

DEPRESSION AND PTSD AS PREDICTORS OF DEMENTIA AND OTHER COGNITIVE
DISORDERS AMONG VETERANS BASED ON RACE AND SEX

BY

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ABSTRACT

In the literature, depression (especially major depressive disorder [MDD]) and posttraumatic disorder (PTSD) have been known to significantly increase individuals' risk for dementia. Dementia affects 5 to 7 percent of the population across the world. Compared to the general U.S. population, the Veteran population experiences significantly greater risk factors associated with dementia and other forms of cognitive impairment. As this population continues to age and diversify in the upcoming years, risk factors specific to their circumstances must be examined. Importantly, similar patterns of health disparities that persist in the general population among men, women, and different racial groups, also exist among the Veteran population. Thus, despite minimization of financial barriers in VA healthcare systems, there are still certain groups with a greater likelihood of developing certain diseases. The aim of this study was to examine MDD and PTSD as predictors of dementia and other forms of cognitive impairment (cognitive impairment not demented [CIND]) among Veterans aged ≥ 60 years ($N = 4,800$) with sex and race analyzed as potential moderators. Hierarchical and backward logistic regression analyses were conducted to determine significant predictors of dementia/CIND. When controlling for the other, a history of MDD and PTSD both were associated with almost double the risk for developing dementia/CIND. Moreover, when a history of MDD was indicated, Black Veterans' risk of dementia/CIND increased almost twofold. Additional findings and implications are also discussed.

Keywords: dementia, cognitive impairment, CIND, depression, MDD, PTSD, race, sex, Veterans, health disparities

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CHAPTER 1

Abstract

Dementia is prevalent among 5 to 7 percent of the population worldwide, and 3.4 million persons aged ≥ 71 in the U.S. A history of depression and/or PTSD has been associated with a greater risk of dementia, yet the relationship between these conditions with dementia remains unclear. Depression is the most notable contributor to the worldwide burden of disease, and PTSD has been found to be more common in the U.S. than other countries, especially considering recent conflicts in which U.S. Veterans have been involved, such as Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF). The U.S. Veteran population has been recognized for being at a greater risk for depression/PTSD and cognitive difficulties, making them an important group to consider for research. Importantly, as the Veteran population rapidly diversifies, health care providers must develop and maintain cultural competency across areas of assessment, diagnosis, and treatment. This is particularly important given that substantial sex and racial health disparities have endured in the U.S. for several decades. Due to the complex relationship between depression/PTSD and dementia, as well as the increased risk among Veterans, additional research is needed to understand psychiatric risk factors of dementia and how Veterans' demographic characteristics may influence this risk.

Keywords: dementia, depression, posttraumatic stress disorder (PTSD), disparities, Veteran population

CHAPTER 1

Predictors of Dementia for Veterans with and without Preexisting Depression and PTSD:

A Review

The worldwide economic burden of dementia in 2010 was approximately \$604 billion, which is one percent of the worldwide gross domestic product (GDP; World Health Organization, 2015). There are approximately 47.5 million people worldwide living with dementia, and 7.7 million others are diagnosed with dementia each year. The *World Alzheimer Report 2010*, published by Alzheimer's Disease International (2010), demonstrated how significant the impact of dementia is: “If dementia care were a country, it would be the world’s 18th largest economy (ranking between Turkey and Indonesia)...If dementia were a company, it would be the world’s largest by annual revenue, exceeding Wal-Mart (\$414 billion) and Exxon Mobil (\$311 billion)” (p. 5). In the United States (U.S.), the economic cost of dementia was estimated to be \$226 billion in 2015, and expected to rise as high as \$1.1 trillion by 2050 (Alzheimer's Association, 2015).

Dementia is a disorder characterized by cognitive and behavioral symptoms that “interfere with the ability to function at work or at usual activities; represent a decline from previous levels of functioning and performing; are not explained by delirium or major psychiatric disorder; and, cognitive impairment is detected and diagnosed...” (National Institute on Aging’s Alzheimer’s Associated Workgroups; McKhann et al., 2011, p. 265). Cognitive impairment must be detected through a clinical interview about the patient’s history and objective cognitive assessment. Examples of cognitive impairment include the following (McKhann et al., 2011, p. 265): changes in behavior/personality (e.g., uncharacteristic mood fluctuations); impaired language and/or visuospatial abilities, and; impaired reasoning and

handling of complex tasks, poor judgement, and impaired ability to acquire and remember new information.

The prevalence rate of dementia increases with age, with the overall U.S. national rate being 13.93 percent, with higher rates among women (15.74 percent) compared to men (11.4 percent; Plassman et al., 2007). In fact, approximately two thirds of Americans diagnosed with Alzheimer's disease (the most common form of dementia) are women (Alzheimer's Association, 2015). Prevalence rates by age groups are 4.97 percent for individuals aged 71 to 79 years, 24.19 percent for individuals aged 80 to 89 years, and 37.36 percent for individuals aged 90 years or older (Plassman et al., 2007). Dementia is the six leading cause of mortality in the U.S. (Alzheimer's Association, 2015).

Although there is no cure for dementia, scientists have developed treatments that delay cognitive decline and help individuals and their caretakers manage symptoms (Farlow, Miller, & Pejovic, 2008). Treatment options include pharmacological approaches, cognitive training, and preventative efforts (e.g., lifestyle changes, exercise, healthy eating, and early and efficient diagnosis). Many researchers have also identified potential risk factors of dementia (Byers & Yaffe, 2011; Chen, Lin, & Chen, 2009; Reddy & Beal, 2008). The APOE gene, particularly the variant APOE4, is the strongest genetic risk factor for dementia (Chen et al., 2009). The literature shows that beta-amyloid is a major component of the neuritic plaques or amyloid deposits found in the brain of persons diagnosed with dementia, particularly Alzheimer's disease (Reddy & Beal, 2008). Notably, a risk factor that is consistent across all ethnic groups is age; as individuals get older, their risk for dementia increases (Chen et al., 2009). Byers and Yaffe (2011) indicated that persons with a history of depression have double the risk of getting dementia compared to those without a history of depression. Additional identified risk factors

include level of physical activity, education, body mass index, alcohol and drug use, smoking, and comorbidity with various diseases (e.g., HIV, hepatitis C virus, traumatic brain injury, and hypertension).

It is important to note that researchers have identified U.S. Veterans as having an increased risk of developing dementia (Lohr et al., 2015; Sibener et al., 2014). They have mentioned several reasons why Veterans may be at greater risk, with the demographic characteristics of the group being a significant factor. On average, Veterans are older than non-Veterans and the Veteran population consists of a higher proportion of Black individuals than the overall U.S. population (Sibener et al., 2014). As people get older, their risk of dementia increases. Further, Black persons are at greater risk for dementia compared to other racial groups (Plassman et al., 2007). Specifically, the incidence of Alzheimer's disease among Black individuals is double that of their White counterparts (Sibener et al., 2014). Moreover, the incidence of traumatic brain injury (TBI) and posttraumatic stress disorder (PTSD) is increasing among the Veteran population, and researchers identified both as risk factors of dementia (Shively & Perl, 2012). Veterans are also at a higher risk for depression, as this condition shares many symptoms with PTSD, and depression has been identified by scholars as a major risk for dementia (Barnes et al., 2012; Byers & Yaffe, 2011; Sibener et al., 2014).

Despite identified risk factors, there are no definite indicators for dementia. In fact, there are some individuals who have risk factors that are strongly associated with dementia, yet they never exhibit symptoms (Bennett et al., 2006; Tomlinson, 1968). For instance, Bennett et al. (2006) found Alzheimer's disease pathology (e.g., neuritic plaques) in the brains of a large number of persons without dementia or mild cognitive impairment. This suggests that even the risk factors with the most scientific evidence do not guarantee the later development or absence

of dementia. Hence, there exists a great need for additional research involving the examination of the risk factors of dementia. In addition, given the increased risk U.S. Veterans have, it is important to investigate factors unique to this population (e.g., PTSD, depression, TBI, demographic characteristics, and more) that act as significant risks.

Depression

Depression is characterized by a change in mood (e.g., sadness, loneliness, apathy), negative self-concept (e.g., self-blame), regressive and self-punitive wishes, vegetative changes, and different activity levels (Beck, 2009). Numerous environmental and biological factors may increase people's risk for depression, including the following: familial environment and adverse experiences in childhood, social/cultural environment and people's roles within their environment (e.g., poor social support), adverse life events, genetic and hereditary factors, co-morbidity with other conditions (e.g., sleep disorders and cognitive impairment), and more (Piccinelli & Wilkinson, 2000). Importantly, risk factors for depression among older adults aged ≥ 50 years are slightly different than the risks for the general population, and include bereavement, sleep disturbance, disability, cognitive decline, prior depression, and female gender (Cole & Dendukuri, 2003).

Depression is the most noteworthy contributor to the global burden of disease, and it is the most frequently encountered women's mental health problem (WHO; World Health Organization, 2002). The lifetime prevalence rates of depression among women are significantly higher than the rates for men, and this remains consistent across racial groups; the approximate lifetime prevalence of MDD is 21.3 percentage for women, and 12.7 percentage for men (Kessler, 2003; Mielke, Vemuri, & Rocca, 2014; Piccinelli & Wilkinson, 2000; WHO, 2002). There are some inconsistent findings on depression prevalence rates among older men and

women, yet more recently, researchers determined that women continue to be at a greater risk for depression even later in life (Barefoot, Mortensen, Helms, Avlund, & Schroll, 2001; Djernes, 2006; Hybels, Blazer, & Pieper, 2001; Meeks, Vahia, Lavretsky, Kulkarni, & Jeste, 2011).

Treatment options for depression have advanced over the decades and individuals now have several treatment choices, such as psychopharmacology, psychotherapy, and electroconvulsive therapy (ECT; Beck, 2009). Due to the extant prevalence of depression worldwide, researchers continue to investigate additional treatment options, and future directions include transcranial magnetic stimulation and pharmacogenomics (Beck, 2009; Hamilton, 2015). Transcranial magnetic stimulation, also known as repetitive transcranial magnetic stimulation (rTMS), is a variation of ECT that stimulates the brain non-convulsively and is associated with fewer side effects compared to ECTs (Vallejo-Torres et al., 2015). Psychiatric pharmacogenomics is the study of how peoples' genetics influence how they respond to certain medications (Hamilton, 2015) and it has the potential to make a profound impact on the effectiveness of antidepressants for the larger population. Recent controversial research findings demonstrate that benefits of antidepressants compared with placebos are nonexistent to minimal for patients with mild to moderate depression (Fournier et al., 2010), and pharmacogenomics could potentially help scientists discover types of antidepressants that are more effective for certain individuals compared to others. Nonetheless, rTMS and pharmacogenomics still require further vigorous investigation prior to being widely accepted and employed as common treatments for depression (Vallejo-Torres et al., 2015).

Posttraumatic Stress Disorder (PTSD)

The *International Classification of Diseases, Ninth Revision* (ICD-9; Centers for Disease Control and Prevention, 2011) outlines the criteria for posttraumatic stress disorder (PTSD) as a

reaction to experiencing or being exposed to a traumatic experience which results in impaired functioning manifesting in the following: re-experiencing the event (e.g., nightmares, recollections, and flashbacks); thoughts, feelings, and activities of traumatic circumstances; changes in affective functioning (e.g., unable to experience certain emotions), and; irritability, hypervigilance, insomnia, etc. Numerous risk factors for PTSD have been identified, with women consistently being at a higher risk compared to their male counterparts (Breslau, 2009). Women have greater odds of developing PTSD following a traumatic incident compared to men. Moreover, women in the military have a higher risk of experiencing traumatic incidents compared to women in the general community, thus making them more likely to develop PTSD (Breslau, 2009; Haskell et al., 2010). The female Veteran population is rising in the U.S., and this has many significant implications for health care providers who work with this particular group (Breslau, 2009; Dobie et al., 2004).

Sandica and Pop (2014) found that, similar to depression, smaller hippocampal volume in the brain may be associated with more susceptibility to PTSD. Additional risk factors include prior affective, anxiety, substance use, and/or personality disorders (Sandica & Pop, 2014). The existing options for PTSD treatment include evidence-based interventions, with Cognitive Behavioral Therapies being the most common (e.g., Cognitive Processing Therapy, Prolonged Exposure, etc.; Gradus, 2007). Psychopharmacology and eye movement desensitization and reprocessing (EMDR) are also common approaches for PTSD treatment.

The U.S. population has higher prevalence rates of PTSD compared to other countries, with higher rates of women diagnosed with PTSD than men in the general public (Breslau, 2009). However, researchers are expecting PTSD rates for women to increase even more as the population of female U.S. Veterans also grows. In addition, Seal and colleagues (2009) found

that active duty Veterans who are less than 25 years old are at a higher risk for PTSD compared to active duty Veterans who are older than 40 years of age.

Racial differences in PTSD rates are also significant, with Black persons consistently having greater risks compared to other racial groups (Asnaani, Richey, Dimaite, Hinton, & Hofmann, 2010; Himle, Baser, Taylor, Campbell, & Jackson, 2009; Roberts, Gilman, Breslau, Breslau, & Koenen, 2011). Lifetime prevalence rates of PTSD are highest among Black individuals when compared to White, Hispanic, and Asian populations (Roberts et al., 2011). However, Black individuals, and all other minority groups, are less likely to seek PTSD treatment compared to their White counterparts (Roberts et al., 2011).

Relationship between Dementia, Depression, and PTSD

The existing knowledgebase on the relationship between dementia, depression, and PTSD remains inconclusive, and many researchers present varying conclusions regarding whether one can cause the other, act as a risk factor, etc. Depression has been examined by countless researchers for decades to better understand its association with dementia, and many hypotheses have been offered (Butters et al., 2008; Byers & Yaffe, 2011; Jorm, 2001; Korczyn & Halperin, 2009). Depression can be a possible reaction to dementia, or a prodrome (i.e., an early symptom) of dementia (Byers & Yaffe, 2011). Depression can also be a reaction of people experiencing decline in their memory (Korczyn & Halperin, 2009). One finding, however, that the majority of researchers seem to agree on is that a history of depression increases the risk of dementia (Korczyn & Halperin, 2009), particularly for older adults (Chodosh, Kado, Seeman, & Karlamangla, 2007).

It can be difficult for even the most skilled clinicians to distinguish between dementia and depression due to similarities in their features, particularly the presentations of cognitive

symptoms (Casey, 2012). Hence, depression and dementia are commonly misdiagnosed as the other, especially in older adults (Casey, 2012). Older adults with depression and/or dementia both exhibit forgetfulness, lack of concentration, reasoning, and other cognitive impairment. Nebes and colleagues (2000) found that decreased working memory and processing speed mediated cognitive impairment in geriatric depression. Importantly, people with depression are usually able to recall memories if they try, whereas those with dementia typically try to conceal the fact that they are unable to recall anything. Reasoning and memory are impaired in both dementia and depression, and this cannot be treated for in dementia. In depression, poor concentration and other cognitive impairments are reversible with treatment or when the depression is in remission. Further, Byers and Yaffe (2011) identified a condition called pseudodementia, which occurs when depression impairs cognitive impairment so severely that symptoms present as dementia.

In a meta-analysis of studies on the association between depression and dementia, Jorm (2001) offered the following hypotheses:

Depression treatments are a risk factor for dementia; depression and dementia share common risk factors; depression is a prodrome of dementia; depression occurs as an early reaction to cognitive decline; depression brings forward the clinical manifestation for dementing disease, and; depression leads to damage of the hippocampus through a glucocorticoid cascade. (pp. 778-779)

Recently, the association between PTSD and dementia has received much consideration from researchers (Lohr et al., 2015; Yaffe et al., 2010). Yaffe and colleagues (2010) reported that Veterans with PTSD have a twofold greater risk of developing dementia compared to Veterans without PTSD. An explanation for Veterans' [with PTSD] higher risk for dementia is the co-

occurrence of depression with both PTSD and dementia. Further, PTSD and dementia both involve depressive symptoms. Notably, Wild and Gur (2008) reported that even after controlling for comorbidity (e.g., depression, substance use, lower IQ, and inattention), PTSD was still associated with verbal memory deficits, which are some of the hallmark indicators of depression and dementia.

Depression as a Risk Factor for Dementia

As researchers have clearly established the existence of some type of relationship between depression and dementia, scholars are now examining if depression may be a potential risk factor for depression. The literature indicates that certain changes occurring in the brain (e.g., neurotransmitter changes, vascular brain disease, white matter changes, and hippocampal changes) support the notion that depression is indeed a risk factor for dementia (Byers & Yaffe, 2011; Chen et al., 2008; Hirono, Kitagaki, Kazui, Hashimoto, & Mori, 2000; Korczyn & Halperin, 2009; Sheline, Gado, & Kraemer, 2003). In the general population, depression usually occurs before dementia, and it is also associated with approximately double the risk of developing dementia or cognitive impairments (Barnes et al., 2012). For women 65 years and older, compared to their male counterparts, clinically significant depressive symptoms are associated with greater incidence of mild cognitive impairment (MCI) and probable dementia (Goveas, Espeland, Woods, Wassertheil-Smoller, & Kotchen, 2011).

Researchers are finding that the time of onset of depression may influence its relationship with dementia (Barnes et al., 2012; Byers & Yaffe, 2011; Geerlings, den Heijer, Koudstaal, Hofman, & Breteler, 2008). The onset of depression varies from individual to individual and there is an increase in the number of instances of depression that occur in individuals from young adulthood to middle age (Byers & Yaffe, 2011). Early- or mid-life depression has been identified

as a significant risk for dementia, whereas late-life depression may act as a prodrome of dementia (Barnes et al., 2012; Byers & Yaffe, 2011). Additional research is necessary to clarify the differences between earlier- or later-onset of depression and its relationship with dementia. Exploring further the impact of an earlier onset of depression could also contribute to preventative treatment efforts for dementia.

PTSD as a Risk Factor for Dementia: Recent Discoveries

Consistent with the data on comorbidity among PTSD, depression, and dementia, researchers have recently found associations between PTSD and dementia, with some identifying PTSD as a significant risk for dementia (Lohr et al., 2015; Sandica & Pop, 2014; Wild & Gur, 2008; Yaffe et al., 2010). Similar to depression, individuals with smaller hippocampal volume are at greater risk of PTSD (Sandica & Pop, 2014). Lohr and colleagues (2015) found that a history of PTSD is associated with accelerated aging, including a greater risk for dementia and other aging-related diseases. Specifically for Veterans 65 years or older, those with PTSD had significantly higher chances of developing dementia compared to those without PTSD (Qureshi et al., 2010). Moreover, even after controlling for several other disorders, researchers found that PTSD was still associated with lower verbal memory (Wild & Gur, 2008).

Diversification of the Population

Important to consider when examining prevalence rates and risk factors for the three disorders is the rapid diversification of the U.S. population (U.S. Census Bureau, 2008). The U.S. Census Bureau (2008) estimated that by 2043, ethnic minorities as a whole group will outnumber their White counterparts. However, each ethnic minority subgroup population within the larger group of minorities will continue to be smaller than the White population. The overall

Veteran population will decrease, yet the number of women and ethnic minority Veterans will increase (National Center for Veterans Analysis and Statistics (NCVAS), 2014).

Including diverse participant samples in future research is imperative, as the existing literature is more representative of certain groups than others (Mindt, Byrd, Saez, & Manly, 2010; Ramirez, Ford, Stewart, & Teresi, 2005). Further, neglecting to include diverse populations (e.g., women and ethnic minorities) in research may result in detrimental health consequences, as the U.S. population is very different than how it was just one decade ago. Treatment may look different from group to group, or individual to individual, men to women, etc. (Ramirez et al., 2005). Notably, Burchard and colleagues (2003) indicated that ignoring race in research and clinical practice can be rather damaging for minorities, as it overlooks or minimizes existing disparities and the experiences of minorities, and Oh et al. (2015) contended that it is a “missed scientific opportunity to fully understand the factors that lead to disease or health” (p. 1). Significant racial disparities relating to quality of health care and health outcomes also exist in the U.S.; thus, problems such as limited research findings applicable to the population as a whole and the lack of culturally appropriate assessments, must be addressed (Ramirez et al., 2005). Disparities between men and women have also been highlighted in the literature, with women having higher risks than men for a large number of mental conditions (Breslau, 2009; Kessler, 2003; WHO, 2002).

Sex Disparities in Diagnoses

Over a decade ago, researchers were finding that women are more likely than men to be diagnosed with dementia (Launer et al., 1999; Letenneur et al., 2000), and this finding is also accepted among most contemporary scholars (Katz et al., 2012; Mielke et al., 2014). In the general population, women also have higher prevalence rates of depression (Kessler, 2003;

Piccinelli & Wilkinson, 2000), and this pattern also has not changed in the last decade (Bouchard & Shih, 2013; Essau, Lewinsohn, Seeley, & Sasagawa, 2010; Van de Velde, Bracke, & Levecque, 2010). The WHO (2002) provided an explanation for the sex disparities in depression rates, stating that the same qualities characterizing depression (e.g., “behaving in submissive ways, experiencing a sense of defeat, wanting to escape but being trapped, perceptions of the self as inferior”, and more) are the same ones that are encouraged in women as desirable qualities of femininity (p. 12).

Depression prevalence rates among older men and women are inconsistent in the existing literature (Barefoot et al., 2001; Sonnenberg, Beekman, Deeg, & Tilburg, 2000). Barefoot and colleagues (2001) indicated that disparity in prevalence rates of depression between men and women declines in late-life, whereas Sonnenberg et al. (2000) found that prevalence rates were almost twice as high for women aged 55 to 85 compared to their male counterparts. Interestingly, Shoevers and colleagues (2000) found that although the prevalence rates of depression for women was double that of men, men showed higher mortality risks than women, which could be a possible explanation for the variability in findings. Overall, the findings indicate that women continue to have higher rates of depression than men in late-life, yet men experience increased mortality risk compared to women despite having similar depressive symptoms.

More recently, researchers have confirmed that the female gender has consistently been identified as a significant risk factor for late-life depression (Chen, Chong, & Tsang, 2007; Meeks et al., 2011). Importantly, however, many older adults may be experiencing depressive symptoms, yet not meeting the full criteria for a depressive disorder (e.g., MDD or adjustment disorder). Depressive symptoms potentially impact these persons in a significant way, yet without a proper classification system, they become difficult to diagnose and treat (Chen et al.,

2007), thus potentially leading to discrepancies in prevalence rates of depression among older men and women. Now, scholars use terms such as subthreshold depression, minor depression, or subsyndromal depression to describe such phenomena (Meeks et al., 2011).

Considering the comorbidity of PTSD and depression, it is not surprising that women are at greater risk for PTSD compared to men (Frans, Rimmo, Aberg, & Fredrikson, 2005). In the general population, PTSD rates among women are twice as high compared to men, even though men report greater trauma exposure (Frans et al., 2005). Breslau (2009) indicated that women are more likely to develop PTSD following a traumatic incident, which could be an explanation for the inconsistency in prevalence rates and the number of trauma exposures found by Frans and colleagues (2005). These findings have noteworthy implications for women in the military, as they are more likely to experience trauma compared to women in the general population (Breslau, 2009; Haskell et al., 2010). Hence, as the female U.S. Veteran population rises, the prevalence rates of PTSD for this population is likely to increase as well.

Racial Disparities in Diagnoses

Countless researchers have established that significant health disparities exist between ethnic minority and White individuals in the U.S. (Manly & Mayeux, 2004). Black individuals have a greater risk for dementia than White individuals, even after controlling for education, gender, and ApoE4 genotype (Plassman et al., 2007), which is a variant of the apolipoprotein E (ApoE) genotype and the most significant genetic risk for late-onset Alzheimer's disease (AD; Cheng et al., 2005). From the *Multi-Institutional Research in Alzheimer's Genetic Epidemiology Study*, Green and colleagues (2002) determined that the overall risk of dementia by age 85 was higher among first-degree relatives of Black individuals with AD (43.7 percent) compared to the risk for first-degree relatives of White individuals with AD (26.9 percent). Similarly, Shadlen

and others (2006) found that White individuals with low levels of education and Black individuals with high levels of education had twice the risk compared to White individuals with high levels of education. Notably, the risk for dementia increased fivefold for Black individuals with low education. Overall, researchers consistently suggest that Black and Hispanic individuals are at greater risk of developing dementia compared to White individuals (Manly & Mayeux, 2004). It is important to note that the research is limited regarding prevalence rates of dementia among other racial minority groups, as the majority of the existing literature in this area involves Black, White, and sometimes Hispanic populations (Manly & Mayeux, 2004).

The findings for rates of depression across racial groups, however, are not as straightforward as they are for dementia. Some scholars have indicated that major depressive disorder (MDD) is more prevalent in the White population, whereas dysthymic disorder is more common in Black and Mexican American populations (Riolo, Nguyen, Greden, & King, 2005; Williams et al., 2007). Others have stated that, among adults aged 54 to 65 years, MDD and other depressive factors are more prevalent in racial minority populations (Dunlop, Song, Lyons, Manheim, & Chang, 2003).

Scholars provided evidence to explain the inconsistent findings in depression prevalence rates. McGuire and Miranda (2008) discussed how ethnicity, race, culture, and language all can impact symptom expressions and behaviors, as well as how health care providers interpret such expressions and behaviors. Due to the underrepresentation of ethnic minorities, particularly in medical research and care, it is likely that lower depression rates among minorities may be an inaccurate reflection of their experiences. Akincigil and colleagues (2012) conducted a study with adult Medicare patients, ranging in age from less than 45 to more than 85 years, to examine racial and ethnic disparities in depression care. Consistent with past research findings (Alegria et

al., 2008; McGuire & Miranda, 2008; Mezuk et al., 2010), the researchers concluded that ethnic minorities, including Black, Hispanic, and other non-Hispanic groups, were less likely to be diagnosed with and treated for depression, when compared to the majority group (i.e., non-Hispanic White persons). Consequently, the researchers highlighted the “underrecognition and undertreatment of depression among minority elders,” as well as “the net of differences in underlying symptoms” (Akincigil et al., 2012, p. 323).

Mezuk and colleagues (2010) found that Black individuals experience more life stressors and engage in more poor health behaviors (PHB) than White individuals, yet Black individuals still had a lower prevalence of depression than their White counterparts. Interestingly, when measuring how PHB affected the positive link between life stress and depression risk, the PHB of Black individuals moderated this link [between stress and depression], whereas the PHB of White individuals did not. These findings provide a rationale for health care providers to assess mental and physical health together, because racial groups may express symptoms and behaviors differently than others.

The results support the relationship between social disadvantage, exposure to stress, coping via poor health behaviors, and the existence of mental and physical health racial disparities (Mezuk et al., 2010). For instance, rather than utilizing mental health treatments, it is possible that racial minorities cope via poor health behaviors in response to the chronic and higher levels of life stressors they experience (compared to their White counterparts). Mezuk et al. (2010) concluded that such differences in coping behaviors potentially account for racial disparities in health outcomes, despite lower rates of mental health diagnoses among racial minorities. Importantly, since the majority of the racial comparisons made in research studies involve Black and White populations, researchers must consider the limitations when applying

these findings to other racial minority groups, particularly those remaining largely underrepresented in the literature.

Similar trends in prevalence rates of PTSD have also been reported. Black individuals had greater odds of being diagnosed with PTSD, and also had greater lifetime prevalence rates of PTSD compared to their White, Asian, and Hispanic counterparts (Asnaani et al., 2010). Unfortunately, Black individuals were less likely to seek treatment for PTSD and other mental health disorders, when compared to White individuals (Himle et al., 2009; Roberts et al., 2011).

Explanations for Disparities

Across the majority of disease categories, members of racial minority groups had higher morbidity and mortality rates than their White counterparts (Ramirez et al., 2005). The U.S. Department of Health and Human Services (2010) attributed these persisting disparities to barriers and discrimination that disadvantaged groups, such as women and ethnic minorities, encounter. In 2010, the U.S. Surgeon general proclaimed that members of ethnic and racial minority groups in the U.S. “face a social and economic environment of inequality that includes greater exposure to racism, discrimination, violence, and poverty, all of which take a toll on mental health” (American Psychiatric Association, 2016).

Causes of such inequity cannot be determined by the types of studies that have been conducted thus far to analyze health disparities across groups, resulting in uncertainty about the determinants (Ramirez et al., 2005). Further, utilizing assessments that lack cultural sensitivity leads to misrepresentative data, particularly if norms have not yet been developed for certain groups (Ramirez et al., 2005). Nonetheless, scholars have offered several hypotheses in efforts to understand and eliminate such disparities.

Health Care Providers' Roles

Van Ryn and Fu (2003) stated “Public health, medical care, and human service providers may influence race/ethnicity and class health disparities in several interconnected ways” (p. 249). Provider communications impact patients’ health-related cognition and behavior (e.g., lower or high expectations, mechanisms of access, loss of benefits; Van Ryn & Fu, 2003). For instance, health care providers can influence patients’ view of themselves (e.g., deservingness of treatment, fundamental value to the community) and their society, culture, and community (Van Ryn & Fu, 2003).

Likewise, patients’ demographic characteristics (e.g., race/ethnicity, sex, age, diagnostic history, and sexual orientation) also significantly affect providers’ beliefs and expectations (Dovidio et al., 2008). This, in turn, can influence patients’ perceptions of themselves and of their providers (Dovidio et al., 2008; Van Ryn & Fu, 2003). Dovidio and colleagues (2008) emphasized the importance of considering how “potential racial biases of providers, which may be subtle and unintentional, and the sensitivity of Black patients to possible cues of bias jointly influence the nature and outcomes of the medical encounter” (p. 5).

For instance, White physicians exhibited more verbally dominant and less patient-centered characteristics with Black versus White patients (Johnson, Roter, Powe, & Cooper, 2004). When working with breast cancer patients, White physicians spent much less time involved in relationship-building activities with Black versus White patients (Siminoff, Graham, & Gordon, 2006). Female patients were more likely to be diagnosed with depression than male patients, even if they reported or presented with identical symptoms (WHO, 2002). However, the source of these phenomena are difficult to identify, as personal perceptions are influenced by

several different contextual factors (Van Ryn & Fu, 2003). Thus, causes cannot be determined and the research in this area remains inconclusive.

Another area researchers explored to understand racial health disparities are the inequities related to treatment. There is undertreatment of depression, that also results from underrecognition, among older minority adults (Akincigil et al., 2012). Researchers found that all racial minority groups are less likely to have access to depression treatment compared to their White counterparts (Alegria et al., 2008; Simpson, Krishnan, Kunik, & Ruiz, 2007). Dovidio et al. (2008) presented their findings from a comprehensive review of the literature on the existing race- and gender-related health disparities, specific racial groups' distrust in the health care system, and how health care providers contribute to racial health inequities. They identified numerous examples of how providers' racial biases can impact their treatment of minority patients. It is also important to note that in 2010, the Institute of Medicine Panel identified race-based prejudice as a key determinant of the existing health disparities in the U.S. (U.S. Department of Health and Human Services, 2010).

Neuropsychology and Universalism

When examining conditions such as dementia, depression, and PTSD, the field of neuropsychology deserves mention based on the altered or impaired cognitive functioning that characterizes these disorders. Neuropsychologists are charged with assessing patients' brain functioning to understand their cognitions and behaviors (Strauss, Sherman, & Spreen, 2006). Mindt and others (2010) underscored the limits to universalism in neuropsychology, which holds that cognitive processes are similar across all persons. The researchers contended that this notion is false in the context of neuropsychological functioning across diverse groups. Further, when universalism is accepted as true, the cognitive processes of the founder(s) of the field become

regarded as “normal,” and cognitive processes departing from the founders’ are considered abnormal, impaired, or pathological.

Applying the notion of universalism in neuropsychology has been detrimental for racial minorities due to their underrepresentation as patients and providers in the field (Manly, 2008; Mindt et al., 2010). Although the research on minorities’ cognitive test performance is increasing, the clinical tools and guidelines for neuropsychological assessment of these groups, especially American Indian and Alaska Native individuals, are very limited (Manly, 2008). Hence, neuropsychologists are faced with a dilemma when working with ethnic minority patients; it is well known that it is unethical to use inappropriate measures with culturally different individuals, yet refusing service for large groups of people based on demographic characteristics also violates the field’s ethics. In addition to the existing racial health disparities in the general U.S. population, there are disparities in the availability and/or use of neuropsychological services, resulting in an increased risk for minorities not receiving the appropriate diagnosis or treatment. Neuropsychology, along with several other health subspecialty fields, require further vigorous testing of its approaches and methods to assure equal health access, assessment, and treatment across racial groups.

Differences in Coping Mechanisms

The literature shows how different groups of people use varying coping mechanisms for their health problems, which scholars hypothesize may be playing a role in the existing health disparities (Ford & Airhihenbuwa, 2010; Gerrard et al., 2012). For example, women are more likely to go to their primary care physician for mental health problems, whereas men are more likely to go to a mental health specialist (WHO, 2002). Moreover, people’s expectations based on gender can influence their disclosure of health information. For example, men are more

likely to disclose alcohol or drug usage, whereas women are more likely to disclose emotional problems (WHO, 2002), as these problems prove to be more stereotypically accepted for men and women, respectively. With respect to racial differences in coping mechanisms, historical events, socioeconomic status, and cultural or religious beliefs can play a major role. For example, Conner and others (2010) determined that due to a lifetime of discrimination and racism experienced by older Black adults, their lack of trust in the health care system often results in them seeking culturally endorsed strategies to “push through” (p. 979) the problem, rather than seeking official medical care for potentially serious medical conditions. Gerrard et al. (2012) also highlighted how adverse experiences, such as racial discrimination, can influence racial minorities’ to use illicit substances as a method of coping.

The Public Health Critical Race (PHCR) Praxis

In an attempt to explain racial disparities in health care, Ford and Airhihenbuwa (2010) developed the Public Health Critical Race (PHCR) Praxis, which was adapted from Critical Race Theory (CRT; Delgado, Stefancic, & Liendo, 2012). The researchers identified PHCR as a tool to promote health equity that “combines theory, experiential knowledge, science, and action” to actively counter existing health inequities (Ford & Airhihenbuwa, 2010, p. 1391). Although segregation and other overt forms of discrimination are outlawed, subtle forms of discrimination, such as “not being offered the same follow-up care that other patients are offered” are common occurrences today (Thrasher, Clay, Ford, & Stewart, 2012, p. 1025). PHCR demonstrates how negating to consider race in health care research and clinical work dismisses the systemic and institutional racism that largely prevails in the U.S. today, thus, turning the disparities into the result of characteristics or deficits of certain groups (e.g., focusing on race as a biological category). The researchers give emphasis to the importance of race consciousness via four

primary foci: contemporary patterns of racial relations, knowledge production, conceptualization and measurement, and action (Ford & Airhihenbuwa, 2010). The model can be applied in research and clinical practice across various contexts (e.g., gender inequities) to demonstrate how such inequities are perpetuated in the current system and the PHCR would be an invaluable tool for examination of racial inequalities across health-related contexts.

Veteran Population

There are approximately 21 million Veterans in the U.S., 72 percent of whom are 50 years or older (National Center for Veterans Analysis and Statistics (NCVAS), 2014). Further, the number of women and ethnic minority U.S. Veterans is steadily rising. The National Center for PTSD reported that the lifetime prevalence of PTSD is significantly higher among Veterans compared to American adults in the general population (Gradus, 2007). Among all adults, the lifetime prevalence of PTSD is estimated to be 3.6 percent for men and 9.7 percent for women. In the Veteran population, the lifetime prevalence is 30.9 percent among men, and 26.9 percent among women. Researchers determined that Veterans with PTSD are twice as likely to develop dementia when compared with Veterans without PTSD (Yaffe et al., 2010). Yaffe and colleagues (2010) reported that both PTSD and dementia are associated with a higher co-occurrence risk of depression. Parallel patterns of disparities in health care and outcomes exist within the Veteran population (Ramirez et al., 2005). Based on these findings, Veterans have higher risks for PTSD, as well as depression and dementia, hence, making them an important group to study (Shively & Perl, 2012; Sibener et al., 2014).

Summary and Conclusions

Despite proliferation of research in the area, the relationship between depression, PTSD, and dementia remains uncertain. Dementia affects 3.4 million individuals aged ≥ 71 years in the

U.S. and people's risk for dementia increases by age (Plassman et al., 2007). Although age has been identified as the biggest risk factor for dementia, there are no current methods for health care providers to utilize to determine with certainty whether an individual will later develop dementia. Importantly, researchers provided evidence that the pathophysiological changes associated with dementia, specifically Alzheimer's disease, starts much earlier than when overt symptoms are observed (Sperling et al., 2011). Sperling and colleagues (2011) identified this earlier stage as "preclinical", and stressed that it would be one of the most critical opportunities for intervention (i.e., preventative methods).

Exploring the role of depression and PTSD in predicting dementia would be advantageous in providing additional information on what types of symptoms individuals may exhibit in the "preclinical" stage. Depression is the most common mental health problem encountered by women, and it is the most notable contributor to the worldwide burden of disease (Essau et al., 2010; WHO, 2002). Importantly, a large body of evidence shows that a history of depression doubles the risk of dementia (Barnes et al., 2012). PTSD is more common in the U.S. than in other countries, especially following the September 11 attacks and Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) in Iraq and Afghanistan, respectively. Due to the recent literature in which researchers identify PTSD as a risk factor for accelerated aging (which includes increased risk for dementia; Lohr et al., 2015; Sibener et al., 2014) and the increasing minority population of U.S. Veterans (U.S. Census Bureau, 2008), PTSD also proves to be an important disorder to consider when studying dementia.

The population is rapidly changing and health care providers must develop and maintain cultural competency with regard to assessment, diagnosis, and treatment. In addition to the known risk factors of dementia, scholars have also demonstrated how race and sex may play a

role in assessment, diagnosis and treatment of dementia and related conditions. Compared to their White counterparts, racial minorities encounter additional barriers when attempting to access health care, which then directly affects health outcomes. This also proves to be true among Veterans, as persons in this group are at greater risk of developing dementia compared to non-Veterans (Sibener et al., 2014). Due to the complex relationship among the three conditions and societal factors unique to the Veteran population that may influence health care and outcomes, additional research is needed to better understand psychiatric risk factors of dementia and how Veterans' demographic characteristics may influence their level of risk.

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CHAPTER 2

Abstract

The objective of this study was to investigate major depressive disorder (MDD) and posttraumatic stress disorder (PTSD) first diagnosed at age < 55 years, as predictors of dementia and other forms of cognitive impairment not demented (CIND) in Veteran subjects aged ≥ 60 years ($N = 4,800$). Sex (male or female) and race (Black or White) were analyzed as potential moderators. Based on the literature, it was hypothesized that subjects with MDD or PTSD history would have an increased risk of dementia/CIND compared to those without a history. Hypotheses related to sex and race were exploratory. There were twelve groups in this study, determined by psychiatric history (e.g., MDD, PTSD, or no psychiatric history), sex, and race. Two sets of hierarchical and backward logistic regression analyses were conducted to determine significant predictors of dementia/CIND. The outcome variable in the first set of analyses was dementia/CIND diagnosed at age ≥ 60 , and the findings of these data were largely insignificant. In the second set of analyses (dementia/CIND diagnosed at age ≥ 56), a history of MDD or PTSD both were associated with almost double the risk for developing dementia/CIND. When a history of MDD was indicated, Black Veterans' risk of dementia/CIND increased almost twofold. Further, given the differences in results from the first and second set of analyses, it is probable that Veteran subjects began experiencing dementia and cognitive impairment at an earlier age compared to the general population. Additional findings, limitations, and implications are also discussed.

Keywords: dementia, cognitive impairment, CIND, MDD, PTSD, race, and sex

CHAPTER 2

History of MDD and PTSD as Risk Factors for Dementia and Cognitive Impairment Not Demented (CIND) among U.S. Veterans: A Retrospective Cohort Study based on Demographic Characteristics

Dementia and depression have a complex relationship, and this relationship has been receiving increased attention in the existing literature (Dotson, Beydoun, & Zonderman, 2010; Korczyn & Halperin, 2009). Due to the similarity between the two diagnoses, particularly the cognitive symptoms (e.g., reasoning and memory), one is commonly misdiagnosed as the other (Casey, 2012). Both disorders are common occurrences in older individuals. Dementia is most common among adults aged ≥ 65 years, and older adults are at risk for depression due to age-associated neurobiological changes, stressful events, role changes associated with loss, and more (Fiske, Wetherell, & Gatz, 2009). Depression can possibly be a reaction to individuals experiencing a decline in memory, or it can also be an early symptom of dementia; thus, it is unclear if one can cause the other (Korczyn & Halperin, 2009).

More recently, researchers have been studying the relationship between posttraumatic stress disorder (PTSD) and dementia, as symptoms of PTSD are related to depression and depression has been known to co-occur with PTSD. Notably, Yaffe et al. (2010) found that Veterans with PTSD have a two-fold higher risk of developing dementia when compared to Veterans without PTSD, which can be explained by the co-occurrence of depression associated with both PTSD and dementia. Likewise, Lohr et al. (2015) conducted a comprehensive review of empirical studies examining PTSD and the role it plays in aging, and determined that in a majority of studies, persons with PTSD have an increased risk of comorbidity of dementia, as

well as several other conditions associated with aging (e.g., cardiovascular aging, type 2 diabetes, and gastrointestinal ulcer disease).

Cognitive Impairment Not Demented (CIND)

It is worthwhile to note that conditions involving cognitive impairment extending beyond memory difficulties have been a significant focus of researchers in recent years (Albert et al., 2011; McKhann et al., 2011; Yaffe et al., 2011). Across research and clinical populations, professionals are noticing large numbers of individuals experiencing cognitive difficulties, yet do not meet criteria for dementia (Chodosh, Kado, Seeman, & Karlamangla, 2007; Farias, Mungas, Reed, Harvey, & DeCarli, 2009; Yaffe et al., 2011). Hence, data on diagnostic and evaluative criteria for various forms of cognitive impairment, such as cognitive disorder not demented (CIND) and mild cognitive impairment (MCI), have proliferated in the literature (Albert et al., 2011; Rosenberg, Johnston, & Lyketsos, 2006). Researchers identified persons meeting criteria for cognitive impairment not demented (CIND), such as MCI, as having an increased risk of developing dementia compared to those without CIND (Meyer, Xu, Thornby, Chowdhury, & Quach, 2002; Rosenberg et al., 2006).

Reisberg and Gauthier (2008) found, from a thorough review of the literature, that subjective cognitive impairment (SCI) is a stage prior to mild cognitive impairment (MCI), which then increases odds for the eventual development of dementia. Considering these data, researchers have been highlighting the importance of recognizing deficits in a range of cognitive functions across research and clinical settings (Katz et al., 2012). Such findings also demonstrate that patients reporting cognitive difficulties, although unobservable to providers and/or loved ones, are an important group to target for preventative treatment.

Further, deficits in cognitive functioning (not classified as dementia) are important to examine when studying the impact of psychiatric disorders (Byers, Covinsky, Barnes, & Yaffe, 2012; Casey, 2012; Yaffe et al., 2010). A greater cumulative burden of depression, including more severe and chronic symptoms, has been linked with a higher likelihood of cognitive impairment (Kaup et al., 2016). More chronic and severe depressive symptoms are the hallmark features of major depressive disorder (MDD), which is a condition specifically identified as a key predictor of dementia (Byers & Yaffe, 2011). In fact, Byers et al. (2012) reported that dementia and mortality are two outcomes that are associated with MDD, yet they remain largely underrecognized. PTSD is also associated with an increased risk of dementia, and well as overall worse cognitive performance particularly in domains of processing speed, learning/memory, and executive functions (Lohr et al., 2015).

Chronic Stress: The Link between MDD and PTSD

A characteristic found in both MDD and PTSD is the presence of chronic stress (Butters et al., 2008; Veitch, Friedl, & Weiner, 2013). Due to its link in many different facets of the aging process (Lohr et al., 2015), chronic stress connects MDD with PTSD as substantial risk factors of dementia and other forms of cognitive impairment. For example, in the U.S., military deployment has been linked to chronic and acute stress, and MDD and PTSD are the two most common mental health illnesses found in the military and Veteran population (Veitch et al., 2013).

Neurotransmitter changes, vascular brain disease, white matter changes in the brain, and hippocampal changes also provide evidence regarding how MDD, and other forms of depression, may be a risk factor for dementia/CIND (Byers & Yaffe, 2011; Chen et al., 2008; Hirono, Kitagaki, Kazui, Hashimoto, & Mori, 2000; Korczyn & Halperin, 2009; Sheline, Gado, &

Kraemer, 2003). Scholars are finding that early-life and mid-life (40 to 55 years of age) depression may act as a significant risk-factor for dementia and related conditions, whereas late-life depression may act as a prodrome for dementia (Barnes et al., 2012; Byers & Yaffe, 2011; Geerlings, den Heijer, Koudstaal, Hofman, & Breteler, 2008). Similar conclusions have been reported for persons with a history of PTSD, which is not surprising considering the high comorbidity between the two disorders (Angelakis & Nixon, 2015; Spinhoven, Penninx, van Hemert, de Rooij, & Elzinga, 2014). For example, persons with MDD and those with PTSD were found to have smaller hippocampal volume; however, it remains unclear whether this leads to symptoms or such symptoms lead to decreased hippocampal volume (Byers & Yaffe, 2011; Sandica & Pop, 2014).

Changes in the Population

An important aspect to consider when studying relationships between dementia and related conditions is the rapidly changing demographic characteristics of the U.S. population. The U.S. Census Bureau (2008) projected that ethnic minorities will become the majority group by 2043, rising from about 33 to 54 percent of the country's population. However, since some of these groups are underrepresented in research, there is a strong necessity to include diverse populations in studies in order to deliver up-to-date information to health care providers, as well as the general public (Mindt, Byrd, Saez, & Manly, 2010; Ramirez, Ford, Stewart, & Teresi, 2005). Due to this underrepresentation, the research is somewhat limited, and inconsistent, regarding prevalence rates of certain diagnoses among diverse groups.

Similar to the general population, the U.S. Veteran population is also expected to become more diverse. The National Center for Veterans Analysis and Statistics (NCVAS; 2014) published the *Projected Veteran Population 2013 to 2043* report demonstrating that, although the

size of the Veteran population is predicted to decline, the percentage of female and ethnic minority Veteran population will gradually increase. Thus, as this population increases, there is a growing need for health care providers who are competent in working with diverse individuals. Veterans are an important group to study, as scholars have identified them as having greater risk for dementia/CIND than the general population (Lohr et al., 2015; Shively & Perl, 2012; Sibener et al., 2014). For example, increased age, Black racial background, and other disorders of the brain (e.g., depression) have been recognized as some of the key risk factors of dementia and related cognitive deficits (Lohr et al., 2015; Shively & Perl, 2012). Compared to the general U.S. population, the Veteran population, on average, consists of older individuals, greater proportion of Black individuals, and has higher incidence rates of TBI and PTSD, which are also related to depression (Sibener et al., 2014).

Prevalence Rates

Dementia and CIND

General Population. Among persons aged ≥ 60 years, the estimated prevalence rate of dementia worldwide is between 5 to 7 percent (Prince et al., 2013). Scholars have reported varying rates of dementia across demographic groups in the U.S. (Hebert, Weuve, Scherr, & Evans, 2013; Manly & Mayeux, 2004; Plassman et al., 2007). The findings from the *Aging, Demographics, and Memory Study* (the *ADAMS* study; Plassman et al., 2007) indicated that among participants aged ≥ 71 years, Black individuals were at a greater risk for dementia than White individuals even after controlling for education, gender, and ApoE4 genotype. The ApoE (apolipoprotein E) genotype has three major alleles, with variant E4 being the largest genetic risk factor of late-onset Alzheimer's disease (AD; Cheng et al., 2005; Reddy & Beal, 2008).

The *ADAMS* study results did not indicate significant differences in rates of dementia between men and women (Plassman et al., 2007). Nonetheless, other studies have long demonstrated the increased risk for women in the general population for developing dementia (Viña & Lloret, 2010). For instance, Mielke, Vemuri, and Rocca (2014) reported that women are disproportionately affected by dementia, particularly Alzheimer's disease, and it is possible men are more likely to be impacted by mild cognitive impairment (MCI). Other scholars have found that women have an increased risk for dementia compared to men at age ≥ 90 years, and that dementia rates among men and women younger than 90 were not significantly different (Katz et al., 2012).

CINDs have been difficult to measure due to lack of diagnostic clarity (Albert et al., 2011). To illustrate, Plassman et al. (2008) found estimates ranging from 3 to 29 percent from a comprehensive review of the literature. In their study, they found cognitive impairment to be present in 22.2 percent of individuals aged ≥ 71 years, which is approximately 70 percent higher than the rate of dementia (Plassman et al., 2008). The researchers also reported that compared to women, men were at a greater risk of having CIND. They did not find a significant relationship between racial background and CIND (Plassman et al., 2008).

Veteran Population. Dementia rate estimates vary slightly for the Veteran population, yet they are largely consistent with the rates (5 to 8 percent) reported for the general population (Veitch et al., 2013; Wray, Wade, Beehler, Hershey, & Vair, 2014). Across disciplines, researchers are expecting this rate in the Veteran population to increase due to the aging population of the U.S. Specifically, among persons aged ≥ 60 years in the general U.S. population, 22 percent are Veterans. Moreover, half of the men in this population are Veterans. Due to the significant amount of comorbidity found in mental and cognitive disorders in this

population, CIND rates have not clearly been established but are thought to follow similar trends (Veitch et al., 2013).

Depression and PTSD

General Population. The lifetime prevalence rate of MDD in the general population is between 5.2 to 6.7 percent (Veitch et al., 2013). Researchers indicated that White individuals have higher rates of MDD whereas Black and Mexican American individuals have higher rates of dysthymic disorder, which involves a chronic state of dysphoria (Riolo, Nguyen, Greden, & King, 2005; Williams et al., 2007). Riolo and colleagues (2005) attributed this to possible effects of poverty, lack of education, less access to health care, and more. However, for adults between 54 to 65 years of age, Dunlop, Song, Lyons, Manheim, and Chang (2003) found that MDD and associated factors were more prevalent in ethnic minority populations than White populations. Thus, although some literature exists that estimates the rates of these disorders across minority groups, the research is scant, and sometimes contradictory, due to small sample sizes across specific groups, lack of culturally appropriate measures, and more (Ramirez et al., 2005).

Among men and women, scholars determined that women generally have greater rates of depression compared to their male counterparts (Essau, Lewinsohn, Seeley, & Sasagawa, 2010; Piccinelli & Wilkinson, 2000; Van de Velde, Bracke, & Levecque, 2010). Such differences could be attributed to various factors, including but not limited to societal and cultural gender norms, higher risk of certain traumatic incidents, help seeking tendencies, and more (Bouchard & Shih, 2013). Among older adults aged ≥ 65 years, the data on rates of depression is inconsistent (Djernes, 2006). Barefoot, Mortensen, Helms, Avlund, and Schroll (2001) found that the disparity in rates of depression decreases in late-life, whereas Hybels, Blazer, and Pieper (2001) reported that among persons aged > 65 years, women consistently had greater rates of depression

compared to men. Similarly, among persons 55 to 85 years of age, the prevalence rate of depression in women was almost twice as high as it was for men (Sonnenberg, Beekman, Deeg, & Tilburg, 2000). Schoevers and others (2000) also found the rate of depression for women was double that for men, though men showed higher mortality risks than women amongst persons with severe levels of depression. More recently, researchers have determined that the female gender acts as a prominent risk factor for late-life depression (Meeks, Vahia, Lavretsky, Kulkarni, & Jeste, 2011).

There is a higher prevalence of PTSD in the U.S. compared to other countries, with lifetime prevalence rates of 6 to 12 percent in the general population (Breslau, 2009; Veitch et al., 2013). Men reported experiencing more traumatic incidents than do women, yet women were twice as likely as men to develop PTSD after a traumatic incident (Breslau, 2009; Dobie et al., 2004). In the general population, Black individuals were more likely to have PTSD compared to their White counterparts, and all ethnic minorities were less likely to seek treatment for PTSD compared to White individuals (Asnaani, Richey, Dimaite, Hinton, & Hofmann, 2010; Roberts, Gilman, Breslau, Breslau, & Koenen, 2011). Furthermore, Black persons in the general population have higher lifetime prevalence rates of PTSD compared to other racial groups (Himle, Baser, Taylor, Campbell, & Jackson, 2009).

Veteran Population. The Veteran population has greater prevalence rates of mental health diagnoses compared to the general population, with MDD and PTSD being the most common (Veitch et al., 2013). The lifetime prevalence of PTSD among U.S. combat Veterans is between 6 to 31 percent, which is significantly greater than the rate of 6 to 12 percent for the general population. Compared to active duty Veterans aged > 40 years, Veterans aged < 25 have a greater risk for PTSD (Seal et al., 2009). The rates of MDD in the Veteran population has been

difficult to measure, with estimates ranging from 12 to 30 percent (Veitch et al., 2013). Female Veterans have been found less likely to screen positive for PTSD, yet more likely to screen positive for depression and military sexual trauma (Haskell et al., 2010). Dobie et al. (2004) found a 21 percent prevalence rate of PTSD for female Veterans, and 20 percent for male Veterans; however, additional research is necessary to determine more accurate estimates between male and female Veterans.

In their analysis of a subsample of Veterans from the *National Vietnam Veterans Readjustment Study (NVVRS)*, Dohrenwend, Turner, Turse, Lewis-Fernandez, and Yager (2008) found that Black Veterans had elevated rates of chronic PTSD, which they explained could potentially be due to greater exposure to war-zone stressors. Black persons were also identified as having a greater risk in a study of Veterans involved in recent Operation Enduring Freedom/Operation Iraqi Freedom conflicts (Dursa, Reinhard, Barth, & Schneiderman, 2014). Importantly, Villa (2002) determined that Black Veterans have continually been disadvantaged with respect to health and other factors associated with daily living across all war cohorts prior to Operation Enduring Freedom (OEF), Operation Iraqi Freedom (OIF), and Operation New Dawn (OND).

The comorbidity of MDD and PTSD among Veterans has been an important topic for researchers, as the exact relationship between the two has been described as “likely to be complex, involving bidirectional causality, common risk factors, and common vulnerabilities” (Angelakis & Nixon, 2015, p. 2). As two of the most common mental health disorders found in this population, it is not a surprising finding that the comorbidity rates of MDD and PTSD is very high for Veterans (Veitch et al., 2013).

Role of Sex and Race

Examining the role of sex and race in dementia/CIND diagnosis is crucial due to the enduring health disparities that exist among these groups. However, the literature is lacking consistent data on prevalence rates of dementia and many other major conditions across different populations (Katz et al., 2012). The U.S. Department of Health and Human Services (2010) published the *National Healthcare Disparities Report 2010*, and found that although quality of health care in the U.S. is improving, access and disparities are not improving. Such disparities were related to disadvantaged groups based on race, SES, and more.

Specifically, Black, American Indian, and Alaska Native individuals received worse care compared to their White counterparts in almost half of the core measures of health care (e.g., preventative care, chronic disease management). Fewer than 20% of these disparities showed evidence of lessening between periods ranging from 2000-2002 to 2006-2008. For example, the quality of and access to preventative care related to women's health (e.g., mammograms, pap smears) worsened over time. Further, the U.S. D.H.H.S. (2010) underscored how racial and ethnic minorities, as well as persons from low SES backgrounds, often receive lower quality of care and encounter more barriers when trying to access health care.

Regrettably, similar patterns of racial disparities in health care and health outcomes have been found among Veterans (Ramirez et al., 2005; Saha et al., 2008). For example, Saha et al. (2008) found worse quantity and quality of health care for racial minorities, particularly Black Veterans, across many clinical content areas (e.g., arthritis/pain management, heart and vascular disease, mental health/substance abuse, and more) as well as by utilization or outcome measure (e.g., medication prescribing and adherence, basic services and processes of care, intermediate outcomes, patient care, and more).

Providers' diagnostic and treatment decisions were also found to vary based on patients' race (Lagomasino, Stockdale, & Miranda, 2015). Ramirez and colleagues (2005) asserted that among the Veteran and the general populations, older racial minority groups have higher incidences of several diseases (e.g., hypertension, heart disease, diabetes, and more) compared to their White counterparts. It is important to note that scholars have also identified studies based on secondary and administrative Veterans Health Administration (VHA) data that are often missing race/ethnicity data (Long, Bamba, Ling, & Shea, 2006), leaving researchers with an incomplete picture of existing disparities.

Patients' Demographic Characteristics and Providers' Impressions

Patients' demographic features were found to be associated with variations in providers' diagnostic and treatment impressions, which researchers have recognized as one of the leading causes of the existing health disparities (Alarcón et al., 2009; Gara, Vega, Arndt, & et al., 2012; Hyde, Mezulis, & Abramson, 2008). It is widely known now that women under 65 are more likely to be diagnosed with depression than men, which can be attributed to various factors, such as emotional expression, gender stereotypes, willingness to seek help, and more (Angst et al., 2002; Hyde et al., 2008). Health care providers are more likely to diagnose women with depression compared with men, even when they report similar symptoms (WHO; World Health Organization, 2002). It is also probable that women are more likely to be diagnosed with depression and dementia due to their increased willingness to express emotion-related symptomology and help-seeking behaviors compared to their male counterparts (Hyde et al., 2008). For greater diagnostic accuracy, it is important for researchers and clinicians to consider how sex may influence their impressions and conclusions, particularly because many conditions such as depression and dementia have similar symptoms.

Race is another important demographic variable for researchers and clinicians to consider, particularly because racial health disparities have persisted in the U.S. for many decades (U.S. Department of Health and Human Services, 2010). For example, many scholars have provided evidence for the greater risk of misdiagnosis that Black individuals have compared to other racial groups (Alarcón et al., 2009; Neighbors, Trierweiler, Ford, & Muroff, 2003). In a seminal article by Neighbors and colleagues (2003), Black individuals were more likely to be diagnosed with schizophrenia whereas White individuals were more often diagnosed with mood disorders. Since then, the examination of how patients' race/ethnicity influences providers' diagnostic impressions has grown in the literature (Dovidio et al., 2008; Gara et al., 2012; Lagomasino et al., 2015; McLean et al., 2014). Notably, almost one decade later, Gara et al. (2012) found that "clinicians appeared to minimize the possibility of mood disorder diagnosis or failed to carefully apply the diagnostic criteria of these disorders" for Black individuals, and also that symptoms were interpreted as "psychotic" for Black persons more than for other racial groups (p. 598). In another study, Eack, Bahorik, Newhill, Neighbors, and Davis (2012) reported that providers' perceptions of patients' honesty was significant in predicting a schizophrenia diagnosis only among Black individuals. Findings such as these have significant implications in health care (Oh, Galanter, Thakur, Pino-Yanes, Barcelo, et al., 2015).

Interestingly, Kales and others (2005) contended that providers may also be forming diagnostic impressions based on factors related to socioeconomic status (SES) of certain groups, rather than racial characteristics. Indeed, the *National Health Disparities Report 2010*, reported that individuals of lower SES encounter barriers to accessing health care, and also receive lower quality of care (U.S. D.H.H.S., 2010, p. 214). However, Diemer and Ali (2009) asserted that due to the intertwining of socioeconomic status and race in historical and contemporary U.S. society,

it is difficult to disentangle the complex relationship between the two. Hence, ignoring racial/ethnic background and/or highlighting other factors instead that are nevertheless related to race (e.g., SES), can be rather detrimental, as apparent racial disparities have persisted across varying health care contexts for numerous decades (Burchard et al., 2003; Oh, Galanter, Thakur, Pino-Yanes, White, et al., 2015). Researchers have also emphasized the damage that it can cause for minority populations because they are already underrepresented in research (Burchard et al., 2003; Mindt et al., 2010). Ignoring race/ethnicity in research would minimize such inequities and the experiences of ethnic minority group members, thus hindering the progress that has been made thus far in eliminating racial disparities in the U.S. health care system (Burchard et al., 2003; Oh, Galanter, Thakur, Pino-Yanes, White, et al., 2015).

Objectives and Rationale of the Present Study

The objectives of this study included: (1) examine major depressive disorder (MDD) and posttraumatic stress disorder (PTSD) as predictors of dementia/CIND, and; (2) explore how sex and race moderated the relationship between the disorders. The acronym CIND (cognitive impairment not demented) is used to identify diagnoses primarily characterized by cognitive impairment selected for this study (see Appendix A for a complete list). Although definitions are slightly varied across studies, researchers commonly use CIND to denote cognitive decline and “mild impairment on memory tests and/or other cognitive domains, with at least most mild functional impairment in daily activities” (Williams, Plassman, Burke, Holsinger, & Benjamin, 2010, p. 29).

The objectives were based on the following rationale: (1) the relationship between MDD and PTSD with dementia/CIND is still not clear (Williams et al., 2010; Wilson, Arnold, Beck, Bienias, & Bennett, 2008); (2) the general population (U.S. Census Bureau, 2008) and the

Veteran population (NCVAS, 2014) are rapidly diversifying; (3) racial minorities experience lower quality of health care and additional barriers to access of health care, compared to their White counterparts (U.S. Department of Health and Human Services, 2010; Yaffe et al., 2013), and this has been found in the Veteran population as well (Saha et al., 2008), and; (4) patients' demographic characteristics may influence health care providers' diagnostic impressions and treatment (Dovidio et al., 2008).

The participants of this study were U.S. Veterans, as this group has a higher likelihood of developing dementia/CIND when compared to the general population, particularly due to the unique circumstances they encounter (e.g., greater incidents of traumatic brain injury and PTSD; Lohr et al., 2015; Shively & Perl, 2012; Sibener et al., 2014). Racial health disparities have been found across a wide range of clinical service areas within the VA system, despite being a system where financial barriers are minimized (Saha et al., 2008). Importantly, race/ethnicity information has been missing from VHA data in past decades (Long et al., 2006), and this study intended to aid in efforts to close this gap. The existing literature on U.S. Veterans' risk of dementia/CIND includes largely male samples, who predominantly self-identify as White (Byers et al., 2012; Yaffe et al., 2013). Research on female Veterans has increased in recent years, yet due to the missing data on race/ethnicity, it has been a difficult task for researchers to include a sample that is representative of different racial groups (Long et al., 2006). This is particularly an important endeavor for future researchers as the Veteran population increasingly diversifies.

Based on the existing literature, it was hypothesized that Veteran subjects with a history of MDD or PTSD at age < 55 would have a greater likelihood of receiving a diagnosis of dementia/CIND at age > 55, compared to subjects without a history of MDD or PTSD. The predictive utility of race and sex were also analyzed. Further, the relationship between these

factors and the chronicity (i.e., number of years since the first diagnosis) of MDD and PTSD was assessed.

Methods

This was a retrospective cohort study consisting of a review of Veterans' medical records, which were obtained through the Department of Veterans Affairs (VA) Informatics and Computing Infrastructure (VINCI; U.S. Department of Veterans Affairs, 2014) and the Corporate Data Warehouse (CDW). The purpose of VINCI is to provide researchers with access to integrated national VA datasets, while ensuring Veterans' privacy and data security. A Veteran's data is entered into the VA database through Veterans Health Information Systems and Technology Architecture (VISTA), and/or the Computerized Patient Record System (CPRS). It is then stored nightly in the CDW, and VINCI is then used to extrapolate information from patient medical records as stored in the CDW.

Based on the inclusion and exclusion criteria outlined below, the final dataset for this study consisted of 4,800 Veterans' medical records retrieved via Microsoft SQL Server in the VINCI workspace. Structured Query Language (SQL), a standard interactive programming language designed for managing and manipulating data in relational database management systems, was used to select and organize relevant data. Veteran information (e.g., age, race, sex, and marital status) were retrieved from consolidated datasets from national clinical and administrative VA data sets (U.S. Department of Veterans Affairs, 2014).

Data related to Veterans' diagnostic history (e.g., ICD-9 codes and descriptions and dates of diagnosis) used for this study were obtained specifically from Veterans' outpatient visits at VA medical centers across the nation. The visits were from a variety of clinical service areas, such as psychiatry or psychology (individual or group treatment methods). Generally, only

licensed independent providers (LIP) can generate new diagnoses for Veterans. Other service providers, such as social workers, can verify that their work with a Veteran targeted a given diagnosis. Inpatient diagnoses were not included given that it is typically mandated for all Veterans with inpatient visits to have a follow-up outpatient visit within seven days of their discharge from the inpatient unit.

Inclusion and Exclusion Criteria

According to the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; DSM-5), the prevalence rates of dementia, across all subtypes, gradually increase with age for individuals aged ≥ 60 (American Psychological Association [APA], 2013). Taking this into consideration, the following inclusion criteria were applied: (1) Veterans aged ≥ 60 years [born before January 1, 1954]; (2) Veterans who identified as male or female; and (3) Veterans who self-identified as having a Black or White racial background. Secondly, for each of the four groups (sex by race), subjects were included who met the following criteria at age < 55 years: (1) diagnosed with MDD, or (2) diagnosed with PTSD, or (3) had no psychiatric history (ICD-9 codes 290.00 to 319.00).

Exclusion criteria for this study included: (1) Veterans aged < 60 years [born after January 1, 1954]; (2) Veterans diagnosed with dementia/CIND at age < 56 , (3) Veterans who did not self-identify as either Black or White; (4) Veterans who did not fit into the three identified groups based on psychiatric history (e.g., second set of inclusion criteria outlined above), and; (5) Veterans aged ≥ 60 years were excluded from the study if they were diagnosed with MDD or PTSD at age ≥ 55 .

Classifications of dementia and CINDs (Appendix A), depression (Appendix B), and PTSD (Appendix B) were outlined using the *International Classification of Diseases, Ninth*

Revision (ICD-9; Centers for Disease Control and Prevention, 2011) because the ICD-9 was used by VA employees nationwide for coding diagnoses prior to October 1st, 2015. Veterans who did not meet diagnostic criteria based on the ICD-9 codes listed in Appendix A and Appendix B were excluded from the study, such as Veterans diagnosed with any other mental health condition (e.g., bipolar disorder or schizophrenia) at age < 55.

The second exclusion criteria (i.e., Veterans diagnosed with dementia/CIND at age < 56) was defined in order to maintain at least a one year gap between the first MDD or PTSD diagnosis and the first dementia or CIND diagnosis, thus allowing for the analysis of the predictive utility of MDD and PTSD. Although dementia generally increases in persons aged \geq 60 years, researchers have highlighted the larger prevalence rates of CINDs in the population, which is seen prior to dementia onset (Williams et al., 2010). Persons with CINDs are at a greater risk of developing dementia compared to those without (Artero, Petersen, Touchon, & Ritchie, 2006; Visser, Kester, Jolles, & Verhey, 2006).

There are more people in the general and Veteran populations with pathological cognitive decline than persons diagnosed with dementia, and due to their increased risk, they are an important group to include in research (Artero et al., 2006; Chodosh et al., 2007; Rosenberg et al., 2006). It has been estimated that there are 70 percent more individuals with cognitive impairment than there are persons with dementia (Plassman et al., 2008). Artero and colleagues (2006) outlined the development of new criteria to identify those with cognitive deficits (not limited to memory) that do not meet dementia diagnostic criteria, and emphasized that such conditions could be associated with “early and subtle changes” that could potentially lead to more serious conditions. With the aim of identifying Veterans who potentially fall in this category, subtypes of dementias and additional ICD-9 code diagnoses primarily characterized by

memory and cognitive impairment (referred to as CIND) were included in this study (e.g., 310.89 Mild memory disturbance, 331.83 Mild cognitive impairment, 294.90 Cognitive Disorder NOS, 294.80 Dementia NOS, and 780.83 Memory loss; see Appendix A).

In the U.S., the onset of MDD typically occurs as individuals enter puberty and tends to peak in their 20's (APA, 2013). Moreover, due to the growing incidence of MDD in individuals from young adulthood to middle age, as well as the variable nature of depression onset, studying the role of early-life to mid-life depression onset in predicting dementia and other forms of cognitive impairment is advantageous (Byers & Yaffe, 2011). Hence, Veterans who were first diagnosed with MDD any time before age 55 were considered for this study. Likewise, Veterans first diagnosed with PTSD prior to age 55 were also considered to examine the predictive value of having a PTSD history.

Veterans diagnosed with MDD or PTSD at age ≥ 55 were excluded from the present study. The existing literature provides evidence that late-life depression may be a prodrome of dementia rather than a risk factor (Barnes et al., 2012; Byers & Yaffe, 2011; Geerlings et al., 2008). However, scholars indicate that the duration of the prodromal phase of dementia is unclear (Wilson et al., 2008). In their study, Wilson and colleagues (2008) examined depression as a prodrome to dementia in terms of three to four years before the onset of Mild Cognitive Impairment (MCI). The rationale for this was to ensure as much as possible that they assessed depressive symptoms prior to the onset of dementia, and measuring symptoms years before MCI reduced the risk of missing prodromal symptoms that may begin earlier than expected.

Similarly, Qureshi et al. (2010) found that for Veterans with an average age of 61, those who met criteria for PTSD had twice the incidence and prevalence of dementia compared to Veterans who did not have PTSD. The researchers stated that PTSD could possibly be “an early

marker of dementia” (Qureshi et al., 2010, p. 1632). To ensure a minimum of a one year gap between the first MDD or PTSD diagnosis and dementia/CIND diagnosis, and also to gather data on varying forms of cognitive impairment before the typical onset of dementia (i.e., 60 years of age), Veterans diagnosed with MDD or PTSD at age ≥ 55 and/or diagnosed with dementia/CIND at age ≤ 55 were omitted from the final sample.

The strong association between MDD and PTSD was an important consideration when evaluating inclusion and exclusion criteria for this study (Yaffe et al., 2010). It is important to note that Veterans diagnosed with *both* MDD and PTSD were omitted in efforts to examine the role of each condition exclusively. To meet criteria, a Veteran could have only been diagnosed with one or the other at age < 55 . Further, Veterans diagnosed with any other mental health conditions (ICD-9 codes 290.00 to 319.00) except those specified for each group in Appendix B were not included in this study.

Younger Veterans (circa 25 years of age) are known to be at a greater risk for PTSD than older Veterans (Seal et al., 2009). Many of these younger Veterans are involved in Operation Enduring Freedom/Operation Iraqi Freedom (OIF/OEF) and are an important group to target for PTSD treatment; in 2007, approximately 300,000 OEF/OIF Veterans were diagnosed with PTSD or depression (Qureshi et al., 2010). Studying how early- or mid-life PTSD, as well as depression, may influence dementia and CINDs later in life will provide findings that may aid in the treatment of younger Veterans, particularly with regard to MDD/PTSD treatment as a preventative treatment of dementia and related conditions.

A Priori Statistical Power Analysis

G*Power was utilized to compute an a priori statistical power analysis for sample size estimation before data was extracted through VINCI. The power analysis indicated a sample size

of 1,680 would be adequate to detect small to medium changes in the logistic regression model ($OR = 2.25$; $1 - \beta = .95$; $p < .05$). In logistic regression, the best effect size measure has been identified as the odds ratio (OR) by many researchers (Faul, Erdfelder, Buchner, & Albert-Georg, 2009; Field, 2013; Rosenthal, 1996). The OR has become particularly important when studying diseases with lower than a 10 percent prevalence rate (Chen, Cohen, & Chen, 2010), making it an appropriate measure of effect size for this study with the prevalence rate of dementia/CIND in the Veteran and general population being approximately 7 percent (Dotson et al., 2010; Plassman et al., 2007; Veitch et al., 2013; Yaffe et al., 2010). Chen et al. (2010) calculated equivalent OR values for Cohen's d (Cohen, 1992) across studies where disease rates were low (less than 10 percent), with Cohen's interpretation recommendations of $d = .2$ (small), $.5$ (medium), and $.8$ (large) considered within the context of the study. For a disease with a prevalence rate of 7 percent, Chen et al. (2010) presented odds ratio values with equivalent Cohen's d values as the following: 1.1 to 1.4 equivalent to $d < 0.20$ ("weak association"); 1.5 to 4.0 with $d > 0.20$ and $d < 0.80$ ("moderate association"); and 5.0 to 30.0 with $d > 0.80$ ("strong association"; see Tables 1 and 2 on pp. 862-863 for more information).

Participants were divided into two racial categories, Black and White, due to the demographic data of the U.S. Veteran population. The U.S. Census Bureau (2012) reported that the Veteran population comprised of 11 percent Black and 80 percent White individuals, leaving 9 percent for other minority groups. Grouping all the minority subgroups into one group may have been the only way to obtain adequate statistical power for purposes of this study, as data with a sufficient number of participants in each minority subgroup was not available. However, due to the variability between, as well as within, specific minority subgroups (Oh, Galanter,

Thakur, Pino-Yanes, Barcelo, et al., 2015; Pinquart & Sorensen, 2005), only Black and White individuals were included in this study.

Sampling Procedures

Initial sample. The initial cohort consisted of 13,812,853 Veteran subjects whose records were obtained through VINCI (U.S. Department of Veterans Affairs, 2014). From this cohort, 7,723,634 subjects were omitted due to possible invalid identifiers and/or for not meeting inclusion criteria related to sex (i.e., male or female) and race (i.e., Black or White). Five subjects were removed from the sample due to having multiple sex identifiers (e.g., identifying as both male and female), and 20,941 records were omitted for having multiple race identifiers (e.g., identifying as both Black and White). This resulted in a final sample of 6,068,273 subjects.

Creation of three cohort tables. From the sample of 6,068,273, subjects meeting criteria for MDD, PTSD, and no mental health history were selected and a separate table was created for each cohort in Microsoft SQL Server. Cohort 1 included 115,245 subjects meeting criteria for MDD, as outlined in Appendix B. Cohort 2 consisted of 146,688 subjects meeting criteria for PTSD, also listed in Appendix B. Cohort 3 consisted of 861,905 subjects without any mental health diagnosis (ICD-9 codes 290 to 319) prior to age 55. Then, subjects with dementia/CIND diagnosis (listed in Appendix A) prior to age 56 were removed from each cohort. Thus, the final sample for Cohort 1 consisted of 55,076 subjects after exclusion of 60,169 with dementia/CIND prior to age 56. The final sample for Cohort 2 included 84,853 subjects after exclusion of 61,835 with dementia/CIND prior to age 56. Cohort 3 had a final sample of 620,403 after exclusion of 241,502 subjects with dementia/CIND prior to age 56.

Twelve subgroups. From each of the three final cohort tables, four separate tables were created for Veterans with distinct demographic backgrounds (resulting in a total of 12 tables): (1)

Black/female, (2) White/female, (3) Black/male, and (4) White/male. Then, for the final sample of this study, an equal number of Veterans were randomly selected from each of these 12 tables in Microsoft SQL Server using standardized SQL query language statements of random selection of information from databases. An a priori power analysis was previously employed for sample size estimation also considering that most U.S. Veterans aged ≥ 60 are White and male (U.S. Census Bureau, 2012), thus it was possible that there would not be enough data for female Veterans aged ≥ 60 who self-identified as Black. Further, considering the low prevalence rates of dementia (5 to 8 percent), a larger sample than specified by the power analysis ($N = 1,680$) was intended to be selected [if available] to increase the likelihood of detecting varying levels of predictive ability of the IVs. The smallest of the 12 tables (Black/female group in Cohort 2 – PTSD) consisted of 495 Veterans' records, thus, a total of 400 subjects from each of the 12 tables were randomly selected, resulting in a total sample size 4,800 Veteran subjects.

Initially, using equal sample sizes was implemented in research studies to make casual inferences. Recently, scholars have used this method for other objectives, such as conducting observational epidemiological studies (Rubin, 1973). Many have attempted to achieve equal group sizes particularly when examining topics such as racial health disparities, sex, socioeconomic status, etc. (Dore, Waldstein, Evans, & Zonderman, 2015; Polednak, 2001). Accordingly, given that demographic variables such as race were examined in this study, an equal number of Veterans per subgroup was intended to reduce bias (Rubin, 1973). A flowchart of the sampling procedures and numbers of subjects at each step can be found in Figure 1.

Participants

The sample for this study consisted of 4,800 Veterans aged ≥ 60 years. The participants were randomly selected from cohort tables for MDD, PTSD, and no mental health history (i.e.,

None) in order to create 12 separate subgroups based on demographic characteristics (see Table 1). Baseline age, in years, was calculated for all subjects on March of 2016. Participant ($N = 4,800$) age ranged from 61 to 71 ($M = 64.57$, $SD = 2.58$), with age rounded to the nearest year. The 12 subgroups included an equal number of subjects in each demographic group ($n = 2,400$ per each), and the age range (rounded to the nearest year) for Veterans in each subgroup was also 61 to 71 years. The mean (with standard deviation) age, in years, for women ($n = 2,400$) and men ($n = 2,400$) were 63.94 ($SD = 2.41$) and 65.20 ($SD = 2.60$), respectively. The mean (with standard deviation) ages, in years, for Black ($n = 2,400$) and White ($n = 2,400$) Veterans were 64.31 ($SD = 2.53$) and 64.83 ($SD = 2.61$). Marital status (with mean age, in years, and standard deviations) was reported as 38.5% married ($n = 1,853$; $M = 64.81$, $SD = 2.67$), 39.5% divorced or separated ($n = 1,896$; $M = 64.48$, $SD = 2.52$), 14.4% single or never married ($n = 693$; $M = 64.17$, $SD = 2.48$), widowed ($n = 306$; $M = 64.54$, $SD = 2.57$), and 1.1% unknown or missing ($n = 52$; $M = 64.75$, $SD = 2.15$).

Cohort 1 (C1): History of MDD before age 55. The age range for subjects in C1 ($n = 1,600$) ranged from 61 to 71 ($M = 64.05$, $SD = 2.39$). C1 consisted of subgroups 1 to 4, with 400 (8.3% of N) in each. Age during the first MDD diagnosis ranged from 45 to 54 ($M = 50.80$, $SD = 2.47$), and the number of years since the first MDD diagnosis ranged from 7 to 17 ($M = 13.25$, $SD = 2.39$). Marital status of subjects in C1 was reported as 32.7% ($n = 523$) married, 44.6% ($n = 712$) divorced or separated, 15.1% ($n = 241$) single or never married, and 7.6% ($n = 122$) widowed.

Cohort 2 (C2): History of PTSD before age 55. The age range for subjects in C2 ($n = 1,600$) ranged from 61 to 71 ($M = 64.94$, $SD = 2.59$). C2 consisted of subgroups 5 to 8, with 400 (8.3% of N) in each. Age during the first PTSD diagnosis also ranged from 45 to 54 ($M = 51.34$,

$SD = 2.29$), and the number of years since the first PTSD diagnosis ranged from 7 to 17 ($M = 13.60$, $SD = 2.46$). Marital status of subjects in C2 was reported as 40.1% ($n = 639$) married, 39.9% ($n = 636$) divorced or separated, 14.4% ($n = 230$) single or never married, and 5.6% ($n = 90$) widowed.

Cohort 3 (C3): No mental health diagnosis before age 55. The age range for subjects in C3 ($n = 1,600$) ranged from 61 to 71 ($M = 64.72$, $SD = 2.68$). C3 consisted of subgroups 9 to 12, with 400 (8.3% of N) in each. Marital status of subjects in C3 was reported as 44.4% ($n = 691$) married, 35.2% ($n = 548$) divorced or separated, 14.3% ($n = 222$) single or never married, and 6.0% ($n = 94$) widowed.

Additional information on participant characteristics are presented in Table 2. Differences between participants based on cohorts, subgroups, and other characteristics are reported in the Results section below.

Data Analysis

The data for this study were analyzed in three sequential steps, beginning with the a priori statistical power analysis. The first dataset included Veterans diagnosed with dementia/CIND at age ≥ 60 years, and the second dataset included Veterans diagnosed at age ≥ 56 years. The findings from the second dataset will be the main focus of this study. G*Power, a statistical power analysis program, Microsoft Excel, and the Statistical Package for the Social Sciences (SPSS) were used to examine the data.

First analysis: Veterans diagnosed with dementia/CIND at age ≥ 60 . Descriptive analyses and crosstabulations with chi-square were conducted to gather demographic and baseline characteristics of the sample. Chi-square (χ^2) and independent samples t -tests were employed to examine differences between groups. The Pearson product moment correlation

coefficient (r) was used to determine correlations between the outcome and predictor variables. The variance inflation factor (VIF) value, tolerance value, and variance proportions were analyzed to determine if there was collinearity among the study variables. Linearity of the logit and potentially influential outliers (using Cook's distance and Mahalanobis distance) were also inspected to discover if the assumptions of logistic regression were met.

The primary analysis consisted of binary logistic regression to examine preexisting MDD and PTSD as predictors of dementia/CIND. Additional covariates that were examined for their predictive utility included race, sex, and their interactions with MDD and PTSD. Other risk factors of dementia/CIND identified in the literature were also studied, including subjects' current age and approximate duration of MDD/PTSD symptoms (Byers & Yaffe, 2011; Kaup et al., 2016). The first logistic regression analysis included the examination of MDD, PTSD, race, and sex as predictors of dementia/CIND diagnosed in Veterans aged ≥ 60 years. Sampling procedures for this initial dataset involved removing subjects from each Cohort who were diagnosed with dementia/CIND prior to age 60, rather than age 56 (as described in the Methods – Sampling Procedures section).

There were 210 subjects in the initial sample diagnosed with dementia/CIND at age ≥ 60 . Although the overall logistic regression model was statistically significant, the predictive utility of individual variables were weak. Based on the Nagelkerke R^2 value of .14, which resembles the R^2 in linear regression, the overall model accounted for a very small amount variance in the DV. This statistic should, however, be interpreted with caution, as it is considered a pseudo R^2 value. The model was able to correctly classify 45.2% of the dementia/CIND cases, suggesting a less than 50-50 chance of accurately identifying persons with dementia/CIND.

Second analysis: Veterans diagnosed with dementia/CIND at age ≥ 56 . Given that the results from the first set of analyses were largely insignificant, data obtained through VINCI were further analyzed for variables that could potentially have an impact on dementia/CIND. A second dataset was created, which included Veterans diagnosed with dementia/CIND at age ≥ 56 , rather than age ≥ 60 . This ensured that there would remain a one year gap between MDD/PTSD and potential dementia/CIND, which would be important to examine predictive utility of the disorders. It also included a total of 336 subjects with positive dementia/CIND status, which was 126 more subjects with dementia/CIND within a four year duration (from ages 56 to 59) who were not included in the first analysis. This dataset was also extracted from the same three cohorts created from the initial sample of 6,068,273. Information about the three tables for Cohorts 1, 2, and 3 are highlighted in gray in Figure 1.

The finding that difficulties with cognitive functioning were present in this Veteran population earlier than the typical age of onset of dementia in the general population (age ≥ 60) is not surprising, considering that many scholars have reported Veterans are at an increased risk of senescence-associated medical conditions at an earlier age (Lohr et al., 2015; Sibener et al., 2014). Therefore, the rationale for the second set of analyses was the growing need to study an increasing population of aging Veterans who are at a higher risk for accelerated cognitive decline that potentially onsets earlier than observed in the general population (Sibener et al., 2014).

Descriptive data, group differences, and correlations among all variables were analyzed with this second dataset of Veterans diagnosed with dementia/CIND after age 55. Variables that were significant in the bivariate analyses or relevant to the hypothesis of this study were then analyzed using logistic regression, which consisted of dementia/CIND as the dependent variable (DV), and MDD history, PTSD history, race, and sex as the predictor variables. It should be

noted that because age has been well-established as a risk factor of dementia/CIND (Chen, Lin, & Chen, 2009; World Health Organization, 2015), it was adjusted for in all the logistic regression models unless otherwise stated. In addition, scholars have found that the type of depressive symptoms may also influence the amount of risk a person has of developing dementia and related conditions. Specifically, depressive symptoms that were more severe and continued to increase were predictive of the highest level of dementia risk (Kaup et al., 2016). Accordingly, in this study, the number of years since the first MDD/PTSD diagnosis were calculated to discover the impact, if any, the chronicity or duration of MDD/PTSD had on the development of dementia/CIND. The amount of time since the first MDD/PTSD diagnosis was used to measure chronicity because symptoms of both conditions are known to typically endure throughout a person's life, sometimes despite efforts to obtain treatment or occurrence of remission periods (Kaup et al., 2016; Veitch et al., 2013).

After the bivariate analyses, binary logistic regression was employed to test the predictive utility of MDD and PTSD, with dementia/CIND diagnosis as the dichotomous DV. The two conditions were examined separately, and then together. These set of analyses were repeated a second time adjusting for the influence of CurrentAge. The remaining logistic regression analyses involved three separate models, all with dementia/CIND diagnosis as the DV. The steps taken during the analyses are denoted with superscript alphabetical letters, such as Model 1^a, 1^b, and 1^c, and are based on recommended model building strategies from the literature. Three common model building strategies used for logistic regression include direct, hierarchical, and stepwise methods (Peng, Lee, & Ingersoll, 2002). The direct model building approach is typically employed when a priori hypotheses are lacking, whereas the hierarchical method is suitable for clarifying patterns of casual relationships between predictor and outcome variables

(Stoltzfus, 2011). Further, although stepwise regression techniques have been considered controversial by some researchers, they have nonetheless been worthwhile for preliminary screening and hypothesis testing (Reed & Wu, 2013; Stoltzfus, 2011). Based on the current knowledgebase of prevalence rates and predictors of dementia/CIND among the general and Veteran populations, hierarchical and stepwise logistic regression methods were selected in this study for the logistic regression analyses.

Age, MDD, and recently PTSD, are well-established risk factors of dementia and CINDs (Byers et al., 2012; Qureshi et al., 2010; Yaffe et al., 2010). In contrast, data on race and sex as risk factors varies and additional research is necessary for clarification (Akincigil et al., 2012; Breslau, 2009; Katz et al., 2012; Plassman et al., 2008; Plassman et al., 2007). Therefore, each of the three models were originally built using hierarchical logistic regression to clarify the role of race and sex in predicting dementia/CIND, and also to determine whether the addition of new interaction variables added to the predictive validity of the model (Reed & Wu, 2013).

Then, backward stepwise methods were employed in the last step of each model to further inspect the impact of individual variables, particularly the interactions between demographic variables and psychiatric history or chronicity. The stepwise method proved valuable for this purpose, especially due to the lack of consistent evidence in the literature about demographic variables as risk factors of dementia/CIND (Katz et al., 2012; Reed & Wu, 2013; Stoltzfus, 2011). Research on the *chronicity* of MDD and PTSD as risk factors is also limited, and most existing studies have considered depressive symptoms only at one point in time (Barnes et al., 2012; Kaup et al., 2016). In this study, Models 2^{duration} and 3^{duration} were built with similar methods as those implemented for Model 2 and 3, respectively. However, MDD_{duration}

and PTSDduration were the main predictor variables under investigation in Models 2^{duration} and 3^{duration}, rather than MDD and PTSD history.

Hierarchical logistic regression was used for Model 1^a, which included MDD history, PTSD history, sex, and race as the predictors, while adjusting for current age. Age was entered in the first block, MDD and PTSD into the second block, and race and sex into the third block. In the second step (Model 1^b), the interactions between sex with MDD (Sex*MDD) and PTSD (Sex*PTSD), and the interactions between race with MDD (Race*MDD) and PTSD (Race*PTSD) were included in the subsequent block.

Finally, all nine variables from Model 1^b were entered into one block using the backward stepwise method in Model 1^c. Researchers have indicated that the backward, versus the forward, stepwise method is preferred when conducting exploratory analyses for logistic regression, because it begins with all predictors in the model and removes those based on their impact on the -2LL value (Reed & Wu, 2013). If the -2LL value of the model significantly decreased after a certain variable was initially removed, then that variable was kept in the model. Provided that the existing findings on relevant demographic predictors of dementia/CIND are inconsistent, and that the individual predictors were largely significant in Model 1^a, yet insignificant in Model 1^b, the backward stepwise method was beneficial in Model 1^c for identifying if any of the new interaction variables were stronger than others in predicting dementia/CIND (Reed & Wu, 2013).

Sex, MDD, PTSD, and the interactions between sex with MDD (sex*MDD) and sex with PTSD (sex*PTSD), while adjusting for current age, were examined in Model 2. In Model 2^a, MDD and PTSD were entered into one block, and sex was entered in the following block. Then, the two interaction variables were added to the model in the subsequent block (Model 2^b). The

third step, Model 2^c, entailed entering all five variables in one block using the backward stepwise method.

The same methods were implemented for Model 3, however, race was the demographic variable under investigation. An additional analysis was conducted for both Models 2 and 3 that involved MDDduration and PTSDduration as the main predictors (rather than MDD and PTSD history) using the same procedures. The final step of these analyses [of MDD/PTSD duration] will be reported in the Results – Logistic Regression Analysis section below and presented in corresponding tables. These models are denoted with “duration” written in superscript format after the model number (e.g., Model 2^{duration} and Model 3^{duration}).

Classification cutoff and Model Validity. It should be noted that a classification cutoff of .07 was used for the logistic regression analysis based on the rate of positive dementia/CIND cases in the current study sample (7 percent). Researchers estimated prevalence rates for Veterans in similar age groups to be approximately 7.3 percent (Wray et al., 2014). In addition to disease prevalence rates, sensitivity and specificity should be considered when determining the optimal cutoff criterion (Hanley & McNeil, 1982). Accordingly, a receiver operating characteristic (ROC) curve analysis was conducted and the area under the curve (AUC) was analyzed to determine the optimal classification cutoff for the analysis.

The ROC curve is one of the most common methods for inspecting the discrimination ability of a model or test, and the AUROC (area under the ROC curve) has been described as the best quantitative index to describe the curve (Hanley & McNeil, 1982; Kumar & Indrayan, 2011). The AUROC denotes “the probability of correctly identifying” positive and negative cases (Hanley & McNeil, 1982, p. 29), and it continues to be used frequently, especially in biomedical research (Dalrymple-Alford et al., 2010; Dujardin et al., 2010). The ROC curve

shows the “full picture of trade-off between the sensitivity and specificity across a series of cutoff points” (Kumar & Indrayan, 2011, p. 277).

For this study, the ROC curve indicated the probability that individuals who had dementia/CIND were correctly being classified as having the condition, and individuals who did not have dementia/CIND were correctly being identified as not having been diagnosed with dementia/CIND. The classification cutoff of .07 was applied based on the predicted probability values obtained from a logistic regression analysis with MDD, PTSD, race, and sex as the predictors, and then used for the ROC curve analysis. The cutoff was chosen because it maximized sensitivity (.631) and specificity (.490). After conducting the logistic regression analyses, the AUROC curve analysis was conducted again to determine the discrimination validity of Models 1, 2, and 3.

Results

Demographic Characteristics

Descriptive statistics of Veterans’ demographic characteristics were calculated separately for all groups, including those with and without a dementia/CIND diagnosis (see Table 2). This retrospective study consisted of a total sample of 4,800 Veteran subject ($M = 64.57$, $SD = 2.58$), with 336 subjects having a dementia/CIND diagnosis at age > 55 . The mean age (with standard deviation) during which subjects ($n = 336$) were first diagnosed with dementia/CIND was 60.83 ($SD = 3.18$). The prevalence rate of positive dementia/CIND cases (7 percent) was consistent with the rates reported in the existing literature among the general and Veteran population (Hebert et al., 2013; Lohr et al., 2015; Prince et al., 2013).

Current age. There was a significant difference between the current age of Veterans diagnosed with dementia/CIND ($n = 336$; $M = 65.64$, $SD = 2.50$) and those without

dementia/CIND ($n = 4,464$; $M = 64.49$, $SD = 2.57$), $t(4798) = -7.95$, $p < .000$, with Veterans diagnosed with dementia/CIND being older.

History of MDD (Cohort 1). Of the Veterans with a history of MDD prior to age 55 ($n = 1,600$), 124 (7.8%) were diagnosed with dementia/CIND. These individuals made up 36.9% of the sample with dementia/CIND ($n = 336$), and 2.6% of the total sample ($N = 4,800$). The percentage of Veterans diagnosed with dementia/CIND after age 55 did not differ based on history of MDD, $\chi^2(1, N = 4800) = 2.07$, $p = .150$. The mean chronicity of MDD, in years, was 13.76 ($SD = 2.24$) in positive cases of dementia/CIND, and 13.21 ($SD = 2.40$) in cases without dementia/CIND, which were found to be significantly different, $t(1598) = -2.48$, $p = .013$. The average number of years between the first MDD diagnosis and first dementia/CIND diagnosis was 8.95 ($SD = 3.40$). Subjects with dementia/CIND were first diagnosed with MDD at a slightly older age ($M = 51.26$, $SD = 2.30$) compared to the age that subjects without dementia/CIND were first diagnosed with MDD ($M = 50.76$, $SD = 2.48$).

History of PTSD (Cohort 2). Among Veterans with a history of PTSD prior to age 55 ($n = 1,600$), 131 (8.2%) were diagnosed with dementia/CIND, which was 39.0% of the positive dementia/CIND cases ($n = 336$), and 2.7% of the total sample ($N = 4,800$). The percentage of Veterans diagnosed with dementia/CIND after age 55 were significantly different based on history of PTSD, $\chi^2(1, N = 4800) = 5.20$, $p = .023$. Likewise, the mean chronicity of PTSD, in years, was determined to be statistically different among Veterans with ($M = 14.28$, $SD = 2.26$) and without ($M = 13.54$, $SD = 2.47$) dementia/CIND, $t(159) = -3.58 = p < .000$. Levene's test indicated unequal variances ($F = 6.76$, $p = .009$), thus degrees of freedom were adjusted from 1598 to 159. The average number of years between first PTSD diagnosis and first dementia/CIND diagnosis was 9.52 ($SD = 3.29$). Subjects with dementia/CIND were first

diagnosed with PTSD at a slightly older age ($M = 51.70$, $SD = 1.89$) compared to the age that subjects without dementia/CIND were first diagnosed with PTSD ($M = 51.31$, $SD = 2.32$).

Sex: Female or male. Veteran subjects diagnosed with dementia/CIND differed significantly by sex, $\chi^2(1, N = 4800) = 17.52$, $p < .000$. There were 131 (5.5%) women and 205 (8.5%) men diagnosed with dementia/CIND. Among the positive dementia/CIND cases ($n = 336$), 39% were women and 61% were men.

Race: White or Black. The proportion of subjects with dementia/CIND also differed significantly by race, $\chi^2(1, N = 4800) = 5.12$, $p = .024$. There were 148 (6.2%) Black individuals and 188 (7.8%) White individuals diagnosed with dementia/CIND. Among the positive dementia/CIND cases ($n = 336$), 44% self-identified as Black whereas 56% of them self-identified as White.

Marital status: Single/unmarried, married, divorced/separated, and widowed. The percentage of individuals with dementia/CIND did not differ significantly by marital status, $\chi^2(3, N = 4748) = 3.98$, $p = .263$. There were 58 (8.4%) single/unmarried, 117 (6.3%) married, 136 (7.2%) divorced/separated, and 25 (8.2%) widowed subjects diagnosed with dementia/CIND. Among the 336 individuals with dementia/CIND, 17.3% were reported as single/unmarried, 34.8% as married, 40.5% as divorced/separated, and 7.4% as widowed. It should be noted that there were 52 (1.1% of N) cases with missing or unknown marital status, and these were coded as missing in the SPSS dataset. Additional information on demographic characteristics can be found in Table 2, including frequency (percentage), mean (standard deviation), and chi-square or t values.

Subgroup Characteristics

Frequency (with percentage) and chi-square values were calculated for each of the 12 subgroups (Table 3). Each subgroup ($n = 400$) was compared to the rest of the sample ($n = 4,400$ in the 11 other subgroups). The percentage of subjects with and without dementia/CIND were significantly different for 2 of the 12 subgroups, one of which was the C2G8 (Cohort 2, Group 8) White/Male subgroup, $\chi^2(1, N = 4800) = 20.28, p < .000$. Among the 400 men in C2G8, 50 (12.5%) subjects had dementia/CIND and 350 (87.5%) did not. Veterans in C2G8 had the highest rate of dementia/CIND compared to the rest of the sample, which suggested that among Veterans aged ≥ 60 years, White male Veterans with a history of PTSD were at greater risk compared to other Veterans (e.g., female Veterans, Veterans who self-identified as Black, and/or other White male Veterans who did not have a history of PTSD).

Subjects with and without dementia/CIND also significantly differed based on the C3G9 (Cohort 3, Group 9) Black/Female subgroup, $\chi^2(1, N = 4800) = 12.11, p = .001$. There were 11 (2.8%) Veterans in C3G9 with dementia/CIND, which was the lowest rate found compared to the rest of the sample. This finding indicated that Black female Veterans without a psychiatric history prior to age 55 had lower chances of getting dementia/CIND when compared to other Veterans (e.g., male Veterans, White Veterans, and/or other Black female Veterans with a psychiatric history prior to age 55).

Although the chi-square tests did not reveal additional significant associations, patterns in prevalence rates of dementia/CIND were nonetheless observed across subgroups. For example, the three White/Male groups had the highest number of dementia/CIND cases ($n = 114$) when compared to the three Black/Male groups ($n = 91$), then White/Female groups ($n = 74$), and Black/Female groups ($n = 57$). Greater dementia/CIND rates were consistently observed for men

compared to women across all three cohorts. With the exception of C1 (history of MDD), White men and women had higher rates compared to Black men and women, respectively. Importantly, the Black/Male group ($n = 36$, 9.0%) with a history of MDD (C1) had greater rates of dementia/CIND compared to the White/Male group ($n = 34$, 8.5%) in C1. The Black/Female and White/Female groups in C1 had the same rate of dementia/CIND ($n = 27$, 6.8% for both racial groups).

Further, the rate of dementia/CIND for White male Veterans without a psychiatric history (C3G12) was greater than the rate for both Black and White female Veterans with a history of MDD or PTSD. However, when a history of MDD was considered, rates for both Black and White female Veterans were 6.8%, which is not significantly lower than the rate for (7.5%) White male Veterans without a psychiatric history. When comparing the rates of subgroups to the overall dementia/CIND prevalence rate found in this study (7%), White male Veterans across all Cohorts had higher rates, and Black male Veterans had higher rates if a history of MDD or PTSD was present. Interestingly, all six groups consisting of female Veterans had lower rates than 7%, except that in some instances, rates were only slightly lower (e.g., 6.8%). It is important to note that although White Veteran groups had higher rates than Black Veterans in Cohorts 2 and 3, Black male Veterans appeared to be at an increased risk if a history of MDD was present (Cohort 1). The number (with percentages) of positive and negative dementia/CIND cases within each of the 12 groups are reported in Table 3 and are presented in a bar graph format in Figure 2.

Relationships among Predictor and Outcome Variables

Results from the chi-square analyses and independent samples *t*-tests revealed statistically significant differences between Veterans with and without dementia/CIND based on the following variables (with descriptions): (1) CurrentAge (participants' current age, in years),

(2) MDDduration (number of years since the first MDD diagnosis), (3) PTSD (history of PTSD prior to age 55) as a dichotomous predictor coded as “0” (no PTSD history) and “1” (with PTSD history), (4) PTSDduration (number of years since the first PTSD diagnosis), (5) sex coded as “0” (male) or “1” (female), and (6) race coded as “0” (White) or “1” (Black). These six variables were selected for analysis in the logistic regression models.

Although MDD history was not found to be statistically significant, it was nonetheless included in the logistic regression models based on the study hypothesis, and also the robust evidence that exists in the literature identifying it as a significant risk factor of dementia and other forms of cognitive impairment (Barnes et al., 2012; Byers et al., 2012; Byers & Yaffe, 2011). MDD as a predictor variable was coded in the same manner as PTSD, with “0” (no MDD history prior to age 55) and “1” (with MDD history prior to age 55). The dichotomous outcome variable, dementia/CIND diagnosed after age 55, was coded as “0” (without dementia/CIND) and “1” (with dementia/CIND). The predictor variables included in the logistic regression analyses and their frequency (χ^2) or mean (t statistic) values as a function of dementia/CIND are presented in Table 4.

Pearson product moment correlation coefficients (r) were also calculated for predictor and outcome variables (see Table 5). The coefficients for this study were interpreted as recommended by Cohen (1992)—an r value of .10 indicates a small effect (1 percent of the total variance), .30 indicates a medium effect (9 percent of the total variance), and .50 and above indicates a large effect (25 percent of the total variance). Contrary to the existing literature, the relationship between dementia/CIND and history of MDD was not statistically significant in the current study, $r(4798) = .021, p = .150$. However, although small, the correlation between dementia/CIND and MDDduration was statistically significant, $r(1598) = .06, p < .05$.

The relationship between CurrentAge and the other variables were all statistically significant ($p < .01$). CurrentAge was strongly correlated with MDDduration, $r(1598) = .465, p < .01$, and PTSDduration, $r(1598) = .590, p < .01$, which is to be expected because the duration of psychiatric symptoms depends on an individual's age. CurrentAge had smaller, yet significant positive relationships with dementia/CIND, $r(4798) = .114, p < .01$, and PTSD history, $r(4798) = .101, p < .01$. In contrast, it was negatively related to MDD history, $r(4798) = -.142, p < .01$, sex, $r(4798) = -.244, p < .01$, and race, $r(4798) = -.100, p < .01$.

Although MDD was not significantly related to the outcome variable, it had a strong negative correlation with PTSD, $r(4798) = -.500, p < .01$. PTSD, $r(4798) = .033, p < .05$, and PTSDduration, $r(1598) = .083, p < .01$, were both significantly related to dementia/CIND, though both of their effects were small. Sex, $r(4798) = -.060, p < .01$, and race, $r(4798) = -.033, p < .05$, were both negatively correlated with dementia/CIND, potentially suggesting that female Veterans (female was coded as "1" and male as "0"), and Black Veterans (Black was coded as "1" and White as "0"), were at lower risk of developing dementia/CIND when compared to male Veterans, and White Veterans, respectively.

Neither sex nor race were correlated with MDD, $r(4798) = .000, p = 1.00$, or PTSD, $r(4798) = .000, p = 1.00$. In addition, sex did not have a significant relationship with MDDduration, $r(1598) = -.021, p = .397$. Race, however, was negatively correlated with MDDduration, and this effect was statistically significant, $r(1598) = -.104, p < .000$. Both demographic variables were negatively related to PTSDduration, with a statistically significant moderate effect for sex, $r(1598) = -.292, p < .01$) and a statistically significant small effect for race, $r(1598) = -.060, p < .05$. The demographic variables were not correlated with each other, $r(4798) = .000, p = 1.00$.

Although the r coefficients indicated generally small effects and weak relationships between the variables, there were nonetheless many statistically significant correlations between the study variables. Moreover, many of the odds ratio (OR) values interpreted as effect size in the logistic regression analysis (which will be discussed in the next section) were significant and ranged from having small to medium effect sizes (based on Chen et al., 2010; Cohen, 1992).

Logistic Regression Analysis

Assumptions. Veterans' data were first examined to ensure the assumptions of logistic regression were met. The assumptions, which are similar to those of linear regression, include absence of multicollinearity, independence of errors, linearity of the logit (for continuous variables), and lack of strongly influential outliers (Mertler & Vannatta, 2013; Stoltzfus, 2011).

Absence of multicollinearity. Employing a linear regression analysis in SPSS with the predictor variables, the variance inflation factor (VIF), tolerance values, and variance proportions were inspected for potential multicollinearity among the variables. Collinearity occurs when two variables are strongly correlated, whereas multicollinearity occurs when more than two predictor variables are intercorrelated (Field, 2013). Generally, an r of .80 or higher is suggestive of two predictors measuring similar occurrences (Field, 2013; Mertler & Vannatta, 2013).

The strongest significant correlation among the variables in this study was $r = -.500$ between MDD and PTSD, indicating that about 25 percent of the variance in the predictors were related (Cohen, 1992). Additionally, the variance proportions of MDD, PTSD, and CurrentAge were .41, .42, and .96, respectively, on condition 5, which had the smallest eigenvalue (see Table 6). Researchers have stated that if multiple variables have high variance proportions on the same small eigenvalue (typically at the bottom of a Collinearity Diagnostics table), it is possible that dependency among the variables may be a problem (Field, 2013). However, the tolerance values

for all variables were greater than .1, VIF values were all less than 10, and the mean of VIF values was 2.55, all of which researchers have recognized as indicators that multicollinearity is likely not a significant problem for the model (Field, 2013; Mertler & Vannatta, 2013; Stoltzfus, 2011).

Linearity of the logit. The continuous variables included in the logistic regression analyses (i.e., CurrentAge, MDDduration, and PTSDduration) were examined to ensure each was linearly related to the log of the outcome variable, dementia/CIND diagnosed after age 55 (Field, 2013). Each variable was interacted with the log of itself, and the resulting interaction variables were examined in a logistic regression analysis. The three interaction variables were not statistically significant, thus, demonstrating that the main effects did not violate the assumption of linearity of the logit.

Influential outliers. Cook's distance was used to analyze the overall influence of each case in the model. Values greater than 1 indicate there may be a case that is exerting additional influence on the model compared to other cases (Cook & Weisberg, 1983). The Cook's distance values for the variables of this study ranged from .000 to .106, which did not suggest a problem.

The Mahalanobis distance (D^2) was also inspected to discover any potential multivariate outliers (Mertler & Vannatta, 2013). This statistical procedure determines the distance of a case from the centroid (the point created by the means of all the variables) of the remaining cases. The distance is calculated as a chi-square (χ^2) statistic with degrees of freedom (df) equal to the number of variables in the analysis (p. 31). Researchers identify outliers as cases with a D^2 value greater than the chi-square critical value significant beyond $p < .001$ (Cousineau & Chartier, 2015; Mertler & Vannatta, 2013). In this study, there were no cases exceeding $\chi^2(5) = 20.515$ at $p < .001$, thus suggesting a lack of outliers.

MDD and PTSD. Prior to examining demographic risk factors, binary logistic regression analysis was conducted to determine the predictive utility of MDD and PTSD separately, and together, with and without the adjusting for CurrentAge. When the model only included MDD, it was not statistically significant, $\chi^2(1, N = 4800) = 2.04, p = .153$. After adjusting for age, the model was significant when compared to a constant only model, $\chi^2(2, N = 4800) = 67.98, p < .000$. This model correctly predicted 65.8% of positive dementia/CIND cases, and 56.9% of cases without dementia/CIND, for an overall classification success rate of 57.5%.

In accordance with Chen and colleagues' (2010) recommendations for understanding the magnitude of odds ratio (*OR*) values as approximate equivalents to Cohen's *d* (Cohen, 1992), the odds ratios of the predictor variables in the logistic regression analyses were interpreted as effect size based on the dementia/CIND disease rate of .07. *OR* values of 1.49 ("weak association"), 2.62 ("moderate association"), and 4.42 ("strong association") were recognized as being equivalent to Cohen's *d* of .2 (small), .5 (medium), and .8 (large), respectively (p. 862).

When MDD history and CurrentAge were both included in the model, the risk of dementia/CIND increased significantly, *OR* = 1.38, 95% CI [1.09, 1.75], *p* .007. An *OR* of 1.38 is indicative of a weak association, with *d* > 0.13 and *d* < 0.17. The same methods were then employed to examine the predictive utility of a history of PTSD, and interestingly, results for PTSD history were in contrast to those found for MDD history. A binomial logistic regression model with only PTSD was statistically significant, $\chi^2(1, N = 4800) = 5.08, p = .024$. The odds ratio value of PTSD, *OR* = 1.30, 95% CI [1.04, 1.64], *p* = .023, was similar to that of MDD, suggesting a weak association among the conditions and dementia/CIND. When adjusting for age, the model with PTSD was considered statistically significant, $\chi^2(2, N = 4800) = 63.09, p < .000$, yet PTSD was not independently significant, *p* = .133.

A model with both MDD and PTSD was statistically significant compared to a constant only model, $\chi^2(2, N = 4800) = 14.78, p = .001$. Further, MDD ($b = .46$, Wald $\chi^2(1) = 9.50, p = .002$) and PTSD ($b = .51$, Wald $\chi^2(1) = 12.40, p < .000$) were also both significant in predicting dementia/CIND. Notably, Veterans with a history of MDD prior to age 55 experienced one and a half times as much increased risk of developing dementia/CIND when PTSD was held constant, $OR = 1.58$, 95% CI [1.18, 2.10]. Moreover, a history of PTSD (when controlling for MDD) resulted in almost double the chances of getting dementia/CIND, $OR = 1.67$, 95% CI [1.27, 2.25]. This analysis demonstrated that when controlling for the other, both MDD and PTSD had moderate associations with dementia/CIND. This model accurately classified 75.9% of individuals with dementia/CIND, and 34.0% of those without, with an overall classification success rate of 37.0%.

To further examine the predictive utility of MDD and PTSD, another model was built adjusting for CurrentAge. This model was statistically significant, $\chi^2(3, N = 4800) = 79.40, p < .000$. When age and PTSD were both held constant, a history of MDD almost doubled the risk of dementia/CIND, $OR = 1.82$, 95% CI [1.36, 2.44], and showed a moderate association with the outcome. In contrast, when MDD and age were controlled for, the predictive utility of PTSD slightly decreased, yet remained statistically significant with a moderate association with dementia/CIND, $OR = 1.63$, 95% CI [1.22, 2.18].

To demonstrate the impact of MDD and PTSD with and without adjustment for CurrentAge, a line graph was created to represent the mean predicted probabilities by Veterans' current age, including both adjusted and unadjusted models of MDD and PTSD (see Figure 3). In the unadjusted model, the risk of dementia/CIND based on MDD history generally declined as subjects' age increased. The PTSD line was indicative of a higher risk as age increases, and then

a significant drop in risk the closer Veterans were to 70 year of age. This potentially suggested that MDD was a significant risk for dementia/CIND despite a Veteran's age, whereas PTSD (when controlling for age) increased the risk of dementia/CIND as Veterans become older. PTSD appeared to be the greatest risk factor in the unadjusted model, whereas MDD was the greatest risk factor in the adjusted model.

Model 1: MDD, PTSD, sex, and race. A hierarchical logistic regression analysis was conducted to examine the predictive utility of MDD, PTSD, and demographic variables as risk factors of dementia/CIND, adjusting for subjects' current age (Model 1^a). CurrentAge, PTSD, sex, and race were entered into this model based on their significance in prior bivariate analyses. MDD was also included based on the literature in which several researchers have determined it to be a significant risk factor of dementia/CIND (Barnes et al., 2012; Byers & Yaffe, 2011; Chen et al., 2009; Kaup et al., 2016).

CurrentAge was entered into block 1, MDD and PTSD into block 2, and race and sex into block 3. Block 2 (MDD and PTSD) significantly contributed to the model, with a change in χ^2 value of 18.55, $p < .000$. Adding race and sex to the model resulted in a smaller, yet significant change in χ^2 value of 7.42, $p = .024$, with an overall statistically significant model, $\chi^2(5, N = 4800) = 86.83, p < .000$). However, the Nagelkerke R^2 of .05 indicated a weak relationship between prediction and grouping. The Hosmer-Lemeshow test was not significant $\chi^2(8, N = 4800) = 6.53, p = .589$, thus supporting the assumption that the model adequately fit the data. With a classification cutoff of .07, the model was able to correctly classify 59.8% of subjects with dementia/CIND and 61.3% of subjects without dementia/CIND, for an overall success rate of 61.2%.

When a .05 criterion of statistical significance was employed, three of the four variables, MDD ($p < .000$), PTSD ($p = .001$), and sex ($p = .022$), were statistically significant when all other variables in the model were held constant (as shown in Table 7). A history of MDD was moderately associated with dementia/CIND, and Veterans with a history of MDD had almost twice the risk, $OR = 1.80$, 95% CI [1.34, 2.42]. Subjects with a history of PTSD ($OR = 1.62$, 95% CI [1.21, 2.16]) had over one and a half times the odds of getting dementia/CIND ($b = .48$, Wald $\chi^2(1) = 10.63$, $p = .001$) when compared to those without a history. While statistically significant ($p = .022$), the odds for male Veterans were only slightly greater than the odds for female Veterans, $OR = .76$, 95% CI [.60, .96].

In the next step, Model 1^b, interactions between sex (female = “1” and male = “0”) and MDD, and sex and PTSD were added. Interactions between race and MDD, and race and PTSD were also included. CurrentAge was entered into the first block, MDD, PTSD, and the demographic variables into the second block, and the new interaction variables into the third block. Although the model as a whole was statistically significant, $\chi^2(9, N = 4,800) = 91.81$, $p < .000$, the interactions did not significantly improve the model’s prediction validity, $\chi^2(4, N = 4,800) = 4.98$, $p = .289$. When examining the effect of each variable when all others were held constant, only CurrentAge was statistically significant ($p < .000$). Model 1^b was able to correctly classify 60.1% of dementia/CIND incidents and 60.2% of non-dementia/CIND incidents, for an overall classification success rate of 60.2%.

To discover optimal grouping and achieve parsimony, all predictors from Model 1^b were entered into one block using a backward LR method for Model 1^c. This method yielded the following predictors: CurrentAge, MDD, PTSD, sex, race, and Race*MDD (see Model 1^c in Table 7). The model was statistically significant, $\chi^2(6, N = 4,800) = 91.50$, $p < .000$, however, the

overall models with this particular set of variables had similar predictive utility as Models 1^a and 1^b.

When examining individual variables' predictive utility, five out of six variables were statistically significant ($p < .05$), with MDD ($p = .058$) being the only variable not significantly contributing to the model. Model 1^c was able to correctly classify 58.6% of dementia/CIND cases and 60.9% of non-dementia/CIND cases, for an overall success rate of 60.8% (see Table 10 for observed and predicted frequencies). Similar to Model 1^a, a history of PTSD was associated with a 1.62, 95% CI [1.21, 2.16], greater likelihood of developing dementia/CIND ($b = .48$, Wald $\chi^2(1) = 10.69$, $p = .001$) in Model 1^c. Men were .76, 95% CI [.60, .96], times more at risk of dementia/CIND compared to women. Interestingly, the strongest significant predictor of dementia/CIND in Model 1^c was Race*MDD, $b = .52$, Wald $\chi^2(1) = 4.66$, $p = .031$, which showed that when compared to their White counterparts, Black Veterans had almost twice the risk of getting dementia/CIND when a history of MDD was also present, $OR = 1.67$, 95% CI [1.05, 2.67].

Model 2: Sex, MDD, PTSD, MDDduration, and PTSDduration. With the aim of specifying risk factors based on demographic characteristics, Model 2 was built using sex, MDD, PTSD, and interactions between the predictors (sex*MDD and sex*PTSD), continuing to adjust for CurrentAge (see Table 8). In Model 2^a, a hierarchical logistic regression analysis was used in which CurrentAge was entered into the first block, MDD and PTSD into the second, and sex into the third. Adding sex to the model significantly improved the model, based on the increase in the chi-square value, $\chi^2(1, N = 4800) = 5.16$, $p = .023$.

Model 2^a, overall, was also statistically significant, $\chi^2(4, N = 4800) = 84.56$, $p < .000$, with a Nagelkerke R^2 of .044. When examining individual variables' impact on the model, all

three variables were statistically significant ($p < .05$), with similar effects of MDD, $OR = 1.81$, 95% CI [1.35, 2.43], and PTSD, $OR = 1.61$, 95% CI [1.21, 2.15], as those found in Model 1^a. However, sex was found to have a weak association with dementia/CIND, $OR = 0.76$, 95% CI [0.60, 0.97]. Model 2^a was able to correctly classify 60.7% of dementia/CIND incidents and 61.2% of non-dementia/CIND incidents, for an overall classification success rate of 61.1% (see Table 10).

Model 2^b consisted of the examination of the two interaction variables between sex and MDD/PTSD. CurrentAge was entered into block 1, MDD, PTSD, and sex into block 2, and sex*MDD, and sex*PTSD into block 3. Although the overall model, when compared to a constant only model, was statistically significant, $\chi^2(6, N = 4800) = 85.77, p < .000$), adding the interactions did not result in a significant improvement in the predictive validity of the model $\chi^2(2, N = 4800) = 0.22, p = .898$. Model 2^b also yielded the same classification success rates as Model 2^a. In the third step, a backward LR method was used to enter all the predictors from Model 2^b. However, this method yielded a model identical to Model 2^a, hence it was not included in Table 8.

Similar procedures were employed to analyze sex and MDDduration and PTSDduration. The steps taken in Model 2^{duration} yielded comparable outcomes to steps taken in Model 2, but with smaller associations between predictor and outcome variables. The final step of Model 2^{duration} is also included in Table 8. Overall, Models 2 and 2^{duration} suggested that when the effects of MDD and PTSD were held constant, male Veterans had a slightly greater risk for dementia/CIND compared to their female counterparts.

Model 3: Race, MDD, PTSD, MDDduration, and PTSDduration. As demonstrated in Table 9, Model 3 consisted of similar procedures as those in Model 2, but with race as the

demographic variable under investigation. Model 3^a, which was adjusted for age and included race, MDD, and PTSD, was statistically significant when compared to a constant only model, $\chi^2(4, N = 4800) = 81.52, p < .000$, with a Nagelkerke R^2 of 0.04. However, adding race to the model did not significantly improve its prediction utility, $\chi^2(1, N = 4800) = 2.11, p = .146$, nor was it statistically significant when holding all other predictors constant, $p = .147$. MDD, $OR = 1.81, 95\% CI [1.35, 2.42]$, and PTSD, $OR = 1.64, 95\% CI [1.23, 2.18]$, however, were significant and had moderate associations with dementia/CIND, with OR values comparable to those found in Models 1^a and 2^a. Model 3^a was able to correctly classify 65.2% of dementia/CIND incidents and 58.7% of non-dementia/CIND incidents, for an overall classification success rate of 59.1%.

Race*MDD and Race*PTSD were included in Model 3^b, using the same block entry procedures as in Model 2^b, which resulted in a statistically significant model, $\chi^2(6, N = 4800) = 86.28, p < .000$, with a Nagelkerke R^2 value of .05. However, adding the interactions to the model did not significantly improve its predictive utility, $\chi^2(2, N = 4800) = 4.76, p = .092$. Further, although neither interaction variable was statistically significant, the p value for Race*MDD was .058, which was slightly greater than the criterion for statistical significance.

In Model 3^c, all the variables from 3^b were entered using backward LR method, which yielded CurrentAge, MDD, PTSD, race, and Race*MDD in the last step. These variables resulted in a statistically significant model, $\chi^2(5, N = 4800) = 86.18, p < .000$, yet the models predictive utility decreased from that of Model 3^a. Nonetheless, this model revealed a statistically significant moderate association between race and history of MDD, $OR = 1.67, 95\% CI [1.05, 2.67]$. A history of PTSD was also associated with similar risks of developing dementia/CIND, $OR = 1.64, 95\% CI [1.23, 2.19]$. Hence, although race was not found to be statistically

significant in previous models (e.g., Models 1^a and 3^a), its interaction with MDD (Race*MDD) was associated with a 1.67, 95% CI [1.05, 2.67], increase in risk among Black Veterans for dementia/CIND.

The significant moderate association of Race*MDD with dementia/CIND was also found in Model 1^c where sex was also included in the model (Table 7). In Model 3^{duration}, the same methods from Model 3 were employed and Race*MDDduration was also the only interaction variable yielded in the backward LR analysis. The findings for the steps in Model 3^{duration} were also similar to those of Model 3, yet with smaller associations among predictor and outcome variables. Model 3^c correctly classified 62.2% of dementia/CIND incidents and 61.6% of non-dementia/CIND incidents, for an overall classification success rate of 61.7% (see Table 10).

To further demonstrate the predictive validity of the logistic regression models with sex (Model 2²) and race (Model 3^c), line graphs with mean predicted probabilities for dementia/CIND were created (see Figure 4). The line graph for Model 2^a shows the higher risk for male Veterans compared to female Veterans, despite differences in psychiatric history. The line graph for Model 3^c displays the increased risk for Black Veterans when a history of MDD was present. Consistent in both line graphs, Veterans who were male, and White, had the highest risk if a history of PTSD was present.

Model Validity and Discrimination Power

The overall logistic regression models of this study were statistically significant in predicting dementia/CIND. The study hypothesis—Veterans with a history of MDD or PTSD (first diagnosed before age 55) would have a greater likelihood of dementia/CIND—was supported by the findings. However, Veterans' current age had an important influence on the amount of risk associated with each disorder. When controlling for the other, MDD and PTSD

increased the risk of dementia/CIND 1.5 to 2.0 times compared those without a history of the diagnoses. When age was adjusted for, the predictive ability of MDD increased, whereas the risk of PTSD decreased slightly. When demographic variables were examined for predictive ability, Black Veterans were 1.67 more likely to develop dementia/CIND if a history of MDD was present. The interaction between race and history of PTSD however, was not significant in this study. Further, male Veterans had a slightly greater risk than female Veterans.

To assess the overall effectiveness of the final models, receiver operating characteristic (ROC) curve analyses were conducted to obtain a visual of the proportion of true positives plotted against the proportion of false positives. The area under the ROC (AUROC) curve values for Model 1^c (AUC = .654, 95% CI [.626, .683]), Model 2^a (AUC = .648, 95% CI [.619, .677]), and Model 3^c (AUC = .651, 95% CI [.623, .680]) are shown in Figure 5. An AUC of 0.5 suggests a 50-50 chance of accurate discrimination among diagnosis (Kumar & Indrayan, 2011). The closer the AUC is to 1.00, the better the diagnostic accuracy of the model or measure. AUC values from .70 to .80 have been considered fair/good in the existing literature (Maroco et al., 2011).

Researchers have identified an AUROC median value of 0.72 as “acceptable” in research studies focusing on risk factors of dementia and related conditions (Maroco et al., 2011). In this study, all three models had similar AUROC values ranging from .648 to .654, which fall below the “good” range of .70 to .80 (Hanley & McNeil, 1982). However, all three models showed statistically significant predictive power ($p < .000$), and the AUROC values fell slightly below the discrimination ability considered suitable within the context of this study. Further, based on the classification cutoff of .07 that was determined from disease rate, sensitivity values of 58%, 61%, and 62%, and specificity values of 62%, 61%, and 62% were determined for Models 1^c, 2^a,

and 3^c, respectively. Predictive accuracy of the models did not differ based on history of MDD or PTSD, duration of MDD or PTSD, sex, and race, although the variables included in each model varied.

Discussion

Researchers have made great strides in the inclusion of minority groups in recent studies involving the general population (Akincigil et al., 2012; Alegria et al., 2008; Mezuk et al., 2010; Yaffe et al., 2013). The current knowledgebase on risks of dementia/CIND, especially for different groups, has also proliferated (Barnes et al., 2012; Mielke et al., 2014; Plassman et al., 2007). For example, it has been established that a substantial risk factor of dementia and other forms of cognitive impairment is hypertension, which disproportionately impacts Black individuals (Manly & Echemendia, 2007). With the recent efforts of the VA to include women and racial minorities in research has also lead to an increase in studies including minority Veteran groups (Long et al., 2006). However, there continues to be a need for further rigorous testing of risk factors of dementia and related conditions for the Veteran population, especially among racial minority groups (Long et al., 2006; Saha et al., 2008).

The current study is one of the few examining dementia/CIND risk factors for the Veteran population aged ≥ 60 and including equal numbers of persons from various demographic groups, such as Black, White, female, or male. The findings of this study further confirmed the significant risk that depression, specifically MDD (Byers et al., 2012), and PTSD (Yaffe et al., 2010) pose for this particular population, and also contributed to the larger efforts for VA studies to include minority groups (Long et al., 2006) in studies related to dementia and other forms of cognitive impairment.

The hypothesis (Veterans with a history of MDD or PTSD would be at greater risk of dementia/CIND) was confirmed by the findings. Specifically, when controlling for the other, MDD and PTSD increased Veterans' risk of developing dementia/CIND almost twofold. Regarding the predictive utility of race and sex, Black Veterans had almost double the risk of developing dementia/CIND compared to their White counterparts, if a history of MDD was indicated. Sex was a significant risk, which indicated that male Veterans had a greater risk compared to female Veterans; yet, the effects for sex were very small. Further, having a history of MDD or PTSD did not affect risk for dementia/CIND based on Veterans' sex (e.g., interactions between sex and the psychiatric conditions were not significant).

It is worthwhile to note that the interaction between race and PTSD was not statistically significant, and this finding was contrary to recent studies that show PTSD rates are significantly higher in Black Veterans than their White counterparts (Dursa et al., 2014). For example, research on racial differences in PTSD rates among Veterans from OEF/OIF conflicts shows significantly higher PTSD rates among Black Veterans (Dursa et al., 2014). Further, when Dohrenwend et al. (2008) studied PTSD prevalence rates of Vietnam Veterans utilizing record-based exposure measures and clinical diagnoses of sub-samples, they also found greater rates of PTSD among Black (and Hispanic) Veterans for this age group. The researchers emphasized that previous research on racial differences in PTSD rates relied on retrospective self-reports and also focused on the presence of the disorder at the time the study was conducted, which frequently was several years after the Vietnam War.

Importantly, David, Kutcher, and Mellman (1999) assessed comorbidities found among male Veterans, 91% of whom were from the Vietnam era, reporting psychotic symptoms of PTSD. They found psychotic symptoms were associated with MDD and that this comorbidity

was more common among Black and Hispanic Veterans compared to White Veterans. Such findings are noteworthy in the context of this study due to the age group (60 years or older) of the Veteran participants [in this study], as well as the war era in which they served. To attribute for the discrepancies between the current study and other recent research on racial differences in PTSD rates, consideration of David and colleagues' (1999) findings is important. For instance, it is possible that Black Veterans in this age group were more likely to be diagnosed with MDD associated with psychotic features, whereas PTSD may have been a diagnosis that was more commonly found among White Veterans. However, additional studies addressing the limitations of inconsistent findings regarding PTSD rates are needed to fully understand the risk for different groups of Veterans.

Prevalence Rates

The rates of dementia/CIND diagnosis in this Veteran population were similar to that of the general population, which is consistent with most of the existing literature (Veitch et al., 2013; World Health Organization, 2015). Although the numbers are slightly varied, researchers have also recently found similar prevalence rates of dementia in the Veteran population (Sibener et al., 2014; Yaffe et al., 2010). However, findings comparing prevalence rates of dementia/CIND in the general population versus the Veteran population is somewhat inconsistent and robust findings have yet to be reported (Veitch et al., 2013). Prince and colleagues (2013) reported that the worldwide prevalence rate of dementias range from 5 to 7 percent in the general population. It is probable there are 7 percent [the high end of the rates for the general population] of positive cases in the current study due to the inclusion of CINDs, as well as the additional risk U.S. Veterans have for developing memory impairment (Lohr et al., 2015).

Although slightly varied, the current prevalence rate of dementia of Veterans is expected to be similar to that of the general population; nonetheless, researchers are in agreement concerning the increased risk that U.S. Veterans are at of developing cognitive impairment and dementia (Veitch et al., 2013). This is particularly so considering the “baby boomer” generation that makes up a large portion of the Veteran population and the increased risks they encounter (Sibener et al., 2014; Veitch et al., 2013). Of the U.S. population 60 years of age and older, 22 percent are Veterans. More specifically, almost half of the men aged 60 or older are Veterans (Veitch et al., 2013), part of the “baby boomer” generation (Hebert et al., 2013).

The “baby boomer” generation has been identified as anyone born between 1946 and 1964 (U.S. Census Bureau, 2008). Researchers have already documented the steady rise in prevalence rates of dementia; for example, from about 4.5 million individuals in 2000 (Hebert, Scherr, Bienias, Bennett, & Evans, 2003) to 4.7 million in 2010, and estimated to be 13.8 million by 2050 (Hebert et al., 2013). This number is expected to continually rise as “baby boomers” approach age 70 and older (Hebert et al., 2013). All subjects in this study are considered to be part of the “baby boomer” population given the U.S. Census Bureau’s (2008) definition of the term.

The findings of this study demonstrated that individuals diagnosed with dementia/CIND are older than those without, which is also consistent with the literature. However, important to highlight is that the first set of analyses conducted with Veterans diagnosed with dementia/CIND at age ≥ 60 ($n = 210$) were largely insignificant. Yet, analyses of Veterans with dementia/CIND diagnosed at age ≥ 56 ($n = 336$) resulted in generally significant findings and a much higher rate of dementia/CIND. The age subjects were diagnosed with dementia ranged from 60 to 70 ($M = 63.13$, $SD = 2.52$) in the first set of analyses, and 56 to 70 ($M = 60.83$, $SD = 3.18$) in the second

set. Hence, across a span of four years (when subjects were diagnosed with dementia/CIND between ages 56 to 59), 126 additional Veterans were diagnosed. This potentially indicates that Veterans begin experiencing cognitive impairments earlier (at age 56) than the general population (at age 60; Prince et al., 2013), which is not surprising given the increased risk this population has for diseases found among older adults.

MDD and PTSD

In general, PTSD and MDD were both significant risk factors of dementia/CIND for Veterans, increasing their odds anywhere from about 1.5 to 2.0 times. Importantly, there were other factors, such as current age, that moderated these risk levels. MDD as a risk factor, when other variables were not considered, did not pose a significant threat. However, when the age of subjects was controlled for, MDD was associated with almost a twofold risk of dementia/CIND. Conversely, a history of PTSD, when other variables were not considered, was a strong risk factor. Yet, when controlling for Veterans' age, PTSD was not a statistically significant risk. This potentially indicated that PTSD as a significant risk varied based on a Veterans' age. A history of MDD alone [prior to age 55] acted as a significant risk for dementia and related conditions, whereas a history of PTSD acted as a strong risk factor especially later in life.

When each disorder (MDD and PTSD) was examined while holding the other constant, they were both significant risk factors and had a moderate association with dementia and related conditions. Notably, when current age, and either PTSD or MDD, were also controlled for, MDD became an even greater risk, whereas the risk that PTSD posed decreased slightly. Specifically, when controlling for PTSD and age, MDD almost doubled the risk of dementia/CIND, whereas PTSD increased the risk over one and a half times. Comparable, yet smaller, associations were found for MDD and PTSD chronicity.

Sex and Race

A history of MDD or PTSD independently posed a greater risk for dementia/CIND compared to Veterans' demographic characteristics. Nevertheless, sex and race still were significant risk factors in different ways. Male Veterans were at a slightly higher risk of developing cognitive difficulties compared to female Veterans. Independently (when holding all other variables in the model constant), sex acted as a significant risk whereas race did not. Black Veterans' risk of dementia/CIND almost doubled when they had a history of MDD. This is an important finding, because researchers have found that Black individuals are less likely to have a depression diagnosis, and receive treatment for depression, compared to their White counterparts (Akincigil et al., 2012). It is possible this phenomenon also occurs in the Veteran population, and that is why a combination of Black racial identification and a history of MDD resulted in a significantly greater risk. The relationship between sex and MDD, and sex and PTSD were not significant.

Without adjusting for other variables, men were at slightly greater risk compared to women. As age increased though, women's risk became greater, particularly at age 70 or older. White Veterans had generally higher rates of dementia/CIND than Black Veterans when a history of PTSD was present, whereas Black Veterans had greater risks if a history of MDD was present. Both female and male Black Veterans' risk increased almost twofold if a history of MDD was present.

Findings Unique to Veterans of Age \geq 60 Years

It is important to note particular findings that were unique to the Veteran population aged 60 or older, when compared to the general U.S. population. When studying the number of dementia/CIND cases in this study, White male Veterans with a history of PTSD had the higher

number of diagnoses, with Black male Veterans with a history of MDD following. Women consistently had lower rates of dementia/CIND diagnosis, and the rates were similar for most of the Black female and White female Veteran groups.

In the general population, Black persons have a greater risk compared to their White counterparts for dementia and related conditions (Plassman et al., 2007; Yaffe et al., 2013). Race alone did not significantly affect risk for dementia/CIND in this study. However, Black Veterans had much greater odds of developing cognitive problems when a history of MDD was present. In a setting (VA medical centers) where barriers to health care costs are minimized and the population (Veterans) is unique in that it is exposed to greater amounts of adverse circumstances, Black Veterans nonetheless continue to be at a greater risk provided they have a history of MDD.

Further, male Veterans continually had greater risks for dementia/CIND compared to their female counterparts, which is understandable considering the different roles male and female Veterans (current age of ≥ 60) had when serving in the military (Vogt et al., 2011). In the past, women's role in the military have been characterized as primarily clerical or nursing staff, whereas their roles in current conflicts in Afghanistan and Iraq entail much higher levels of combat exposure (Street, Vogt, & Dutra, 2009; Vogt et al., 2011). Nevertheless, this is a unique finding provided that most of the research on dementia prevalence rates identifies women as having significantly greater probabilities. There are some researchers, however, who have reported the higher rates could be due to women's longer longevity compared to that of men's, and others who indicate many other factors also influence women's higher levels of risk (Viña & Lloret, 2010).

Limitations

Despite the significant impact that dementia and related conditions have on affected persons and their loved ones, it is a condition that is seen in older individuals and is rare among the general population. The World Health Organization (2015) reported the prevalence rate of dementia for those aged 60 and older to be approximately 5 to 8 percent. Although this rate is expected to increase, particularly within the Veteran population (Veitch et al., 2013), the current prevalence rate makes dementia and related conditions difficult to investigate and determine concrete findings. Thus, this study is not without its limitations.

Dementia and cognitive impairment not demented (CIND) were grouped together in this study, hence, it is possible potential differences or patterns among those diagnosed with dementia versus CINDs may have existed. This will be an important objective in future research—to examine how subtypes of dementia and related conditions differ with respect to risk factors. Although all specifiers were considered for major depressive disorder (duration, severity, presence of psychotic behavior, and remission status) and posttraumatic stress disorder (acute, brief, and chronic), these were two exclusive psychiatric conditions examined in this study. These disorders are known to impact Veterans at a greater rate, intensity, and duration (Veitch et al., 2013), nonetheless, researchers should investigate other related psychiatric conditions as risks of dementia/CIND. Further, examination of the comorbidity of these conditions across diverse Veteran groups is also needed, especially due to the similarity in symptoms and high rates of comorbidity (Angelakis & Nixon, 2015).

Likewise, other factors with strong predictive utility of dementia and related conditions identified in the literature, such as hypertension for Black individuals (Yaffe et al., 2013), traumatic brain injury (TBI) for Veterans (Veitch et al., 2013), and genetic risks of dementia

(Chen et al., 2009), were not examined in this study. It would be advantageous for researchers to study the influence of these variables on Veterans of various demographic backgrounds. Scholars have found that treatment of mental health conditions, such as MDD, can improve cognitive functioning in some persons (Herrera-Guzmán et al., 2010), thus, researchers should also examine the potential impact that obtaining treatment for depression and PTSD might have on the outcome of risk of dementia/CIND. Moreover, the *diagnosis* of MDD and PTSD made by licensed independent providers were examined in this study, yet actual depressive or PTSD symptoms were not assessed. Thus, readers must remember that the findings are solely based on diagnoses that were made rather than the observation of actual symptoms via mood questionnaires (e.g., Geriatric Depression Scale), clinical interviews, etc.

In order to obtain adequate statistical power, this study included only Veterans who self-identified as Black or White, thus, omitting other racial groups such as Veterans who identified as having more than one race (e.g., “mixed” or both Black and White). It should also be noted that the final sample in each of the 12 groups were randomly selected from the larger Cohort tables, which consisted of fewer records for women, particularly those who self-identified as Black, compared to the medical data available for men. As the Veteran population continues to diversify and data for other racial groups becomes available, it will be imperative for researchers to include data of these Veterans in future studies to provide findings applicable to more Veteran subpopulations.

Although statistically significant, the logistic regression models had small pseudo R^2 values (e.g., Nagelkerke R^2) ranging from .04 to .05. Further, the ROC curve analysis showed the discrimination ability of the models were slightly less than what is considered “acceptable” in the context of this study. To increase the chances of detecting prediction validity of study variables

based on a low disease rate of 7%, a larger sample than what was indicated by the a priori statistical power analysis was included in this study. This resulted in having statistical tests that were “overpowered,” and smaller values or effects may have been determined to be statistically significant by inflated p values.

Taking this into consideration, the study findings were also largely interpreted using effect size as measured by the *odds ratio* values (Chen et al., 2010; Cohen, 1992), which were found to be in the weak to moderate range. This way, the amount of association that existed among variables were examined rather than basing the findings solely on p values. Furthermore, when statistical tests are potentially “overpowered,” the clinical significance of the statistically significant results are called into question. Thus, both the statistical and clinical significance of the study findings will be considered when discussing implications.

Implications

The findings of the current study have important implications for both clinicians and researchers. Notably, Veterans in this study were at an accelerated risk of cognitive difficulties—they were more likely to experience cognitive impairment earlier than persons in the general population. Sperling and others (2011) identified a “preclinical stage” that can be a major target for preventative treatment approaches of dementia/CIND, as changes in the brain are suspected to begin several years prior to the actual onset of symptoms related to cognitive impairment. Clinicians must take this, as well as the accelerated risk of Veterans, into consideration. Preventative efforts in this regard would be very advantageous, particularly for younger Veterans. For researchers, it is important to include Veterans from younger age groups to further examine the typical onset of cognitive difficulties for this special population. Researchers have determined younger Veterans are at a greater risk for PTSD, hence, these findings overall have

significant implications particularly for those Veterans involved in recent OEF/OIF conflicts (Qureshi et al., 2010; Seal et al., 2009).

Based on the significance of both MDD and PTSD as risk factors for Veterans aged ≥ 60 years, greater attention to the assessment and treatment of depression and PTSD is warranted. MDD was a risk factor despite Veterans' current age, whereas PTSD generally appeared to be a significant risk factor as Veterans increased in age. Despite the examination of these conditions separately in this study, MDD and PTSD nonetheless have comparable symptoms (Asnaani et al., 2010; Spinhoven et al., 2014). Taking into consideration the significant effects of both conditions, it would be advisable for clinicians to conduct brief depression/PTSD screens especially for older Veterans (Byers et al., 2012; Casey, 2012; Djernes, 2006); that way, if further assessment or treatment is warranted, there are increased chances it will be detected.

Important to note about MDD and PTSD symptoms is the difference in emotion and symptom expression among men and women, particularly for older adults and Veterans (Djernes, 2006). Bouchard and Shih (2013) emphasized how men are less likely to express depressive symptoms compared to women, potentially due to societal gender stereotypes (Essau et al., 2010). Women are more interpersonally oriented and have greater chances of experiencing interpersonal stress compared to their male counterparts, which researchers have attributed as one of the significant causes of such disparities in rates of depression (Bouchard & Shih, 2013). For that reason, psychoeducation related to psychiatric symptoms and the differences in symptom expression among demographic groups is important to include in patient/Veteran treatment care. This is not to suggest that all male Veterans may attempt to conceal their psychiatric symptoms, but rather that due to socialization and gender stereotypes, men and

women express these symptoms quite differently and it may be difficult to recognize symptoms in one versus the other (Essau et al., 2010).

Time and time again, scholars have provided evidence of persons' racial background playing a significant role in their health outcomes (Alegria et al., 2008; Oh, Galanter, Thakur, Pino-Yanes, White, et al., 2015), and this proves to be no different for the Veteran population (Saha et al., 2008). Specifically, Black Veterans with a history of MDD should be given additional consideration with respect to health care due to their increased risk of cognitive impairment. In this study, the interaction variable between history of MDD and race (Race*MDD) was statistically significant and almost doubled the odds of a Black Veteran developing dementia or a related condition. This is particularly critical considering the racial disparities in diagnosis that disproportionately impact Black individuals (Eack et al., 2012). Further, researchers must also consider the relationship between MDD and race in future studies, especially when studying the Veteran population.

Although the potentially “overpowered” statistical analyses of this study may have produced inflated *p* values resulting in statistical significance of smaller differences, it is important to inspect such results for their clinical significance. For example, the difference in mean PTSD duration among Veterans with dementia/CIND ($M = 14.28$ years, $SD = 2.26$) compared to those without ($M = 13.54$ years, $SD = 2.47$) was statistically significant, yet the absolute difference between the two age means, in years, is less than one year. This may cause readers to question the clinical significance of such a finding, however, it is important to consider the difference within the context of the study. Specifically, experiencing PTSD symptoms for an additional six months for a Veteran may be quite devastating and potentially result in a significantly lower quality of life, which could lead to higher risks for various medical

conditions. The findings for MDD duration were similar. Thus, when working with Veterans experiencing mental health conditions, clinicians must be cautious not to minimize the toll that an additional six months of adverse mental symptoms can take. Likewise, researchers should also further inspect findings typically considered to be “small” based on the context of their study.

Conclusion

As one of the few studies including various demographic groups of the Veteran population, the findings related to risk factors of dementia and related conditions can hopefully lay the groundwork for future researchers to investigate how risk factors of cognitive difficulties in the Veteran population differ from those found in the general population. MDD and PTSD were both identified as significant risk factors, particularly when the other was controlled for. Male Veterans had a slightly greater risk of developing cognitive difficulties compared to female Veterans of this study. Black Veterans had almost double the risk of developing dementia or related conditions when a history of MDD was indicated. The findings also indicated that the Veteran population may be more likely to experience an earlier onset of cognitive difficulties compared to the general population.

Continual brief assessment and treatment of symptoms [if warranted] related to depression, especially MDD, and PTSD will be an important initiative for providers working with Veterans (Casey, 2012; Fanning & Pietrzak, 2013; Kaup et al., 2016). Practices such as these can potentially act as one of the greatest preventative treatment approaches for dementia and related conditions. As the aging Veteran population also diversifies based on sex and race (U.S. Census Bureau, 2012), an essential task for researchers and clinicians is to consider such

demographic variables in their work to provide care employing best practices and better serve those who have served the country—U.S. Veterans.

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Table 1

Groups of Veterans by Sex, Race, and History of Psychiatric Disorder (N = 4,800)

	Cohort 1	Cohort 2	Cohort 3
Race/Sex	(MDD)	(PTSD)	(No MH history)
Black/Female	C1G1	C2G4	C3G9
White/Female	C1G2	C2G5	C3G10
Black/Male	C1G3	C2G6	C3G11
White/Male	C1G4	C2G7	C3G12

Note. C# = cohort number. G# = group number. Cohorts were based on psychiatric history diagnosed at age < 55. Cohort 1 = major depressive disorder (MDD) was the only psychiatric diagnosis. Cohort 2 = posttraumatic stress disorder (PTSD) was the only psychiatric diagnosis. Cohort 3 = no psychiatric history. Individuals with a history of both MDD and PTSD were excluded from the study. Individuals who identified as having more than one sex and/or race were also excluded.

Table 2

Characteristics of Veterans with and without Dementia/CIND (N = 4,800)

Veteran Characteristic	n (% of N)	DEM/CIND Status		With DEM/CIND	
		Yes (n = 336)	No (n = 4,464)	% of DEM	% of N
^a Current age**	—	65.64 (2.50)	64.49 (2.57)	—	—
^a DEM/CIND dx age	—	60.83 (3.18)	—	—	—
<u>MDD (Cohort 1)</u>	1,600 (33.3%)	124 (7.8%)	1,476 (92.3%)	36.9%	2.6%
^a MDD dx age	—	51.26 (2.30)	50.76 (2.48)	—	—
^a MDD duration*	—	13.76 (2.24)	13.21 (2.40)	—	—
^a DEM/CIND-MDD dx	—	8.95 (3.40)	—	—	—
<u>PTSD (Cohort 2)*</u>	1,600 (33.3%)	131 (8.2%)	1,469 (91.8%)	39.0%	2.7%
^a PTSD dx age	—	51.70 (1.89)	51.31 (2.32)	—	—
^a PTSD duration**	—	14.28 (2.26)	13.54 (2.47)	—	—
^a DEM/CIND-PTSD dx	—	9.52 (3.29)	—	—	—
<u>Sex**</u>					
Female	2,400 (50.0%)	131 (5.5%)	2,269 (94.5%)	39.0%	2.7%
Male	2,400 (50.0%)	205 (8.5%)	2,195 (91.5%)	61.0%	4.3%
<u>Race*</u>					
Black	2,400 (50.0%)	148 (6.2%)	2,252 (93.8%)	44.0%	3.1%
White	2,400 (50.0%)	188 (7.8%)	2,212 (92.2%)	56.0%	3.9%
<u>Marital Status</u>					
Single/Unmarried	693 (14.6%)	58 (8.4%)	635 (91.6%)	17.3%	1.2%
Married	1,853 (39.0%)	117 (6.3%)	1,736 (93.7%)	34.8%	2.5%
Divorced/Separated	1,896 (39.9%)	136 (7.2%)	1,760 (92.8%)	40.5%	2.9%
Widowed	306 (6.4%)	25 (8.2%)	281 (91.8%)	7.4%	0.5%
TOTAL	4,800 (100%)	336 (7.0%)	4,464 (93.0%)	—	—

Note. DEM/CIND dx age = first dementia/CIND diagnosis at age > 55. MDD/PTSD dx age = first MDD/PTSD diagnosis at age < 55. MDDduration and PTSDduration = # of years since first MDD or PTSD diagnosis, respectively. DEM/CIND-MDD/PTSD dx = number of years between the first DEM/CIND and the first MDD/PTSD diagnosis. Individuals with a history of both MDD and PTSD were excluded from the study. Subjects who identified as having more than one sex and/or race were also excluded.

^aContinuous variables expressed as mean (with standard deviation). All other variables were categorical and expressed as frequency (percentage).

* $p < .05$. ** $p < .01$. Values based on χ^2 or t tests for categorical and ^acontinuous variables, respectively.

Table 3

Characteristics of Veterans in Each of the 12 Subgroups with and without Dementia/CIND (N = 4,800)

Group	n (% of N)	DEM/CIND Status		With DEM/CIND		$\chi^2(1)$
		Yes (n = 336)	No (n = 4,464)	% of DEM	% of N	
<u>Cohort 1 - MDD</u>						
C1G1 Black/Female	400 (8.3%)	27 (6.8%)	373 (93.3%)	8.0%	0.6%	0.04
C1G2 White/Female	400 (8.3%)	27 (6.8%)	373 (93.3%)	8.0%	0.6%	0.04
C1G3 Black/Male	400 (8.3%)	36 (9.0%)	364 (91.0%)	10.7%	0.8%	2.68
C1G4 White/Male	400 (8.3%)	34 (8.5%)	366 (91.5%)	10.1%	0.7%	1.51
<u>Cohort 2 - PTSD</u>						
C2G5 Black/Female	400 (8.3%)	19 (4.8%)	381 (95.3%)	5.7%	0.4%	3.93
C2G6 White/Female	400 (8.3%)	27 (6.8%)	373 (93.3%)	8.0%	0.6%	0.04
C2G7 Black/Male	400 (8.3%)	35 (8.8%)	365 (91.3%)	10.4%	0.7%	2.05
C2G8 White/Male	400 (8.3%)	50 (12.5%)	350 (87.5%)	14.9%	1.0%	20.28**
<u>Cohort 3 - None</u>						
C3G9 Black/Female	400 (8.3%)	11 (2.8%)	389 (97.3%)	3.3%	0.2%	12.11**
C3G10 White/Female	400 (8.3%)	20 (5.0%)	380 (95.0%)	6.0%	0.4%	2.68
C3G11 Black/Male	400 (8.3%)	20 (5.0%)	380 (95.0%)	6.0%	0.4%	2.68
C3G12 White/Male	400 (8.3%)	30 (7.5%)	370 (92.5%)	8.9%	0.6%	0.17
TOTAL	4,800 (100%)	336 (7.0%)	4,464 (93.0%)	—	—	—

Note. Values are frequency (percentage) with p value by $\chi^2(1)$ test comparing one subgroup ($n = 400$) with the other 11 subgroups ($n = 4,400$). DEM/CIND Status = whether dementia/CIND was diagnosed at age > 55. Cohort 1 = MDD was the only psychiatric diagnosis at age < 55. Cohort 2 = PTSD was the only psychiatric diagnosis at age < 55. Cohort 3 = no psychiatric history at age < 55. Individuals with a history of both MDD and PTSD were excluded from the study. Individuals who identified as having more than one sex and/or race were also excluded.

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

Table 4

Frequency or Mean Values for Predictor Variables of Dementia/CIND included in Logistic Regression Analyses

Categorical Predictor	With DEM/CIND (<i>n</i> = 336)	Without DEM/CIND (<i>n</i> = 4,464)	$\chi^2(1)$ value	<i>p</i>
MDD	124 (7.8%)	1,476 (92.3%)	2.07	.150
PTSD	131 (8.2%)	1,469 (91.8%)	5.20*	.023
<u>Sex</u>				
Male ^a	205 (8.5%)	2,195 (91.5%)	17.52**	.000
Female	131 (5.5%)	2,269 (94.5%)		
<u>Race</u>				
White ^a	188 (7.8%)	2,212 (92.2%)	5.12*	.024
Black	148 (6.2%)	2,252 (93.8%)		

Continuous Predictor	With DEM/CIND (<i>n</i> = 336)	Without DEM/CIND (<i>n</i> = 4,464)	<i>t</i> value	<i>p</i>
CurrentAge	65.54 (2.50)	64.49 (2.57)	<i>t</i> (4798) -7.95**	.000
MDDduration	13.76 (2.24)	13.21 (2.40)	<i>t</i> (1598) -2.48*	.013
PTSDduration	14.28 (2.26)	13.54 (2.47)	<i>t</i> (159) ^b -3.58**	.000

Note. DEM/CIND = first dementia/CIND diagnosis at age > 55. MDD and PTSD coded as “0” (no history of MDD/PTSD at age < 55) or “1” (with a history of MDD/PTSD at age < 55). Reference group for MDD and PTSD was Cohort 3 (no psychiatric history at age < 55). Sex included Female (coded as “1”) and Male (coded as “0”). Race included Black (coded as “1”) and White (coded as “0”). MDDduration and PTSDduration = # of years since first MDD/PTSD diagnosis, respectively. Categorical predictor variables are reported as frequency (with percentage) and continuous predictor variables are reported as mean (with standard deviation).

^aReference group for the categorical predictor variables of sex and race.

^bLevene’s test indicated unequal variances ($F = 6.76$, $p = .009$). Degrees of freedom were adjusted from 1598 to 159.

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

Table 5

Intercorrelations for Dementia/CIND and Predictor Variables

Variable	1	2	3	4	5	6	7	8
1. Dementia/CIND	–							
2. MDD	.021	–						
3. MDDduration ^c	.062*	^c	–					
4. PTSD	.033*	-.500**	^c	–				
5. PTSDduration ^c	.083**	^c	^c	^c	–			
6. Sex	-.060**	.000	-.021	.000	-.292**	–		
7. Race	-.033*	.000	-.104**	.000	-.060*	.000	–	
8. CurrentAge	.114**	-.142**	.465**	.101**	.590**	-.244**	-.100**	–

Note. $N = 4,800$ unless otherwise stated. Dementia/CIND = first dementia/CIND diagnosis at age > 55. MDD and PTSD coded as “0” (no history of MDD/PTSD at age < 55) or “1” (with a history of MDD/PTSD at age < 55). MDDduration and PTSDduration = # of years since first MDD/PTSD diagnosis, respectively ($n = 1,600$ per cohort). Sex included Female (coded as “1”) and Male (coded as “0”). Race included Black (coded as “1”) and White (coded as “0”).

^cCould not be computed because at least one of the variables was constant and represented only one Cohort of subjects ($n = 1,600$).

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

Table 6

Collinearity Diagnostics for Predictor Variables of Dementia/CIND

Variable	Collinearity Statistics			Dimension	Eigenvalue	Condition Index	Variance Proportions				
	Tolerance	VIF					MDD	PTSD	Sex	Race	CurrentAge
MDD	.506	1.98		1	2.95	1.00	.020	.020	.040	.040	.020
PTSD	.499	2.00		2	1.00	1.72	.250	.250	.000	.000	.000
Sex	.510	1.96		3	0.50	2.43	.000	.000	.520	.500	.000
Race	.505	1.98		4	0.41	2.69	.310	.310	.290	.290	.010
CurrentAge	.208	4.82		5	0.14	4.53	.410	.420	.160	.170	.960

Note. Linear Regression through the Origin.

Table 7

Model 1: Logistic Regression Predicting Dementia/CIND at Age > 55 (including Sex and Race)

Model	Predictor Variable	B	SE	OR	95% CI	Wald statistic	p
1 ^a	CurrentAge	0.16	0.02	1.18	[1.12, 1.23]	48.85**	.000
	MDD	0.59	0.15	1.80	[1.34, 2.42]	15.36**	.000
	PTSD	0.48	0.15	1.62	[1.21, 2.16]	10.63**	.001
	Sex	-0.28	0.12	0.76	[0.60, 0.96]	5.25*	.022
	Race	-0.17	0.12	0.84	[0.67, 1.05]	2.26	.133
1 ^b	CurrentAge	0.16	0.02	1.18	[1.12, 1.23]	47.82**	.000
	MDD	0.27	0.24	1.32	[0.83, 2.09]	1.36	.244
	PTSD	0.41	0.22	1.51	[0.98, 2.35]	3.43	.064
	Sex	-0.36	0.24	0.70	[0.44, 1.11]	2.28	.131
	Race	-0.42	0.24	0.66	[0.41, 1.04]	3.20	.074
	Sex*MDD	0.14	0.30	1.15	[0.64, 2.08]	0.21	.644
	Sex*PTSD	0.08	0.31	1.08	[0.59, 1.96]	0.06	.805
	Race*MDD	0.57	0.30	1.77	[0.98, 3.20]	3.59	.058
Race*PTSD	0.09	0.30	1.10	[0.61, 1.98]	0.10	.756	
1 ^c	CurrentAge	0.16	0.02	1.18	[1.12, 1.23]	49.58**	.000
	MDD	0.36	0.19	1.43	[0.99, 2.06]	3.60	.058
	PTSD	0.48	0.15	1.62	[1.21, 2.16]	10.69**	.001
	Sex	-0.28	0.12	0.76	[0.60, 0.96]	5.26*	.022
	Race	-0.36	0.15	0.70	[0.52, 0.93]	6.18*	.013
	Race*MDD	0.52	0.24	1.67	[1.05, 2.67]	4.66*	.031

Note. $N = 4,800$. CI = confidence interval for odds ratio (OR). MDD and PTSD coded as “0” (no history of MDD/PTSD at age < 55) or “1” (with a history of MDD/PTSD at age < 55). Sex included Female (coded as “1”) and Male (coded as “0”). Race included Black (coded as “1”) and White (coded as “0”). Model 1^c variables were entered using Backward LR method.

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

Table 8

Model 2: Logistic Regression Predicting Dementia/CIND at Age > 55 (including Sex)

Model	Predictor Variable	<i>B</i>	<i>SE</i>	<i>OR</i>	95% CI	Wald statistic	<i>p</i>
2 ^a	CurrentAge	.165	.023	1.18	[1.13, 1.23]	51.71**	.000
	MDD	.592	.150	1.81	[1.35, 2.43]	15.57**	.000
	PTSD	.479	.147	1.61	[1.21, 2.15]	10.57**	.001
	Sex	-.271	.120	0.76	[0.60, 0.97]	5.10*	.024
2 ^b	CurrentAge	.164	.023	1.18	[1.13, 1.23]	50.03**	.000
	MDD	.533	.195	1.71	[1.16, 2.50]	7.45**	.006
	PTSD	.446	.187	1.56	[1.08, 2.26]	5.67*	.017
	Sex	-.355	.236	0.70	[0.44, 1.11]	2.26	.133
	Sex*MDD	.140	.303	1.15	[0.64, 2.08]	0.22	.642
	Sex*PTSD	.081	.305	1.09	[0.60, 1.97]	0.07	.790
2 ^{duration}	CurrentAge	.151	.023	1.16	[1.11, 1.22]	43.66**	.000
	MDDduration	.041	.010	1.04	[1.02, 1.06]	15.57**	.000
	PTSDduration	.032	.010	1.03	[1.01, 1.05]	10.45**	.001
	Sex	-.270	.120	0.76	[0.60, 0.97]	5.06*	.024

Note. $N = 4,800$. CI = confidence interval for odds ratio (*OR*). MDD and PTSD coded as “0” (no history of MDD/PTSD at age < 55) or “1” (with a history of MDD/PTSD at age < 55). Sex included Female (coded as “1”) and Male (coded as “0”). In Model 2^b, interactions between Sex and MDD and PTSD were added. A third step was taken using the Backward LR method, which yielded the same variables as Model 2^a, thus results were not included in this table. The same methods were used to examine MDDduration and PTSDduration, and the steps in Model 2^{duration} yielded similar results as the steps in Model 2. MDDduration and PTSDduration = # of years since the first MDD/PTSD diagnosis, respectively.

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

Table 9

Model 3: Logistic Regression Predicting Dementia/CIND at Age > 55 (including Race)

Model	Predictor Variable	<i>B</i>	<i>SE</i>	<i>OR</i>	95% CI	Wald statistic	<i>p</i>
3 ^a	CurrentAge	.174	.022	1.19	[1.14, 1.24]	60.75**	.000
	MDD	.594	.150	1.81	[1.35, 2.43]	15.70**	.000
	PTSD	.492	.147	1.64	[1.23, 2.18]	11.19**	.001
	Race	-.167	.115	0.85	[0.68, 1.06]	2.11	.147
3 ^b	CurrentAge	.175	.022	1.19	[1.14, 1.25]	61.39**	.000
	MDD	.338	.200	1.40	[0.95, 2.08]	2.87	.091
	PTSD	.456	.190	1.58	[1.09, 2.29]	5.73*	.017
	Race	-.415	.236	0.66	[0.43, 1.05]	3.10	.078
	Race*MDD	.572	.302	1.77	[0.98, 3.20]	3.60	.058
	Race*PTSD	.094	.300	1.10	[0.61, 1.98]	0.10	.754
3 ^c	CurrentAge	.175	.022	1.19	[1.14, 1.25]	61.45**	.000
	MDD	.361	.187	1.44	[1.00, 2.07]	3.73	.053
	PTSD	.494	.147	1.64	[1.23, 2.19]	11.25**	.001
	Race	-.358	.146	0.70	[0.53, .093]	5.98*	.015
	Race*MDD	.515	.239	1.67	[1.05, 2.67]	4.65*	.031
3 ^{duration}	CurrentAge	.162	.022	1.18	[1.13, 1.23]	52.06**	.000
	MDDduration	.024	.013	1.02	[1.00, 1.05]	3.40	.065
	PTSDduration	.034	.010	1.03	[1.01, 1.06]	11.25**	.001
	Race	-.356	.145	0.70	[0.53, 0.93]	6.01*	.014
	Race*MDDduration	.038	.017	1.04	[1.01, 1.07]	5.00*	.025

Note. $N = 4,800$. CI = confidence interval for odds ratio (*OR*). MDD and PTSD coded as “0” (no history of MDD/PTSD at age < 55) or “1” (with a history of MDD/PTSD at age < 55). Race included Black (coded as “1”) and White (coded as “0”). In Model 3^b, interactions between Race and MDD and PTSD were added. In Model 3^c, all the variables from 3^b were entered using Backward LR method, and Model 3^c included all the variables from the final step of the backward LR logistic regression analysis. The same methods were used to examine MDDduration and PTSDduration, and the steps in Model 3^{duration} yielded similar results as the steps in Model 3. MDDduration and PTSDduration = # of years since the first MDD/PTSD diagnosis, respectively.

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

Table 10

Observed and Predicted Frequencies for Dementia/CIND by Logistic Regression Models

Model	Observed	Predicted Dementia		% Correct
		No	Yes	
1 ^c	DEM/CIND No	2,719	1,745	60.9
	Yes	139	197	58.6
	Overall %			60.8
2 ^a	DEM/CIND No	2,730	1,734	61.2
	Yes	132	204	60.7
	Overall %			61.1
3 ^c	DEM/CIND No	2,752	1,712	61.6
	Yes	127	209	62.2
	Overall %			61.7

Note. $N = 4,800$. Classification cut off = .07. Model 1^c variables = CurrentAge, MDD, PTSD, Sex, Race, and Race*MDD. Model 2^a variables = CurrentAge, MDD, PTSD, and Sex. Model 3^c variables = CurrentAge, MDD, PTSD, Race, and Race*MDD.

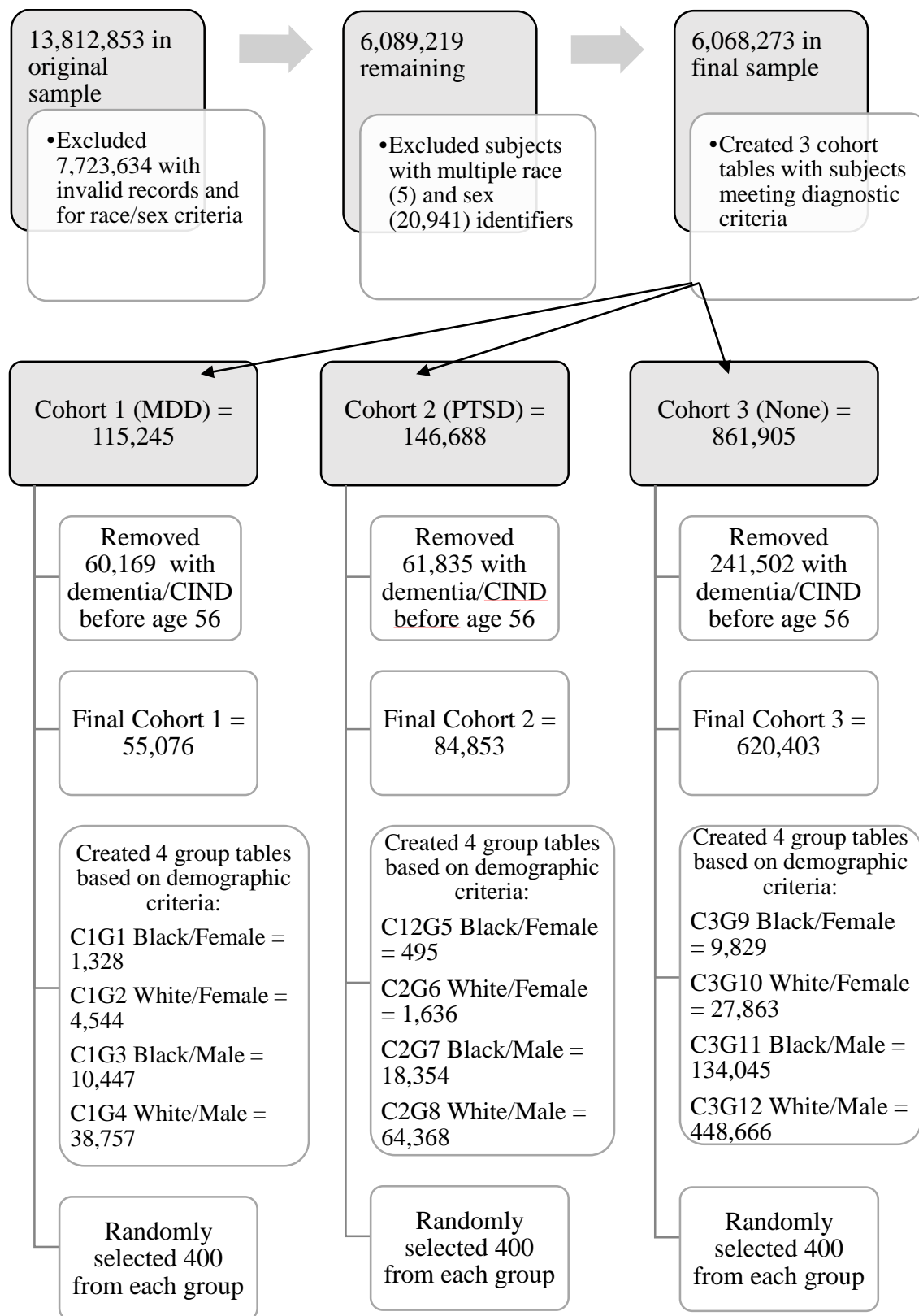


Figure 1. Flowchart of Study Participant Selection with Inclusion/Exclusion Criteria.

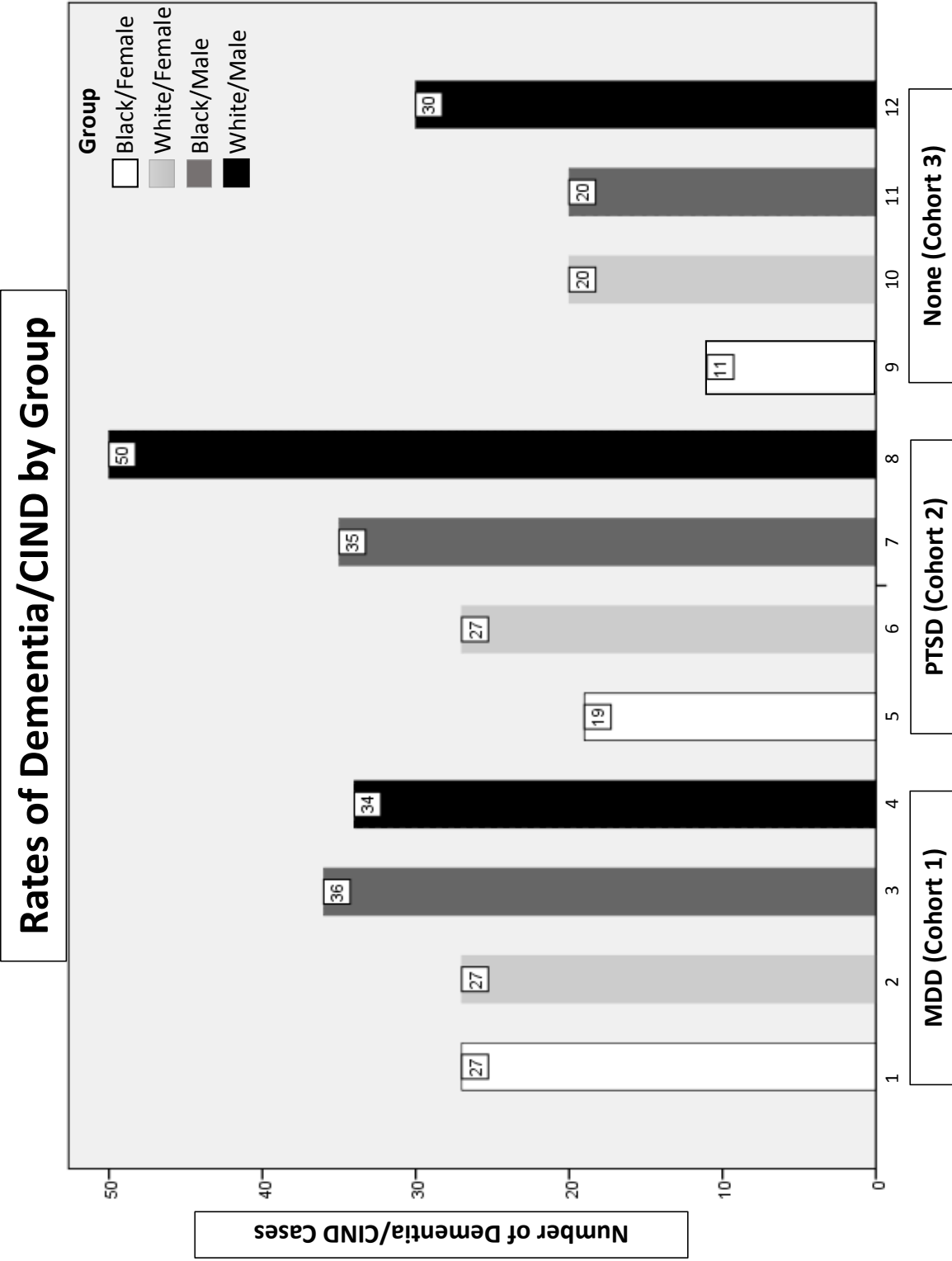


Figure 2. Number of Dementia/CIND Cases (diagnosed at age > 55) per Subgroup, divided by Cohorts 1, 2, and 3.

Risk of Dementia/CIND based on MDD/PTSD History

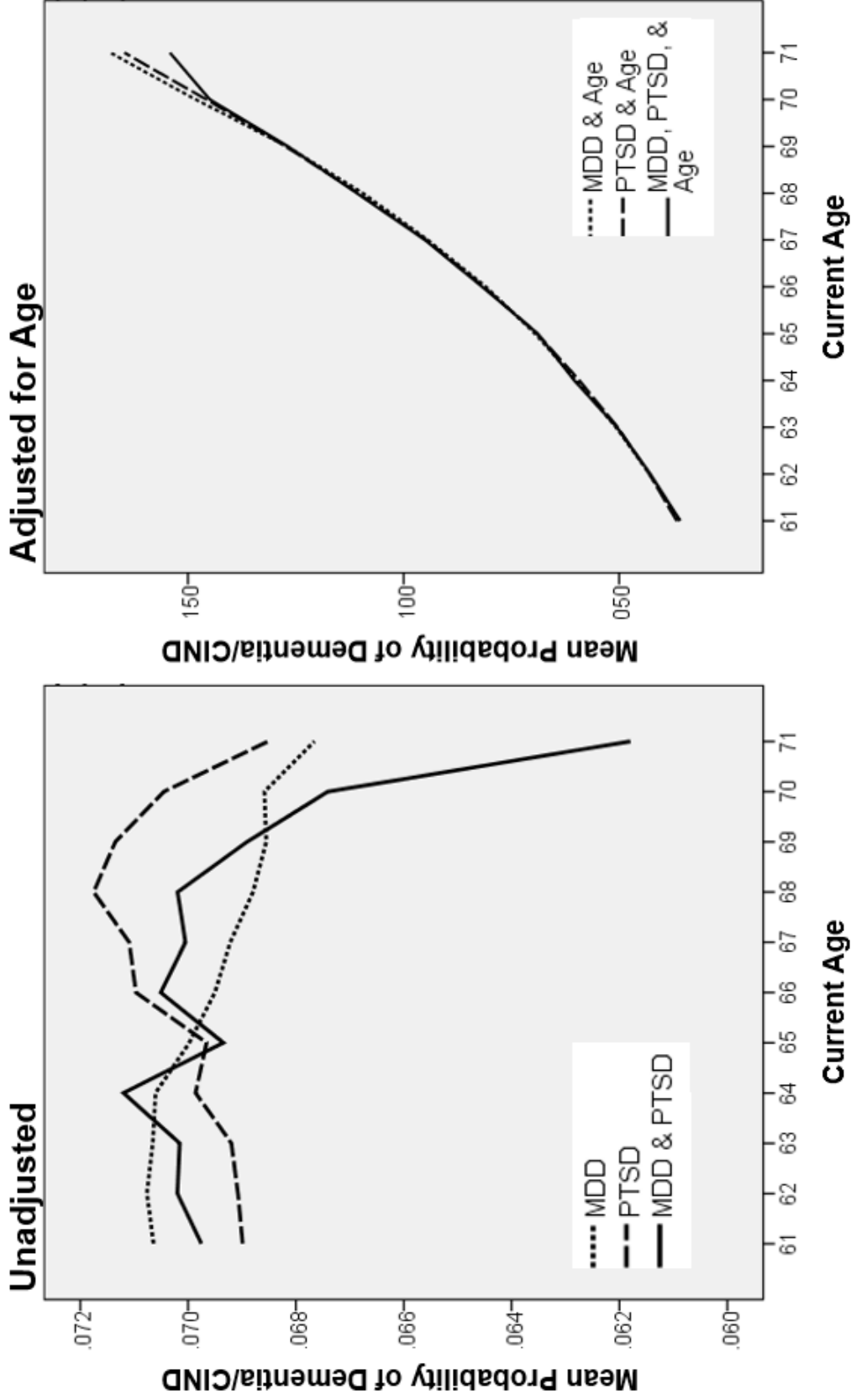


Figure 3. Comparison of Risk of Dementia/CIND (mean predicted probabilities) based on MDD/PTSD History by Logistic Regression Models Adjusted and Unadjusted for Current Age.

Risk of Dementia/CIND based on Sex and Race

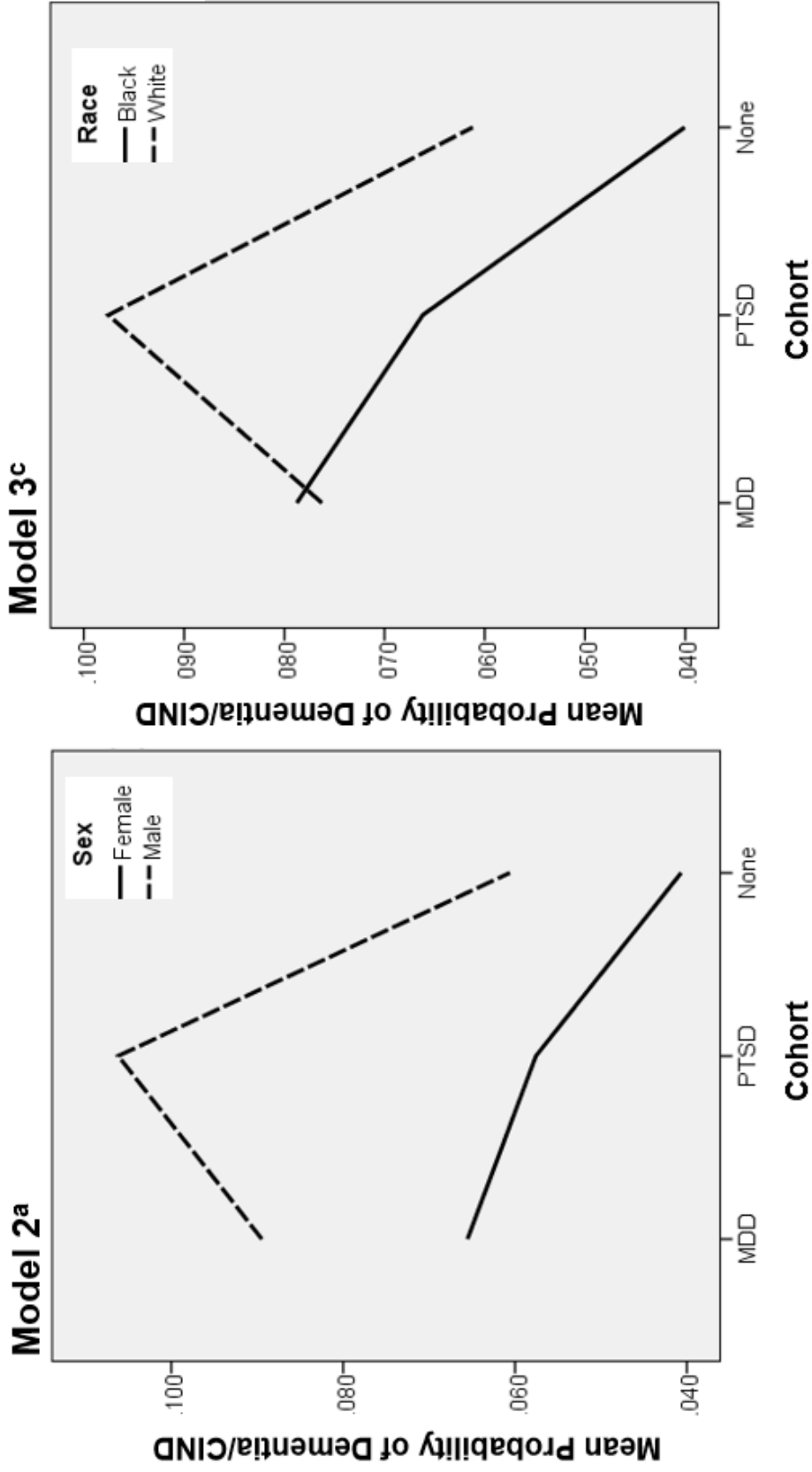


Figure 4. Risk of Dementia/CIND based on Sex and Race. Model 2^a predictors = CurrentAge, MDD, PTSD, and Sex (see Table 8). Model 3^c predictors = CurrentAge, MDD, PTSD, Race, and Race*MDD (see Table 9).

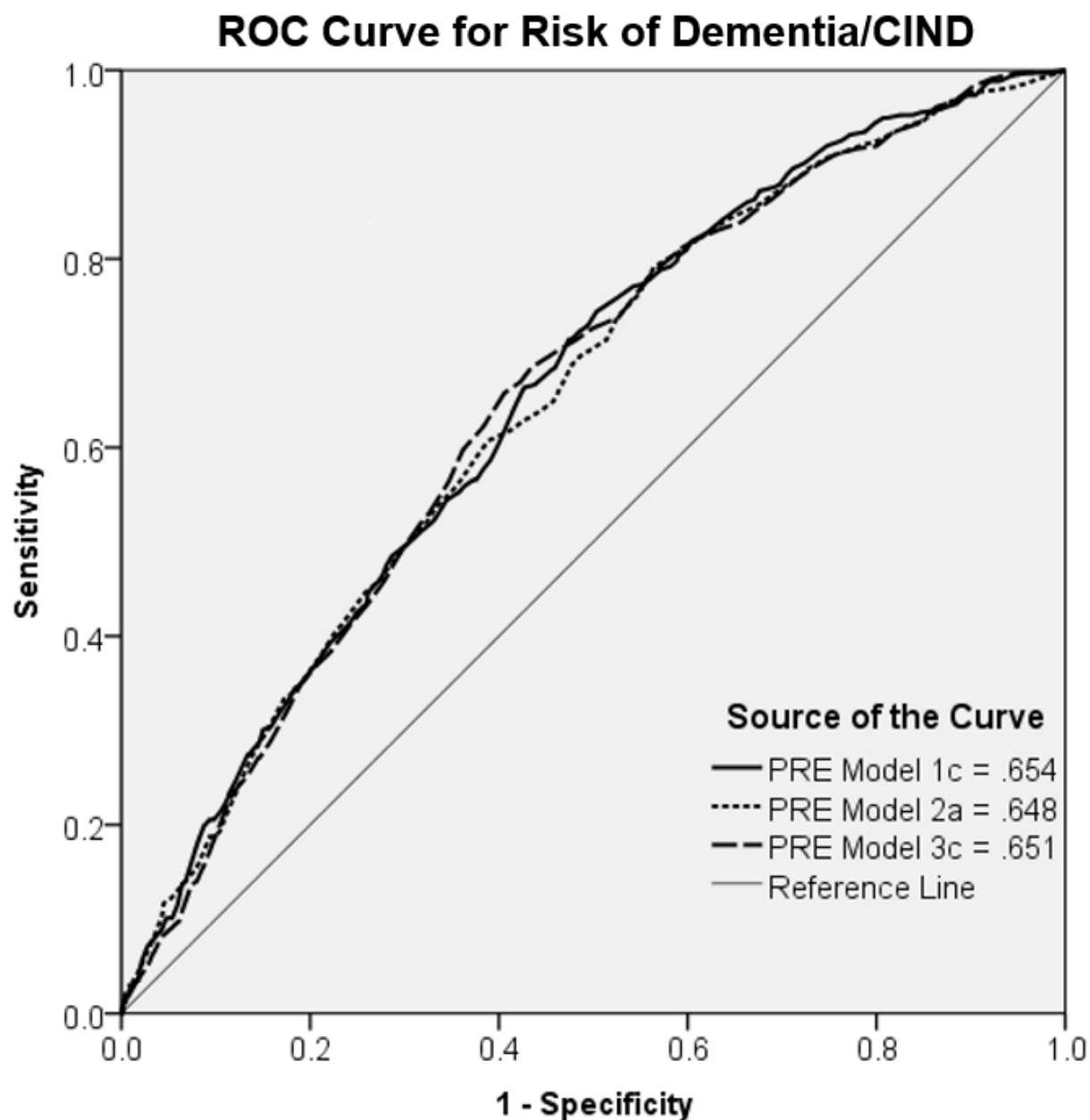


Figure 5. Receiver Operating Characteristic (ROC) Curve for Risk of Dementia/CIND (diagnosed at age > 55) based on Logistic Regression Models 1^c, 2^a, and 3^c. Model 1^c (Table 7) variables = CurrentAge, MDD, PTSD, Sex, Race, and Race*MDD. Model 2^a (Table 8) variables = CurrentAge, MDD, PTSD, and Sex. Model 3^c (Table 9) variables = CurrentAge, MDD, PTSD, Race, and Race*MDD.

Appendix A

ICD-9 Dementia and Cognitive Impairment Not Demented (CIND) Codes and Descriptions

290.00 Senile dementia, uncomplicated	310.10 Senility with mental changes of nonpsychotic severity
290.10 Presenile dementia, uncomplicated	310.80 Mild memory disturbance
290.11 Presenile dementia, with delirium	310.89 Mild memory disturbance, not amounting to dementia, associated with senile brain disease (other specified nonpsychotic mental disorders following organic brain damage)
290.12 Presenile dementia, with delusional features	323.90 Leukoencephalopathies
290.13 Presenile dementia, with depressive features	331.00 Alzheimer's disease
290.20 Senile dementia, with delusional features	331.10 Frontotemporal dementia
290.21 Senile dementia, with depressive features	331.11 Pick's Disease
290.30 Senile dementia, with delirium	331.19 Other frontotemporal dementia
290.40 Vascular dementia, uncomplicated	331.20 Senile degeneration of brain
290.41 Vascular dementia, with delirium	331.80 Other cerebral degeneration
290.42 Vascular dementia, with delusions	331.82 Dementia with Lewy bodies
290.43 Vascular dementia, with depressed mood	331.83 Mild cognitive impairment, so stated
291.10 Wernicke-Korsakoff syndrome (alcoholic)	331.89 Other cerebral degeneration
291.20 Alcohol-induced persisting dementia	331.90 Cerebral degeneration unspecified
292.82 Drug-induced persisting dementia	388.00 Degenerative and vascular disorders, unspecified
294.00 Persistent mental disorders due to conditions classified elsewhere	437.00 Cerebral atherosclerosis
294.10 Dementia in conditions classified elsewhere, without behavioral disturbance	437.10 Other generalized ischemic cerebrovascular disease
294.11 Dementia in conditions classified elsewhere, with behavioral disturbance	437.20 Hypertensive encephalopathy
294.20 Dementia, unspecified, without behavioral disturbance	437.80 Other ill-defined cerebrovascular disease
294.21 Dementia, unspecified, with behavioral disturbance	437.90 Unspecified cerebrovascular disease
294.80 Persistent Mental Disorders Due to Conditions Classified Elsewhere, Other; Amnesic Disorder NOS, Dementia NOS	438.00 Late effect of cerebrovascular disease, cognitive deficits
294.90 Other specified mental disorders due to known physiological condition; Cognitive Disorder NOS	780.83 Memory loss
	797.00 Senility without mention of psychosis
	799.55 Frontal lobe and executive function deficit
	799.59 Other signs and symptoms involving cognition

Appendix B

ICD-9 Major Depressive Disorder (MDD) and Posttraumatic Stress Disorder (PTSD)
Codes and Descriptions

- 296.2 Major depressive affective disorder, single episode, unspecified degree
- 296.21 Major depressive affective disorder, single episode, mild degree
- 296.22 Major depressive affective disorder, single episode, moderate degree
- 296.23 Major depressive affective disorder, single episode, severe degree, without psychotic behavior
- 296.24 Major depressive affective disorder, single episode, severe degree, specified as with psychotic behavior
- 296.25 Major depressive affective disorder, single episode, in partial or unspecified remission
- 296.26 Major depressive affective disorder, single episode, in full remission
- 296.3 Major depressive affective disorder, recurrent episode, unspecified degree
- 296.31 Major depressive affective disorder, recurrent episode, mild degree
- 296.32 Major depressive affective disorder, recurrent episode, moderate degree
- 296.33 Major depressive affective disorder, recurrent episode, severe degree without psychotic behavior
- 296.34 Major depressive affective disorder, recurrent episode, severe degree, specified as with psychotic behavior
- 296.35 Major depressive affective disorder, recurrent episode, in partial or unspecified remission
- 296.36 Major depressive affective disorder, recurrent episode, in full remission

- 309.81 Post-traumatic stress disorder, acute
- 309.81 Posttraumatic stress disorder, brief
- 309.81 Posttraumatic stress disorder, chronic