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Associations Between Pain Interference and Late-Life Cognitive Function Among Diverse Community-Dwelling Older Adults

By

CLAIRE MINH NGUYEN
DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

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DAVIS

Approved:

Janice F. Bell, Chair

Heather M. Young

Philippe R. Goldin

Christiana M. Drake

Oanh L. Meyer

Committee in Charge

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ABSTRACT

There is increasing interest in identifying modifiable risk factors for cognitive decline and dementia. Emerging evidence suggests that chronic pain, also known as persistent pain, may be a potentially modifiable risk factor for cognitive decline and dementia. Previous studies, however, provided mixed findings on the relationship between persistent pain and cognitive decline in older adults; and few studies specifically examined pain interference and domain-specific cognition. Notably, there is a paucity of research examining how the intersection of persistent pain and cognitive decline affects older adults belonging to ethnoracially diverse groups. As such, the primary aim of this dissertation was to investigate the cross-sectional associations between pain interference and cognitive performance in the specific cognitive domains of verbal episodic memory and executive functioning among older adults aged 65 and older. A secondary aim of the study was to examine potential effect modification from sex, ethnoracialized group membership, and educational attainment.

Data for this secondary analysis came from the Kaiser Healthy Aging and Diverse Life Experiences (KHANDLE) Study, a prospective cohort of ethnoracially-diverse, community-dwelling older adults aged 65 and older residing in Northern California. The analytic sample comprised 952 participants. The outcome measures were verbal episodic memory and executive functioning. The primary exposure of interest was pain interference, which was defined as having persistent pain that made it difficult to do usual activities such as household chores or work. Multiple linear regression was used to examine the cross-sectional associations between pain interference and verbal episodic memory and executive functioning, while controlling for important sociodemographic, health-related, and lifestyle variables.

Compared with participants without persistent pain or without pain interference, older adults in the pain interference group were more likely to be women; have non-Latinx Black group membership; have lower mean years of educational attainment; and more likely to be unpartnered. In adjusted multiple linear regression models, the effect of having pain interference was statistically significant and negatively associated with executive functioning *z*-score. However, the study did not find a significant association between pain interference and verbal episodic memory. Additionally, moderation analysis indicated that the relationship between pain interference and executive functioning score did not appear to differ statistically by sex, ethnoracialized group membership, or by educational attainment.

In this prospective cohort of diverse older adults, this study found a negative association between pain interference and executive functioning composite score, and, more specifically, a negative association between pain interference and phonemic (letter) fluency score. While this study contributes to the growing body of research on the relationship of pain and cognitive function in older adults, additional research is warranted to elucidate the complex factors and potential causal mechanisms of the relationship.

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CHAPTER 1: INTRODUCTION

1.1 Background and problem statement

A substantial body of literature highlights the pressing challenges of rapidly diversifying and aging populations living with age-related cognitive decline and dementia in the United States and worldwide (GBD 2019 Collaborators, 2021; Nichols et al., 2022; World Health Organization [WHO], 2017). Individuals from racially and ethnically minoritized groups are projected to comprise approximately 45% of the U.S. older adult population by 2060 (U.S. Census Bureau, 2018). Many of these diverse older persons will be at increased risk of developing, or being affected by, cognitive impairment and dementia (Farina et al., 2019; García et al., 2019). Evidence points to significant disparities in Alzheimer's disease and related dementia (ADRD) prevalence among racially minoritized populations in the U.S. (Brewster et al., 2019; Matthews et al., 2019; Weuve et al., 2018). Emerging research indicates that Black and Latinx subgroups may bear the highest ADRD burden through the year 2060 (Matthews et al., 2019; Mayeda et al., 2016). However, we do not yet have a complete picture of the ADRD burden and disparities as there is a paucity of dementia research on certain subgroups such as Asian Americans. What is clear, though, is that these demographic changes present enormous burden and costs to individuals, families, healthcare systems, and societies (Alzheimer's Association, 2022; Aranda et al., 2021; WHO, 2012, 2017).

At the same time, mounting evidence in the past few decades suggests that chronic pain, also known as persistent pain, is highly prevalent among U.S. older adults; is increasingly associated with comorbidities and disability; and also incurs significant costs to individuals, families, healthcare systems, and societies (Institute of Medicine [IOM], 2011; Rice et al., 2016). Using data from the 2019 National Health Interview Survey, researchers found that among adults

aged 65 years and older, 30.8% reported having chronic pain, compared with 25.8% adults aged 45 to 64 years, and 14.6% adults aged 30 to 44 years (Zelaya et al., 2020). The estimated annual cost of pain in the U.S. in 2010, in terms of healthcare resources, disability, and lost productivity, was over $630 billion (in 2010 dollars), exceeding the cost for heart disease and cancer (Gaskin & Richard, 2012).

Despite the staggering economic costs and burden posed by chronic pain, pain prevention continues to be conceptually underdeveloped and clinically underpromoted, particularly in older adults (Johnson & Booker, 2021; Miaskowski et al., 2020). Johnson and Booker (2021) attribute the neglect partly to the failure to acknowledge chronic pain as a condition worth preventing. Instead of pain prevention, past pain research focused mostly on the pathophysiological disease process and clinical manifestations of chronic pain disorders. However, there has been a shift in recent decades towards understanding psychosocial factors that influence chronic pain in the general adult populations (e.g., Cohen et al., 2021; Edwards et al., 2016; Meints & Edwards, 2018) and in older adult subpopulations (Gagliese et al., 2018; Miaskowski et al., 2020). Relatedly, there is growing recognition of the need to examine the social drivers and upstream factors of chronic pain (Johnson & Booker, 2021; Wallace et al., 2021; Zajacova et al., 2021a).

Similarly, cognitive aging and dementia research has traditionally been conducted within a biomedical framework. However, recent research has expanded to examine lifestyle and social risk factors, cognitive health disparities, and social determinants of cognitive health (Aranda et al., 2021; Baumgart et al., 2015; Brewster et al., 2019; Livingston et al., 2020). Yet, despite research demonstrating associations between persistent pain and cognitive function, and increasing interest in examining persistent pain as a potentially modifiable risk factor for cognitive decline in older adults, we still have a limited understanding of the exact nature of the

relationships (Gagliese et al., 2018; Innes & Sambamoorthi, 2020; Yuan et al., 2023; Zhang et al., 2022). The exact number adults aged 65 and older who are affected by both persistent pain and cognitive dysfunction in unknown. However, a systematic review by van Kooten et al. (2016) examining the prevalence of pain in older adults with dementia found that estimates in the literature ranged from 46-56%, depending on the dementia subtypes. Arguably, there is a critical need to examine the co-occurrence of these two conditions in aging populations to better understand the possible links between these two comorbid conditions, potential interrelated risk factors, and any causal mechanisms and specific pathways underlying their associations. Moreover, with the changing demographics of the older adult population, there is also an urgent need to understand the social factors, such as education and ethnoracialized group membership, that may influence the relationships between persistent pain and cognitive decline. Notably, there is a paucity of research examining how the intersection of persistent pain and cognitive decline affects older adults belonging to ethnoracially diverse groups in the United States. Greater understanding of the relationships between these two overlapping problems may aid the development of effective, targeted interventions, clinical guidelines, and policies to improve the quality of life and well-being of diverse older adults and to mitigate the immense burden posed by these two growing public health challenges.

1.2 Research aims and hypotheses

To better understand the relationship between persistent pain and cognitive performance among ethnoracially-diverse older adults, this study used data collected for the Kaiser Healthy Aging and Diverse Life Experiences (KHANDLE) Study. A notable feature of the KHANDLE Study is its multiethnic cohort, comprising community-living persons aged 65 and older who self-identify as non-Latinx Asian, non-Latinx Black, Latinx, or non-Latinx White, the four major

ethnoracialized subgroups in the United States. This dissertation study investigated the following specific aims and hypotheses.

Aim 1. Examine the cross-sectional associations between pain interference and executive functioning (EF) and verbal episodic memory (VEM) scores among all study participants.

Hypothesis 1a. Pain interference will be negatively associated with EF score across all study participants.

Hypothesis 1b. Pain interference will be negatively associated with VEM score across all study participants.

Aim 2. Investigate whether sex, ethnoracialized group membership, and educational attainment moderate the associations in Aim 1.

Hypothesis 2a. There will be a significant interaction effect of sex and pain interference on EF and VEM scores such that female sex will have a stronger inverse association compared with male sex.

Hypothesis 2b. There will be a significant interaction effect of ethnoracialized group membership and pain interference on EF and VEM scores. The negative associations between pain interference and EF and VEM scores will be stronger for participants who have non-Latinx Black or Latinx group membership compared with those identifying as non-Latinx White and non-Latinx Asian.

Hypothesis 2c. There will be a significant interaction effect of educational attainment and pain interference on EF and VEM scores. The inverse associations between pain interference and EF and VEM scores will be stronger for participants with lower levels of educational attainment (i.e., education will have a protective effect).

1.3 Conceptual frameworks

Acknowledging the complex, interrelated, and multifactorial dimensions of pain, cognitive functioning, and cognitive aging disparities, this study drew on theoretical insights from the Biopsychosocial (BPS) Model of Chronic Pain and the Biopsychosocial Framework of Minority Aging to understand the relationships between persistent pain, pain interference, and cognitive functioning in ethnoracially diverse older adults. In contrast to the biomedical approach to pain, which primarily focuses on biological processes and pathophysiology, the Biopsychosocial Model of Chronic Pain posits chronic pain development as the result of dynamic interactions among physiologic, psychological, and sociocultural factors within individuals (Gatchel et al., 2007). While the BPS Model of Chronic Pain has contributed greatly to understanding the multidimensionality of pain experiences, there are critiques of the model's inherent linearity: the underlying assumption of the model is that the causes of pain originate with the biological factors and then expand sequentially to the psychological and social factors (Quintner et al., 2008). Extending Quintner et al.'s critique of the BPS Model of Chronic Pain, Booker and colleagues (2023b) highlighted the challenges in elucidating how these multiple biopsychosocial factors interact, and the strength to which these relationships contribute to pain experiences in different populations. To elucidate how the multiple biopsychosocial factors interact in the pain experiences of older adults, Miakowski and colleagues (2020) drew on empiric research and literature review to further modify the BPS Model of Chronic Pain to critically account for age-related changes and variability in pain experiences among older persons. The result is their Biopsychosocial Model of Chronic Pain for Older Adults, which provides a conceptual framework to guide research in geriatric pain and inform clinical geriatric pain management (Miakowski et al., 2020). The model proposed by Miakowski and colleagues

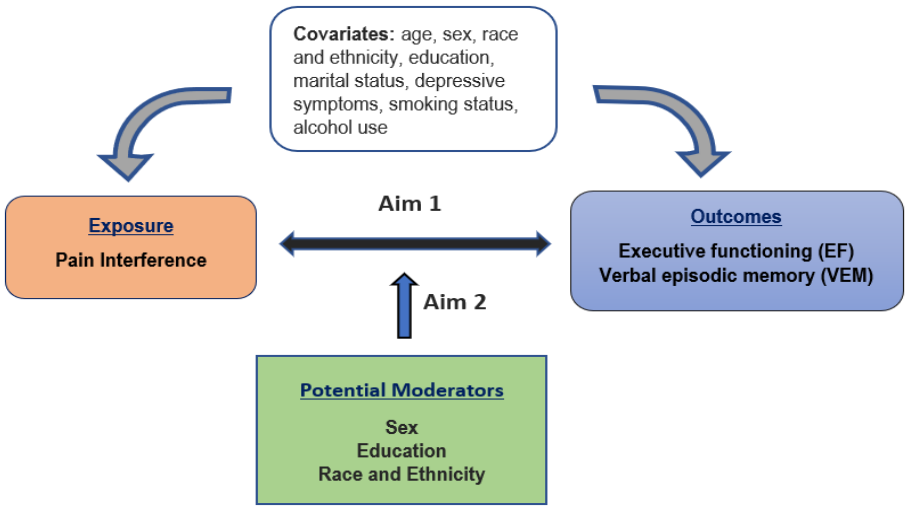
moves beyond biomedical reductionism by conceptualizing the different factors and domains constitutive of the pain experience (biological, psychological, and social) as being interrelated and mutually interacting in a dynamic, circular process. Importantly, Miakowski and colleagues (2020) acknowledged the need to extend beyond individual-level factors to examine structural-level factors that impact pain experiences and pain care in diverse older adult populations. This crucial point is expounded by Booker and colleagues (2023b) who noted that the BPS Model of Chronic Pain focuses heavily on factors and interventions aimed at the individual level (e.g., pain coping strategies, lifestyle modifications), rather than factors at the provider level (e.g., provider bias, over- or under-treatment of pain) or at the system level (e.g., access to pain care, structural racism) that have much greater downstream effects on pain experiences and pain-related outcomes. Accordingly, Booker and colleagues (2023b) argue for a shift towards examining the crucial structural-level factors and interventions that are needed to bring about health equity in pain prevalence, pain care, and pain-related outcomes among subpopulations that have been disproportionately impacted by pain and pain-related disabilities.

Similar critiques, albeit implicit, have been made of Spector and Orrell's (2010) biopsychosocial conceptualization of cognitive health and dementia. Using the biopsychosocial approach, their model posits that cognitive health is not solely determined by biological and physical health factors; psychological and social factors also impact cognitive aging and dementia risk (Spector & Orrell, 2010). However, their model focuses mostly on the individual-level factors that influence cognitive aging and dementia. In response, Forrester and colleagues (2019) adapted Spector and Orrell's (2010) biopsychosocial model of cognitive health, but expanded beyond the individual level to include system-level factors in their proposed Biopsychosocial Framework of Minority

Aging. In the Biopsychosocial Framework of Minority Aging, social and structural factors—particularly stressors, such as racialization, unequal access and quality of education, and discrimination—are upstream causes of downstream physiological dysregulation and allostatic load burden, which then negatively impacts cognitive aging outcomes and cognitive disparities in minoritized older adults (Forrester et al., 2019). Forrester and colleagues' Biopsychosocial Framework of Minority Aging informs this study's understanding of cognitive aging in ethnoracially-diverse older adults. A conceptual model of this study's variables is presented below in Figure 1.

Figure 1

Conceptual Model of Study Variables



1.4 Significance of the research

This study builds on recent research that examines persistent pain as a possible modifiable risk factor of cognitive decline in older adults (Innes & Sambamoorthi, 2020; Yuan et al., 2023; Zhang et al., 2021). The aim of this study was to examine how pain interference operates differentially among older persons and how it may have differential associations with cognitive performance in different subpopulations, including ethnoracialized subgroups. While numerous studies published in the past few decades point to racial and ethnic disparities and inequities in cognitive aging (e.g., Barnes, 2022; Brewster et al., 2019; Mayeda et al., 2016, 2017; Weuve et al., 2018), as well as racial and ethnic disparities and inequities in pain experiences and pain care (e.g., Booker et al., 2023b; Meghani et al., 2012; Meints et al., 2019; Zajacova et al., 2021b), there has been limited research on the intersection of pain and cognitive aging in ethnoracially-diverse older adults in the U.S. Notably, cross-sectional and longitudinal studies examining associations of chronic pain and/or pain interference with cognitive performance rarely include diverse samples of older adults beyond non-Latinx Black and non-Latinx White participants. To our knowledge, no published, population-based studies have examined the pain-cognition relationships among non-Latinx Asian older adults; and few studies have examined the pain-cognition relationships among Latinx older adults (Bell et al., 2022a; Milani et al., 2024). This study addressed this research gap by using data from a prospective cohort study that contains a large sample of Asian participants (n = 415), with representation from different Asian ethnicities (e.g., Chinese, Japanese, Filipino, and South Asians) (Eng et al., 2019; Meyer et al., 2023).

In addition, many past studies examining the pain-cognition relationship in older adults relied on global cognitive screening tests for the outcome measures (Warner et al., 2023). These

cognitive screening tests are not as accurate in detecting subtle changes in cognitive performance as neuropsychological assessment (Warner et al., 2023i). By contrast, this study's cognitive measures were from the Spanish and English Neuropsychological Assessment Scales (SENAS), which assess domain-specific cognition and can detect subtle changes in cognitive performance. Moreover, the SENAS was developed as a culturally and linguistically-informed neuropsychological assessment tool, making it more suitable for use among ethnoracially and linguistically diverse U.S. populations (Mungas et al., 2000, 2004, 2005).

With the rapidly shifting demographics and the public health challenges presented by persistent pain and cognitive decline in older adults, it is important to investigate further the pain-cognition relationship to identify the modifiable risk factors for cognitive decline and dementia. The goals of this study align with the larger goals of health equity research in cognitive aging: to understand potential heterogeneity in cognitive aging; identify the factors and drivers of health inequities in cognitive aging; develop targeted, effective interventions for diverse aging populations; and inform public policies (Aranda et al., 2021; Brewster et al., 2019; Gilmore-Bykovskyi et al., 2022).

CHAPTER II: REVIEW OF LITERATURE

2.1 Overview of cognitive decline

Cognitive functioning is a key factor in quality of life and contributes to older adults' ability to maintain functional independence and well-being (Beaton et al., 2015; Gross et al., 2011). Older persons, however, are at greater risk of experiencing cognitive decline, which can progress to cognitive impairment and dementia (Alzheimer's Association, 2022; WHO, 2017). Research suggests that neuropathologic changes associated with Alzheimer's disease (AD) may begin 20 or more years before the onset of clinical symptoms (Reiman et al., 2012; Villemagne et al., 2013). Given the prolonged period before symptom manifestations and the lack of effective treatments currently, compelling arguments underwritten by public health approaches have called for shifting the focus to prevention and intervening at much earlier stages to change and alter the progression and outcome of AD and other dementias (Alzheimer's Association, 2022; Livingstone et al., 2020). The result is the growing research interest in examining the asymptomatic and prodromal stages of AD, constructs such as subjective cognitive decline and mild cognitive impairment, and dementia prevention (National Academies of Sciences, Engineering, and Medicine [NASEM], 2017). Consequently, there is growing consensus on the need to examine risk factors for cognitive decline to identify and develop prevention and treatment strategies for cognitive impairment and dementia (Baumgart et al., 2015; Livingston et al., 2020; NASEM, 2017). Along this line, this literature review situates the following discussion of cognitive decline and risk factors for cognitive decline within the larger context of dementia and dementia prevention.

Encouraging evidence in recent years points to declining prevalence and age-specific incidence of dementia in the United States and some high-income countries, possibly due to

improvements in dementia modifiable risk factors, such as gains in education attainment across generations (Farina et al., 2022; Grasset et al., 2016; Langa et al., 2017). Despite this declining trend, however, recent gains in life expectancy in many countries have fueled aging population growth, resulting in a greater number of people living with age-related cognitive decline and dementia (Brayne & Miller, 2017; Nichols et al., 2022; WHO, 2017). Moreover, while there may be a general decline in dementia prevalence in the U.S., recent research suggests noticeable heterogeneity and disparities in age-adjusted dementia prevalence in the U.S. by sex and gender (Zhu et al., 2021), educational attainment (Hayward et al., 2021), and ethnoracialized group membership (Chen & Zissimopoulos, 2018; Kornblith et al., 2022; Mayeda et al., 2016; Zhu et al., 2021).

The two drivers behind the increasing numbers of individuals living with cognitive decline and/or dementia—population aging and increased life expectancy—are also drivers of the rising numbers of people living with persistent pain in the U.S. and globally (Blyth et al., 2019). Many high-income countries face not only the challenges and burden presented by an increasing number of older adults living with cognitive impairment and dementia, but also the challenges and burden posed by the number of adults living with chronic pain. It is well-established that chronic or persistent pain constitutes a major public health crisis and poses an enormous burden on individuals, families, healthcare systems, and societies (Blyth et al., 2019; Goldberg & McGee, 2011; IOM, 2011). The “invisible crisis” of chronic pain (Morris, 1993) has become visible and urgent in the past two decades in the U.S.. The crisis is particularly noticeable in older adult populations, in which persistent pain is often underdiagnosed and undertreated for a variety of reasons. One contributing reason is the widespread—albeit erroneous—perception among many individuals and health professionals that pain is an

inevitable part of aging (Barkin et al., 2005; Thielke et al., 2012). At the same time, persistent pain is underdiagnosed in older adults due to higher prevalences of cognitive impairment and dementia in this age group (Bullock et al., 2019; Gagliese et al., 2018; Haasum et al., 2011). Neuropathological changes that occur with cognitive impairment and dementia impact pain perception and the ability to verbally express pain, resulting in underdiagnosis (Achterberg et al., 2021; Gagliese et al., 2018; Kaufmann et al., 2021). Additionally, due to the complexity of pharmacological treatment in the context of comorbidities, polypharmacy, and the increased risks of adverse drug effects in this age group, many older adults experience undertreatment of their pain by health professionals (Domenichiello & Ramsden, 2019; Ferrell et al., 2002; Prostran et al., 2016). In many ways, the challenges of understanding and addressing persistent pain in older adults arguably parallel the challenges of the equally complex crisis of cognitive decline and dementia.

Cognitive decline is common in older ages and can affect a single domain, such as memory; or multiple cognitive domains beyond memory, such as attention, processing speed, and executive functioning (Deary et al., 2009). Age-related cognitive decline varies greatly across individuals and usually occurs on a continuum from mild to severe (Deary et al., 2009). In general, normal, age-related cognitive changes do not result in functional impairment and are not considered to be pathological (Deary et al., 2009). Mild cognitive impairment, on the other hand, is considered pathological and is characterized by cognitive deficits beyond normal healthy aging but does not cause functional impairment. It is viewed as a preclinical, transitional phase between healthy cognitive aging and dementia; however, not all individuals with mild cognitive impairment will go on to develop dementia (Anderson, 2019; Petersen, 2004).

Dementia is a complex syndrome characterized by progressive deterioration in more than one cognitive domain; moreover, the deterioration leads to impairment in activities of daily living (WHO, 2012, 2017). There are several diseases that cause dementia, and each subtype of dementia differs in etiology and pathophysiology (Alzheimer's Association, 2022; WHO, 2012). Alzheimer's disease (AD) is the most common cause of dementia, comprising about 60-70% of dementia cases, followed by vascular dementia, which accounts for 15-20% of all cases of dementia in North America and Europe (Alzheimer's Association, 2022; Rizzi et al., 2014). Other causes of dementia include dementia with Lewy bodies, several diseases that cause frontotemporal dementia, Parkinson's disease, and mixed dementia (WHO, 2012).

Currently, there is no single definitive diagnostic test for neurodegenerative dementia. Post-mortem neuropathological examination is considered the gold standard to diagnose and score age-related neuropathological findings, although there have been calls to abandon this gold standard in favor of integrating multiple sources of information to make the dementia diagnosis (Scheltens & Rockwood, 2011). In clinical settings, a dementia diagnosis is made based on many criteria, including symptoms, medical evaluation, neuropsychological assessment, blood tests, and neuroimaging (Alzheimer's Association, 2022; American Psychiatric Association, 2013). However, diagnosing dementia is quite complex and challenging for many reasons. One of the biggest challenges to diagnosing conditions involving cognitive impairment is the persisting stigma surrounding dementia and the related reluctance to seek diagnosis for cognitive change (Parker et al., 2022). To complicate matters, early symptoms of dementia may resemble "normal" age-related cognitive decline; and some affected individuals mask the symptoms in the early stages (Karantzoulis & Galvin, 2011; Robinson et al., 2015). Additionally, the standard and diagnostic criteria used to diagnose AD and other etiologic subtypes of dementia are poorly

operationalized (McKhann et al., 2011). These challenges often result in misclassification, misdiagnosis, and delayed diagnosis of dementia (Ryan et al., 2018), particularly in individuals belonging to minoritized groups (Brewster et al., 2019; Lin et al., 2021). Additionally, there are many methodological challenges in researching cognitive health and dementia, including neuropsychological assessment variability, measurement error, selection, and bias (Brewster et al., 2019; Glymour et al., 2008; Weuve et al., 2015).

Neuropsychological assessment

Neuropsychological assessment plays an important role in research and clinical care related to cognitive aging and cognitive health. It entails a systematic approach to evaluating cognitive functioning and is usually performed with a battery approach, which involves tests of a variety of cognitive ability areas, with more than one test per ability area (Harvey, 2022). These ability areas include skills such as memory, attention, processing speed, reasoning, judgment, and problem-solving, spatial, and language functions (Harvey, 2022). Two cognitive functions known to be very sensitive to cognitive aging are episodic memory and executive function (Buckner et al., 2006). Episodic memory, which refers to the conscious recollection of personal experiences that contains information on what has happened, where, and when it happened, is usually the first memory system to decline in both normal and pathological aging, such as AD (Pause et al., 2013; Tromp et al., 2015). Domain-specific cognitive tests for learning and memory usually require individuals to learn a set of words and freely recall them over a short or long delay (e.g., the Rey Auditory Verbal Learning Test). Some memory tests assess not only verbal memory, but also visual and auditory memory (e.g., the Wechsler Memory Scale).

Executive functioning (EF) is an umbrella term that refers to numerous, complex cognitive processes necessary for goal-directed behaviors, including planning, inhibition, task

switching, memory updating, cognitive flexibility, and performance monitoring (Moriarty et al., 2011; Phillips & Henry, 2008). There are many tests to evaluate executive functioning; these tests involve problem solving, planning, manipulating mazes, and other complex tasks (Harvey, 2019). Some commonly used tests of executive function include the Rey-Osterrieth Complex Figure Test, the Stroop Test, the Trail Making Test-Part B, and the Wisconsin Card Sorting Test (Harvey, 2019). Of note, cognitive functioning in individuals with chronic pain have been studied traditionally using neuropsychological measures of attention, working memory, and psychomotor speed (Berryman et al., 2013; Sjøgren et al., 2005).

Neuropsychological tests have been derived traditionally from research that usually involved small samples that were not demographically diverse, a factor that likely contributed to limited reliability and generalizability (Howieson, 2019; Poreh, 2002). Moreover, some researchers have raised issues of measurement bias and susceptibility to confounding demographic and cultural factors when these tests are applied in cross-cultural and multilingual contexts; they note the challenges of harmonizing neuropsychological measures across cultural groups (Ardila, 2007; Manly et al., 1998; Mungas et al., 2005). Recent research has shown the strong influence of diversity-related factors, such as education, culture, and language, on an individual's performance on traditional neuropsychological tests that have normative standards derived from non-Latinx White, English-speaking populations (Arce Rentería et al., 2023; Byrd, & Rivera-Mindt, 2022; Franzen et al., 2023). To address cross-cultural and language limitations in existing neuropsychological tests, Mungas and colleagues (2000, 2004, 2005) developed the Spanish and English Neuropsychological Assessment Scales (SENAS), using item response theory methodology for valid comparisons of cognition and cognitive change across ethnoracially and linguistically diverse groups. While the SENAS contributes to the development

of demographically adjusted norms, few studies to date have established robust norms for neuropsychological tests in older adults identifying as Asian or Asian American and are secondary English speakers (Kapoor et al., 2024).

2.2 Risk factors for cognitive decline and dementia

While we currently do not have a definitive understanding of the multifactorial etiologies of dementia, extensive research has shown that nonmodifiable and modifiable risk factors are implicated in this complex, heterogenous disease category (Rockwood et al., 2019). Nonmodifiable risk factors include advanced age, sex, family history, and being carriers of certain genetic variants, such the apolipoprotein E ε4 allele (Rockwood et al., 2019). Advanced age has been shown to be a significant risk modifier (Livingston et al., 2020; van der Flier & Scheltens, 2005).

While epidemiological research indicates that Alzheimer's disease disproportionately affects women in both prevalence and severity (partly because women tend to live longer), we still do not fully understand the underlying biologic mechanisms (Ferretti et al., 2020; Mielke et al., 2022; Podcasy & Epperson, 2022). It has been hypothesized that sex differences in biological factors (e.g., sex hormones, age-related declined in brain volume) may play a role in AD heterogeneity (Carter et al., 2012). However, sex differences in dementia risk remain unclear, and more research is needed to elucidate sex and gender differences in AD risk (Ferretti et al., 2020; Levine et al., 2021; Mielke et al., 2022; Podcasy & Epperson, 2022).

Certain health conditions, many of which can be modified through lifestyle and environmental changes, are associated with an increased risk of developing MCI and dementia; these conditions include depression, cancer, cardiovascular disease, type 2 diabetes mellitus, delirium, thyroid disorders, chronic kidney disease, and loss of hearing and/or vision (Kane et

al., 2017). While there is growing research examining specific health conditions and their relationships to dementia, the extent to which each of these health conditions drive dementia development, and how genetic, individual health, and lifestyle-related and social factors interact is still not fully known (Deckers et al., 2014; Rockwood et al., 2019). Despite substantial research investment in the past several decades, we do not yet have highly effective interventions that can considerably impact neurocognitive disease risk and progression (Cummings et al., 2014; Kane et al., 2017). Moreover, epidemiological studies suggest complex links between multiple factors (demographic, socioeconomic, lifestyle, and health-related factors) and risks of dementia (Baumgart et al., 2015; Livingston et al., 2020). In the absence of curative treatments, research and intervention strategies have focused on identifying potentially modifiable risk factors for cognitive decline, dementia, and dementia-related outcomes (Baumgart et al., 2015; Livingston et al., 2020).

2.2.1 *Modifiable risk factors for cognitive decline and dementia*

In 2020, the Lancet Commission identified twelve modifiable risk factors with strong evidence within a life course framework of being causally related to dementia onset: low education, hearing loss, traumatic brain injury, hypertension, excessive alcohol consumption, obesity, smoking, depression, social isolation, physical inactivity, diabetes, and air pollution (Livingston et al., 2020). Education is an early life factor for participants ages 45 years and younger per the Lancet Commission's findings. Hearing loss, traumatic brain injury, hypertension, excessive alcohol consumption, and obesity were identified as midlife factors for those ages 45 to 64 years. Later life factors affecting those ages 65 years and older include smoking, depression, social isolation, physical inactivity, diabetes, and air pollution. The Lancet Commission also analyzed risk ratios from meta-analyses and global prevalence estimates of

each risk factor to conclude that approximately 40% of dementia cases globally could be attributable to these twelve potentially modifiable risk factors (Livingston et al., 2020). In a follow up analysis of some of the meta-analyses included in the Lancet Commission report, Lee et al. (2022) found that 41% of dementia cases in the U.S. were associated with these 12 potentially modifiable risk factors. These studies bolster the conviction that identifying and addressing modifiable risk factors in older adults—indeed, all adults—may reduce the risks of cognitive decline and dementia incidence (Aranda et al., 2021; Barnes, 2022; Penninkilampi et al., 2018).

Recent research examining the relationships between persistent pain and cognitive decline suggests that persistent pain maybe be a modifiable risk factor of cognitive function, cognitive decline, and dementia development (Berryman et al., 2013, 2014; Whitlock et al., 2017; Zhang et al., 2021). Persistent pain is posited as a modifiable risk factor because there are treatment options (if not definitive cures) and psychosocial interventions available at the individual level to address the physiological factors; the psychological factors (e.g., depression, coping skills/resiliency); and the social factors (e.g., social isolation) associated with persistent pain. However, while pain research has moved away from examining pain from a strictly biomedical framework to embracing a biopsychosocial approach (Gagliese et al., 2018; Gatchel et al., 2007; Miakowski et al., 2020), the social dimensions of pain have yet to be fully elucidated (Guillemin et al., 2014).

2.3 Overview of persistent pain

Persistent or chronic pain is now recognized as a distinct disease entity, rather than merely a symptom (Raffaeli & Arnaudo, 2017). According to the International Association for the Study of Pain, chronic pain is defined as pain that continues for a prolonged period beyond

the normal tissue healing time of three months and may or may not be associated with a well-defined disease process (Treede et al., 2015). While pain has traditionally been understood as involving sensory and physiological processes, recent research employing neuroimaging studies suggests pain experiences are deeply embedded in complex neurocognitive pathways and are significantly associated with cognitive, emotional, and social dysfunction (Malfliet et al., 2017; Ng et al., 2018). Recognizing the multidimensionality of pain beyond the sensory dimension, the Institute of Medicine's 2011 report, titled *Relieving Pain in America,* noted that pain experiences are more than just the biological output of tissue damage; an individual's attitudes, emotional disposition, and belief systems can profoundly shape the experience of pain.

In addition to highlighting the multidimensionality of pain, the IOM report (2011) called attention—and action—to the widespread prevalence of non-cancer chronic pain. More recent studies using U.S. nationally representative adult samples have found prevalence rates of around 20%, with a higher prevalence in women than in men, and higher pain intensity or severity in individuals with lower education attainment and income; and the higher prevalence rates among these sociodemographic groups seem to hold among older adult subpopulations (Fliesser et al., 2017; Grol-Prokopczyk, 2017; Janevic et al., 2017; Zelaya et al., 2020). Notably, however, past pain research has mostly focused on populations under the age of 65, and primarily sampled individuals with relatively little comorbidity and with good cognitive skills (Degnino & Campos, 2022). When epidemiological pain studies do include community-living adults aged 65 and older in the sample, the resultant estimates of persistent pain prevalence in this age population vary widely, ranging from 30% to 75% (Molton & Terrill, 2014; Patel et al., 2013; Sawyer et al., 2006; Tsang et al., 2008). The wide range in estimates can be attributed to varying survey methods, different study samples and data sources, reliance on self-reported data, and the lack of

standardized methods for defining and measuring chronic pain in clinical, experimental, and population-based studies; (IOM, 2011; Steingrímsdóttir et al., 2017). Numerous and diverse scales are used to measure pain, and most of these scales rely on self-report (Herr et al., 2019). These pain assessment scales may or may not include all components of pain experiences, such as pain intensity, pain duration, pain interference, and emotional regulation of pain. These methodological limitations, along with heterogeneity in study designs, hinder the ability to compare pain findings across different studies (Zimmer & Zajacova, 2020).

Several lines of evidence indicate that pain prevalence rates increase with advancing age (Schofield, 2007). Aging is often associated with slower healing and recovery from injury or disease (Docking et al., 2016; Fayaz et al., 2016; Molton et al., 2014; Tsang et al., 2008). Older adults are at particular risk of experiencing persistent pain (Dahlhamer et al., 2018; IOM, 2011; Zimmer & Zajacova, 2020). The higher prevalence of chronic medical comorbidities among older adults is thought to contribute to the higher chronic pain prevalence (IOM, 2011). A recent study found an increase in the prevalence of chronic pain in a nationally representative sample of older adults (Grol-Prokopczyk, 2017). However, an earlier study suggests that pain prevalence rates level off beyond the seventh decade of life (Cole et al., 2010). A possible explanation for the plateauing effect in pain prevalence in older persons could be cohort differences or mortality selection (Grol-Prokopczyk, 2017). Most importantly, it has been noted that the pain prevalence rates in older individuals may be underestimated—and thus undertreated—due to numerous challenges related to properly assessing pain in this population (Herr, 2011; Miakowski et al., 2020), especially in older persons experiencing cognitive impairment and dementia (Bullock et al., 2019; Gagliese et al., 2018; Herr et al., 2019; Hunt et al., 2015). Indeed, much more research

is need in the area of pain assessment in the older adult population (Hadjistavropoulos et al., 2007; Herr et al., 2011).

Pain assessment

The two common subdomains of self-reported pain are pain intensity and pain interference (Fillingim et al., 2016). Pain intensity refers to the magnitude of the self-reported pain (e.g., on a numeric scale of 1 to 10, with 10 being the worst pain experienced). Pain interference, also known as "pain impact," refers to the extent to which pain limits or interferes with one's abilities to complete daily-related, work-related, and/or social-related activities (Amtmann et al., 2010). One challenge in using the pain intensity construct in clinical and research contexts is that persistent pain often fluctuates greatly depending on the time of day, the activity level, and other associated factors (Kerns et al., 1988; Schneider et al., 2012; Von Korff et al., 1990). In contrast, the pain interference construct is viewed as having more temporal stability as it is more closely tied to functional abilities and quality of life (Broderick et al., 2010; Dworkin et al., 2005; Von Korff et al., 1990). Thus, pain interference, rather than pain intensity, has been shown to be associated with less measurement variability and is considered the primary measure in clinical trials and clinical pain treatment (Dworkin et al., 2009; Patel et al., 2021).

When the subdomain of pain interference is disaggregated from pain intensity in pain research, research findings often point to differential prevalence of pain interference versus pain intensity. For instance, a cross-sectional study of community-living adults aged 50 and older found that while pain prevalence was steady across cohorts in their 50s, 60s, 70s, and 80s, the degree of pain interference increased markedly with each increase in age group (Thomas et al., 2004, 2007). Gender is also associated with differential levels of pain interference: women tend to report higher levels of pain interference than men in population studies (Barry et al., 2012;

Tripp et al., 2006). Moreover, lower socioeconomic status has been found to be more strongly associated with self-report of increased pain interference but not pain intensity (Dahlhamer et al., 2018).

When relationships between pain interference and ethnoracialized identities were examined in the limited published studies, the findings have been inconsistent. An earlier study examining pain and disability in 115 community-dwelling, urban, older adults (M_{age} = 74 years; 52% non-Latinx Black older adults, 48% non-Latinx White older adults) found that the association between pain interference (defined in the study as disability arising from chronic pain) was stronger for non-Latinx White older adults than for non-Latinx Black older adults, after controlling for health and economic status (Horgas et al., 2008). A recent study using the Health and Retirement Study to examine pain intensity and interference among adults aged 50 and above and who self-identified as non-Latinx White, non-Latinx Black, and Latinx, found, on average, non-Latinx Black and Latinx adults experienced greater pain intensity and pain-related interference than non-Latinx White adults (Yang et al., 2022). Yang and colleagues (2022) found that racial and ethnic disparities in pain intensity, and some of the differences in pain interference, remained salient even after controlling for sociodemographic characteristics and other health conditions. This finding is concordant with research that finds that racial and ethnic disparities in various health conditions sometimes persist, albeit reduced, across all levels of socioeconomic status (Braveman et al., 2010; Williams et al., 2016).

2.4 Prevalences of persistent pain

Population-based studies indicate that certain demographic groups (e.g., female sex, older adults) and socioeconomic factors (e.g., low educational attainment, low socioeconomic status/position) have higher correlation with chronic pain and specific

chronic pain conditions (Mills et al., 2019; Mullins et al., 2022; Zajacova et al., 2021b). A study by Mullins et al. (2022) using the 2019 National Health Interview Survey, found, after accounting for all other demographic factors, age, female sex, lower educational attainment, and nonmarried status were associated with higher odds of having chronic pain. When severity of pain was examined, the researchers found female sex was associated with an adjusted odds ratio of 1.41 (95% CI: 1.25–1.59) for severe pain compared with male sex (Mullins et al., 2022). Notably, Mullins et al. (2022) concluded that lower educational attainment was an independent risk factor for both the development of chronic pain as well as increased pain severity among U.S. adults with chronic pain; individuals with the lowest level of education were found to have the highest odds of pain affecting life, work, and family most days.

Similarly, studies have found that individuals with lower socioeconomic status (SES) were more likely to experience more severe pain and a greater level of pain-related disability compared with those from higher SES (Boyd et al., 2016; Mills et al., 2019). Using data from the Health and Retirement Study to examine the distribution of non-cancer chronic pain among adults 51 years of age and older from 1998-2010, Grol-Prokopczyk (2017) found that individuals with lower income were more likely to report pain and experience more severe pain. Relatedly, Janevic et al. (2017) used a subsample (n = 1,925) of the Health and Retirement Study 2010 data and found that pain intensity and pain impact decreased as wealth increased. Likewise, an analysis of the 2016 National Health Survey data by Dahlhamer et al. (2018) found that adults living in or near poverty were more likely to experience chronic pain and high-impact chronic pain that limits life or work activities. Lastly, women with lower SES reported higher rates of severe chronic pain compared with

those with higher SES in studies that used data from the Health and Retirement Study (Grol-Prokopczyk, 2017; Janevic et al., 2017).

Findings of ethnoracialized disparities in pain prevalence have been mixed and not as consistent as for SES. Dahlhamer and colleagues (2018) analyzed the 2016 National Health Interview Survey data and found that non-Latinx White adults had a significantly higher age-adjusted prevalence of chronic pain than did all other ethnoracialized groups; however, the study did not find any significant differences in high-impact chronic pain prevalence by race and ethnicity. Similarly, a study by Zajacova and colleagues (2021b) that also used the National Health Interview Survey, but covering the period of 2002–2018 and for adults aged 25–84 (N = 441,707), found that non-Latinx White adults aged 65–84 years had 17% higher odds of reporting any pain than non-Latinx Black Americans, but were no more likely to report this outcome than other ethnoracialized subgroups. Similarly, a study by Mullins et al. (2022) using the 2019 National Health Interview Survey found that across ethnoracialized groups, non-Latinx White adults had the highest reported rates of chronic pain at 23.7% (22.9%–24.4%), compared with Latinx and non-Latinx Black adults. However, adult respondents who identified as belonging to Latinx or non-Latinx Black subgroups had higher odds of reporting more severe pain, compared with non-Latinx White adults (Mullins et al., 2022).

While pain prevalence rates by ethnoracialized subgroups may be inconsistent across trend studies, studies have found more consistent findings pointing to ethnoracialized disparities in pain assessment, pain care, and pain-related outcomes and disability (Campbell & Edwards, 2012; Green et al., 2005; Jefferson et al., 2019; Maly, 2020; Maly & Vallerand, 2018; Mossey, 2011). For instance, a study using a subsample of the 2010 Health and

Retirement Study found that adults from non-Latinx Black and Latinx subgroups were more likely to report greater pain severity and pain-related disability compared with non-Latinx White adults (Janevic et al., 2017). A recent study using the U.S. Census Bureau for the National Center for Health Statistics data found that individuals who self-identified as Black/African American, Native American, and Asian Indian had a higher likelihood of experiencing chronic pain that significantly interfered with important activities (i.e., work, social, and/or self-care activities), compared with individuals who self-identified as non-Latinx White, Latinx, Asian, or American Indian/Inuit (Pitcher et al., 2019). Lastly, a meta-analysis of 28 quantitative studies by Vaughn et al. (2019) focusing on adults with osteoarthritis found that the clinical pain severity was significantly higher among non-Latinx Black adults compared with non-Latinx White adults. Moreover, the non-Latinx Black participants had greater self-reported disability from the pain (i.e., pain interference) and greater disability in performing functional physical tasks compared with non-Latinx White adults (Vaughn et al., 2019).

Studies examining ethnoracialized disparities in pain care found that non-Latinx Black and Latinx subgroups face barriers to pain diagnosis and treatment, are more likely to receive inadequate pain management (Ly, 2019; Mossey, 2011); and experience lower quality pain care compared with non-Latinx White adults (Cintron & Morrison, 2006; Meghani et al., 2012). Moreover, studies have shown that non-Latinx Black and Latino patients were less likely to receive pain medication, particularly opioid analgesics, than non-Latinx White patients (Ly, 2019; Meghani et al., 2012; Pletcher et al., 2008; Singhal et al., 2016). Notably, a recent systematic review of cross-sectional, longitudinal, and interventional studies published from 2000 onward found that Latinx and non-Latinx Black adults have poorer outcomes and

management of their chronic pain conditions compared with non-Latinx White adults (Morales & Yong, 2021). Morales and Yong (2021) noted that there are many factors and underlying mechanisms that could contribute to ethnoracialized differences in the treatment of chronic pain at the individual, provider, and system levels.

2.5 Persistent pain and cognition in older adults

Numerous experimental and population-based studies have demonstrated that persistent pain is associated with adverse cognitive functioning in older adults, although the results have been inconsistent and substantial methodological limitations have been highlighted, including the predominance of cross-sectional, rather than longitudinal, study designs (see systematic reviews by Innes & Sambamoorthi, 2020; Yuan et al., 2023; Zhang et al., 2022). A widely cited model used to explain this pain-cognition association, the cognitive-affective model of the interruptive function of pain, posits that pain processing demands and competes for attention and limited cognitive resources (Eccleston & Crombez, 1999). As such, cognitive resources are consistently diverted to pain perception and maladaptive emotional and behavioral coping strategies (Eccleston & Crombez, 1999). This model was later further developed into the Neurocognitive Model of Attention to Pain (Legrain et al., 2009). Van der Leeuw et al. (2016) suggested the Neurocognitive Model of Attention to Pain as an explanation for their findings from a cross-sectional study of community-dwelling adults aged 70 and older (N = 765). The researchers found that older adults with more severe chronic pain or more pain interference had worse performance on memory tests and executive functioning tests compared with those with none or less severe pain; however, the strength of the associations diminished after adjusting for demographic and health measures (van der Leeuw et al., 2016).

Several longitudinal studies have also found negative associations between chronic pain and subsequent cognitive decline. For example, Whitlock and colleagues (2017) analyzed the Health and Retirement Study cohort data and found an inverse association between baseline persistent pain and accelerated 10-year memory decline; persistent pain was associated with 9.2% (95% CI [2.8%-15.0%]) more rapid decline in memory score compared with participants without persistent pain. A recent longitudinal study by Rong et al. (2021) using the English Longitudinal Study of Ageing provided additional evidence of this longitudinal association, although only for participants with moderate-to-severe persistent pain; compared with the no pain group, the moderate-to-severe persistent pain group demonstrated a significantly faster decline rate in global cognitive abilities. Interestingly, the relationships of moderate-to-severe persistent pain with verbal memory, temporal orientation, and semantic fluency were similar. Moreover, the study found that participants with severe pain status demonstrated faster cognitive decline in a dose-response pattern, and this relationship was demonstrated throughout multiple cognitive domains (Rong et al., 2021). Similarly, a prospective longitudinal study by Rouch et al. (2021) examined the influence of chronic pain on the 12-year change of neuropsychological performance in a population of community dwellers aged 65 years and older (n = 693) from the PAQUID cohort in France. The researchers found that the presence of moderate-to-severe persistent pain for more than six months was associated with lower levels in the latent global cognitive performance within 15 years of follow-up when compared with older adults with no or mild chronic pain, controlled for age, sex, education, comorbidities, depression, and analgesic medications. When the different neuropsychological test scores were assessed separately, the study found a greater decline in processing speed alone in older adults with moderate-to-severe persistent pain (Rouch et al., 2021).

Associations between pain and processing speed were also found in a longitudinal study by Bell et al. (2022b), which examined the associations of baseline pain, pain persistence, and incident pain with changes in cognition across 10 years in a sample of healthy community-living older adults (n = 688; M_{age} = 74, SD = 6.05) from the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial. Bell et al. (2022b) used multilevel models that adjusted for baseline age, time (years after follow-up), race, gender, education, marital status, and depressive symptoms at baseline and over time. The researchers found that 31 percent of participants reported pain at baseline which was associated with worse baseline memory and accelerated decline in processing speed. Additionally, 42 percent of older adults who reported incident pain had accelerated decline in complex processing speed, divided attention, memory, reasoning, and cognitive status. On average, older adults reported a mean of two waves of pain persistence related to accelerated decline in memory (Bell et al., 2022b).

Differences in cognitive outcomes associated with pain intensity versus pain interference have been noted in more recent longitudinal studies involving adults aged 65 and older. For instance, a study by Bell et al. (2022a) using 10 biennial waves of the Health and Retirement Study (n = 8,515; M_{age} = 74.17, SD = 6.87), examined the longitudinal associations of persistence of pain with cognitive performance, cognitive impairment, and subjective memory decline. The researchers found that duration of pain interference, rather than pain severity, was associated with worse cognitive performance in older adults over time; for every 2 years of persistence of pain interference (especially interference in daily housework and chores), there was an associated 21% higher odds of cognitive impairment (Bell et al., 2022a). Similarly, a longitudinal study involving older Puerto Rican adults (N = 2,349; M_{age} = 69.9; SD = 7.2 years) by Milani et al. (2023) found that higher pain interference over four years was associated with

lower cognitive function at follow-up; moreover, those adults with better baseline cognitive performance reported less pain at follow-up. Another longitudinal study by Milani et al. (2024) found that among very old community-dwelling Mexican American adults (aged ≥80) residing in the Southwestern U.S., both untreated and treated pain interference were associated with incident cognitive impairment.

Longitudinal studies that specifically examined persistent pain and dementia risk have also found positive associations. For example, Ezzati and colleagues (2019) examined 1,114 individuals aged 70 years and older from the Einstein Aging Study and found that pain intensity had no significant effect on time to developing dementia, whereas higher levels of pain interference were associated with a higher risk of dementia. A retrospective cohort study by Wang and Liu (2021) using the Framingham Heart Study data found that widespread pain—a common subtype of chronic pain that may reflect musculoskeletal disorders, such as fibromyalgia—was associated with 43% increase in all-cause dementia risk, and 47% increase in Alzheimer's disease dementia risk, adjusting for age and sex. A retrospective cohort study of older Appalachian Medicare beneficiaries (N = 161,573) found that baseline common non-cancer chronic pain conditions had a strong, positive, dose–response relationship to odds for incident ADRD after adjustment for covariates (AOR = 1.26; 95% CI [1.20, 1.32]); and this association appeared partially mediated by depression and anxiety (Khalid et al., 2022).

Attention, memory, and pain

Empirical research indicates that individuals with chronic pain often display cognitive deficits in the domains of attention and memory (Moriarty et al., 2011). A study looking at individuals with chronic pain disorders (fibromyalgia, rheumatoid arthritis, or musculoskeletal pain), found that those with chronic pain performed significantly worse than pain-free controls in

the domains of selective attention, sustained attention, and auditory-verbal working memory, controlling for age, depression, and anxiety (Dick et al., 2002). In another study, Dick and Rashiq (2007) examined attention and working memory performance in persons with chronic pain disorders; this study demonstrated that these individuals were significantly impaired on tasks of attention also revealed significantly worse working memory processes. Other studies have shown impaired memory in individuals with chronic low back pain compared with pain-free individuals (Ling et al., 2007; Mazza et al., 2018; Simon et al., 2016). A systematic review of 24 studies involving working memory deficits in adults with chronic pain found that those without chronic pain performed significantly better on working memory tasks (Berryman et al., 2013).

Other studies, however, found no associations between chronic pain and specific cognitive domains. A longitudinal study by van der Leeuw et al. (2018) examined the longitudinal association between pain (measured with the Medical Outcomes Study pain severity scale) and major cognitive impairment in participants (N = 441) without dementia enrolled in the prospective cohort study Central Control of Mobility in Aging. The researchers found that persistent pain was not associated with incident cognitive impairment in the three cognitive domains evaluated (attention, memory, and executive functioning), adjusted for age, gender, ethnicity, and education. However, the study noted that among those with chronic pain, the risk for developing major memory impairment was higher in individuals with high levels of pain intensity than those with low levels of pain intensity (van der Leeuw et al., 2018). Notable limitations of the study by van der Leeuw et al. (2018) were the small sample size (441 total participants, of which only 285 reported pain) and short follow-up duration (a mean follow-up of 2.75 years; SD = 1.94). Another longitudinal study using the English Longitudinal Study of

Ageing (N = 6,515; M_{age} = 65 years) investigated whether the presence and severity of pain at baseline could predict a decline in cognitive function over four years of follow-up. After adjusting for 26 potential confounders, the researchers found no association between pain presence and verbal fluency, memory, or processing speed in a four-year follow-up (Veronese et al., 2018). Only individuals with severe pain intensity were found to have marginally worsening memory tests in this study by Veronese et al. (2018). Taken together, however, these two studies share common research challenges such as variability in the definition and measurement of chronic pain, lack of generalizability in the findings, and insufficient length of follow-up time of less than five years to observe meaningful cognitive changes. Thus, it is not surprising that results from these studies have been inconsistent.

Evidence suggests a close association between chronic pain and executive functioning; individuals with chronic pain demonstrate deficits in executive functioning relative to adults without pain (Berryman et al., 2014). A recent systematic review of 57 studies involving chronic pain, the researchers found that executive functioning performance was reduced in individuals with chronic pain compared with pain-free controls, with all three subdomains of executive functioning delineated by Miyake et al. (2000)—response inhibition, complex "frontal lobe" or "executive" tasks, and set shifting—being similarly affected (Bunk et al., 2019). Similarly, in a meta-analysis of 22 studies, Berryman et al. (2014) examined chronic pain in relation to these same three subdomains of executive functioning. The pooled results from this meta-analysis showed small to moderate impairments in all three subdomains of executive functioning in adults with chronic pain relative to adults without pain. However, Berryman et al. noted that many of the studies in the meta-analysis did not control for the

potential effects of medications or sleep. Additionally, there was heterogeneity across study designs and a high risk of bias (Berryman et al., 2014).

Systematic reviews of the pain-cognition relationships

Notably, a systematic review and meta-analysis pooling data from 10 longitudinal studies and 57,495 participants concluded that persistent pain was not associated with the development of cognitive decline in older adults (*OR* = 1.05 95% CI [0.92-1.21]; de Aguiar et al., 2020). However, in discussing the limitations of their study, de Aguiar and colleagues (2020) pointed to lack of standardization in the measurement of pain and cognition in the studies included in their systematic review, which made it difficult to compare studies. Moreover, they also noted that differences in study design and duration, age range of the study samples, and recruitment methods may have contributed to the inconsistent findings in the literature. These challenges and limitations were raised also in the systematic review of the chronic pain-cognition relationship by Innes and Sambamoorthi (2020). Like de Aguiar and colleagues (2020), Innes and Sambamoorthi (2020) stressed the need for long-term prospective studies to investigate the effects of chronic pain and specific chronic pain conditions on cognitive decline and conversion to ADRD.

Yuan and colleagues (2023) conducted a more recent systematic review and meta-analysis of the relationship between persistent pain and cognitive decline and dementia, pooling data from 35 cohort studies containing 1,122,503 participants. The researchers found that persistent pain (*OR* = 1.24; 95% CI [1.17, 1.31]) was a risk factor for subsequent cognitive decline or dementia (Yuan et al., 2023). Moreover, in their meta-analysis, Yuan et al. (2023) found that chronic pain increased the risk of all-cause dementia, Alzheimer's disease, and

vascular dementia. Specifically, the study found that pain interference was associated with an increased risk of cognitive decline or dementia, while pain intensity was not (Yuan et al., 2023). Compared with the systematic review and meta-analysis by de Aguiar et al. (2020), Yuan and colleagues (2023) included more cohort studies (35 vs. 10); the proportion of studies with sample sizes less than 2000 was smaller (20% vs. 50%); and the number of studies of low quality was lower (3% vs. 10%). Moreover, Yuan and coauthors noted that in the two years after the publication of de Aguiar et al.'s (2020) systematic analysis, several new cohort studies were published, most of which have shown that chronic pain in older adults can significantly increase the risk of cognitive decline or dementia (e.g., Khalid et al., 2022; Wang & Liu, 2021). However, the systematic review by Innes and Sambamoorthi (2020) and the systematic reviews and meta-analyses by Yuan et al. (2023) and de Aguiar et al. (2020) concluded that the linkages between persistent pain and cognitive decline are likely multifactorial and involve many potential confounders, mediators, and moderators that were not measured in most of the studies reviewed.

Lastly, research highlights an additional dimension of the pain-cognition relationship beyond the theory of limited cognitive resources initially posited by Eccleston & Crombez, 1999. Increasing evidence suggests that the relationship between persistent pain and cognitive decline is bidirectional and multifactorial (Moriarty et al., 2011; de Aguiar et al., 2020; Zhang et al., 2022). More recent advances and findings from functional imaging and electrophysiological measures indicate pain and cognition are interdependent through a reliance on shared neural networks (Legrain et al., 2011; Moriarty et al., 2011). Recent research in neuroplasticity indicates that prolonged duration of persistent pain may have long-term effects on brain structure and networks necessary for intact cognitive processing, and these two systems may affect one

another reciprocally (Higgins et al., 2018). However, the relationships and causal mechanisms of persistent pain and cognitive decline remain unclear and underexamined (de Aguiar et al., 2020; Innes & Sambamoorthi, 2020; Zhang et al., 2022).

Education as a confounder in the pain-cognition relationship

Education is one important confounder and potential moderator and/or mediator in both pain research and cognitive health research. Education is a well-established social determinant of health over the life course; it is closely linked to health disparities (Braveman et al., 2011; Zajacova & Lawrence, 2018) and is a potentially modifiable risk factor of dementia (Livingston et al., 2020; Peterson et al., 2020) and chronic pain (Case & Deaton, 2022). Ample studies indicate positive associations between individuals with more years of education and a lower risk of dementia or delayed onset of ADRD-related accelerated declines (Clouston et al., 2020; Maccora et al., 2020; Meng & D'Arcy, 2012). However, because certain racial and ethnic subgroups, on average, tend to have less education attainment, it has been suggested that the higher prevalence of dementia rates in these subpopulations may reflect these educational disparities (Rodriguez et al., 2018; Zahodne et al., 2017, 2021). For instance, Peterson and colleagues (2020) conducted a narrative review of the evidence of associations between six modifiable risk factors (education, smoking, physical inactivity, obesity, social isolation, and psychosocial stress) and Alzheimer's disease risk in non-Latinx Black and non-Latinx White subgroups. Of the six examined risks, education provided the strongest evidence of association with cognitive outcomes in these two subgroups (Peterson et al., 2020).

More research is needed in this area to elucidate the influence of educational attainment on ethnoracialized differences in pain prevalence rates, and the intersection of chronic pain and cognitive decline in older adults. Since education interacts with other contextual factors in health

disparities, the health benefits of education may have differential returns across different sociodemographic subgroups, which can be explained by theories of resource substitution and intersectionality (Vable et al., 2018). Differential returns to education may arise because groups that are socially marginalized (e.g., due to race and ethnicity, gender, SES, immigration status, etc.) have less access to health-promoting alternatives to education (e.g., power, authority, earning, social capital, etc.), which may result in greater dependence on the resources to which one has access (e.g., education)—potentially contributing to larger returns to education for socially marginalized groups (Vable et al., 2018).

2.6 Racial and ethnic disparities in cognitive health and pain experiences

Ethnoracialized disparities in cognitive function and Alzheimer's disease and related dementia prevalence in U.S. older adults are well documented (Lin et al., 2021; Matthews et al., 2019; Mayeda et al., 2016; Seblova et al., 2022). Likewise, there is an emerging evidence base of the influence of ethnoracialized group membership on older adults' pain experiences and resulting ethnoracialized disparities in pain prevalence in older adult populations (Miaskowski et al., 2020; Zimmer & Zajacova, 2020). However, linkages of persistent pain and cognitive decline remain under investigated in certain ethnoracialized groups.

While more research is needed, researchers have cautioned against reducing racial and ethnic disparities in health risks and health conditions to racial and ethnic essentialism (Adkins-Jackson et al., 2022; Bailey et al., 2017, 2021; Tsai, 2022). That is, race—a social construct and not a biological category—is not a risk factor for racialized health disparities; rather, race is a risk marker of racism and structural inequities (Krieger, 2000; Tsai, 2022). Indeed, an understanding of racial and ethnic disparities in cognitive decline and dementia requires understanding the structural and contextual factors of cognitive health, such as differential access

to healthcare, educational attainment and education quality, and cumulative advantages and disadvantages between different groups from longstanding structural inequities (Barnes, 2022; Glymour & Manly, 2008; Zahodne et al., 2016, 2021). In other words, we need to understand how these contextual factors and structural inequities may "get under the skin" and become "embodied" in biological processes (Krieger, 2000, 2021) to engender bodies in pain and neurodegenerative pathologies.

2.7 Gaps in the literature

The factors driving racial and ethnic disparities in pain experiences and cognitive aging and how they may be related remain under studied. To our knowledge, very limited research has been carried out to investigate racial and ethnic disparities in the intersection of pain and cognitive functioning in demographically diverse older adults. Published studies examining the associations of persistent pain with cognitive decline rarely include adults aged 65 and older from racially and ethnically minoritized groups. Very few cohort studies include sufficient sampling of older adults identified as non-Latinx Asian and Latinx to evaluate the persistent pain-cognition associations by multiethnic group membership; and fewer studies include multiple racial and ethnic subgroups to examine potential effect modification by race and ethnicity. In addition, few observational studies have examined the relationships between persistent pain and cognitive decline in the context of education attainment. This study addressed this gap in the literature by examining potential effect modification of the pain-cognition associations by sex, education attainment, and multiethnic group membership. The study's approach to data analysis was informed by three guiding questions for health disparity investigation proposed by Ward and colleagues (2019): Is there a difference in the prevalence of the outcome between groups? Is there a difference in the prevalence of the exposure between

groups? Does the relationship between the exposure and outcome differ between groups? Accounting for multifactorial heterogeneity may advance our understanding of whether differences in pain experiences may contribute to late-life cognitive health disparities, particularly ethnoracialized health disparities, and cognitive decline risk in diverse older adults.

CHAPTER 3: METHODS

3.1 Overview

This study aimed to understand the relationships between pain interference and objective measures of cognitive function among ethnoracially-diverse older adults residing in Northern California. To achieve this goal, the study conducted secondary data analysis to investigate the following specific aims.

Aim 1. Examine the cross-sectional associations between pain interference and executive functioning (EF) and verbal episodic memory (VEM) scores among all study participants.

Aim 2. Investigate whether sex, ethnoracialized group membership, and educational attainment moderate the associations in Aim 1.

3.2 Data source and study sample

Data for this secondary analysis came from the Kaiser Healthy Aging and Diverse Life Experiences (KHANDLE) Study. KHANDLE is an ongoing prospective cohort study being conducted by research teams from Kaiser Permanente Northern California (KPNC) Division of Research and the University of California, Davis Alzheimer's Disease Center (Eng et al., 2019; Mungas et al., 2021). KHANDLE aims to evaluate how race and ethnic group membership, early-life experiences, life course health, and sociocultural factors influence racial and ethnic cognitive differences in late-life brain health and cognitive aging among community-dwelling older adults residing in Northern California in the San Francisco Bay area and Sacramento Valley (Eng et al., 2019; Mungas et al., 2021). To achieve these aims and enroll a diverse cohort, the KHANDLE research team carried out stratified random sampling by race, ethnicity, and educational attainment on KPNC member population. Eligible participants were long-term

members of KPNC; aged 65 years and older on January 1, 2017; had participated in one or more multiphasic health checkups at KPNC between 1964 and 1985; were English or Spanish speakers; and did not have a medical records diagnosis of dementia at the time of study enrollment in 2017 (Mungas et al., 2021). A total of 1,712 community-dwelling older adults were recruited for the baseline cohort, with approximately equal proportions of Asian, Black, Latinx, and White participants. Prior research indicated that the KPNC older adult population aged 65 and older share similar health characteristics to the population of older adults residing in Northern California with respect to medical history of chronic conditions, and behavioral factors, including smoking, obesity, and sedentary lifestyle (Gordon, 2015).

The primary study includes the collection of data from the KPNC multiphasic health checkups (MHC), baseline study assessments and interviews, and follow up interviews. Between 1964 and 1985, KPNC conducted voluntary multiphasic health checkups (MHC), a series of wellness assessments, at Kaiser Permanente Oakland and San Francisco Medical Centers. Through the patient self-reported questionnaires and clinical assessments of the MHCs, Kaiser collected information on demographics, health-related activities, and health indicators and risk factors. For the KHANDLE study, trained Kaiser research interviewers conducted the baseline study assessments and interviews of the selected participants in 2017. Follow-up interviews have been conducted, on average, 17.4 months after baseline assessment. Participants in wave 1 (2017-2018) and wave 2 (2019-2020) had in-person interviews in their residences or at a KPNC facility. In the interviews, participants are asked about life course environment exposures and psychosocial factors.

3.2.1 Protection of human subjects

The original KHANDLE Study was approved by the Kaiser Permanente Northern California and University of California, Davis, Institutional Review Boards (IRB Number: CN-16-2786). All enrolled participants provided written informed consent according to the IRB-approved protocol. The Institutional Review Board at the University of California, Davis determined that because the present study used de-identified data from a previously approved study, this research was exempt from review.

3.2.2 Sampling and eligibility criteria of the original KHANDLE study

The primary study enrolled 1,712 individuals at wave 1. Three enrollees who self-identified primarily as Native American were excluded due to concerns about small numbers and identifiability (Eng et al., 2019). Average baseline age of the participants was 76 years. Over half (56.8%) of participants self-identified as female sex. Ethnoracialized composition of the 1,709 participants was as follows: 503 non-Latinx White (29.4%), 441 non-Latinx Black (25.8%), 415 Asian (24.3%), and 350 Latinx (20.5%) participants (Eng et al., 2019). Most non-Latinx White (84.1%) and non-Latinx Black (96.4%) participants were born in the U.S., while about half of non-Latinx Asian (50.6%) and Latinx (58%) participants were U.S. born (Eng et al., 2019).

Inclusion criteria of the primary study. Individuals eligible for KHANDLE were long-term members of Kaiser Permanente Northern California (KPNC); were age 65 years or older on January 1, 2017; spoke English or Spanish; had previously participated in KPNC multiphasic health checkups; and did not have a current diagnosis of dementia in their electronic medical record at the time of study enrollment in 2017.

Exclusion criteria of the primary study. Individuals were excluded if they had an electronic health record diagnosis of dementia or other neurodegenerative disease

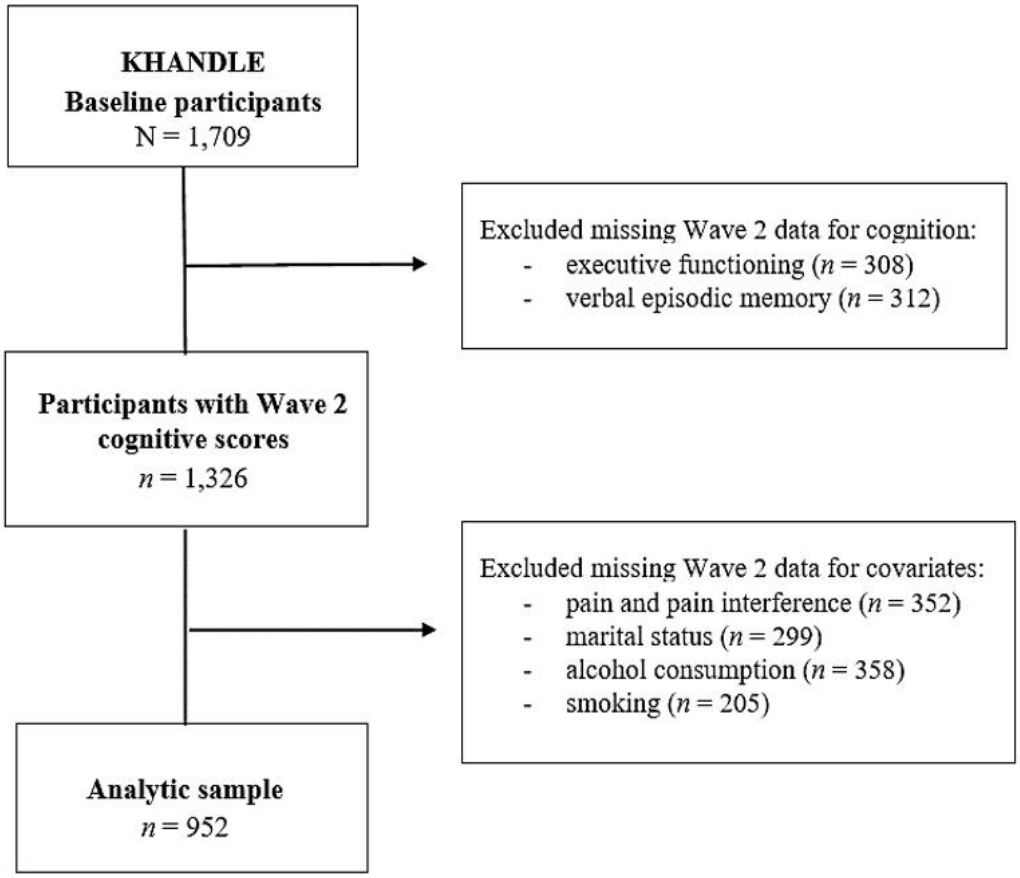
(frontotemporal dementia, Lewy body disease, Pick's disease, Parkinson's disease with dementia, Huntington's disease); and presence of health conditions that would impede participation in study interviews (e.g., hospice activity in the past 12 months, history of severe chronic obstructive pulmonary disease in the past 6 months, congestive heart failure hospitalizations in the past 6 months, and history of end stage renal disease or dialysis in the past 12 months).

3.2.3 Analytic sample

For the current analysis, individuals from the baseline cohort sample of 1,709 were excluded if they were missing scores for verbal episodic memory (n = 312) and executive functioning (n = 308) at wave 2; missing responses to the pain questions in both wave 1 and wave 2 (n = 352); or missing wave 2 data on the primary model covariates. Figure 3.1 presents the flow diagram showing the distillation of the final analytic sample (n = 952).

Figure 3.1

Flow Diagram of the Analytic Sample Selection



3.3 Measures

3.3.1 Outcome variables: Executive functioning and verbal episodic memory

The cognitive domains of executive functioning (EF) and verbal episodic memory (VEM) comprise a subset of the SENAS neuropsychological tests, which have undergone extensive development as a battery of cognitive tests (Mungas et al., 2000, 2004, 2005). SENAS was developed with the use of modern psychometric methods based on item response theory (IRT) to create psychometrically matched measures across different cognitive domains and across English and Spanish versions (Mungas et al., 2000, 2004). Notably, SENAS was explicitly developed for research purposes and is designed to measure small, subtle changes in cognition without limitation due to floor or ceiling effects (Mungas et al., 2000, 2004). Details of the administration procedures, development, and psychometric characteristics of SENAS have been extensively described in previous publications (Mungas et al., 2000, 2004, 2005).

The SENAS is administered in each wave in either English or Spanish. Language of test administration is determined by an algorithm that combined information regarding each participant's language preference and language usage in several specific contexts (e.g., conversing at home, listening to radio or television, conversing outside the home, preferred language for reading). As the SENAS and interview questions are not administered in other languages besides English or Spanish in the different waves of data collection, individuals who spoke other languages besides Spanish (e.g., Cantonese, Mandarin, Tagalog) needed English proficiency to participate in the KHANDLE study.

Due to the COVID-19 pandemic and the implementation of safety protocols, 4% of participants in wave 2 had the SENAS administered by telephone interviews, while the rest had completed the SENAS in person prior to the change in study protocols. As the assessment of

semantic memory in SENAS includes visual stimuli, the four percent of participants who had telephone interviews in wave 2 had data collected only for verbal episodic memory and executive function neuropsychological assessments. For this reason, this study utilized wave 2 cognitive domain scores and restricted the outcome measures to the cognitive domains of verbal episodic memory and executive functioning. Moreover, prior studies suggest that the domains of attention, memory, and executive functioning are more strongly associated with persistent pain than other cognitive domains (Berryman et al., 2014; Moriarty et al., 2011; van der Leeuw et al., 2018).

In SENAS, the VEM and EF scores are constructed as composite scores (Mungas et al., 2011). The VEM score is an item response theory score derived from a multi-trial 15-item word-list learning test. The interviewer reads the word list out loud to the participants over five learning trials. The number of words recalled across each of these five trials signifies specific indices of learning. Also administered as part of the episodic memory assessment is a delayed free recall trial following a distractor task. Scores from the five learning trials and delayed recall trial combine to constitute the VEM composite score.

The EF composite score is calculated from item response theory scores for component tasks of category fluency, phonemic fluency, and working memory. Category fluency, also known as semantic fluency, is a traditional verbal fluency task requiring participants to name as many animals as possible for 60 seconds. Phonemic fluency, also known as letter fluency, is a traditional letter fluency task that has been modified in SENAS so that it is applicable to illiterate persons. Participants are asked to name as many words as possible that begin with specific sounds for 60 seconds. Lastly, working memory is a composite measure derived from three tasks: Digit Span Backwards, Visual Span Backwards, and List Sorting. In the Digit Span

Backwards task, participants are asked to repeat number sequences backwards. Visual Span Backwards is a backward variant of Visual Attention Span task; participants are asked to point to dots on a page in reverse order from that presented by the examiner. List Sorting is comprised of two parts. In part 1, participants are presented with a list of fruits or animals and are asked to repeat all of the elements on the list, in order from smallest to largest. In part 2, the lists include both fruits and animals. Participants are instructed to repeat fruits first, sorted from smallest to largest, and then animals in order from smallest to largest. Details of the cognitive assessment performed in the KHANDLE Study can found in Hernandez Saucedo et al. (2022).

Lower scores in each cognitive domain and subdomain indicate worse cognitive functioning. The present study used wave 2 cognitive scores. The composite scores in each cognitive domain (VEM and EF) and the scores in the subdomains of EF (category fluency, phonemic fluency, and working memory) were *z*-standardized for analysis using the wave 2 sample mean and standard deviation (*SD*) to represent standard deviation units (mean of 0 and *SD* of 1, range of −3.3 to 3.3).

3.3.2 Primary exposure: Pain interference

The primary exposure of interest was pain interference, which was defined as having persistent pain that made it difficult to do usual activities such as household chores or work. To operationalize the pain interference variable, I first categorized persistent pain. As the KHANDLE Study does not directly assess persistent pain (i.e., no assessment of pain duration and chronicity), I used the responses to the pain presence question from both waves 1 and 2. Participants were asked at wave 1 and wave 2 interviews, “Are you often troubled with pain?” The two possible responses are “yes” or “no.” I categorized participants who responded “no” to the pain presence question in both waves 1 and 2 as having “no persistent pain.” Similarly,

participants who responded “no” to the pain presence question in either wave 1 or wave 2 were categorized as having “no persistent pain.” I categorized individuals who responded “yes” to having pain presence in both waves 1 and 2 as having persistent pain.

Participants who respond “yes” to the pain presence question were subsequently asked in the KHANDLE wave 1 and wave 2 interviews, “Does the pain make it difficult for you to do your usual activities such as household chores or work?” The two possible responses are “yes” or “no.” I constructed a 3-level ordinal pain interference variable using persistent pain status (yes/no) and pain interference (yes/no). Individuals categorized in the “No Persistent Pain” group were deemed not to have pain interference; this group served as the reference group and was assigned a score of 0. Individuals who were deemed to have persistent pain status but reported that the pain did not interfere with usual activities were assigned to the “No Pain Interference” group and assigned a score of 1. Individuals who were deemed to have persistent pain and reported that the pain interfered with usual activities were assigned to the “Pain Interference” group and given a score of 2.

3.3.3 Covariates

The present study included several individual-level sociodemographic, health, and behavioral factors as *a priori* potential confounders. Previous studies have shown that sex, age, marital status, depressive symptoms, alcohol use, and smoking status have been associated with persistent pain and cognitive functioning (Innes & Sambamoorthi, 2020; Whitlock et al., 2017; Yuan et al., 2023; Zhang et al., 2022). Additionally, substantial evidence suggests cognitive performance scores are strongly influenced by racial and ethnic group membership (Brewster et al., 2014; Masel & Peek, 2009; Quiñones et al., 2022; Weuve et al., 2019) and educational attainment (Eng et al., 2021; Gross et al., 2015; Quiñones et al., 2022; Sisco et al., 2015).

Age, a continuous variable, was calculated at time of wave 2 interview date from the participant's date of birth (obtained from the health record data). Age was top coded to 90 years.

Sex, a binary variable, corresponded to whether the respondent self-identified as female or male at wave 1 interview. Participants who self-reported "other" or "refused" had values for biologic sex imputed from their Kaiser Permanente electronic health records.

Race and ethnicity, a categorical variable, was determined from the participant's self-reported ethnoracialized group membership at wave 1 interview, or from the participant's Kaiser Permanente health record if missing. This study employed the race and ethnicity assignment of participants following the method described in previously published KHANDLE studies (e.g., Eng et al., 2021; Meyer et al., 2023). Participants were classified as Latinx, non-Latinx Asian, non-Latinx Black, or non-Latinx White through a specific race and ethnicity assignment algorithm to account for individuals who reported multiple ethnicities and/or multiple races. Thus, participants reporting multiple ethnicities within the same major racialized group were categorized as belonging to a single racialized group. For persons reporting multiple ethnicities across major ethnoracialized groups, duplicate observations were created for each additionally reported ethnoracialized group of that individual and assigned a weight of 1 divided by the number of reported racial and ethnic groups (Eng et al., 2021). For details of the algorithm for race and ethnicity assignment utilized in KHANDLE, see Eng et al. (2021) and Meyer et al. (2023).

Marital status, based on wave 2 interview, was categorized as dichotomous: married/partnered or unpartnered, with the latter including participants who reported being divorced, separated, widowed, or never married.

Educational attainment, a continuous variable, was measured by self-reported years of education at wave 2. This study operationalized education attainment according to the method by Calmasini et al. (2022). For participants with greater than a high school education, years of education was calculated from a categorical variable coded so that some college, but no degree = 13 years; Associate's degree = 14 years; Bachelor's degree = 16 years; Master's degree = 18 years; and Doctoral or equivalent degree = 20 years. Following the method by Corlier et al. (2020), for participants with vocational degrees and certificates but no Associate's degrees, each certificate attainment was counted as an additional year of education.

Depressive symptoms were measured using the 4-item Patient-Reported Outcomes Measurement Information System® (PROMIS®) Depression assessment (Short Form 4a) computer adaptive testing (CAT) v1.0, and was administered through the National Institutes of Health (NIH) Toolbox. The four questions in the NIH PROMIS® Depression short form questionnaire query emotional, cognitive, and behavioral manifestations of depression experienced by participants in the last seven days. The responses range on a 5-point Likert scale from 1 ("Never") to 5 ("Always"). The NIH PROMIS® Depression assessment has demonstrated strong convergent validity with the Center for Epidemiological Studies Depression Scale (CESD) and the Patient Health Questionnaire-9, commonly known as PHQ-9 (Pilkonis et al., 2014). The total raw score of depressive symptoms was then standardized to a theta score per convention (Chapman, 2022).

Smoking status, a categorical variable (current smoker, past smoker, and never smoker), was measured by participants' self-report to the question of whether they ever smoked cigarettes in the past and/or currently smoke cigarettes.

Alcohol use, a continuous variable, was measured by a combination of the participants' self-report of the number of drinks on days in which they drank and the frequency with which they drank. To calculate the quantity of weekly alcohol use, this study followed the convention established by Calmasini et al. (2022). If both volume and frequency values were missing, I used the answer to the question "Do you ever drink alcoholic beverages such as beer, wine or liquor?". If participants responded no, we assigned 0 drinks for volume and none or less than once a week for frequency. If participants responded yes, but did not respond to the frequency and volume questions, I set weekly alcohol use to missing.

*Phone interview***.** To account for the 4% of participants who had phone interviews in place of in-person interviews in wave 2, I added an indicator variable called "phone" and assigned the value 1 to those participants who had phone interviews; while the value 0 was assigned to those who had in-person interviews. The *phone* variable was included in all adjusted models as a covariate.

3.4 Statistical analysis

All analyses were conducted using R statistical software, version 4.3.3 (R Project for Statistical Computing, Vienna, Austria). All *p*-values presented were from 2-tailed analyses, with $p < .05$ considered statistically significant.

Data cleaning was conducted using the following R packages: "tidyverse," "naniar," and "finalfit." Statistical analysis was performed using the following R packages: "lessR," "car", and "emmeans." Graphs, tables and figures were created using the following R packages: "Hmisc," "ggplot2," "ggstatsplot," "PerformanceAnalytics," "performance," "sjPlot," "gt" and "gtsummary."

3.4.1 Missing data

Missing data analysis was carried out to generate counts and frequencies of missing values, and to visualize patterns of missingness with heat maps and correlation matrices. I performed Little's chi-square test (using "naniar" R package) to assess whether the missing values were missing completely at random (MCAR) (Little, 1988). The resultant high statistic value ($\chi^2 = 521$) and low *p*-value (< .001) of Little's test indicated that the missing values were not MCAR. I conducted further analysis by creating a binary variable (called "missing") that represented whether the data value was missing (1) or not missing (0) for each predictor variable and used logistic regression to regress all predictor variables on to the "missing" variable to obtain *z*-values for all predictor variables. I then calculated the *p*-values from the *z*-values for each predictor variable. All resultant *p*-values were non-significant, indicating that the missing values in the variables of interest were MAR. While there was a high number of missing values for the pain-related questions in wave 2, I decided not to use multiple chain imputation procedures as this method did not seem likely to give good estimates of the missing pain values. Instead, I opted to use complete-case analysis to handle missing data. The analytic sample of 952 complete cases provided sufficient power for the study.

3.4.2 Data analysis

I performed data diagnostics using histograms, scatterplots, and other data visualization to assess for outliers and data distribution. Preliminary data analyses included univariate distributions of all variables. Raw numbers and percentages were used for categorical variables; and means and standard errors were used for continuous variables. I performed bivariate analysis to evaluate the relations among variables of interest. To test for significant associations between categorical variables, I used chi-square test. To test for significant correlations between

continuous variables, I used Pearson's correlation coefficient. Nonparametric equivalences were used in cases in which there were violations of normality. To test whether there were statistically significant differences in the means of VEM and EF scores across the ethnoracialized subgroups, I employed one-way analysis of variance (ANOVA).

For linear regression analyses, I first performed unadjusted modeling to examine the associations between pain status and each cognitive domain separately. VEM and EF scores were regressed on pain interference status, and the magnitude of the association was determined by the pain interference coefficient. Next, I repeated each of the linear regression analyses to adjust for covariates. I used Pearson correlation coefficients and variance inflation factor (VIF < 2.0) diagnostic methods to screen for multicollinearity among variables included in the models. Model 1 minimally adjusted for age, sex, and race and ethnicity. Model 2 further adjusted for educational attainment, marital status, smoking status, and alcohol use. I used the *F*-test to assess the overall model significance, and the adjusted *R* square values to assess how much variance in the respective outcome can be accounted for by the predictors.

For research aim 2, I investigated effect modification by introducing the following interaction terms into the linear regression models: pain interference*race, pain interference*sex, and pain interference*education. If the omnibus test of the interaction effect was statistically significant, I retained that specific interaction term in the model and performed stratum-specific moderation analysis using the "emmeans" package for R, which utilizes estimated marginal means for multiple comparisons.

CHAPTER 4: RESULTS

4.1. Descriptive statistics

Table 4.1 presents a descriptive summary of the demographic characteristics and other variables for the study participants overall as well as stratified by pain status. The analytic sample (N = 952) was 59.1% female with a mean age of 76.79 (SD = 6.21); 31.8% of the participants identified as non-Latinx White; 24.5% as non-Latinx Asian; 25.1% as non-Latinx Black; and 19.5% identified as belonging to Latinx ethnic group. The average years of educational attainment was 14.98 (SD = 2.90). The majority of participants reported being married or in a relationship (56.6%) and having never smoked (57.5%). Overall, 56.1% of participants reported having no persistent pain; 19.0% reported having persistent pain but no pain interference on a regular basis; and 24.9% reported having persistent pain that interfered with usual activities such as work and house chores. Compared with participants without persistent pain or without pain interference, older adults in the pain interference group were more likely to be women (67.9%); have non-Latinx Black group membership (29.5%); have lower mean years of educational attainment (M = 14.31, SD = 3.09); more likely to be unpartnered (52.7%); and more likely to be former smokers (49.4%).

Table 4.1

Demographic Characteristics and Other Variables of the Study Participants

Characteristics	Overall	Pain Status			*p*-value [a]
		No Persistent Pain	No Pain Interference	Pain Interference	
Total, *n* (%)	952 (100)	534 (56.1)	181 (19.0)	237 (24.9)	
Sex, *n* (%)					**.004**
Female	563 (59.1)	294 (55.1)	108 (59.7)	161 (67.9)	
Age (yrs), mean (*SD*)	76.79 (6.19)	76.93 (6.33)	76.50 (5.74)	76.70 (6.21)	.898
Range	67.27 – 90.00	67.30 – 90.00	67.89 – 90.00	67.27 – 90.00	
Race and ethnicity					**.004**
Latinx	186 (19.5)	93 (17.4)	43 (23.8)	50 (21.1)	
Non-Latinx Asian	224 (23.5)	152 (28.5)	33 (18.2)	39 (16.5)	
Non-Latinx Black	239 (25.1)	124 (23.2)	45 (24.9)	70 (29.5)	
Non-Latinx White	303 (31.8)	165 (30.9)	60 (33.1)	78 (32.9)	
Education (yrs), mean (*SD*)	14.98 (2.90)	15.28 (2.69)	14.95 (3.11)	14.31 (3.09)	**.001**
Range	0.00 – 20.00	1.00 – 20.00	2.00 – 20.00	0.00 – 20.00	
Marital status, *n* (%)					**.002**
Married/partnered	539 (56.6)	325 (60.9)	102 (56.4)	112 (47.3)	
Unpartnered	413 (43.4)	209 (39.1)	79 (43.6)	125 (52.7)	
Smoking status, *n* (%)					
Never smoker	547 (57.5)	335 (62.7)	103 (56.9)	109 (46.0)	
Current smoker	20 (2.1)	6 (1.1)	3 (1.7)	11 (4.6)	
Former smoker	385 (40.4)	193 (36.1)	75 (41.4)	117 (49.4)	
Alcohol use, mean (*SD*)	2.69 (4.54)	2.92 (4.81)	2.98 (4.61)	1.97 (3.74)	**.005**
Range	0.00 – 28.00	0.00 – 28.00	0.00 – 21.00	0.00 – 28.00	

Notes. Alcohol is calculated as total number of drinks per week. Abbreviation: *SD* = standard deviation.

[a] Kruskal-Wallis rank sum test; Pearson's chi-square test. *P*-value was not calculated for current smoker status variable due to small cell sizes.

Table 4.2 displays the descriptive summary of the cognitive score distributions for the outcome variables: verbal episodic memory and executive functioning, including the EF subdomains of category fluency, phonemic fluency, and working memory. Participants categorized as having pain interference had a significantly lower mean EF score (M = -0.10, SD = 0.97; p = .028) compared with participants without persistent pain or without pain interference. Similarly, they also had a significantly lower mean scores in the EF subdomains of phonemic fluency (M = -0.12, SD = 1.00; p = .015) compared with participants without persistent pain or without pain interference. Comparison of the mean scores of category fluency (M = -0.05, SD = 0.96; p = .066) and working memory (M = -0.07, SD = 0.97; p = .107) were statistically non-significant. Likewise, for verbal episodic memory, participants in the pain interference group had statistically non-significant mean score (M = 0.09, SD = 0.99; p = .540) compared with participants without persistent pain or without pain interference.

Table 4.2

Descriptive Summary of Cognitive Domain Scores

Characteristics	Overall	Pain Status			*p*-value[a]
		No Persistent Pain	No Pain Interference	Pain Interference	
Total, *n* (%)	952 (100)	534 (56.1)	181 (19.0)	237 (24.9)	
Executive Function					**.028**
Mean (*SD*)	0.05 (0.99)	0.09 (1.00)	0.14 (0.97)	-0.10 (0.97)	
Median (*IQR*)	0.01 (-0.60, 0.73)	0.04 (-0.58, 0.76)	0.13 (-0.52, 0.84)	-0.10 (-0.71, 0.48)	
Range	-2.79 – 3.07	-2.63 – 3.07	-2.24 – 2.37	-2.79 – 2.74	
Category Fluency					.066
Mean (*SD*)	0.03 (0.98)	0.03 (1.02)	0.15 (0.86)	-0.05 (0.96)	
Median (*IQR*)	0.04 (-0.57, 0.62)	0.04 (-0.64, 0.66)	0.18 (-0.40, 0.77)	-0.01 (-0.59, 0.51)	
Range	-2.98 – 2.96	-2.81 – 2.96	-2.14 – 2.30	-2.98 – 2.96	
Phonemic Fluency					**.015**
Mean (*SD*)	0.06 (1.00)	0.12 (1.00)	0.11 (0.99)	-0.12 (1.00)	
Median (*IQR*)	0.03 (-0.59, 0.73)	0.14 (-0.54, 0.74)	0.00 (-0.48, 0.88)	-0.10 (0.83, 0.52)	
Range	-2.92 – 2.39	-2.92 – 2.39	-1.95 – 2.39	-2.92 – 2.39	
Working Memory					.107
Mean (*SD*)	0.03 (1.00)	0.06 (0.97)	0.08 (1.08)	-0.07 (0.97)	
Median (*IQR*)	0.03 (-0.59, 0.67)	0.04 (-0.45, 0.72)	0.15 (-0.72, 0.79)	-0.10 (-0.73, 0.55)	
Range	-2.85 – 2.42	2.70 – 2.42	-2.70 – 2.42	-2.85 – 2.42	
Verbal Episodic Memory					.540
Mean (*SD*)	0.03 (.96)	-0.01 (0.99)	0.04 (0.86)	0.09 (0.99)	
Median (*IQR*)	-0.01 (-0.62, 0.65)	-0.04 (-0.64, 0.64)	0.03 (-0.53, 0.60)	0.07 (-0.61, 0.71)	
Range	-2.45 – 3.02	-2.38 – 2.51	-1.83 – 3.02	-2.45 – 2.82	

Note. Abbreviations: *SD* = standard deviation; *IQR* = interquartile range

[a] Kruskal-Wallis rank sum test

4.2. Preliminary analysis

Assessment of data normality with scatterplots, histograms, Q-Q plots, and skewness and kurtosis values was conducted as part of preliminary data analysis. No gross non-normality was detected in exploratory data visualization. Normality was assessed further with the Shapiro-Wilk test of normality. For executive functioning (EF) score distribution, all *p*-values for the three pain status groups were >.05 from the Shapiro-Wilk tests. For verbal episodic memory score (VEM) distribution, *p*-values for two pain status groups (No Pain Interference and Pain Interference) were >.05 from the Shapiro-Wilk tests. However, for the No Persistent Pain group, the VEM score data were not normally distributed ($p = .03$). However, this violation of normality is acceptable given that linear regression models with a Gaussian error structure are generally robust to violations of the normality assumption (Knief & Forstmeier, 2021); and inference in least-squares linear regression does not require assumption of normal distribution if the sample sizes are sufficiently large (Lumley et al., 2002).

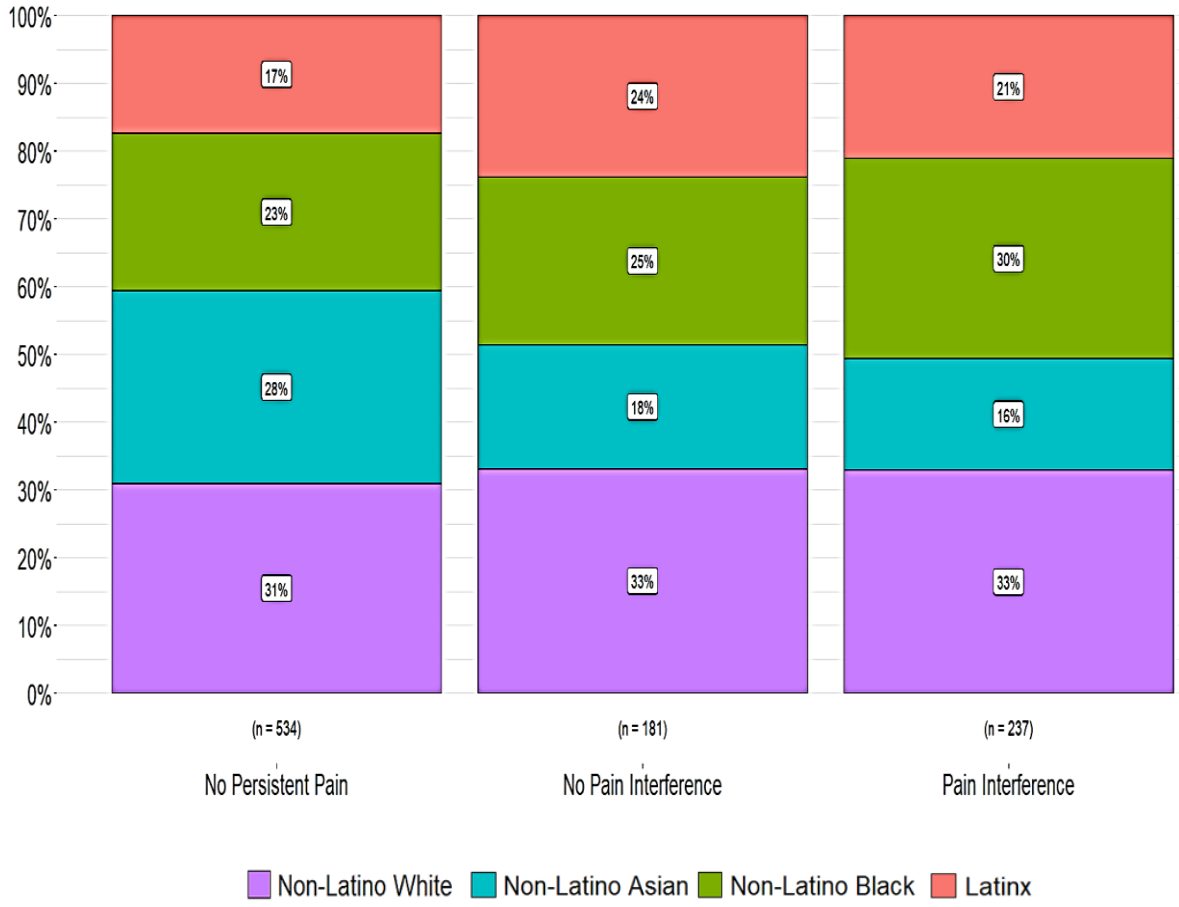
Bivariate correlation analysis was conducted to assess the strength of associations between variables. Pearson's chi-square test of association was used to examine the relations between categorical variables. The association between pain status and sex was significant ($p = .004$). The association between pain status and marital status was significant ($p = .002$). The association between pain status and ethnoracialized group membership was significant ($p = .004$) with a small effect size (Cramer's $V = 0.08$).

To determine whether there is a statistical difference in the prevalence of pain interference between the ethnoracialized groups, chi-square tests of goodness fit was conducted. The results were statistically significant for all three pain status groups, indicating that the distributions of participants within the pain status categories by ethnoracialized group

membership were not equal. See Figure 4.1 below.

Figure 4.1

Frequency Distribution of Pain Status by Ethnoracialized Groups



Note. Data source: Kaiser Healthy Aging and Diverse Life Experiences (KHANDLE), Wave 2

Associations between continuous variables were examined using Pearson's product-moment correlation. Table 4.3 presents a correlation table with Pearson's correlation coefficients. Age was negatively but significantly associated with education attainment (r = -.13; p < .001), EF score (r = -.33; p < .001), and VEM score (r = -.35; p < .001). Education attainment was positively and significantly associated with alcohol use (r = .09; p = .006), EF score (r = .30; p < .001), and VEM score (r = .16; p < .001). Depressive symptoms score was significantly and negatively associated with EF score (r = -.09; p =.01); with alcohol use (r = -.12; p < .001); and with education attainment (r = -.08; p = .01). However, it was not significantly associated with VEM score (r = -.04; p = .30). Cohen (1988) established the following criterion for Pearson's correlation coefficient: for small effect size, $0 \leq r \leq 0.29$; for medium effect size, $.30 \leq r \leq 0.49$; and for large effect size, $r \geq .50$. Pearson's r values in the correlation table 4.3 below are in the small and medium effect size ranges.

Due to the very small r value and small effect size for the variable depressive symptoms as well as the non-significant correlation with verbal episodic memory score, depressive symptoms score was not included in the multiple linear regression models. Moreover, substantial research points to the comorbidity and bidirectional relationship between depressive symptoms and chronic pain, and possible shared neurobiological bases (Boakye et al., 2016; Hooten, 2016; Makino et al., 2020; Sheng et al., 2017). Evidence of high neural and clinical correlations between persistent pain and depressive symptoms in the literature provided additional rationale for excluding depressive symptoms from the regression analysis.

Table 4.3

Correlations for Continuous Variables

Variables	Age	Education	Depression	Alcohol	EF	VEM
Age	–					
Education	-.13***	–				
Depression	.02	-.08**	–			
Alcohol	-.02	.09**	-.12***	–		
EF	-.33***	.30***	-.09**	.12***	–	
VEM	-.35***	.16***	-.04	-.01	.52***	–

Notes. Values shown are Pearson's *r*.

Abbreviations: Depression = depressive symptoms score. Alcohol use = total number of drinks per week. EF = executive function *z*-score. VEM = verbal episodic memory *z*-score.

*$p < .05$ **$p < .01$ ***$p < .001$

Multicollinearity among predictors was also assessed, as it can result in less reliable statistical inferences (Daoud, 2017; Shrestha, 2020). Variance inflation factor (VIF) and tolerance are two diagnostic tools of multicollinearity (Daoud, 2017). VIF values between 1 and 5 suggest low to moderate correlation among variables. VIF values greater than 5 and tolerance of less than .10 indicate severe multicollinearity (Daoud, 2017). The VIF values for all explanatory variables in this study were below 2 and tolerance ranged between .80 and .97; thus, multicollinearity was not a concern.

Homogeneity of variances of the outcome variables was assessed using Bartlett's test and Levene's test. Results of Bartlett's test indicate homogeneity of variances for executive functioning score (p = .84) and for verbal episodic memory score (p = .06). Results of Levene's test suggest the population variances of the executive functioning score for the ethnoracialized groups are equal (p = .53). However, Levene's test suggests heteroskedasticity for the verbal episodic memory score (p = .04). Thus, to accommodate any unequal variances, the Welch F-test was used for one-way analysis of variance (ANOVA) in this study.

4.3 Analysis of variance

A one-way ANOVA was conducted to examine possible differences in the mean cognitive domain-specific scores between the ethnoracialized groups, with race and ethnic group membership as the groups factor and EF and VEM scores as the dependent variables. The results suggest that the mean EF composite z-score differ significantly between the four ethnoracialized groups, Welch $F(3, 505.89) = 44.36$, $p = <.001$, $\omega^2 = 0.20$, 95% CI [0.15, 1.00]. Post-hoc pairwise comparison was conducted using the Games-Howell method to account for the unbalanced samples among the ethnoracialized groups, and the Holm-Bonferroni correction test to guard against Type I error. Figure 4.3 below shows violin plots of the mean EF z-scores

between the four ethnoracialized groups. The bars at the top in Figure 4.2 depict statistically significant pairwise comparisons of the mean EF *z*-scores of participants in the non-Latinx White group in relation to each of the other three ethnoracialized groups, with adjusted *p*-values from the Holm-Bonferroni correction test. Post-hoc comparisons indicate that older adults in the non-Latinx White group had a significantly higher mean EF *z*-score (M = 0.58, SD = 1.00), compared with those in the non-Latinx Asian group (M = -0.16, SD = 0.90, adjusted p <.001), the non-Latinx Black group (M = -0.24, SD = 0.87, adjusted p <.001), and the Latinx group (M = -0.18, SD = 0.87, adjusted p <.001).

Figure 4.2

One-way ANOVA Between Ethnoracialized Groups by Executive Functioning z-Score

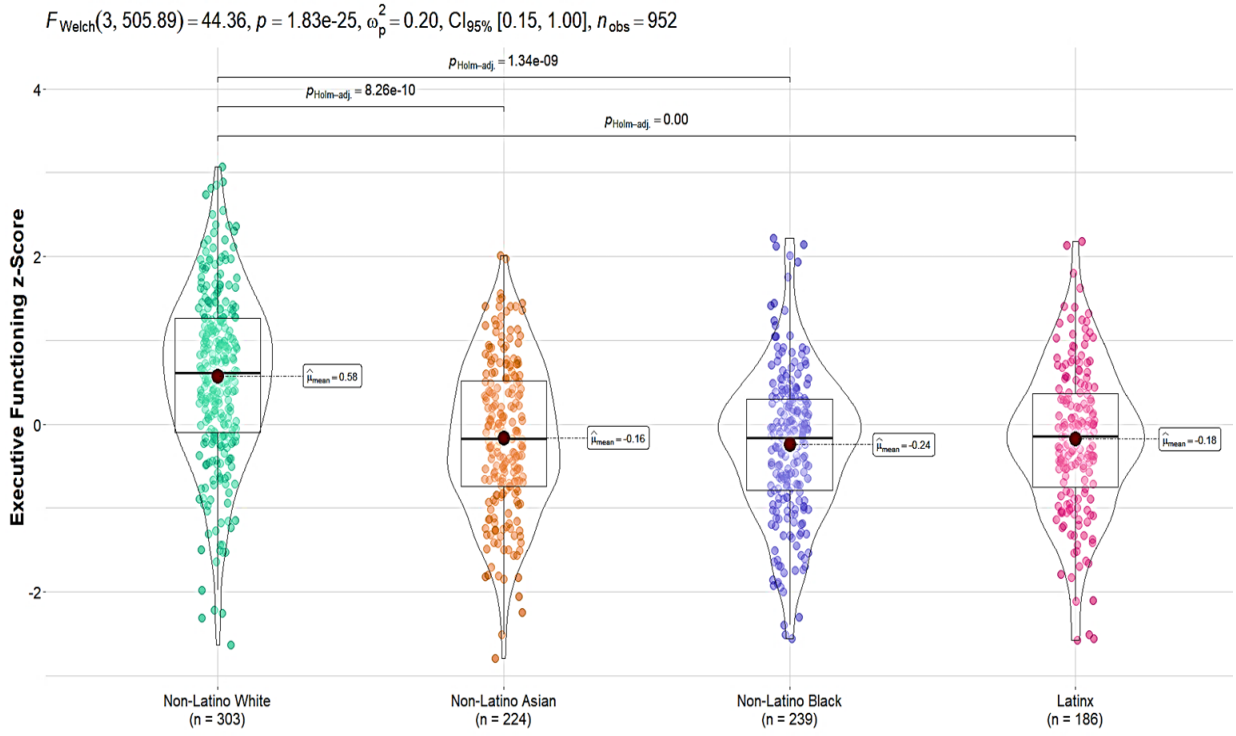
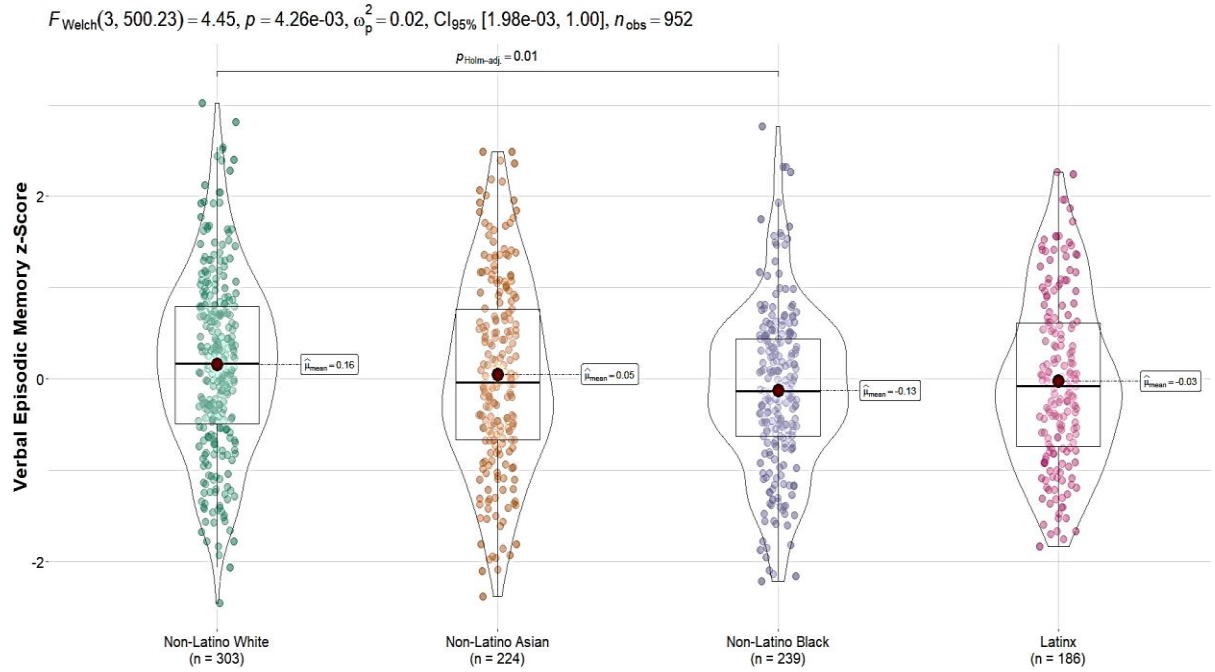


Figure 4.3 illustrates violin plots of the mean VEM *z*-scores across the four ethnoracialized groups. The sole bar at the top in Figure 4.3 depicts the only significant pairwise comparison. Older adults in the non-Latinx White group had significantly higher mean verbal episodic scores (M = 0.16, SD = 0.88) than individuals in the non-Latinx Black group (M = -0.13, SD = 0.98, adjusted p = .01). The pairwise comparisons of mean VEM scores between the non-Latinx White group and each of the other two ethnoracialized groups are statistically non-significant, however.

Figure 4.3

One-way ANOVA Between Ethnoracialized Groups by Verbal Episodic Memory z-Score



4.4 Multiple linear regression analysis

4.4.1 Adjusted models

The first research aim of this study was to examine the cross-sectional associations between pain interference and EF and VEM *z*-scores among an ethnoracially diverse sample of community-dwelling older adults. I hypothesized that having pain interference will be inversely associated with EF and VEM *z*-scores. For each cognitive domain, ordinary least squares (OLS) linear regression models were fitted to predict the effects of pain interference on cognitive domain-specific z-scores. Model 1 adjusted for age, sex, race and ethnicity, and mode of study interview (in-person versus phone). Model 2 included the covariates from Model 1 with additional adjustment for education attainment, marital status, smoking status, and alcohol use.

After fitting the models, linear regression assumptions of multicollinearity, normality, linearity, and homoscedasticity were examined to ensure that the models worked well for the data. All models were examined post hoc for collinearity of predictors, with no evidence of multicollinearity in any of the models (no VIFs >2). Diagnostic plots of regression analysis, including residuals plots, Q-Q plots, spread-location plots were reviewed to assess for linearity, homoscedasticity, and autocorrelation of errors (see Appendices C and D for the regression diagnostic plots). Twenty observations in the dataset had Cook's distance of greater than 0.015. Refitting the models without these 20 influential points did not change the regression results or affect the linear regression assumptions; thus, these 20 observations were retained in the data. Additionally, I conducted the Breusch-Pagan test to assess homoscedasticity, and the result was statistically non-significant. Linear regression assumptions of multicollinearity, normality, linearity, and homoscedasticity were met.

Table 4.4 below presents the results of multiple linear regression analysis of the independent effect of pain status on EF composite *z*-score. The partially-adjusted Model 1 was statistically significant, $F(8, 943) = 49.21$, $p < .001$, and it explained about 29% of the variance in EF z-score (adjusted $R^2 = 0.29$). By contrast, the fully-adjusted Model 2 explained a statistically significant and substantial proportion (36%) of variance ($F(13, 938) = 42.85$, $p < .001$, adjusted $R^2 = 0.36$). Compared with the No Persistent Pain group (reference group), the effect of having pain interference in Model 2, after adjusting for covariates, was statistically significant and negatively associated with EF *z*-score (Std. $\beta = -0.16$, standardized 95% CI [-0.29, -0.03], $p < .05$). For the No Pain Interference group, the association with EF score was not statistically significant, however.

Table 4.4

Linear Regression of the Effect of Pain Status on Executive Functioning z-Score

	Model 1					Model 2				
Predictor	***b***	***Std.* β**	***Std. SE***	***std. 95% CI***		***b***	***Std.* β**	***Std. SE***	***std. 95% CI***	
				LL	***UL***				***LL***	***UL***
(Intercept)	4.77 ***	0.42	0.06	0.29	0.54	4.03 ***	0.29	0.07	0.16	0.43
No Persistent Pain	*Ref*					*Ref*				
No Pain Interference	0.00	0.00	0.07	-0.14	0.15	0.02	0.02	0.07	-0.11	0.16
Pain Interference	-0.25 ***	-0.25	0.07	**-0.38**	**-0.12**	-0.16 *	-0.16		**-0.29**	**-0.03**
Non-Latinx White	*Ref*					*Ref*				
Non-Latinx Asian	-0.76 ***	-0.77	0.08	**-0.91**	**-0.62**	-0.75 ***	-0.76	0.07	**-0.90**	**-0.61**
Non-Latinx Black	-0.90 ***	-0.91	0.07	**-1.06**	**-0.77**	-0.79 ***	-0.80	0.07	**-0.94**	**-0.67**
Latinx	-0.76 ***	-0.77	0.08	**-0.93**	**-0.61**	-0.60 ***	-0.61	0.08	**-0.76**	**-0.46**
Age	-0.06 ***	-0.35	0.03	**-0.41**	**-0.30**	-0.05 ***	-0.30	0.03	**-0.36**	**-0.25**
Male	*Ref*					*Ref*				
Female	0.35 ***	0.35	0.06	**0.24**	**0.47**	0.48 ***	0.49	0.06	**0.37**	**0.60**
Education						0.09 ***	0.26	0.03	**0.21**	**0.32**
Married/Partnered	*Ref*					*Ref*				
Unpartnered						-0.15 **	-0.16	0.06	**-0.27**	**-0.04**
Alcohol Use						0.02 **	0.07	0.03	**0.02**	**0.12**
Never smoker	*Ref*					*Ref*				
Former smoker						0.07	0.07	0.06	-0.04	0.18
Current smoker						0.01	0.01	0.19	-0.35	0.37
Observations	952					952				
R^2 / R^2 adjusted	0.30 / 0.29					0.37 / 0.36				

Note. b = unstandardized coefficients; *std.* β = standardized coefficients; *SE* = standard error; CI = confidence interval. Model 1 adjusted for age, sex, race and ethnicity, and mode of interview. Model 2 additionally adjusted for educational attainment, marital status, smoking status, and alcohol use. Reference groups are italicized.

** p<.05 ** p<.01 *** p<.001*

Because the EF score is a composite score that includes scores from the subdomains of category fluency, phonemic fluency, and working memory, additional linear regression analysis was undertaken to test the associations of having pain interference with each of these cognitive subdomains. The regression results indicated that the separate independent effects of having pain interference on category fluency and working memory scores were not statistically significant. However, a statistically significant association was found between having pain interference and phonemic fluency *z*-score (see Table 4.5). The fully-adjusted Model 2 explained a statistically significant and moderate proportion of variance ($F(13, 938) = 20.67$, $p < .001$, adjusted $R^2 = 0.21$). Compared with the No Persistent Pain group (reference group), the effect of having pain interference in Model 2, after adjusting for covariates, was statistically significant and negatively associated with phonemic fluency *z*-score ($\beta = -0.19$, $p = .009$; standardized $\beta = -0.19$, standardized 95% CI = [-0.33, -0.05]). For the No Pain Interference group, the association with phonemic fluency was not statistically significant, however.

With regard to verbal episodic memory, linear regression analysis indicated that the association between having pain interference and VEM *z*-score was not statistically significant. Thus, for the first research aim of this study, only one of the hypotheses was supported.

Hypothesis 1a. Pain interference will be inversely associated with EF score across all study participants. *(Supported only for phonemic fluency − 1 of 3 subdomains of EF)*

Hypothesis 1b. Pain interference will be inversely associated with VEM score across all study participants. *(Not supported)*

Table 4.5

Linear Regression of the Effect of Pain Status on Phonemic Fluency z-Score

	Model 1					Model 2				
Predictor	***b***	**Std. β**	**Std. *SE***	**std. 95% CI**		***b***	**Std. β**	**Std. *SE***	**std. 95% CI**	
				LL	**UL**				**LL**	**UL**
(Intercept)	2.52 ***	0.46	0.07	0.32	0.60	1.79 ***	0.30	0.08	0.15	0.45
No Persistent Pain	*Ref*					*Ref*				
No Pain Interference	-0.03	-0.03	0.08	-0.19	0.12	-0.02	-0.02	0.08	-0.17	0.13
Pain Interference	-0.26 ***	-0.26	0.07	**-0.41**	**-0.12**	-0.19 **	-0.19	0.07	**-0.33**	**-0.05**
Non-Latinx White	*Ref*					*Ref*				
Non-Latinx Asian	-0.60 ***	-0.60	0.08	**-0.77**	**-0.44**	-0.59 ***	-0.59	0.08	**-0.74**	**-0.43**
Non-Latinx Black	-0.78 ***	-0.78	0.08	**-0.94**	**-0.62**	-0.67 ***	-0.67	0.08	**-0.83**	**-0.52**
Latinx	-0.65 ***	-0.65	0.09	**-0.82**	**-0.48**	-0.48 ***	-0.48	0.09	**-0.65**	**-0.31**
Age	-0.03 ***	-0.16	0.03	**-0.22**	**-0.10**	-0.02 ***	-0.12	0.03	**-0.18**	**-0.06**
Male	*Ref*					*Ref*				
Female	0.14 *	0.14	0.06	**0.02**	**0.27**	0.26 ***	0.26	0.06	**0.14**	**0.39**
Education						0.09 ***	0.27	0.03	**0.21**	**0.33**
Married/Partnered	*Ref*					*Ref*				
Unpartnered						-0.11	-0.11	0.06	-0.23	0.02
Alcohol use						0.01 *	0.06	0.03	**0.00**	**0.12**
Never smoker	*Ref*					*Ref*				
Former smoker						0.12	0.12	0.06	-0.00	0.24
Current smoker						0.12	0.12	0.20	-0.29	0.52
Observations	952					952				
R^2 / R^2 adjusted	0.14 / 0.14					0.22 / 0.21				

Note. b = unstandardized coefficients; *std.* β = standardized coefficients; *SE* = standard error; CI = confidence interval. Model 1 adjusted for age, sex, race and ethnicity, and mode of interview. Model 2 additionally adjusted for education attainment, marital status, smoking status, and alcohol use. Reference groups are italicized.

** p< .05 ** p< .01 *** p< .001*

4.4.2 Interaction effects

The second aim of this study was to investigate the potential effect modification by ethnoracialized group membership, sex, and educational attainment in the relationships between pain status and EF and VEM scores. Interaction analysis was carried out with the fully-adjusted linear regression models. Since the association between pain interference and VEM *z*-score was found to be statistically non-significant (see section 4.4.1), moderation analysis was carried out only for the relationship between pain status and EF *z*-score. Results from moderation analysis indicated that the relationship between pain interference and EF score did not appear to differ statistically by sex, ethnoracialized group membership, or by educational attainment. There was a significant main effect of ethnoracialized group membership on EF score ($p < .001$), but no significant interaction effect between ethnoracialized group membership and pain interference ($p = .55$). Likewise, there was a significant main effect of sex on EF score ($p < .001$), but no significant interaction effect between sex and pain interference ($p = .88$). Lastly, there was a significant main effect of educational attainment on EF score ($p < .001$), but no significant interaction effect between educational attainment and pain interference ($p = .78$).

All three hypotheses of Aim 2 were not supported in this study.

Hypothesis 2a. There will be a significant interaction effect of sex and pain interference on EF and VEM scores such that female sex will have a stronger magnitude of negative association compared with male sex. *(Not supported)*

Hypothesis 2b. There will be a significant interaction effect of ethnoracialized group membership and pain interference on EF and VEM scores. The negative associations between pain interference and EF and VEM scores will be stronger for participants who have non-Latinx

Black or Latinx group membership compared with those who identified as non-Latinx White and non-Latinx Asian. *(Not supported)*

Hypothesis 2c. There will be a significant interaction effect of educational attainment and pain interference on EF and VEM scores. The inverse associations between pain interference and EF and VEM scores will be stronger for participants with lower levels of educational attainment (i.e., education will have a protective effect). *(Not supported)*

CHAPTER 5: DISCUSSION

5.1 Summary and Explanation of Findings

This cross-sectional study investigated the relationship between pain interference from persistent pain and cognitive function in a prospective cohort of diverse community-dwelling older adults residing in Northern California. The study found conclusive evidence of a negative association between pain interference and phonemic (letter) fluency, a subdomain of executive functioning, in partially and fully adjusted models. In the fully adjusted model, controlling for educational attainment, marital status, and behavioral covariates of smoking status and alcohol use attenuated the unadjusted estimates only slightly.

While these findings are from cross-sectional analysis, they are consistent with findings from previous longitudinal studies that found significant associations between pain interference from persistent pain, rather than merely the presence or intensity of the persistent pain, with worse cognitive performance in community-dwelling older adults (Bell et al., 2022a; Milani et al., 2023; Milani et al., 2024). It is worth highlighting, however, some differences between the present study and some of the longitudinal studies in the literature. While the present study had a multi-ethnic analytical sample, the analytical sample in the Bell et al. study (2022a) consisted predominantly of White participants (85%) with smaller representation from Black participants (12%) and from participants categorized as "Other" (3%). Similarly, the Milani et al. (2023) study sample comprised exclusively of Puerto Rican adults aged 60 and older, thus limiting the study's generalization to ethnoracially diverse population. Additionally, both the Bell et al. (2022a) study and Milani et al. (2023) study examined global cognitive function as the outcome measure, rather than looking at domain-specific cognitive performance. By contrast, a strength of the present study is the granular examination of domain-specific cognitive performance.

Contrary to observational studies that found a link between persistent pain (although not specifically pain interference) and deficits in executive functioning domains (Berryman et al., 2014; Bunks et al., 2019; Moriarty et al., 2011), this study found no conclusive evidence of a negative association between having persistent pain (but no pain interference) and executive functioning score compared with the No Persistent Pain group (control group). There are some possible explanations for this null finding. Many previous studies investigating the persistent pain-executive functioning performance relationship did not specifically examine pain interference, only the presence of chronic pain and/or pain intensity (Berryman et al,, 2014; Bunks et al., 2019). Second, there is great variability in the definition and operationalization of chronic pain or persistent pain in previous studies due to the numerous types of pain questionnaires employed and pain assessment tools available (de Aguiar et al., 2020). Since the operationalization of persistent pain and pain interference in this dissertation was not identical to previous studies, there are methodological challenges to making direct comparisons with other studies. Not surprising, pain researchers have advocated for adoption of standardized pain assessment and measures which would greatly facilitate pain research (Gatchel et al., 2018; Patel et al., 2021). Additionally, researchers have called for the development and use of pain assessment and pain measures that are specific to the needs and characteristics of older adults, who have not been well represented in past pain research (Booker et al., 2020; Dagino & Campos, 2022; Herr, 2011). To compound matters further, there are numerous types and subtypes of pain (e.g., nociceptive pain, neuropathic pain, and centralized neuropathic pain); wide-ranging pain etiologies; and different body sites that can be affected by pain (e.g., low back, knees, hands), including multiple affected sites. Expanding research of the pain-cognition relationship to include the location and number of affected pain sites and how these factors may

contribute to changes in brain structure, cognitive decline, and dementia risk is a promising line of inquiry (Tian et al., 2023; Zhao et al., 2023; Zheng et al., 2024).

Finally, executive functioning is a very broad and diverse construct that encompasses heterogeneous cognitive processes and numerous tasks (Friedman & Miyake, 2017; Miyake et al., 2000; Packwood et al., 2011). Miyake and colleagues' (2000) proposal to categorize the many components and subcomponents of executive functioning into three functional groups (updating, shifting, and inhibition) provides a useful framework for systematic reviews (Bunks et al., 2019) and meta-analyses (Berryman et al., 2014) involving executive functioning processes; however, direct comparison of findings from individual studies involving pain and executive functioning remains challenging due to the inherent heterogeneity in the measurement of both constructs. In the KHANDLE Study, the composite executive functioning score is comprised of three specific subdomains (category fluency, phonemic fluency, and working memory), with each subdomain being assessed by specific neuropsychological tests (Mungas et al., 2000, 2004, 2005). These specific neuropsychological tests may be different from the executive functioning subdomains and the battery of neuropsychological tests used to evaluate executive functioning performance in other studies.

When the three KHANDLE subdomains of executive functioning were examined in regression analysis, this study found conclusive evidence of a negative association between pain interference and phonemic (letter) fluency score after adjusting for covariates. In the literature, there has been very limited research conducted on pain and phonemic fluency; and most investigated the effects of experimentally-induced pain (i.e., acute pain) on phonemic fluency rather than examining persistent pain (Oosterman et al., 2010; Zhou et al., 2015). For the association between persistent pain (but no pain interference) and phonemic fluency score, the

finding in this study was equivocal. Likewise, there were inconclusive findings in the present study for category (semantic) fluency and working memory; the regression coefficients were small in magnitude and statistically non-significant for both the Pain Interference and the No Pain Interference groups compared with the No Persistent Pain group. The null finding for category fluency is consistent with a longitudinal study by Veronese et al. (2018) that found no significant associations between pain presence and category fluency among community-dwelling adults aged 50 and over. The null finding for working memory in this dissertation was somewhat surprising, however, as previous studies have found that adults of varying age groups with chronic pain often demonstrated working memory deficits (Berryman et al., 2013; Legrain et al., 2011; Mendonça et al., 2021; Rathbone et al., 2016). A possible explanation is that most of these studies involved cohorts who were younger than 65 years (Berryman et al., 2013; Legrain et al., 2011). Pain research involving adults aged 65 and older is limited, as this age group is under-represented in research (Boyd et al., 2024; Scholfield, 2007). Another possible explanation is that some studies utilized different sets of neuropsychological tests to assess working memory, rather than the Digit Span Backwards, Visual Span Backwards, and List Sorting tests that were used in the KHANDLE study. These factors could contribute to the dissimilar findings in this study from previous studies.

Likewise, contrary to my hypothesis, I did not find a statistically significant negative association between pain interference and verbal episodic memory (VEM) score, or between persistent pain (No Pain Interference group) and VEM score compared with the No Persistent Pain group. In contrast, a longitudinal study by Rong et al. (2021) found that compared with the no persistent pain group, the moderate-to-severe persistent pain group demonstrated a significantly faster decline rate in verbal memory.

Taken together, the inconsistent findings in this study compared with the literature could be attributed to the aforementioned heterogeneity of measuring and operationalizing persistent pain and pain interference, and the methodological challenges in comparing different study designs with varying operationalization of pain measure and heterogeneous study populations (de Aguiar et al., 2020; Innes & Sambamoorthi, 2020). Additionally, there may be potential confounders unaccounted for in this study, such as use of pain analgesics and/or other pain treatment modalities which may affect both pain as well as cognition (Warner et al., 2023); physical activity and physical function status (Ritchie et al., 2022); and sleep duration and quality (Chen et al., 2024; Curtis et al., 2021). Relatedly, the KHANDLE participants in the analytic sample may have been physically healthier with fewer comorbidities at the time of data collection than participants in other studies that had conclusive findings for the pain-cognition relationship. (For further discussion of the study's limitations, see section 5.3 below.)

Aim 2 investigated effect modification in the relationship between pain interference and cognitive performance (EF and VEM scores). It was hypothesized that there would be significant interaction effects by sex, ethnoracialized group membership, and educational attainment. Contrary to my hypotheses, however, I did not find conclusive evidence of effect modification by these three sociodemographic categories. While there was a significant positive association between female sex and composite EF score compared with male sex in the main effects models, when the interaction term pain interference*sex was introduced, the omnibus test was statistically non-significant. It should be noted, however, that the possible moderating effect of sex in the persistent pain-cognition relationship has not been well researched, despite a growing body of evidence of sex and gender differences in pain experiences (Cohen et al., 2021; Mogil, 2012; Osborne & Davis, 2022), as well as emerging studies of sex and gender differences in

cognitive function and cognitive impairment (Ferreti et al., 2020; Levine et al., 2021; Mielke et al., 2022; Podcasy & Epperson, 2022). Future research is needed to examine possible underlying sex and gender identity differences in this area.

Evidence for effect modification from ethnoracialized group membership was also equivocal in this study. The ANOVA results indicated that the mean EF composite score differed significantly between the four ethnoracialized groups, and there were significant associations between the different ethnoracialized subgroups and EF score in the main effects models; however, when the interaction term of pain interference*race was introduced in the adjusted models, the omnibus test was statistically non-significant. As ethnoracialized identity is a social construct and is often used as proxy for racism, examining direct markers of structural racism and their effects on cognitive function (e.g., Seblova et al., 2022), such as allostatic load (e.g., D'Amico et al., 2020) and discrimination (e.g., Burgess et al., 2009; Zahodne et al., 2020) in future research may yield some insight into effect heterogeneity from ethnoracialized group membership in the pain-cognition relationship.

Similarly, the findings from this study were inconclusive with regard to whether educational attainment moderated the association between pain interference and EF score. While there was a significant positive association between educational attainment and composite EF score in the main effects model, the interaction analysis did not yield conclusive evidence of education effect heterogeneity in the pain interference-EF association. The null finding may be partly explained by recent research that suggests that single assessment of educational attainment may not be the best predictor of late-life cognitive function and cognitive decline. Rather, a more nuanced examination of both the level and timing of educational attainment (Soh et al., 2024) and the quality of the education, particularly for older adults who were likely to have received

primary education during periods of segregated schooling (Eng et al., 2021; Seblova et al., 2023; Sisco et al.,, 2015; Soh et al., 2023), may provide better insight into late-life cognitive function.

5.2 Implications

While the findings in this dissertation were inconsistent, they contribute to the growing research into examining persistent pain as a possible modifiable exposure and risk of late-life cognitive dysfunction and cognitive decline (Berryman et al., 2013, 2014; Whitlock et al., 2017; Zhang et al., 2021). Such research has implications for the ways in which we approach persistent pain and highlights the importance of early intervention and management of persistent pain and pain interference, particularly in subpopulations that have been shown to be at increased risk for cognitive decline and dementia (e.g., older adults, women, ethnoracially minoritized persons, and individuals with lower education attainment). Interdisciplinary research on the public health problem of persistent pain and pain interference in the past few decades suggests that the problem should be addressed using multifaceted approaches at multiple levels: the individual, clinical practice, and broader health systems and policies (Booker et al., 2023b; Johnson & Booker, 2021; Wallace et al., 2021; Zajacova et al., 2021a).

At the individual level, we need to provide better, culturally-informed patient education about pain as well as appropriate information about evidence-based strategies for self-management that individuals can employ to manage their own pain (e.g., pain coping skills, exercise, diet, and sleep hygiene). Concomitantly, we need to increase public health awareness about the risk factors and consequences of pain-related conditions so that individuals can make informed decisions and, when possible, make personal and lifestyle changes (Gatchel et al., 2018). As we gain better and more precise understanding of the relationships between pain and cognition, it is crucial to share the research findings with the public in ways that reduce the many

forms of stigma surrounding not just persistent pain (De Ruddere & Craig, 2016; Perugino et al., 2022) but also cognitive decline and ADRD (Herrmann et al., 2018; Rosin et al., 2020).

At the level of clinical practice, it is imperative that clinicians gain competency in providing individualized, comprehensive pain assessment and pain management for diverse populations, given the substantial number of individuals currently, as well as projected to be, affected by pain and pain-related limitations (Case et al., 2020; Zajacova et al., 2021b; Zelaya et al., 2020). This can be achieved by ensuring that core competencies in pain management are consistently taught across health care disciplines to close the pain education gap (Fishman & Young, 2016; Fishman et al., 2013). Pain management competency should extend to awareness of the negative impact of clinician-based bias and discrimination on pain assessment, pain care, and pain-related outcomes (Eze et al., 2022; Hoffman et al., 2016; Mathur et al., 2022; Meints et al., 2019). One crucial way to mitigate clinician-based bias and move toward greater equity in pain care is to equip clinicians with the knowledge and skills of cultural sensitivity and perspective-taking to contextualize clinical pain care in accordance with the cultural values and behaviors of their increasingly diverse patient populations (Booker et al., 2022; Eze et al., 2022; Wang & Jacobs, 2023).

More importantly, we need to expand beyond individual-level and clinician-level interventions if we are to effectively mitigate the immense societal challenges and burden of persistent pain. This requires addressing social and structural determinants that contribute to disparities in pain prevalences and pain-related disabilities, as well as disparities across multiple levels of pain care (Baker et al., 2023; Janevic et al., 2022; Mathur et al., 2022). There is consensus that we need to increase access to evidence-based multimodal and interdisciplinary pain treatment, particularly for certain subgroups that have experienced inadequate pain care

and/or barriers to receiving timely quality pain management (Booker et al., 2023b; Gatchel et al., 2018; Meghani et al., 2012). However, the path toward equitable pain care necessitates moving beyond the confines of healthcare institutions to consider structural and multisectoral interventions and policy initiatives. Critical steps in this direction include reforming payment structures for pain care (Mathur et al., 2022); expanding coverage of non-opioid pharmacotherapy and non-pharmacological interventions (Interagency Pain Research Coordinating Committee, 2016; Lentz et al., 2023); and increasing and diversifying the pain clinician workforce (Hood et al., 2022; Strand et al., 2021).

5.3 Strengths, limitations and future directions

The study has several strengths. This study utilized secondary data from an ethnoracially diverse study cohort that includes Asian participants, a subgroup that has not been well represented in previous pain research. Second, the cognitive scores in this study were derived from the SENAS battery of neuropsychological tests, which, in addition to having been validated in culturally, linguistically, and educationally diverse populations, were designed to measure changes in cognition with minimal limitations in floor or ceiling effects (Mungas et al., 2000, 2004).

Several limitations of the study should be noted. First, due to the study's cross-sectional design, neither causality nor the temporal order of the associations between pain interference and cognitive performance can be determined. Longitudinal analysis of pain interference and cognitive decline in the KHANDLE Study cohort is warranted to understand potential causal pathways underlying the relationships. Additionally, there is a need to conduct large-scale prospective clinical studies in middle-aged adults to determine whether effective interventions

and management of persistent pain in this age group can help prevent and delay the onset of cognitive decline and cognitive impairment in older adults (Chen et al., 2023).

Second, the study's analyses were limited by the ways in which the exposure variable pain interference was measured and operationalized from the five pain-related questions in the KHANDLE Study interview administered to participants at each wave. These pain-related questions are not validated pain scales. Since the five pain-related questions do not directly ask about pain frequency and duration, this study used an indirect method for determining "persistent pain" (see operationalization of the variable "pain presence" in section 3.3.2 of Chapter 4: Methods). Another limitation is that the five pain-related questions query only general aspects of pain experiences and may not fully capture the multidimensionality of persistent pain and pain interference in older adults. Moreover, the pain-related questions are administered only English and Spanish; these pain-related questions have not been validated in ethnoracially, culturally, and linguistically diverse populations. These limitations may contribute to measurement error. For instance, some KHANDLE participants may interpret the survey questions of pain intensity and pain interference as asking about overlapping constructs; other participants may view these two questions as having disparate meanings. It is important to note that there is currently an absence of validated instruments that measure culturally relevant behaviors and indicators of pain in older adult population (Booker et al., 2023b; Herr et al., 2019). Future research would benefit from using multidimensional assessment of self-reported pain, such as the Brief Pain Inventory, which assesses both pain intensity and pain interference (Cleeland & Ryan, 1994), or the McGill Pain Questionnaire, which measures the sensory, affective, and evaluative dimensions of pain (Melzack, 1975). Additionally, it would be worthwhile to explore the different types of pain interference and develop culturally informed assessments of pain presence and pain interference

in diverse older adult populations. Relatedly, future research would benefit from the use of pain questionnaires and neuropsychological tests that are administered in languages other than English or Spanish.

Another limitation is the possibility of recall bias. The pain-related questions rely to a large extent on retrospective reports of pain experiences. Participants with better memory may have better recall of pain experiences and thus more likely to report having pain. Also, social desirability response bias is another consideration. Due to the pervasive stigma associated with persistent pain, participants with pain might be less likely to complete the pain-related questions, or to respond to the questions in ways that differed from their pain experiences, such as under-reporting or over-reporting their pain and pain interference (De Ruddere & Craig, 2016; Boring et al., 2022).

Lastly, there are restrictions to this study's generalizability, as the KHANDLE cohort was recruited from long-term Kaiser Permanente Northern California (KPNC) health plan members and not from nationally-representative older adult populations. Notable differences in the characteristics of KPNC member population compared with the non-Kaiser Permanente population have been discussed elsewhere (Gordon, 2015). For instance, while KP members demographically reflect residents in the Northern California region, the mean household income of KP members is significantly higher than that of the non-KP population; these differences remained after adjusting for age and gender, and these differences in income were significant among both men and women (Gordon, 2015). Furthermore, as individuals eligible for KHANDLE cohort were long-term KPNC members, the participants likely have had consistent health care access in KP integrated health system for an extended period (Mungas et al., 2021). This continuity of care and care access is not necessarily the norm for other older adults,

particularly those residing in more rural settings of California and other U.S. geographical areas and potentially contribute to membership bias. Thus, study participants may have differential access to health care or types of pain treatment. Their study retention rate may also be different from non-KPNC members. Given these differences, it may be important for future research to utilize prospective longitudinal studies with geographically diverse participants to expand external validity, and cohorts comprising middle-aged adults.

5.4 Conclusion

Persistent pain, pain interference and cognitive decline affect many older adults. In this prospective cohort of diverse community-dwelling older adults residing in Northern California, this study found a negative association between pain interference and executive functioning composite score, and, more specifically, a negative association between pain interference and phonemic fluency performance (a subdomain of executive functioning). This study did not find conclusive evidence for effect modification by sex, ethnoracialized group membership, or educational attainment. While this study contributes to the growing body of research on the relationship of pain and cognitive function in older adults, additional research is warranted to elucidate the complex factors and potential causal mechanisms of the relationship. Future research in this area may increase our understanding of modifiable risk factors for cognitive decline and Alzheimer's disease and related dementia. Findings from such research may contribute to the development of preventative efforts and targeted interventions, establishment of relevant clinical guidelines, and implementation of impactful policies to improve the quality of life and well-being of diverse older adults suffering from pain and who might be at increased risk of cognitive decline and dementia.

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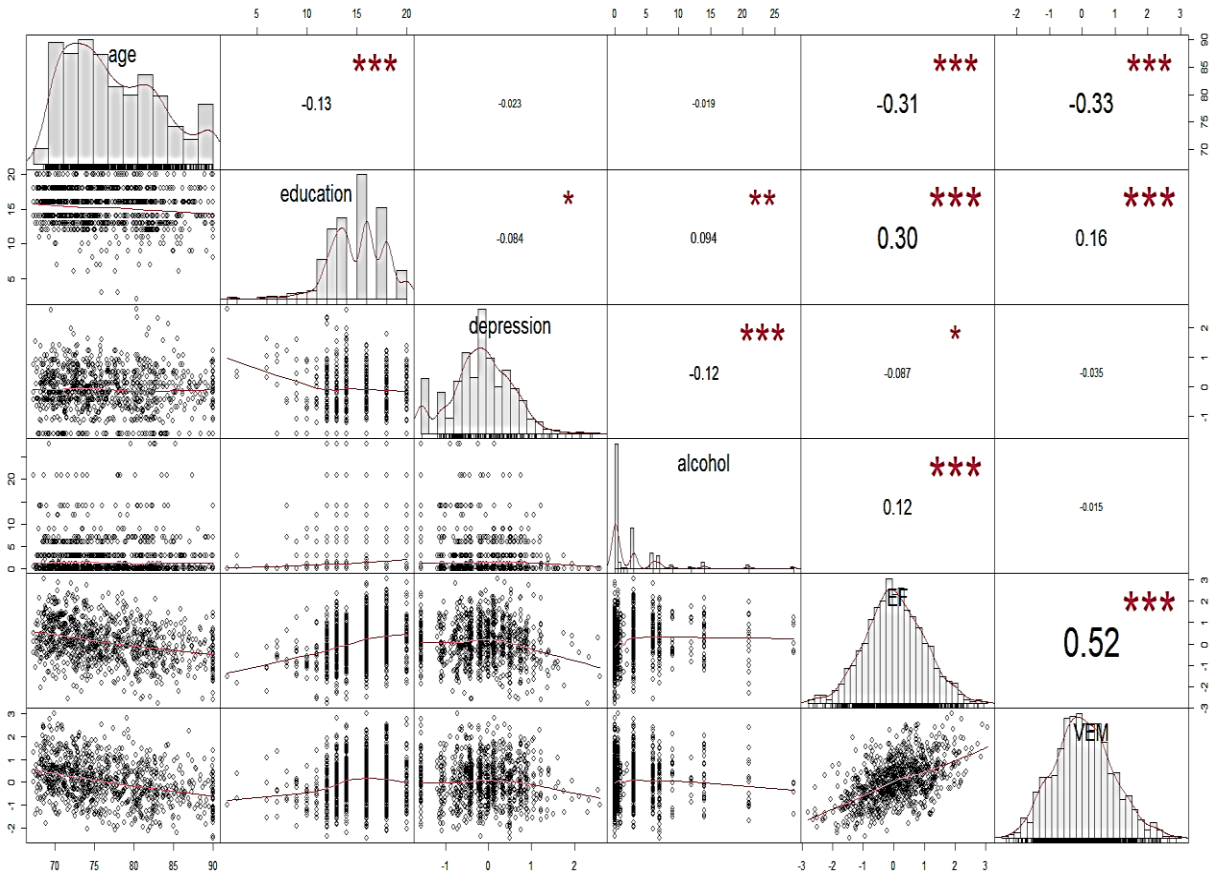
Appendices

Appendix A: Measurement Matrix of Study Variables

	Measure	Operational Definition	Specification
Outcome	Executive functioning (EF) Verbal episodic memory VEM)	VEM score is derived from a multi-trial 15-item word-list learning test. EF composite score is derived from component tasks of category fluency, phonemic fluency, and working memory.	*Continuous/Ratio* EF score range: -3.3 – 3.3 VEM score range: -3.3 – 3.3 A higher total score indicates better cognitive function
Exposure	Pain interference	Participants were asked at wave 1 and wave 2 interviews, "Are you often troubled with pain?" The two possible responses are "yes" or "no." Participants who respond "yes" to the pain presence question were subsequently asked: "Does the pain make it difficult for you to do your usual activities such as household chores or work?" The two possible responses are "yes" or "no." Pain interference variable was operationalized using the sum of persistent pain status (yes/no) and pain interference (yes/no).	*Categorical/Ordinal* No persistent pain = 0 No pain interference = 1 Pain interference = 2
Confounders and Covariates	Age	Age in years at wave 2 interview date from the participant's date of birth.	*Continuous/Ratio*
	Sex	Sex corresponds to whether the respondent self-identified as female or male.	*Categorical/Nominal* • Male • Female
	Race and ethnicity	Self-reported data. KHANDLE utilizes an algorithm for race and ethnicity assignment. See Eng et al. (2021) and Meyer et al. (2023).	*Categorical/Nominal* • Latinx • Non-Latinx Asian • Non-Latinx Black • Non-Latinx White
	Marital status	Marital status is based on is self-reported data.	*Categorical/Nominal* • Married/partnered • Unpartnered
	Education	Education attainment in years at Wave 1	*Continuous/Ratio*

	Depressive symptoms	Measured using the National Institutes of Health (NIH) Patient-Reported Outcomes Measurement Information System® (PROMIS®) Depression (Short Form 4a) assessment. The four questions correspond to emotional, cognitive, and behavioral manifestations of depression symptoms experienced in the last seven days, with responses reported using a 5-point Likert scale.	*Continuous/Ratio* Response options: Likert scale 1 = never 2= rarely 3 = sometimes 4 = often 5= always Score range: 2-38. A higher score indicates more depressive symptoms. Per NIH Toolbox convention, the raw scores were converted to standardized theta scores, ranging from -3.0 to 3.0.
	Smoking status	Participants' self-report to the question of whether they ever smoked cigarettes and whether they currently smoked.	*Categorical/Nominal* Current smoker = 2 Past smoker = 1 Never smoked = 0
	Alcohol use (weekly)	Measured by a combination of the participants' self-report of the number of drinks on days in which they drank and the frequency with which they drank.	*Continuous/Ratio*

Appendix B: Correlation Coefficient Matrix of Continuous Variables

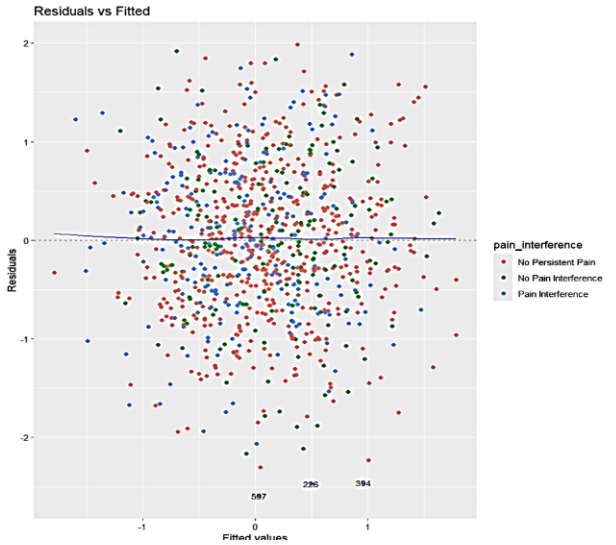


Note. Values shown are Pearson's *r*. Variable coding is as follows: depression = depressive symptoms score; alcohol = total number of drinks per week; EF = executive function *z*-score; VEM = verbal episodic memory *z*-score.

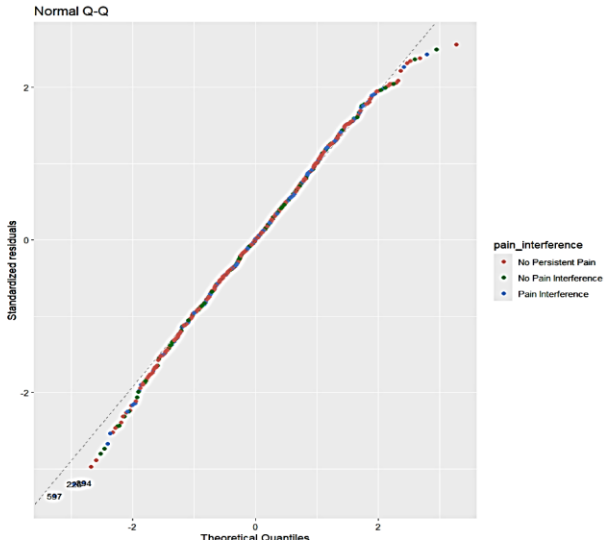
*$p < .05$ **$p < .01$ ***$p < .001$

Appendix C: Plots of the Regression Model for Executive Functioning

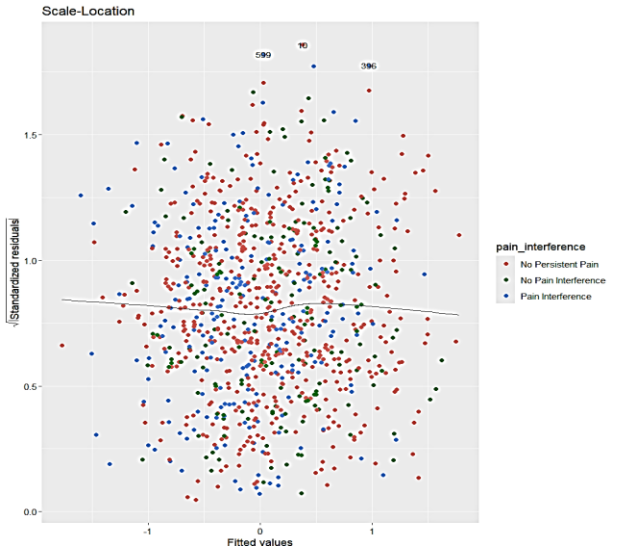
Residuals vs Fitted Scatterplot



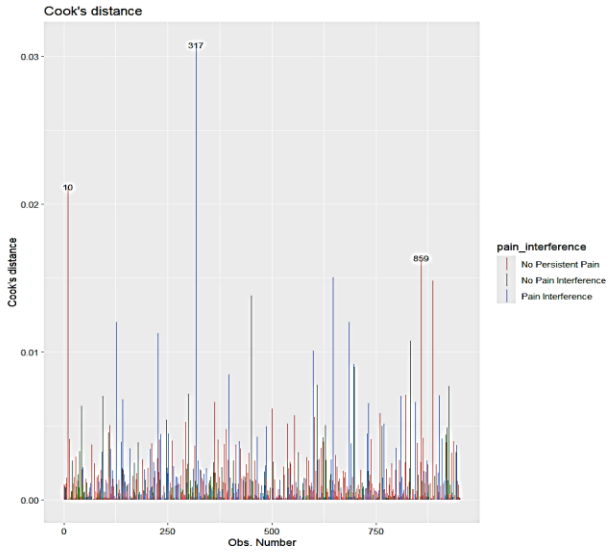
Q-Q Plot



Scale-Location Plot

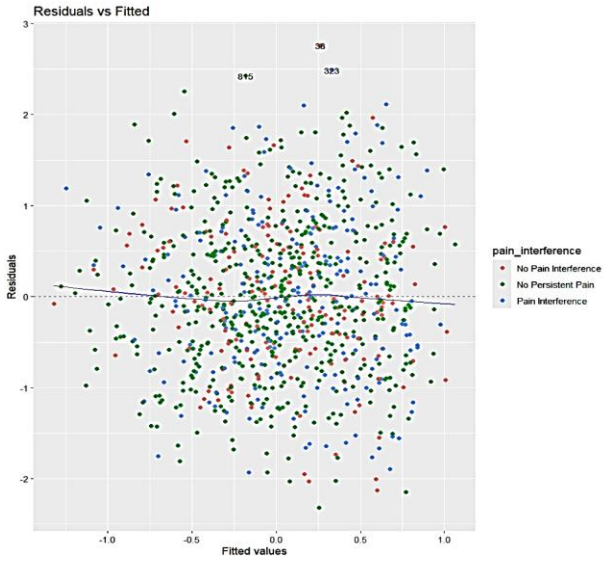


Cook's Distance

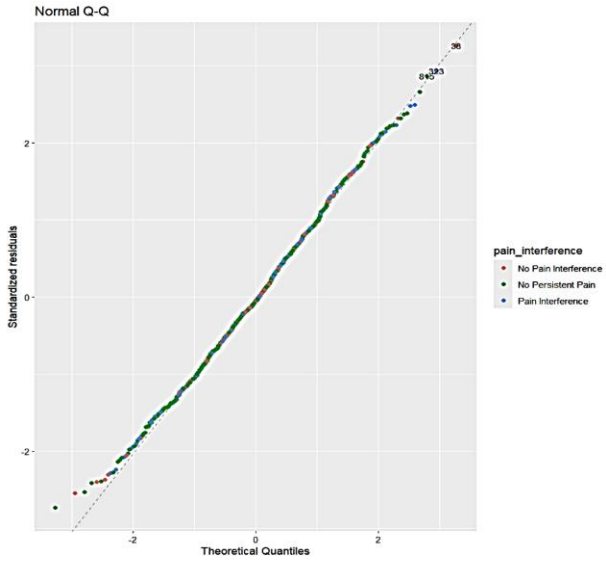


Appendix D: Plots of the Regression Model for Verbal Episodic Memory

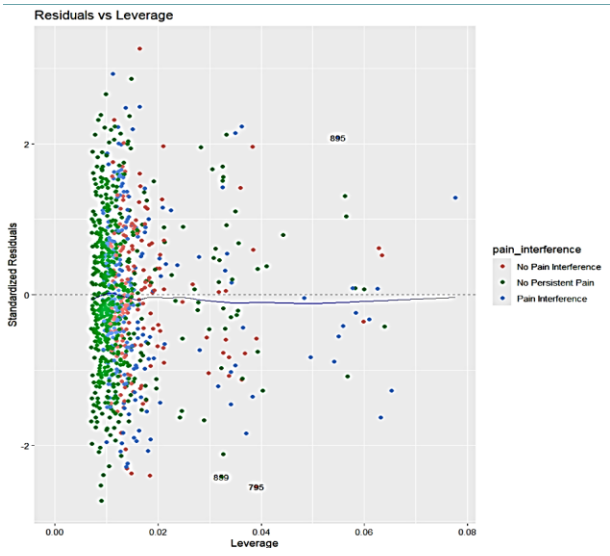
Residuals vs Fitted Scatterplot



Q-Q Plot



Scale-Location Plot



Cook's Distance

