1.12)	0.517
Model IV[d] (N=742)		
Pain severity	1.01 (0.93- 1.10)	0.862
Model V[e] (N=742)		
Pain severity	1.01 (0.92- 1.10)	0.864

[1]Hazard ratios and 95% confidence intervals (CI) calculated from Cox proportional hazard regression modeling
[2] Pain severity was measured using Brief Pain Inventory (BPI) severity subscale (Cleeland & Ryan, 1994), at baseline. Pain severity was a continuous independent variable. Time to death (yrs.) was the outcome variable. No pain was the reference group
[a]**Model I** without adjustments. [b]**Model II** adjusted for age, gender, race, and education. [c]**Model III** additionally adjusted for BMI, PASE, and MMSE. [d]**Model IV** additionally adjusted for heart disease, diabetes mellitus, lung disease, and depression. [e]**Model V** additionally adjusted for psychiatric drug and analgesics.

Table 20.
Relationship Between Pain Interference at Baseline and Mortality Among Community-Dwelling Older Adults at 12.4 Years (Total Observation=765, Deaths=144)

	Mortality	
Predictor[2]	HR (95% CI)[1]	p-value
[a]Model I (N= 762)		
Pain interference	1.02 (0.95-1.10)	0.618
[b]Model II (N=760)		
Pain interference	0.99 (0.92-1.07)	0.886
[c]Model III (N= 742)		
Pain interference	0.97 (0.90-1.05)	0.491
[d]Model IV (N=742)		
Pain interference	0.95 (0.87-1.03)	0.202
[e]Model V (N=742)		
Pain interference	0.94 (0.86-1.03)	0.182

[1]Hazard ratios and 95% confidence intervals (CI) calculated from Cox proportional hazard regression modeling
[2] Pain interference was measured using Brief Pain Inventory (BPI) subscale, at baseline. Pain interference subscale comprises of 7-items that measured the level of interference with general activity, mood, walking ability, performing normal work, relations with other people, sleep, and enjoyment of life (Cleeland & Ryan, 1994). Pain interference was a continuous independent variable. Time to death (yrs.) was the dependent variable. No pain was the reference group.
[a]**Model I** without adjustments. [b]**Model II** adjusted for age, gender, race, and education. [c]**Model III** additionally adjusted for BMI, PASE, and MMSE. [d]**Model IV** additionally adjusted for heart disease, diabetes mellitus, lung disease, and depression. [e]**Model V** additionally adjusted for psychiatric drug and analgesics.

Table 21.

Relationship Between Multisite Pain at Baseline and Mortality Among Community-Dwelling Older Adults at 9.8 Years (Total Observation=765, Deaths=126)

	Mortality[3]	
Predictor[2]	HR (95%CI)[1]	p-value
[a]Model I (N=764)		
Single-site pain	1.25(0.78- 2.02)	0.359
Persistent multisite pain	1.41(0.93- 2.14)	0.103
[b]Model II (N=762)		
Single-site pain	1.26(0.78-2.03)	0.341
Persistent multisite pain	1.33(0.87- 2.02)	0.190
[c]Model III (N=744)		
Single-site pain	1.33(0.82 – 2.16)	0.254
Persistent multisite pain	1.36(0.88-2.10)	0.166
[d]Model IV (N=744)		
Single-site pain	1.25(0.77- 2.04)	0.368
Persistent multisite pain	1.22(0.78-1.91)	0.382
[e]Model V (N=744)		
Single-site pain	1.25(0.77-2.04)	0.371
Persistent multisite pain	1.22(0.77-1.93)	0.394
[f]Model VI (N=744)		
Single-site pain	1.21(0.74-1.98)	0.443
Persistent multisite pain	1.04(0.65-1.67)	0.878

[1]Hazard ratios and 95% confidence intervals (CI) calculated from Cox proportional hazard regression modeling
[2] A 13-item joint pain questionnaire (JPQ) assessed persistent musculoskeletal pain (Hochberg et al., 1995), at baseline. Persistent pain was categorized as a three-level independent variable. Time to death (yrs.) was the independent variable. No pain was the reference group. [3]Because there was more extensive ascertainment of death until 06/06/2015 (9.8yrs.), therefore for this second analysis, 06/06/2015 was selected as the censoring date.

[a]Model I without adjustments. **[b]Model II** adjusted for age, gender, race, and education. **[c]Model III** additionally adjusted for BMI, PASE, and MMSE. **[d]Model IV** additionally adjusted for heart disease, diabetes mellitus, lung disease, and depression. **[e]Model V** additionally adjusted for psychiatric drug and analgesics. **[f]Model VI** additionally adjusted for ADL.

Table 22.
Relationship Between Pain Severity at Baseline and Mortality Among Community-Dwelling Older Adults at 9.8 Years[3] (Total Observation=765, Deaths=126)

	Mortality	
Predictor[2]	HR (95%CI)[1]	p-value
[a]Model I (N=762)		
Pain severity	1.07(0.99-1.15)	0.107
[b]Model II (N=760)		
Pain severity	1.06(0.97-1.15)	0.195
[c]Model III (N=742)		
Pain severity	1.05(0.96- 1.14)	0.315
[d]Model IV (N=742)		
Pain severity	1.02(0.93-1.12)	0.626
[e]Model V (N=742)		
Pain severity	1.02(0.93-1.12)	0.681

[1]Hazard ratios and 95% confidence intervals (CI) calculated from Cox proportional hazard regression modeling
[2] Pain severity was measured using Brief Pain Inventory (BPI) severity subscale (Cleeland & Ryan, 1994), at baseline. Pain severity was a continuous independent variable. Time to death (yrs.) was the independent variable. No pain was the reference group. [3]Because there was more extensive ascertainment of death until 06/06/2015 (9.8yrs.), therefore for this second analysis, 06/06/2015 was selected as the censoring date
[a]Model I without adjustments. **[b]Model II** adjusted for age, gender, race, and education. **[c]Model III** additionally adjusted for BMI, PASE, and MMSE. **[d]Model IV** additionally adjusted for heart disease, diabetes mellitus, lung disease, and depression. **[e]Model V** additionally adjusted for psychiatric drug and analgesics.

Table 23.
Relationship Between Pain Interference at Baseline and Mortality Among Community-Dwelling Older Adults at 9.8 Years (Total Observation=765, Deaths=126)

	Mortality[3]	
Predictor[2]	HR (95%CI)[1]	p-value
[a]Model I (N=762)		
Pain interference	1.05(0.97-1.13)	0.225
[b]Model II (N=760)		
Pain interference	1.03(0.95-1.11)	0.512
[c]Model III (N= 742)		
BPI interference	0.99(0.91-1.08)	0.860
[d]Model IV (N=742)		
Pain interference	0.97(0.89-1.05)	0.437
[e]Model V (N=742)		
Pain interference	0.96(0.87-1.05)	0.373

[1]Hazard ratios and 95% confidence intervals (CI) calculated from Cox proportional hazard regression modeling
[2] Pain interference was measured using Brief Pain Inventory (BPI) subscale, at baseline. Pain interference subscale comprises of 7-items that measured the level of interference with general activity, mood, walking ability, performing normal work, relations with other people, sleep, and enjoyment of life (Cleeland & Ryan, 1994). Pain interference was a continuous independent variable. Time to death (yrs.) was the independent variable. No pain was the reference group.
[3]Because there was more extensive ascertainment of death until 06/06/2015 (9.8yrs.), therefore for this second analysis, 06/06/2015 was selected as the censoring date.
[a]**Model I** without adjustments. [b]**Model II** adjusted for age, gender, race, and education. [c]**Model III** additionally adjusted for BMI, PASE, and MMSE. [d]**Model IV** additionally adjusted for heart disease, diabetes mellitus, lung disease, and depression. [e]**Model V** additionally adjusted for psychiatric drug and analgesics.

Table 24.
Relationship Between Multisite Pain at Baseline and Mortality Among Community-Dwelling Older Adults During the 12.4 Years According to Gender (Total Observation=765, Deaths=144)

	Mortality				
	Men (n=276)			**Women (n=489)**	
Predictor[2]	HR (95%CI)[1]	p-value	Predictor[2]	HR (95%CI)[1]	p-value
Model I[a] (N= 275)			**Model I[a] (N=489)**		
Single-site pain	1.18(0.61-2.25)	0.625	Single-site pain	1.04(0.57-1.91)	0.893
Persistent multisite pain	1.14(0.61-2.13)	0.691	Persistent multisite pain	1.37(0.84- 2.24)	0.205
Model II[b] (N=274)			**Model II[b] (N=488)**		
Single-site pain	1.16(0.60-2.23)	0.653	Single-site pain	1.07(0.58-1.96)	0.837
Persistent multisite pain	1.15(0.60-2.20)	0.666	Persistent multisite pain	1.21(0.74-1.99)	0.455
Model III[c] (N=268)			**Model III[c] (N=476)**		
Single-site pain	1.13(0.58-2.18)	0.717	Single-site pain	1.17(0.63-2.18)	0.613
Persistent multisite pain	1.15(0.60-2.20)	0.667	Persistent multisite pain	1.25(0.74-2.12)	0.398
Model IV[d] (N=268)			**Model IV[d] (N= 476)**		
Single-site pain	1.10(0.57-2.15)	0.773	Single-site pain	1.11(0.59-2.08)	0.739
Persistent multisite pain	1.09(0.55-2.16)	0.813	Persistent multisite pain	1.13(0.66-1.94)	0.650
Model V[e] (N=268)			**Model V[e] (N=476)**		
Single-site pain	1.15(0.59-2.26)	0.680	Single-site pain	1.10(0.58-2.06)	0.772
Persistent multisite pain	1.14(0.57-2.27)	0.712	Persistent multisite pain	1.11(0.63-1.93)	0.725
Model VI[f] (N=268)			**Model VI[f] (N=476)**		
Single-site pain	0.99(0.50-1.95)	0.981	Single-site pain	1.09(0.58-2.04)	0.799
Persistent multisite pain	0.76(0.36-1.62)	0.476	Persistent multisite pain	1.07(0.61- 1.87)	0.826

[1]Hazard ratios and 95% confidence intervals (CI) calculated from Cox proportional hazard regression modeling
[2] A 13-item joint pain questionnaire (JPQ) assessed persistent musculoskeletal pain (Hochberg et al., 1995), at baseline. Persistent pain was categorized as a three-level independent variable. Time to death (yrs.) was the outcome variable. No pain was the reference group.
[a]**Model I** without adjustments. [b]**Model II** adjusted for age, race, and education. [c]**Model III** additionally adjusted for BMI, PASE, and MMSE. [d]**Model IV** additionally adjusted for heart disease, diabetes mellitus, lung disease, and depression. [e]**Model V** additionally adjusted for psychiatric drug and analgesics. [f]**Model VI** additionally adjusted for ADL.

Table 25.
Relationship Between Pain Severity at Baseline and Mortality Among Community-Dwelling Older Adults During the 12.4 Years According to Gender (Total Observation=765, Deaths=144)

	Mortality				
	Men (N=276)			**Women (N=489)**	
Predictor[2]	HR (95%CI)[1]	p-value	Predictor[2]	HR (95%CI)[1]	p-value
Model I[a] (N=275)			**Model I[a] (N= 487)**		
Pain severity	0.93(0.81-1.08)	0.353	Pain severity	1.11(1.01-1.22)	**0.024**
Model II[b] (N=274)			**Model II[b] (N= 486)**		
Pain severity	0.95(0.81-1.10)	0.476	Pain severity	1.07(0.98-1.18)	0.131
Model III[c] (N=268)			**Model III[c] (N=474)**		
Pain severity	0.96(0.82-1.12)	0.571	Pain severity	1.07(0.97-1.19)	0.151
Model IV[d] (N=268)			**Model IV[d] (N=474)**		
Pain severity	0.94(0.80-1.1)	0.455	Pain severity	1.05 (0.95-1.16)	0.359
Model V[e] (N=268)			**Model V[e] (N=474)**		
Pain severity	0.95(0.80-1.13)	0.563	Pain severity	1.04(0.94-1.16)	0.433

[1]Hazard ratios and 95% confidence intervals (CI) calculated from Cox proportional hazard regression modeling
[2] Pain severity was measured using Brief Pain Inventory (BPI) severity subscale (Cleeland & Ryan, 1994), at baseline. Pain severity was a continuous independent variable. Time to death (yrs.) was the outcome variable. No pain was the reference group
[a]**Model I** without adjustments. [b]**Model II** adjusted for age, race, and education. [c]**Model III** additionally adjusted for BMI, PASE, and MMSE. [d]**Model IV** additionally adjusted for heart disease, diabetes mellitus, lung disease, and depression. [e]**Model V** additionally adjusted for psychiatric drug and analgesics.

Table 26.
Relationship Between Pain Interference at Baseline and Mortality Among Community-Dwelling Older Adults During the 12.4 Years According to Gender (Total Observation=765, Deaths=144)

	Mortality				
	Men (n=276)			**Women (n=489)**	
Predictor[2]	HR (95%CI)[1]	p-value	Predictor[2]	HR (95%CI)[1]	p-value
Model I[a] (N=275)			**Model I[a] (N=487)**		
Pain interference	1.01(0.88-1.16)	0.879	Pain interference	1.03 (0.94-1.13)	0.524
Model II[b] (N=274)			**Model II[b] (N=486)**		
Pain interference	1.00(0.87-1.15)	0.987	Pain interference	1.00(0.92-1.10)	0.969
Model III[c] (N=268)			**Model III[c] (N=474)**		
Pain interference	1.01(0.87-1.17)	0.908	Pain interference	0.97(0.88-1.07)	0.574
Model IV[d] (N=268)			**Model IV[d] (N=474)**		
Pain interference	0.99(0.86-1.16)	0.946	Pain interference	0.93(0.84-1.03)	0.177
Model V[e] (N=268)			**Model V[e] (N=474)**		
Pain interference	1.01(0.86-1.18)	0.924	Pain interference	0.91(0.81-1.02)	0.100

[1]Hazard ratios and 95% confidence intervals (CI) calculated from Cox proportional hazard regression modeling
[2] Pain interference was measured using Brief Pain Inventory (BPI) subscale, at baseline. Pain interference subscale comprises of 7-items that measured the level of interference with general activity, mood, walking ability, performing normal work, relations with other people, sleep, and enjoyment of life (Cleeland & Ryan, 1994). Pain interference was a continuous independent variable. Time to death (yrs.) was the dependent variable. No pain was the reference group.
[a]**Model I** without adjustments. [b]**Model II** adjusted for age, race, and education. [c]**Model III** additionally adjusted for BMI, PASE, and MMSE. [d]**Model IV** additionally adjusted for heart disease, diabetes mellitus, lung disease, and depression. [e]**Model V** additionally adjusted for psychiatric drug and analgesics.

Table 27.
Relationship Between Multisite Pain at Baseline and Mortality Among Community-Dwelling Older Adults During the 9.8 Years According to Gender (Total Observation=765, Deaths=126)

	Mortality[3]				
	Men (n=276)			**Women (n=489)**	
Predictor[2]	HR (95%CI)[1]	p-value	Predictor[2]	HR (95%CI)[1]	p-value
Model I[a] (N=275)			**Model I[a] (N=489)**		
Single-site pain	1.45(0.72-2.94)	0.297	Single-site pain	1.10(0.58- 2.12)	0.765
Persistent multisite pain	1.41(0.71-2.78)	0.327	Persistent multisite pain	1.44(0.85-2.43)	0.180
Model II[b] (N=274)			**Model II[b](N=488)**		
Single-site pain	1.45(0.71-2.95)	0.303	Single-site pain	1.11(0.58-2.14)	0.747
Persistent multisite pain	1.45(0.72-2.91)	0.302	Persistent multisite pain	1.30(0.76-2.22)	0.335
Model III[c] (N=268)			**Model III[c] (N=476)**		
Single-site pain	1.41(0.69-2.88)	0.346	Single-site pain	1.21(0.62-2.36)	0.575
Persistent multisite pain	1.47(0.73-2.96)	0.286	Persistent multisite pain	1.32(0.75-2.32)	0.342
Model IV[d] (N=268)			**Model IV[d] (N= 476)**		
Single-site pain	1.38(0.67-2.84)	0.379	Single-site pain	1.17(0.59- 2.30)	0.652
Persistent multisite pain	1.41(0.68-2.95)	0.360	Persistent multisite pain	1.19(0.67-2.12)	0.556
Model V[e] (N=268)			**Model V[e] (N=476)**		
Single-site pain	1.42(0.69-2.93)	0.347	Single-site pain	1.15(0.58-2.27)	0.683
Persistent multisite pain	1.45(0.69-3.06)	0.325	Persistent multisite pain	1.16(0.64-2.10)	0.633
Model VI[f] (N=268)			**Model VI[f] (N=476)**		
Single-site pain	1.16(0.56-2.41)	0.695	Single-site pain	1.14(0.58-2.24)	0.712
Persistent multisite pain	0 .91(0.41-2.06)	0.828	Persistent multisite pain	1.08(0.59-1.99)	0.796

[1]Hazard ratios and 95% confidence intervals (CI) calculated from Cox proportional hazard regression modeling.
[2] A 13-item joint pain questionnaire (JPQ) assessed persistent musculoskeletal pain (Hochberg et al., 1995), at baseline. Persistent pain was categorized as a three-level independent variable. Time to death (yrs.) was the outcome variable. No pain was the reference group.
[3]Because there was more extensive ascertainment of death until 06/06/2015 (9.8yrs.), therefore for this second analysis, 06/06/2015 was selected as the censoring date.
[a]**Model I** without adjustments. [b]**Model II** adjusted for age, race, and education. [c]**Model III** additionally adjusted for BMI, PASE, and MMSE. [d]**Model IV** additionally adjusted for heart disease, diabetes mellitus, lung disease, and depression. [e]**Model V** additionally adjusted for psychiatric drug and analgesics. [f]**Model VI** additionally adjusted for ADL.

Table 28.
Relationship Between Pain Severity at Baseline and Mortality Among Community-Dwelling Older Adults During the 9.8-Years According to Gender (Total Observation=765, Deaths=126)

	Mortality[3]				
	Men (N=276)		**Women (N=489)**		
Predictor[2]	HR (95%CI)[1]	p-value	Predictor[2]	HR (95%CI)[1]	p-value
Model I[a] (N=275)			**Model I[a] (N=487)**		
Pain severity	0.95 (0.81-1.10)	0.466	Pain severity	1.14(1.04-1.26)	**0.006**
Model II[b] (N=274)			**Model II[b] (N=486)**		
Pain severity	0.96 (0.82-1.13)	0.623	Pain severity	1.11(1.01-1.22)	**0.037**
Model III[c] (N=268)			**Model III[c] (N=474)**		
Pain severity	0.97 (0.82-1.14)	0.700	Pain severity	1.09(0.98-1.21)	0.097
Model IV[d] (N=268)			**Model IV[d] (N=474)**		
Pain severity	0.95 (0.80-1.14)	0.595	Pain severity	1.06 (0.96-1.18)	0.256
Model V[e] (N=268)			**Model V[e] (N=474)**		
Pain severity	0.96 (0.80-1.15)	0.632	Pain severity	1.06(0.94-1.19)	0.329

[1]Hazard ratios and 95% confidence intervals (CI) calculated from Cox proportional hazard regression modeling
[2] Pain severity was measured using Brief Pain Inventory (BPI) severity subscale (Cleeland & Ryan, 1994), at baseline. Pain severity was a continuous independent variable. Time to death (yrs.) was the outcome variable. No pain was the reference group
[3]Because there was more extensive ascertainment of death until 06/06/2015 (9.8yrs) therefore for this second analysis, 06/06/2015 was selected as the censoring date.
[a]**Model I** without adjustments. [b]**Model II** adjusted for age, race, and education. [c]**Model III** additionally adjusted for BMI, PASE, and MMSE. [d]**Model IV** additionally adjusted for heart disease, diabetes mellitus, lung disease, and depression. [e]**Model V** additionally adjusted for psychiatric drug and analgesics.

Table 29.
Relationship Between Pain Interference at Baseline and Mortality Among Community-Dwelling Older Adults During the 9.8 Years According to Gender (Total Observation=765, Deaths=126)

	Mortality[3]				
	Men (n=276)		**Women (n=489)**		
Predictor[2]	HR (95%CI)[1]	p-value	Predictor[2]	HR (95%CI)[1]	p-value
Model I[a] (N=275)			**Model I[a] (N=487)**		
Pain interference	1.03(0.89-1.18)	0.694	Pain interference	1.07(0.97-1.17)	0.178
Model II[b] (N=274)			**Model II[b](N=486)**		
Pain interference	1.02(0.88-1.19)	0.768	Pain interference	1.04(0.94-1.14)	0.461
Model III[c] (N=268)			**Model III[c] (N=474)**		
Pain interference	1.03(0.89-1.20)	0.689	Pain interference	0.99(0.89-1.09)	0.814
Model IV[d] (N=268)			**Model IV[d] (N=474)**		
Pain interference	1.02(0.87-1.20)	0.783	Pain interference	0.95(0.85-1.05)	0.317
Model V[e] (N=268)			**Model V[e] (N=474)**		
Pain interference	1.03(0.88-1.21)	0.730	Pain interference	0.92(0.82-1.04)	0.189

[1]Hazard ratios and 95% confidence intervals (CI) calculated from Cox proportional hazard regression modeling
[2] Pain interference was measured using Brief Pain Inventory (BPI) subscale, at baseline. Pain interference subscale comprises of 7-items that measured the level of interference with general activity, mood, walking ability, performing normal work, relations with other people, sleep, and enjoyment of life (Cleeland & Ryan, 1994). Pain interference was a continuous independent variable. Time to death (yrs.) was the dependent variable. No pain was the reference group.
[3]Because there was more extensive ascertainment of death until 06/06/2015, therefore for this second analysis, 06/06/2015 was selected as the censoring date.
[a]**Model I** without adjustments. [b]**Model II** adjusted for age, race, and education. [c]**Model III** additionally adjusted for BMI, PASE, and MMSE. [d]**Model IV** additionally adjusted for heart disease, diabetes mellitus, lung disease, and depression. [e]**Model V** additionally adjusted for psychiatric drug and analgesics.

Table 30.
Relationship Between Baseline Persistent Multisite Pain and Mortality Among Community-Dwelling Older Adults at 12.4 Years and 9.8 Years

Pain Distribution	**12.4 years**			**9.8 years[2]**		
	No of death	Total person years of follow-up	Death rate/100 person-years	Number of deaths	Total person years of follow-up	Death rate/100 person-years
Total	44	7725.00	1.86	125	6062.54	2.07
No pain	46	2804	1.64	37	2190.50	1.69
Single-site pain	34	1876.15	1.81	31	1470.43	2.11
Persistent multisite pain[1]	63	3041.66	2.07	57	2398.42	2.38

A 13-item joint pain questionnaire (JPQ) assessed persistent musculoskeletal pain (Hochberg et al., 1995), at baseline. Persistent pain was categorized as a three-level independent variable. Time to death (yrs.) was the independent variable. No pain was the reference group.
[2]Because there was more extensive ascertainment of death until 06/06/2015 (9.8 years), therefore for this second analysis, 06/06/2015 was selected as the censoring date.

Table 31.
Relationship Between Baseline Persistent Multisite Pain and Mortality Among Community-Dwelling Older Adults at 12.4 Years and 9.8 Years According to Gender

Gender[1]	**12.4 years**			**9.8 years[2]**		
	Number of deaths	Total person years of follow-up	Death rate/100 person-years	Number of deaths	Total person years of follow-up	Death rate/100 person-years
Men	56	2753.17	2.03	49	2162.52	2.27
Women	88	4971.83	1.77	77	3900.01	1.97

[1]Gender as a binary variable.
[2]Because there was more extensive ascertainment of death until 06/06/2015 (9.8 years), therefore for this second analysis, 06/06/2015 was selected as the censoring date to make the comparison between two time-points.

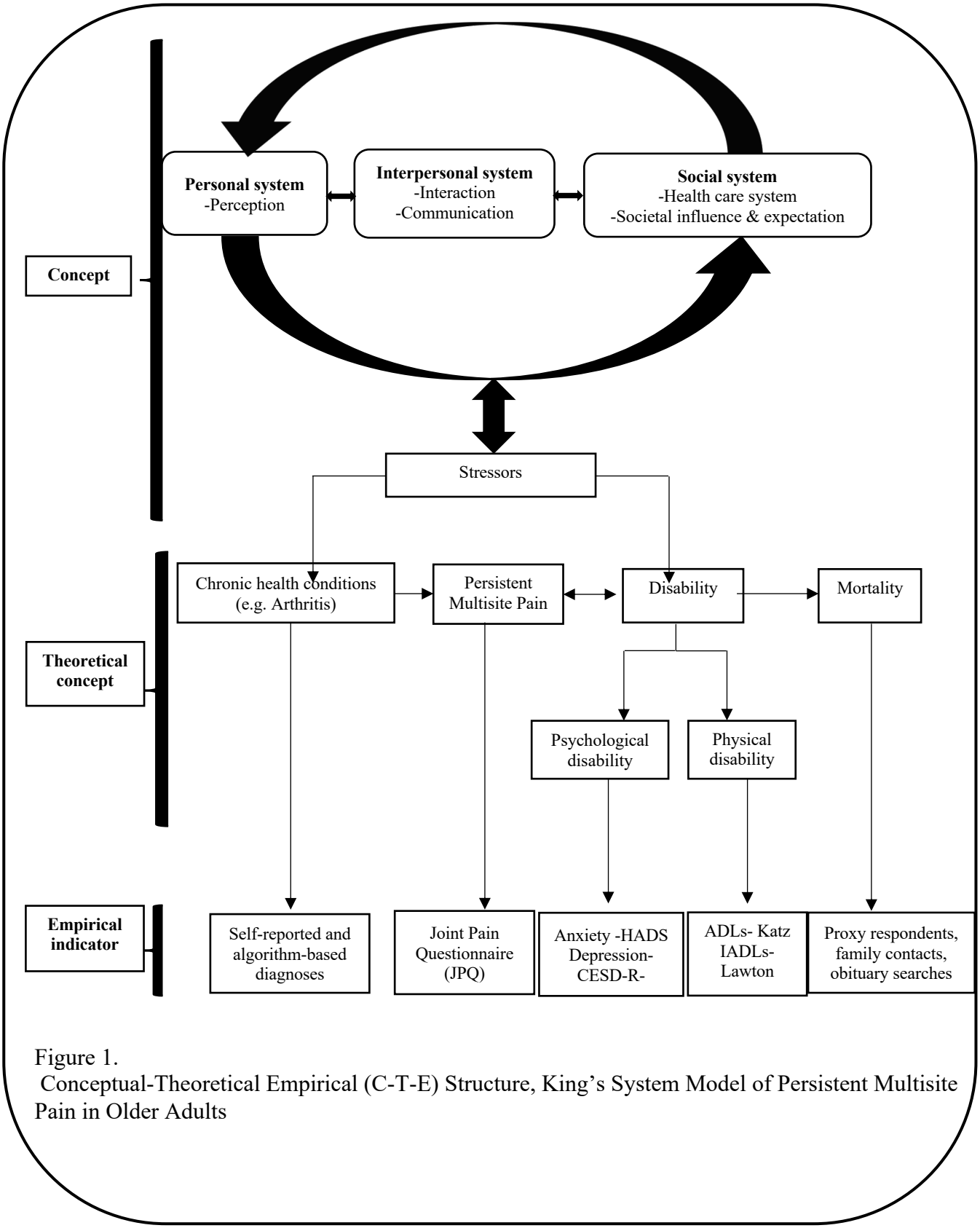


Figure 1.
Conceptual-Theoretical Empirical (C-T-E) Structure, King's System Model of Persistent Multisite Pain in Older Adults

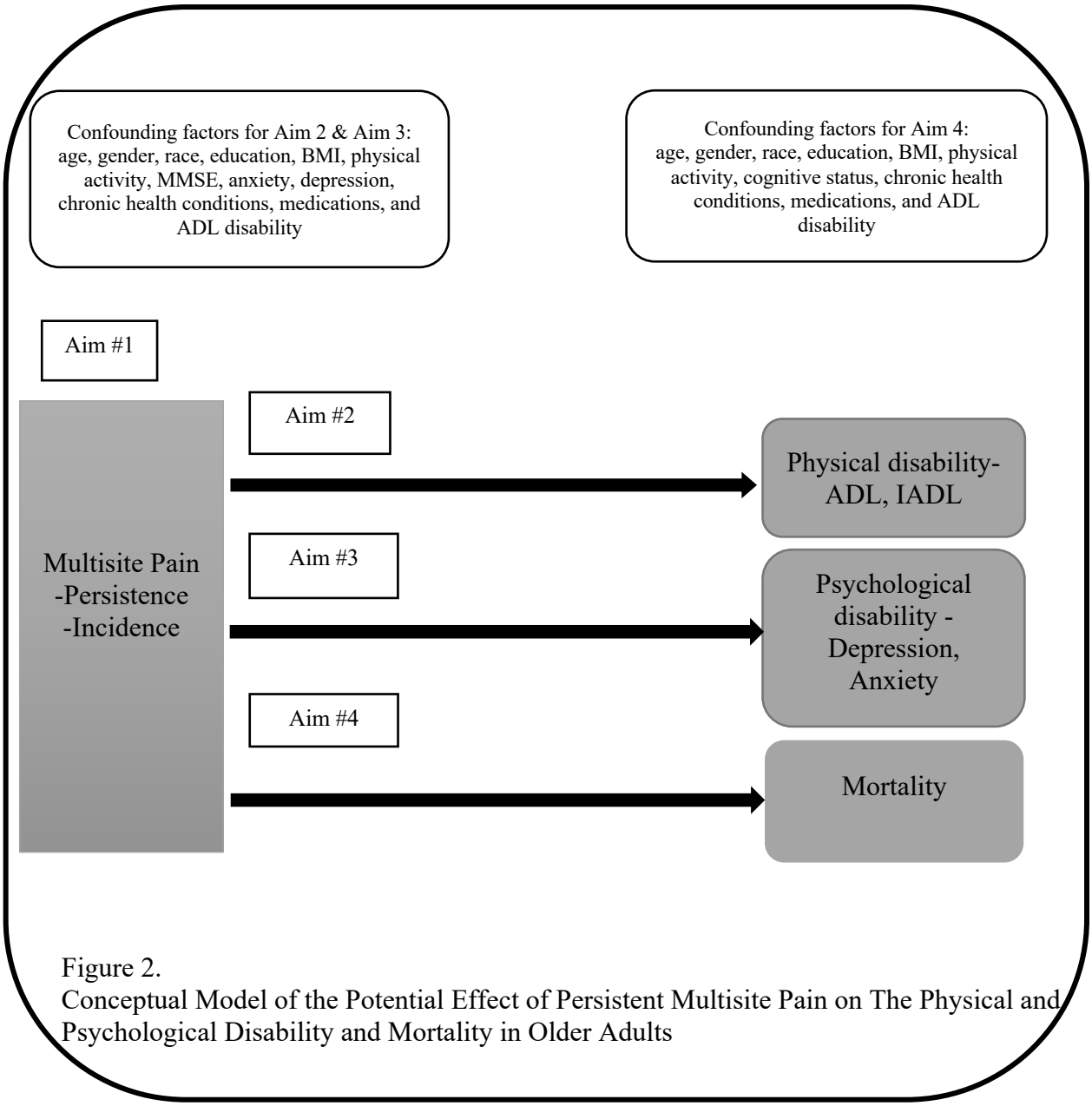


Figure 2.
Conceptual Model of the Potential Effect of Persistent Multisite Pain on The Physical and Psychological Disability and Mortality in Older Adults

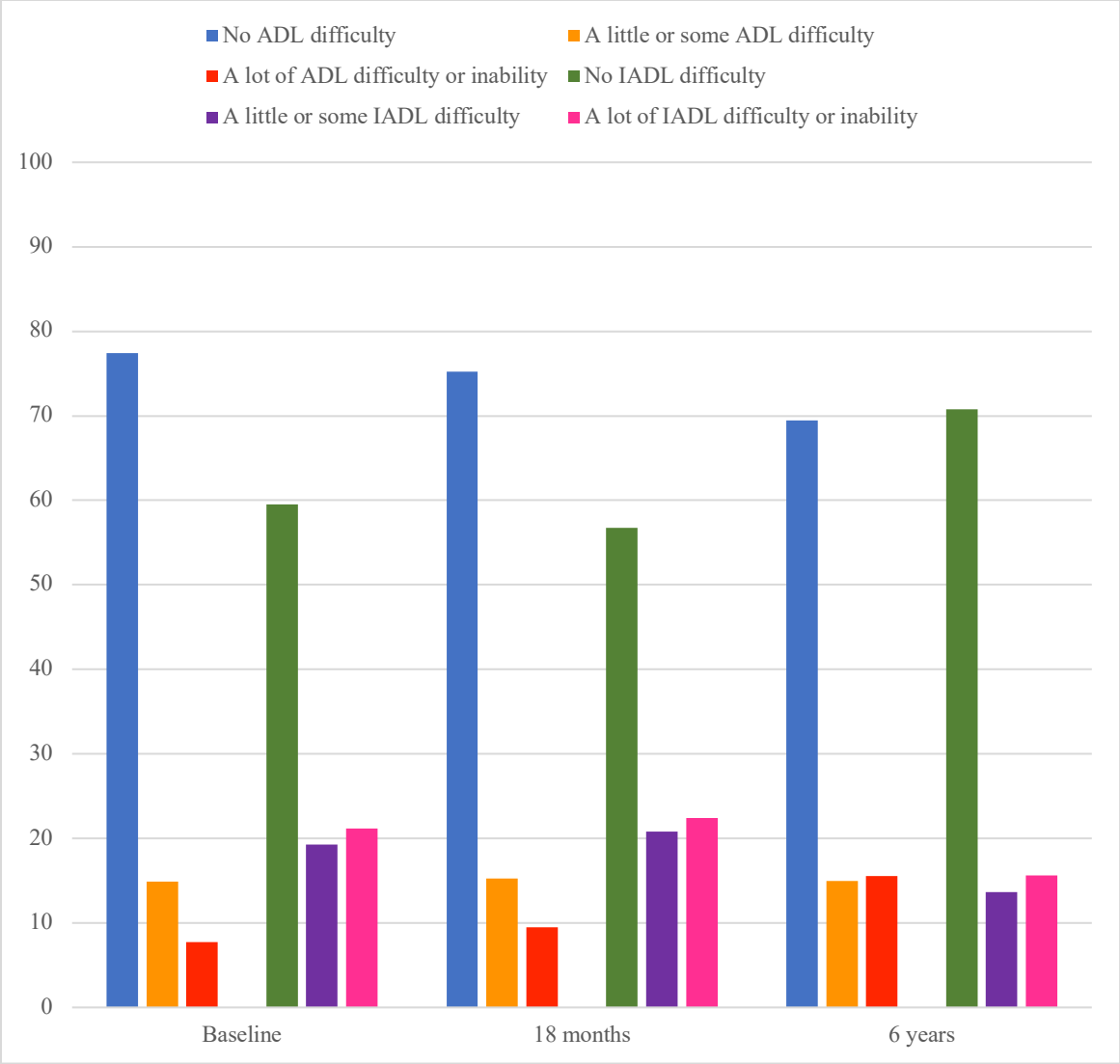


Figure 3.
Prevalence of ADL and IADL Difficulty at Baseline, 18 Months, and 6 Years from MOBILIZE Boston Study (I and II)

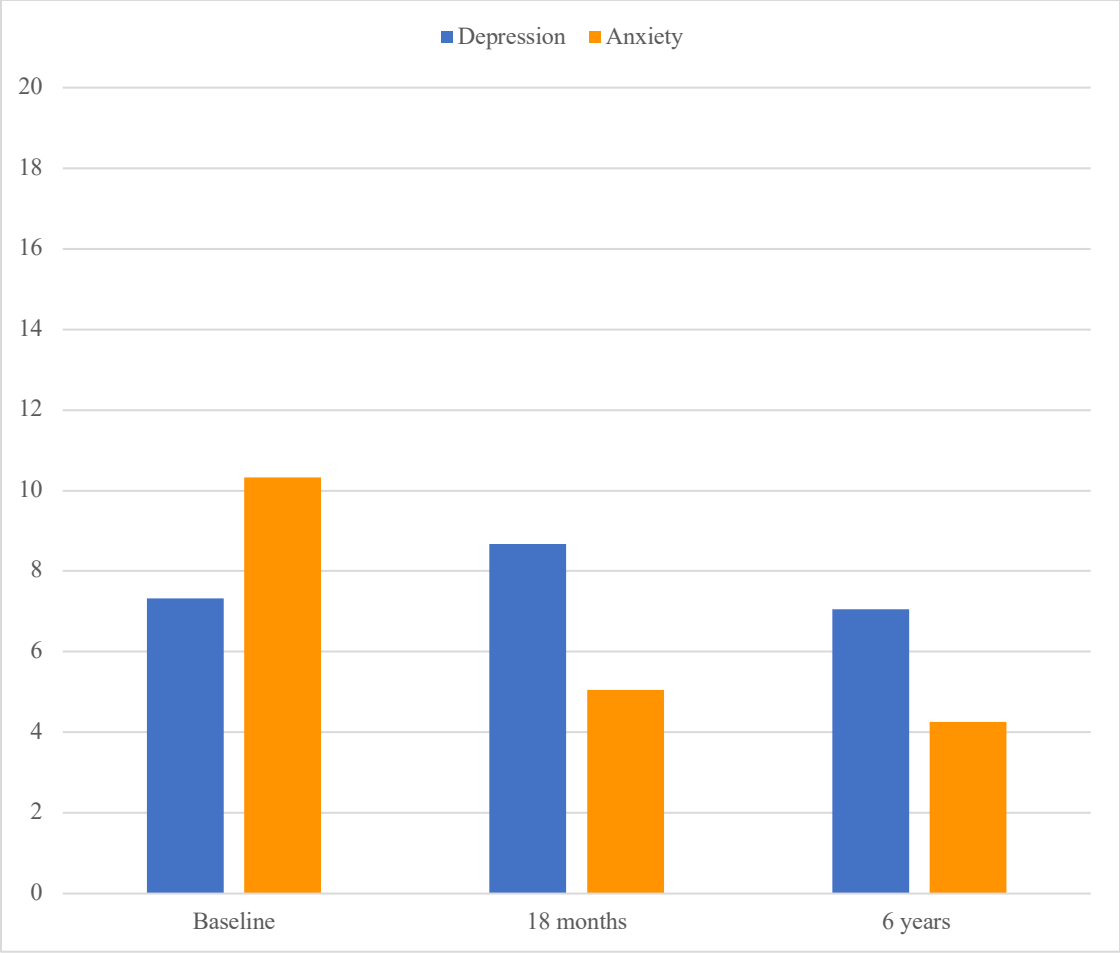


Figure 4.
Prevalence of Depression and Anxiety at Baseline, 18 Months, and 6 Years from MOBILIZE Boston Study (I and II)

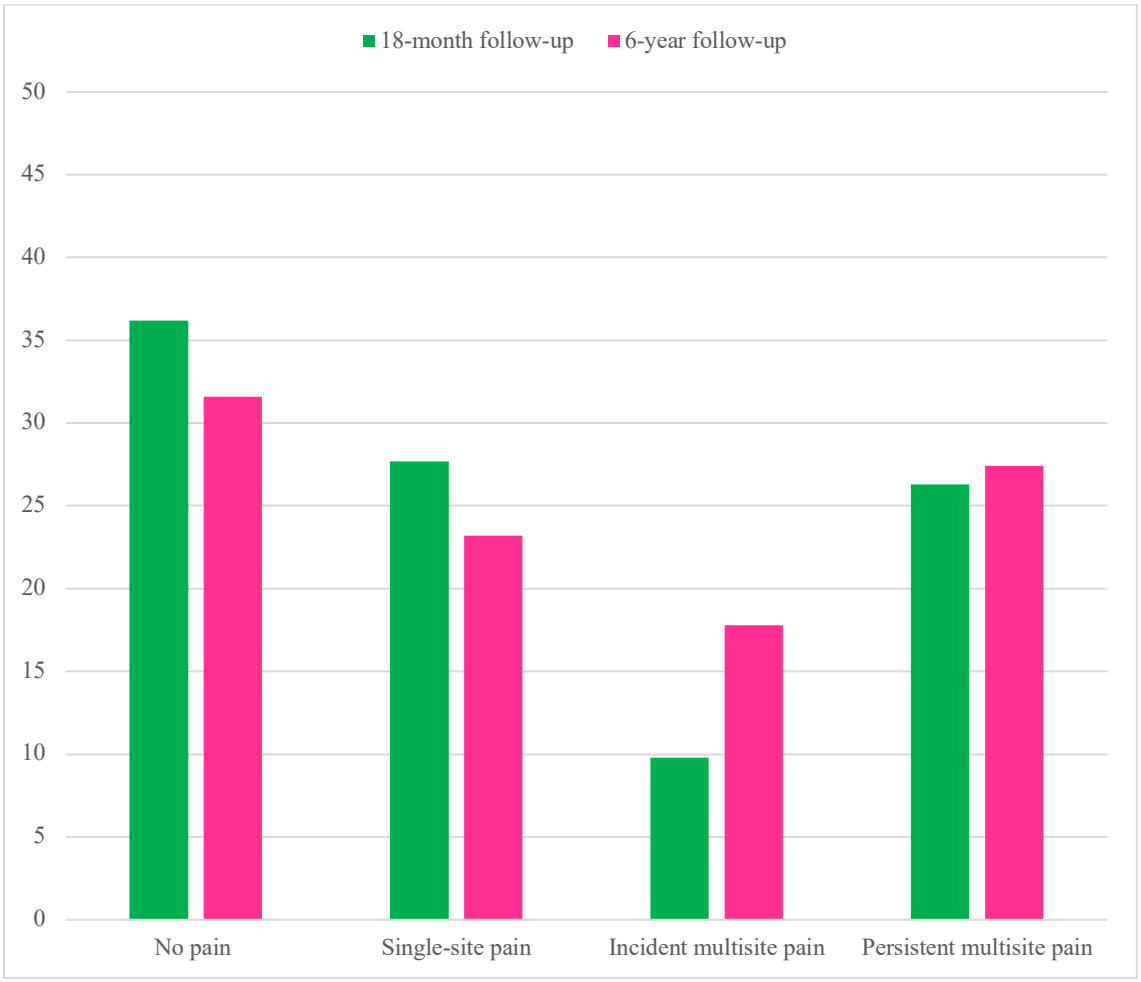


Figure 5.
Prevalence of Longitudinally Assessed Pain Distribution from Baseline to 18 Months, and 6 Years.

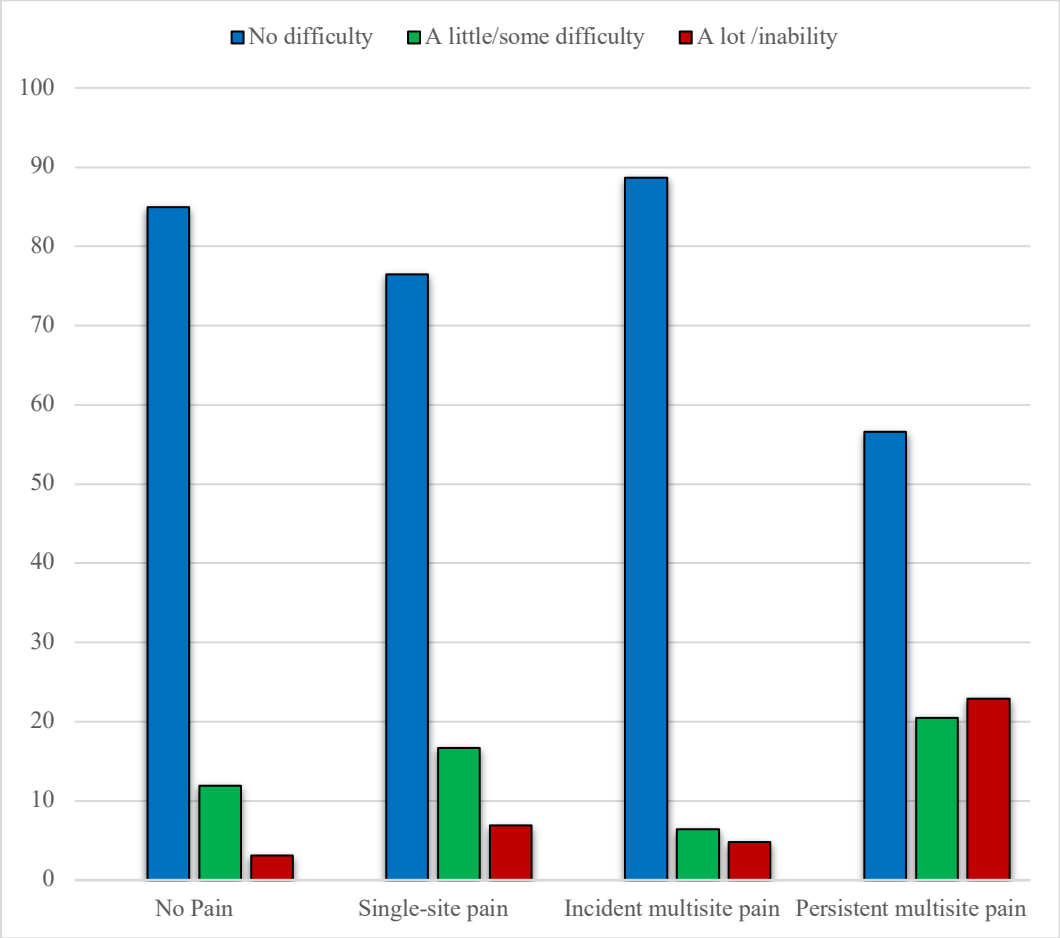


Figure 6.
Prevalence of ADL Difficulty According to Longitudinally Assessed Pain Characteristics in an Older Population at the 18-Month Follow-Up (N=632)

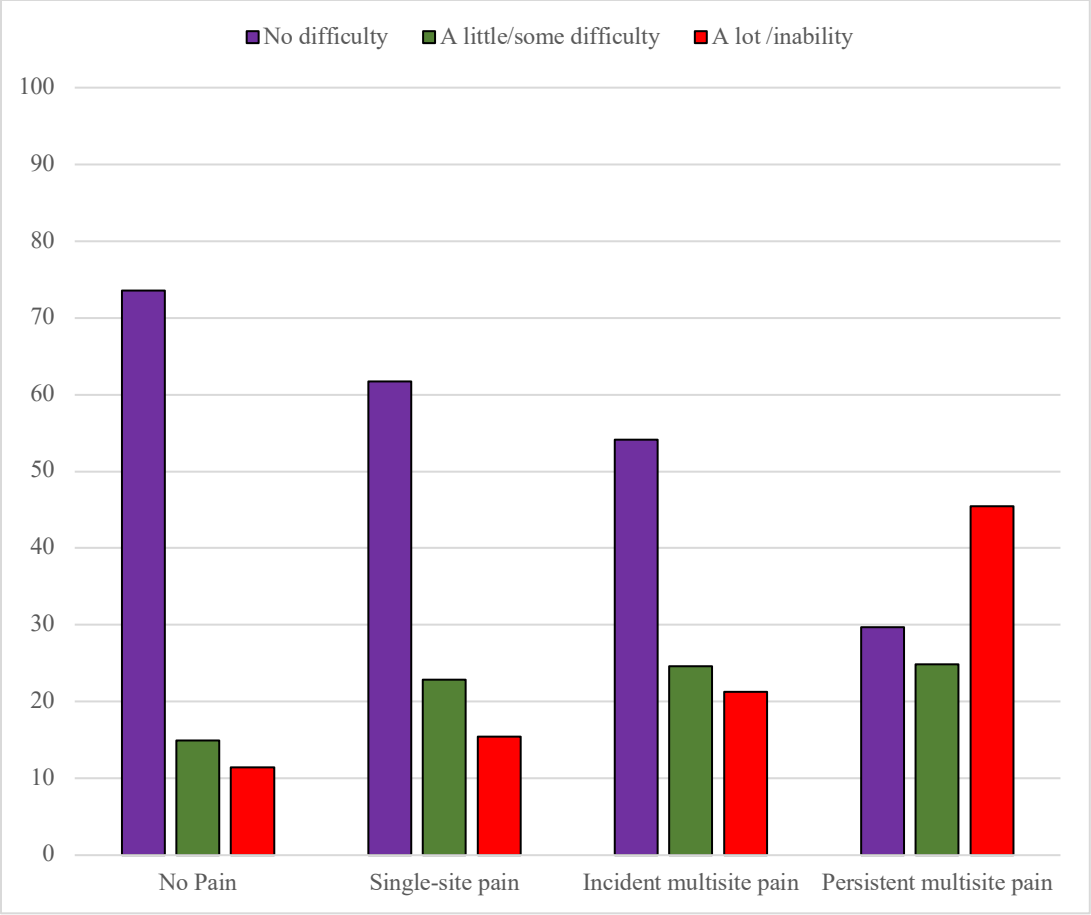


Figure 7.
Prevalence of IADL Difficulty According to Longitudinally Assessed Pain Characteristics in an Older Population at the 18-Month Follow-Up (N=632)

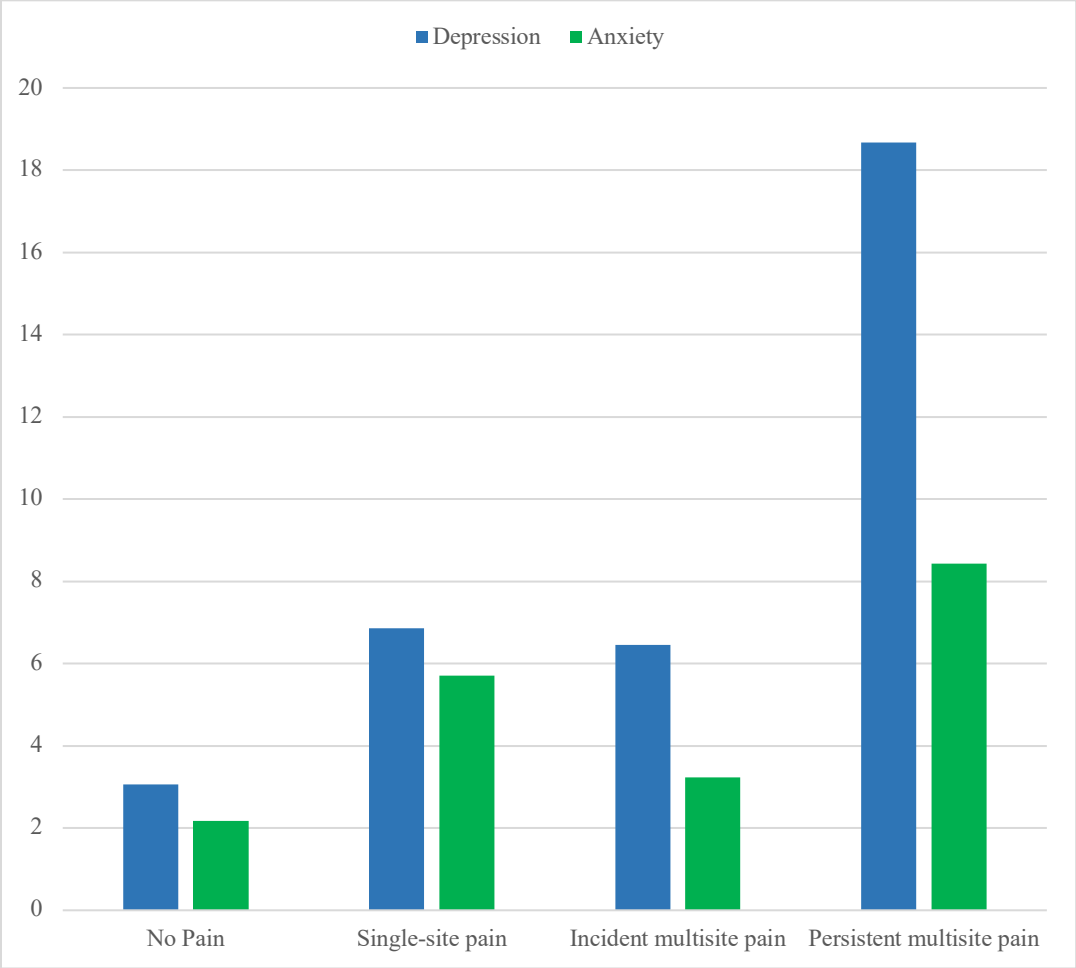


Figure 8.
Prevalence of Depression and Anxiety According to Longitudinally Assessed Pain Characteristics in an Older Population at the 18-Month Follow-Up (N=632)

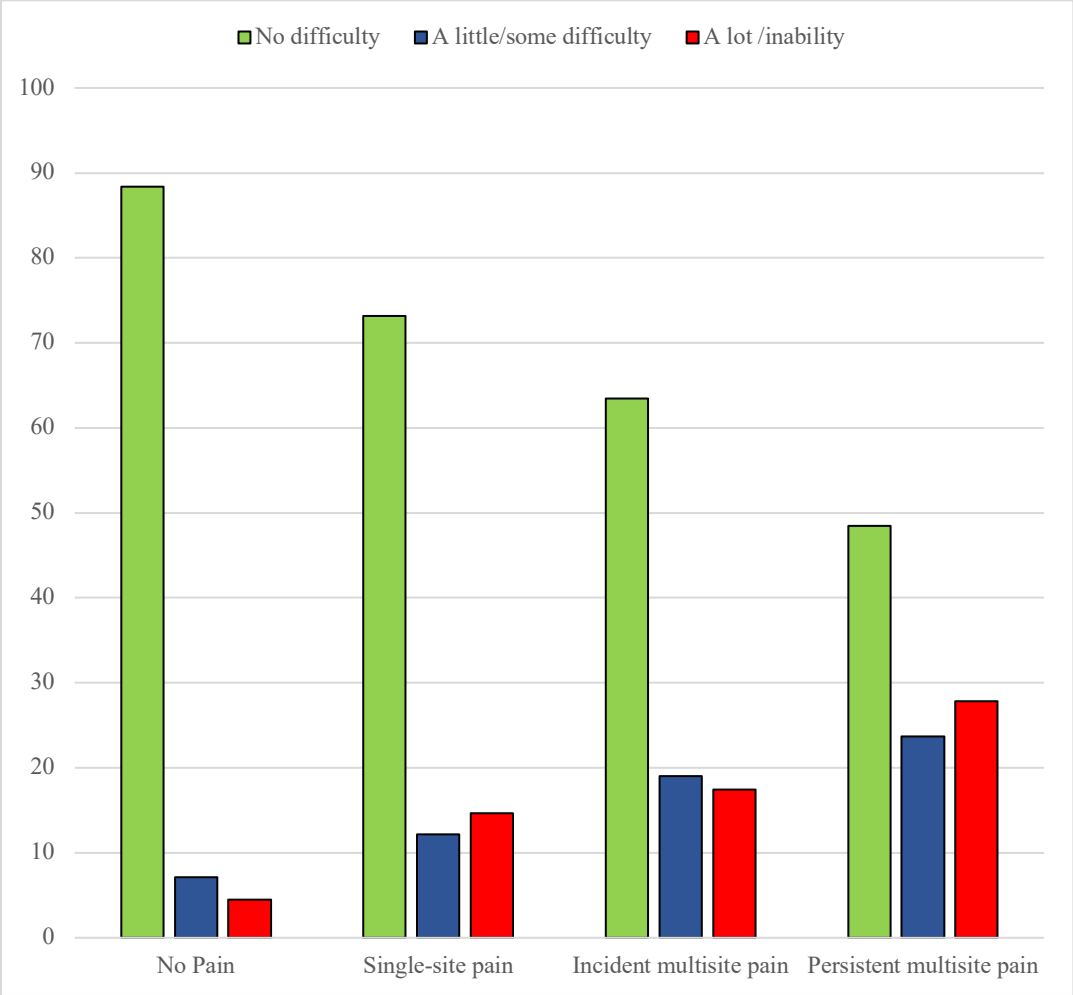


Figure 9.
Prevalence of ADL Difficulty According to Longitudinally Assessed Pain Distribution in an Older Population at the 6-Year Follow-Up (N=354)

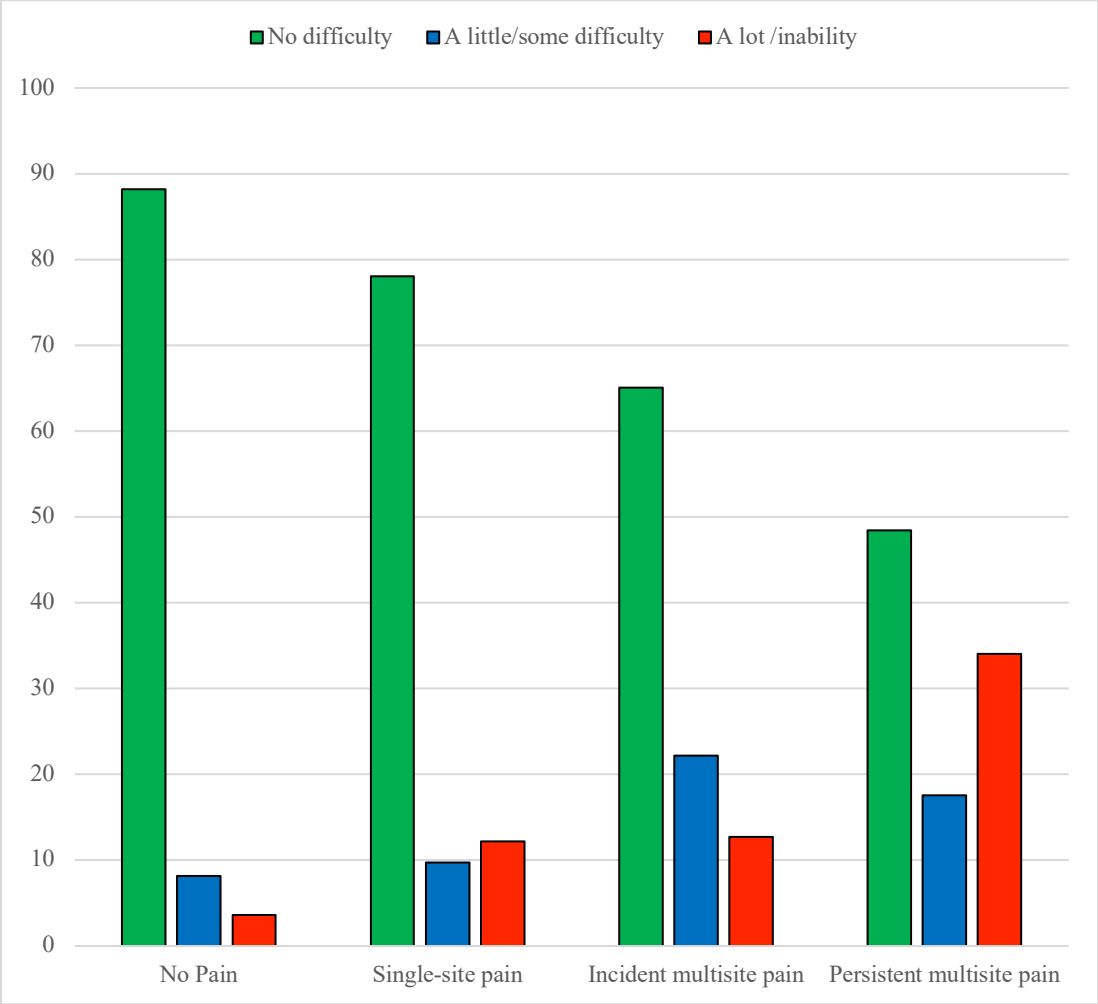


Figure 10.
Prevalence of IADL Difficulty According to Longitudinally Assessed Pain Distribution in an Older Population at the 6-Year Follow-Up (N=354)

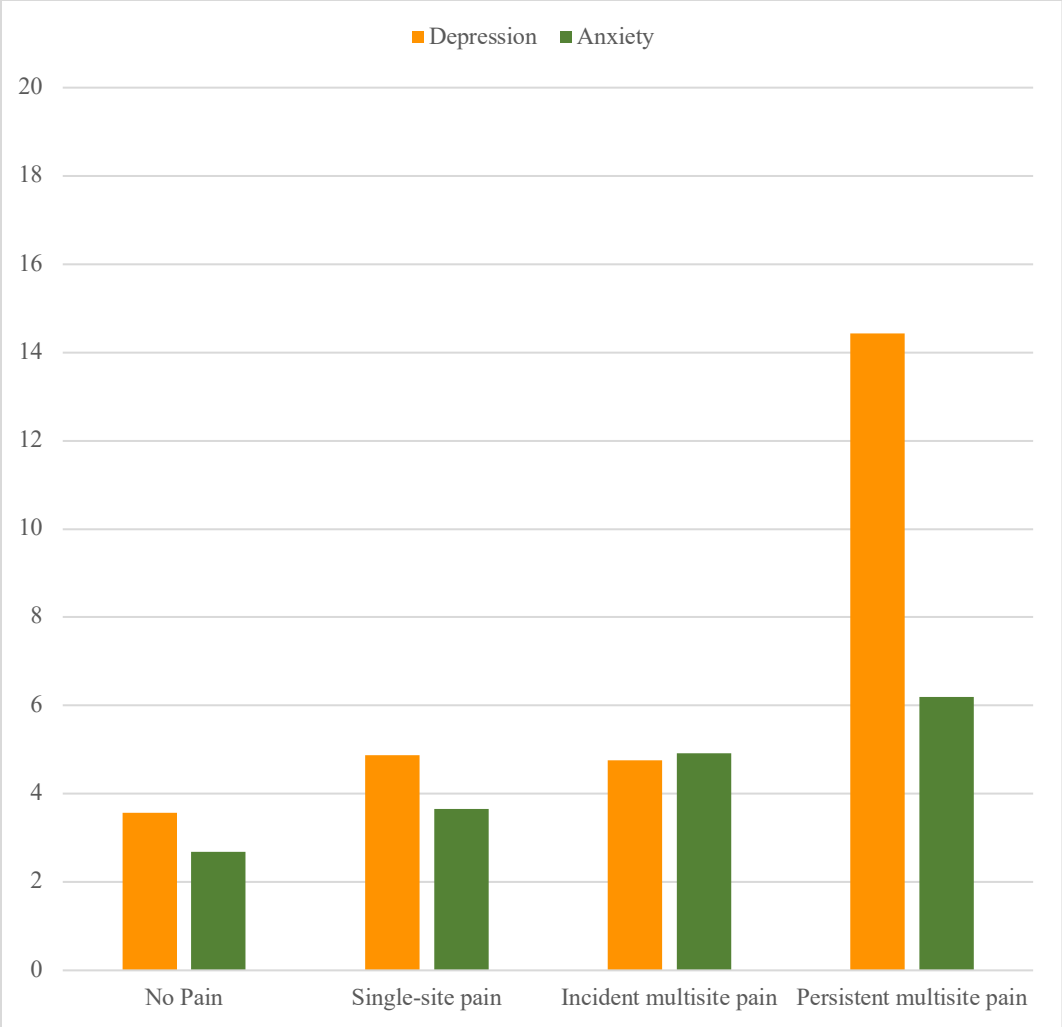
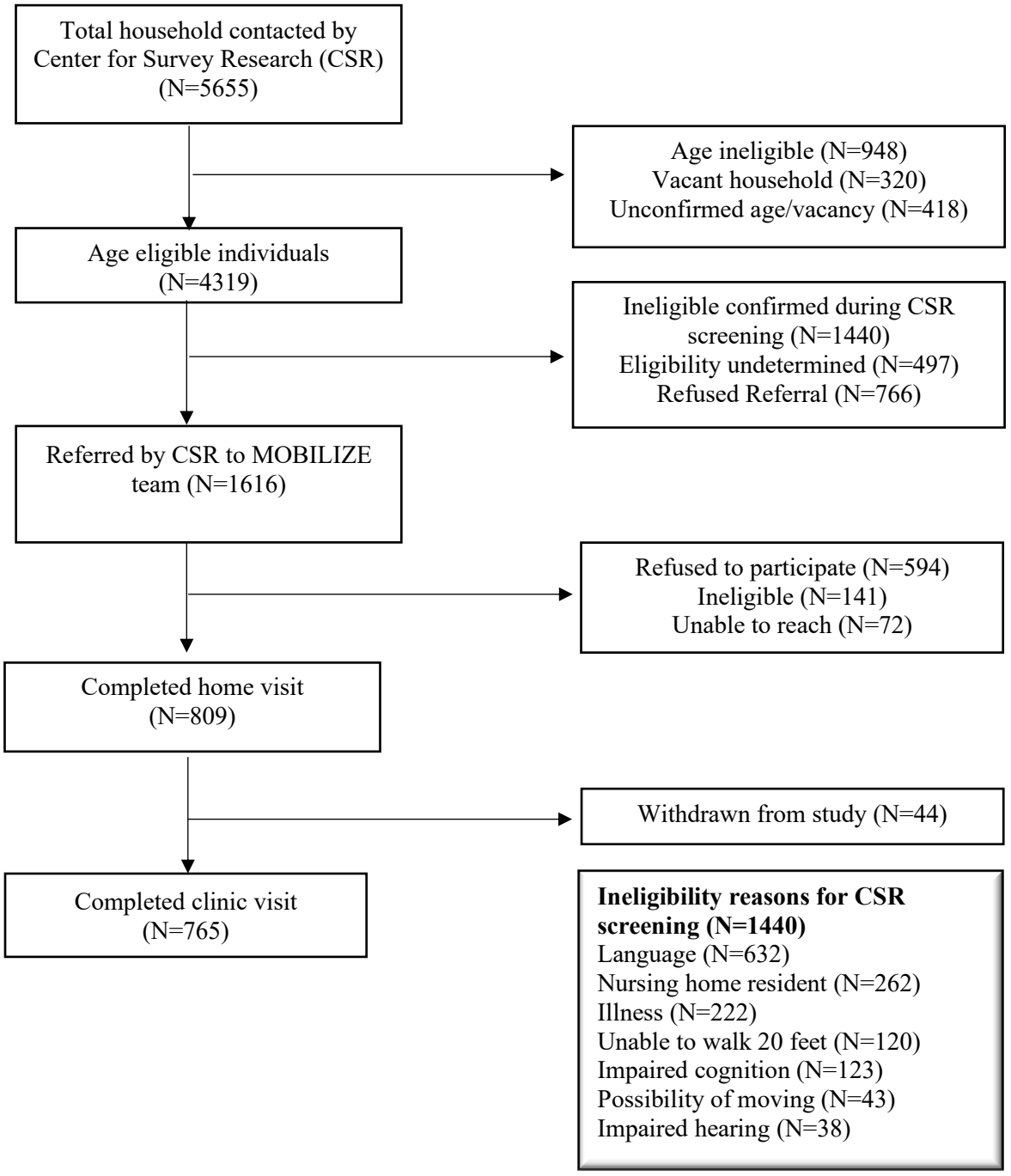


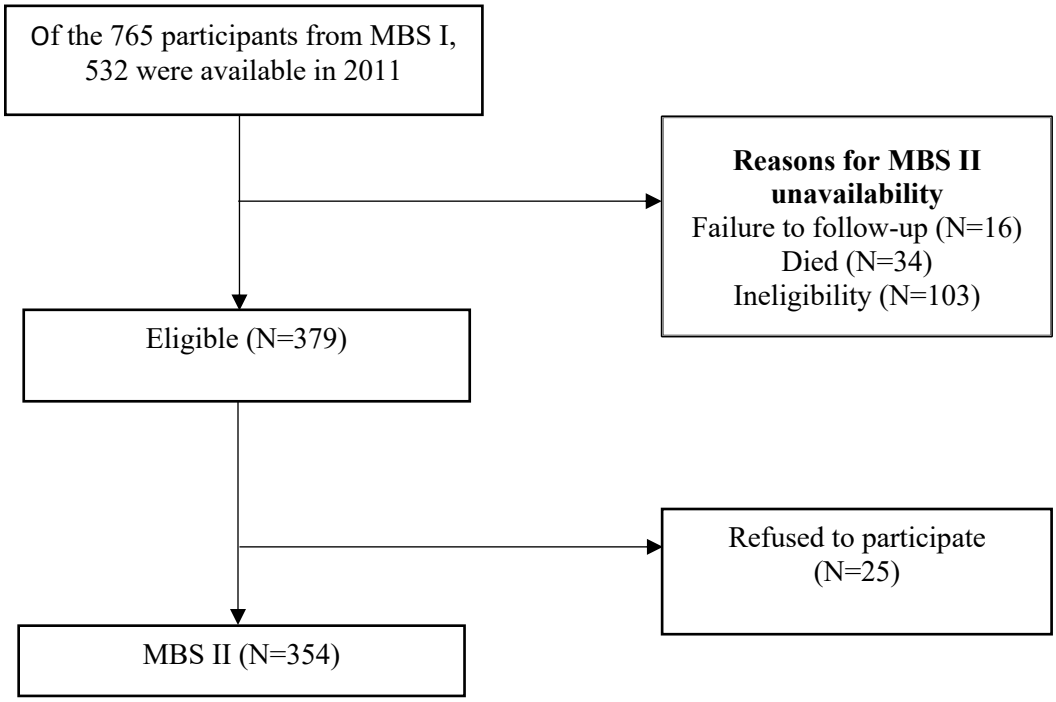
Figure 11.
Prevalence of Depression and Anxiety According to Longitudinally Assessed Pain Distribution in an Older Population at the 6-Year Follow-Up (N=354)

APPENDIX

A1. FLOWCHART OF RECRUITMENT AND ENROLLMENT, MOBILIZE BOSTON STUDY I



A2. FLOWCHART OF RECRUITMENT AND ENROLLMENT MOBILIZE BOSTON STUDY II



Ineligibility reasons for MBS II (N=103)
1. Severe health problems (N=46)
2. Relocation (N=38)
3. Admission to nursing home (N=10)
4. New diagnosis of Advanced dementia (N=7)
5. New diagnosis of terminal illness (N=1)
6. Deafness/blindness (N=1)

REFERENCES

Abdulla, A., Adams, N., Bone, M., Elliott, A. M., Gaffin, J., Jones, D., … Schofield, P. (2013). Guidance on the management of pain in older people. *Age and Ageing*, *42*, i1–i57. https://doi.org/10.1093/ageing/afs200

American Geriatric Society (AGS). (2009). Pharmacological management of persistent pain in older persons. *Pain Medicine*, *10*(6), 1062–1083. https://doi.org/10.1111/j.1526-4637.2009.00699.x

American Geriatric Society (AGS). (2002). The management of persistent pain in older persons. *Journal of American Geriatrics Society*, *50*(S205), 1–20. https://doi.org/10.1046/j.1532-5415.50.6s.1.x

American Geriatrics Society (AGS). (2009). Pharmacological management of persistent pain in older persons. *Pain Medicine*, *10*(6), 1062–1083. https://doi.org/10.1111/j.1526-4637.2009.00699.x

Andersson, H. I. (2004). The course of non-malignant chronic pain: A 12-year follow-up of a cohort from the general population. *European Journal of Pain*, *8*(1), 47–53. https://doi.org/10.1016/S1090-3801(03)00064-8

Andersson, H. I. (2009). Increased mortality among individuals with chronic widespread pain relates to lifestyle factors: A prospective population-based study. *Disability and Rehabilitation*, *31*(24), 1980–1987. https://doi.org/10.3109/09638280902874154

Asberg, A. N., Stovner, L. J., Zwart, J. A., Winsvold, B. S., Heuch, I., & Hagen, K. (2016). Chronic musculoskeletal complaints as a predictor of mortality - The HUNT study. *Pain*, *157*(7), 1443–1447. https://doi.org/10.1097/j.pain.0000000000000537

Asmundson, G. J. G., Coons, M. J., Taylor, S., & Katz, J. (2002). PTSD and the experience of pain: Research and clinical implications of shared vulnerability and mutual maintenance models. *Canadian Journal of Psychiatry*, *47*(10), 930–937. https://doi.org/10.1177/070674370204701004

Asmundson, G. J. G., & Katz, J. (2009). Understanding the co-occurrence of anxiety disorders and chronic pain: State-of-the-art. *Depression and Anxiety*, *26*(10), 888–901. https://doi.org/10.1002/da.20600

Bandura, A. (2004). Health promotion by social cognitive means. *Health Education and Behavior*, *31*(2), 143–164. https://doi.org/10.1177/1090198104263660

Bean, J. F., Latham, N. K., Holt, N., Kurlinksi, L., Ni, P., Leveille, S., … Jett, A. (2013). Which neuromuscular attributes are most associated with mobility among older primary care patients? *Archives of Physical Medicine and Rehabilitation*, *94*(12), 1–15. https://doi.org/doi:10.1016/j.apmr.2013.07.026.

Beaton, K., Mcevoy, C., & Grimmer, K. (2015). Identifying indicators of early functional decline in community-dwelling older people: A review. *Geriatrics and Gerontology International*, *15*(2), 133–140. https://doi.org/10.1111/ggi.12379

Berkman, L. F., Berkman, C. S., Kasl, S., Freeman, D. H., Leo, L., Ostfeld, A. M., … Brody, J. A. (1986). Depressive symptoms in relation to physical health and functioning in the elderly. *American Journal of Epidemiology*, *124*(3), 372–388. https://doi.org/10.1093/oxfordjournals.aje.a114408

Bjelland, I., Dahl, A. A., Haug, T. T., & Neckelmann, D. (2002). The validity of the Hospital Anxiety and Depression Scale. *Journal of Psychosomatic Research*, *52*(2), 69–77. https://doi.org/10.1016/S0022-3999(01)00296-3

Blazer, D. G. (2003). Depression in late Life: Review and commentary. *Journal of Gerontology: Medical Sciences*, *58A*(3), 249–265. https://doi.org/10.1176/foc.7.1.foc118

Blyth, F. M., March, L. M., Brnabic, A. J. M., Jorm, L. R., Williamson, M., & Cousins, M. J. (2001). Chronic pain in Australia: A prevalence study. *Pain*, *89*(2), 127–134. https://doi.org/10.1016/s0304-3959(00)00355-9

Blyth, F. M., & Noguchi, N. (2017). Chronic musculoskeletal pain and its impact on older people. *Best Practice and Research: Clinical Rheumatology*, *31*(2), 160–168. https://doi.org/10.1016/j.berh.2017.10.004

Boehlen, F. H., Herzog, W., Schellberg, D., Maatouk, I., Schoettker, B., Brenner, H., & Wild, B. (2020). Gender-specific predictors of generalized anxiety disorder symptoms in older adults: Results of a large population-based study. *Journal of Affective Disorders*, *262*, 174–181. https://doi.org/10.1016/j.jad.2019.10.025

Bonura, K. B., & Tenenbaum, G. (2014). Effects of yoga on psychological health in older adults. *Journal of Physical Activity and Health*, *11*, 1334–1341. https://doi.org/10.1123/jpah.2012-0365

Booth, F. W., Roberts, C. K., & Laye, M. J. (2012). Lack of exercise is a major cause of chronic diseases. *Comprehensive Physiology*, *2*(2), 1143–1211. https://doi.org/10.1002/cphy.c110025

Bressler, R., & Bahl, J. J. (2003). Principles of drug therapy for the elderly patient. *Mayo Clinic Proceedings*, *78*(12), 1564–1577. https://doi.org/10.4065/78.12.1564

Brewster, G. S., Peterson, L., Roker, R., Ellis, M. L., & Edwards, J. D. (2017). Depressive symptoms, cognition, and everyday function among community-residing older adults. *Journal of Aging and Health*, *29*(3), 367–388. https://doi.org/10.1177/0898264316635587

Briggs, A. M., Cross, M. J., Hoy, D. G., Sànchez-Riera, L., Blyth, F. M., Woolf, A. D., & March, L. (2016). Musculoskeletal health conditions represent a global threat to healthy aging: A report for the 2015 World Health Organization world report on ageing and health. *Gerontologist*, *56*(suppl_2), S243–S255. https://doi.org/10.1093/geront/gnw002

Brown, S. T., Kirkpatrick, M. K., Swanson, M. S., & McKenzie, I. L. (2011). Pain experience of the elderly. *Pain Management Nursing*, *12*(4), 190–196. https://doi.org/10.1016/j.pmn.2010.05.004

Bryant, C., Jackson, H., & Ames, D. (2008). The prevalence of anxiety in older adults: Methodological issues and a review of the literature. *Journal of Affective Disorders*, *109*(3), 233–250. https://doi.org/10.1016/j.jad.2007.11.008

Bryant, C., Mohlman, J., Gum, A., Stanley, M., Beekman, T. A., Wetherell, J. L., & Thorp, R. S. (2013). Anxiety disorders in older adults: Looking to DSM5 and beyond…. *The American Journal of Geriatric Psychiatry*, *21*(9), 872–876. https://doi.org/110.1016/j.jagp.2013.01.011.

Buchman, A. S., Shah, R. C., Leurgans, S. E., Boyle, P. A., Wilson, R. S., & Bennett, David, A. (2010). Musculoskeletal pain and incident disability in community-dwelling elders. *Arthritis Care and Research*, *62*(9), 1287–1293. https://doi.org/10.1038/jid.2014.371

Burke, L. E., Wang, J., & Sevick, M. A. (2011). Self-monitoring in weight loss: A systematic review of the literature. *Journal of the American Dietetic Association*, *111*(1), 92–102. https://doi.org/10.1016/j.jada.2010.10.008.Self-Monitoring

Burston, J. J., Valdes, A. M., Woodhams, S. G., Mapp, P. I., Stocks, J., Watson, D. J. G., … Chapman, V. (2019). The impact of anxiety on chronic musculoskeletal pain and the role of astrocyte activation. *Pain*, *160*(3), 658–669. https://doi.org/10.1097/j.pain.0000000000001445

Butera, K. A., Roff, S. R., Buford, T. W., & Cruz-Almeida, Y. (2019). The impact of multisite pain on functional outcomes in older adults: Biopsychosocial considerations. *Journal of Pain Research*, *12*, 1115–1125. https://doi.org/10.2147/JPR.S192755

Cai, L., & Lubitz, J. (2007). Was there compression of disability for older Americans from 1992 to 2003? *Demography*, *44*(3), 479–495. https://doi.org/10.1353/dem.2007.0022

Canuto, A., Weber, K., Baertschi, M., Andreas, S., Volkert, J., Dehoust, M. C., … Härter, M. (2018). Anxiety disorders in old age: Psychiatric comorbidities, quality of life, and prevalence according to age, gender, and country. *American Journal of Geriatric Psychiatry*, *26*(2), 174–185. https://doi.org/10.1016/j.jagp.2017.08.015

Carman, K. L., Pam, D., Maureen, M., Sofaer, S., Adams, K., Bechtel, C., … Patient. (2013). Patient and family engagement: A framework for understanding the elements and developing interventions and policies. *Health Affairs*, *32*(2), 223–231. https://doi.org/10.1097/nna.0000000000000317

Cecchi, F., Molino-Lova, R., Di Iorio, A., Conti, A. A., Mannoni, A., Lauretani, F., … Ferrucci, L. (2009). Measures of physical performance capture the excess disability associated with hip pain or knee pain in older persons. *Journals of Gerontology - Series A Biological Sciences and Medical Sciences*, *64*(12), 1316–1324. https://doi.org/10.1093/gerona/glp125

Chapman, D. P., & Perry, G. S. (2008). Depression as a major component of public health for older adults. *Preventing Chronic Disease*, *5*(1).

Chen, J., Devine, A., Dick, I. M., Dhaliwal, S. S., & Prince, R. L. (2003). Prevalence of lower extremity pain and its association with functionality and quality of life in elderly women in Australia. *The Journal of Rheumatology*, *30*(12), 2689–2693.

Chen, Q., Hayman, L. L., Shmerling, R. H., Bean, J. F., & Leveille, S. G. (2011). Characteristics of chronic pain associated with sleep difficulty in the older population: The MOBILIZE Boston study. *Journal of the American Geriatrics Society*, *59*(8), 1385–1392. https://doi.org/10.1111/j.1532-5415.2011.03544.x.Characteristics

Cleeland, C. S., & Ryan, K. M. (1994). Pain Assessment: Global use of the brief pain inventory. *Annals Academy of Medicine, Singapore*, *23*(2), 129–138.

Clifford, K. M., Duncan, N. A., Heinrich, K., & Shaw, J. (2015). Update on managing generalized anxiety disorder in older adults. *Journal of Gerontological Nursing*, *41*(4), 10–20. https://doi.org/10.3928/00989134-20150313-03

Cole, M. G., & Dendukuri, N. (2003). Risk factors for depression among elderly community subjects: A systematic review and meta-analysis. *American Journal of Psychiatry*, *160*(6), 1147–1156. https://doi.org/10.1176/appi.ajp.160.6.1147

Colón-Emeric, C. S., Whitson, H. E., Pavon, J., & Hoenig, H. (2013). Functional decline in older adults. *American Family Physician*, *88*(6), 388–394.

Covinsky, K. E., Lindquist, K., Dunlop, D. D., & Yelin, E. (2009). Pain, functional limitations, and aging. *Journal of American Geriatrics Society*, *57*(9), 1556–1561. https://doi.org/10.1111/j.1532-5415.2009.02388.x.

Coyne, R. (2019). The Lawton Instrumental Activities of Daily Living (IADL) scale. *Try This: Best Practice in Nursing Care to Older Adults*, (23), 52–62.

Crimmins, E. M., Hayward, M. D., Hagedorn, A., Saito, Y., & Brouard, N. (2009). Change in disability-free life expectancy for Americans 70 years old and older. *Demography*, *46*(3), 627–646.

Crimmins, E. M., & Saito, Y. (2001). Trends in healthy life expectancy in the United States, 1970-1990: Gender, racial, and educational differences. *Social Science & Medicine*, *52*(11), 1629–1641.

Crimmins, E. M., Zhang, Y., & Saito, Y. (2016). Trends over 4 decades in disability-free life expectancy in the United States. *American Journal of Public Health*, *106*(7), 1287–1293. https://doi.org/10.2105/AJPH.2016.303120

Croft, P., Dunn, K. M., & Von Korff, M. (2007). Chronic pain syndromes: You can't have one without another. *Pain*, *131*(3), 237–238. https://doi.org/10.1016/j.pain.2007.07.013

Croft, P., Jordan, K., & Jinks, C. (2005). "Pain elsewhere" and the impact of knee pain in older people. *Arthritis and Rheumatism*, *52*(8), 2350–2354. https://doi.org/10.1002/art.21218

Cromwell, D. A., Eagar, K., & Poulos, R. G. (2003). The performance of instrumental activities of daily living scale in screening for cognitive impairment in elderly community residents. *Journal of Clinical Epidemiology*, *56*(2), 131–137. https://doi.org/10.1016/S0895-4356(02)00599-1

Culpepper, L. (2009). Generalized anxiety disorder and medical illness. *Journal of Clinical Psychiatry*, *70*(SUPPL. 2), 20–24. https://doi.org/10.4088/JCP.s.7002.04

Damsa, C., Kosel, M., & Moussally, J. (2009). Current status of brain imaging in anxiety disorders. *Current Opinion in Psychiatry*, *22*(1), 96–110. https://doi.org/10.1097/YCO.0b013e328319bd10

DaSilva, J. A. P., Geenen, R., & Jacobs, J. W. G. (2018). Chronic widespread pain and increased mortality: Biopsychosocial interconnections. *Annals of the Rheumatic Diseases*, *77*(6), 790–792. https://doi.org/10.1136/annrheumdis-2017-211893

Davies, H. T., Crombieb, I. K., & Macrae, W. A. (1998). Where does it hurt ? Describing the body locations of chronic pain. *European Journal of Pain*, *2*(1), 69–80. https://doi.org/10.1016/S1090-3801(98)90048-9

De Heer, E. W., Gerrits, M. M. J. G., Beekman, A. T. F., Dekker, J., Van Marwijk, H. W. J., De Waal, M. W. M., … Van Der Feltz-Cornelis, C. M. (2014). The association of depression and anxiety with pain: A study from NESDA. *PLOS ONE*, *9*(10), 1–11. https://doi.org/10.1371/journal.pone.0106907

de Oliveira, C. M. B., Sakata, R. K., Issy, A. M., Gerola, L. R., & Salomão, R. (2011). Cytokines and pain. *Revista Brasileira de Anestesiologia*, *61*(2), 255–265. https://doi.org/10.1016/S0034-7094(11)70029-0

de Oliveira, L. D. S. S. C. B., Souza, E. C., Rodrigues, R. A. S., Fett, C. A., & Piva, A. B. (2019). The effects of physical activity on anxiety, depression, and quality of life in elderly people living in the community. *Trends in Psychiatry and Psychotherapy*, *41*(1), 36–42. https://doi.org/10.1590/2237-6089-2017-0129

Denkinger, M. D., Lukas, A., Nikolaus, T., Peter, R., Franke, S., Geiger, H., … Rapp, K. (2014). Multisite pain, pain frequency and pain severity are associated with depression in older adults: Results from the ActiFE Ulm study. *Age and Ageing*, *43*(4), 510–514. https://doi.org/10.1093/ageing/afu013

Di Iorio, A., Abate, M., Guralnik, J. M., Bandinelli, S., Cecchi, F., Cherubini, A., … Ferrucci, L. (2007). From chronic low back pain to disability, a multifactorial mediated pathway: The InCHIANTI study. *Spine*, *32*(26), 0–14. https://doi.org/10.1097/BRS.0b013e31815cd422

Divo, M. J., Martinez, C. H., & Mannino, D. M. (2014). Ageing and the epidemiology of multimorbidity. *European Respiratory Journal*, *44*(4), 1055–1068.

Djernes, J. K. (2006). Prevalence and predictors of depression in populations of elderly : A review. *Acta Psychiatrica Scandinavica*, *113*(5), 372–387. https://doi.org/10.1111/j.1600-0447.2006.00770.x

Djukanovic, I., Carlsson, J., & Årestedt, K. (2017). Is the Hospital Anxiety and Depression Scale (HADS) a valid measure in a general population 65-80 years old? A psychometric evaluation study. *Health and Quality of Life Outcomes*, *15*(1), 1–10. https://doi.org/10.1186/s12955-017-0759-9

Docking, R. E., Fleming, J., Brayne, C., Zhao, J., Macfarlane, G. J., & Jones, G. T. (2015). The relationship between back pain and mortality in older adults varies with disability and gender: Results from the Cambridge City over-75s Cohort (CC75C) study. *European Journal of Pain (United Kingdom)*, *19*(4), 466–472. https://doi.org/10.1002/ejp.568

Donald, I. P., & Foy, C. (2004). A longitudinal study of joint pain in older people. *Rheumatology*, *43*(10), 1256–1260. https://doi.org/10.1093/rheumatology/keh298

Dong, X., Chang, E. S., & Simon, M. A. (2014). Physical function assessment in a community-dwelling population of U.S. Chinese older adults. *Journals of Gerontology - Series A Biological Sciences and Medical Sciences*, *69*, S31–S38. https://doi.org/10.1093/gerona/glu205

Duchowny, K. A., Clarke, P. J., & Peterson, M. D. (2018). Muscle weakness and physical disability in older Americans: Longitudinal findings from the U.S. health and retirement study. *Journal of Nutrition, Health and Aging*, *22*(4), 501–507. https://doi.org/10.1007/s12603-017-0951-y

Eaton, W. W., Muntaner, C., Smith, C., Tien, A., & Ybarra, M. (2004). Center for epidemiologic studies depression scale: Review and revision (CESD and CESDR). In M. E. Maruish (Ed.), *The use of psychological testing for treatment planning and outcomes assessment: Instruments for adults* (pp. 363–377). London: Lawrence Erlbaum.

Eggermont, L. H. P., Bean, J. F., Guralnik, J. M., & Leveille, S. G. (2009). Comparing pain severity versus pain location in the MOBILIZE Boston study: Chronic pain and lower extremity function. *Journals of Gerontology - Series A Biological Sciences and Medical Sciences*, *64*(7), 763–770. https://doi.org/10.1093/gerona/glp016

Eggermont, L. H. P., Leveille, S. G., Shi, L., Kiely, D. K., Shmerling, R. H., Jones, R. N., … Bean, J. F. (2014). Pain characteristics associated with the onset of disability in older adults: The MOBILIZE Boston study. *Journal of American Geriatrics Society*, *62*(6), 1007–1016. https://doi.org/10.1111/jgs.12848

Eggermont, L. H. P., Milberg, W. P., Lipsitz, L. A., Scherder, E. J. A., & Leveille, S. G. (2009). Physical activity and executive function in aging: The MOBILIZE Boston study. *Journal of the American Geriatrics Society*, *57*(10), 1750–1756. https://doi.org/10.1111/j.1532-5415.2009.02441.x

Eggermont, L. H. P., Penninx, B. W. J. H., Jones, R. N. J., & Leveille, S. G. (2012). Depressive symptoms, chronic pain, and falls in older community-dwelling adults: The MOBILIZE Boston study. *Journal of American Geriatrics Society*, *60*(2), 230–237. https://doi.org/10.1038/jid.2014.371

Engel, L. G. (1977). The need for a new medical model: A challenge for biomedicine. *Science*, *196*(4286), 129–136. https://doi.org/10.1126/science.847460

Fabbri, E., An, Y., Zoli, M., Simonsick, E. M., Guralnik, J. M., Bandinelli, S., … Ferrucci, L. (2015). Aging and the burden of multimorbidity: Associations with inflammatory and anabolic hormonal biomarkers. *Journals of Gerontology - Series A Biological Sciences and Medical Sciences*, *70*(1), 63–70. https://doi.org/10.1093/gerona/glu127

Farrell, M. J. (2012). Age-related changes in the structure and function of brain regions involved in pain processing. *Pain Medicine*, *13*(SUPPL. 2), S37–S43. https://doi.org/10.1111/j.1526-4637.2011.01287.x

Farrokhi, S., Chen, Y. F., Piva, S. R., Fitzgerald, G. K., Jeong, J. H., & Kwoh, C. K. (2016). The influence of knee pain location on symptoms, functional status, and knee-related quality of life in older adults with chronic knee pain: Data from the osteoarthritis initiative. *Clinical Journal of Pain*, *32*(6), 463–470. https://doi.org/10.1097/AJP.0000000000000291

Federal Interagency Forum on Aging-Related Statistics. (2016). Older Americans: key indicators of well-being. Washington, DC: Government Printing Office.

Felger, J. C., & Lotrich, F. E. (2013). Inflammatory cytokines in depression: Neurobiological mechanisms and therapeutic implications. *Neuroscience*, *246*, 199–229. https://doi.org/10.1016/j.neuroscience.2013.04.060

Filho, A. M. C., Mambrini, J. V. de M., Malta, D. C., Lima-Costa, M. F., & Peixoto, S. V. (2018). Contribution of chronic diseases to the prevalence of disability in basic and instrumental activities of daily living in elderly Brazilians: The national health survey (2013). *Cadernos de Saude Publica*, *34*(1), 1–12. https://doi.org/10.1590/0102-311x00204016

Fiske, A., Wetherell, J. L., & Gatz, M. (2009). Depression in older adults. *Annual Review of Clinical Psychology*, *5*, 363–389. https://doi.org/10.1146/annurev.clinpsy.032408.153621.Depression

Flint, A. J. (2005). Anxiety and its disorders in late life: Moving the field forward. *American Journal of Geriatric Psychiatry*, *13*(1), 3–6. https://doi.org/10.1176/appi.ajgp.13.1.3

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). Mini-mental state: A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, *12*(3), 189–198. https://doi.org/10.1016/0022-3956(75)90026-6

Fong, J. H. (2019). Disability incidence and functional decline among older adults with major chronic diseases. *BMC Geriatrics*, *19*(1), 323. https://doi.org/10.1186/s12877-019-1348-z

Fong, J. H., Mitchell, O. S., & Koh, B. S. K. K. (2015). Disaggregating activities of daily living limitations for predicting nursing home admission. *Health Services Research*, *50*(2), 560–578. https://doi.org/10.1111/1475-6773.12235

Forjaz, M. J., Rodriguez-Blazquez, C., Ayala, A., Rodriguez-Rodriguez, V., De Pedro-Cuesta, J., Garcia-Gutierrez, S., & Prados-Torres, A. (2015). Chronic conditions, disability, and quality of life in older adults with multimorbidity in Spain. *European Journal of Internal Medicine*, *26*(3), 176–181. https://doi.org/10.1016/j.ejim.2015.02.016

Fowler-Brown, A., Wee, C., Marcantonio, E., Ngo, L., & Leveille, S. (2013). The mediating effect of chronic pain on the relationship between obesity and physical function and disability in older adults. *Journal of American Geriatrics Society*, *61*(12), 2079–2086. https://doi.org/10.1111/jgs.12512

Freedman, V. A., & Spillman, B. C. (2016). Active life expectancy in the older US population, 1982–2011: Black-white differences persisted. *Health Affairs*, *35*(8), 1351–1358. https://doi.org/10.1377/hlthaff.2015.1247

Freedman, V. A., Wolf, D. A., & Spillman, B. C. (2016). Disability-free life expectancy over 30 years: A growing female disadvantage in the US population. *American Journal of Public Health*, *106*(6), 1079–1085. https://doi.org/10.2105/AJPH.2016.303089

Fried, L. P., & Guralnik, J. M. (1997). Disability in older adults: Evidence regarding significance, etiology, and risk. *Journal of the American Geriatrics Society*, *45*(1), 92–100. https://doi.org/10.1111/j.1532-5415.1997.tb00986.x

Fries, F. J. (1980). Aging, natural death, and the compression of morbidity. *Bulletin of the World Health Organization*, *303*(3), 245–250.

Fries, J. F. (1996). Physical activity, the compression of morbidity, and the health of the elderly. *Journal of the Royal Society of Medicine*, *89*(2), 64–68. https://doi.org/10.1177/014107689608900202

Fuller-Thomson, E., Yu, B., Nuru-Jeter, A., Guralnik, J. M., & Minkler, M. (2009). Basic ADL disability and functional limitation rates among older americans from 2000-2005: The end of the decline? *Journals of Gerontology - Series A Biological Sciences and Medical Sciences*, *64*(12), 1333–1336. https://doi.org/10.1093/gerona/glp130

Gagliese, L., Gauthier, R. L., Narain, N., & Freedman, T. (2018). Pain, aging and dementia: Towards a biopsychosocial model. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *87*, 207–215. https://doi.org/10.1016/j.pnpbp.2017.09.022

Gallo, J. J., Anthony, J. C., & Muthen, B. O. (1994). Age differences in the symptoms of depression: A latent trait analysis. *Journals of Gerontology*, *49*(6). https://doi.org/10.1093/geronj/49.6.P251

Garland, E. L. (2013). Pain processing in the nervous system. *Prim Care*, *39*(3), 561–571. https://doi.org/10.1016/j.pop.2012.06.013.Pain

Gatchel, R. J., Peng, Y. B., Peters, M. L., Fuchs, P. N., & Turk, D. C. (2007). The biopsychosocial approach to chronic pain: Scientific advances and future directions. *Psychological Bulletin*, *133*(4), 581–624. https://doi.org/10.1037/0033-2909.133.4.581

Gaugler, J. E., Duval, S., Anderson, K. A., & Kane, R. L. (2007). Predicting nursing home admission in the U.S: A meta-analysis. *BMC Geriatrics*, *7*(13). https://doi.org/10.1186/1471-2318-7-13

Gerrits, M. M. J. G., Vogelzangs, N., Van Oppen, P., Van Marwijk, H. W. J., Van Der Horst, H., & Penninx, B. W. J. H. (2012). Impact of pain on the course of depressive and anxiety disorders. *Pain*, *153*(2), 429–436. https://doi.org/10.1016/j.pain.2011.11.001

Gibson, J. S. (2006). Older people's pain. *Pain Clinical Updates*, *15*(3), 1–4. https://doi.org/10.1016/j.pain.2004.01.023

Gopinath, B., Schneider, J., McMahon, C. M., Teber, E., Leeder, S. R., & Mitchell, P. (2012). Severity of age-related hearing loss is associated with impaired activities of daily living. *Age and Ageing*, *41*(2), 195–200. https://doi.org/10.1093/ageing/afr155

Grachev, I. D., Fredrickson, B. E., & Apkarian, A. V. (2002). Brain chemistry reflects dual states of pain and anxiety in chronic low back pain. *Journal of Neural Transmission*, *109*(10), 1309–1334.

Grenier, S., Payette, M. C., Gunther, B., Askari, S., Desjardins, F. F., Raymond, B., & Berbiche, D. (2019). Association of age and gender with anxiety disorders in older adults: A systematic review and meta-analysis. *International Journal of Geriatric Psychiatry*, *34*(3), 397–407. https://doi.org/10.1002/gps.5035

Grichnik, K. P., & Ferrante, F. M. (1991). The difference between acute and chronic pain. *The Mount Sinai Journal of Medicine, New York*, *58*(3), 217–220.

Griffin, D. W., Harmon, D. C., & Kennedy, N. M. (2012). Do patients with chronic low back pain have an altered level and/or pattern of physical activity compared to healthy individuals? A systematic review of the literature. *Physiotherapy*, *98*(1), 13–23. https://doi.org/10.1016/j.physio.2011.04.350

Gruenberg, E. M. (1977). The failures of success. *The Milbank Memorial Fund Quarterly. Health and Society*, *55*(1), 3–24. https://doi.org/10.1111/j.1468-0009.2005.00400.x

Gruman, J., Rovner, M. H., French, M. E., Jeffress, D., Sofaer, S., Shaller, D., & Prager, D. J. (2010). From patient education to patient engagement: Implications for the field of patient education. *Patient Education and Counseling*, *78*(3), 350–356. https://doi.org/10.1016/j.pec.2010.02.002

Guralnik, J. M., Fried, L. P., & Salive, M. E. (1996). Disability as a public health outcome in the aging population. *Annual Review of Public Health*, *17*(1), 25–46. https://doi.org/10.1146/annurev.pu.17.050196.000325

Guralnik, J. M., Simonsick, E. M., Ferrucci, L., Glynn, R. J., Berkman, L. F., Blazer, D. G., … Wallace, R. B. (1994). A short physical performance battery assessing lower extremity function: Association with self-reported disability and prediction of mortality and nursing home admission. *Journal of Gerontology*, *49*(2), M85-94. https://doi.org/10.1093/geronj/49.2.M85

Hadjistavropoulos, H. D., & Lachapelle, D. L. (2000). Extent and nature of anxiety experienced during physical examination of chronic low back pain. *Behaviour Research and Therapy*, *38*(1), 13–29. https://doi.org/10.1016/S0005-7967(99)00024-8

Hadjistavropoulos, T., Herr, K., Turk, D. C., Fine, P. G., Dworkin, R. H., Helme, R., … Williams, J. (2007). An interdisciplinary expert consensus statement on assessment of pain in older persons. *Clinical Journal of Pain*. https://doi.org/10.1097/AJP.0b013e31802be869

Hall, A., Copsey, B., Richmond, H., Thompson, J., Ferreira, M., Latimer, J., & Maher, C. G. (2017). Effectiveness of tai chi for chronic musculoskeletal pain conditions: Updated systematic review and meta-analysis. *Physical Therapy*, *97*(2), 227–238. https://doi.org/10.2522/ptj.20160246

Hamer, M., Bates, C. J., & Mishra, G. D. (2011). Depression, physical function, and risk of mortality: National diet and nutrition survey in adults older than 65 years. *American Journal of Geriatric Psychiatry*, *19*(1), 72–78. https://doi.org/10.1097/JGP.0b013e3181df465e

Hasin, S. D., Goodwin, D. R., Stinson, S. F., & Grant, F. B. (2005). Epidemiology of major depressive disorder: Results from the national epidemiologic survey on alcoholism and related conditions. *Archives of General Psychiatry*, *62*(10), 1097–1106. https://doi.org/10.1001/archpsyc.62.10.1097

Haynie, D. A., Berg, S., Johansson, B., Gatz, M., & Zarit, S. H. (2001). Symptoms of depression in the oldest old : A longitudinal study. *Journal of Gerontology: Psychological Sciences*, *56B*(2), 111–118. https://doi.org/10.1093/geronb/56.2.P111

Helme, R. D., & Gibson, S. J. (2001). The epidemiology of pain in elderly people. *Clinics in Geriatric Medicine*, *17*(3), 417-431,. https://doi.org/https://doi.org/10.1016/S0749-0690(05)70078-1

Helvik, A. S., Engedal, K., Skancke, R. H., & Selbæk, G. (2011). A psychometric evaluation of the Hospital Anxiety and Depression Scale for the medically hospitalized elderly. *Nordic Journal of Psychiatry*, *65*(5), 338–344. https://doi.org/10.3109/08039488.2011.560684

Herbolsheimer, F., Schaap, L. A., Edwards, M. H., Maggi, S., Otero, Á., Timmermans, E. J., … Peter, R. (2016). Physical activity patterns among older adults with and without knee osteoarthritis in six European countries. *Arthritis Care and Research*, *68*(2), 228–236. https://doi.org/10.1002/acr.22669

Herr, K. A., & Mobily, P. R. (1992). Chronic pain and depression. *Journal of Psychosocial Nursing and Mental Health Services*, *30*(9), 7–9. https://doi.org/10.3928/0279-3695-19920901-05

Heun, R., Papassotiropoulos, A., & Ptok, U. (2000). Subthreshold depressive and anxiety disorders in the elderly. *European Psychiatry*, *15*(3), 173–182. https://doi.org/10.1016/S0924-9338(00)00228-5

Hicks, G. E., Shardell, M., Alley, D. E., Miller, R. R., Bandinelli, S., Guralnik, J., … Ferrucci, L. (2012). Absolute strength and loss of strength as predictors of mobility decline in older adults: The InCHIANTI study. *Journals of Gerontology - Series A Biological Sciences and Medical Sciences*, *67 A*(1), 66–73. https://doi.org/10.1093/gerona/glr055

Hochberg, M. C., Corti, C. M., Ferrucci, L., & Guralnik, J. M. (1995). Musculoskeletal Disease. In M. Guralnik, JM, Fried LP, Simonsick EM, Kasper JD, Lafferty (Ed.), *The women's health and aging study: Health and social characteristics of older women with disability* (pp. 128–139). Bethesda, MD: National Institutes on Aging.

Hochberg, M. C., Lawrence, R. C., Everett, D. F., & Cornoni-Huntley, J. (1989). Epidemiologic associations of pain in osteoarthritis of the knee: Data from the national health and nutrition examination survey and the national health and nutrition examination-i epidemiologic follow-up survey. *Seminars in Arthritis and Rheumatism*, *18*(4 SUPPL.2), 4–9. https://doi.org/10.1016/0049-0172(89)90008-5

Holden, M. A., Nicholls, E. E., Young, J., Hay, E. M., & Foster, N. E. (2015). Exercise and physical activity in older adults with knee pain: A mixed methods study. *Rheumatology (United Kingdom)*, *54*(3), 413–423. https://doi.org/10.1093/rheumatology/keu333

Holmes, A., Christelis, N., & Arnold, C. (2012). Depression and chronic Pain. *Medical Journal of Australia*, *1 Suppl*(4), 17–20. https://doi.org/10.5694/mjao12.10589

Holzschneider, K., & Mulert, C. (2011). Neuroimaging in anxiety disorders. *Dialouges in Clinical Neuroscience*, *13*(4), 453–461.

Horton, S., & Johnson, R. J. (2010). Improving access to health care for uninsured elderly patients. *Public Health Nursing*, *27*(4), 362–370. https://doi.org/10.1111/j.1525-1446.2010.00866.x

Hung, W. W., Ross, J. S., Boockvar, K. S., & Siu, A. L. (2012). Association of chronic diseases and impairments with disability in older adults: A decade of change? *Medical Care*, *50*(6), 501–507. https://doi.org/10.1097/MLR.0b013e318245a0e0

Hunt, I. M., Silman, A. J., Benjamin, S., Mcbeth, J., & Macfarlane, G. J. (1999). The prevalence and associated features of chronic widespread pain in the community using the ‘ Manchester ’ definition of chronic widespread pain. *Rheumatology (United Kingdom)*, *38*(3), 275–279. https://doi.org/10.1093/rheumatology/38.3.275

Institute of Medicine (IOM). (2011). *Relieving pain In America: A blueprint for transforming prevention, care, education, and research* (Vol. 26). Washington, DC: National Academies Press. https://doi.org/10.17226/13172

Irwin, M., Artin, K. H., & Oxman, M. N. (1999). Screening for depression in the older adult. *Archives of Internal Medicine*, *159*(15), 1701–1704. https://doi.org/10.1001/archinte.159.15.1701

Ishak, N. A., Zahari, Z., & Justine, M. (2017). Kinesiophobia, pain, muscle functions, and functional performances among older persons with low back pain. *Pain Research and Treatment*, *2017*. https://doi.org/10.1155/2017/3489617

Jakicic, J. M., & Davis, K. K. (2011). Obesity and physical activity. *Psychiatric Clinics of North America*, *34*(4), 829–840. https://doi.org/10.1016/j.psc.2011.08.009

Jang, Y., Haley, W. E., Small, B. J., & Mortimer, J. A. (2002). The role of mastery and social resources in the associations between disability and depression in later life. *Gerontologist*, *42*(6), 807–813. https://doi.org/10.1093/geront/42.6.807

Jinks, C., Jordan, K., & Croft, P. (2002). Measuring the population impact of knee pain and disability with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). *Pain*, *100*(1–2), 55–64. https://doi.org/10.1016/S0304-3959(02)00239-7

Johannes, C. B., Le, T. K., Zhou, X., Johnston, J. A., & Dworkin, R. H. (2010). The prevalence of chronic pain in United States adults: Results of an internet-based survey. *Journal of Pain*, *11*(11), 1230–1239. https://doi.org/10.1016/j.jpain.2010.07.002

Jordan, K. P., & Croft, P. (2010). Mortality and cancer in patients with new musculoskeletal episodes: A cohort study. *British Journal of General Practice*, *60*(572), e105–e112. https://doi.org/10.3399/bjgp10x483526

Kahana, B., Kahana, E., Namazi, K., Kercher, K., & Stange, K. (1997). The role of pain in the cascade from chronic illness to social disability and psychological distress in late life. In D. . Mostofsky & J. Lomranz (Eds.), *Handbook of Pain and Aging* (pp. 185–206). New York, NY: Plenum Publishing Co. https://doi.org/10.1007/978-1-4899-0283-2_9

Kaplan, M. S., Huguet, N., Newsom, J. T., & McFarland, B. H. (2003). Characteristics of physically inactive older adults with arthritis: Results of a population-based study. *Preventive Medicine*, *37*(1), 61–67. https://doi.org/10.1016/S0091-7435(03)00059-8

Kåreholt, I., & Brattberg, G. (1998). Pain and mortality risk among elderly persons in Sweden. *Pain*, *77*(3), 271–278. https://doi.org/10.1016/S0304-3959(98)00103-1

Katz, S. (1983). Assessing self-maintenance: Activities of daily living, mobility, and instrumental activities of daily living. *Journal of the American Geriatrics Society*, *31*(12), 721–727. https://doi.org/10.1111/j.1532-5415.1983.tb03391.x

Katz, S., Ford, A., Moskowitz, R., Jackson, B., & Jaffe, M. (1963). Studies of illness in the aged. The index of ADL: A standarized measure of biological and psychosocial function. *JAMA*, *185*(12), 914–919. https://doi.org/10.1001/jama.1963.03060120024016

Kaye, A. D., Baluch, A., & Scott, J. T. (2010). Pain management in the elderly population: A review. *The Ochsner Journal*, *10*(3), 179–187. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/21603375%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC3096211

Keefe, F. J., Kashikar-Zuck, S., Opiteck, J., Hage, E., Dalrymple, L., & Blumenthal, J. A. (1996). Pain in arthritis and musculoskeletal disorders: The role of coping skills training and exercise interventions. *Journal of Orthopaedic & Sports Physical Therapy*, *24*(4), 279–290. https://doi.org/10.2519/jospt.1996.24.4.279

Keenan, A. M., Tennant, A., Fear, J., Emery, P., & Conaghan, P. G. (2006). Impact of multiple joint problems on daily living tasks in people in the community over age fifty-five. *Arthritis Care and Research*, *55*(5), 757–764. https://doi.org/10.1002/art.22239

Kendler, K. S., Gatz, M. G., Gardner, C. O., & Pedersen, N. L. (2006). A Swedish national twin study of lifetime major depression. *American Journal of Psychiatry*, *163*(1), 109–114.

King-Kallimanis, B., Gum, A. M., & Kohn, R. (2009). Comorbidity of depressive and anxiety disorders for older Americans in the national comorbidity survey-replication. *American Journal of Geriatric Psychiatry*, *17*(9), 782–792. https://doi.org/10.1097/JGP.0b013e3181ad4d17

King, I. M. (1981). *A theory for nursing : Systems, concepts, process*. New York: John Wiley & Sons, Inc.

Kochanek, D. K., Murphy, L. S., Xu, J., & Arias, E. (2017). Mortality in the United States. *The Boston Medical and Surgical Journal*, *22*(3), 46–47. https://doi.org/10.1056/nejm184002260220306

Koltyn, K. F. (2002). Using physical activity to manage pain in older adults. *Journal of Aging and Physical Activity*, *10*(2), 226–239. https://doi.org/10.1123/japa.10.2.226

Koychev, I., & Ebmeier, K. P. (2016). Anxiety in older adults often goes undiagnosed. *The Practitioner*, *260*(1789), 17–20.

Krishnan, K. R. R., Delong, M., Kraemer, H., Carney, R., Spiegel, D., Gordon, C., … Wainscott, C. (2002). Comorbidity of depression with other medical diseases in the elderly. *Biological Psychiatry*, *52*(6), 559–588. https://doi.org/10.1016/S0006-3223(02)01472-5

Kroenke, K., Bair, M., Damush, T., Hoke, S., Nicholas, G., Kempf, C., … Sutherland, J. (2007). Stepped Care for Affective Disorders and Musculoskeletal Pain (SCAMP) study. Design and practical implications of an intervention for comorbid pain and depression. *General Hospital Psychiatry*, *29*(6), 506–517. https://doi.org/10.1016/j.genhosppsych.2007.08.005

Kroenke, K., Bair, M. J., Damush, T. M., Wu, J., Hoke, S., Sutherland, J., & Tu, W. (2009). Optimized antidepressant therapy and pain self-management in primary care patients with depression and usculoskeletal pain: A randomized controlled trial. *JAMA - Journal of the American Medical Association*, *301*(20), 2099–2110. https://doi.org/10.1001/jama.2009.723

Laird, K. T., Krause, B., Funes, C., & Lavretsky, H. (2019). Psychobiological factors of resilience and depression in late life. *Translational Psychiatry*, *9*(1), 1–18. https://doi.org/10.1038/s41398-019-0424-7

Lampinen, P., Heikkinen, R. L., & Ruoppila, I. (2000). Changes in intensity of physical exercise as predictors of depressive symptoms among older adults: An eight-year follow-up. *Preventive Medicine*, *30*(5), 371–380. https://doi.org/10.1006/pmed.2000.0641

Landi, F., Liperoti, R., Russo, A., Capoluongo, E., Barillaro, C., Pahor, M., … Onder, G. (2010). Disability, more than multimorbidity, was predictive of mortality among older persons aged 80 years and older. *Journal of Clinical Epidemiology*, *63*(7), 752–759. https://doi.org/10.1016/j.jclinepi.2009.09.007

Landi, F., Russo, A., Liperoti, R., Danese, P., Maiorana, E., Pahor, M., … Onder, G. (2009). Daily pain and functional decline among old-old adults living in the community: Results from the ilSIRENTE study. *Journal of Pain and Symptom Management*, *38*(3), 350–357. https://doi.org/10.1016/j.jpainsymman.2008.10.005

Lane, P., & Smith, D. (2018). Culture, ageing and the construction of pain. *Geriatrics (Switzerland)*, *3*(1), 1–13. https://doi.org/10.3390/geriatrics3030040

Larsson, A., Palstam, A., Löfgren, M., Ernberg, M., Bjersing, J., Bileviciute-Ljungar, I., … Mannerkorpi, K. (2015). Resistance exercise improves muscle strength, health status and pain intensity in fibromyalgia-a randomized controlled trial. *Arthritis Research and Therapy*, *17*(1), 1–15. https://doi.org/10.1186/s13075-015-0679-1

Larsson, C., Ekvall Hansson, E., Sundquist, K., & Jakobsson, U. (2016). Impact of pain characteristics and fear-avoidance beliefs on physical activity levels among older adults with chronic Pain: A population-based, longitudinal study. *BMC Geriatrics*, *16*(1), 1–8. https://doi.org/10.1186/s12877-016-0224-3

Larsson, C., Hansson, E., Sundquist, K., & Jakobsson, U. (2017). Chronic pain in older adults: Prevalence, incidence, and risk factors. *Scandinavian Journal of Rheumatology*, *46*(4), 317–325. https://doi.org/10.1080/03009742.2016.1218543

Laslett, L. L., Quinn, S. J., Winzenberg, T. M., Sanderson, K., Cicuttini, F., & Jones, G. (2012). A prospective study of the impact of musculoskeletal pain and radiographic osteoarthritis on health related quality of life in community dwelling older people. *BMC Musculoskeletal Disorders*, *13*(1), 168. https://doi.org/10.1186/1471-2474-13-168

Lawton, P. M., & Brody, E. (1969). Assessment of older people: Self-maintaining and instrumental activities of daily living. *The Gerontologist*, *9*(3), 179–186. https://doi.org/10.1001/jama.1949.02900240052023

Ledoux, É., Dubois, J. D., & Descarreaux, M. (2012). Physical and psychosocial predictors of functional trunk capacity in older adults with and without low back pain. *Journal of Manipulative and Physiological Therapeutics*, *35*(5), 338–345. https://doi.org/10.1016/j.jmpt.2012.04.007

Lee, S. J., Lindquist, K., Segal, M. R., & Covinsky, K. E. (2006). Development and validation of a prognostic index for 4-year mortality in older adults. *Journal of the American Medical Association*, *295*(7), 801–808. https://doi.org/10.1001/jama.295.7.801

Lee, Y., & Park, K. (2008). Does physical activity moderate the association between depressive symptoms and disability in older adults? *International Journal of Geriatric Psychiatry*, *23*(3), 249–256. https://doi.org/10.1002/gps

Leeuw, M., Goossens, M. E. J. B., Linton, S. J., Crombez, G., Boersma, K., & Vlaeyen, J. W. S. (2007). The fear-avoidance model of musculoskeletal pain: Current state of scientific evidence. *Journal of Behavioral Medicine*, *30*(1), 77–94. https://doi.org/10.1007/s10865-006-9085-0

Lenze, E. J., Mulsant, B. H., Shear, M. K., Houck, P., & Reynolds, C. F. (2006). Anxiety symptoms in elderly patients with depression. *Drugs & Aging*, *19*(10), 753–760. https://doi.org/10.2165/00002512-200219100-00004

Lenze, E. J., Rogers, J. C., Martire, L. M., Mulsant, B. H., Rollman, B. L., Dew, M. A., … Reynolds, C. F. (2001). The association of late-life depression and anxiety with physical disability: A review of the literature and prospectus for future research. *American Journal of Geriatric Psychiatry*, *9*(2), 113–135. https://doi.org/10.1097/00019442-200105000-00004

Lenze, E. J., Schulz, R., Martire, L. M., Zdaniuk, B., Glass, T., Kop, W. J., … Reynolds, C. F. (2005). The course of functional decline in older people with persistently elevated depressive symptoms: Longitudinal findings from the cardiovascular health study. *Journal of the American Geriatrics Society*, *53*(4), 569–575. https://doi.org/10.1111/j.1532-5415.2005.53202.x

Leveille, S. G., Bean, J., Ngo, L., McMullen, W., & Guralnik, J. M. (2007). The pathway from musculoskeletal pain to mobility difficulty in older disabled women. *Pain*, *128*(1–2), 69–77. https://doi.org/10.1016/j.pain.2006.08.031

Leveille, S. G., Guralnik, J. M., Ferrucci, L., Hirsch, R., Simonsick, E., & Hochberg, M. C. (1998). Foot pain and disability in older women. *American Journal of Epidemiology*, *148*(7), 657–665.

Leveille, S. G., Jones, R. N., Kiely, D. K., Hausdorff, J. M., Shmerling, R. H., Guralnik, J. M., … Bean, J. F. (2009). Chronic musculoskeletal pain and the occurrence of falls in an older population. *Journal of the American Medical Association*, *302*(20), 2214–2221. https://doi.org/10.1001/jama.2009.1738

Leveille, S. G., Kiel, D. P., Jones, R. N., Roman, A., Hannan, M. T., Sorond, F. A., … Lipsitz, L. A. (2008). The MOBILIZE Boston Study: Design and methods of a prospective cohort study of novel risk factors for falls in an older population. *BMC Geriatrics*, *8*, 1–14. https://doi.org/10.1186/1471-2318-8-16

Leveille, S. G., Ling, S., Hochberg, M. C., Resnick, H. E., Bandeen-Roche, K. J., Won, A., & Guralnik, J. M. (2001). Widespread musculoskeletal pain and the progression of disability in older disabled women. *Annal of Internal Medicine*, *135*(12), 1038–1046.

Leveille, S. G., Zang, Y., McMullen, W., Kelly-Hayes, M. K.-H., & Felson, D. T. (2005). Sex differences in musculoskeletal pain in older adults. *Pain*, *116*(3), 332–338. https://doi.org/10.1016/j.pain.2005.05.002

Ling, S. M., Fried, L. P., Garrett, E. S., Fan, M. Y., Rantanen, T., & Bathon, J. M. (2003). Knee osteoarthritis compromises early mobility function: The Women's Health and Aging Study II. *Journal of Rheumatology*, *30*(1), 114–120.

Llamas-Velasco, S., Villarejo-Galende, A., Contador, I., Lora Pablos, D., Hernández-Gallego, J., & Bermejo-Pareja, F. (2016). Physical activity and long-term mortality risk in older adults: A prospective population based study (NEDICES). *Preventive Medicine Reports*, *4*, 546–550. https://doi.org/10.1016/j.pmedr.2016.10.002

Loeser, J. D., & Black, R. G. (1975). A taxonomy of pain. *Pain*, *1*(1), 81–84. https://doi.org/10.1016/0304-3959(75)90007-X

Lorig, K. R., & Holman, H. R. (2003). Self-management education : History, definition, outcomes, and mechanisms. *The Society of Behavioral Medicine.*, *26*(1), 1–7.

Luppa, M., Sikorski, C., Luck, T., Ehreke, L., Konnopka, A., Wiese, B., … Riedel-Heller, S. G. (2012). Age- and gender-specific prevalence of pepression in latest-life - systematic review and meta-analysis. *Journal of Affective Disorders*, *136*(3), 212–221. https://doi.org/10.1016/j.jad.2010.11.033

Macfarlane, G. J., Barnish, M. S., & Jones, G. T. (2017). Persons with chronic widespread pain experience excess mortality: Longitudinal results from UK Biobank and meta-Analysis. *Annals of the Rheumatic Diseases*, *76*(11), 1815–1822. https://doi.org/10.1136/annrheumdis-2017-211476

Macfarlane, G. J., Croft, P. R., Schollum, J., & Silman, A. J. (1996). Widespread pain: Is an improved classification possible? *Journal of Rheumatology*, *23*(9), 1628–1632.

Macfarlane, G. J., Jones, G. T., Knekt, P., Aromaa, A., McBeth, J., Mikkelsson, M., & Heliovaara, M. (2007). Is the report of widespread body pain associated with long-term increased mortality? Data from the Mini-Finland Health Survey. *Rheumatology*, *46*(5), 805–807. https://doi.org/10.1093/rheumatology/kel403

Macfarlane, G. J., McBeth, J., & Silman, Alan, J. (2001). Widespread body pain and mortality: Prospective population based study, *323*(7314), 662–665. https://doi.org/10.1136/bmj.323.7314.662

Macfarlane, Pye, S. R., Finn, J. D., Wu, F. C. W., Silman, A. J., Bartfai, G., … Jiang, M. (2009). Investigating the determinants of international differences in the prevalence of chronic widespread pain: Evidence from the European Male Ageing Study. *Annals of the Rheumatic Diseases*, *68*(5), 690–695. https://doi.org/10.1136/ard.2008.089417

Mackichan, F., Adamson, J., & Gooberman-Hill, R. (2013). “Living within your limits”: Activity restriction in older people experiencing chronic pain. *Age and Ageing*, *42*(6), 702–708. https://doi.org/10.1093/ageing/aft119

Maes, M., Song, C., Lin, A., de Jongh, R., van Gastel, A., Kenis, G., … Smith, R. (1998). The effects of psychological stress on humans: increased production of pro-inflammatory cytokines and a Th1-like response in stress-induced anxiety. *Cytokine*, *10*(4), 313–318. Retrieved from http://anet.ua.ac.be/record//c:irua:20392

Majer, I. M., Nusselder, W. J., Mackenbach, J. P., Klijs, B., & Van Baal, P. H. M. (2011). Mortality risk associated with disability: A population-based record linkage study. *American Journal of Public Health*, *101*(12), 9–15. https://doi.org/10.2105/AJPH.2011.300361

Makris, U. E., Paul, T. M., Holt, N. E., Latham, N. K., Ni, P., Jette, A., … Bean, J. F. (2016). The relationship among neuromuscular impairments, chronic back pain, and mobility in older adults. *Physical Medicine and Rehabilitation*, *8*(8), 738–747. https://doi.org/10.1016/j.pmrj.2016.01.007

Manini, T. (2011). Development of physical disability in older adults. *Current Aging Science*, *4*(3), 184–191. https://doi.org/10.2174/1874609811104030184

Manini, T., & Pahor, M. (2009). Physical activity and maintaining physical function in older adults. *British Journal of Sports Medicine*, *43*(1), 28–31. https://doi.org/10.1136/bjsm.2008.053736

Manthorpe, J., & Iliffe, S. (2010). Suicide in later life: Public health and practitioner perspectives. *International Journal of Geriatric Psychiatry*, *25*(12), 1230–1238. https://doi.org/10.1002/gps.2473

Manton, K. G. (1982). Changing concepts of morbidity and mortality in the elderly population. *The Milbank Memorial Fund Quarterly. Health and Society*, *60*(2), 183–244. https://doi.org/10.2307/3349767

Manton, K. G., Gu, X. L., & Lowrimore, G. R. (2008). Cohort changes in active life expectancy in the U.S. elderly population: Experience from the 1982-2004 National Long-Term Care Survey. *Journals of Gerontology - Series B Psychological Sciences and Social Sciences*, *63*(5), 269–281. https://doi.org/10.1093/geronb/63.5.S269

Mänty, M., Thinggaard, M., Christensen, K., & Avlund, K. (2014). Musculoskeletal pain and physical functioning in the oldest old. *European Journal of Pain*, *18*(4), 522–529. https://doi.org/10.1038/jid.2014.371

Martin, R. R., Hadjistavropoulos, T., & McCreary, D. R. (2005). Fear of pain and fear of falling among younger and older adults with musculoskeletal pain conditions. *Pain Research and Management*, *10*(4), 211–218. https://doi.org/10.1155/2005/919865

McBeth, J., Silman, A. J., & Macfarlane, G. J. (2003). Association of widespread body pain with an increased risk of cancer and reduced cancer survival: A prospective, population-based study. *Arthritis and Rheumatism*, *48*(6), 1686–1692. https://doi.org/10.1002/art.10973

McBeth, J., Symmons, D. P., Silman, A. J., Allison, T., Webb, R., Brammah, T., & MacFarlane, G. J. (2009). Musculoskeletal pain is associated with a long-term increased risk of cancer and cardiovascular-related mortality. *Rheumatology*, *48*(1), 74–77. https://doi.org/10.1093/rheumatology/ken424

McCarthy, H. L., Bigal, E. M., Mindy, K., Derby, C., & Lipton, B. R. (2009). Chronic pain and obesity in the elderly: Results from the Einstein Aging Study. *Journal of American Geriatrics Society*, *57*(1), 115–119. https://doi.org/10.1111/j.1532-5415.2008.02089.x.Chronic

McGrath, R., Robinson-Lane, S. G., Peterson, M. D., Bailey, R. R., & Vincent, B. M. (2018). Muscle strength and functional limitations: Preserving function in older Mexican Americans. *Journal of the American Medical Directors Association*, *19*(5), 391–398. https://doi.org/10.1016/j.jamda.2017.12.011

McKinstry, B., Hammersley, V., Burton, C., Pinnock, H., Elton, R., Dowell, J., … Sheikh, A. (2010). The quality, safety and content of telephone and face-to-face consultations: A comparative study. *Quality and Safety in Health Care*, *19*(4), 298–303. https://doi.org/10.1136/qshc.2008.027763

McWilliams, L. A., Cox, B. J., & Enns, M. W. (2003). Mood and anxiety disorders associated with chronic pain: An examination in a nationally representative sample. *Pain*, *106*(1–2), 127–133. https://doi.org/10.1016/S0304-3959(03)00301-4

McWilliams, L. A., Goodwin, R. D., & Cox, B. J. (2004). Depression and anxiety associated with three pain conditions: Results from a nationally representative sample. *Pain*, *111*(1–2), 77–83. https://doi.org/10.1016/j.pain.2004.06.002

Meerwijk, E. L., Ford, J. M., & Weiss, S. J. (2013). Brain regions associated with psychological pain: Implications for a neural network and its relationship to physical pain. *Brain Imaging and Behavior*, *7*(1), 1–14. https://doi.org/10.1007/s11682-012-9179-y

Mehta, M. K., Simonsick, M. E., Penninx, B. W. J. H. B., Schulz, R., Rubin, M. S., Satterfield, S., & Yaffe, K. (2003). Prevalence and correlates of anxiety symptoms in well-functioning older adults: Findings from the health aging and body composition study. *Journal of the American Geriatrics Society*, *51*(4), 499–504.

Melzack, R., & Wall, P. D. (1965). Pain mechansims: A new theory. *Science*, *150*(3699), 971–979.

Merskey, H., & Bogduk, N. (1994). *Classification of chronic pain*. (IASP Task Force on Taxonomy, Ed.) (2nd ed.). Seattle: IASP Press.

Miaskowski, C. (2000). The impact of age on a patient's perception of pain and ways it can be managed. *Pain Management Nursing*, *1*(3), 2–7. https://doi.org/10.1053/jpmn.2000.9760

Mitchell, A. J., & Subramaniam, H. (2005). Prognosis of depression in old age compared to middle age: A systematic review of comparative studies. *American Journal of Psychiatry*, *162*(9), 1588–1601. https://doi.org/10.1176/appi.ajp.162.9.1588

Molton, I. R., & Terrill, A. L. (2014). Overview of persistent pain in older adults. *American Psychologist*, *69*(2), 197–207. https://doi.org/10.1037/a0035794

Mor, V., Wilcox, V., Rakowski, W., & Hiris, J. (1994). Functional transitions among the elderly: Patterns, predictors, and related hospital use. *American Journal of Public Health*, *84*(8), 1274–1280. https://doi.org/10.2105/AJPH.84.8.1274

Morone, N. E., Karp, J. F., Lynch, C. S., Bost, J. E., El Khoudary, S. R., & Weiner, D. K. (2009). Impact of chronic musculoskeletal pathology on older adults: A study of differences between knee OA and low back pain. *Pain Medicine*, *10*(4), 693–701. https://doi.org/10.1111/j.1526-4637.2009.00565.x

Mottram, S., Peat, G., Thomas, E., Wilkie, R., & Croft, P. (2008). Patterns of pain and mobility limitation in older people: Cross-sectional findings from a population survey of 18,497 adults aged 50 years and over. *Quality of Life Research*, *17*(4), 529–539. https://doi.org/10.1007/s11136-008-9324-7

Murabito, J. M., Pencina, M. J., Zhu, L., Kelly-Hayes, M., Shrader, P., & D'Agostino, R. B. (2008). Temporal trends in self-reported functional limitations and physical disability among the community-dwelling elderly population: The Framingham Heart Study. *American Journal of Public Health*, *98*(7), 1256–1262. https://doi.org/10.2105/AJPH.2007.128132

Murata, S., Doi, T., Sawa, R., Nakamura, R., Isa, T., Ebina, A., … Ono, R. (2019). Association between objectively measured physical activity and the number of chronic musculoskeletal pain sites in community-dwelling older adults. *Pain Medicine (United States)*, *20*(4), 717–723. https://doi.org/10.1093/pm/pny112

Murtagh, K. N., & Hubert, H. B. (2004). Gender differences in physical disability among an elderly cohort. *American Journal of Public Health*, *94*(8), 1406–1411. https://doi.org/10.2105/AJPH.94.8.1406

Nagi, S. (1976). An epidemiology of disability among adults in the United States. *Health and Society*, *54*(4), 439–467.

National Council of Aging. (2018). Healthy aging: Fact sheet. Retrieved July 5, 2020, from https://d2mkcg26uvg1cz.cloudfront.net/wp-content/uploads/2018-Healthy-Aging-Fact-Sheet-7.10.18-1.pdf

National Institute of Mental Health. (2016). Depression basics. Retrieved from https://www.nimh.nih.gov/health/publications/depression/index.shtml

Nawai, A. (2017). *Is pain catastrophizing associated with poor physical performance and falls in older adults with chronic pain? The Mobilize Boston Study II (Doctoral Dissertation)*. Retrieved from https://scholarworks.umb.edu/doctoral_dissertations/370

Newman, A. B., Kupelian, V., Visser, M., Simonsick, E. M., Goodpaster, B. H., Kritchevsky, S. B., … Harris, T. B. (2006). Strength, but not muscle mass, is associated with mortality in the health, aging and body composition study cohort. *Journals of Gerontology - Series A Biological Sciences and Medical Sciences*, *61*(1), 72–77. https://doi.org/10.1093/gerona/61.1.72

Ogden, C. L., Carroll, M. D., Kit, B. K., & Flegal, K. M. (2013). Prevalence of obesity among adults: United States, 2011-2012. *National Center for Health Stastistics Data Brief*.

Olfson, M., & Gameroff, M. J. (2007). Generalized anxiety disorder, somatic pain and health care costs. *General Hospital Psychiatry*, *29*(4), 310–316. https://doi.org/10.1016/j.genhosppsych.2007.04.004

Onder, G., Cesari, M., Russo, A., Zamboni, V., Bernabei, R., & Landi, F. (2006). Association between daily pain and physical function among old-old adults living in the community: Results from the ilSIRENTE study. *Pain*, *121*(1–2), 53–59. https://doi.org/10.1016/j.pain.2005.12.003

Onubogu, U. D. (2014). Pain and depression in older adults with arthritis. *Orthopaedic Nursing*, *33*(2), 102–108. https://doi.org/10.1097/NOR.0000000000000035

Ostir, G. V., Carlson, J. E., Black, S. A., Rudkin, L., Goodwin, J. S., & Markides, K. S. (1999). Disability in older Adults 1: Prevalence, causes, and consequences. *Behavioral Medicine*, *24*(4), 147–156. https://doi.org/10.1080/08964289.1999.11879271

Overdorf, V., Kollia, B., Makarec, K., & Alleva Szeles, C. (2016). The relationship between physical activity and depressive symptoms in healthy older women. *Gerontology and Geriatric Medicine*, *2*, 1–8. https://doi.org/10.1177/2333721415626859

Pan, F., Laslett, L., Blizzard, L., Cicuttini, F., Winzenberg, T., Ding, C., & Jones, G. (2017). Associations between fat mass and multisite pain: A five-year longitudinal study. *Arthritis Care and Research*, *69*(4), 509–516. https://doi.org/10.1002/acr.22963

Patel, K., Guralnik, J. M., Dansie, E. J., & Turk, D. C. (2013). Prevalence and impact of pain among older odults in the United States: Findings from the 2011 National Health and Aging Trends Study. *Pain*, *154*(12), 1–22. https://doi.org/10.1016/j.pain.2013.07.029

Patel, K., & Turk, D. (2015). Chronic pain and the risk of death: Findings from the 1999-2004 NHANES mortality follow-up study. *The Journal of Pain*, *16*(4), S11. https://doi.org/10.1016/j.jpain.2015.01.054

Peat, G., Thomas, E., Wilkie, R., & Croft, P. (2006). Multiple joint pain and lower extremity disability in middle and old age. *Disability and Rehabilitation*, *28*(24), 1543–1549. https://doi.org/10.1080/09638280600646250

Pelletier, R., Higgins, J., & Bourbonnais, D. (2015). Is neuroplasticity in the central nervous system the missing link to our understanding of chronic musculoskeletal disorders? *BMC Musculoskeletal Disorders*, *16*(1), 1–13. https://doi.org/10.1186/s12891-015-0480-y

Penninx, B. W. J. H., Geerlings, S. W., & Deeg, D. J. H. (1999). Minor and major depression and the risk of death in older persons. *Primary Care Companion to the Journal of Clinical Psychiatry*, *1*(6), 196.

Porensky, K. E., Dew, M. A., Karp, F. J., Skidmore, E., Rollman, L. B., Shear, M. K., & Lenze, J. E. (2009). The burden of late-life generalized anxiety disorder: Effects on disability, health-related quality of life, and healthcare utilization. *American Journal of Geriatric Psychiatry*, *17*(6), 473–482. https://doi.org/doi:10.1097/jgp.0b013e31819b87b2

Radloff, L. S. (1977). The CES-D Scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement*, *1*(3), 385–401. https://doi.org/10.1177/014662167700100306

Reid, M. C., Eccleston, C., & Pillemer, K. (2015). Management of chronic pain in older adults. *BMJ*, *350*, h532. https://doi.org/10.1136/bmj.h532

Reyes-Gibby, C. C., Aday, L., & Cleeland, C. (2002). Impact of pain on self-rated health in the community-dwelling adults. *Pain*, *95*(1–2), 75–82.

Reynolds, K., Pietrzak, R. H., El-Gabalawy, R., Mackenzie, C. S., & Sareen, J. (2015). Prevalence of psychiatric disorders in U.S. older adults: Findings from a nationally representative survey. *World Psychiatry*, *14*(1), 74–81. https://doi.org/10.1002/wps.20193

Riebe, D., Blissmer, B. J., Greaney, M. L., Ewing Garber, C., Lees, F. D., & Clark, P. G. (2009). The relationship between obesity, physical activity, and physical function in older adults. *Journal of Aging and Health*, *21*(8), 1159–1178. https://doi.org/10.1177/0898264309350076

Ritchie, K., Artero, S., Beluche, I., Ancelin, M., Mann, A., Dupuy, A., … Boulenger, J. . (2004). Prevalence of DSM -IV psychiatric disorder in the French elderly population. *British Journal of Psychiatry*, *184*(2), 147–152.

Rodda, J., Walker, Z., & Carter, J. (2011). Depression in older adults. *BMJ*, *343*, d5219. https://doi.org/10.1136/bmj.d5219

Rose, G. A. (1962). The diagnosis of ischaemic heart pain and intermittent claudication in field surveys. *Bull World Health Organ*, *27*(6), 645–658.

Rubin, H. R., Pronovost, P., & Diette, G. B. (2001). The advantages and disadvantages of process-based measures of health care quality. *International Journal for Quality in Health Care*, *13*(6), 469–474. https://doi.org/10.1093/intqhc/13.6.469

Rubio, J. M., Pérez-Fuentes, G., Liu, S.-M., Markowitz, J. C., Alegría, A., Blanco, C., & Lin, K.-H. (2011). Epidemiology of chronic and nonchronic major depressive disorder: Results from the national epidemiologic survey on alcohol and related conditions. *Depression and Anxiety*, *28*(8), 622–631. https://doi.org/10.1002/da.20864

Sale, J. E. M., Gignac, M., & Hawker, G. (2006). How "bad" does the pain have to be? A qualitative study examining adherence to pain medication in older adults with osteoarthritis. *Arthritis Care and Research*, *55*(2), 272–278. https://doi.org/10.1002/art.21853

Samelson, E. J., Kelsey, J. L., Kiel, D. P., Roman, A. M., Cupples, L. A., Freeman, M. B., … Lipsitz, L. A. (2008). Issues in conducting epidemiologic research among elders: Lessons from the MOBILIZE Boston Study. *American Journal of Epidemiology*, *168*(12), 1444–1451. https://doi.org/10.1093/aje/kwn277

Samper-Ternent, R., & Al Snih, S. (2012). Obesity in older adults: Epidemiology and implications for disability and disease. *Review in Clinical Gerontology*, *1*(22), 10–34. https://doi.org/10.1038/jid.2014.371

Santos, K. A. da S., Cendoroglo, M. S., & Santos, F. C. (2017). Anxiety disorder in elderly persons with chronic pain: Frequency and associations. *Brazilian Journal of Geriatrics and Gerontology*, *20*(1), 91–98.

Sareen, J., Cox, B. J., Clara, I., & Asmundson, G. J. G. (2005). The relationship between anxiety disorders and physical disorders in the U.S. National Comorbidity Survey. *Depression and Anxiety*, *21*(4), 193–202. https://doi.org/10.1002/da.20072

Schulman, E., Gairola, G., Kuder, L., & McCulloch, J. (2002). Depression and associated characteristics among community-based elderly people. *Journal of Allied Health*, *31*(3), 140–146.

Scudds, R. J., & Østbye, T. (2001). Pain and pain-related interference with function in older Canadians: The Canadian study of health and aging. *Disability and Rehabilitation*, *23*(15), 654–664. https://doi.org/10.1080/09638280110043942

Scudds, R. J., & Robertson, J. M. (2000). Pain factors associated with physical disability in a sample of community-dwelling senior citizens. *Journals of Gerontology - Series A Biological Sciences and Medical Sciences*, *55A*(7), M393–M399. https://doi.org/10.1093/gerona/55.7.M393

Seifert, F., & Maihöfner, C. (2011). Functional and structural imaging of pain-induced neuroplasticity. *Current Opinion in Anaesthesiology*, *24*(5), 515–523. https://doi.org/10.1097/ACO.0b013e32834a1079

Shah, R. C., Buchman, A. S., Boyle, P. A., Leurgans, S. E., Wilson, R. S., Andersson, G. B., & Bennett, D. A. (2011). Musculoskeletal pain is associated with incident mobility disability in community-dwelling elders. *Journals of Gerontology - Series A Biological Sciences and Medical Sciences*, *66 A*(1), 82–88. https://doi.org/10.1093/gerona/glq187

Shega, J. W., Andrew, M., Kotwal, A., Lau, D. T., Herr, K., Ersek, M., … Dale, W. (2013). Relationship between persistent pain and 5-year mortality: A population-based prospective cohort study. *Journal of the American Geriatrics Society*, *61*(12), 2135–2141. https://doi.org/10.1111/jgs.12554

Sheng, J., Liu, S., Wang, Y., Cui, R., & Zhang, X. (2017). The link between depression and chronic pain: Neural mechanisms in the brain. *Neural Plasticity*, *2017*, 1–10. https://doi.org/10.1155/2017/9724371

Sherman, S. E., & Reuben, D. (1998). Measures of functional status in community-dwelling elders. *Journal of General Internal Medicine*, *13*(12), 817–823. https://doi.org/10.1046/j.1525-1497.1998.00245.x

Siddall, P. J. (2013). Neuroplasticity and pain: What does it all mean? *Medical Journal of Australia*, *198*(4), 177–178. https://doi.org/10.5694/mja13.10100

Silva, E. (2016). Here come the baby boomers. *Journal of the American College of Radiology*, *13*(3), 242. https://doi.org/10.1016/j.jacr.2015.12.002

Sloan, F. A., Ostermann, J., Brown, D. S., & Lee, P. P. (2005). Effects of changes in self-reported vision on cognitive, affective, and functional status and living arrangements among the elderly. *American Journal of Ophthalmology*, *140*(4), 618.e1-618.e12. https://doi.org/10.1016/j.ajo.2005.01.019

Smith, B. H., Elliott, A. M., & Hannaford, P. C. (2003). Pain and subsequent mortality and cancer among women in the Royal College of General Practitioners Oral Contraception Study. *British Journal of General Practice*, *53*(486), 45–46.

Smith, D., Wilkie, R., Croft, P., & McBeth, J. (2018). Pain and mortality in older adults: The influence of pain phenotype. *Arthritis Care and Research*, *70*(2), 236–243. https://doi.org/10.1002/acr.23268

Smith, D., Wilkie, R., Croft, P., Parmar, S., & McBeth, J. (2018). Pain and mortality: Mechanisms for a relationship. *Pain*, *159*(6), 1112–1118. https://doi.org/10.1097/j.pain.0000000000001193

Smith, D., Wilkie, R., Uthman, O., Jordan, J. L., & McBeth, J. (2014). Chronic pain and mortality: A systematic review. *PLoS ONE*, *9*(6), 1–17. https://doi.org/10.1371/journal.pone.0099048

Snaith, P. R. (2003). The Hospital Anxiety And Depression Scale. *Health and Quality of Life Outcomes*, *1*, 1–4. https://doi.org/10.1186/s12955-014-0173-5

Sofaer, B., Moore, A. P., Holloway, I., Lamberty, J. M., Thorp, T. A. S., & O'Dwyer, J. (2005). Chronic pain as perceived by older people: A qualitative study. *Age and Ageing*, *34*(5), 462–466. https://doi.org/10.1093/ageing/afi139

Solé-Auró, A., Beltrán-Sánchez, H., & Crimmins, E. M. (2014). Are differences in disability-free life expectancy by gender, race, and education widening at older ages? *Population Research and Policy Review*, *34*(1), 1–18. https://doi.org/10.1007/s11113-014-9337-6

Solhaug, H. I., Romuld, E. B., Romild, U., & Stordal, E. (2012). Increased prevalence of depression in cohorts of the elderly : An 11-year follow-up in the general population – the HUNT. *International Psychogeriatrics*, *24*(1), 151–158. https://doi.org/10.1017/S1041610211001141

Stein, M. B., & Sareen, J. (2015). Generalized anxiety disorder. *The New England Journal of Medicine*, *373*(7), 2059–2068. https://doi.org/10.7326/AITC201904020

Stewart, C., Schofield, P., Elliott, A. M., Torrance, N., & Leveille, S. (2014). What do we mean by “Older Adults’’ Persistent Pain Self-management"? A concept analysis.” *Pain Medicine*, *15*(2), 214–224. https://doi.org/10.1111/pme.12251

Stubbs, B., Binnekade, T. T., Soundy, A., Schofield, P., Huijnen, I. P. J., & Eggermont, L. H. P. (2013). Are older adults with chronic musculoskeletal pain less active than older adults without pain? A systematic review and meta-analysis. *Pain Medicine (United States)*, *14*(9), 1316–1331. https://doi.org/10.1111/pme.12154

Stubbs, B., Patchay, S., Soundy, A., & Schofield, P. (2014). The Avoidance of Activities due to Fear of Falling Contributes to Sedentary Behavior among Community-Dwelling Older Adults with Chronic Musculoskeletal Pain: A Multisite Observational Study. *Pain Medicine (United States)*, *15*(11), 1861–1871. https://doi.org/10.1111/pme.12570

Stubbs, B., Schofield, P., Patchay, S., & Leveille, S. (2016). Musculoskeletal pain characteristics associated with lower balance confidence in community-dwelling older adults. *Physiotherapy*, *102*(2), 152–158. https://doi.org/10.1016/j.physio.2015.03.3721

Studenski, S., Perera, S., Wallace, D., Chandler, J. M., Duncan, P. W., Rooney, E., … Guralnik, J. M. (2003). Physical performance measures in the clinical setting. *Journal of the American Geriatrics Society*, *51*(3), 314–322. https://doi.org/10.1046/j.1532-5415.2003.51104.x

Tatsuya, H., Hideki., K., Shigeru., I., Jiro., N., Junya., S., & Minoru., O. (2017). Factors associated with chronic musculoskeletal pain in Japanese community-dwelling older adults. *Medicine*, *96*(23), 1–5. https://doi.org/10.1097/MD.0000000000007069

Taylor, D. (2014). Physical activity is medicine for older adults. *Postgraduate Medical Journal*, *90*(1059), 26–32. https://doi.org/10.1136/postgradmedj-2012-131366

Thakral, M. (2015). *Pain qualities and their persistence in the elder population (Doctoral Dissertation)*. Retrieved from https://search.proquest.com/docview/1766154614?accountid=27797

Thakral, M., Shi, L., Foust, J. B., Patel, K., Shmerling, R. H., Bean, J. F., & Leveille, S. G. (2019). Persistent pain quality as a novel approach to assessing risk for disability in community-dwelling elders with chronic pain. *Journals of Gerontology - Series A Biological Sciences and Medical Sciences*, *74*(5), 733–741. https://doi.org/10.1093/gerona/gly133

Thapa, S., Shmerling, R. H., Bean, J. F., Cai, Y., & Leveille, S. G. (2018). Chronic multisite pain: Evaluation of a new geriatric syndrome. *Aging Clinical and Experimental Research*, *0*(0), 1–11. https://doi.org/10.1007/s40520-018-1061-3

Thielke, S., Sale, J., & Reid, M. C. (2012). Aging: Are these 4 pain myths complicating care? *The Journal of Family Practice*, *61*(1), 666–670.

Thomas, E., Dunn, K. M., Mallen, C., & Peat, G. (2008). A prognostic approach to defining chronic pain: Application to knee pain in older adults. *Pain*, *139*(2), 389–397. https://doi.org/10.1016/j.pain.2008.05.010

Thomas, E., Peat, G., Harris, L., Wilkie, R., & Croft, P. R. (2004). The prevalence of pain and pain interference in a general population of older adults: Cross-sectional findings from the North Staffordshire Osteoarthritis Project (NorStOP). *Pain*, *110*(1–2), 361–368. https://doi.org/10.1016/j.pain.2004.04.017

Tsai, P. F., Tak, S., Moore, C., & Palencia, I. (2003). Testing a theory of chronic pain. *Journal of Advanced Nursing*, *43*(2), 158–169.

Turk, D. C., Fillingim, R. B., Ohrbach, R., & Patel, K. (2016). Assessment of psychosocial and functional impact of chronic pain. *Journal of Pain*, *17*(9), T21–T49. https://doi.org/10.1016/j.jpain.2016.02.006

Turk, D. C., & Flor, H. (1999). Chronic pain: A biobehavioral perspective. In R. J. Gatchel & D. C. Turk (Eds.), *Psychosocial factors in pain: Critical perspectives* (pp. 18–34). New York: The Guilford Press.

Turk, D. C., & Okifuji, A. (2002). Psychological factors in chronic pain: Evolution and revolution. *Journal of Consulting and Clinical Psychology*, *70*(3), 678–690. https://doi.org/10.1037/0022-006X.70.3.678

U.S. Census Bureau. (2014). *An aging nation: The older population in the United States*.

Valvanne, J., Juva, K., & Erkinjuntti, T. (1996). Major depression in the elderly : A population study in Helsinki. *International Psychogeriatrics*, *8*(3), 437–443.

van't Veer-Tazelaar, P. J. (Nelleke., van Marwijk, H. W. J., Jansen, A. P. D. (Daniëlle., Rijmen, F., Kostense, P. J., van Oppen, P., … Beekman, A. T. F. (2008). Depression in old age (75+), the PIKO study. *Journal of Affective Disorders*, *106*(3), 295–299. https://doi.org/10.1016/j.jad.2007.07.004

Verbrugge, L., & Jette, A. M. (1994). The disablement process. *Social Science & Medicine*, *38*(1), 1–14.

Verbrugge, L., Lepkowski, J. M., & Konkol, L. L. (1991). Levels of disability among U.S. adults with arthritis. *Journals of Gerontology*, *46*(2), S71–S83. https://doi.org/10.1093/geronj/46.2.S71

Verbrugge, L., & Patrick, D. L. (1995). Seven chronic conditions: Their impact on US adults' activity levels and use of medical services. *American Journal of Public Health*, *85*(2), 173–182. https://doi.org/10.2105/ajph.85.2.173

Vlaeyen, J. W. S., & Linton, S. J. (2000). Fear-avoidance and its consequences in muscle skeleton pain: A state of the art. *Pain*, *85*(3), 317–332.

Washburn, R. A., Smith, K. W., Jette, A. M., & Janney, C. A. (1993). The physical activity scale for the elderly (PASE): Development and evaluation. *Journal of Clinical Epidemiology*, *46*(2), 153–162. https://doi.org/10.1016/0895-4356(93)90053-4

Weiner, D. K., Sakamoto, S., Perera, S., & Breuer, P. (2006). Chronic low back pain in older adults: Prevalence, reliability, and validity of physical examination findings. *Journal of the American Geriatrics Society*, *54*(1), 11–20. https://doi.org/10.1111/j.1532-5415.2005.00534.x

Welsh, V. K., Clarson, L. E., Mallen, C. D., & McBeth, J. (2019). Multisite pain and self-reported falls in older people: Systematic review and meta-analysis. *Arthritis Research and Therapy*, *21*(1), 67. https://doi.org/http://dx.doi.org/10.1186/s13075-019-1847-5

Whitson, H. E., Landerman, L. R., Newman, A. B., Fried, L. P., Pieper, C. F., & Cohen, H. J. (2010). Chronic medical conditions and the sex-based disparity in disability: The cardiovascular health study. *Journals of Gerontology - Series A Biological Sciences and Medical Sciences*, *65 A*(12), 1325–1331. https://doi.org/10.1093/gerona/glq139

Wolfe, F., Smythe, H. A., Yunus, M. ., Bennett, R. M., Bombardier, C., Goldenberg, D. L., … Sheon, R. P. (1990). The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. *Arthritis & Rheumatism*, *33*(2), 160–172.

Wolitzky-Taylor, K. B., Castriotta, N., Lenze, E. J., Stanley, M. A., & Craske, M. G. (2010). Anxiety disorders in older adults: A comprehensive review. *Depression and Anxiety*, *27*(2), 190–211. https://doi.org/10.1002/da.20653

Woo, A. K. (2010). Depression and anxiety in pain. *Anaesthesia*, *4*(1), 8–12. https://doi.org/10.1111/j.1365-2044.1986.tb12803.x

Wu, L. W., Chen, W. L., Peng, T. C., Chiang, S. T., Yang, H. F., Sun, Y. S., … Kao, T. W. (2016). All-cause mortality risk in elderly individuals with disabilities: A retrospective observational study. *BMJ Open*, *6*(9). https://doi.org/10.1136/bmjopen-2016-011164

Yang, Y., & George, L. K. (2005). Functional disability, disability transitions, and depressive symptoms in late life. *Journal of Aging and Health*, *17*(3), 263–292. https://doi.org/10.1177/0898264305276295

Yezierski, R. P. (2012). The effects of age on pain sensitivity: Pre-clinical studies. *Pain Medicine*, *13*(Suppl 2), S27–S36. https://doi.org/10.1111/j.1526-4637.2011.01311.x

You, T., Ogawa, E. F., Thapa, S., Cai, Y., Zhang, H., Nagae, S., … Leveille, S. G. (2018). Tai chi for older adults with chronic multisite pain: A randomized controlled pilot study. *Aging Clinical and Experimental Research*, *30*(11), 1335–1343. https://doi.org/10.1007/s40520-018-0922-0

Young, A. (1993). Current issues in arthrogenous inhibition. *Annals of the Rheumatic Diseases*, *52*(11), 829–834. https://doi.org/10.1136/ard.52.11.829

Zigmond, A. S., & Snaith, R. P. (1983). The Hospital Anxiety and Depression Scale. *Acta Psychiatrica Scandinavica*, *67*(6), 361–370. https://doi.org/10.1111/j.1600-0447.1983.tb09716.x

Zis, P., Daskalaki, A., Bountouni, I., Sykioti, P., Varrassi, G., & Paladini, A. (2017). Depression and chronic pain in the elderly: Links and management challenges. *Clinical Interventions in Aging*, *12*, 709–720. https://doi.org/10.2147/CIA.S113576