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Pain, Disablement Process and Frailty among Older Adults in the United States: Findings from the National Health and Aging Trends Study

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Pain, Disablement Process and Frailty among Older Adults in the United States: Findings from the National Health and Aging Trends Study

by

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Dedication

This dissertation is dedicated to my father Jagir Singh Sodhi, my mother Balbeer Kaur Sodhi, my sisters Pawandeep Sodhi, and Gagandeep Sodhi, and brother Charandeep Singh Sodhi.

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Pain, Disablement Process and Frailty among Older Adults in the United States: Findings from the National Health and Aging Trends Study

Publication No.______________

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Background: Musculoskeletal pain is highly prevalent among older adults and the most common cause of disability. **Objectives:** To examine 1) whether sociodemographic characteristics, comorbidities, depression, obesity and sleep complaints are independently associated with pain; 2) the effect of pain on upper-lower extremity functional limitation and disability; and 3) the effect of pain on frailty over 6-years pf follow-up among older adults. **Design:** Longitudinal study. **Subjects:** 5,716 participants aged 65 years and older from the National Health and Aging Trends Study (2011-2017) with complete information on pain and all the covariates of interest. **Measures:** Pain and pain location (shoulder, wrist, hand, hips, knees, ankle, neck, and back) are the independent variables**.** Socio-demographics (age, gender, marital status, race/ethnicity and years of formal education), sleep complaints, depression, body mass index, and comorbidities are covariates. The outcome measures were: pain, upper-lower extremity functional limitation, limitations in activities of daily living (ADL's), and frailty. **Analysis:** Descriptive statistics were used to compare sample characteristics by pain and outcome variables. General estimation equations models were performed to examine predictors of pain and pain as predictor of upper-lower extremity functional limitations, ADL disability, and frailty over time. **Results:** Prevalence of pain in American older adults was 52.3% at baseline. The most prevalent pain location was knee (41.3%), followed by back (37.4%) and shoulder (32.3%). The odds of reporting pain were 0.99 (95% CI 0.97-1.01) over time. Pain was an independent predictor of upper extremity (UE) functional limitations (OR 1.90, 95% CI-1.66-2.16), lower extremity (LE) functional limitations (OR 1.52, 95% CI 1.42-1.63), ADL disability (OR 1.82, 95% CI 1.58-2.09), and frailty (OR 1.86, 95% CI 1.60-2.16) over time. **Conclusions:** Prevalence of pain among American older adults was high (52%). Pain is a strong independent predictor of functional limitations, ADL disability, and frailty. These findings suggest that early intervention and better management of pain is needed to prevent/delay disability and frailty, enhance patient management, allocation of health care resources, maintain independence and lower the burden of pain in this population.

Keywords: Pain; Functional limitation; Disability; Frailty; American older adults.

TABLE OF CONTENTS

List of Tables

List of Figures

List of Abbreviations

ACS	American Community Survey
ADL	Activities of Daily Living
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
DV	Dependent Variable
GEE	General estimation Equation
HRS	Health and Retirement Study
ICIDH	International Classification of Impairments, Disabilities and Handicaps
IOM	Institute of Medicine
IV	Independent Variable
Kg	Kilograms
LE	Lower- Extremity
LEFL	Lower-Extremity Functional Limitation
LSOA	Longitudinal Study on Aging
m	Meters
NCIHH	National Center for Complementary and Integrative Health
NHATS	National Health and Aging Trends Study
NHB	Non-Hispanic Blacks

OR	Odds Ratio
SD	Standard Deviation
SP	Sample Person
SP	Sample Person
UE	Upper-Extremity
UEFL	Upper-Extremity Functional Limitation
U-LE	Upper-Lower Extremity
US	United States (United States of America)

CHAPTER 1

SPECIFIC AIMS

The purpose of this study is to investigate the predictors of pain and pain as a predictor of Upper-Lower Extremity (ULE) functional limitations, Activities of Daily Living (ADL) disability, and frailty over 6-years of follow-up among American older adults using the National Health and Aging Trends Study (NHATS). Pain was defined as self-reported pain in the body and pain locations (shoulder, hand, wrist, hip, knee, foot, back and neck). ULE functional limitations were determined with a series of self-reported questions such as carry 20 pounds, carry 10 pounds, grasp small objects, open sealed jar with hands, reach overhead, carry heavy objects above head, able to walk 6 blocks, able to walk 3 blocks, able to walk up 20 stairs, able to walk up 10 stairs or able to get down on knees. Limitations in activities of daily living (ADL) was determined by asking the asking the participants whether in the last month anyone helped them in performing self-care activities such as eating, bathing, transferring, dressing, moving out of the bed, and moving inside. Frailty was assessed using the Phenotype developed by Fried et al.[1] which include the following five components: exhaustion, low physical activity, weakness, slowness, and shrinking.

Previous studies conducted were mostly of cross-sectional design and evidence regarding the effect of pain on functional limitations, disability and frailty among American older adults over time is scarce. Therefore, the objective of this study was to investigate predictors of pain, and pain as a predictor of upper-lower extremity functional limitations, ADL disability, and frailty over 6-years of follow-up among American older adults from a national representative of Medicare Beneficiaries aged 65 years and older. The study has three specific aims.

SPECIFIC AIMS AND HYPOTHESES

Specific Aim 1

To examine the extent to which sociodemographic characteristics, comorbidities, depression, obesity, and sleep complaints are associated with pain over 6-years of follow-up.

Hypothesis 1.a. Older adults with comorbidities will be more likely to experience pain than those without comorbidities.

Hypothesis 1.b. Older adults with depression will be more likely to experience pain than those without depression.

Hypothesis 1.c. Older adults with sleep complaints will be more likely to experience pain than those without sleep complaints.

Specific Aim 2

To examine the effect of pain on upper-lower extremity (ULE) functional limitations and ADL disability over 6-years of follow-up.

Hypothesis 2.a. Older adults with pain will be more likely to experience ULE functional limitations and ADL disability than those without pain.

Hypothesis 2.b. Depression will mediate the relationship between pain and ULE functional limitations and ADL disability.

Hypothesis 2.c. Obesity will moderate the relationship between pain and ULE functional limitations and ADL disability.

Specific Aim 3

To examine the effect of pain as a predictor of frailty over 6-years of follow-up.

Hypothesis 3.a. Older adults with pain will be more likely to experience frailty than those without pain.

Hypothesis 3.b. Depression will mediate the relationship between pain and frailty.

Data employed are from the National Health and Aging Trends Study (NHATS), an ongoing nationally representative sample of Medicare beneficiaries aged 65 years and older. It was designed to study functioning in later life and is intended to advance research that will guide efforts to reduce disability, maximize health and independent functioning, and enhance quality of life at older ages. Study participants were first interviewed in 2011 and annual re-interviews were conducted to document changes over time. The NHATS sample study design, which is drawn from the Medicare enrollment file, oversamples persons at older ages and Black individuals.

SIGNIFICANCE OF RESEARCH

Pain has been reported as one of the most common and expensive medical problem, currently facing the United States. Approximately 100 million Americans are living with some level of pain. [2] Musculoskeletal pain is most prevalent among older adults and it is associated with restrictions in ADL's, instrumental activities of daily livings (IADL's), mobility limitations, frailty, and decreased quality of life. [3-7] Studies have shown prevalence of pain ranging from 24% to 72% among adults. [8-10] Older adults are in general at higher risk of chronic pain. Population-based surveys have found that the prevalence of widespread pain is highest in those 60 to 80 years of age and approximately 60%–75% of people over the age of 65 reported persistent pain.[11]

This study presents an approach to examine the factors associated with pain and how pain is related to the disablement process and frailty over six-years of follow-up, using a nationally representative sample of older adults in the U.S. This approach will help us: 1) identify which factors are predictors of pain to implement preventive strategies to reduce the burden of pain in this population; 2) identify which pain locations are more affected; 3) determine the relationship between pain and the disablement process; 4) determine the relationship between pain and frailty; and 5) provide knowledge to help physicians/clinicians to identify targets for intervention and design better pain management protocols to prevent early disability and frailty among older adults.

Understanding the relationship between pain, the disablement process and frailty will help increase independence and improve quality of life in older adults. Determining these relationships is important for enhancing patient management, allocation of health care resources, maintain older adult independence and lower the burden of pain in this population and their caregivers.

CHAPTER 2

BACKGROUND

Chapter 2 is organized into five sections. The first section presents an overview of pain, including definition, epidemiology, risk factors, and consequences. The second section is an overview of upper - lower extremity (ULE) functional limitations, including definition, epidemiology and relationship between pain and functional limitations. The third section is an overview of disability, including definition, measures, conceptual frameworks proposed to study disability, epidemiology and relationship between pain and disability. The fourth section is an overview of frailty, including definition, measures, epidemiology and the relationship between pain and frailty. The fifth section is an overview of economic burden of pain in older adults and the need of this study.

PAIN

Definition

Pain is defined as a "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage."[1] The US Commission on the Evaluation of Pain defines pain as a "complex experience, embracing physical, mental, social, and behavioral processes, which compromises the quality of life of many individuals." Pain is a complex experience but unique to each individual and across life span it is one of the frequent causes for taking medications, physician visits and work disability. Severe chronic pain affects the physical and mental wellbeing of an individual and eventually impacts the quality of life. Although each individual experience pain at some point, older adults in general are at higher risk of chronic pain.[4] Musculoskeletal pain is one of the most common problems reported in older adults, and it is associated with restrictions in activities of daily living (ADL), instrumental activities of daily living (IADL), mobility, and decreased quality of life.[4-7]

Epidemiology

Studies have shown prevalence of pain ranging from 24% to 72% among adults.[3-5] Some studies have shown higher prevalence of pain with increasing age while others a plateau or lower prevalence with advancing age. Much of the variance in prevalence estimates can be attributed to inadequate sampling of the oldest-old in the community, and due to differences in survey methods and case definitions.

According to the National Health Interview Survey (NHIS) data, conducted by Center for Disease Control and Prevention, (CDC) in 2016, 20.4% U.S. adults reported chronic pain and 8% reported high impact chronic pain. The prevalence was reported higher in older adults, women, and individuals with low socio-economic status. The age adjusted prevalence of chronic pain was reported also lower in those with higher education (Bachelor's degree), compared to those with lower education.[12]

These findings were almost similar to results reported previously by few studies that have looked at the prevalence of pain. For example, a recent study conducted by Korff and colleagues reported a prevalence of 13.7% on the U.S. adults. [13] Similarly, a study conducted in 2001 on adults living in Scotland reported an estimated 14% of adults with chronic pain and 6.3 % of adults reported severe chronic pain.[14] Another study conducted on adults living in Australia found that 17% of men and 20% of women reported chronic pain and the prevalence increased in older adults with a rate of at 27 % in the age group (65-69) years old and 31 % in the age group (80-84 years).[15]

Risk Factors

Several factors are known to be associated with a greater risk of musculoskeletal pain. Those factors can be nonmodifiable and modifiable factors. Nonmodifiable factors are older age, female gender and family history of pain.[8,9] Modifiable factors are diabetes,[16] stroke,[17] osteoarthritis,[18] back pain,[19] joint pains,[20] obesity,[11] sleep disorders/ discomforts, anxiety, and depressive symptoms.[21,22]

Nonmodifiable factors

1) ***Women***

The prevalence of chronic pain has been reported higher in women as compared to men, and the trend exists between gender across different ethnicities and comorbid conditions. [23]Women are also more likely to report higher pain severity and chronic painful conditions such as fibromyalgia, chronic fatigue syndrome, carpel tunnel syndrome, and arthritis as compared to men.[24,25]

2) ***Older age***

Aging has been shown to be associated with increased risk of pain. Older adults in general reported increased prevalence of chronic pain and the rate of disabling pain rises with age. The prevalence of widespread pain is highest in those 60-80 years of age, and approximately 60%–75% of people over the age of 65 reported persistent pain. [26, 8]

3) ***Socioeconomic status***

Socioeconomic variances such as education, poverty, and health insurance coverage may contribute to the differences in the pain prevalence.[27] Population-based studies have shown that individuals with lower education, and higher poverty levels, have higher odds of reporting pain as compared to those with higher socio-economic status.[26] Findings from the NHANES data from 2003-2004, concluded the same results that individuals with low-socioeconomic status experience more pain compared to those with higher-socioeconomic status.[28]

4) ***Family history of pain***

Various studies have shown that chronic pain is an outcome of an interaction between environment and genetic factors. [29,30]A study conducted in Norway on Family Linkage Data using the Nord-Trøndelag Health Study (HUNT Study) showed that history of chronic pain in parents is associated with higher odds of nonspecific pain and chronic multisite pain in their children. [29] Recent systematic review and metanalysis conducted on offspring of parents with pain reported higher pain complaints among those with a genetic history of painful conditions.[31]

Although nonmodifiable factors cannot be changed, knowledge of their presence helps in identifying the population groups at greater risk for developing pain and hence guide for the appropriate interventions to target.

Modifiable factors

1) ***Obesity and overweight***

Both obesity and pain are serious public health concerns and studies have shown a bidirectional association between them.[32,33] Older adults who are overweight an obese are at greater risk of developing pain at multiple sites in the body.[34] According to the longitudinal study using the Veterans Health Administration, individuals with obesity were significantly twice more likely to report pain complaints as compared to those who were not obese.[35]

2) ***Comorbid conditions***

Studies have shown that higher risk of prevalent comorbid conditions in older age is associated with higher odds of pain.[16,17] Older adults with diabetes have been shown to have higher odds of pain than those without diabetes. A population-based study conducted on individuals diagnosed with stroke found that the prevalence of moderate to severe pain was almost 21% after a year and half of stroke.[17]

3) ***Sleep disorders and sleep complaints***

Sleep complaints including trouble sleeping is associated with increased prevalence of pain among older adults. Sleep disorders and sleep discomforts including non-restorative sleep have been shown to be independent predictors of widespread pain among cohorts above 50 years of age.[36,37]

4) ***Psychological distress***

Psychological factors including anxiety, and depressive symptoms have been found as predictors of onset of persistent chronic widespread pain.[25] Patients with depressive symptoms are more likely to suffer from both neuropathic and non-neuropathic pain as compared to those without depressive disorders.[2]

Consequences of Pain

1) ***Physical symptoms***

Physical symptoms of pain include mobility restrictions, loss of joint motion, and fatigue. Older individuals who suffer from chronic and musculoskeletal pain are more likely to be less active and have higher overall incidence of comorbid conditions including cardiovascular diseases[17], diabetes[16], hypertension[17], and obesity[34].

2) ***Functional Limitations***

Pain in the upper and lower extremity has been shown to be associated with functional limitations in daily activities among older adults.[4] Burner and colleagues found that, severe shoulder pain is associated with difficulty performing daily activity tasks and leads to reduced shoulder internal rotation in older adults by almost 36%.[38] Pain reduces the ability to perform daily activity tasks such as walking one or several blocks, climbing stairs, pushing, pulling, lifting, stooping, jogging one mile, and heavy household work.[4,39] Musculoskeletal pain in older adults with diabetes is associated with higher prevalence of limitations in shoulder movements, decreased grip and pinch muscle strength, limitations in opening jars and carrying grocery bags.[40,41]

3) ***Disability***

Several studies have found a significant relationship between pain and disability, especially in older adults .[42-44] Peat and colleagues found that pain at multiple sites in the lower extremity is significantly associated with disability.[45] Another study conducted among older Mexicans Americans found that pain on weight bearing was a significant independent predictor of subsequent disability and inability to perform lower extremity function tasks.[46] Findings from the Health Retirement Study showed that subjects with overall pain were 1.7 times more likely to develop ADL disability over 10-years of follow-up than those without pain.[47]

4) *Frailty*

Recent studies have reported an association between pain and frailty.[10,48-50] Shega et al., found that individuals with moderate to severe pain were 2.5 times more likely of being prefrail and 5.5 times of being frail than those without pain.[10] Castenda and colleagues conducted a study on Mexican older adults and showed that chronic pain is linked to higher incidence of frailty among Mexican older adults.[51] Individuals diagnosed with osteoarthritis (with and without pain) with pain were significantly more likely to report frailty than those without pain.[52] Psychosocial factors, such as depression mediates the relationship between pain and frailty among Chinese community-dwelling older adults.[53] Persistent pain advances the progression of frailty in older adults through a variety of mechanisms, such as reduced mobility, decreased nutritional intake, depression, insufficient sleep and increased number of comorbidities.

5) *Lower social wellbeing*

Individuals with chronic widespread and persistent pain have been reported to have higher psychological restrictions such as depression, and anxiety, and marked decline in their physical, social and psychological wellbeing as compared to those with mild pain. [54] [26]

6) *Quality of life*

Individuals with moderate to severe chronic pain shows poor perceived health, including the ability to perform ADL's, work, and maintain societal relationships and reduced quality of life compared to those with no pain. [14,54] Overall, the debilitating effects of chronic pain interferes with work and often a leading cause of unemployment, early retirement and hence lowered quality of life.[26]

Overall, understanding various risk factors associated with pain and their consequences will help increase independence and improve quality of life among older adults. Determining the relationship between pain and various factors is important for enhancing patient management, allocation of health care resources, and eventually aids in maintaining independence and lower the burden of pain in this population. Also, earlier assessment and better management of pain may prevent long-term disability among older adults.

FUNCTIONAL LIMITATION

Definition

A functional limitation is a restriction in the ability to perform an action or activity in the manner or within the range considered 'normal' and which is attributable to impairment. [55] Functional limitations caused by comorbid conditions increase with age. More than one third of individuals 65 years of age and older identify a comorbid condition that imposes some limitation on everyday living and causes limitation in functional activity.[56]

Epidemiology

According to the 2014 Census Bureau report on Americans with Disabilities, it has been reported that 48.2 million U.S older adults reported functional limitation. Out of which, 12.4% of adults reported upper body functional limitations, and 17.6% reported lower body functional limitation. Among adults with either upper or lower extremity limitation, lower body functional limitations was found to be higher (87.7%) than upper body functional limitations (61.7%).[57]

The most common upper body functional limitation among adults in 2014 was difficulty in lifting a 10-pound object (10.2%), with 5.2% of adults unable to do the activity at all. Furthermore, 5.6 % of adults had difficulty using their fingers to do activities using upper extremities such as picking up a glass or grasp an object, and 0.5 % of individuals could not perform the activity.[57]

In the lower extremity, the most commonly reported lower body functional limitation for older adults is difficulty walking a quarter mile. According to the National Center for Complementary and Integrative Health report in 2014, 13.4% of adults had difficulty walking a quarter mile in 2014, and 7.6% (18.3 million) were unable to walk a quarter mile at all. Approximately 12.1% of adults had difficulty climbing a flight of stairs, and 3.9% were unable to perform this activity. Among individuals aged 65 and older, 39% reported difficulty walking or climbing stairs, and10% were unable to do the activity at all.[57]

The incidence of functional limitation has been shown to increase markedly with age.[58,59] The findings from Longitudinal Study of Aging (LSOA) conducted by Dunlop and colleagues on a sample of 4,205 elderly subjects showed that gender predicted the onset of severe functional limitation in older adults. Also, earlier history of moderate functional limitation, cardio vascular disease and vision impairment predicted onset of severe functional limitation after controlling for the socio-demographic factors.[60]

The relationship between pain and Upper-Lower Extremity Functional Limitation

Pain in the upper-extremity is associated with functional limitations in daily activities among older adults.[4] . A systematic review conducted by Luime and colleagues showed that the shoulder pain is as one of the most common painful joints in the upper-extremity, with a lifetime prevalence ranging from 6.7-66.7%. and is associated with limitations in movement. [61] Covinsky and colleagues using Health and Retirement Study (HRS), reported that older adults with significant pain were at higher risk of developing functional limitations, mobility limitations, tasks of upper extremity and stair climbing, and ADL functions.[4] Burner and colleagues found that, severe shoulder pain is associated with difficulty performing daily activity tasks and leads to reduced shoulder internal rotation in older adults by almost 36%.[38] Musculoskeletal pain in older adults with diabetes is associated with higher prevalence of limitations in shoulder movements, decreased grip and pinch muscle strength, limitations in opening jars and carrying grocery bags.[40,41]

Pain in the lower extremity and back reduces the ability to perform daily tasks such as walking one or several blocks, climbing stairs, pushing, pulling, lifting, stooping, jogging one mile, and heavy household work.[4,39] A study by Leveille and colleagues found that women with widespread pain experience more difficulty with walking or lifting than those women without pain.[62] Patel et al, using the National Health and Ageing Trend Study showed that older adults with pain at multiple sites in the lower extremity reported more difficulty in performing kneeling, bending, walking three blocks and climbing stairs.[63] Findings from a cross-sectional survey conducted in community-dwelling older adults with pain reported significantly reduced gait speed and inability to walk 3 blocks, leading to lower extremity disability.[4]

DISABILITY

Definition

Disability is a complex and dynamic process that can be difficult to define and measure. It has been described as “any restriction or lack of ability to perform an activity in the manner or within the range considered normal for a human being”.[64] Some of the most acceptable definitions are “the difference, or gap, between an older individual's capability to complete a particular task and the demand imposed by the task.”[16] or “inability or limitation in performing socially defined roles and tasks accepted of an individual within a socio-cultural and physical environment”.[65] Most studies define disability by self-reported need of assistance with one or more activities of daily living such as walking across a small room or personal grooming.[16, 17]

Measures

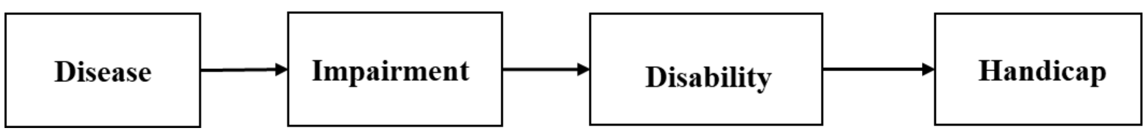
Several instruments are available to assess the level of physical limitation in older adults. The most commonly used measure to assess the physical functioning is the self-care activities also called as activities of daily living (ADL's). These measures are extensively used in community-dwelling population and have a good reliability in order to identify the individuals with disability. The items of ADL disability include: eating, bathing, transferring from bed to chair, toileting, and dressing. However, the ADL Index proposed by Katz also included the item of incontinence. Each ADL item is further divided in three levels of functioning: no need to help, help needed and unable to be do. These three levels are further divided into independence (no need to help) and dependence (help needed and unable to do). [66]

Other scales used to assess the physical functioning in older adults are Rosow-Breaslau scale that includes two mobility items: 1) walking up and down the stairs to second floor and, 2) walking half a mile. [67] Nagi scale used a mix of number of activities to assess the group of tasks. These include handling small objects, lifting small objects, lifting weights over 10 pounds, moving large objects, stooping, crouching, or kneeling.[68]

Conceptual frameworks

There are several conceptual frameworks that have been proposed to determine the impact of a disease/pathology on disability. These models serve as a platform towards the development of research in the field of disability. The figure 1 shows the International classification of impairments, disabilities and handicap (ICIDH), proposed by the World Health Organization in 1980.[64] This model was designed in corresponding to the International Classification of Diseases and comprises of three main components: impairment, disability and handicap. Impairments are the outcomes of the diseases present in specific organs or systems; disability refers to the overall person experience; and handicap denotes to the social barriers that restricts the people who are disabled from performing activities which they can do otherwise.

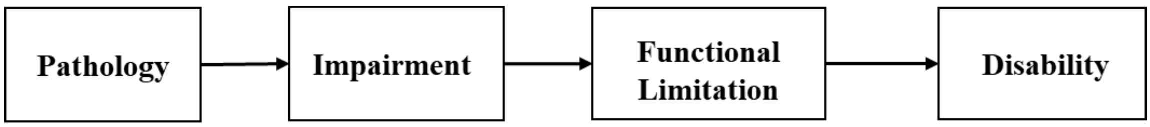
Figure 1: International classification of Impairments, Disabilities and Handicap (ICIDH).



Source- World Health Organization. The International Classification of Functioning, Disability and Handicaps. Geneva, 1980.

The other model was proposed by a sociologist named Saad Nagi in 1965. [65] The schematic representation of the disablement process is presented in figure 2 and outlines the pathway from active pathology to its consequences (impairment, functional limitation, and disability). The concepts of functional limitation and disability descried by Nagi represents the same scope as described in the ICICH model. However, the functional limitation concept doesn't specify if the limitation in the activities is associated to the consequences of impairment.

Figure 2: The Disablement process by Nagi.



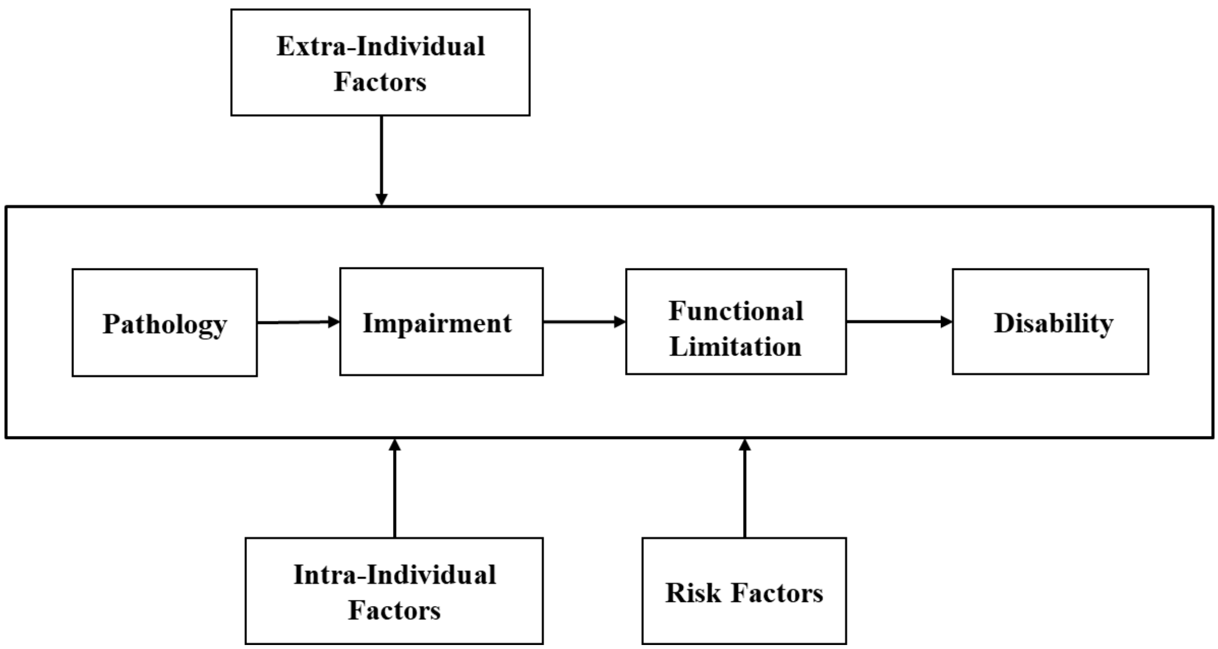
Source- Nagi S Z. Some conceptual issues in disability and rehabilitation. Sociology and rehabilitation, M B Sussman. American Sociological Association, Washington, DC 1965; 100–113.

Verbrugge and Jette [55] proposed the model of disablement process in 1994 shown in figure 3. The model was mainly an expansion of the Nagi model and draws the details of the ICIDH model. The disablement process proposed by Verbrugge and Jette is a sociomedical model, paying attention to both medical and social aspects of disability with the introduction of factors that may accelerate or delay the process of disability.

The main pathway includes pathology and its functional consequences (impairment, functional limitation and disability) with three fundamental characteristics: 1) the incorporation of predisposing factors such as demographic, social, psychological, behavioral, and biological; 2) the incorporation of extra individual factors such as medical care and rehabilitation, medications and other therapeutic regimens, external support, physical and social environment; and 3) the incorporation of intra- individual factors such as lifestyle and behavioral changes, psychosocial attribute and coping, and activity accommodations that acts as an aggravating factors for functional limitation.

This model visibly shows that the factors such as biological, environmental and behavioral are involved in reversing the process of disability. The enabling factors refers to the factors that are associated with the increase in the likelihood of an individual towards less limitation, hence improvement. However, the disabling factors are the risk factors that increases the likelihood of an individual towards functional limitation from a disabling condition.

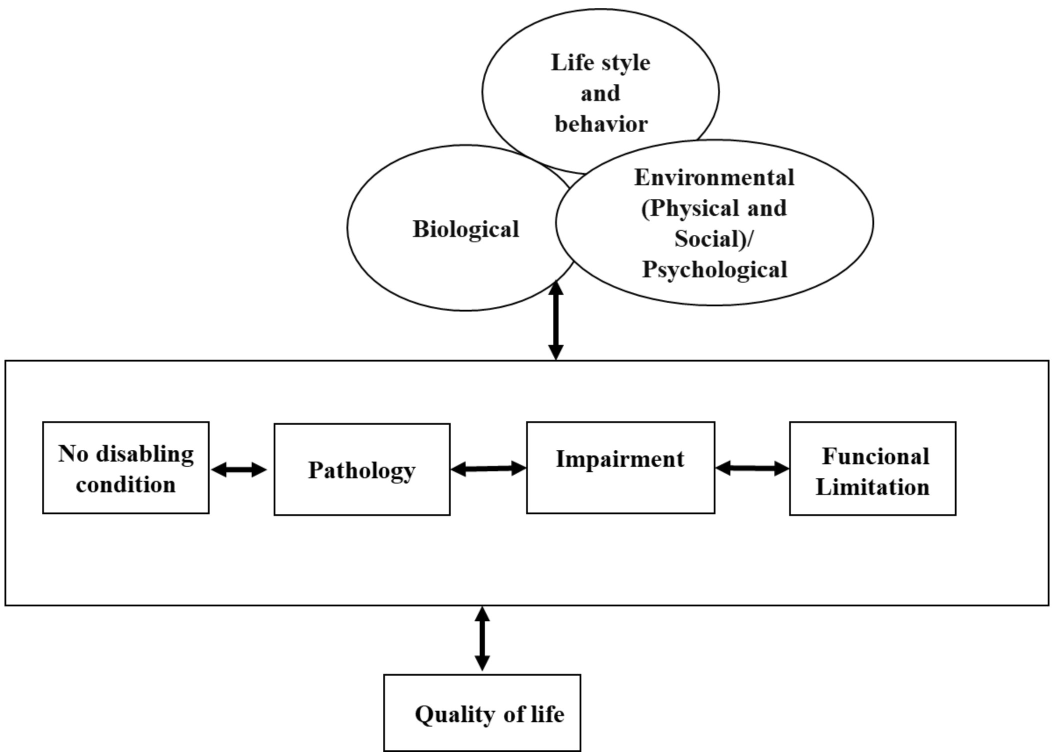
Figure 3: The Disablement process model by Verbrugge and Jette.



Source- Verbrugge LM, Jette AM. The disablement process. Social science & medicine (1982). 1994;38:1-14

Another model is the enabling disabling model proposed by the Division of Health Sciences at the Institute of Medicine (IOM) in 1991.[69] This model was different from the previously proposed models as it includes bidirectional arrows and has a “no disabling condition”. Furthermore, in this model they proposed that disability is not characteristic of an individual rather it’s an interaction between the individual and the environment.

Figure 4: The Enabling Disabling Model by Institute of Medicine.



Source- Brandt EM, Pope A. 1997. Enabling America: Assessing the Role of Rehabilitation Science and Engineering: Washington DC: National academics Press.

Epidemiology

According to 2017 Disability Statistics Annual Report, the rate of individuals with disabilities was 12.8% with the highest rate reported among individuals aged 65 and above (35.2%).[70] Furthermore, the need for assistance increases with age and has been reported significantly higher among those 80 years or older compared to those 65-69 years.[71]

According to 2017 American Community Survey (ACS), conducted by US Census Bureau report, the prevalence of severe disability and the need for personal assistance also increase with age. Adults 75 years and older needed assistance performing certain activities about two times more often than adults between 55 and 64 years and about seven times more often than adults between 18 and 24 years. [72]

Differences in disability prevalence are exist also exist among different race/ethnicity origin groups. Among adults, Blacks had a higher prevalence of disability (35%) than non-Hispanic Whites (31.5 %) and Hispanics (24.6 %) in 2014. Black adults are also most likely to have a severe disability (26.4 %), whereas Asians are least likely to have a severe disability with 11% prevalence rate.[72]

Relationship between pain and disability

Several studies have found a relationship between pain and disability.[42-44] For example, Peat and colleagues found that pain at multiple sites in the lower extremity is significantly associated with disability.[45] Another study conducted among older Mexicans

Americans found that pain on weight bearing was a significant independent predictor of subsequent disability and inability to perform lower extremity function tasks.[46] Findings from the Health Retirement Study showed that subjects with overall pain were 1.7 times more likely to develop ADL disability over 10-years than those without pain.[47]

A cross-sectional study conducted in Canadian seniors found that those with higher pain intensity were two times more likely to report ADL disability than those with lower pain intensity and those with use of pain medications were 1.6 times more likely to report ADL disability.[73] Rejeski et al. examining older adults with knee pain found that obesity is a significant moderator and influences the transitional states of disability in disablement process.[74] A recent randomized controlled trial conducted on low-income, home-dwelling older adults using the "Community Aging in Place: Advancing Better Living for Elders," CAPABLE data, showed that depression fully mediated the relationship between pain intensity and ADL disability.[75]

FRAILTY

Definition

Frailty is defined as "a physiologic state of increased vulnerability to stressors that results from decreased physiologic reserves, and even dysregulation, of multiple physiologic systems."[1] Frailty is highly prevalent in older adults and is associated with adverse health outcomes, including disability, cognitive decline, institutionalization and mortality.[76] With the aging population, there is an increasing rate of frailty each year, with almost 25%-50% becoming frail over the age of 85. [77,78]

Measures

There are two primary models of frailty, the frailty phenotype model developed by Fried and colleagues and the frailty index developed by Rockwood and colleagues.[1,79] The frailty phenotype defines frailty based on 3 or more of the following components: poor grip strength, slow walking speed, low physical activity, exhaustion and unintentional weight loss. The frailty index defines frailty as the collection of "deficits" over time including signs, symptoms, diseases and disabilities.[80]

Both of these measures are based on two different conceptual frameworks. The Fried group has suggested that frailty represents a phenotype which reflects underlying age-related changes in multiple systems. Frailty phenotype consists of five components: exhaustion, low physical activity, weakness, slowness, and shrinking.

Most of the researchers agree with the Frailty Phenotype as the standard measure of frailty, however some consider the Frailty Index as the measure of choice for frailty.[81] The decision of choosing a frailty measure depend on the definition and outcomes that best suit the researchers/clinicians for testing their hypothesis. However, the Fried's phenotype has been the most extensively tested for its validity and reliability and is the most widely used measure in frailty research. [82]

Epidemiology

Frailty is highly common in older adults. Previous studies have shown that the prevalence of frailty in community-dwelling older adults ranges between 4% to 59 %. This prevalence increases with age and has been reported higher among women as compared to men.[83] Also, studies have shown that the prevalence of frailty is higher in older adults with low socio-economic status, those with poor health, and with increased number of medical conditions, and disability.[77,84]

The prevalence of frailty has been shown to increase with each 5-year age group in older adults before reaching a plateau with a prevalence of 15.3% in the age group 65–69 years old to 23.5% in the age group (75-79) years old. Fried and colleagues also agree with this increase of frailty with each 5-year age group with a prevalence of 3.2% among (65–70 years) to 9.5% among (75–79 years) old. Furthermore, differences exist between the individuals of various race/ethnicity. Hispanics and Blacks are more likely to be frail as compared to the Whites.[1,85]

Prevalence of frailty has been shown to be higher among nursing home residents than in community dwelling people with an overall prevalence of 10.7%, specifically 34.9% in a Polish cohort[86], 48% in a Canadian cohort [87], and 68% in a Spanish cohort. A recent systematic review and metanalysis study conducted in 2018 by Siriwardhana and colleagues, showed higher prevalence of frailty and prefrailty in community-dwelling older adults living in upper middle-income countries as compared to those living in the high-income countries.[88]

This could be explained because institutionalization could be a consequence of frailty. Finally, several studies show that the prevalence of pre-frailty is much higher than the frailty in older adults and the differences could be due to different definitions and measure of frailty used.[88]

Relationship between pain and frailty

Recent studies have reported an association between pain and frailty.[10,48-50] For example, Shega et al., found that people with moderate to severe pain were 2.5 times more likely of being prefrail and 5.5 times of being frail than those without pain.[10] Studies also have shown that persistent pain accelerate the progression of frailty via several mechanisms including decreased mobility, reduced sleep, depression and increased number of comorbidities. [11,89]

A study conducted on individuals diagnosed with osteoarthritis (with and without pain) found that those with pain were significantly more likely to have frailty than those without pain. [52] Similarly, Castaneda and colleagues conducted a study on Mexican older adults and showed that chronic pain is linked to higher incidence of frailty among Mexican older adults. [51] A longitudinal study conducted on Chinese community-dwelling older adults showed that depression mediates the relationship between pain and frailty.[53]

ECONOMIC BURDEN OF PAIN

The rampant increase in the health care cost is one of the greatest challenges faced by the U.S health care system and the public health programs. The exact estimation of the cost of pain is problematic as its associated with the cost of several other comorbidities that contributes to pain and it's difficult to detangle. According to the latest report by Bone and Joint initiative USA on the burden of musculoskeletal diseases in the U.S, three out of the four older adults over the age of 65 suffer from a musculoskeletal disease and the annual cost of treating these musculoskeletal diseases, is much higher than the treatment itself. Pain has been reported as one of the most prevalent and expensive medical problem in the US, with an estimated 100 million Americans living with some level of pain.

The number of individuals suffering from pain itself is greater than the collective number of individuals affected by cancer, heart disease and diabetes. [3] The overall economic burden of chronic pain costs approximately $560-630 billion annually, together with health care expenses and lost productivity in the United States.[2] The cost of medical expenditures for pain to the federal and state government in 2008 was approximately 99 billion.

Additionally, previous studies have shown that the annual costs of headache, backache, arthritis and other musculosketalal conditions were reported $61 billion annually and from back pain is $150-200 billion in terms of lost productivity and reduced wages in 2006 and 2009 respectively. [90,91] The estimates of annual costs from other prevalent medical conditions including headache, low back problems and spine problems are 200-300 billion annually.[92] The overall disability cost from all the causes that's leads to chronic pain was reported $300 billion annually with the pain related conditions of back and arthritis as the most common causes of disability as reported by the Center for Disease Control (CDC, 2018). [93,94]

NEED OF THE STUDY

Pain is a significant public health concern considering its high prevalence, incidence, seriousness, disparities, vulnerable populations, and its importance of prevention at both individual and population levels. Considering the Healthy People 2020 pain relief objective which is to lower the number of individuals suffering from untreated pain due to their lack of access to the pain treatment, the need to assess the various predictors of pain and its effect on the health outcomes in older adults is utmost important. Also, the previous studies conducted were mostly of cross-sectional design and evidence regarding the effect of pain on functional limitations, disability and frailty among American older adults over time is scarce and our study aims to fulfill this gap.

Therefore, the objective of this study was to investigate predictors of pain, and pain as a predictor of upper-lower extremity functional limitations, ADL disability, and frailty over 6-years of follow-up among American older adults. Understanding the relationship between pain, the disablement process and frailty will help increase independence and improve quality of life of older adults. Determining these relationships is important for enhancing patient management, allocation of health care resources, and lower the burden of pain in this population. This study will help physicians/clinicians identify targets for intervention and design better pain management protocols to prevent early disability and frailty in this population.

CHAPTER 3

METHODS

The primary aim of the study was to examine the relationship between pain and the disablement process and frailty in American older adults. Guided by the literature review, three specific aims are presented below. This is followed by 1) the conceptual model; 2) key hypothesis tested; 3) description of the data and sample; 4) description of the variables; and 5) an outline of the analysis.

Specific Aim 1**:** To examine the extent to which sociodemographic characteristic, comorbidities, depression, obesity, and sleep complaints are associated with pain over 6-years of follow-up.

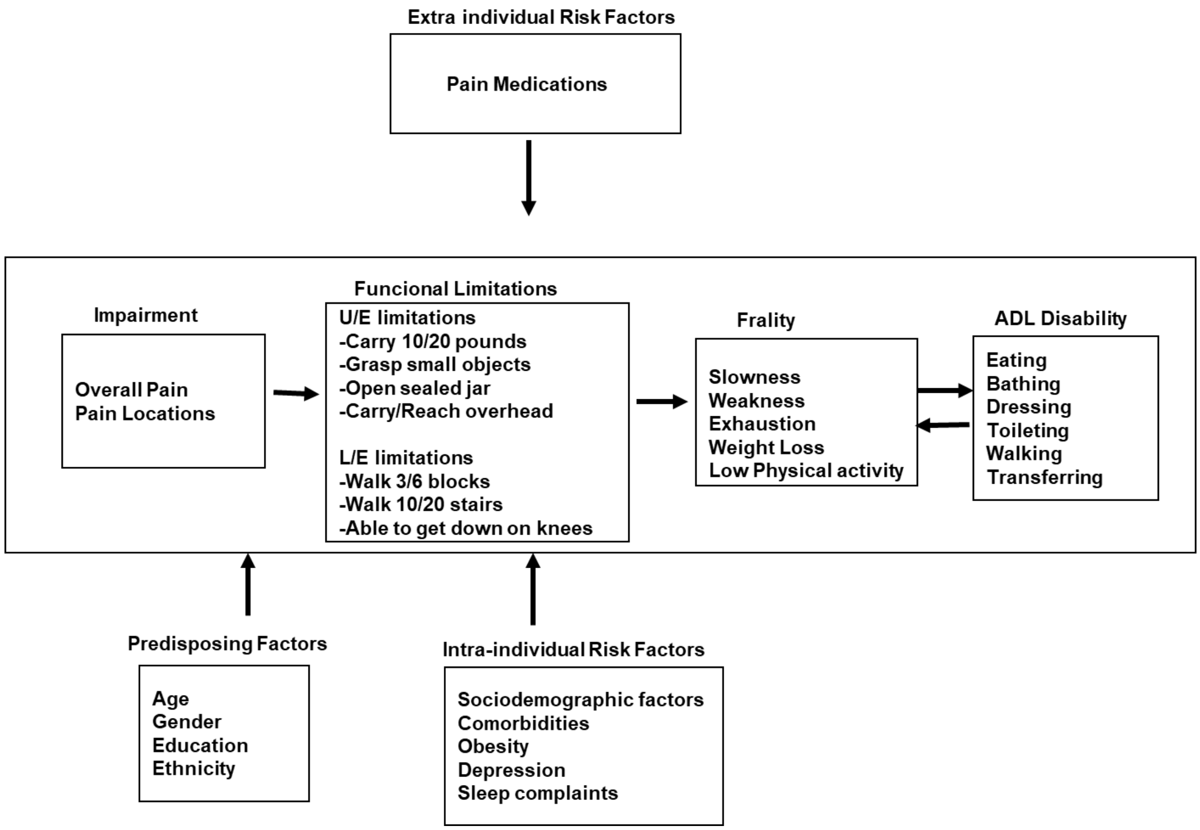
Specific Aim 2**:** To examine the effect of pain on upper-lower extremity functional limitations and ADL disability over 6-years of follow-up.

Specific Aim 3**:** To examine the effect of pain as a predictor of frailty over 6-years of follow-up.

CONCEPTUAL MODEL

The proposed research used the model of the disablement process proposed by Verbrugge and Jette[55] as a conceptual framework to guides all the analyses. This research will start from the stage of impairment, represented by overall pain in the body and pain locations (hand, wrist, shoulder, neck, back, hip, knee, or foot).

Figure 5: The Diagram of proposed model of the Pain-Frailty-Disability Conceptual Framework



Source- Verbrugge LM, Jette AM. The disablement process. Social science & medicine *(1982).*

The second stage is functional limitation, which occurs as a direct consequence of impairments and it is represented by functional limitations in upper extremities (e.g., carry 20 or 10 pounds, grasp small objects, open sealed jar with hands, reach overhead or carry heavy objects above head) and lower extremities (e.g., walk 6 or 3 blocks, walk up

20 or 10 stairs or able to get down on knees). The third stage is represented by frailty (slowness, weakness, low physical activity, exhaustion and weight loss). The fourth stage is disability, which reflects difficulty, limitation, or inability to perform the activities of daily living (ADL).

The main pain-frailty-disability pathway is itself influenced by phenomena that are not strictly part of the disease or impairments and can be considered as external factors. These factors were analyzed in this proposed research and they are: a) predisposing factors (age, gender, education or ethnicity); b) intra-individual factors (comorbidities, depression, obesity or sleep complaints); c) and extra-individual factors (pain medications). (figure 5)

The conceptual model implies several hypotheses that can be tested given the large sample size with longitudinal data. As the specific aims outlined, three specific hypotheses are proposed for Specific Aims 1 and 2; and two for the Specific Aim 3.

Hypothesis 1.a. Older adults with comorbidities will be more likely to experience pain than those without comorbidities.

Hypothesis 1.b. Older adults with depression will be more likely to experience pain than those without depression.

Hypothesis 1.c. Older adults with sleep complaints will be more likely to experience pain than those without sleep complaints.

Hypothesis 2.a. Older adults with pain will be more likely to experience upper-lower extremity functional limitations and ADL disability than those without pain.

Hypothesis 2.b. Depression will mediate the relationship between pain and upper-lower extremity functional limitations and ADL disability.

Hypothesis 2.c. Obesity will moderate the relationship between pain and upper-lower extremity functional limitations and ADL disability.

Hypothesis 3.a. Older adults with pain will be more likely to experience frailty than those without pain.

Hypothesis 3.b. Depression will mediate the relationship between pain and frailty.

DATA AND SAMPLE SELECTION

Data for the study are from the National Health and Aging Trends Study (NHATS). The NHATS is an ongoing nationally representative sample of Medicare beneficiaries aged 65 years and older. It is designed to study functioning in later life and is intended to advance research that will guide efforts to reduce disability, maximize health and independent functioning, and enhance quality of life at older ages. Study participants were first interviewed in 2011 and were re-interviewed annually to document changes over time.

The NHATS sample study design, which is drawn from the Medicare enrollment file, oversamples persons at older ages and Black individuals. The Medicare enrollment database served as the sampling frame. At baseline (round 1), a sample size of 8,500 respondents was targeted, a sufficient number to track disability trends by age and race/ethnicity. Round 1 of NHATS used a stratified three-stage sample design: 1) selection of 95 primary sampling units (PSUs); 2) selection of 655 secondary sampling units (SSUs); and 3) selection of beneficiaries within sampled SSUs as of September 30, 2010. This data is publicly available.

The probabilities of selection at each of the three stages were designed to yield equal probability samples and targeted sample sizes by age groups (65-69, 70-74, 75-79, 80-84, 85-89, and 90+) and race/ethnicity (non-Hispanic Black and White/Other). A total of 14,643 beneficiaries were sampled altogether and 12,411 cases released to the field. The overall target sample size was 8,500 responding beneficiaries. NHATS achieved a 71% response rate, yielding 8,245 complete cases. NHATS is supported by the National Institute on Aging under a cooperative agreement with the Johns Hopkins University Bloomberg School of Public Health (U01AG032947), with data collection by Westat.

The disability measures included in the NHATS[95] were guided by a conceptual framework that combined the language of the World Health Organization's International Classification of Functioning[96] with the Nagi model of disablement[97] emphasizing the role of accommodations or compensatory strategies such as the use of adopting devices, changes in behavior (e.g. reducing frequency of an activity), environment (e.g., modifications in the bathroom), and getting help or services. Study participants were first interviewed in 2011 (N=8,245) and annual re-interviews are conducted to document change over time. Seven rounds of data have been collected. Replenishment took place in round 5 to study disability trends as well as individual trajectories.

The NHATS survey collects data on socio-demographics, early life factors, health conditions, physical impairments, cognitive and physical capacity, mobility and self-care activities, anthropometric measures, environment, activities and participation, compensatory strategies, health care utilization, and economic and social consequences at each interview.

Study Population

The present study included data collected from baseline (2011/2012) to round six (2016/2017). The distribution of sample size and status of follow-up at each interview of the NHATS survey is presented in Table 1. Wave 1 included a sample of 8,245, out of which a total of 3,675 were follow-up till wave 6. We included a sample of 5,716 participants at baseline after excluding those with missing information on pain and the covariates. The cumulative number of deaths reported by the end of wave 6 was 2,006. Table 1 shows the sample size and status of follow-up from baseline to wave 6.

Table 1: Summary of the NHATS sample at each follow-up (N=8,245).

Status	Baseline 2011-2012	Wave 2 2012-2013	Wave 3 2013-2014	Wave 4 2014-2015	Wave 5 2015-2016	Wave 6 2016-2017
Sample Person	8245	7075	5799	4737	4152	3675
Participants included	5716	4699	3882	3289	2990	2673
Proxy	583	964	897	722	556	497
Deaths		503	523	404	296	280

This study included participants who were interviewed in person and lived in the community in 2011 (N=5,716). Participants excluded were those who were not living in community, had missing information on pain and other covariates, and those with proxy interviews (N=2,529). For Aim 2, participants who reported any ULE functional limitations at baseline were excluded leaving a sample size of 4,430 to analyze the effect of pain on upper-extremity functional limitations, and a sample size of 1,717 to analyze the effect of pain on lower extremity functional limitations.

To analyze the effect of pain on ADL disability, participants with any ADL limitations at baseline were excluded leaving a sample size of 5,023. For Aim 3, participants with frailty at baseline were excluded leaving a sample size of 5,019. Figure 6 shows the flowchart of the sample selection.

Figure 6 : Flowchart of the Sample Selection.

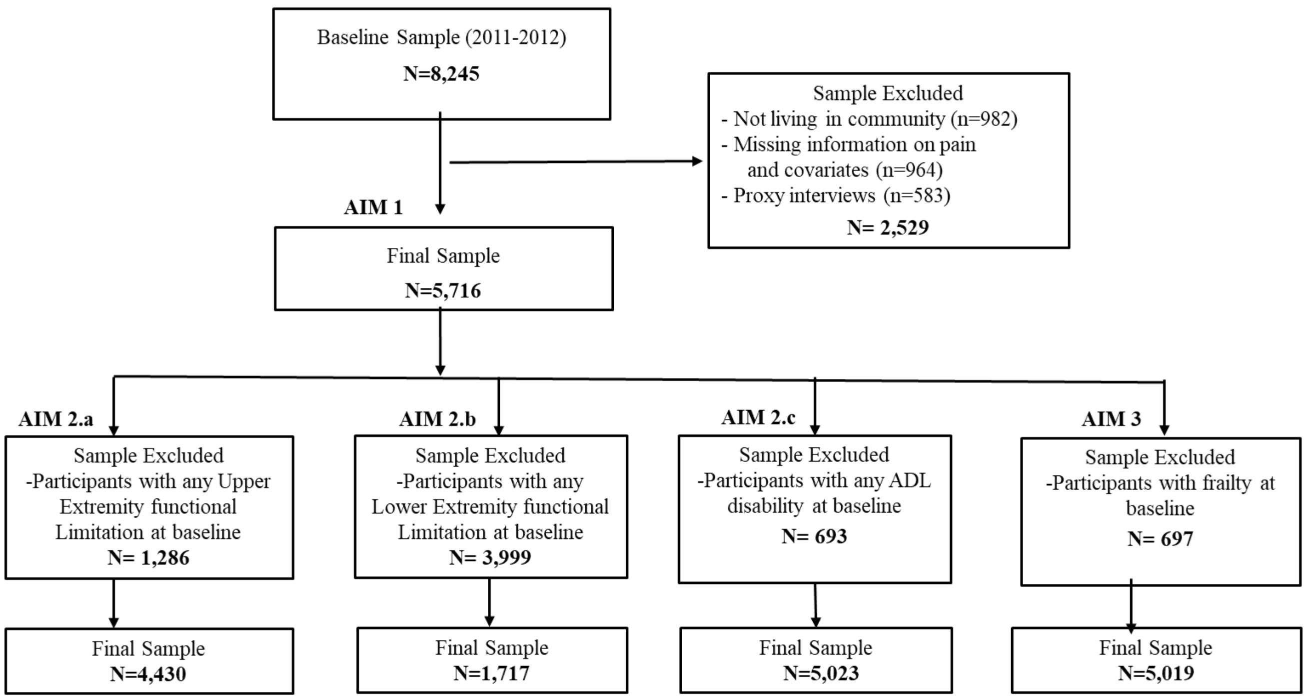


Table 2 presents the descriptive characteristics of the participants who were excluded versus included at baseline. Excluded participants were more significantly more likely to be older, female, unmarried, of Hispanic origin, to have lower level of education, BMI < 18.5 Kg/m^2, to report stroke, diabetes, cancer, dementia, depression, any functional limitations in upper extremities, ADL disability, and poorer performance in handgrip strength and walking speed than those included in the study.

Table 2 : Baseline characteristics of the sample by excluded and included participants among American older adults (N=6,680).

Predictor variables	Excluded N (%)	Included N (%)	P-Value
Total	964 (13.4)	5716 (86.6)	
Age (Years)			<.0001
65-74	327 (48.7)	2519 (57.5)	
75-84	400 (35.5)	2292 (33.2)	
85 +	237 (15.8)	905 (9.3)	
Gender (Female)	612 (61.8)	3223 (54.9)	0.0006
BMI (Kg/m2)			<.0001
<18.5	26 (3.02)	116 (1.7)	
18.5-25	296 (38.7)	1820 (30.3)	
25-30	232 (31.8)	2173 (39.2)	
30-34	117 (16.1)	1056 (19.2)	
35+	80 (10.2)	1056 (9.6)	
Marital Status (Married)	405 (49.7)	2972 (58.3)	<.0001
Race/Ethnicity			<.0001
Whites	452 (78.1)	4155 (85.3)	
Blacks	206 (11.3)	1233 (8.1)	
Hispanics	63 (10.6)	328 (6.6)	
Education Status			0.0002
1-8th grade	149 (13.7)	616 (8.6)	
8th- 12th grade	119 (11.0)	810 (11.4)	
High School	410 (46.0)	2757 (49.6)	
Bach/MS degree	219 (29.3)	1533 (30.4)	
Sleep Complaints			
Trouble Sleep	425 (41.9)	2465 (41.8)	0.96
Sleep over	454 (45.1)	2631 (43.6)	0.459
Sleep med	197 (29.2)	1194 (21.9)	0.647
Comorbid Conditions			
Heart attack	164 (15.6)	828 (13.3)	0.073

Stroke	119 (10.6)	570 (8.5)	0.055
Hypertension	642 (64.2)	3829 (63.4)	0.67
Arthritis	532 (54.2)	3148 (53.1)	0.573
Diabetes	267 (26.6)	1416 (22.9)	0.033
Cancer	212 (21.4)	1507 (26.6)	0.002
Dementia	37 (3.2)	136 (1.8)	0.004
Lung Disease	135 (14.8),	884 (15.4)	0.656
Hip Fracture	45 (4.3)	231 (3.2)	0.125
Depression	154 (15.5)	787 (12.5)	0.024
Any UEFL	284 (28.2)	1286 (17.8)	<.0001
Any LEFL	591 (72.2)	3999 (68.9)	0.115
ADL Disability	164 (13.7)	693 (10.0)	0.001
Pain	521 (51.7)	3036 (52.3)	0.728
Grip total (Mean ± SD)			<.0001
Male	25.9 (13.6)	31.8 (13.3)	
Female	15.6 (9.7)	18.2 (8.9	
Walk total	4.4 (3.7)	4.1 (3.2)	<.0001

Means and percents were obtained after adjusting for sampling weights used in National Health and Aging Trends Study (NHATS)
Values are presented as means ± standard deviation (SD) or n (%)
Chi-square tests are used for categorical variables and t-tests for continuous variables
UEFL upper-extremity functional limitation, *LEFL* lower extremity functional limitation, *BMI* body mass index, *ADL* activities of daily living

MEASURES

Independent Variables

Any pain: Assessed by the following question; "In the last month, have you been bothered by pain"? (Yes/No).

Pain Location: Assessed by the following question: "where you have had pain in the last month -hand, wrist, shoulder, neck, back, hip, knee, or foot? (Yes/No).

Pain Severity: Pain severity index was created using two questions that were asked to the participants who reported pain. 1) In the last month, has pain ever limited your activities? (Yes/No); and 2) In the last month, how often did you take medication for pain? Would you say every day, most days, some days, rarely or never? Based on participants response, two categories were created: 1) Yes (every day, most days, or some days and 2) No (rarely, or never). Participants who responded yes for the above two questions were considered to have severe pain.

Outcome Variables

Upper-Extremity Function Limitations: Assessed by 6 questions: In the last month, were you able to carry 20 pounds, carry 10 pounds, grasp small objects, open sealed jar with hands, reach overhead or carry heavy objects above head. (Yes/No). Any upper-extremity functional limitations were dichotomized as having difficulty or no difficulty in performing one or more of the six activities.

Lower-Extremity Function Limitations: Assessed by 6 questions: In the last month, were you able to walk 6 blocks, able to walk 3 blocks, able to walk up 20 stairs, able to walk up 10 stairs or able to get down on knees. (Yes/No). Any lower extremity functional limitations were dichotomized as having difficulty or no difficulty in performing one or more of the five activities.

Activities of Daily Living Disability: Assessed by asking the following question: In the last month, whether anyone helped them in performing these self-care activities: eating, bathing, transferring, dressing, moving out of the bed, and moving inside. Any ADL disability was dichotomized as yes or no in performing one or more of the six self-care activities.[98] (Yes/No).

Frailty: Frailty was assessed by frailty phenotype measure described by Fried et al.[1] Five frailty items were used: exhaustion, low physical activity, weakness, slowness, and shrinking. Participants who reported low energy or being easily exhausted to limit their activities were considered positive for the exhaustion criterion. Participants who never walked for exercise or engaged in vigorous activities were considered positive for the low physical activity criterion. Participants with a body mass index (BMI) less than 18.5 Kg/m^2 or reported losing 10 or more pounds unintentionally in the last year were considered positive for the criterion of shrinking. Low walking speed was defined using the first two walking trials, as below the 20th percentile of the weighted population distribution adjusted by sex and height. Weakness was defined using the maximum dominant hand grip strength over two trials, as below the 20th percentile adjusted by sex and BMI. [99,100] Non-frail status was defined as participants not meeting any criteria. Participants with one to two criterions were considered pre-frail. Participants with three or more criterions were considered frail.[1]

Covariates

Age: Age was categorized into three groups of 65 -74, 75-84, and ≥ 85 years old.

Gender: was dichotomized as female vs. male

Race/Ethnicity: Race was categorized into three groups; Non-Hispanic Whites, Non-Hispanic Blacks, and Hispanics.

Education: Education was categorized into four groups of 1-8th grade, 8th-12th grade, high school graduate, and college graduate with a bachelor's or a master's degree.

Body Mass Index (BMI): Self-reported weight and height was used to calculate BMI. BMI was be grouped in <18.5 (underweight), 18.5- 25 (normal), 25-30 (overweight), 30-35 (obesity type I), >35 (obesity type II), with 18.5-25 as the reference group.

Marital status: Assessed by asking the following question "Are you currently married, living with a partner, separated, divorced, widowed, or never married? Based on the participants response, two categories were created: 1) Yes (Married) and 2) No (living with a partner, separated, divorced, widowed, or never married.

Comorbid conditions: Assessed by asking the following question "I will read a list of some diseases and conditions that a doctor may have said you have/had. Please tell me if a doctor ever told you that you had heart attack, stroke, arthritis, diabetes, hypertension, dementia, lung disease, hip fracture, or cancer." (Yes/No)

Sleep Complaints: Assessed using three self-reported questions on sleep in the last month: how often it takes more than 30 minutes to fall asleep at night; how often person had trouble falling back asleep on nights he/she woke up; and how often he/she took medication to sleep. Response categories were: every night, most nights, some nights, rarely, and never. Based on participants response, two categories were created: 1) Yes (every night, most nights, or some nights) and 2) No (rarely, or never).[101]

Depression: Assessed with the Patient Health Quuestionnaire-2 (PHQ-2). Participants were asked the following questions: Over the last month, how often have you: 1) Had little interest or pleasure in doing things? and 2) Felt down, depressed, or hopeless? With responses of: not at all, several days, more than half the days, or nearly every day. Each item is scored ranging from 0 to 3 with a maximum score of 6. PHQ-2 score ≥ 3 was used to define substantial depressive symptoms as it has been shown to have a 100% sensitivity and 77% specificity for the diagnosis of major depression among older adults.[102]

STATISTICAL ANALYSIS

Multiple analyses were conducted for each aim using a variety of statistical techniques including descriptive analyses, tables, graphs, and box plots. We inspected for normality, identify outliers, and perform transformations on data as needed. Collinearity between variables were tested using the variance decomposition proportions and standard error inflation factors. Weights were applied to all analyses to account for the NHATS sampling design. To determine the validity of our findings for each analysis, we identified predictors of missing data and subject attrition to determine where bias is greatest. We examined responses and information collected from participants to determine if missing data occurs randomly or systematically. This was performed by comparing analyses including and excluding subjects with missing data for variables to determine the effects of subject attrition. If estimates are similar using both methods, we can assume that subject attrition did not greatly affect our results. Several statistical procedures have been developed that help investigators understand the extent to which subject attrition and missing data produce bias in results by constructing unbiased confidence intervals even when the missing data mechanism cannot be ignored. NHATS investigators have performed multiple imputations in some variables such as hand grip strength and short physical performance battery (SPPB) that was used in this application. To adjust for the sampling weights used in the NHATS study, SAS survey procedures were applied.

General Estimation Equation (GEE) [103] models with a binomial distribution and logit link were used to estimate 1) the odds ratio of pain as a function of sociodemographic, sleep complaints, depression, obesity, comorbidities, and sleep complains; 2) the odds ratio of any upper-lower extremity functional limitations and ADL disability as a function of pain; and 3) the odds ratio of frailty as a function of pain over 6-years of follow-up after controlling for all covariates. The GEE model is a known function of the marginal expectation of the dependent variable as a linear function of one or more predictor variables. [104]

The GEE procedure offers consistent estimates of the regression coefficients and of their variances under weak assumptions about the actual correlation among a subject's observation. This approach bypasses the need of the multivariate analysis by assuming a functional form for the marginal distribution at each point. The GEE procedure also implements the weighted GEE method to handle missing responses that are caused by loos to follow up, dropouts or attrition in the longitudinal studies.[105,106] All the variables were analyzed as time varying except for age, gender, education, and race/ethnicity.

Statistical Analyses for Specific Aim 1

Aim 1: *To examine the extent to which sociodemographic characteristic, comorbidities, depression, obesity, and sleep complaints are associated with pain over 6-years.*

> ***Hypothesis 1a:*** Older adults with comorbidities will be more likely to experience pain when than those without comorbidities.
>
> ***Hypothesis 1b:*** Older adults with depression will be more likely to experience pain than those without depression.
>
> ***Hypothesis 1c:*** Older adults with sleep complaints will be more likely to experience pain than those without sleep complaints.

Methods: Descriptive analysis were conducted and reported as frequency, percent, mean, standard deviation or standard error. Students T-test and Chi-square tests were used to examine the distribution of sociodemographic, comorbidities, depression, sleep complaints and obesity by pain. To test the hypotheses 1.a. to 1.c., the GEE models with a binomial distribution and logit link were used to estimate the odds ratio of pain as a function of sociodemographic, sleep complaints, depression, obesity, comorbidities, and sleep complains over 6-years of follow-up.

Statistical Analyses for Specific Aim 2

Aim 2: *To examine the effect of pain on upper-lower extremity functional limitations and ADL disability over 6-years of follow-up.*

Hypothesis 2a: Older adults with pain will be more likely to experience any upper-lower extremity functional limitations and ADL disability than those without pain.

Hypothesis 2b: Depression will mediate the relationship between pain and any upper-lower extremity functional limitations and ADL disability.

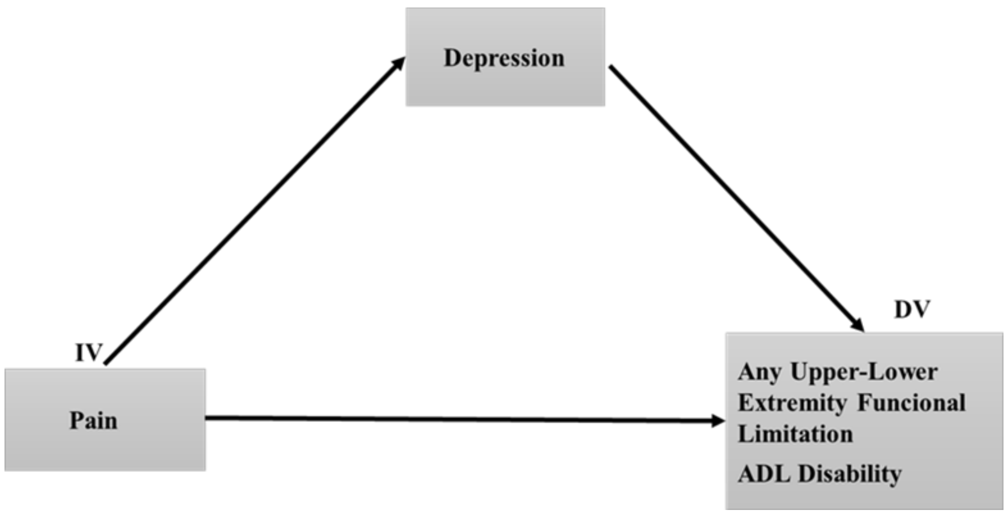
Hypothesis 2c: Obesity will moderate the relationship between pain and upper-lower extremity function limitation and ADL disability.

Methods: Descriptive analysis were conducted and reported as frequency, percent, mean, standard deviation or standard error. Students T-test and Chi-square tests were used to examine the distribution of upper-lower extremity functional limitations and ADL disability by pain.

To test hypothesis 2.a. Generalized Estimation Equation model with a binomial distribution and logit link were used to estimate the odds ratio of any upper-lower extremity functional limitations and ADL disability as a function of pain over 6-years of follow-up, controlling for all covariates. Analyses for any upper-extremity functional limitations were conducted among those who reported no upper-extremity functional limitations at baseline. Analyses for any lower extremity functional limitations were conducted among those who reported no lower extremity functional limitations at baseline. Analyses for ADL disability were conducted among those who reported no ADL disability at baseline.

To test hypothesis 2.b. Generalized Estimation Equation model were used, and four models were performed to test the mediating effect of depression on the relationship between pain and any upper-lower extremity functional limitations and ADL disability. Model 1 included time, and pain. Model 2 included time, and depression. Model 3 included time, pain, and depression. Model 4 included all variables (time, pain, sociodemographic, sleep complaints, depression, obesity, and comorbidities).

Figure 7: The Mediator model for depression in the relationship between pain and any upper-lower extremity functional limitations and ADL disability.

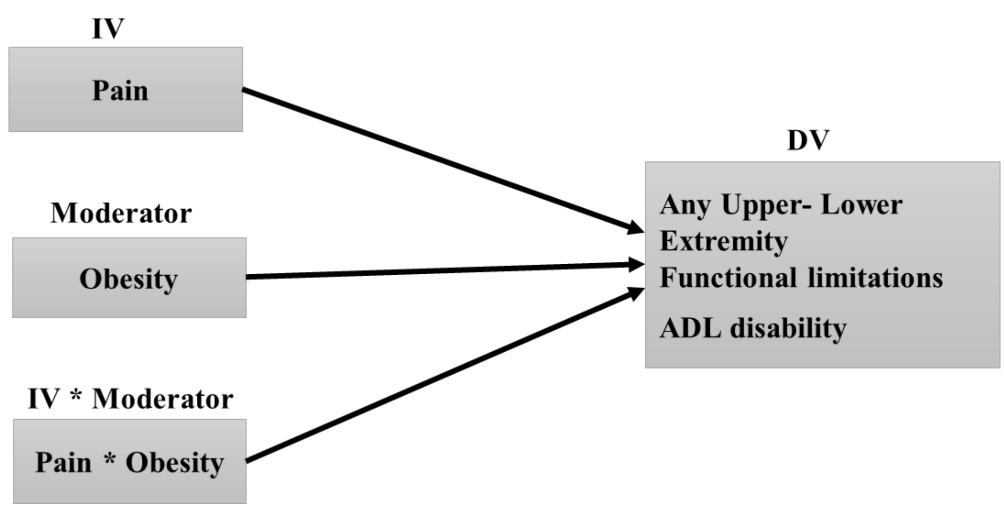


Note: IV=Independent Variable; DV=Dependent variable

To test hypothesis 2.c. Generalized Estimation Equation models were used, and two models were performed to test the moderator effect of obesity on the relationship between pain and any upper-lower extremity functional limitations and ADL disability. Model 1 included time, pain, sociodemographic, sleep complaints, depression, obesity, and comorbidities. Model 2 included all variables in Model 1 and an interaction term between pain and obesity.

To test the moderator effect of obesity on the relationship between pain and any upper-lower extremity functional limitations and ADL disability was investigated with an interaction effect between pain and obesity. Figure 8 shows the path diagram representation of the moderator effect where IV is the independent variable; obesity is the moderator variable; DV is the dependent variable (any upper-lower extremity functional limitations and ADL disability); and the interaction between IV and the moderator variable (obesity – BMI ≥ 30 Kg/m2).

Figure 8: The Moderator model for obesity in the relationship between pain, and upper-lower extremity functional limitations and ADL disability.



Note: IV=Independent Variable; DV=Dependent variable

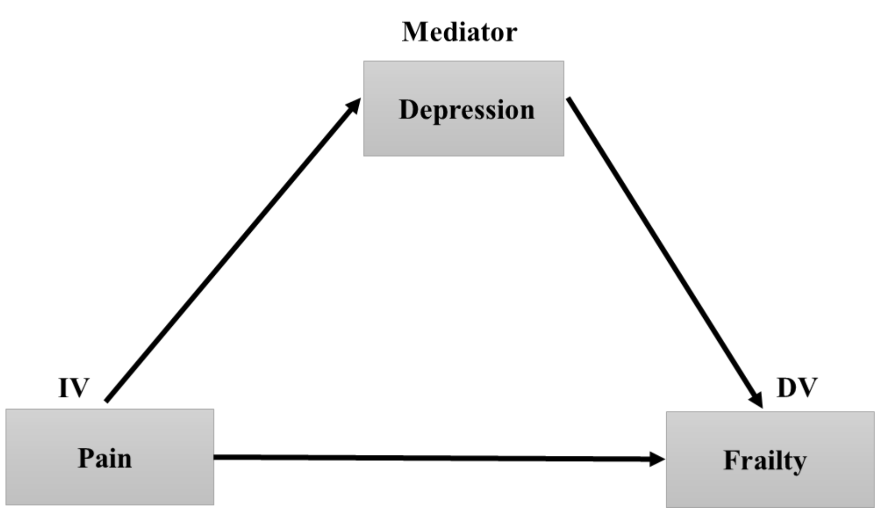
Statistical Analyses for Specific Aim 3

Aim 3: *To examine the effect of pain as a predictor of frailty over 6-years of follow-up.*

> ***Hypothesis 3.a:*** Older adults with pain will be more likely to experience frailty than those without pain.
>
> ***Hypothesis 3.b:*** Depression will mediate the relationship between pain and frailty.

Methods: Descriptive analysis were conducted and reported as frequency, percent, mean, standard deviation or standard error. Students T-test and Chi-square tests were used to examine the distribution of frailty by pain.

Figure 9: The mediator model for depression in the relationship between pain and frailty.



Note: IV=Independent Variable; DV=Dependent variable

To test hypothesis 3.a. Generalized Estimation Equation models with a binomial distribution and logit link were used to estimate the odds ratio of frailty as a function of pain over 6-years of follow-up among those who were not frail at baseline, controlling for all covariates.

To test hypothesis 3.b. Generalized Estimation Equation models were performed, and four models tested the mediating effect of depression on the relationship between pain and frailty. Model 1 included time and pain. Model 2 included time and depression. Model 3 included time, pain, and depression. Model 4 included all variables (time, pain, sociodemographic, sleep complaints, depression, obesity, and comorbidities).

All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

CHAPTER 4

AIM 1 RESULTS: Effect of sociodemographic characteristics, comorbidities, depression, obesity, and sleep complaints on pain over 6-years of follow-up in American older adults.

In this chapter we examined whether sociodemographic characteristic, comorbidities, depression, obesity, and sleep complaints are predictive of pain over 6-years of follow-up in American older adults. We hypothesized that older adults with comorbidities, depression and sleep complaints will be more likely to experience pain than those without pain.

RESULTS OF DESCRIPTIVE ANALYSES

Table 3 presents the descriptive characteristics of the sample at baseline by pain. The overall prevalence of pain was 52.3 %. Participants reporting pain were significantly more likely to be female, unmarried, have high school education, BMI $\geq$ 30 Kg/m^2, reported more comorbid conditions, depression, sleep complaints, any ULE functional limitations, ADL disability and perform poorer in handgrip strength and walk speed than those without pain. No significant differences were observed by age and race/ethnicity.

Table 3: Descriptive characteristics of the overall sample by pain among American older adults at baseline (N=5,716).

Predictor variables	No Pain N (%)	Pain N (%)	P-Value
Total	2680 (47.6)	3036 (52.3)	
Age at baseline			
65-74	1184 (57.4)	1335 (57.5)	0.948
75-84	1078 (33.6)	1214 (33.0)	0.691
85 +	418 (9.0)	487 (9.5)	0.508
Gender (Female)	1365 (49.4)	1858 (59.8)	<.0001
BMI (Kg/m^2)			<.0001
<18.5	63 (2.1)	53 (1.4)	
18.5<25	951 (33.6)	869 (27.3)	
25<30	1077 (41.7)	1096 (40.0)	
30<34	417 (16.2)	639 (21.8)	
>35	172 (6.4)	379(12.5)	
Marital Status (Married)	1473 (61.4)	1499 (55.6)	<.0001
Race/Ethnicity			0.287
Whites	1976 (85.7)	2179 (85.0)	
NHB	546 (7.5)	687 (8.5)	
Hispanics	158 (6.8)	170 (6.5)	
Education Status			0.0001
1-8th grade	273 (8.1)	343 (8.9)	
8th- 12th grade	343 (10.4)	467 (12.3)	
High School	1273 (48.0)	1484 (51.1)	
Bach/MS degree	791 (33.5)	742 (27.7)	
Sleep Complaints			
Trouble Sleep	950 (34.1)	1515 (48.8)	<.0001
Sleep over	999 (35.5)	1632 (50.9)	<.0001
Sleep med	383 (15.5)	811 (27.6)	<.0001
Comorbid Conditions			
Heart attack	322 (11.1)	506 (15.3)	<.0001
Stroke	208 (6.7)	362 (10.1)	<.0001
Hypertension	1633 (57.3)	2196 (68.9)	<.0001
Arthritis	968 (35.1)	2180 (69.4)	<.0001
Diabetes	549 (19.0)	867 (26.6)	<.0001
Cancer	648 (23.8)	859 (29.0)	<.0001
Dementia	46 (1.2)	90 (2.3)	0.0011
Lung Disease	292 (10.7)	592 (19.7)	<.0001
Hip Fracture	84 (2.4)	147 (3.9)	0.0025

Depression	237 (8.3)	550 (16.3)	<.0001
Any UEFL	334 (8.9)	952 (25.8)	<.0001
Any LEFL	1913 (71.7)	2086 (66.2)	<.0001
ADL Disability	171 (4.7)	522 (14.7)	<.0001
Grip total (Kg, Mean ± SD)			<.0001
Male	34.1 (11.7)	29.3 (14.5)	
Female	20.3 (7.5)	16.6 (9.6)	
Walk total (seconds, Mean ± SD)	3.8 (2.7)	4.3 (3.5)	<.0001

Means and percents were obtained after adjusting for sampling weights used in National Health and Aging Trends Study (NHATS)
Values are presented as means ± standard deviation (SD) or n (%)
Chi-square tests are used for categorical variables and t-tests for continuous variables
UEFL upper-extremity functional limitation, *LEFL* lower extremity functional limitation *BMI* body mass index, *NHB* Non-Hispanic Blacks, *ADL* activities of daily living

Figure 10 presents the prevalence of pain at each wave. The prevalence of pain ranged from 52.3 % at baseline to 57.4 % in wave 6.

Figure 10: Prevalence of pain across 6 waves of follow-up.

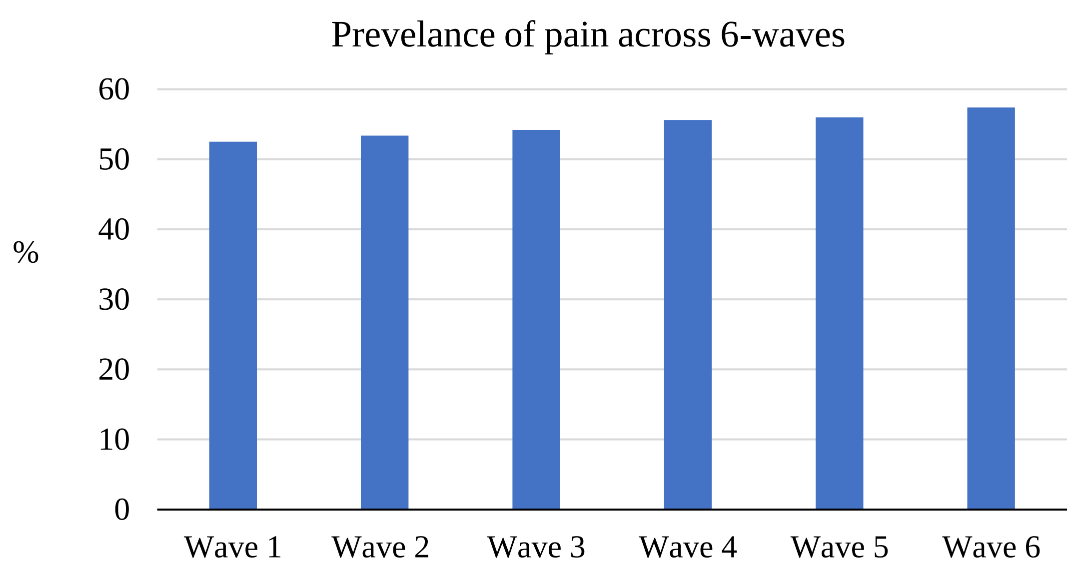


Figure 11 presents the prevalence of participants taking pain medications among those with pain at each wave. The prevalence of participants taking pain medications ranged from 60 % at baseline to 57.4 % in wave 6.

Figure 11: Prevalence of participants taking pain medications across 6 waves of follow-up.

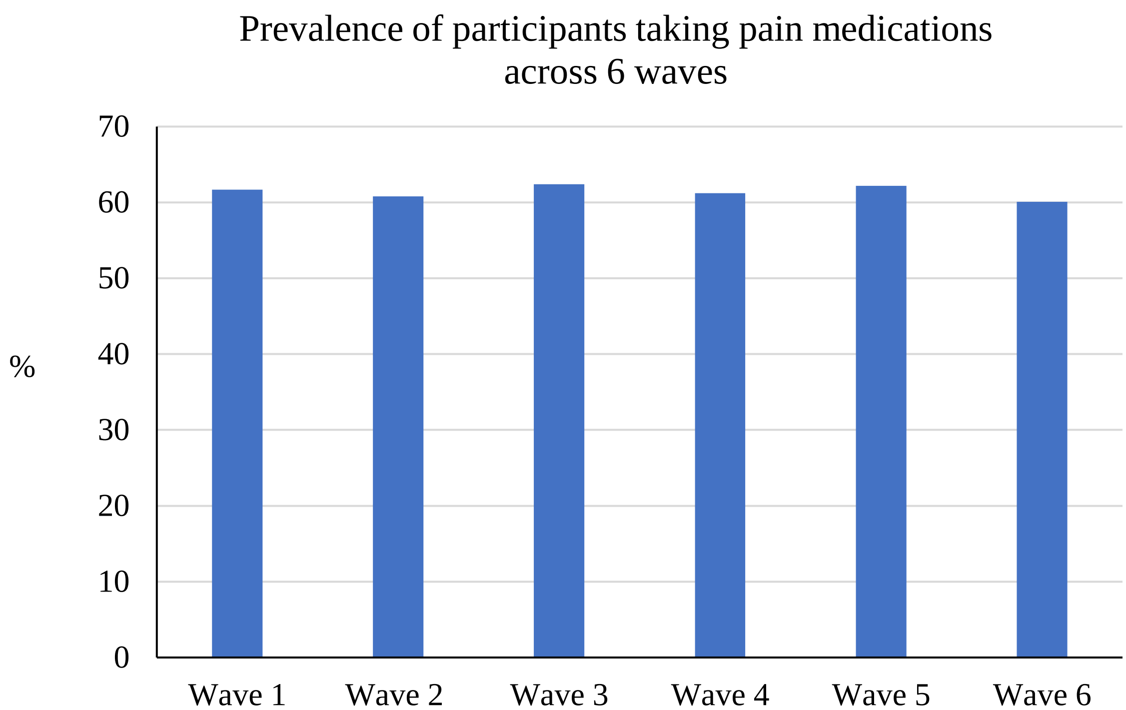
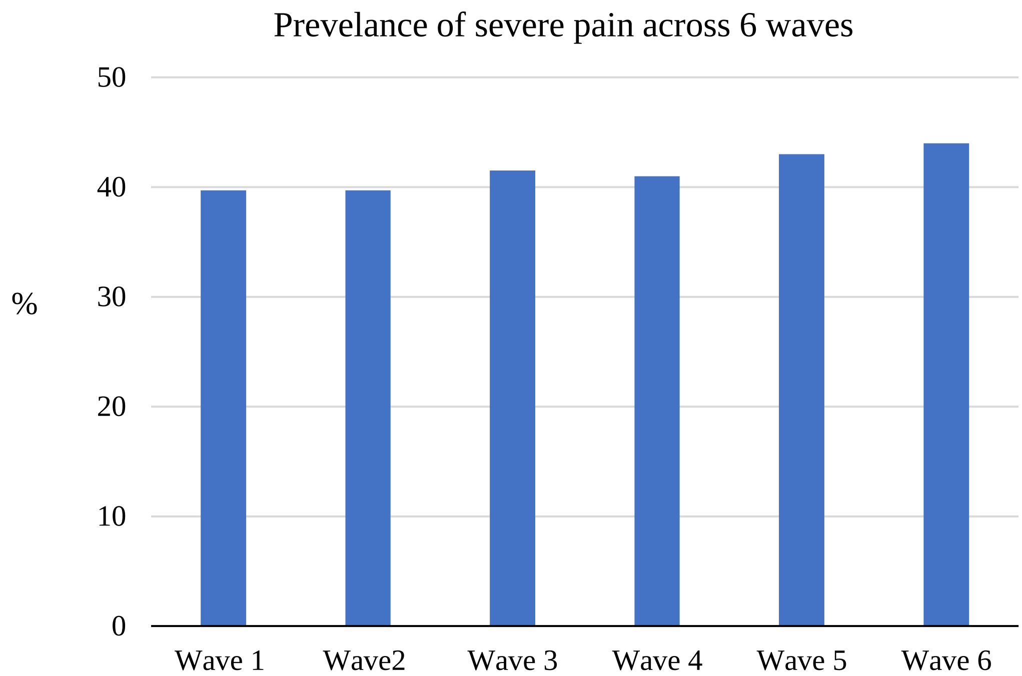


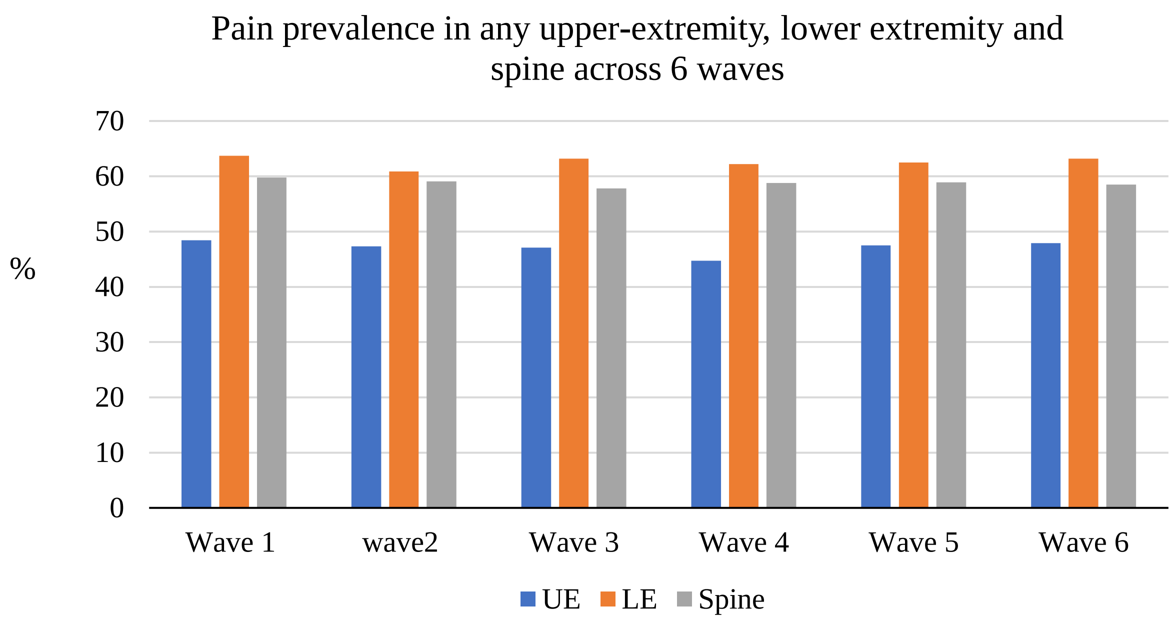
Figure 12 presents the prevalence of severe pain (taking pain medications and pain limiting activities) over 6-years of follow up among those who reported pain at each wave. Severe pain ranged from 39.7% at baseline to 44% in wave 6.

Figure 12: Prevalence of severe pain in American older adults with pain over 6-years of follow-up.



The prevalence of pain in any upper-extremity, any lower extremity and any spine locations over 6-years of follow up among those who reported pain is presented in Figure 13. The prevalence of any upper-extremity pain ranged from 48.4 % at baseline to 47.9 % in wave 6. The prevalence of any lower extremity pain ranged from 63.7 % at baseline to 63.2 % in wave 6. The prevalence of any spine pain ranged from 59.8 % at baseline to 53.5 % in wave 6.

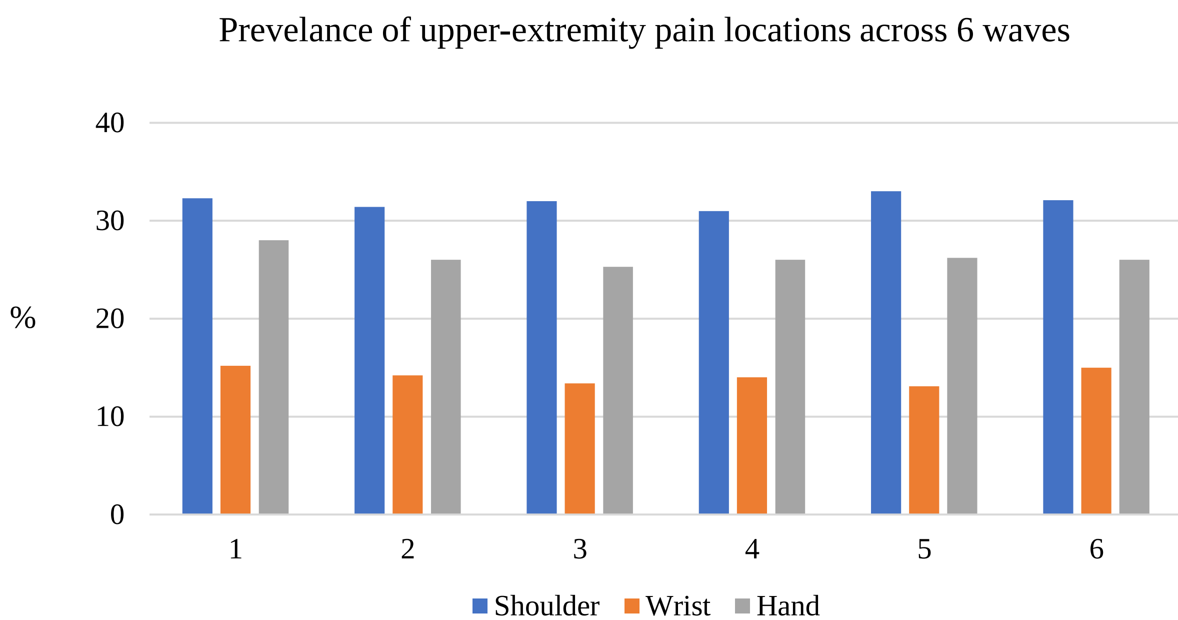
Figure 13: Prevalence of any upper-extremity, any lower extremity and any spine pain in American older adults with pain over 6-years of follow-up.



UE upper-extremity, *LE* lower extremity

The prevalence of pain in upper-extremity locations (shoulder, wrist and hand) over 6-years of follow up is presented in Figure 14. The prevalence of shoulder pain ranged from 32.3% at baseline to 32.1% in wave 6. The prevalence of hand pain ranged from 28% at baseline to 26% in wave 6. The prevalence of wrist pain ranged from 15.2 % at baseline to 15% in wave 6.

Figure 14: Prevalence of pain in upper-extremity locations (shoulder, wrist, and hand) in American older adults with pain over 6-years of follow-up.



The prevalence of pain in lower extremity locations (hip, knee, and foot) over 6-years of follow up is presented in Figure 15. The prevalence of hip pain ranged from 28.5 % at baseline to 29.2 % in wave 6. The prevalence of knee pain ranged from 41.3% at baseline to 40.2 % in wave 6. The prevalence of foot pain ranged from 28.6 % at baseline to 26.4 % in wave 6.

Figure 15: Pain prevalence in lower extremity locations (hip, knee, and foot) in American older adults with pain over 6-years of follow-up.

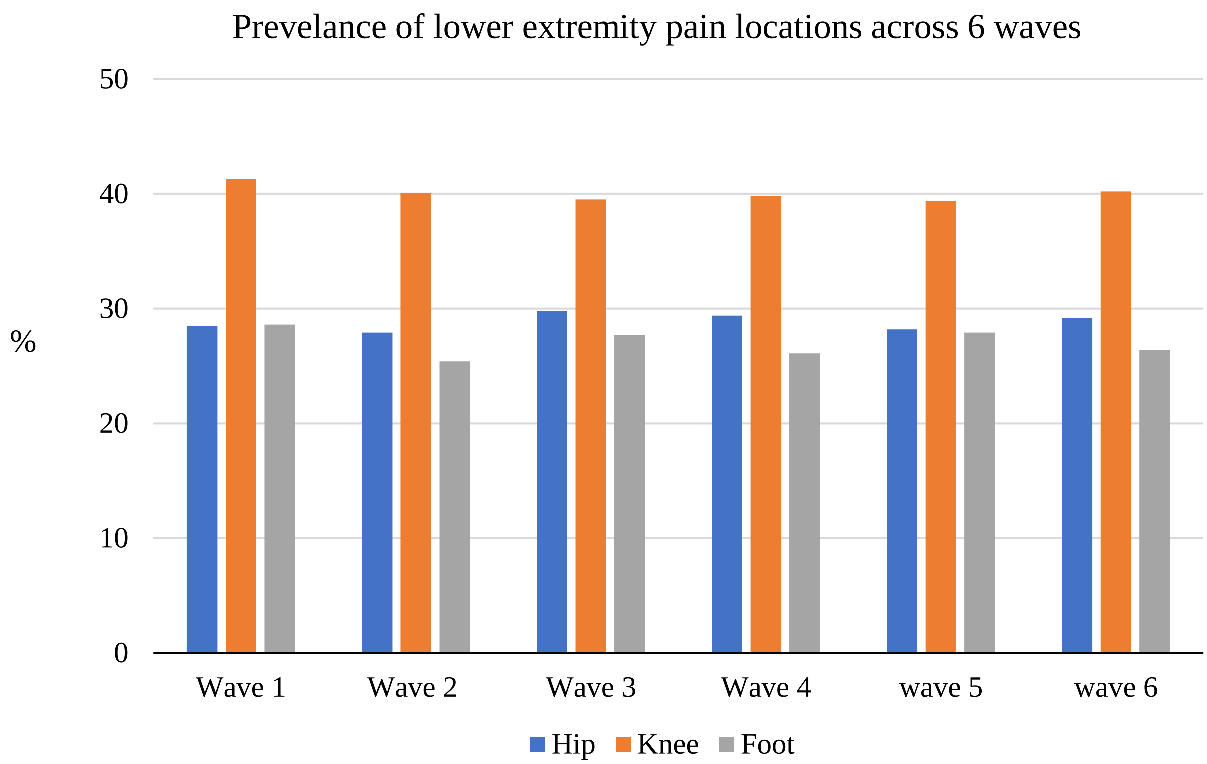
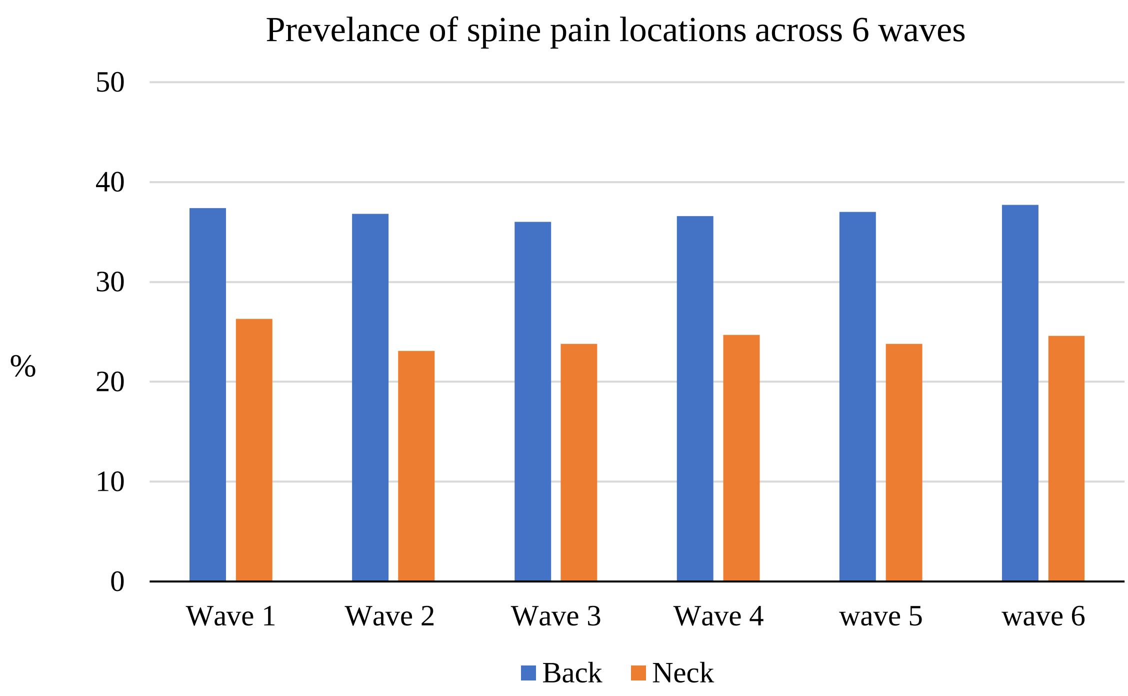


Figure 16 presents the prevalence of pain in spine locations (back, and neck) over 6-years of follow up among those who reported pain at each wave. Pain in the back ranged from 37.4% at baseline to 37.7% in wave 6. Pain in the neck ranged from 26.3 % at baseline to 24.6 % in wave 6.

Figure 16: Prevalence of pain in spine locations (back, and neck) in American older adults with pain over 6-years of follow-up.



RESULTS OF LONGITUDINAL ANALYSES

Table 4 presents the results of the General Estimation Equation models of pain over 6-years of follow-up as a function of sociodemographic characteristics, comorbidities, depression, BMI, and sleep complaints. The odds ratio of reporting pain was 0.99 (95% CI 0.97-1.01) over time. Female participants, being married, BMI ≥30 Kg/m^2, hypertension, arthritis, lung disease, cancer, any sleep complaints and depressive symptoms were factors with high odds ratio of reporting pain over time. Older age (75-84 years) was predictive of lower odds of reporting pain over time.

Table 4: General Estimation Equation models for pain over 6-years of follow-up among American older adults (N=5,716).

Predictor variables	OR (95% CI)
Time (Years)	0.99 (0.97-1.01)
Age at baseline	
65-74	Reference
75-84	0.88 (0.80-0.97)
85 +	0.94 (0.82-1.07)
Gender (Female)	1.23 (1.12-1.35)
Marital Status (Married)	1.17 (1.07-1.29)
Education Status (1-8th grade)	Reference
8th- 12th grade	0.98 (0.82-1.17)
High School	0.98 (0.84-1.14)
Bach/MS degree	0.97 (0.82-1.14)
Race/Ethnicity	
Whites	Reference
NHB	0.99 (0.89-1.11)
Hispanics	0.98 (0.80-1.19)
BMI (Kg/m^2)	
18.5<25	Reference
<18.5	0.89 (0.67-1.19)
25<30	1.01 (0.91-1.12)
30<35	1.32 (1.17-1.50)
>35	1.57 (1.32-1.87)
Comorbid Conditions	
Heart attack	1.12 (0.98-1.28)
Stroke	1.07 (0.91-1.25)
Hypertension	1.24 (1.13-1.36)
Arthritis	3.48 (3.20-3.80)
Diabetes	1.12 (1.01-1.24)
Dementia	1.05 (0.87-1.27)

Lung Disease	1.30 (1.17-1.44)
Hip Fracture	1.15 (0.92-1.43)
Cancer	1.18 (1.07-1.31)
Sleep Complaints	
Trouble Sleep	1.35 (1.25-1.45)
Sleep over	1.24 (1.15-1.34)
Sleep med	1.48 (1.35- 1.63)
Depression	1.61 (1.45-1.78)

OR odds ratio, *CI* confidence interval, *NHB* Non-Hispanic Blacks, *BMI* body mass index

Table 5 presents the results of the General Estimation Equation models for any upper-extremity pain, any lower extremity pain and any spine pain over 6-years of follow-up as a function of sociodemographic characteristics, comorbidities, depression, BMI, and sleep complaints. The odds ratio of reporting any upper-extremity pain was 0.97 (95% CI 0.95-0.99), any lower extremity pain was 0.98 (95% CI 0.96-1.00), and any spine pain was 0.97 (95% CI 0.95-0.99) over time. Female participants, being married, BMI (30-34) Kg/m^2, heart attack, hypertension, stroke, arthritis, lung disease, sleep complaints and depressive symptoms were factors with high odds ratio of reporting any pain in upper extremities over time. Older age was predictor of lower odds of reporting any upper-extremity pain. Female participants, being married, BMI $\geq$ 25 Kg/m^2, heart attack, hypertension, arthritis, diabetes, lung disease, hip fracture, sleep complaints and depressive symptoms were factors with high odds ratio of reporting any lower extremity pain. Those participants in the age group of 75 to 84 years were less likely to report any lower extremity pain. Female participants, BMI $\geq$30 Kg/m^2, heart attack, hypertension, arthritis, lung disease, high depressive symptoms and sleep complaints were factors with high odds ratio of reporting any pain in spine. Older age (85 years and older), Non-

Hispanic blacks and Hispanics participants were significantly less likely to report any pain in spine over time.

Table 5: General Estimation Equation models for any upper-extremity, any lower-extremity and any spine pain over 6-years of follow-up among American older adults (N=5,716).

Predictor variables	Any upper-extremity pain OR (95%CI)	Any lower extremity pain OR (95% CI)	Any spine pain OR (95% CI)
Time (Years)	0.97 (0.95-0.99)	0.98 (0.96-1.00)	0.97 (0.95-0.99)
Age at baseline			
65-74	Reference	Reference	Reference
75-84	0.86 (0.78-0.95)	0.90 (0.82-0.99)	0.93 (0.84-1.03)
85 +	0.86 (0.75-0.99)	0.99 (0.86-1.13)	0.85 (0.73-0.99)
Gender (Female)	1.26 (1.15-1.39)	1.41 (1.29-1.55)	1.13 (1.02-1.25)
Marital Status (Married)	1.13 (1.03-1.24)	1.19 (1.09-1.30)	0.98 (0.88-1.09)
Education Status			
1-8th grade	Reference	Reference	Reference
8th- 12th grade	0.89 (0.75-1.07)	0.92 (0.77-1.10)	0.96 (0.79-1.17)
High School	0.92 (0.79-1.06)	0.92 (0.79-1.08)	0.99 (0.83-1.17)
Bach/MS degree	0.93 (0.79-1.09)	0.88 (0.74-1.04)	0.90 (0.75-1.08)
Race/Ethnicity	Reference	Reference	Reference
Whites	Reference	Reference	Reference
NHB	0.99 (0.89-1.12)	1.06 (0.94-1.18)	0.74 (0.66-0.84)
Hispanics	1.10 (0.91-1.32)	1.15 (0.95-1.40)	0.67 (0.54-0.82)
BMI (Kg/m^2)			
18.5<25	Reference	Reference	Reference
<18.5	0.98 (0.71-1.35)	0.77 (0.55-1.07)	0.83 (0.58-1.19)
25<30	1.06 (0.95-1.18)	1.19 (1.07-1.32)	1.07 (0.95-1.20)
30<35	1.33 (1.17-1.51)	1.77 (1.56-2.01)	1.21 (1.05-1.39)
>35	1.14 (0.96-1.34)	2.16 (1.83-2.56)	1.24 (1.03-1.48)
Comorbid Conditions			

Heart attack	1.16 (1.02-1.33)	1.13 (1.00-1.29)	1.21 (1.05-1.40)
Stroke	1.17 (1.01-1.36)	1.05 (0.90-1.22)	0.94 (0.80-1.11)
Hypertension	1.21 (1.10-1.34)	1.15 (1.05-1.27)	1.15 (1.03-1.29)
Arthritis	3.40 (3.09-3.74)	3.44 (3.15-3.76)	1.71 (1.54-1.89)
Diabetes	1.07 (0.97-1.18)	1.16 (1.05-1.28)	1.02 (0.91-1.14)
Dementia	0.95 (0.80-1.14)	0.96 (0.81-1.14)	0.94 (0.76-1.15)
Lung Disease	1.32 (1.19-1.47)	1.19 (1.07-1.32)	1.31 (1.16-1.47)
Hip Fracture	1.02 (0.83-1.26)	1.77 (1.43-2.21)	0.89 (0.72-1.11)
Cancer	1.07 (0.96-1.18)	1.05 (0.95-1.16)	1.06 (0.95-1.19)
Sleep Complaints			
Trouble Sleep	1.22 (1.13-1.31)	1.24 (1.15-1.33)	1.09 (1.00-1.18)
Sleep over	1.20 (1.11-1.30)	1.15 (1.07-1.25)	1.11 (1.02-1.21)
Sleep med	1.47 (1.34- 1.61)	1.42 (1.29- 1.55)	1.36 (1.23- 1.50)
Depression	1.40 (1.28-1.54)	1.29 (1.16-1.42)	1.25 (1.12-1.39)

OR odds ratio, *CI* confidence interval, *NHB* Non-Hispanic Blacks, *BMI* body mass index

CHAPTER 5

AIM 2 RESULTS: Effect of pain on upper-lower extremity functional limitations and ADL disability over 6-years of follow-up among American older adults.

In this chapter, the effect of pain on ULE functional limitations and ADL disability in American older adults who had no functional limitation and were non-disabled at baseline was examined. We hypothesized that: 1) older adults with pain will be more likely to experience ULE functional limitation and ADL disability than those without pain; 2) depression will mediate the relationship between pain and ULE functional limitations, and between pain and ADL disability; and 3) obesity will moderate the relationship between pain and ULE functional limitations and ADL disability.

Descriptive analysis was conducted and reported as frequency, percent, mean, standard deviation or standard error. Students T-test and Chi-square tests were used to examine the descriptive characteristics of the sample by upper-lower extremity functional limitations and ADL disability.

General Estimation Equation model with a binomial distribution and logit link was used to estimate the odds ratio of ULE functional limitations and ADL disability as a function of pain over 6-years, controlling for all covariates. To test the mediating effect of depression on the relationship between pain and ULE functional limitations and ADL disability, four models were performed. Model 1 included time, and pain. Model 2 included time, and depression. Model 3 included time, pain, and depression. Model 4 included all variables (time, pain, sociodemographic, comorbidities, sleep complaints, depression, and obesity). To test whether the relation between pain and ULE functional limitation and ADL disability was mediated by depression, the percentage reduction in the odds ratio in models with and without the proposed mediators was estimated (i.e., % reduction = [(OR without mediators − OR with mediators/OR without mediators − 1) × 100]). To test the moderator effect of obesity on the relationship between pain and ULE functional limitations and ADL disability, two models were performed. Model 1 included time, pain, sociodemographic, comorbidities sleep complaints, depression and obesity. Model 2 included an interaction term between pain and obesity along with all the variables in Model 1.

RESULTS FOR DESCRIPTIVE ANALYSES

Table 6 presents the descriptive characteristics of the sample at baseline by any upper-extremity functional limitations. The overall prevalence of any upper-extremity functional limitations was 17.8 %. Participants reporting any upper-extremity functional limitations were significantly more likely to be older age, female, married, BMI (≥30 Kg/m^2), reported more comorbid conditions, depression, sleep complaints, any lower-extremity functional limitations, ADL disability and perform poorer in handgrip strength and walk speed than those without any upper-extremity functional limitations.

Table 6: Descriptive characteristics of the overall sample by any upper-extremity functional limitations among American older adults at baseline (N=5,716).

Predictor variables	Without any Upper-extremity Functional Limitations N (%)	With any Upper-extremity Functional Limitations N (%)	P-Value
Total	4430 (82.2)	1286 (17.8)	
Age at baseline			<.0001
65-74	2130 (60.8)	389 (42.3)	
75-84	1763 (32.3)	529 (37.9)	
85 +	537 (6.9)	368 (19.8)	
Gender (Female)	2266 (50.8)	957 (73.4)	<.0001
Marital Status (Married)	2524 (62.0)	448 (41.6)	<.0001
Race/Ethnicity			<.0001
Whites	3394 (87.9)	761 (73.4)	
Blacks	847 (6.9)	386 (13.1)	
Hispanics	189 (5.2)	139 (13.5)	
Education Status			<.0001
1-8th grade	351 (6.2)	265 (19.2)	
8th- 12th grade	537 (10.1)	273 (17.7)	
High School	2195 (50.0)	562 (47.8)	
Bach/MS degree	1347 (33.7)	186 (15.3)	
Sleep Complaints			
Trouble Sleep	1762 (38.7)	703 (56.4)	<.0001
Sleep over	1847 (39.6)	784 (62.2)	<.0001
Sleep med	805 (19.6)	389 (32.5)	<.0001
Comorbid Conditions			
Heart attack	559 (11.5)	269 (21.2)	<.0001
Stroke	335 (6.7)	235 (17.1)	<.0001
Hypertension	2822 (60.5)	1007 (76.5)	<.0001
Arthritis	2177 (48.3)	971 (75.3)	<.0001
Diabetes	966 (20.5)	450 (34.5)	<.0001
Cancer	1164 (26.2)	343 (30.0)	0.284
Dementia	54 (1.0)	82 (5.5)	<.0001
Lung Disease	585 (13.4)	299 (24.8)	<.0001
Hip Fracture	112 (2.2)	119 (8.1)	<.0001
BMI (Kg/m^2)			<.0001
<18.5	81 (1.5)	35 (2.5)	
18.5<25	1432 (30.7)	388 (28.4)	

25<30	1757 (40.6)	416 (32.9)	
30<35	788 (18.7)	268 (21.0)	
>35	372 (8.5)	179 (15.2)	
Depression	433 (9.2)	354 (28.0)	<.0001
Any LEFL	2886 (65.7)	1113 (83.5)	<.0001
ADL Disability	208 (4.4)	485 (35.8)	<.0001
Grip total (Kg, Mean ± SD)			<.0001
Male	33.3 (12.6)	22.5 (14.1)	
Female	20.1 (8.2)	13.7 (9.1)	
Walk total (Seconds, Mean ± SD)	3.7 (1.9)	5.7 (5.4)	<.0001

BMI body mass index, SD standard deviation, UEFL upper-extremity functional limitation LEFL lower-extremity functional limitation, ADL activities of daily living

Table 7 presents the descriptive characteristics of the sample at baseline by any lower-extremity functional limitations. The overall prevalence of any lower-extremity functional limitations was 68.9 %. Participants reporting any lower-extremity functional limitations were significantly more likely to be older age, female, Blacks, BMI (25-30 Kg/m^2), reported hypertension, arthritis, dementia, depression, any upper-extremity functional limitations, ADL disability and perform poorer in handgrip strength and walk speed than those without any lower-extremity functional limitations.

Table 7: Descriptive characteristics of the overall sample by any lower extremity functional limitations among American older adults at baseline (N=5,716).

Predictor variables	Without any Lower Extremity Functional Limitations N (%)	With any Lower Extremity Functional Limitations N (%)	P-Value
Total	1717 (31.1)	3999 (68.9)	
Age at baseline			<.0001

65-74	772 (57.1)	1747 (57.7)	
75-84	733 (35.5)	1559 (32.2)	
85 +	212 (7.4)	693 (10.1)	
Gender (Female)	1118 (65.3)	2105 (50.2)	<.0001
Marital Status (Married)	910 (57.6)	2062 (58.8)	0.461
Race/Ethnicity			0.042
Whites	1309 (86.9)	2846 (84.6)	
Blacks	315 (6.8)	918 (8.7)	
Hispanics	93 (6.3)	235 (6.7)	
Education Status			<.0001
1-8th grade	138 (7.2)	478 (9.2)	
8th- 12th grade	232 (11.3)	578 (11.4)	
High School	899 (54.5)	1858 (47.4)	
Bach/MS degree	448 (27.0)	1085 (32.0)	
Sleep Complaints			
Trouble Sleep	750 (43.1)	1715 (41.2)	0.233
Sleep over	838 (47.9)	1793 (41.6)	<.0001
Sleep med	352 (21.7)	842 (21.9)	0.861
Comorbid Conditions			
Heart attack	221 (12.2)	607 (13.8)	0.138
Stroke	142 (7.5)	428 (8.9)	0.101
Hypertension	1189 (67.0)	2640 (61.7)	0.0008
Arthritis	1023 (60.4)	2125 (49.7)	<.0001
Diabetes	424 (23.7)	992 (22.6)	0.419
Cancer	465 (26.7)	1042 (26.4)	0.847
Dementia	19 (0.8)	117 (2.2)	0.0002
Lung Disease	240 (14.4)	644 (15.9)	0.221
Hip Fracture	53 (2.9)	178 (3.3)	0.517
BMI (Kg/m^2)			<.0001
<18.5	19 (0.9)	97 (2.1)	
18.5<25	461 (24.9)	1359 (32.7)	
25<30	647 (37.2)	1526 (40.2)	
30<35	387 (24.2)	669 (16.8)	
>35	203 (12.8)	348 (8.2)	
Depression	194 (10.7)	593 (13.4)	0.01
Any UEFL	173 (9.4)	1113 (21.6)	<.0001
ADL Disability	102 (5.8)	591 (11.8)	<.0001
Grip total (Kg, Mean ± SD)			<.0001
Male	30.1 (13.2)	32.4 (13.3)	
Female	19.1 (8.6)	17.7 (9.1)	
Walk total (Seconds, Mean ± SD)	3.8 (1.8)	4.2 (3.6)	<.0001

BMI body mass index, SD standard deviation, UEFL upper-extremity functional limitation, ADL activities of daily living

Table 8 presents the descriptive characteristics of the sample at baseline by ADL disability. The overall prevalence of ADL disability was 9.9 %. Participants reporting any ADL disability were significantly more likely to be older age, female, Blacks and Hispanics, BMI (25-30 Kg/m^2), reported more comorbid conditions, depression, sleep complaints, any ULE functional limitations, and perform poorer in handgrip strength and walk speed than those without any ADL disability.

Table 8: Descriptive characteristics of the overall sample by ADL disability among Americans older adults at baseline (N=5,716).

Predictor variables	**No ADL Disability N (%)**	**ADL Disability N (%)**	**P-Value**
Total	5023 (90.1)	693 (9.9)	
Age at baseline			<.0001
65-74	2302 (58.8)	217 (45.3)	
75-84	2022 (33.1)	270 (35.0)	
85 +	699 (8.1)	206 (19.7)	
Gender (Female)	2759 (53.8)	464 (64.5)	<.0001
Marital Status (Married)	2623 (58.2)	349 (59.9)	0.446
Race/Ethnicity			<.0001
Whites	3725 (86.4)	430 (75.7)	
Blacks	1049 (7.8)	184 (10.5)	
Hispanics	249 (5.8)	79 (13.8)	
Education Status			<.0001
1-8th grade	475 (7.5)	141 (17.9)	
8th- 12th grade	681 (11.0)	129 (15.5)	
High School	2449 (49.8)	308 (47.7)	
Bach/MS degree	1418 (31.7)	115 (18.9)	
Sleep Complaints			
Trouble Sleep	2071 (40.1)	394 (57.3)	<.0001

Sleep over	2214 (41.7)	417 (60.2)	<.0001
Sleep med	958 (20.4)	236 (35.5)	<.0001
Comorbid Conditions			
Heart attack	675 (12.5)	153 (20.5)	<.0001
Stroke	417 (7.4)	153 (19.1)	<.0001
Hypertension	3279 (61.8)	550 (78.0)	<.0001
Arthritis	2625 (50.8)	523 (73.4)	<.0001
Diabetes	1148 (21.1)	268 (40.0)	<.0001
Cancer	1301 (26.0)	206 (31.2)	0.011
Dementia	72 (1.2)	64 (7.3)	<.0001
Lung Disease	715 (14.4)	169 (24.9)	<.0001
Hip Fracture	147 (2.4)	84 (10.5)	<.0001
BMI (Kg/m^2)			<.0001
<18.5	92 (1.6)	24 (3.0)	
18.5<25	1631 (30.9)	189 (24.3)	
25<30	1943 (39.8)	230 (34.1)	
30<35	912 (18.8)	144 (21.8)	
>35	445 (8.9)	106 (16.8)	
Depression	573 (2.4)	214 (31.3)	<.0001
Any UEFL	801 (12.6)	485 (63.9)	<.0001
Any LEFL	3408 (67.4)	591 (81.6)	<.0001
Grip total (Kg, Mean ± SD)	32.7 (12.9)	22.6 (13.8)	<.0001
Male	19.0 (8.6)	13.3 (9.0)	
Female	3.8 (2.4)	6.0 (6.1)	
Walk total (seconds, Mean ± SD)	3.2 (12.9)	2.6 (13.8)	<.0001

UEFL upper-extremity functional limitation *LEFL* lower extremity functional limitation

Figure 17 presents the prevalence of the any upper-extremity functional limitations by pain over 6 years of follow up. The prevalence of any upper-extremity functional limitations ranged from 28.7% in wave 1 to 26.9% in wave 6 among those with pain. The prevalence of any upper-extremity functional limitations ranged from 11.1% at baseline to 14.3% in wave 6 among those without pain.

Figure 17: Prevalence of any upper-extremity functional limitations by pain over 6-years of follow-up.

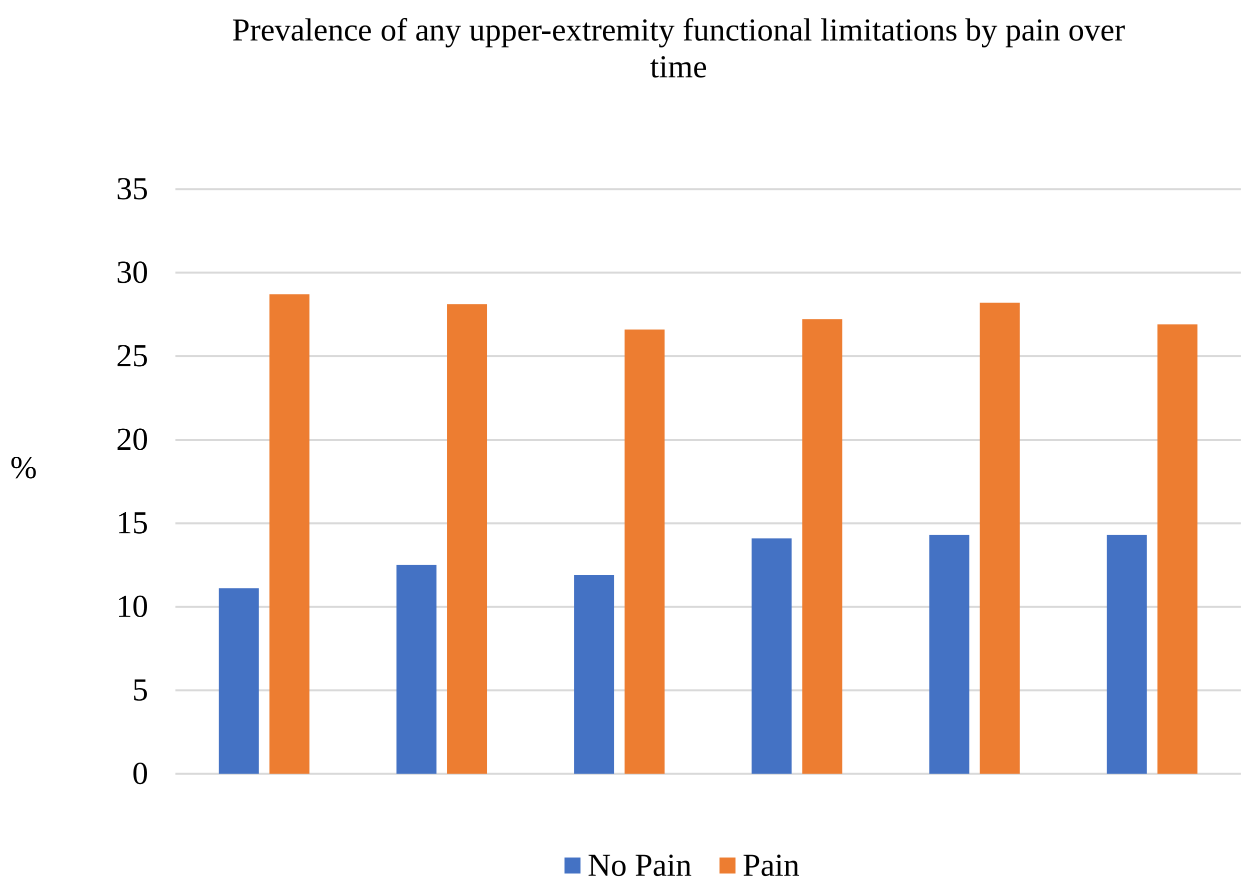


Figure 18 presents the prevalence of the any lower extremity functional limitations by pain over 6 years of follow up. The prevalence of any lower extremity functional limitations ranged from 67.5 % in wave 1 to 70.4 % in wave 6 among those with pain. The prevalence of any upper-extremity functional limitations ranged from 72.2 % at baseline to 50.6 % in wave 6 among those without pain.

Figure 18: Prevalence of any lower extremity functional limitations by pain over 6-years of follow-up.

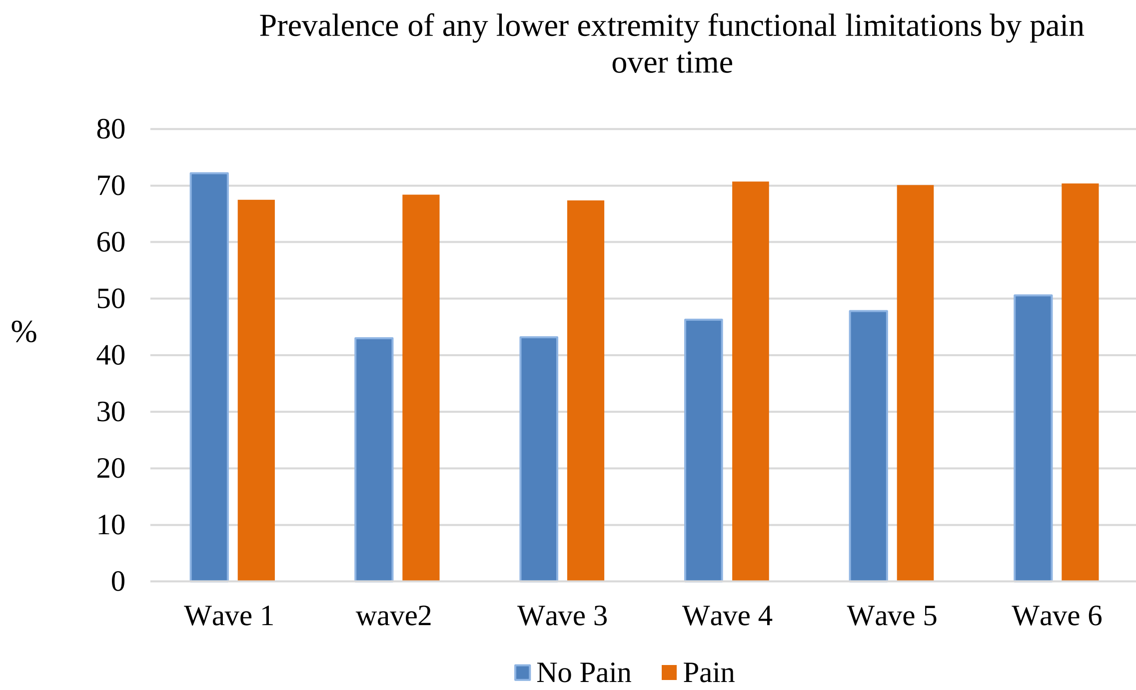
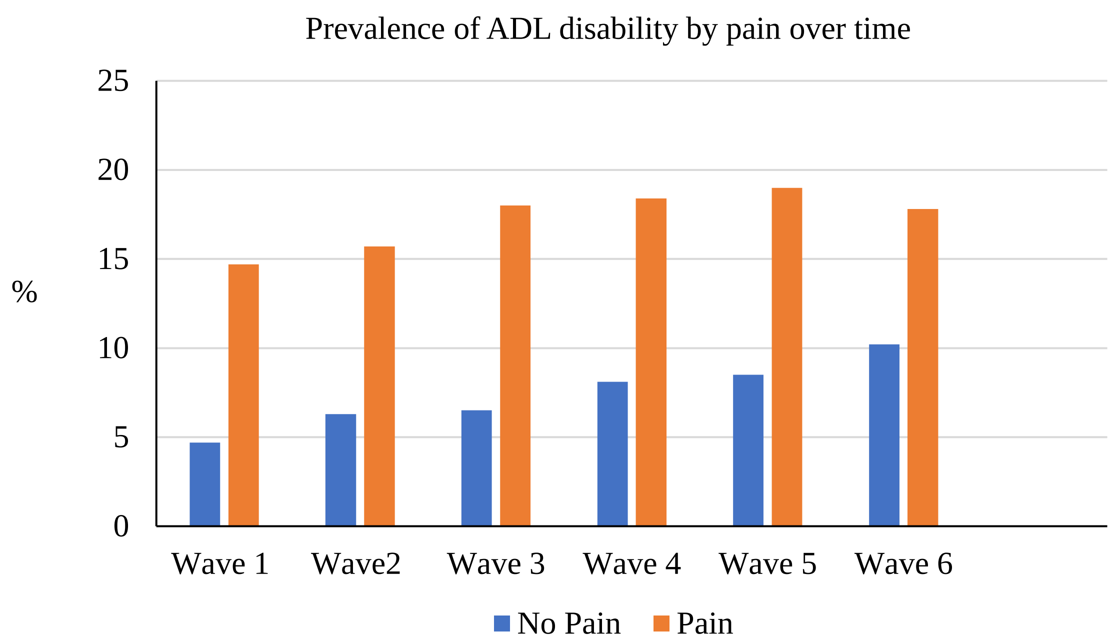


Figure 19 presents the prevalence of ADL disability by pain over 6 years of follow up. The prevalence of ADL disability ranged from 14.7 % in wave 1 to 17.8 % in wave 6 among those with pain. The prevalence of ADL disability ranged from 4.7 % at baseline to 10.2 % in wave 6 among those without pain.

Figure 19: Prevalence of ADL disability by pain over 6-years of follow-up.



RESULTS FOR LONGITUDINAL ANALYSES

Table 9 presents the results of the General Estimation Equation model for any upper-extremity functional limitations as a function of pain among those who reported no upper-extremity functional limitations at baseline over 6-Years of follow-up. Two models were performed. Model 1 included sociodemographic variables (age, gender, marital status, education and race) and pain. In Model 2, comorbid conditions were added along with the variables in model 1. Model 1 shows that per year of follow-up participants had an OR of 1.17 (95 % CI 1.13-1.22) of reporting any upper-extremity functional limitations, and those with pain had an odds ratio of 2.30 (95 % CI 2.02-2.61) of reporting any upper-extremity functional limitations over time. In Model 2, after controlling for comorbidities, pain remained a significant predictor of any upper-extremity functional limitations (OR 1.90, 95% CI 1.66-2.16). Those aged 75 and older, being female participants, non-Hispanic blacks, and Hispanics were also predictor factors of any upper-extremity functional limitations. Married participants and those with higher education were less likely to report any upper-extremity functional limitations over time.

Table 9: General Estimation Equation models for any upper-extremity functional limitations as a function of pain among those without upper-extremity functional limitations at baseline over 6-years of follow-up (N=4,430).

Predictor variables	**Model 1** **OR (95%CI)**	**Model 2** **OR (95% CI)**
Time (years)	1.17 (1.13-1.22)	1.13 (1.09-1.17)
Age at baseline		
65-74	Reference	Reference
75-84	2.44 (2.05-2.89)	2.41 (2.02-2.86)
85 +	5.32 (4.24-6.68)	5.59 (4.44-7.03)
Gender (Female)	1.61(1.36-1.90)	1.59 (1.34-1.88)
Marital Status (Married)	0.75 (0.64-0.89)	0.79 (0.67-0.93)
Education Status		
1-8th grade	Reference	Reference
8th- 12th grade	0.80 (0.59-1.10)	0.78 (0.56-1.07)
High School	0.64 (0.48-0.84)	0.65 (0.49-0.86)
Bach/MS degree	0.41 (0.30-0.55)	0.44 (0.32-0.60)
Race/Ethnicity		
Whites	Reference	Reference
NHB	1.62 (1.34-1.96)	1.49 (1.23-1.80)
Hispanics	1.80(1.26-2.55)	1.71 (1.16-2.52)
Pain	2.30 (2.02-2.61)	1.90 (1.66-2.16)
Comorbid Conditions		1.55 (1.45-1.65)

OR odds ratio, *CI* confidence interval, *NHB* Non-Hispanic Blacks

Table 10 presents the results of the General Estimation Equation models testing for the mediating effect of depression on any UEFL among those without any UEFL at baseline over 6-years of follow-up. In model 1, the OR of any UEFL as a function of pain was 2.30 (95% CI 2.02-2.61). In model 2, the OR of any UEFL was 3.04 (95% CI 2.59-3.58) as a function of depression. In model 3, both pain and depression were entered in the equation. The OR of any UEFL as a function of pain was 2.18 (95% CI 1.91-2.48) and as a function of depression was 2.73 (95% CI 2.32-3.21). The percent reduction in odds ratio of any UEFL in pain after adding depression was 9.2 %. Depression and pain remained as significant predictors of any UEFL after controlling for all covariates (1.83, 95% CI 1.60-2.08 and 2.45, 95% CI 2.09-2.89, respectively). The relationship between pain and any upper extremity functional limitation was partially mediated by depression.

Table 10: General Estimation Equation models testing the mediating effect of depression between pain and any UEFL among those without any UEFL at baseline over 6-years of follow-up (N=4,430).

Predictor variables	**Model 1 OR (95%CI)**	**Model 2 OR (95% CI)**	**Model 3 OR (95% CI)**	**Model 4 OR (95% CI)**
Time (years)	1.17 (1.13-1.22)	1.18 (1.14-1.22)	1.17 (1.13-1.21)	1.13 (1.09-1.18)
Age at baseline				
65-74	Reference	Reference	Reference	Reference
75-84	2.44 (2.05-2.89)	2.36 (1.98-2.80)	2.41 (2.03-2.86)	2.38 (2.00-2.83)
85 +	5.32 (4.24-6.68)	5.16 (4.10-6.48)	5.44 (4.32-6.85)	5.67 (4.49-7.15)
Gender (Female)	1.61(1.36-1.90)	1.79 (1.52-2.11)	1.67 (1.42-1.98)	1.65 (1.39-1.95)
Marital Status (Married)	0.75 (0.64-0.89)	0.82 (0.70-0.97)	0.79 (0.67-0.93)	1.17 (1.06-1.28)
Education Status				
1-8th grade	Reference	Reference	Reference	Reference
8th- 12th grade	0.80 (0.59-1.10)	0.84 (0.61-1.14)	0.82 (0.60-1.12)	0.80 (0.58-1.10)
High School	0.64 (0.48-0.84)	0.68 (0.52-0.90)	0.67 (0.51-0.88)	0.68 (0.51-0.91)
Bach/MS degree	0.41 (0.30-0.55)	0.45 (0.34-0.61)	0.45 (0.33-0.61)	0.49 (0.36-0.66)
Race/Ethnicity				
Whites	Reference	Reference	Reference	Reference
NHB	1.62 (1.34-1.96)	1.57 (1.30-1.91)	1.58 (1.31-1.91)	1.46 (1.21-1.77)
Hispanics	1.80(1.26-2.55)	1.71 (1.20-2.44)	1.74 (1.21-2.50)	1.68 (1.12-2.50)
Pain	2.30 (2.02-2.61)		2.18 (1.91-2.48)	1.83 (1.60-2.08)
Depression		3.04 (2.59-3.58)	2.73 (2.32-3.21)	2.45 (2.09-2.89)
Comorbid Conditions				1.51 (1.42-1.61)

OR odds ratio, *CI* confidence interval, *NHB* Non-Hispanic Blacks

Table 11 presents the results of the General Estimation Equation model testing the moderating effect of obesity on the relationship between pain and any upper-extremity functional limitations among those without upper-extremity functional limitations at baseline over 6-years of follow. In model 1 the presence of pain and obesity (BMI≥30 Kg/m^2) was predictive of any upper-extremity functional limitation at follow-up (OR 1.86, 95% CI 1.63-2.13 and OR 1.24, 95%CI 1.04-1.46, respectively) after controlling for sociodemographic variables and comorbidities. In model 2, the interaction effect between pain and obesity was non-significant for any upper-extremity functional limitation

Table 11: General Estimation Equation models testing the moderating effect between pain and obesity on any upper-extremity functional limitations among those without upper-extremity functional limitations at baseline over 6-years of follow-up, (N=4,430).

Predictor variables	Model 1 OR (95%CI)	Model 2 OR (95% CI)
Time (years)	1.13 (1.09-1.17)	1.13 (1.09-1.17)
Age at baseline		
65-74	Reference	Reference
75-84	2.39 (2.00-2.86)	2.39 (2.00-2.86)
85 +	5.92 (4.65-7.54)	5.93 (4.65-7.55)
Gender (Female)	1.63 (1.37-1.93)	1.63 (1.37-1.93)
Marital Status (Married)	0.82 (0.69-0.98)	0.82 (0.69-0.98)
Education Status		
1-8th grade	Reference	Reference

8th- 12th grade	0.74 (0.53-1.02)	0.74 (0.53-1.03)
High School	0.65 (0.48-0.87)	0.65 (0.48-0.87)
Bach/MS degree	0.46 (0.34-0.64)	0.46 (0.34-0.64)
Race/Ethnicity		
Whites	Reference	Reference
NHB	1.43 (1.17-1.74)	1.43 (1.17-1.74)
Hispanics	1.48 (1.00-2.19)	1.48 (1.00-2.19)
Comorbid Conditions	1.48 (1.39-1.59)	1.48 (1.39-1.59)
Pain	1.86 (1.63-2.13)	1.84 (1.58-2.15)
Obesity (BMI≥30)	1.24 (1.04-1.46)	1.20 (0.91-1.57)
Pain*Obesity		1.04 (0.77-1.41)

OR odds ratio, CI confidence interval, NHB Non-Hispanic Blacks, BMI body mass index

Table 12 presents the results of the General Estimation Equation models for any lower extremity functional limitations as a function of pain among those without lower extremity functional limitations at baseline over 6-years of follow-up. Two models were performed. Model 1 included sociodemographic variables (age, gender, marital status, education and race) and pain. In Model 2, comorbid conditions were added along with the variables in model 1. The odds ratio of developing any lower extremity functional limitations over time after controlling for all covariates was 0.97 (95% CI 0.94-0.99) in Model 1. The OR of reporting any lower extremity functional limitations as a function of pain was 1.78 (95 % CI 1.51-2.11) in Model 1 and 1.52 (95% CI 1.42-1.63) in Model 2 after controlling for comorbid conditions. Older age, being female, and one or more comorbid conditions were also predictor factors of any lower extremity functional limitations. Being married and those with higher level of education were less likely to report lower extremity functional limitations over time.

Table 12: General Estimation Equation models for any lower extremity functional limitations as a function of pain among those without lower extremity functional limitations at baseline over 6-years of follow-up (N=1,717).

Predictor variables	**Model 1** **OR (95%CI)**	**Model 2** **OR (95% CI)**
Time (years)	1.09 (1.04-1.15)	0.97 (0.94-0.99)
Age at baseline		
65-74	Reference	Reference
75-84	1.34 (1.08-1.68)	1.43 (1.31-1.55)
85 +	1.66 (1.14-2.40)	2.19 (1.89-2.54)
Gender (Female)	1.95 (1.56-2.44)	1.56 (1.43-1.69)
Marital Status (Married)	1.09 (0.88-1.36)	0.90 (0.82-0.98)
Education Status		
1-8th grade	Reference	Reference
8th- 12th grade	1.10 (0.69-1.77)	0.84 (0.69-1.02)
High School	1.00 (0.67-1.50)	0.77 (0.65-0.92)
Bach/MS degree	0.69 (0.45-1.05)	0.58 (0.49-0.70)
Race/Ethnicity		
Whites	Reference	Reference
NHB	0.91 (0.68-1.22)	1.04 (0.93-1.17)
Hispanics	1.15 (0.74-1.81)	1.09 (0.90-1.33)
Pain	1.78 (1.51-2.11)	1.52 (1.42-1.63)
Comorbid Conditions		1.36 (1.31-1.41)

OR odds ratio, *CI* confidence interval, *NHB* Non-Hispanic Blacks

Table 13 presents the results of the General Estimation Equation models testing the mediating effect of depression on the relationship between pain and any lower extremity functional limitations. In model 1, the odds ratio of any lower extremity functional limitations as a function of pain was 1.78 (95% CI 1.51-2.11). In model 2, the odds ratio of any lower-extremity functional limitations as a function of depression was 2.40 (95%

CI 1.75-3.29). In model 3, both pain and depression were added to the equation. The odds ratio of any lower extremity functional limitations as a function of pain was 1.72 (95% CI 1.46-2.04) and as a function of depression was 2.05 (95% CI 1.50-2.82). The percent reduction in odds ratio of any lower extremity functional limitations in pain after adding depression was 7.6 %. Depression and pain remained as significant predictors of any lower extremity functional limitations after controlling for all covariates (OR 2.05, 95% CI 1.50-2.82 and OR 1.57, 95% CI 1.32-1.86), respectively). The relationship between pain and any lower extremity functional limitation was partially mediated by depression. Older age, being female, and comorbid conditions were also predictor factors of any lower extremity functional limitations.

Table 13: General Estimation Equation models testing the mediating effect of depression on the relationship between pain and any lower-extremity functional limitations among those without lower-extremity functional limitations at baseline over 6-years of follow-up (N=1,717).

Predictor variables	**Model 1 OR (95%CI)**	**Model 2 OR (95% CI)**	**Model 3 OR (95% CI)**	**Model 4 OR (95% CI)**
Time (years)	1.09 (1.04-1.15)	1.10 (1.04-1.15)	1.09 (1.03-1.14)	1.06 (1.00-1.11)
Age at baseline				
65-74	Reference	Reference	Reference	Reference
75-84	1.34 (1.08-1.68)	1.31 (1.05-1.64)	1.33 (1.07-1.66)	1.34 (1.07-1.67)
85 +	1.66 (1.14-2.40)	1.67 (1.15-2.42)	1.71 (1.17-2.49)	1.77 (1.20-2.62)
Gender (Female)	1.95 (1.56-2.44)	2.01 (1.60-2.51)	1.97 (1.58-2.47)	2.08 (1.66-2.61)
Marital Status (Married)	1.09 (0.88-1.36)	1.15 (0.93-1.42)	1.11 (0.89-1.38)	1.12 (0.90-1.39)
Education Status				
1-8th grade	Reference	Reference	Reference	Reference

8th- 12th grade	1.10 (0.69-1.77)	1.09 (0.67-1.78)	1.09 (0.67-1.76)	1.05 (0.64-1.69)
High School	1.00 (0.67-1.50)	1.02 (0.67-1.56)	1.01 (0.66-1.53)	1.00 (0.66-1.52)
Bach/MS degree	0.69 (0.45-1.05)	0.72 (0.46-1.11)	0.71 (0.46-1.10)	0.73 (0.47-1.12)
Race/Ethnicity				
Whites	Reference	Reference	Reference	Reference
NHB	0.91 (0.68-1.22)	0.89 (0.66-1.20)	0.87 (0.65-1.17)	0.82 (0.61-1.10)
Hispanics	1.15 (0.74-1.81)	1.05 (0.66-1.66)	1.06 (0.67-1.66)	1.02 (0.65-1.60)
Pain	1.78 (1.51-2.11)		1.72 (1.46-2.04)	1.57 (1.32-1.86)
Depression		2.40 (1.75-3.29)	2.23 (1.62-3.06)	2.05 (1.50-2.82)
Comorbid Conditions				1.35 (1.22-1.49)

OR odds ratio, *CI* confidence interval, *NHB* Non-Hispanic Blacks

Table 14 presents the results of the General Estimation Equation models testing the moderating effect of obesity on the relationship between pain and any lower extremity functional limitations among those without lower extremity functional limitations at baseline over 6-years of follow up. In model 1, pain and obesity (BMI≥ 30 Kg/m^2) were predictors of any lower-extremity functional limitations at follow-up (OR 1.60, 95% CI 1.35-1.91 and OR 1.93, 95% CI 1.54-2.42, respectively). In model 2, an interaction term between pain and obesity was added in the equation and no significant interaction effect was found.

Table 14: General Estimation Equation models testing the moderating effect of obesity on the relationship between pain and obesity on any lower extremity functional limitations among those without lower extremity Functional Limitations at baseline over 6-years of follow-up (N=1,717).

Predictor variables	**Model 1** **OR (95%CI)**	**Model 2** **OR (95% CI)**
Time (years)	1.06 (1.00-1.12)	1.06 (1.00-1.11)

Age at baseline		
65-74	Reference	Reference
75-84	1.54 (1.23-1.94)	1.55 (1.23-1.95
85 +	2.12 (1.44-3.14)	2.12 (1.44-3.13)
Gender (Female)	2.23 (1.77-2.80)	2.23 (1.77-2.81)
Marital Status (Married)	1.15 (0.92-1.43)	1.15 (0.92-1.44)
Education Status		
1-8th grade	Reference	Reference
8th- 12th grade	1.05 (0.67-1.75)	1.09 (0.67-1.76)
High School	0.93 (0.62-1.41)	0.94 (0.62-1.42)
Bach/MS degree	0.66 (0.43-1.01)	0.66 (0.43-1.01)
Race/Ethnicity		
Whites	Reference	Reference
NHB	0.80 (0.59-1.08)	0.80 (0.59-1.09)
Hispanics	1.11 (0.70-1.77)	1.12 (0.70-1.78)
Comorbid Conditions	1.34 (1.21-1.49)	1.34 (1.21-1.49)
Pain	1.60 (1.35-1.91)	1.49 (1.22-1.83)
Obesity (BMI≥30)	1.93 (1.54-2.42)	1.70 (1.27-2.27)
Pain * Obesity		1.28 (0.89-1.84)

OR odds ratio, *CI* confidence interval, *NHB* Non-Hispanic Blacks *BMI* body mass index

Table 15 presents the results of the General Estimation Equation model for any ADL disability as a function of pain among those without ADL disability at baseline over 6-years of follow-up. Two models were performed. Model 1 included sociodemographic variables (age, gender, marital status, education and race/ethnicity) and pain. In Model 2, comorbid conditions were entered along with the variables in Model 1. The odds ratio of becoming ADL disabled over time was 1.22 (95% CI 1.18-1.26) in Model 1 and 1.18 (95% CI 1.13-1.22) in Model 2. The odds ratio of any ADL disability as a function of pain was 2.32 (95% CI 1.95-2.55) in Model 1 and 1.82 ((95% CI 1.58-2.09) in Model 2. Older age, being female, being married, and comorbid conditions were also predictor factors of any ADL disability over time. Participants with higher level of education were less likely to report ADL disability over time.

Table 15: General Estimation Equation models for any ADL Disability as a function of pain among those without ADL disability at baseline over 6-years of follow-up (N=5,023).

Predictor variables	**Model 1** **OR (95%CI)**	**Model 2** **OR (95% CI)**
Time (years)	1.22 (1.18-1.26)	1.18 (1.13-1.22)
Age at baseline		
65-74	Reference	Reference
75-84	2.03 (1.70-2.44)	1.96 (1.64-2.35)
85 +	4.11 (3.28-5.15)	4.31 (3.43-5.41)
Gender (Female)	1.23 (1.03-1.46)	1.22 (1.02-1.45)
Marital Status (Married)	1.17 (0.98-1.38)	1.28 (1.08-1.52)
Education Status		
1-8th grade	Reference	Reference
8th- 12th grade	0.81 (0.60-1.09)	0.79 (0.58-1.08)
High School	0.53 (0.41-0.68)	0.56 (0.43-0.72)
Bach/MS degree	0.53 (0.40-0.69)	0.6 (0.46-0.80)
Race/Ethnicity		
Whites	Reference	Reference
NHB	1.26 (1.04-1.53)	1.12 (0.92-1.37)
Hispanics	1.20 (0.84-1.71)	1.03 (0.70-1.50)
Pain	2.23 (1.95-2.55)	1.82 (1.58-2.09)
Comorbid Conditions		1.63 (1.53-1.74)

OR odds ratio, *CI* confidence interval, *NHB* Non-Hispanic Blacks

Table 16 presents the results of the General Estimation Equation models testing the mediating effect of depression on the relationship between pain and ADL disability. In model 1, the odds ratio of ADL disability as a function of pain was 2.23 (95% CI 1.95-

2.55). In model 2, the odds ratio of ADL disability as a function of depression was 3.26, (95% CI 2.81-3.79). In model 3, both pain and depression were added to the equation. The odds ratio of ADL disability as a function of pain was 2.06 (95% CI 1.80-2.36) and as a function of depression was 2.96 (95% CI 2.55-3.44). The percent reduction in odds ratio of ADL disability in pain after adding depression was 13.8 %. Depression and pain remained as significant predictors of ADL disability after controlling for all covariates (OR 2.63, 95% CI 2.25-3.07 and OR 1.72, 95% CI 1.49-1.97), respectively. The mediating effect of depression on the relationship between pain and ADL disability was partially mediated. Older age, being female, being married and one or more comorbid conditions were also predictor factors of ADL disability.

Table 16: General Estimation Equation models testing the mediating effect of depression on the relationship between pain and ADL disability among those without ADL disability at baseline over 6-years of follow-up (N=5,023).

Predictor variables	Model 1 OR (95%CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)
Time (years)	1.22 (1.18-1.26)	1.23 (1.18-1.27)	1.22 (1.18-1.27)	1.18 (1.14-1.23)
Age at baseline				
75-84	2.03 (1.70-2.44)	1.96 (1.64-2.36)	1.99 (1.66-2.38)	1.92 (1.60-2.30)
85 +	4.11 (3.28-5.15)	3.96 (3.16-4.97)	4.12 (3.29-5.17)	4.29 (3.41-5.40)
Gender (Female)	1.23 (1.03-1.46)	1.33 (1.13-1.58)	1.25 (1.05-1.48)	1.24 (1.04-1.47)
Marital Status (Married)	1.17 (0.98-1.38)	1.25 (1.05-1.49)	1.23 (1.04-1.47)	1.33 (1.12-1.58)
Education Status				
1-8th grade	Reference	Reference	Reference	Reference
8th- 12th grade	0.81 (0.60-1.09)	0.82 (0.61-1.12)	0.82 (0.61-1.12)	0.81 (0.59-1.11)
High School	0.53 (0.41-0.68)	0.56 (0.43-0.73)	0.57 (0.44-0.74)	0.59 (0.45-0.78)

Bach/MS degree	0.53 (0.40-0.69)	0.58 (0.44-0.77)	0.60 (0.46-0.80)	0.69 (0.52-0.92)
Race/Ethnicity				
Whites	Reference	Reference	Reference	Reference
NHB	1.26 (1.04-1.53)	1.21 (1.00-1.48)	1.21 (1.00-1.48)	1.09 (0.89-1.33)
Hispanics	1.20 (0.84-1.71)	1.10 (0.76-1.60)	1.11 (0.77-1.61)	0.96 (0.64-1.45)
Pain	2.23 (1.95-2.55)		2.06 (1.80-2.36)	1.72 (1.49-1.97)
Depression		3.26 (2.81-3.79)	2.96 (2.55-3.44)	2.63 (2.25-3.07)
Comorbid Conditions				1.58 (1.48-1.69)

OR odds ratio, CI confidence interval, NHB Non-Hispanic Black

Table 17 presents the results of the General Estimation Equation models testing the moderating effect of obesity on the relationship between pain and ADL disability among those without ADL disability at baseline over 6-years of follow up. In model 1, pain and obesity (BMI $\geq$ 30 Kg/m^2) were predictors of ADL disability at follow-up (OR 1.87, 95% CI 1.62-2.16 and OR 1.10, 95% CI 0.92-1.31, respectively). In model 2, an interaction term between pain and obesity was added in the equation and no significant interaction effect was found.

Table 17: General Estimation Equation models testing the moderating effect of obesity on the relationship between pain and obesity on ADL disability among those without ADL disability at baseline over 6-years of follow-up (N=5,023)

Predictor variables	Model 1 OR (95%CI)	Model 2 OR (95% CI)
Time (years)	1.17 (1.12-1.22)	1.17 (1.12-1.22)
Age at baseline		
65-74	Reference	Reference
75-84	1.96 (1.62-2.36)	1.96 (1.62-2.36)
85 +	4.47 (3.53-5.65)	4.47 (3.53-5.66)
Gender (Female)	1.21 (1.01-1.45)	1.21 (1.01-1.45)

Marital Status (Married)	1.31 (1.10-1.57)	1.31 (1.10-1.57)
Education Status		
1-8th grade	Reference	Reference
8th- 12th grade	0.79 (0.57-1.08)	0.79 (0.57-1.09)
High School	0.55 (0.42-0.73)	0.56 (0.42-0.73)
Bach/MS degree	0.61 (0.46-0.81)	0.61 (0.46-0.81)
Race/Ethnicity		
Whites	Reference	Reference
NHB	1.08 (0.88-1.33)	1.08 (0.88-1.33)
Hispanics	1.02 (0.70-1.50)	1.02 (0.70-1.50)
Comorbid Conditions	1.63 (1.52-1.74)	1.63 (1.52-1.74)
Pain	1.87 (1.62-2.16)	1.81 (1.53-2.13)
Obesity (BMI≥30)	1.10 (0.92-1.31)	0.99 (0.73-1.33)
Pain*Obesity		1.15 (0.83-1.59)

OR odds ratio, CI confidence interval, NHB Non-Hispanic Blacks

CHAPTER 6

AIM 3 RESULTS: Pain as a Predictor of Frailty over 6-years among American older Adults.

This chapter reports the results for the analyses on the association between pain and frailty in American older adults who were non-frail at baseline. We hypothesized that older adults with pain will be more likely to experience frailty than those without pain and that depression will mediate the relationship between pain and frailty.

Descriptive analysis was conducted and reported as frequency, percent, mean, standard deviation or standard error. Students T-test and Chi-square tests were used to examine the descriptive characteristics of the sample by frailty

General Estimation Equations models with a binomial distribution and logit link was used to estimate the odds ratio of frailty as a function of pain over 6-years. To test for mediation effect of depression on the relationship between pain and frailty four models were performed using the GEE. Model 1 included time and pain. Model 2 included time and depression. Model 3 included time, pain, and depression. Model 4 included all variables (time, pain, sociodemographic, sleep complaints, depression, obesity, comorbidities). To test whether the relation between pain and frailty was mediated by depression, we estimated the percentage of reduction in the odds ratio in models with and without the proposed mediators (i.e., % reduction = [(OR without mediators − OR with mediators/OR without mediators − 1) × 100]).[107]

RESULTS OF DESCRIPTIVE ANALYSES

Table 18 presents the descriptive characteristics of the sample at baseline by frailty phenotype status. The overall prevalence of prefrailty and frailty was 33.3 % and 9 % respectively. Participants with frailty were significantly more likely to be older, female, married, BMI (25-30 Kg/m^2), reported more comorbid conditions, depression, sleep complaints, any ULE functional limitations, ADL disability, and perform poorer in handgrip strength and walk speed than those without frailty.

Table 18: Descriptive characteristics of the sample by frailty status among American older adults at baseline (N=5,019).

Predictor variables	Non-Frail N (%)	Pre-Frail N (%)	Frail N (%)	P-Value
Total	2232 (57.7)	2018 (33.3)	769 (9.0)	
Age at baseline				<.0001
65-74	1128 (67.5)	954 (51.7)	150 (37.6)	
75-84	731 (28.1)	1045 (37.4)	242 (39.6)	
85 +	160 (4.4)	424 (10.9)	185 (22.8)	
Gender (Female)	1050 (50.4)	1379 (56.1)	338 (58.5)	0.0002
Marital Status (Married)	1182 (64.2)	1236 (56.3)	238 (45.9)	<.0001
Race/Ethnicity				<.0001
Whites	1596 (89.1)	1752 (84.9)	361 (77.5)	
Blacks	341 (6.1)	529 (8.2)	168 (12.3)	

Hispanics	82 (4.8)	142 (6.9)	48 (10.2)	
Education Status				<.0001
1-8th grade	118 (4.7)	275 (9.7)	118 (18.2)	
8th- 12th grade	192 (7.7)	359 (12.0)	128 (19.9)	
High School	973 (47.8)	1215 (52.2)	256 (48.8)	
Bach/MS degree	736 (39.8)	574 (26.1)	75 (13.1)	
Sleep Complaints				
Trouble Sleep	720 (34.8)	1064 (42.9)	306 (54.8)	<.0001
Sleep over	699 (32.3)	1193 (48.0)	337 (61.1)	<.0001
Sleep med	287 (15.4)	516 (22.9)	170 (32.5)	<.0001
Comorbid Conditions				
Heart attack	175 (8.3)	383 (14.7)	127 (23.2)	<.0001
Hypertension	1189 (52.3)	1693 (67.9)	432 (73.7)	<.0001
Stroke	101 (4.2)	259 (10.0)	107 (17.8)	<.0001
Arthritis	827 (40.3)	1340 (54.8)	412 (72.0)	<.0001
Diabetes	352 (16.1)	607 (24.4)	206 (37.1)	<.0001
Cancer	490 (24.1)	640 (27.2)	174 (32.0)	0.0022
Dementia	12 (0.49)	55 (1.9)	40 (0.4)	<.0001
Lung Disease	179 (8.9)	392 (16.7)	39 (5.8)	<.0001
Hip Fracture	41 (1.6)	87 (3.2)	54 (8.8)	<.0001
BMI (kg/m2)				<.0001
<18.5		67 (2.7)	32 (5.3)	
18.5<25	706 (33.4)	719 (27.8)	194 (30.7)	
25<30	854 (43.7)	905 (37.2)	174 (31.8)	
30<35	352 (17.5)	455 (20.4)	107 (18.5)	
>35	107 (5.4)	277 (11.9)	7 (13.7)	
Depression	92 (4.2)	335 (13.4)	192 (36.7)	<.0001
Any UEFL	95 (4.0)	480 (16.8)	345 (56.9)	<.0001
Any LEFL	1397 (70.9)	1598 (64.3)	487 (82.8)	<.0001
Grip total (Kg, Mean ± SD)				<.0001
Male	38.7 (7.9)	32.4 (10.1)	24.6 (8.9)	
Female	22.9 (5.3)	20.1 (6.2)	15.2 (6.0)	
Walk total (seconds, Mean ± SD)	3.3 (1.1)	4.3 (2.9)	6.4 (5.6)	<.0001

UEFL upper-extremity functional limitation *LEFL* lower extremity functional limitation, SD standard deviation

Figure 19 presents the percentage of participants for each frailty phenotype components at baseline. A total of 7 % reported exhaustion, 6.7 % low physical activity, 4.6 % shrinking, 4.5 % weakness and 6.1 % slowness.

Figure 20 : Percentage of each frailty phenotype component among American older adults at baseline (N= 5,019)

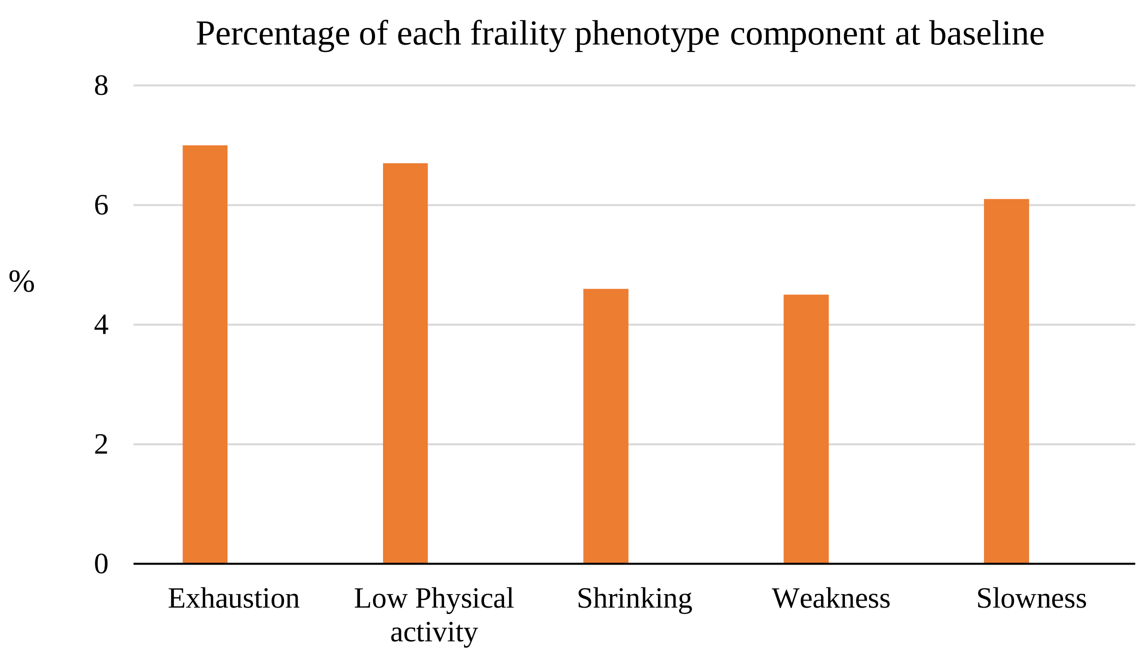
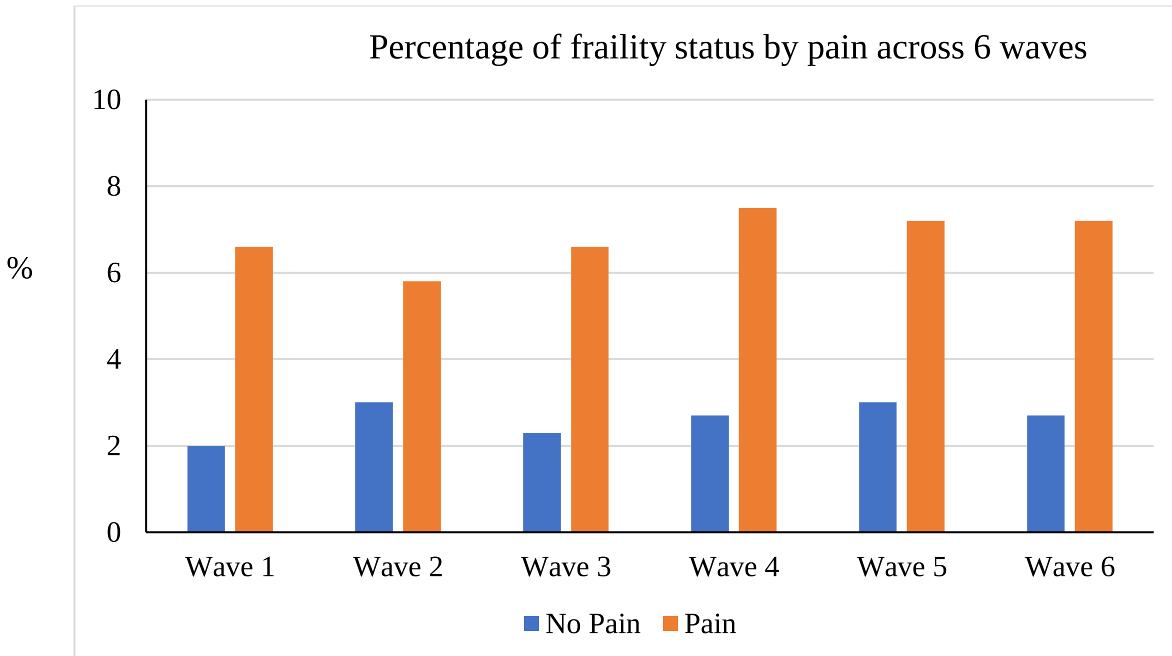


Figure 20 presents the prevalence of frailty status by pain over 6- years of follow up. The prevalence of frailty ranged from 6.6 % at baseline to 7.2 % at wave 6 among those with pain. The prevalence of frailty ranged from 2 % at baseline to 2.7 % at wave 6 among those without pain.

Figure 21 : Prevalence of frailty status among American older adults with pain over 6-years of follow-up.



RESULTS OF LONGITUDINAL ANALYSES

Table 19 presents the results of the GEE models for frailty over 6-years of follow-up as a function of sociodemographic characteristics, comorbid conditions, obesity (BMI≥ 30 Kg/m^2) and depression. The OR for frailty as a function of pain was 1.86 (95% CI 1.60-2.16) over time. Older age, one or more comorbid conditions, and depressive symptoms were factors with high odds ratio of frailty over time. Higher education was predictive of lower odds of frailty over time.

Table 19: General Estimation Equation models for Frailty as a function of Pain among participants who were non-frail at baseline over 6-years of follow-up (N=5,019)

Predictor variables	OR (95% CI)
Time (years)	1.10 (1.06-1.16)
Age at baseline	
65-74	Reference
75-84	1.81 (1.49-2.19)
85 +	3.83 (3.01-4.87)
Gender (Female)	0.90 (0.76-1.08)
Marital Status (Married)	0.84 (0.70-1.00)
Education Status	
1-8^{th} grade	Reference
8th- 12th grade	0.94 (0.69-1.28)
High School	0.77 (0.59-1.01)
Bach/MS degree	0.54 (0.40-0.72)
Race/Ethnicity	
Whites	Reference
NHB	1.09 (0.88-1.34)
Hispanics	1.27 (0.87-1.86)
Comorbid Conditions	1.46 (1.35-1.57)
Obesity (BMI≥30)	0.86 (0.72-1.04)
Depression	2.88 (2.40-3.46)
Pain	1.86 (1.60-2.16)

OR odds ratio, CI confidence interval, BMI body mass index, NHB Non-Hispanic Blacks

Table 20 presents the GEE results for testing the mediating effect of depression on frailty among those without frailty at baseline over 6-years of follow-up. In model 1, the OR of frailty as a function of pain was 2.31 (95% CI 2.01-2.65). In model 2, the OR of frailty was (OR 3.49, 95% CI 2.95-4.13) as a function of depression. In model 3, both pain and depression were entered in the equation. The OR of frailty as a function of pain was 2.17 (95% CI 1.89-2.51) and as a function of depression was 3.16 (95% CI 2.66-3.75). The percent reduction in odds ratio of frailty in pain after adding depression was 10.6 %. Depression and pain remained as significant predictors of frailty after controlling for all covariates (2.85, 95% CI 2.39-3.39 and, 1.84, 95% CI 1.59-2.12 respectively). The relationship between pain and frailty was partially mediated by depression. Older age, and one or more comorbidities were also predictor factors of frailty. Participants with higher level of education were less likely to become frail over time.

Table 20: General Estimation Equation models for testing the mediating effect of depression on the relationship between pain and frailty among those who were non-frail at baseline over 6-years of follow-up (N=5,019).

Predictor variables	**Model 1**	**Model 2**	**Model 3**	**Model 4**
	OR (95%CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Time (years)	1.13 (1.09-1.18)	1.14 (1.10-1.19)	1.13 (1.09-1.18)	1.10 (1.05-1.15)
Age at baseline				
65-74	Reference	Reference	Reference	Reference
75-84	2.04 (1.70-2.45)	1.95 (1.62-2.35)	2.00 (1.66-2.40)	1.89 (1.57-2.28)
85 +	3.84 (3.07-4.81)	3.70 (2.94-4.64)	3.88 (3.09-4.87)	3.93 (3.12-4.94)
Gender (Female)	0.89 (0.75-1.05)	0.98 (0.83-1.15)	0.90 (0.76-1.07)	0.87 (0.73-1.03)

Marital Status (Married)	0.78 (0.65-0.92)	0.86 (0.73-1.02)	0.83 (0.70-0.99)	0.84 (0.70-1.00)
Education Status				
1-8th grade	Reference	Reference	Reference	Reference
8th- 12th grade	1.02 (0.77-1.37)	0.97 (0.73-1.30)	1.00 (0.74-1.35)	1.01 (0.74-1.38)
High School	0.73 (0.57-0.94)	0.73 (0.57-0.94)	0.75 (0.58-0.97)	0.81 (0.62-1.06)
Bach/MS degree	0.48 (0.36-0.64)	0.50 (0.38-0.67)	0.52 (0.39-0.69)	0.59 (0.43-0.79)
Race/Ethnicity				
Whites	Reference	Reference	Reference	Reference
NHB	1.19 (0.97-1.45)	1.17 (0.96-1.44)	1.17 (0.95-1.44)	1.07 (0.87-1.32)
Hispanics	1.44 (1.02-2.03)	1.34 (0.95-1.93)	1.33 (0.93-1.90)	1.23 (0.84-1.79)
Pain	2.31 (2.01-2.65)		2.17 (1.89-2.51)	1.84 (1.59-2.12)
Depression		3.49 (2.95-4.13)	3.16 (2.66-3.75)	2.85 (2.39-3.39)
Comorbid Conditions				1.45 (1.36-1.56)

OR odds ratio, *CI* confidence interval, *NHB* Non-Hispanic Blacks

CHAPTER 7

DISCUSSION

AIM 1: The effect of sociodemographic characteristic, comorbidities, depression, obesity, and sleep complaints on pain over 6-years of follow-up in American older adults.

The purpose of this study was to investigate whether sociodemographic characteristics, comorbidities, depression, obesity, and sleep complaints are predictor factors of pain over 6-years of follow-up among American older adults.

Our findings showed that more than half of the American older adults reported pain in 2011. Participants with arthritis, lung disease, hypertension, hip fracture, cancer and diabetes were significantly more likely to report pain over time. Pain was reported higher among females, married participants and those with higher BMI ($\geq$ 30 Kg/m^2). Older adults in the age group 75-84 reported lower odds of pain over time. Participants with high depressive symptoms and sleep complaints had significantly higher odds of reporting pain over time. There were no significant differences by racial/ethnicity groups and participants education level. This study provides a comprehensive detail on the pain prevalence and predictors factors of pain in the community-dwelling older adults living in the U.S.

The findings of our study showed similar results as reported previously that older adults with comorbidities have higher odds of developing pain over time.[108] Previous literature has shown that almost 65% of older adults have multiple comorbidities and is one of the serious indicator of geriatric medicine.[109] Most of the older adults suffer from four or more comorbid conditions.[110] The relationship between comorbid conditions and self-rated pain has been clearly demonstrated in older adults. However, there might be variation in pain intensity and severity in terms of number and type of comorbid conditions reported in older adults. The emotional distress resulted from comorbidities leads to higher number of Excessive daytime sleepiness (EDS) and awakenings during night in older adults.[111] Also, comorbid conditions are positively associated with the prevalence of sleep disorders, including insomnia, sleep apnea, and restless legs syndrome, which in turn has been shown as an important predictor of pain in older adults.[112]

Consistent with previous studies, we found that older adults with high depressive symptoms had greater risk of reporting pain as compared to those without depression over 6-years of follow-up. Several researchers have shown the association between depressed mood and pain in older adults and vice versa.[113,114] Depressed mood has been shown to be associated with alterations in the central processing of pain, which in turn increases the pain sensitivity in the older adults with pain.[115,116] Given the association between depressive symptoms and pain, early preventive measures, programs to improve social loneliness, should be adopted at early stage to delay the onset of pain in older adults.

Literature has also shown that almost 50% of older adults with sleep disturbances experience pain over time.[117] Our study findings were in accordance with the previous studies showing that the individuals with sleep complaints including insomnia have increased risk of developing chronic pain over time.[118,119] Several mechanisms have been proposed as potential pathways leading to the increased occurrence of pain in persons with sleep problems and vice versa.[120]

The hyperalgesia effects following sleep disturbances might alter the pain endogenous pathways that leads to increased vulnerability to central sensitivity of pain. This association between sleep complaints and pain might be explained better by mechanisms that underlie both conditions. Some studies have shown that altered immune physiology and hypothalamus-pituitary-adrenal (HPA-axis) are related to pain and sleep complaints. [121] It has been shown that normal sleep is associated with reduced muscle tonus, on the other hand disturbed sleep might hinder the muscle recovery process and result in pain.[122]

Finan and colleagues suggest that the sleep disturbances are a stronger predictor of pain than the effect of pain on sleep. However, recent findings from the department of clinical psychology group in Virginia showed that discrepancies in pain might be a better predictor of sleep complaints.[123]

In summary, our findings suggest that there is a complex multilevel association between comorbidities, sleep disturbances and psychological symptoms that might trigger the onset of pain in older adults. There is substantial consensus in the diversity of predictors of pain in older adults. An exhaustive in-depth assessment should be done by physicians when ruling out the causes of persistent pain in older adults. The present study provides evidence in the risk factors of pain in older adults, more innovative and novel approaches should be implemented to reduce the burden of pain and improve the quality of life in older adults. Future studies should focus on considering broader parameters in order to study the epidemiology of pain. Thus, recognition and attention to these factors could lead to improved pain management and quality of life of older adults.

AIM 2: The effect of pain on upper-lower extremity functional limitations and ADL disability over 6-years of follow-up in American older adults.

The purpose of this study was to examine the effect of pain on any ULE functional limitations and ADL disability over 6-years in American older adults who had no functional limitations or ADL disability at baseline.

Our findings showed that participants with pain were 2.3 times more likely to report UE functional limitation, 1.7 times more likely to report LE functional limitation, and 2.2 times more likely to report ADL disability over 6-years of follow-up. The relationship remained significant after adjusting for potentially confounding variables including age, gender, marital status, race/ethnicity (Non-Hispanic Blacks and Hispanics), education, comorbid conditions, obesity (BMI$\geq$30Kg/m^2), and high depressive symptoms. Predictor factors of reporting UE-LE functional limitations over time were participants aged 75 and above, being female, comorbid conditions, obesity, and high depressive symptoms. Similarly, predictor factors of ADL disability were participants aged 75 and above, being female, married, those who reported comorbid conditions, obesity, and high depressive symptoms. Hispanics and Non-Hispanic Blacks were significantly more likely to report UE-LE functional limitation over time as compared to the Non-Hispanic Whites. However, older adults with higher education were less likely to report UE-LE functional limitation and ADL disability over time compared to those with less education.

The findings of our study showed similar results as reported by previous studies. Studies have shown that pain in the upper-extremity is associated with limitations in opening jars and carrying grocery bags.[40,41] Similarly pain in the lower extremity and back reduces the ability to perform daily tasks such as walking one or several blocks, climbing stairs, pushing, pulling, lifting, stooping, jogging one mile, and heavy household work.[4,39] Findings from a cross-sectional survey conducted in community-dwelling older adults with pain reported significantly reduced gait speed and inability to walk 3 blocks, leading to lower extremity disability.[10]

Our findings are somewhat similar to the previous studies that have examined the relationship between pain and disability.[42-44] Findings from the Health Retirement Study showed that participants with overall pain were 1.7 times more likely to develop ADL disability over 10-years of follow-up as compared to those without pain.[47] Peat and colleagues found that pain at multiple sites in the lower extremity is significantly associated with disability.[45] Another study conducted among older Mexicans Americans found that pain on weight bearing was a significant independent predictor of subsequent disability and inability to perform lower extremity function tasks.[46] A cross-sectional study conducted in Canadian seniors found that those with higher pain intensity were two times more likely to report ADL disability than those with lower pain intensity and those with the use of pain medications were 1.6 times more likely to report ADL disability.[73]

Our study examined the longitudinal effect of pain on both ULE functional limitations and disability in a nationally representative sample of American older adults. We analyzed pain as time varying and excluded participants with ULE functional limitations or ADL disability at baseline to capture the effect of pain free of functional limitations or disability at baseline. Our study also showed that the prevalence of UE-LE functional limitations and ADL disability in older adults with pain was much higher compared to those without pain. Also, we found an increasing trend in the prevalence of LE functional limitations over a period of 6-years from 67.5 % to 70.4 % among older adults with pain. This increase is concerning and the reasons for this could be morphological changes associated with aging and prolonged pain over time. However, no increase in the UE functional limitations and ADL disability was reported over time among older adults with pain.

The strong association between pain, functional limitations and ADL disability suggests that it may be part of the same pathophysiological process. The occurrence of pain in this population is at an early age than the occurrence of functional limitation and disablement process, thus suggesting pain as a significant early predictor of functional limitation and disability. This suggests that early evaluation and treatment of pain is an important element in the evaluation of physical functioning in older adults. Also, most of the older adults with pain also have several comorbid conditions such as arthritis, diabetes, hypertension, depression all factors associated with functional limitations and ADL disability.

Previous studies have shown that persistent pain is associated with incidence of suicides among older adults.[124,125] This association between pain and depression could be reciprocal and linked in a causal manner as increase in pain predicting depression and increase in depression predicting pain.[126] Thus, identifying older adults with pain and depression at an early stage could be highly beneficial in order to prevent or delay functional limitations and thus ADL disability in older adults.

As previously published, obesity is also an important predictor of future disability and functional limitations. Rejeski and colleagues examining older adults with knee pain found that obesity is a significant moderator and influences the transitional states of disability in disablement process.[74]. A recent randomized controlled trial conducted on low-income, home-dwelling older adults using the "Community Aging in Place: Advancing Better Living for Elders," CAPABLE data, showed that depression fully mediated the relationship between pain intensity and ADL disability.[75] However, depressive symptoms did not mediate the relationship between pain and ADL disability over time.

In summary, our results indicated that pain is an independent predictor contributing to functional limitations and ADL disability in American older adults. This effect persisted after controlling for socio-demographic factors (age, gender, race, education), physical factors (obesity), psychological factors (depressive symptoms) and comorbid conditions. Our findings suggest that early assessment and proper management of pain may prevent/delay functional limitations and improve the quality of life in this population.

AIM 3: Effect of Pain on Frailty over 6-years of follow-up in American older adults

The purpose of this study was to investigate the effect of pain on becoming frail over 6-years of follow-up among American older adults. Our findings showed that participants who reported pain were 1.86 times more likely to become frail over 6-years of follow-up, after controlling for all covariates. Other predictive factors associated with higher odds of becoming frail over time were participants aged 75 and above, comorbid conditions, and with high depressive symptoms. Participants with higher level of education were less likely to become frail over time.

The findings of our study showed similar results as reported previously using the Concord Health and Ageing in Men Project (CHAMP), and European Male Ageing Study survey. [48-50] Megale and colleagues examined whether pain increases the risk of frailty over time in a sample of 1,705 community dwelling subjects from the CHAMP survey and found that those with chronic pain were at 1.6 times greater risk of developing frailty than those without pain after 5 years of follow-up. [50] Participants in the EMAS study who reported some pain and those who reported chronic widespread pain were 1.5 and 4.3 times more likely, respectively, to become frail after 4 years of follow-up. [48]

However, our findings differ from those reported by Wade and colleagues using the ELSA study, where those with moderate pain and severe pain were 3.1 and 3.8 times more likely, respectively, to become frail over time. [49]

The differences in the results from the ELSA study could be explained due to number of factors. First, each study has different study population characteristics including participants from different region, and diverse features that could explain the difference in the results. Second, the consideration of different confounders in the study. Apart from the sociodemographic, and depressive symptoms they also included lifestyle factors and socioeconomic factors, which could be the reason for the higher odds of frailty among participants with pain. Third reason could be the longer follow up, as they included 8 years of follow-up and that might have led to higher odds of frailty among participants with pain. However, the other two studies had less than 6- years of follow up and reported lower odds of frailty over time compared to our study. Lastly, specific frailty assessment criteria that is used in the study could be different that has led to the differences in the results.

We found that the percent of being pre-frail increased from 25.2% to 30.4 % and being frail increased from 6.6% to 7.4% among those with pain over time. This increase is concerning and the reasons for this are unclear. The association between pain and frailty may be explained by mechanisms that underlie both conditions. It has been shown that pain is associated with weak grip strength [127], reduced gait speed [63] and malnutrition [128], all components of the frailty phenotype.[1] Persistent pain acts as a stressor by triggering the stress mechanism and diminishing physiologic reserves, in turn increasing the risk of developing frailty. [10,51,129]

Previous studies have suggested that pain may led to alterations in the hypothalamic-pituitary-adrenal axis and cellular inflammation that can potentially predisposes the individual to frailty. [130,131] Additionally, older adults are vulnerable to musculoskeletal pain due to progressive age-related pathological changes that impair their ability to cope with pain and eventually predisposes them to a greater risk of adverse health outcomes, comorbidities, functional impairment, disability and frailty. [39,47,132,133] Prevention and early treatment may reduce the burden of pain and delay the onset of frailty in older adults.

In summary, our study establishes that non-frail American older adults with pain are more likely to experience frailty over time than those without pain. This effect persisted after controlling for socio-demographic factors (age, gender, race, education, physical factors (obesity), psychological factors (depressive symptoms) and comorbid conditions. Our findings suggest that early assessment and proper management of pain may reduce frailty and improve the quality of life in this population.

CONCLUSION

This study shows that more than 50% of the American older adults suffer from pain over 6- years of follow up and out of those reporting pain almost 60% were taking pain medications. The most prevalent pain location was knee (41.3%), followed by back (37.4%) and shoulder (32.3%). Comorbidities, obesity, sleep complaints and depression were significant predictors of pain over time. Older adults with pain were 2.3 times more likely to report UE functional limitations, 1.7 times more likely to report LE functional limitations, 2.2 times more likely to report ADL disability, and 1.8 times more likely to become frail after controlling for all covariates. Depression partially mediated the relationship between pain and ULE functional limitations, pain and ADL disability, and pain and frailty. Obesity was not a significant moderator in the relationship between pain and ULE functional limitations, and pain and ADL disability. Our findings suggest that early assessment and proper management of pain may improve functional limitations and delay the risk of developing disability and frailty at later age.

In conclusion, current study examined the factors associated with the pain and how pain is related to the disablement process and frailty using a nationally representative sample of older adults in the US. Findings from this study will 1) help physicians to identify predictors of pain to implement preventive strategies to reduce the burden of pain in this population; 2) identify which pain locations are more affected; 3) determined the degree of the relationship between pain and the disablement process; 4) determined the degree of the relationship between pain and frailty; and 5) provided knowledge to help physicians/clinicians to identify targets for intervention and design better pain management protocols to prevent early disability and frailty among older adults.

LIMITATIONS OF THE STUDY

Our study has several imitations. First, the assessment of pain and comorbid conditions, functional limitations and ADL disability was self-reported. This may lead to recall or response bias as compared to physician assessment. However, population-based studies showed that self-reported data for pain have been shown to be robust, particularly for dichotomous measures such as pain versus no pain. [134] Second, the information on pain frequency, intensity, and pain medications (over the counter or prescribed) was not collected in this data. Third, the participants excluded from the study were less healthy compared to those included, which might have led to the underestimation of functional limitations, disability and frailty. Fourth, attrition, due to death or loss to follow-up is a common problem in longitudinal studies. However, to account for this, general estimation equations was used, and all participants remained in the analysis until their last interview date. Fifth, our study includes older adults living in the U.S., so our findings cannot be generalized to the older adults living in other countries.

STRENGTHS OF THE STUDY

Despite these limitations, this study has several strengths. This study examines the predictors of pain, and the effect of pain on functional limitations, disability and frailty using the nationally representative sample of Medicare beneficiaries living in the U.S. The current study involved a longitudinal data analysis (6-years follow up) and included both male and female participants who were non-disabled and non-frail at baseline to examine the effect of pain among participants free of functional limitations, ADL disability, and frailty. We also analyzed the variables as time varying for comorbid conditions, depression, obesity, and sleep complaints.

FUTURE RESAERCH IMPLICATIONS

Our findings highlight the need for future researchers to consider various biological, lifestyle and socio-economic factors into consideration that play a role in disability and frailty in aging population when examining pain. Also, future studies should include psychological and social factors of frailty in addition to the physical components, hence facilitating the intervention of various effect of different factors on several frailty domains. We also recommend that future studies should assess the effect of pain on frailty using assessment tools that are not restricted to physical, social and psychological factors to assess frailty in community-dwelling older adults. Several studies have already demonstrated high validity and reliability of these tools in this population.[135,136]

With the recent federal rule restricting prescribing of opioid analgesics, there is a need to facilitate access of those living with pain to evidence-based non-opioid modalities like physical therapy, occupational therapy, joint injections and integrative care. These finding suggests a need for development of policy to increase access to appropriate interventions for optimal management of common comorbid conditions (e.g., diabetes, arthritis, and depression shown previously to be associated with pain among older adults. Understanding the complex relationship between pain, the disablement process and frailty will help physicians in designing appropriate intervention programs and hence improve the quality of life in older adults. Our findings highlight the Healthy people 2020 objective of lowering pain burden in older adults. Thus, increasing awareness about pain in older adults is highly important in order to lower adverse health outcomes, reduce institutalizations, promote independence, better allocation of health care resources, and lower the burden of pain in this population.

REFERENCES

1. Fried LP, Tangen CM, Walston J, et al. Frailty in Older AdultsEvidence for a Phenotype. *The Journals of Gerontology: Series A.* 2001;56(3):M146-M157.

2. Gaskin DJ, Richard P. The economic costs of pain in the United States. *The journal of pain : official journal of the American Pain Society.* 2012;13(8):715-724.

3. Huisstede BM, Bierma-Zeinstra SM, Koes BW, Verhaar JA. Incidence and prevalence of upper-extremity musculoskeletal disorders. A systematic appraisal of the literature. *BMC musculoskeletal disorders.* 2006;7:7.

4. Covinsky KE, Lindquist K, Dunlop DD, Yelin E. Pain, functional limitations, and aging. *Journal of the American Geriatrics Society.* 2009;57(9):1556-1561.

5. Lillie AK, Read S, Mallen C, Croft P, McBeth J. Musculoskeletal pain in older adults at the end-of-life: a systematic search and critical review of the literature with priorities for future research. *BMC palliative care.* 2013;12(1):27.

6. Duenas M, Ojeda B, Salazar A, Mico JA, Failde I. A review of chronic pain impact on patients, their social environment and the health care system. *Journal of pain research.* 2016;9:457-467.

7. Ludwig C, Luthy C, Allaz AF, Herrmann FR, Cedraschi C. The impact of low back pain on health-related quality of life in old age: results from a survey of a

large sample of Swiss elders living in the community. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society.* 2018;27(5):1157-1165.

8. Steglitz J, Buscemi J, Ferguson MJ. The future of pain research, education, and treatment: a summary of the IOM report "Relieving pain in America: a blueprint for transforming prevention, care, education, and research". *Translational behavioral medicine.* 2012;2(1):6-8.

9. Andersson HI, Ejlertsson G, Leden I, Rosenberg C. Chronic pain in a geographically defined general population: studies of differences in age, gender, social class, and pain localization. *The Clinical journal of pain.* 1993;9(3):174-182.

10. Shega JW, Dale W, Andrew M, Paice J, Rockwood K, Weiner DK. Persistent pain and frailty: a case for homeostenosis. *Journal of the American Geriatrics Society.* 2012;60(1):113-117.

11. The management of persistent pain in older persons. *Journal of the American Geriatrics Society.* 2002;50(6 Suppl):S205-224.

12. Dahlhamer J, Lucas J, Zelaya, C, et al. Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults — United States, 2016. MMWR Morb Mortal Wkly Rep 2018;67:1001–1006. .

13. Von Korff M, Scher AI, Helmick C, et al. United States National Pain Strategy for Population Research: Concepts, Definitions, and Pilot Data. *The journal of pain : official journal of the American Pain Society.* 2016;17(10):1068-1080.

14. Smith BH, Elliott AM, Chambers WA, Smith WC, Hannaford PC, Penny K. The impact of chronic pain in the community. *Family practice.* 2001;18(3):292-299.

15. Blyth FM, March LM, Brnabic AJ, Jorm LR, Williamson M, Cousins MJ. Chronic pain in Australia: a prevalence study. *Pain.* 2001;89(2-3):127-134.

16. Karjalainen M, Saltevo J, Tiihonen M, Haanpaa M, Kautiainen H, Mantyselka P. Frequent pain in older people with and without diabetes - Finnish community based study. *BMC geriatrics.* 2018;18(1):73.

17. Jonsson AC, Lindgren I, Hallstrom B, Norrving B, Lindgren A. Prevalence and intensity of pain after stroke: a population based study focusing on patients' perspectives. *Journal of neurology, neurosurgery, and psychiatry.* 2006;77(5):590-595.

18. Mailis-Gagnon A, Nicholson K, Yegneswaran B, Zurowski M. Pain characteristics of adults 65 years of age and older referred to a tertiary care pain clinic. *Pain research & management.* 2008;13(5):389-394.

19. Denard PJ, Holton KF, Miller J, et al. Back pain, neurogenic symptoms, and physical function in relation to spondylolisthesis among elderly men. *The spine journal : official journal of the North American Spine Society.* 2010;10(10):865-873.

20. Donald F, Esdaile JM, Kimoff JR, Fitzcharles MA. Musculoskeletal complaints and fibromyalgia in patients attending a respiratory sleep disorders clinic. *The Journal of rheumatology.* 1996;23(9):1612-1616.

21. McBeth J, Macfarlane GJ, Hunt IM, Silman AJ. Risk factors for persistent chronic widespread pain: a community-based study. *Rheumatology (Oxford, England).* 2001;40(1):95-101.

22. Ohayon MM, Stingl JC. Prevalence and comorbidity of chronic pain in the German general population. *Journal of psychiatric research.* 2012;46(4):444-450.

23. Fillingim RB, King CD, Ribeiro-Dasilva MC, Rahim-Williams B, Riley JL, 3rd. Sex, gender, and pain: a review of recent clinical and experimental findings. *The journal of pain : official journal of the American Pain Society.* 2009;10(5):447-485.

24. End Women's Pain. Chronic pain in women: neglect, dismissal, and discrimination. June 2011. .

25. Green CR, Hart-Johnson T, Loeffler DR. Cancer-related chronic pain: examining quality of life in diverse cancer survivors. *Cancer.* 2011;117(9):1994-2003.

26. Institute of Medicine. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Washington, DC: The National Academies Press; 2011.

27. National Research Council (US) Panel on DHHS Collection of Race and Ethnic Data. Eliminating health disparities: measurement and data needs. Ver Ploeg M, Perrin E, eds. Washington, DC: National Academies Press; 2004.

28. Riskowski JL. Associations of socioeconomic position and pain prevalence in the United States: findings from the National Health and Nutrition Examination Survey. *Pain medicine (Malden, Mass).* 2014;15(9):1508-1521.

29. Hoftun GB, Romundstad PR, Rygg M. Association of parental chronic pain with chronic pain in the adolescent and young adult: family linkage data from the HUNT Study. *JAMA pediatrics.* 2013;167(1):61-69.

30. Kato K, Sullivan PF, Evengard B, Pedersen NL. Importance of genetic influences on chronic widespread pain. *Arthritis and rheumatism.* 2006;54(5):1682-1686.

31. Higgins KS, Birnie KA, Chambers CT, et al. Offspring of parents with chronic pain: a systematic review and meta-analysis of pain, health, psychological, and family outcomes. *Pain.* 2015;156(11):2256-2266.

32. Wright LJ, Schur E, Noonan C, Ahumada S, Buchwald D, Afari N. Chronic pain, overweight, and obesity: findings from a community-based twin registry. *The journal of pain : official journal of the American Pain Society.* 2010;11(7):628-635.

33. McCarthy LH, Bigal ME, Katz M, Derby C, Lipton RB. Chronic pain and obesity in elderly people: results from the Einstein aging study. *Journal of the American Geriatrics Society.* 2009;57(1):115-119.

34. Okifuji A, Hare BD. The association between chronic pain and obesity. *Journal of pain research.* 2015;8:399-408.

35. Higgins DM, Kerns RD, Brandt CA, et al. Persistent pain and comorbidity among Operation Enduring Freedom/Operation Iraqi Freedom/operation New Dawn veterans. *Pain medicine (Malden, Mass).* 2014;15(5):782-790.

36. Lautenbacher S, Kundermann B, Krieg JC. Sleep deprivation and pain perception. *Sleep medicine reviews.* 2006;10(5):357-369.

37. Roehrs T, Roth T. Sleep and pain: interaction of two vital functions. *Seminars in neurology.* 2005;25(1):106-116.

38. Burner T, Abbott D, Huber K, et al. Shoulder symptoms and function in geriatric patients. *Journal of geriatric physical therapy (2001).* 2014;37(4):154-158.

39. Weiner DK, Haggerty CL, Kritchevsky SB, et al. How does low back pain impact physical function in independent, well-functioning older adults? Evidence from the Health ABC Cohort and implications for the future. *Pain medicine (Malden, Mass).* 2003;4(4):311-320.

40. Shah KM, Clark BR, McGill JB, Mueller MJ. Upper extremity impairments, pain and disability in patients with diabetes mellitus. *Physiotherapy.* 2015;101(2):147-154.

41. Shah RC, Buchman AS, Boyle PA, et al. Musculoskeletal pain is associated with incident mobility disability in community-dwelling elders. *The journals of*

gerontology Series A, Biological sciences and medical sciences. 2011;66(1):82-88.

42. Cano A, Mayo A, Ventimiglia M. Coping, pain severity, interference, and disability: the potential mediating and moderating roles of race and education. *The journal of pain : official journal of the American Pain Society.* 2006;7(7):459-468.

43. McCracken LM, Eccleston C. A prospective study of acceptance of pain and patient functioning with chronic pain. *Pain.* 2005;118(1-2):164-169.

44. Williams CS, Tinetti ME, Kasl SV, Peduzzi PN. The role of pain in the recovery of instrumental and social functioning after hip fracture. *Journal of aging and health.* 2006;18(5):743-762.

45. Peat G, Thomas E, Wilkie R, Croft P. Multiple joint pain and lower extremity disability in middle and old age. *Disability and rehabilitation.* 2006;28(24):1543-1549.

46. Al Snih S, Markides KS, Ray L, Goodwin JS. Impact of pain on disability among older Mexican Americans. *The journals of gerontology Series A, Biological sciences and medical sciences.* 2001;56(7):M400-404.

47. Andrews JS, Cenzer IS, Yelin E, Covinsky KE. Pain as a risk factor for disability or death. *Journal of the American Geriatrics Society.* 2013;61(4):583-589.

48. Wade KF, Lee DM, McBeth J, et al. Chronic widespread pain is associated with worsening frailty in European men. *Age and ageing.* 2016;45(2):268-274.

49. Wade KF, Marshall A, Vanhoutte B, Wu FC, O'Neill TW, Lee DM. Does Pain Predict Frailty in Older Men and Women? Findings From the English Longitudinal Study of Ageing (ELSA). *The journals of gerontology Series A, Biological sciences and medical sciences.* 2017;72(3):403-409.

50. Megale RZ, Ferreira ML, Ferreira PH, et al. Association between pain and the frailty phenotype in older men: longitudinal results from the Concord Health and Ageing in Men Project (CHAMP). *Age and ageing.* 2018;47(3):381-387.

51. Castaneda Morales VM, Jimenez Garduno AM, Escarcega MV, Sanchez Velazquez LD, Becerra Laparra I. Association between Chronic Pain and Frailty in Mexican Elders. *The Journal of frailty & aging.* 2016;5(1):59-61.

52. Veronese N, Maggi S, Trevisan C, et al. Pain Increases the Risk of Developing Frailty in Older Adults with Osteoarthritis. *Pain medicine (Malden, Mass).* 2017;18(3):414-427.

53. Tian X, Wang C, Qiao X, et al. The association between pain and frailty among Chinese community-dwelling older adults: depression as a mediator and its interaction with pain. *Pain.* 2017.

54. Gureje O, Von Korff M, Simon GE, Gater R. Persistent pain and well-being: a World Health Organization Study in Primary Care. *Jama.* 1998;280(2):147-151.

55. Verbrugge LM, Jette AM. The disablement process. *Social science & medicine (1982).* 1994;38(1):1-14.

56. Manini T. Development of physical disability in older adults. *Current aging science.* 2011;4(3):184-191.

57. United States Census Bureau Americans with Disabilities. 2014.

58. Crimmins EM, Hayward MD, Saito Y. Changing mortality and morbidity rates and the health status and life expectancy of the older population. *Demography.* 1994;31(1):159-175.

59. Guralnik JM, Simonsick EM. Physical disability in older Americans. *Journal of gerontology.* 1993;48 Spec No:3-10.

60. Dunlop DD, Manheim LM, Sohn MW, Liu X, Chang RW. Incidence of functional limitation in older adults: the impact of gender, race, and chronic conditions. *Archives of physical medicine and rehabilitation.* 2002;83(7):964-971.

61. Luime JJ, Koes BW, Hendriksen IJ, et al. Prevalence and incidence of shoulder pain in the general population; a systematic review. *Scandinavian journal of rheumatology.* 2004;33(2):73-81.

62. Leveille SG, Jones RN, Kiely DK, et al. Chronic musculoskeletal pain and the occurrence of falls in an older population. *JAMA: Journal of the American Medical Association.* 2009;302(20):2214-2221.

63. Patel KV, Guralnik JM, Dansie EJ, Turk DC. Prevalence and impact of pain among older adults in the United States: findings from the 2011 National Health and Aging Trends Study. *Pain.* 2013;154(12):2649-2657.

64. World Health Organization. The International Classification of Functioning, Disability and Handicaps. Geneva, 1980.

65. Nagi S Z. Some conceptual issues in disability and rehabilitation. Sociology and rehabilitation, M B Sussman. American Sociological Association, Washington, DC 1965; 100–113.

66. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. STUDIES OF ILLNESS IN THE AGED. THE INDEX OF ADL: A STANDARDIZED MEASURE OF BIOLOGICAL AND PSYCHOSOCIAL FUNCTION. *Jama.* 1963;185:914-919.

67. Rosow I, Breslau N. A Guttman health scale for the aged. *Journal of gerontology.* 1966;21(4):556-559.

68. Nagi SZ. An epidemiology of disability among adults in the United States. *The Milbank Memorial Fund quarterly Health and society.* 1976;54(4):439-467.

69. Brandt EM, Pope A. 1997. Enabling America: Assessing the Role of Rehabilitation Science and Engineering: Washigton DC: National academics Press.

70. Disability Statistics Annual Report 2017. A Publication of the Rehabilitation Research and Training Center on Disability Statistics and Demographics. .

71. Choi H, Schoeni RF, Martin LG. Are Functional and Activity Limitations Becoming More Prevalent among 55 to 69-Year-Olds in the United States? *PloS one.* 2016;11(10):e0164565.

72. American Community Survey (ACS), United States Census Bureau report, 2017.

73. Scudds RJ, Robertson JM. Pain factors associated with physical disability in a sample of community-dwelling senior citizens. *The journals of gerontology Series A, Biological sciences and medical sciences.* 2000;55(7):M393-399.

74. Rejeski WJ, Ip EH, Marsh AP, Zhang Q, Miller ME. Obesity influences transitional states of disability in older adults with knee pain. *Archives of physical medicine and rehabilitation.* 2008;89(11):2102-2107.

75. Smith PD, Becker K, Roberts L, Walker J, Szanton SL. Associations among pain, depression, and functional limitation in low-income, home-dwelling older adults: An analysis of baseline data from CAPABLE. *Geriatric nursing (New York, NY).* 2016;37(5):348-352.

76. Buckinx F, Rolland Y, Reginster JY, Ricour C, Petermans J, Bruyere O. Burden of frailty in the elderly population: perspectives for a public health challenge. *Archives of public health = Archives belges de sante publique.* 2015;73(1):19.

77. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet (London, England).* 2013;381(9868):752-762.

78. Morley JE, Vellas B, van Kan GA, et al. Frailty consensus: a call to action. *Journal of the American Medical Directors Association.* 2013;14(6):392-397.

79. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne.* 2005;173(5):489-495.

80. Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. *The journals of gerontology Series A, Biological sciences and medical sciences.* 2007;62(7):722-727.

81. Cesari M, Gambassi G, van Kan GA, Vellas B. The frailty phenotype and the frailty index: different instruments for different purposes. *Age and ageing.* 2014;43(1):10-12.

82. Buta BJ, Walston JD, Godino JG, et al. Frailty assessment instruments: Systematic characterization of the uses and contexts of highly-cited instruments. *Ageing research reviews.* 2016;26:53-61.

83. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community-dwelling older persons: a systematic review. *Journal of the American Geriatrics Society.* 2012;60(8):1487-1492.

84. Ensrud KE, Ewing SK, Cawthon PM, et al. A comparison of frailty indexes for the prediction of falls, disability, fractures, and mortality in older men. *Journal of the American Geriatrics Society.* 2009;57(3):492-498.

85. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. *The journals of gerontology Series A, Biological sciences and medical sciences.* 2004;59(3):255-263.

86. Matusik P, Tomaszewski K, Chmielowska K, et al. Severe frailty and cognitive impairment are related to higher mortality in 12-month follow-up of nursing home residents. *Archives of gerontology and geriatrics.* 2012;55(1):22-24.

87. Freiheit EA, Hogan DB, Strain LA, et al. Operationalizing frailty among older residents of assisted living facilities. *BMC geriatrics.* 2011;11:23.

88. Siriwardhana DD, Hardoon S, Rait G, Weerasinghe MC, Walters KR. Prevalence of frailty and prefrailty among community-dwelling older adults in low-income and middle-income countries: a systematic review and meta-analysis. *BMJ open.* 2018;8(3):e018195.

89. Rudy TE, Weiner DK, Lieber SJ, Slaboda J, Boston JR. The impact of chronic low back pain on older adults: a comparative study of patients and controls. *Pain.* 2007;131(3):293-301.

90. Stewart WF, Ricci JA, Chee E, Morganstein D, Lipton R. Lost productive time and cost due to common pain conditions in the US workforce. *Jama.* 2003;290(18):2443-2454.

91. Freburger JK, Holmes GM, Agans RP, et al. The rising prevalence of chronic low back pain. *Archives of internal medicine.* 2009;169(3):251-258.

92. Katz JN. Lumbar disc disorders and low-back pain: socioeconomic factors and consequences. *The Journal of bone and joint surgery American volume.* 2006;88 Suppl 2:21-24.

93. Centers for Disease Control and Prevention (CDC). Health and Economic Costs of Chronic Diseases. Atlanta, GA: CDC.

94. Centers for Disease Control and Prevention. The Cost of Arthritis in US Adults. Accessed June 29, 2018.

95. Freedman VA. Adopting the ICF language for studying late-life disability: a field of dreams? In: *J Gerontol A Biol Sci Med Sci.* Vol 64. United States2009:1172-1174; discussion 1175-1176.

96. *World Health Organization. International Classification of Impairments, Disability, and Handicaps. 1980.*

97. Nagi SZ. *Disability concepts revisted: implications for prevention. In: Pope A.M.andTarlov A.R., ed. Disability in America: Toward a National Agenda for*

Prevention. Washington, D.C: Division of Health Promotion and Disease Prevention, Institute of Medicine. National Academy Press, 1991, pp 309-327.

98. Frochen S, Mehdizadeh S. Functional Status and Adaptation: Measuring Activities of Daily Living and Device Use in the National Health and Aging Trends Study. *Journal of aging and health.* 2018;30(7):1136-1155.

99. Guralnik JM, Simonsick EM, Ferrucci L, et al. 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.* 1994;49(2):M85-94.

100. Kasper, J FV, Niefeld MR. *Construction of performance-based summary measures of physical capacity in the National Health and Aging Trends Study. NHATS Technical Paper #4.* Baltimore: Johns Hopkins University School of Public Health2013.

101. Spira AP, Kaufmann CN, Kasper JD, et al. Association between insomnia symptoms and functional status in U.S. older adults. *The journals of gerontology Series B, Psychological sciences and social sciences.* 2014;69 Suppl 1:S35-41.

102. Li C, Friedman B, Conwell Y, Fiscella K. Validity of the Patient Health Questionnaire 2 (PHQ-2) in identifying major depression in older people. *Journal of the American Geriatrics Society.* 2007;55(4):596-602.

103. Shaw AT, Gandhi L, Gadgeel S, et al. Alectinib in ALK-positive, crizotinib-resistant, non-small-cell lung cancer: a single-group, multicentre, phase 2 trial. *The Lancet Oncology.* 2016;17(2):234-242.

104. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics.* 1986;42(1):121-130.

105. Su L, Hogan JW. Bayesian semiparametric regression for longitudinal binary processes with missing data. *Statistics in medicine.* 2008;27(17):3247-3268.

106. Preisser JS, Lohman KK, Rathouz PJ. Performance of weighted estimating equations for longitudinal binary data with drop-outs missing at random. *Statistics in medicine.* 2002;21(20):3035-3054.

107. Preacher KJ, Hayes AF. SPSS and SAS procedures for estimating indirect effects in simple mediation models. *Behavior research methods, instruments, & computers : a journal of the Psychonomic Society, Inc.* 2004;36(4):717-731.

108. Leong IY, Farrell MJ, Helme RD, Gibson SJ. The relationship between medical comorbidity and self-rated pain, mood disturbance, and function in older people with chronic pain. *The journals of gerontology Series A, Biological sciences and medical sciences.* 2007;62(5):550-555.

109. Salive ME. Multimorbidity in older adults. *Epidemiologic reviews.* 2013;35:75-83.

110. Di Bari M, Virgillo A, Matteuzzi D, et al. Predictive validity of measures of comorbidity in older community dwellers: the Insufficienza Cardiaca negli Anziani Residenti a Dicomano Study. *Journal of the American Geriatrics Society.* 2006;54(2):210-216.

111. Stroe AF, Roth T, Jefferson C, et al. Comparative levels of excessive daytime sleepiness in common medical disorders. *Sleep medicine.* 2010;11(9):890-896.

112. Suzuki K, Miyamoto M, Hirata K. Sleep disorders in the elderly: Diagnosis and management. *Journal of general and family medicine.* 2017;18(2):61-71.

113. Zis P, Daskalaki A, Bountouni I, Sykioti P, Varrassi G, Paladini A. Depression and chronic pain in the elderly: links and management challenges. *Clinical interventions in aging.* 2017;12:709-720.

114. Bauer H, Emeny RT, Baumert J, Ladwig KH. Resilience moderates the association between chronic pain and depressive symptoms in the elderly. *European journal of pain (London, England).* 2016;20(8):1253-1265.

115. Sale JE, Gignac M, Hawker G. How "bad" does the pain have to be? A qualitative study examining adherence to pain medication in older adults with osteoarthritis. *Arthritis and rheumatism.* 2006;55(2):272-278.

116. Klauenberg S, Maier C, Assion HJ, et al. Depression and changed pain perception: hints for a central disinhibition mechanism. *Pain.* 2008;140(2):332-343.

117. Taylor DJ, Mallory LJ, Lichstein KL, Durrence HH, Riedel BW, Bush AJ. Comorbidity of chronic insomnia with medical problems. *Sleep.* 2007;30(2):213-218.

118. Mundal I, Grawe RW, Bjorngaard JH, Linaker OM, Fors EA. Psychosocial factors and risk of chronic widespread pain: an 11-year follow-up study--the HUNT study. *Pain.* 2014;155(8):1555-1561.

119. Mork PJ, Vik KL, Moe B, Lier R, Bardal EM, Nilsen TI. Sleep problems, exercise and obesity and risk of chronic musculoskeletal pain: the Norwegian HUNT study. *European journal of public health.* 2014;24(6):924-929.

120. Smith MT, Haythornthwaite JA. How do sleep disturbance and chronic pain inter-relate? Insights from the longitudinal and cognitive-behavioral clinical trials literature. *Sleep medicine reviews.* 2004;8(2):119-132.

121. Irwin MR, Olmstead R, Carroll JE. Sleep Disturbance, Sleep Duration, and Inflammation: A Systematic Review and Meta-Analysis of Cohort Studies and Experimental Sleep Deprivation. *Biological psychiatry.* 2016;80(1):40-52.

122. Li J, Vitiello MV, Gooneratne NS. Sleep in Normal Aging. *Sleep medicine clinics.* 2018;13(1):1-11.

123. Ravyts SG, Dzierzewski JM, Grah SC, et al. Sleep and Pain in Mid- to Late-Life: An Exploration of Day-to-Day Pain Inconsistency. *Clinical gerontologist.* 2018;41(2):123-129.

124. Almeida OP, Draper B, Snowdon J, et al. Factors associated with suicidal thoughts in a large community study of older adults. *The British journal of psychiatry : the journal of mental science.* 2012;201(6):466-472.

125. Tektonidou MG, Dasgupta A, Ward MM. Suicidal ideation among adults with arthritis: prevalence and subgroups at highest risk. Data from the 2007-2008 National Health and Nutrition Examination Survey. *Arthritis care & research.* 2011;63(9):1322-1333.

126. Chou KL. Reciprocal relationship between pain and depression in older adults: evidence from the English Longitudinal Study of Ageing. *Journal of affective disorders.* 2007;102(1-3):115-123.

127. Leveille SG, Fried L, Guralnik JM. Disabling symptoms: what do older women report? *Journal of general internal medicine.* 2002;17(10):766-773.

128. Boulos C, Salameh P, Barberger-Gateau P. Malnutrition and frailty in community dwelling older adults living in a rural setting. *Clinical nutrition (Edinburgh, Scotland).* 2016;35(1):138-143.

129. Karp JF, Shega JW, Morone NE, Weiner DK. Advances in understanding the mechanisms and management of persistent pain in older adults. *British journal of anaesthesia.* 2008;101(1):111-120.

130. McBeth J, Silman AJ, Gupta A, et al. Moderation of psychosocial risk factors through dysfunction of the hypothalamic-pituitary-adrenal stress axis in the onset

of chronic widespread musculoskeletal pain: findings of a population-based prospective cohort study. *Arthritis and rheumatism.* 2007;56(1):360-371.

131. Leng SX, Xue QL, Tian J, Walston JD, Fried LP. Inflammation and frailty in older women. *Journal of the American Geriatrics Society.* 2007;55(6):864-871.

132. Nessighaoui H, Lilamand M, Patel KV, et al. Frailty and Pain: Two Related Conditions. *The Journal of frailty & aging.* 2015;4(3):144-148.

133. Resnick NM, Marcantonio ER. How should clinical care of the aged differ? *Lancet (London, England).* 1997;350(9085):1157-1158.

134. McCahon S, Strong J, Sharry R, Cramond T. Self-report and pain behavior among patients with chronic pain. *The Clinical journal of pain.* 2005;21(3):223-231.

135. Dent E, Kowal P, Hoogendijk EO. Frailty measurement in research and clinical practice: A review. *European journal of internal medicine.* 2016;31:3-10.

136. Gobbens RJ, van Assen MA. The prediction of quality of life by physical, psychological and social components of frailty in community-dwelling older people. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2014;23(8):2289-2300.

VITA

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