

8-2014

DETECTION OF DEMENTIA RISK IN PRIMARY CARE: PRELIMINARY INVESTIGATION OF A COMPOSITE DEMENTIA RISK SCORE IN VETERANS

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Abstract

Dementia is becoming a significant public health concern as the United States population rapidly ages. Veterans, accounting for a substantial portion of the United States population, may be at even higher risk for developing dementia as they generally have more risk factors for dementia than the general population. The current study sought to develop a modifiable composite dementia risk score, based on routinely gathered data from the primary care setting, that would predict an individual's risk for developing dementia in 10 years. A composite risk score—based on age, hypercholesterolemia, hypertension, current smoking, alcohol use disorder, and pulse pressure—was created using 10 years of Veterans' electronic medical record information. The predictive accuracy of the composite risk score was in the “good” range (AUC = 0.78) and less conservative estimates were even more accurate (AUC=0.85). The sensitivity was 50% and the specificity was 80%. This risk score is the first composite dementia risk score created for Veterans and provides optimism for future research in this area. Once further validated, this type of risk score could be seamlessly introduced into the primary care setting where its components are usually available. This type of assessment holds promise of being a considerable step forward in the prevention or delay or dementia onset in a rapidly aging Veteran population.

DETECTION OF DEMENTIA RISK IN PRIMARY CARE:
PRELIMINARY INVESTIGATION OF A COMPOSITE DEMENTIA RISK SCORE IN
VETERANS

by

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Dissertation

Submitted in partial fulfillment of the requirements for the degree of
Doctor of Philosophy in Clinical Psychology.

Syracuse University
August 2014

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Acknowledgments

First, I would like to thank my soon-to-be wife, Jaimie, for being by my side throughout this entire process (and for saying “yes”). Next, I could not have survived this journey without the guidance of Dr. Randall Jorgensen. Special thanks to Dr. Dominic Carone for believing in me not only as a person but also in my potential as a neuropsychologist. I owe a thank you to my fellow graduate cohort for being a much needed source of laughter throughout graduate school. Furthermore, thanks to Drs. Jennifer Funderburk, Laura Wray, and Christina Vair for their help navigating the VA and to the members on my dissertation committee, Drs. Stephen Maisto, Joseph Ditre, Kevin Antshel, Kevin Heffernan, and Peter Vanable. Last, I would like to thank my mother for teaching me the value of hard work, my brothers for teaching me how to take criticism, my grandmother—who was always my biggest fan—and the Shapiro’s for their encouragement and interest in my career.

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Detection of Dementia Risk in Primary Care: Preliminary Investigation of a Composite Dementia Risk Score in Veterans

The Alzheimer's Association (2012A) estimated that 13.9% of people over the age of 70 in the United States have dementia. Dementia is defined in the DSM IV-TR (American Psychiatric Association, 2000) as a disorder that is "characterized by the development of multiple cognitive deficits (including memory impairment) that are due to the direct physiological effects of a general medical condition, to the persisting effects of a substance, or to multiple etiologies." The DSM 5 (American Psychiatric Association, 2013) has redefined dementia as "major neurocognitive disorder," although the key features of severely impaired cognition remain largely the same (Silverman, Zigman, Krinsky-McHale, Ryan, & Schupf, 2013). The most common type of dementia is Alzheimer's disease, which accounts for approximately 60% to 80% of cases, and vascular dementia is the second most common type among at least 10 subtypes of dementia (Alzheimer's Association, 2013A).

The prevalence of dementia in Americans is expected to further increase as the United States population ages in the coming years (Alzheimer's Association, 2012A). Dementia has been described as the modern epidemic of later life and has replaced cancer as the most feared diagnosis by older adults (Bond & Corner, 2001). The number of people with Alzheimer's disease over the age of 65 may nearly triple from 5 million to as many as 16 million by 2050, barring the development of medical breakthroughs to prevent, slow or stop the disease (Alzheimer's Association, 2014). Veterans comprise a significant portion of the United States population with dementia, as over 750,000 Veterans were found to have dementia in 2005 (Krishnan et al., 2005), and this number is expected to increase as Veterans age in the coming years (Figure 1). Veterans may be more at risk for developing dementia due to a combination of

factors including higher likelihood of traumatic brain injuries (Barnes et al., 2011), Post Traumatic Stress Disorder (PTSD; Yaffe et al., 2010), and poorer general health (Agha, Lofgren, VanRuiswyk, & Layde, 2000). Approximately 9 million Veterans are enrolled in the Department of Veterans Affairs (VA) healthcare system and the typical Veteran is rapidly approaching 65 years of age (Department of Veterans Affairs, 2012). Consequently, assessing risk for dementia in Veterans through primary care is an intervention that may contribute to the reduction and/or delay the incidence of dementia in this population (Wilson, Ritchie, Peters & Ritchie, 2011).

Veterans generally have an abundance of risk factors for dementia, making them an important population for the further study of dementia risk (Department of Veterans Affairs, 2012). Moreover, Veterans account for approximately 7% of the entire United States population (Martinez & Bingham, 2011), and the VA (2012) projects that 39% of Veterans will be over the age of 65 and 72% will be over the age of 50 by the year 2036; that is, a considerable number of Veterans will be in the age range that is most associated with dementia diagnosis. Thus, the assessment of dementia risk in Veterans is paramount to the health of a large portion of the aging population in the United States.

Because there is currently no curative treatment for dementia, researchers have focused on methods for early identification and prevention (Kivipelto et al., 2006; Reijmer et al., 2011). These models have attained moderate success using cardiovascular risk factors as predictors for dementia risk; however, research suggests that more risk factors need to be considered and that this type of risk score needs to be validated in other populations (Kivipelto et al., 2006; Reijmer et al., 2011). The risk factor approach has been used to detect undiagnosed dementia in older age (e.g., Wray, Wade, Beehler, Hershey, & Vair, 2013) and to estimate the risk of dementia in midlife (e.g., Coibica, Padurariu, Bild, & Stefanescu, 2011; Debette et al., 2011; Kivipelto et al.,

2006; Reijmer et al., 2011). Recently, Wray and colleagues (2013) evaluated a novel dementia detection paradigm for Veterans over 70 years of age using information from the electronic medical record (EMR). They found that increased utilization of hospital and clinic services (e.g., number of ER visits and history of stroke) were associated with increased detection of dementia. Still, this study was limited in that it focused on detection of existing undiagnosed dementia and did not provide information about the incidence of new dementia within the population (Wray et al., 2013). Although this is an effective endeavor in the management of existing dementia, it does not account for the projected increase in the incidence of dementia in the aging Veteran population. Thus, the Veteran population provides an ample opportunity to assess for dementia risk in a younger population before they start to show signs of the disease. This type of early detection of dementia could significantly prevent crises on both the public health and individual family levels, facilitate adjustment to dementia risk and diagnosis, and provide access to treatments and support (Woods et al., 2003).

Numerous risk factors for dementia have been previously considered. A risk factor is defined as such when its presence, compared with a similar individual without such a factor, causes an increased risk of incurring a certain negative event (Inzitari, 2003). Specifically, modifiable risk factors for cardiovascular disease, such as hypertension and high cholesterol, have been shown to be risk factors for dementia as well (DeBette, 2010; Knopman, 2001). In 2010, the National Institute of Health Conference concluded that there is a need for validated modifiable risk factors to reduce the incidence of dementia (Román, Nash, & Fillit, 2012). With this in mind, the current study sought to determine the optimal method of dementia risk assessment in Veterans under the age of 70 using modifiable (i.e., factors that can be changed or

improved in some way) and routinely collected data (i.e., information that is regularly collected at a primary care visit) before they reach the average age of dementia diagnosis.

Nonmodifiable risk factors for dementia do not allow an individual to reduce their risk for dementia by directly addressing the risk factor itself and are often expensive and time-intensive. Thus, a focus on modifiable risk factors would allow for a reduction of specific dementia risk factors based on routinely gathered and cost-effective methods. Only four previous studies have explored a composite dementia risk score that uses at least some modifiable risk factors; of these four studies, all of which involved the general population, two of the studies used the same risk score paradigm (Kivipelto et al., 2006; Reijmer et al., 2011) and two of them used a combination of modifiable and nonmodifiable risk factors (Barnes et al., 2009; Jessen et al., 2011). Individual cardiovascular risk factors have been associated with dementia on their own, and a clustering of these risk factors may contribute to dementia in an additive or synergistic manner that further augments dementia risk (Pronk et al., 2004; Reijmer et al., 2011). Kivipelto and colleagues (2006) used several modifiable cardiovascular risk factors to create a risk score for dementia. In addition, they employed a second model that added a nonmodifiable (Apolipoprotein ϵ 4 (ApoE4) genotype) risk factor in addition to modifiable cardiovascular risk factors. Jessen and colleagues (2011) used a similar model with a mix of nonmodifiable (family history of dementia and ApoE4) and modifiable risk factors (depression, activities of daily living, smoking status). Variables in a risk score that are not routinely gathered, such as genetic testing for the ApoE4 allele, are not only expensive but are also more difficult to generalize to a large group of patients due to logistical concerns (e.g., labs readily available to conduct large numbers of assays). The purpose of the current study was to create a composite dementia risk

score based on solely modifiable and routinely gathered variables in the Veteran population, which has previously not been researched.

The current study attempted to create a composite dementia risk score by employing a set of modifiable, non-laboratory-based cardiovascular risk factors that are prevalent in Veterans including: hypercholesterolemia diagnosis, hypertension diagnosis, current cigarette smoking, pulse pressure, and alcohol use disorder diagnosis; age was the only non-modifiable risk factor due to its predictive importance and to be consistent with the literature. This model was created using over ten years of health information from EMRs in the VA database. In the following sections, I will discuss the distinction between laboratory- and non-laboratory-based methods for dementia risk assessment. In the course of focusing on simple and efficient risk assessment in Veterans, both empirical and theoretical rationales will be presented to support the creation of a dementia risk score using modifiable, non-laboratory-based risk factors. In a review of the recent literature, I will highlight (a) the associations between various individual cardiovascular risk factors and dementia, (b) the predictive importance of an additive combination of these risk factors, and (c) the prediction of dementia from psychosocial risk factors (e.g., depression) that are common in the Veteran population. Finally, the specific importance of these risk factors in Veterans will directly lead to my expectations for the current study: namely, that (a) risk factors for dementia including age, diabetes mellitus, hypercholesterolemia, body mass index, blood pressure, pulse pressure, smoking, depression, and alcohol use disorder can be combined to create a single composite risk score; and (b) that this composite risk score computed before the age of 70 will subsequently predict diagnosis of dementia 10 years later.

Dementia and Cardiovascular Risk

There are at least eight diseases and syndromes that account for several types of dementia. Alzheimer's disease (AD) is the most common type of dementia, as it is estimated to account for between 60 and 80% of dementia cases (Alzheimer's Association, 2013A). Still, dementia can arise from various etiologically and neuropathologically distinct disorders and reflect diverse patterns of cognitive impairment (Weintraub, Wicklund, & Salmon, 2012). Vascular dementia, previously known as multi-infarct or post-stroke dementia, accounts for approximately 10% of dementia cases and is more directly related to cardiovascular variables as it is often caused by vessel bleeding or blockage in the brain. While AD and vascular dementia were exclusionary differential diagnoses in the past, pathologic evidence has shown that the two can occur simultaneously. Recent evidence from long-term observational studies and autopsy studies has shown that many individuals with dementia often have more than one type of dementia, referred to as "mixed dementia," (combination of Alzheimer's disease and Vascular Dementia) which is commonly found in older individuals (Alzheimer's Association, 2013A).

Román, Nash, and Fillit (2012) suggest that differentiation between the different types of dementia is not necessary when considering dementia risk because most cases are probably a form of vascular dementia or mixed dementia, and thus the risk factors will overlap. They advocate for a broader view in dementia risk assessment and propose that a risk score based on cardiovascular risk factors can be beneficial in preventing heart disease, stroke, and dementia concurrently. The two most common forms of dementia, Alzheimer's disease (AD) and vascular dementia (VaD), share common changes in macro- and microvasculature in the brain that may develop from cardiovascular risk factors (Román, Nash, & Fillit, 2012). Among others, they

reported that hypertension (high blood pressure), hyperlipidemia (high cholesterol) and cigarette smoking are risk factors that can lead to these abnormalities (Román, Nash, & Fillit, 2012).

Strong evidence has emerged for the association between risk factors for cardiovascular disease and the development of dementia over time (Bangen et al., 2010; Knopman, Mosley, Catellier, & Coker, 2009; Román, 2005; Tolppanen, Kettunen, Ahonen, Soininen, & Hartikainen, 2013). Although dementias such as Alzheimer's disease have been frequently linked to individual cardiovascular risk factors, treatments have been relatively ineffective (Qiu, 2012). Qiu (2012) suggests that a multifactorial treatment and prevention strategy might improve intervention efforts. Several studies (e.g., Coibica, Padurariu, Bild, & Stefanescu, 2011; Seshadri et al., 2004) have shown associations between composite cardiovascular risk scores, which are a multifactorial combination of individual cardiovascular risk factors, and dementia. Among these risk factors are blood pressure, BMI, cholesterol, cigarette smoking, and age, which are known to be associated with impaired cognitive functioning.

There are two main routes that can be followed to determine an individual's risk for dementia: laboratory-based methods (e.g., Magnetic Resonance Imaging (MRI), evoked potentials, genetic testing) and non-laboratory-based methods [e.g., body mass index (BMI), cigarette smoking, and hypertension].

Laboratory-based methods. Several biomarkers, including event-related potentials, MRI, genetic testing, and biochemical tests, have been proposed in the prediction of dementia (e.g., Armstrong et al., 2014; Chapman et al., 2011; Dickerson et al., 2011). For example, event-related potentials in the brain have been utilized to predict which individuals with Mild Cognitive Impairment (a possible precursor to dementia) will develop Alzheimer's disease (AD) with fairly good (88%) accuracy (Chapman et al., 2011). A similar model correctly classified

92% of the subjects in the study into either the AD group or the control group with a sensitivity of 1.00 using event-related potentials during a cognitive task (Chapman et al., 2007). In addition to event-related potentials, other biomarkers for dementia in the brain have been found using MRI (Dickerson et al., 2011). Biochemical markers (e.g., beta-amyloid ratios) and genetic markers (e.g., ApoE4 genotype) have been found to be associated with dementia as well (Koyama et al., 2012; Miller, 2012). Pharmacological advancements have been made with drugs such as memantine (Namenda) and donepezil (Aricept) to treat *symptoms* of Alzheimer's disease (Bland, 2012), but there has not been any significant advancement in ceasing its onset or risk assessment that points to earlier intervention efforts. Furthermore, researchers have recently tested a computerized dementia screening tool that can be used by people to self-administer their own dementia screening at home by completing a clock drawing task (Kim, Hsiao, & Do, 2012).

While these are helpful contributions to those immediately at risk for dementia, interventions at this stage may be too late to significantly aid in the reduction of Alzheimer's disease overall (Alzheimer's Association, 2012B). Similarly, screening methods for detecting current dementia have been shown to be relatively accurate, but a recent systematic review offered that there is little evidence for overall improved outcome in these cases (Lin, O'Connor, Rossom, Perdue, & Eckstrom, 2013). Consequently, a blood test for the differential diagnosis of Alzheimer's disease is in the early stages of development, which would be an important step in preventing Alzheimer's disease before its onset (Goldknopf, Park, & Sabbagh, 2012). Despite the relative success that the above laboratory risk factors have had in determining dementia risk, they are not practical for the use in a risk score for a large-population due to high cost in time and money and the invasive nature of the assessments. In an effort to focus on more cardiovascular and lifestyle risk factors that are routinely collected, some researchers have been

moving toward a focus on modifiable risk factors for dementia such as arterial stiffness (Pase, 2012). While these methods are an improvement in that they are modifiable, they are still not regularly gathered in a primary care setting and, consequently, are less optimal components of a risk score than are non-laboratory-based factors.

Non-laboratory-based risk factors.

Non-laboratory-based risk factors for dementia are appropriate for use in a risk score that will be applied to a large population due to their wide availability and ease of communication (Koopman & Mainous, 2008). For example, the interpretation of risk factors is thought to be best understood when simple numbers can be communicated to patients by health care providers (Paling, 2003). Thus, when a patient is presented with numerical findings such as a blood pressure reading, they may be able to more effectively understand these results than the more complex data from an MRI. In addition to cardiovascular risk factors, evidence has been emerging for psychosocial risk factors for dementia, including depression. The combination of these cardiovascular and psychosocial risk factors may be important in creating a dementia risk score for Veterans, who generally possess an abundance of risk factors for cardiovascular disease and dementia (Department of Veterans Affairs, 2012). Interestingly, Kester and colleagues (2014) recently published data that suggest that the combination of small vessel disease with vascular risk factors is likely to be a mechanism that leads to Alzheimer's disease. The following subsections outline the role of individual cardiovascular and psychosocial risk factors for dementia.

Blood pressure. Epidemiological studies have shown an association between chronic high blood pressure and dementia (Feldstein, 2012; Yasar et al., 2013). Aside from its own relation to dementia, some researchers assert that high systolic blood pressure (SBP) may interact

with other risk factors and be the driving force in the association between cardiovascular risk and dementia (Zade et al., 2010). A longitudinal study showed that SBP was inversely related to cognitive test scores that are commonly used to diagnose dementia; as SBP increased, cognitive test scores decreased (Knopman, Mosley, Catellier, & Coker, 2009). Low SBP has also been shown to be a protective factor in the development of dementia; Knopman and colleagues (2001) found that those with the lowest SBP had the slowest cognitive decline over time.

Along with SBP, high diastolic blood pressure (DBP) has been associated with the diagnosis of dementia as well. Shah and colleagues (2012) have noted an association between high DBP and beta-amyloid plaques, which are commonly associated with Alzheimer's disease. They suggest that high midlife DBP may modulate the subclinical changes that eventually lead to dementia (Shah et al., 2012). Even slightly high blood pressure (categorized as prehypertension) may lead to cerebrovascular changes and increase risk for stroke (Huan et al., 2014). Mechanistically, hypertension has been shown to alter the vasculature in the brain by vascular remodeling, impaired cerebral autoregulation, cerebral microbleeds, white matter lesions, unrecognized lacunar infarcts, and Alzheimer's-like plaques (Manolio, Olson, & Longstreth Jr., 2003).

High blood pressure is known to be more prevalent in Veterans than the general population (Department of Veterans Affairs, 2012). According to the Department of Veterans Affairs, 34.5% of Veterans endorsed that they received treatment for high blood pressure (Department of Veterans Affairs, 2001). Preliminary reports from a longitudinal study by the VA are suggesting that Veterans may age faster, in terms of physical changes, and develop problems such as high blood pressure sooner than the general population (Zoroya, 2012). With this in mind, blood pressure is an especially important risk factor for dementia in Veterans.

Pulse Pressure. DBP and SBP are related in a measure known as pulse pressure, which is calculated by SBP minus DBP. Pulse pressure is often utilized as a conventional measure of vascular or arterial stiffness; it is technically a consequence of vascular stiffness, which refers to the loss of elasticity in the vasculature of the circulatory system due to mechanical stress (Mattace-Raso et al., 2006). When pulse pressure is high, the difference between systolic and diastolic blood pressure creates a larger degree of stretching in the elastin of the arteries, which makes them more susceptible to vascular-related events such as stroke. Pulse pressure offers additional information above that obtained from standard blood pressure because of its associations with cardiovascular diseases, such as arterial stiffness and severe atherosclerosis (Qiu, Winblad, Viitanen, & Fratiglioni, 2003). As such, high pulse pressure has been linked to cardiovascular disease (Cockcroft et al., 2005) and dementia (Freitag et al., 2006; Qiu et al., 2003). Research suggests that atherosclerosis and dementia may share common underlying mechanisms that lead to deterioration of brain matter and functioning (Dolan et al., 2010). For this reason, pulse pressure may be a simple and effective component of a dementia risk score along with measures of SBP and DBP.

Diabetes. The literature has highlighted diabetes and hypertension as the two modifiable risk factors that have the greatest impact on cognition (Knopman et al., 2009). These two risk factors have been associated with cognitive deficit even in persons with subclinical symptoms who have not yet experienced clinical signs of stroke or dementia (Elias et al., 2004).

Longitudinal studies have shown that diabetes and hypertension are the most strongly correlated CRFs with poor cognition (Zade et al., 2010) and future cognitive decline (Wadley et al., 2007).

Diabetes has been shown to be a risk factor for cognitive decline in those younger than 58 years old (Knopman et al., 2001) and in elderly diabetics (Knopman et al., 2001; Maineri et al.,

2007), and has been shown to be linked to dementia in general (Carvalho, Katz, Dutta, Katakam, Moreira, & Busija, 2014; Wang et al., 2014). It is estimated that over 18 million Americans have diagnosed diabetes mellitus (8% of adult Americans), not to mention an additional 7 million Americans that are estimated to have undiagnosed diabetes (Roger et al., 2011). Furthermore, diabetes has been linked to impairment in memory (Maineri, Xavier, Berleze, Moriguchi, 2007) and executive function (Knopman et al., 2009), among others. Aside from its direct relationship to cognition, Fotuhi, Do, and Jack (2012) recently used biological evidence to show that diabetes is among eight other modifiable risk factors (e.g., hypertension) that are associated with smaller hippocampi (the brain region commonly associated with memory) and subsequent cognitive decline. This study suggested that treatment of a constellation of risk factors could be most effective in reducing the impact of these risk factors (Fotuhi, Do, & Jack, 2012). Furthermore, individuals with Type II diabetes have been shown to be more susceptible to the genetic risk factors (viz. ApoE4 allele) that underlie Alzheimer's disease and may put the individual at higher risk for cerebral infarcts and stroke (Peila, Rodriguez, & Launer, 2002).

Body Mass Index (BMI). BMI, calculated as the ratio of an individual's height and weight, is a type of risk score on its own that classifies people into categories such as normal weight (18.5 – 25), overweight (25-30), and obese (>30; Centers for Disease Control and Prevention, 2011). BMI provides an indirect measurement of adiposity, which is strongly correlated with total body fat (Xu et al., 2011).

Several studies have shown that as the BMI has a linear relationship with the probability of dementia; as BMI increases, dementia risk increases (Chang, Won, Lee, Kim, & Kweon, 2012; Whitmer, Gunderson, Queensberry, Zhou, & Yaffe, 2007). BMI may negatively affect the brain by increasing the risk for cardiovascular diseases as described above and may affect brain

development and survival on its own (Gustafson, 2008). A recent study showed that risk for dementia increased by over twofold in those with BMI in the overweight or obese ranges (Chang, Won, Lee, Kim, & Kweon, 2012). Numerous studies have classified the typical Veteran enrolled in their research studies as “obese” based on BMI (Anderson et al., 2011; Vieweg et al., 2006). This evidence for higher average BMI in Veterans suggests that Veterans are at higher risk for cardiovascular disease and dementia than the general US population. BMI, as an indirect measure of adiposity, may cause damage associated with dementia through the same mechanism as hypercholesterolemia (i.e. high cholesterol; Schröder et al., 2003).

Hypercholesterolemia. Hypercholesterolemia is defined as a plasma cholesterol level greater than 250 mg/dL (6.5 mmol/L) or greater than 193 mg/dL (5.0 mmol/L) in case of a previous myocardial infarction (Pinto-Sietsma et al., 2003). As a group, Veterans have been shown to be more likely to have elevated cholesterol than the general population (Hoerster et al., 2012). Cholesterol levels have been shown to be higher in those with Alzheimer’s disease than those without the disease, even after adjusting for the ApoE4 allele. Furthermore, the use of statin drugs, which lower total cholesterol, has been shown to slow hippocampal volume reduction and improve cognitive functioning (Sparks et al., 2008). Mechanistically, cholesterol is essential for numerous mechanisms in the brain. For example, cholesterol is used to transport Apolipoprotein E and cholesterol synthesis has been shown to modulate β -amyloid in cells, both of which are strongly associated with Alzheimer’s disease (Wolozin, 2004).

Cigarette smoking. Cigarette smoking has been shown to double an individual’s risk for dementia (Gons et al., 2011). Cigarette smoking has been associated with cognitive decline in numerous studies (Debette et al., 2011; Elias et al., 2005; Smith et al., 2007). Smoking has been linked to neuropsychological deficits (e.g., Debette et al., 2011) and white matter changes in the

brain (Gons et al., 2011; van Dijk et al., 2008) that are common in dementia. While a cardiovascular risk factor in itself, smoking may also cause negative effects that interact with other cardiovascular risk factors to lead to worse cognition over time (Duron & Hanon, 2008). While approximately 20% of Americans over the age of 20 currently smoke cigarettes (Roger et al., 2011), smoking rates are higher for those in the military than the general population (Joseph, Muggli, Pearson, & Lando, 2005; Smith et al., 2008). A recent survey of Veterans indicated that 64% smoked at least 100 cigarettes in their lifetime and almost half of them currently smoke (Department of Veterans Affairs, 2010).

Alcohol Use Disorder. Alcohol Use Disorder is defined in the DSM 5 (American Psychiatric Association, 2014) by a cluster of symptoms including bingeing, difficulty cutting down, large amount of time spent drinking, craving, failure to fulfill major roles due to use, continued use despite consequences, important social, occupation, or recreational dysfunction, recurrent use in hazardous situations, tolerance (i.e. need for markedly increased amounts or diminished effect with the same amount), and withdrawal. Alcohol can lead to its own specific form of dementia known as Korsakoff's syndrome, which involves short-term memory loss primarily due to the deterioration of the mammillary bodies due to extensive alcohol consumption (Kril & Harper, 2012). In addition, extensive alcohol use may lead to other forms of dementia by causing white and grey matter volume loss and complementary increase in cerebrospinal fluid volumes (Pfefferbaum et al., 1995). The resulting neuroanatomical damage caused by alcoholism has also been shown to improve in former alcoholics practicing abstinence (Bartsch et al., 2007; Pfefferbaum et al., 1995). Similar to other risk factors for dementia, Veterans have been shown to be more likely to have extensive alcohol use than the general population (Substance Abuse and Mental Health Services Administration, 2001).

Age. Some degree of cognitive decline is expected in all humans through the normal aging process (Gossard, 2012; Starr, Deary, Inch, Cross, & MacLellan, 1997). Still, age is a significant risk factor for cardiovascular disease on its own and may interact with other risk factors for dementia (Elias et al., 2005). For example, age has been shown to attenuate the body's resistance to other risk factors and amplify the effects of those risk factors more than would be expected through normal aging alone. Age is generally proposed as a moderating risk factor for cognitive decline (Panza et al., 2006). While age is not necessarily modifiable, earlier interventions at midlife may lead to better outcomes for the incidence of dementia. Currently, the Veteran population is aging as a whole and may be more at risk for dementia (Department of Veterans Affairs, 2012).

Depression. Depression (viz., Major Depressive Disorder and related diagnoses) is associated with both cardiovascular risk (Suls & Bunde, 2005) and dementia risk (Ohanna, Golander, & Barak, 2011). In this case, "depression" refers to the diagnoses of a depressive disorder and not simply depressed mood, which is the self-report of depressed feelings. The United States Preventive Services Task Force (2002) has suggested that depression be screened for on a routine basis in Veterans. On its own, depression has been linked to poorer neuropsychological performance and a higher risk for dementia. A 2001 meta-analysis showed that patients with a history of depression were shown to have twice the risk for developing dementia than those who were never diagnosed with depression (Ohanna, Golander, & Barak, 2011). The two most likely explanations were that 1) depression may be an early symptom of dementia, or that 2) depression may enhance the clinical manifestation of diseases that lead to dementia (Ohanna, Golander, & Barak, 2011).

The causal explanations that link depression and dementia are controversial (Ohanna, Golander, & Barak, 2011). The “vascular depression” hypothesis may provide an explanation for the link between depression, cardiovascular risk, and dementia. In this hypothesis, it is postulated that some aspect of vascular disease predisposes affected individuals to depression. It is possible that vascular disease is an intermediary between depression and dementia, while depression and cardiovascular risk factors may also work in synergy to lead to greater dementia risk (Bangen et al., 2010). Indeed, evidence for the interaction between cardiovascular risk factors and depression is continuing to develop. Bangen and colleagues (2010) reported that Alzheimer’s patients who were depressed had a higher degree of stroke risk than cognitively normal individuals. Moreover, stroke risk, based on a composite risk score made up of several cardiovascular risk factors, was more effective at differentiating between depressed and non-depressed Alzheimer’s patients (Bangen et al., 2010).

As a population, Veterans show a high incidence of depression (National Alliance on Mental Illness, 2009). Depression occurs in 10%-15% of the elderly over 65 years old in the general population, while 11% of Veterans over the age of 65 have the diagnosis of major depressive disorder (Petersen, 2011; Yen et al., 2007). Not only is depression the second-most common mental disorder among Veterans (second only to PTSD), but it is also suggested that depression is also under-diagnosed in Veterans (National Alliance on Mental Illness, 2009; Petersen, 2011). For these reasons, depression may be a risk factor for dementia that is especially important in Veterans.

Potential Utility of a Composite Dementia Risk Score in Veterans

The VA has endorsed the identification of cardiovascular risk factors in the past, including cholesterol, blood pressure, smoking, and obesity (Department of Veterans Affairs,

2008), along with similar programs to reduce cardiovascular risk factors are beginning to be implemented (Melnyk et al., 2013). As stated previously, this study's objective was to create a risk score for dementia in Veterans using modifiable, non-laboratory-based measures. A risk score based on these risk factors is beneficial for a number of reasons. First, non-laboratory-based risk factors are less costly, less invasive, and more likely to be understood by primary care providers and the general population, making dissemination of the risk score more efficient. Second, the use of modifiable risk factors will create an opportunity for individuals to determine their risk before the onset of clinical features and seek to lessen their risk over time. Third, dementia care is estimated to cost over \$42,000 per person (Hurd, Martorell, Delavande, Mullen, & Langa, 2013) and dementia has been shown to be significantly more expensive than many other diseases in a sample of Veterans, while the cost to treat hypertension was more than eight times less expensive (Yu et al., 2003). The stark difference in monetary cost to the VA shows that treatment of risk factors of dementia, such as hypertension, earlier in life are likely to be fiscally impactful later. Finally, 75% of all Veterans participated in wartime activities and served in the World War II, Korea, or Vietnam eras; of this 75%, 59% of them are approaching the average age of onset for dementia (Department of Veterans Affairs, 2012; Alzheimer's Association, 2012A). This trend is also apparent in Figure 1, as the population of Veterans over the age of 65 is expected to increase in the coming years.

Veterans are not only becoming older, but they also have a large number of cardiovascular risk factors shown to predict the development of dementia (Kivipelto et al., 2006) and are more likely than the general population to manifest a set of psychosocial risk factors for dementia (e.g., depression; Department of Veterans Affairs, 2010). In addition, they are served by the largest integrated healthcare system in the United States, which could benefit from a

readily available risk score to (a) serve as a marker for more intensive assessment (e.g., ApoE4 or formal cognitive testing) and (b) guide life style interventions towards modifiable risks in order to prevent or slow dementia onset (Axon, Gebregziabher, Echols, Gilbert, & Egede, 2011; Morgan, Teal, Reddy, Ford, & Ashton, 2005). Interventions based on lifestyle changes (viz. increased exercise and self-monitoring) have shown success in reducing cardiovascular risk in the Veteran population (Burke, Dunbar-Jacob, & Hill, 1997; Chapman et al., 2013). In fact, a recent paper by Naci and Ioannidis (2013) provided evidence that exercise and many drug interventions are often similar in their mortality benefits in the secondary prevention of numerous cardiovascular and cerebrovascular illnesses.

Again, due to a large target population of almost 9 million Veterans (Department of Veterans Affairs, 2012), efficient dementia risk assessment is vital. This assessment will be most efficiently calculated if it includes risk factors that are modifiable, routinely assessed for in primary care visits, and non-laboratory-based for ease of calculation, dissemination, and understanding. In addition, because this risk score is modifiable and can be easily calculated, interventions can take place earlier on in life before it is too late to impede the dementia process (Alzheimer's Association, 2012B). For Veterans, dementia is one of the most costly chronic conditions that is treated by the VA (Kunik, 2011). Veterans are an important population for the study of dementia risk because they are part of one of the largest integrated health care systems in the United States. The VA health care system offers more comprehensive health care benefits than Medicare and other managed plans in addition to special programs and long-term care. Despite these offerings, the VA health care system is not without weaknesses. For one, the economic burdens of a health care system that is utilized by millions of Veterans can be extensive and have been attributed to part of the problem with excessive wait times (Geiger,

2014). In 1999, the average cost of dementia for each patient in the VA was \$19,522 when costs for medical/surgical, inpatient services, outpatient services, and outpatient pharmacy were aggregated (Yu et al., 2003). More recent estimates show that the cost of treating Alzheimer's disease alone is \$100 billion annually (Krishnan et al., 2005). Thus, focus on risk detection and prevention of dementia at an earlier age may help lessen the economic burden of dementia on the VA health care system. Furthermore, although memory disturbances are the most common symptom associated with dementia, behavioral disturbances occur in 90% of individuals with dementia, which can be dangerous for both the patients and the caregivers (Kunik, 2011) and are often treated with expensive antipsychotic medications (Bradford et al., 2012). With this in mind, Veterans are an important population for the study of and interventions for dementia risk.

The National Prevention Counsel's (2011) proposition that healthcare providers should focus more on preventative medicine paves the way for the introduction of dementia risk scores that build upon multiple risk factors to create a single score. The transition away from single health risk factors may be more helpful because individuals often report experiencing multiple risk factors, as opposed to just one (Pronk et al., 2004). The ability to identify harmful risk factors is paramount to the early identification and treatment of disease in primary care settings. Over the past decade, government entities such as the United States Preventive Services Task Force (2003) and the National Prevention Counsel (2011) have urged primary care physicians to increase their focus on identifying risk factors for disease before they fully develop into more significant health problems. These risk factors, such as smoking and hypertension, are associated with cardiovascular disease and future cognitive decline. Although these factors are commonly assessed for or diagnosed by physicians, often little is done with the information beyond a medication regimen or frequent monitoring. With this in mind, the use of a single composite

score that delineates dementia risk could be extremely useful for primary care physicians to help their patients understand their risk and ways in which they can modify their lifestyle choices in order to reduce their risk.

An essential part of the Department of Veterans Affairs' mission is to improve the quality of healthcare for Veterans by integrated mental health services into primary care by including behavioral health prevention and treatment services. A recent meta-analysis (N=15,988) showed that risk perceptions should be integrated as core concepts in theories of health behavior change (Brewer et al., 2007). Furthermore, numerous theories of health behavior change such as the Health Belief Model and the Theory of Planned Behavior indicate that perception of risk and alteration of health beliefs can lead to significant positive behavior changes (Champion & Skinner, 2008; Montaña & Kasprzyk, 2008). The primary care setting brings an ability to reach a large number of Veterans, including the fact that many Veterans are seen routinely and their dementia risk scores could be monitored along with their cognitive status. Therefore, an area of importance is to develop a dementia risk score that is specific to the risk factors that are prevalent in the Veteran population. This study sought to determine modifiable and routinely gathered risk factors for dementia prior to the diagnosis of dementia in order to promote the integration of primary care and mental health and potentially leading to better overall health care for Veterans. This type of program is in line with the Primary Care–Mental Health Integration (PC-MHI) initiative outlined by the VA (Wray, Szymanski, Kearney, & McCarthy, 2012).

The Health Belief Model (HBM) has been one of the most widely used theories of health and behavior change since its origin in the 1950s. The HBM integrates several constructs in order to provide a guideline for optimal health behavior change. Individual perceptions of (a) susceptibility to a disease, (b) perceived benefits of change, (c) perceived barriers to change, and

(d) perceived ability to change (i.e. self-efficacy) underlie the decision process of the HBM. These four constructs lead to an individual's perceived threat and desire for change, thereby influencing their individual behaviors. Outside of these factors, there are "cues to action," which are strategies to activate "readiness" for change and can influence health behaviors (Champion & Skinner, 2008). Theoretically, a composite dementia risk score would function in various areas of the health belief model. Most simply, a dementia risk score would be a "cue to action" by promoting both awareness and optimism about the utility of certain health behavior changes. Furthermore, the use of risk factors that are better understood by a patient may aid in perceived susceptibility and self-efficacy, thereby improving health behavior change. For those with some knowledge about nonmodifiable dementia risk factors (e.g., family history or ApoE4 status), a composite dementia risk score based on cardiovascular variables may reduce some of the perceived barriers to change and increase the perceived benefits of such change.

Current State-of-the-Art in Dementia Risk Assessment

Dementia risk factors that are modifiable and routinely gathered in the primary care setting have been included in dementia risk scores alongside nonmodifiable biological risk factors. Several attempts to predict the risk of dementia have employed both nonmodifiable biological factors (e.g., ApoE4 genotype) and modifiable non-laboratory-based risk factors (e.g., BMI; Barnes et al., 2009; Jessen et al., 2011). In 2009, Barnes and colleagues attempted to develop a late-life dementia risk index that could accurately place older adults into low, moderate, or high risk of developing dementia within the next six years. They included modifiable non-laboratory based measures (alcohol consumption and BMI) along with nonmodifiable biological measures (MRI and internal carotid thickness). Their full model showed only slightly more accuracy (c statistic = 0.81) than the non-laboratory-based model of

Kivipelto and colleagues in 2006 (c statistic = 0.78). The c statistic is a measure of how well a predictive model can discriminate between observations at different levels of the model and is the same as the area under the receiver-operating characteristic (ROC) curve (LaValley, 2008). Based on these findings, they suggest that the simple risk factors employed in the Kivipelto et al. (2006) study may provide useful alternatives when time or resources are limited. Jessen and colleagues (2011) also attempted to create a model for predicting Alzheimer's disease risk. They included modifiable non-laboratory based risk factors (depression, activities of daily living, smoking status) and nonmodifiable risk factors (report of memory impairment, family history of dementia and education; Jessen et al., 2011). This model is more widely applicable because it does not include laboratory-based markers in the score; however, it is still not universally modifiable at midlife because family history is not always known and cannot be modified, and subjective memory complaints may present too late in the progression of the disease by the time that biobehavioral risk assessment is employed.

D'Agostino and colleagues (2008) have shown evidence that simpler models can be just as effective as more complex models of risk assessment in cardiovascular risk scores. In their study, they created a risk score for general cardiovascular disease with using both laboratory and non-laboratory risk factors. They determined that a simpler score using age, body mass index, systolic blood pressure, antihypertensive medication use, current smoking, and diabetes diagnosis performed reasonably well as compared to a more comprehensive model that used laboratory-based measures; the c statistic was 0.76 for the model containing cholesterol values and 0.75 for the model with BMI replacing cholesterol (D'Agostino et al., 2008). Along the same lines, because the purpose of a risk score is to aid the clinician in assisting with secondary prevention efforts, nonmodifiable risk factors are not as useful in a risk score for dementia

(Koopman & Mainous, 2008). This reasoning adds even more evidence for the improved efficiency that a risk score that is made up of modifiable, non-laboratory-based risk factors may achieve.

Many researchers are focusing on methods of dementia risk prediction that use non-laboratory methods, such as neuropsychological test scores (e.g., Reckess, Varvaris, Gordon, & Schretlen, 2013) or cardiovascular vital signs (e.g., Debette et al., 2011; Zade et al, 2010). As opposed to risk factors that are invasive or must be collected with special instrumentation in the lab context, researchers have outlined various modifiable non-laboratory-based risk factors for dementia that are routinely collected in the primary care setting and can be modified to reduce risk. While risk factors such as total cholesterol levels technically require a laboratory to determine test results, they are routinely collected in the primary care setting by drawing blood. With this in mind, “non-laboratory-based” in this study refers to risk factors that are routinely collected in the primary care setting and do not require nontraditional and extensive laboratory techniques such as MRI or lumbar puncture (used to test for ApoE4 genotype; Hesse et al., 2000).

Two studies (Kivipelto et al., 2006; Reijmer et al., 2011) have used non-laboratory risk factors such as blood pressure, BMI, and smoking status in their risk scores for dementia. Furthermore, researchers have shown evidence for the link between individual cardiovascular risk factors and dementia, such as cigarette smoking (Debette et al., 2011; Smith et al., 2007) and blood pressure (Duron & Hanon, 2008; Zade et al, 2010). These studies have shown comparable predictive validity to laboratory-based risk models and provide the benefits of routine data collection and modifiable factors that can be reduced over time. The dementia risk models that included nonmodifiable and laboratory-based risk factors, while helpful, may be less practical for

inclusion as a risk score for use in large-scale population studies. Koopman and Mainous (2008) stressed that risk factors contained in a risk score need to be easily measurable in the setting where they will be applied. Kivipelto and colleagues (2006) showed that the model with ApoE4 was only more predictive for the highest of three risk categories; note that this assay non-modifiable risk factor and is an invasive procedure that requires a lumbar puncture and laboratory analyses to determine the results (Hesse et al., 2000). In general, these types of risk factors are not as readily available as those routinely collected in the primary care setting. Moreover, because these risk factors are non-modifiable, they cannot be improved by treatment. By using modifiable risk factors in a risk score, an individual can seek to lower their risk over time. Thus, a dementia risk score that includes only modifiable, non-laboratory-based risk factors, like the one proposed by Kivipelto and colleagues in 2006, may aid in the efficient identification of at risk Veterans in midlife in the large-scale primary care settings associated with the Veterans Health Administration.

The Current Study

The above sections argue for the need for a simple and modifiable dementia risk score in Veterans. In the current study, cardiovascular risk factors were used to create a dementia risk score that was pertinent to Veterans. The current study was an extension of the study by Wray and colleagues (2013). A dementia risk score in this population is important for many reasons. First, the Veteran population has shown to be at more risk for cardiovascular risk factors of dementia than the general population. In a rapidly aging population with these health risks, the ability to predict, prevent, and slow the progression of dementia at earlier stages of life will be crucial. Second, previous dementia risk scores (e.g., Kivipelto et al., 2006) have noted that dementia risk scores should be verified in other populations; thus, the current study also serves a

secondary function for validation of a dementia risk score in a new population. It should be noted, however, that the current study is preliminary in nature in that this is the first study to create and employ a dementia risk score based on modifiable cardiovascular risk factors in the Veteran population.

The expectations for the current study were as follow: that (a) risk factors for dementia including age, diabetes, hypercholesterolemia, body mass index, blood pressure, pulse pressure, smoking, depression, and alcohol use disorder will comprise a single composite risk score; and (b) a composite risk score using specific cardiovascular and psychosocial variables before the age of 70 will be predict dementia 10 years later after the age of 70 years old.

Methods

Sample

This study was reviewed by the Institutional Review Boards from Syracuse University and the Department of Veterans Affairs. Data was obtained from the Veterans who received Veterans Health Administration services in the Veterans Integrated Service Network (VISN) 2. The VISN 2 network was available to over 400,000 Veterans in the Upstate, Central, and Western New York area in 2011, with almost half of the Veterans over the age of 65 (Department of Veterans Affairs, 2012). Veterans' health information is entered into the VA electronic medical record by a health care provider, which makes their information especially helpful in research. In addition to their specific medical needs, primary care clinics in VISN 2 regularly assess areas such as psychiatric distress, body mass, smoking status, and blood pressure (Funderburk, Maisto, Sugarman, & Wade, 2008). Data for the current study was extracted from the VA database, which contains medical information from individuals receiving medical care at VA medical centers or outpatient clinics.

A sample was extracted from the VA database consisting of Veterans seen in VISN 2 clinics during Fiscal Years 1998 and 1999 (FY98 and FY99) with a date of birth later than 9/30/1929 to ensure that they were under 70 years old 10 years prior to the outcome time points; that is, Veterans who were under 70 years old and seen in a VISN-2 clinic 10 years prior to the outcome time points from the RAPID study were of interest so as to maintain a focus on earlier identification and prediction of dementia (Woods et al., 2003). Some variables (height, weight, and blood pressures) also included information from FY00 due to insufficient data in FY98.

RAPID Sample

Wray and colleagues (2013) study described a novel dementia detection paradigm using the Recognizing and Assessing the Progression of cognitive Impairment and Dementia (RAPID) program that was developed by the leadership of VA Healthcare Network Upstate New York (Veterans Integrated Service Network 2; VISN 2). In general, RAPID was designed to complement primary care services by using information from the EMR, pre- appointment brief cognitive screening calls, and Dementia Care Coordinator (DCC) support to Veterans, their families, and their primary care providers. The program was based on concurrent research at VISN-2 that established age greater than 70 years, history of stroke, and two or more ER visits as variables associated with increased risk of dementia diagnosis. These factors were used to generate a list of Veterans who were called by Behavioral Telehealth Center (BTC) technicians and administered the Blessed Orientation Memory and Concentration (BOMC) Scale over the phone. The BOMC is a brief screening tool for dementia that has good predictive validity for early stage dementia (Brooke & Bullock, 1999) and has been validated for telephone use (Kawas, Karagiozis, Resau, Corrada, & Brookmeyer, 1995). Following these screening calls, an experienced Dementia Care Coordinator would review the charts of those who scored above the

cutoff on the BOMC and would administer follow-up phone calls. Finally, the Dementia Care Coordinator would contact the Veteran's primary care provider and discuss their opinion with regard to a dementia diagnosis (Wray et al., 2013). A more detailed description of the RAPID Program and its constituents can be found in Wray et al. (2013).

Data Collection

As previously stated, the current study's data is derived from a study by Wray and colleagues (2013) that utilized a paradigm to detect undiagnosed dementia. Dementia diagnosis was used as the primary outcome measure for the current study. This data was originally obtained for the Wray et al. (2013) study, which consisted of Veterans over the age of 70 who were seen in primary care in FY08 or FY09. Dementia was defined as the incidence of dementia diagnosis in any ICD-9 encounter outpatient or inpatient code during the study period. ICD-9 codes that were used for diagnosis can be found in Appendix A. Veterans with a history of dementia and documented use of anticholinesterase inhibitors or NMDA antagonists from FY05 to FY07 were excluded because the focus of the study was to detect undiagnosed dementia. Because the Alzheimer's Association (2012A) did not differentiate between the different types of dementia in relation to cardiovascular risk, all types of dementia are included under the general "dementia" category in this study. This notion is also in line with suggestions by Román, Nash, and Fillet (2012), who advocated for a broader view of dementia when screening for dementia risk.

Data was derived according to an IRB approved amendment to the RAPID dementia detection study. Data for the current study was pulled according to the specifications outlined below and were cross-referenced with the same population of Veterans identified in the original data pull for the Wray et al. (2013) study; that is, Veterans that were under 70 years old for the

period of FY98 and FY99 and were in the RAPID database were retained. Cardiovascular and dementia risk factors were extracted from the VA database. These components include age, smoking status, systolic blood pressure, diastolic blood pressure, and body mass index. In order to further advance previous research, additional factors such as pulse pressure, depression, and alcohol use disorder were considered as additional risk factors. In addition to these risk factors, encounter codes for visits between FY98 and FY99 were retained in order to utilize ICD-9 diagnostic codes. Diagnoses of depression, hypercholesterolemia, diabetes, and hypertension were established using the ICD-9 codes for their respective disorders (Appendix A).

More specifically, data were extracted for all Veterans from the VA database from FY98 and FY99, unless otherwise specified: 1) smoking status (any indication of smoking status during the given time period), 2) age (in years for the most recent encounter from FY98-FY00), 3) any measurement of height and/or weight during FY98-FY00, 4) depression diagnosis (Appendix A), 5) hypertension diagnosis (Appendix A), 6) diabetes diagnosis (Appendix A), 7) hypercholesterolemia diagnosis (Appendix A), 8) alcohol use disorder diagnosis (Appendix A). Diagnoses were only returned if they were listed as a principle or secondary diagnosis (i.e., the top two listed diagnoses for an encounter). Those who had encounter diagnoses for dementia in FY98/FY99 were excluded from the current study. Encounter ICD-9 codes for all outpatient encounters were retained inclusive in the following clinics: (Primary Care, Primary Care Mental Health, Geriatric Evaluation and Management Clinic, Mental Health Clinic, Substance Abuse Treatment Services Outpatient Clinic, PTSD Treatment Outpatient Clinic, Neuropsychology Clinic, Geropsychology Clinic, Behavioral Medicine Clinic, Neurology Clinic, Dementia Care Management Clinic).

Data from various cardiovascular and dementia risk factors were matched with a possible sample of 4,836 RAPID-eligible Veterans. Dementia diagnoses (positive and negative) were available for 2,238 Veterans from the sample. Initially, 66,014 encounters from FY98, FY99, and FY00 were retained for eligible Veterans. Multiple encounters for each Veteran between FY98 and FY00 were combined into a single average value for each veteran for all information except encounters. For instance, a patient with multiple blood pressure readings during the time period was averaged to a single value. For encounters, any indication of the relevant diagnostic codes (Appendix A) was coded. After averaging multiple encounters for continuous variables and determining RAPID eligibility, all 2,238 Veterans with information regarding dementia diagnosis had encounter data with diagnostic codes. In order to calculate BMI, 7,112 height values were retained, comprising 3,806 unique RAPID-eligible Veterans and 10,417 weights were retained, comprising 2,915 unique RAPID-eligible Veterans. For Veterans with multiple height or weight values, averages were computed. For BMI, 1,356 values were retained overall. Smoking data was retained for 1,655 Veterans, 1,307 of which were RAPID-eligible. Those without indications of current smoking were regarded as not current smokers and history of smoking did not necessarily qualify an individual for current smoking. Finally, 26,334 systolic and diastolic blood pressures were retained, comprising 4,112 unique RAPID-eligible Veterans. For Veterans with multiple blood pressures, averages were computed. Follow-up time was calculated as the index date used to classify dementia diagnosis in FY08/FY09 minus the most recent encounter date from FY98-FY00. The sample was 100% male. Female Veterans only comprised 1% of the sample and were removed to improve homogeneity in the data analyses. No female Veterans had dementia diagnosis and the overall results did not significantly change when they were removed.

As described above, dementia diagnosis was used as the limiting factor for sample size, such that each of the 2,238 individuals that were retained in the final dataset had a dementia diagnosis. An a priori power analysis based on the mean odds ratio of 2.93 from the dementia risk score by Kivipelto and colleagues (2006) determined that a sample size of 650 was needed for 80% power in this study (Demidenko, 2008).

Data Analysis

The current study is a retrospective longitudinal analysis that sought to create a risk score for dementia in Veterans. The main outcome measure was conversion from no diagnosis of dementia at baseline between the years of FY98/FY99 to a diagnosis of dementia in FY08/FY09. Previous studies (Kivipelto et al., 2006; Reijmer et al., 2011) used longitudinal methods spanning approximately 20 years. A period of 10 years was used in this study to limit the effects of survival bias (e.g., those with dementia dying before they were reassessed) that were outlined as a disadvantage of a long follow-up period by Reijmer and colleagues (2011). The current study included Veterans under the age of 70 at baseline and span over 10 years, such that the age range for individuals at the end of the time frame would encompass the average age of dementia symptoms appearing (65 years old) and the average age of a dementia diagnosis (80 years old; Alzheimer's Association, 2012A).

Composite risk score creation.

Composite risk scores were created using the methods outlined by Sullivan, Massaro, and D'Agostino Sr. (2004) and data comprising the scores are provided in Table 1. This method involves the use of statistical models with multiple predictor variables to create a "points system" that enables the creation of useful and easily interpretable risk scores for a dichotomous outcome. Although continuous variables likely allow for more accurate prediction than

categorical factors, the minute differences between continuous data points are easily summarized when split into risk categories without losing statistical validity; that is, presenting risk factors in categories has been shown to not reduce the predictive accuracy of the model and also makes the risk score easier to calculate and interpret (Kivipelto et al., 2006; D'Agostino et al., 2008). Risk scores were calculated using a multiple logistic regression model, which is often used in the creation of risk scores (e.g., Kivipelto et al., 2006; D'Agostino et al., 2008). Multiple risk scores were initially created to determine the optimal combination of variables for the final dementia risk score. The final risk score that was retained had the best predictive validity and made the most intuitive sense for the scoring system.

All predictor variables were first added into a multiple logistic regression model in order to obtain regression coefficients (β_i) to weight the variables. Some predictor variables (BMI, depression, SBP/DBP, and diabetes) were dropped either because they were not significant ($p > .05$; depression and diabetes) or were better accounted for by other risk factors in the model (BMI was better accounted for by hypercholesterolemia and continuous SBP/DBP were better accounted for by pulse pressure and hypertension diagnosis); that is, variables that are thought to directly measure the same risk factor were not both retained due to potential multicollinearity. Predictor variables were then organized into categories that would lend themselves to simple classifications. For dichotomous variables, such as diabetes or hypercholesterolemia diagnoses, categories were either yes or no. For continuous variables, established values or tertiles were used as cutoff points, as done in Kivipelto et al. (2006), which may aid in the relative ease of establishing risk in primary care. After each category was created, reference values (W_{ij}) were established to translate the results of the regression into a points system. For continuous categories, midpoints between the two values (e.g., 64.5 was used for ages between 63 and 66)

were deployed. For continuous variables with an unrestricted range (e.g., “<63 years old”), the midpoints between 1st or 99th percentile and the closest reference values were used. For example, for the age <63 variable, the midpoint between the 1st percentile and 63 (62) was used, as shown in Table 1. Nominal categories had reference values depending on the coding of the variables (e.g., 0 or 1 for hypertension diagnosis). Using a base-category as a reference point for each risk factor (i.e., the category that is assigned 0 points), the distance between the base category and the various risk factor levels ($W_{ij} - W_{iREF}$) was multiplied by the regression coefficient from the multiple logistic regression model. Next, a constant (B) was created for these values in order to establish the number of regression units that would correspond to one point using a linear transformation. The constant (B) is not a statistically derived construct; it is a number that transforms the regression coefficients into an interpretable point system for ease of communication and understanding. Finally, the points associated with each risk factor were computed using the following equation:

$$\text{Points}_{ij} = \beta_i(W_{ij} - W_{iREF})/B .$$

To summarize, the point values for the dementia risk score were created by first establishing a reference value for each risk factor and subsequently calculating the difference between each category and the reference value. This difference was then multiplied by the regression coefficient from the multiple logistic regression model and then divided by a constant in order to make clean point values that can easily be combined into a single composite risk score (Sullivan, Massaro, & D’Agostino Sr., 2004). The final point values for the risk scores are shown in Table 1. Using these point values, a composite dementia risk score was created for each Veteran.

Statistical analysis of the composite risk score.

Once the composite risk score was calculated, the risk score was used in a Cox proportional hazards model to predict dementia diagnosis, with follow-up time as the time component. Cox proportional hazards models are often used to predict risk for dementia and cardiovascular events (D'Agostino et al., 2008; Kivipelto et al., 2006; Whitmer et al., 2005; Wilson et al., 1998). This modeling provides a type of hazard ratio that expresses the rate at which an event occurs (Appendix B). The Cox model is the most commonly used multivariate approach for analyzing the probability of an event occurring over time. It has shown to be more statistically powerful than logistic regression (van der Net et al., 2008), and it allows for a technique known as censoring, which adequately handles the problem of missing data in longitudinal studies by assuming that the subjects who drop out have the same hazard as those who are left in the study (Weuve et al., 2011).

The composite risk score was placed into a Cox proportional hazards regression model with dementia diagnosis and follow-up years. Results from the Cox proportional hazards model were used to calculate risk based on the composite risk score using the Cox proportional hazards regression equation,

$$\hat{p} = 1 - S_0(t)^{\exp\left(\sum_{i=1}^P \beta_i X_i - \sum_{i=1}^P [\beta_i \bar{X}_i]\right)}$$

A Kaplan Meier curve was used to establish the baseline survival rate, $S_0(t)$, using the cumulative survival at the mean composite risk score, as outlined by Sullivan, Massaro, and D'Agostino Sr. (2004). The Kaplan-Meier survival curve is essentially a survival curve that is defined as the probability of surviving in a given length of time while considering time in many small intervals (Goel, Khanna, & Kishore, 2010). Generally, it represents the proportion of

individuals who have “survived” at the end of the time frame (which in this case means that they did not have dementia in FY08/FY09).

Rare event correction. The prevalence of dementia in the current sample (0.1%) was much smaller than the estimated population base rate of 7% in Veterans over the age of 65, although this was commensurate with the prevalence in the Wray et al. (2013) study. Missing data and rare outcomes are a common problem in health outcome research (He, 2010), and there are a number of ways to correct for these differences. Further, because the asymptotic assumptions of traditional logistic regression are unreliable in samples with unbalanced outcome variables (Mehta & Patel, 1995), two alternative methods of logistic regression were run in addition to the traditional logistic regression model.

Exact logistic regression. Because the population base rate of dementia (τ) can be estimated at a fairly accurate level, a correction offered by King and Zeng (2001) provides an alternative procedure by weighting the data to compensate for differences in the sample (\bar{y}) and population (τ). The base rate for dementia in the current study (\bar{y}) was 0.1% while the base rate for dementia in Veterans similar to this sample (τ) is approximately 7%. Further information regarding the mathematical procedures for this weighting process is in Appendix C. This weighting method was used in an exact logistic regression model. Exact logistic regression is most suitable for small, sparse, or skewed datasets in which the asymptotic assumptions of the logistic regression are not met. It produces the log odds of the outcome variable, similar to the traditional maximum-likelihood logistic regression, but do not depend on asymptotic results. Unlike maximum-likelihood logistic regression, inferences from exact logistic regression are based on appropriate permutational distributions of sufficient statistics of the regression parameters of interest, conditional on fixing the sufficient statistics of the remaining parameters

at their observed values (Mehta & Patel, 1995). This conditional approach, while much more computationally intensive, has gained popularity with the rise in high-powered statistical software and efficient models to calculate exact conditional inference (Mehta & Patel, 1995). Exact logistic regression was run utilizing the above weighting procedure to correct for the discrepancy between the observed and population rates of dementia.

Bootstrapping. Another method that can be employed to assess for bias due to an unbalanced outcome is to take numerous subsamples of the data and compare their outcomes. One such method is “bootstrapping,” which compares numerous subsamples of data and provides an estimate of the sampling distribution of the sample in question. The bootstrapping procedure repeatedly compares subsamples of the data in order to estimate the accuracy of predictions about the population based on the sample data (Olatayo, Amahia & Obilade, 2010). Especially in a sample in which subpopulations vary considerably, bootstrapping algorithms are advantageous because they allow for the user to sample each subpopulation (stratum) independently. In addition to the traditional and exact logistic regression models, a bootstrapped sampling technique using 1,000 subsamples stratified by dementia diagnosis were used in the current study with bias-corrected and accelerated (BCa) confidence interval type. Bootstrap validation is commonly used in the establishment of other risk scores (e.g., Morrison et al., 2007; Schnabel et al., 2010; Wong et al., 1999) and protects against overfitting (Babyak, 2004).

Testing group differences. Independent samples t tests and χ^2 tests were employed to determine differences between individuals with and without dementia. As performed in Kivipelto et al. (2006), variables were split into two groups based on dementia diagnosis and into three groups based on tertiles of dementia risk in order to simplify the scoring system, as shown in

Table 1. Kivipelto and colleagues (2006) concluded that this type of simplified scoring system did not lead to a loss of important information.

Validity of risk assessments.

Receiver operating characteristic (ROC) curves mapping sensitivity against 1-specificity were created as a measure of overall usefulness of the models; that is, the proportion of true positives are plotted against the proportion of false positives. The ROC curve, and more specifically, the area under the ROC curve (AUC), is the most popular metric for capturing discrimination of a risk model. In short, the ROC curve provides the probability that a given score will correctly predict the outcome of interest in the future (Pencina, D'Agostino Sr, D'Agostino Jr, & Vasan, 2008). The ideal point on the ROC curve would be (0,100)—meaning that all positive examples are correctly classified and no negative examples are misclassified. Further, the line $y = x$ represents the scenario of randomly guessing the class and represents an AUC of 0.50, which is the worst performance that an ROC curve can have (Chawla, Boyer, Hall, & Kegelmeyer, 2002).

Values for sensitivity (recall), specificity, and precision were calculated as shown in Appendix B to provide measures of accuracy of risk prediction. A cutoff value of 8 was chosen for the composite risk score to classify a Veteran as high or low risk for dementia. This cutoff value was chosen because it maximized sensitivity and specificity, as performed by Kivipelto and colleagues (2006). In addition, two commonly used point estimates—odds ratios and hazard ratios—were supplied for logistic regressions and cox proportional hazard models, respectively, as shown in Tables 1, 4, 5, and 6.

Exploratory Analyses.

Synthetic Minority Over-sampling Technique (SMOTE). A technique known as SMOTE was described by Chawla, Bowyer, Hall, and Kegelmeyer (2002) as a method to handle imbalanced datasets in order to improve predictive accuracy. This approach uses a combination of under-sampling of the majority (larger) class with a special form of over-sampling of the minority (smaller) class in an imbalanced dataset. In a balanced dataset, predictive accuracy is defined as the proportion of true positives and true negatives out of all classifications from a given predictor; that is,

$$Accuracy = \frac{TP + TN}{TP + FP + TN + FN},$$

where TP represents true positives, TN represents true negatives, FP represents false positives, and FN represents false negatives. Thus, in a balanced dataset with relatively equal error costs, the error rate of $1 - Accuracy$ (i.e., proportion of false positives and false negatives) is reasonable as a performance metric; however, imbalanced datasets carry unequal error costs which do not hold the same assumption about accuracy. The ROC curve is thought to represent the family of best decision boundaries for the relative costs of the TP and FP. For an imbalanced dataset in which the above equality of error assumption is not met, the SMOTE technique offers a method that “sweeps out” the ROC curve by manipulating the balance of samples for each class. By creating “synthetic” examples and over-sampling the minority class, SMOTE moves the ROC curve closer to the ideal point on the curve. Synthetic examples are taken from the minority class along line segments from a specified number of neighboring values and the percent increase desired for the sample of can also be specified (Shawla et al., 2002). After applying the SMOTE technique in the current study, the new “synthetic” sample included 176 cases of dementia, which was the same base rate (7%) as the estimated base rate of dementia in

65 year-old Veterans (Wray et al., 2013). This new sample was analyzed with the composite dementia risk score as a predictor and a new ROC curve was created.

Framingham Cardiovascular Risk Scores. Because of the significant associations between composite cardiovascular/stroke risk scores and dementia (Bangen et al., 2010; Coibica et al., 2011; Debette et al., 2011), a modified version of the Framingham General Cardiovascular Risk Profile (D’Agostino et al., 2008) was calculated for the sample. Using the risk factors of age, HDL cholesterol, total cholesterol, systolic blood pressure (treated and untreated), current smoking, and diabetes diagnosis, D’Agostino and colleagues (2008) calculated an individual’s projected 10-year risk for developing cardiovascular disease. Certain limitations from the sample in the current study made it necessary to slightly alter this risk score. Because laboratory values for cholesterol were not available, diagnosis of hypercholesterolemia (based on ICD-9 codes) was substituted for total cholesterol and the points for the value of 240mg/dL, which is the commonly utilized standard for “high cholesterol,” was used in the modified risk score (Solomon, Kivipelto, Wolozin, Zhou, & Whitmer, 2009). The points for HDL cholesterol were not added into the score because this data was not available; however, this factor was mostly a protective factor, as the points for HDL cholesterol can only range from -2 to +2. For the purposes of this risk score, systolic blood pressure values were regarded as “treated” if the individual had a concurrent ICD-9 diagnosis of hypertension and were regarded as “untreated” if the individual did not have a concurrent ICD-9 diagnosis of hypertension.

Results

Overall Sample

Descriptive statistics for the overall sample are shown in Table 2. Out of the 2,238 Veterans from the RAPID sample that had information regarding dementia diagnosis, diagnoses

or indications of diabetes, depression, hypercholesterolemia, hypertension, alcohol use disorder, and current smoking were available for all individuals. Body Mass Index was only available for 60% of the sample and all other variables shown in Table 2 had at least 81% of data available.

The prevalence for diabetes in this sample (10%) was commensurate with that estimated for the general population (8%; Knowler, 2002) and slightly higher than the estimated prevalence of diabetes in Veterans during FY98 (5%; Miller, Safford, & Pogach, 2004). The prevalence for depression in this sample (8%) was similar to that for both Veterans (11%; Yen et al., 2007) and the general population (10%-15%; Petersen, 2011) over the age of 65. Hypertension (50%) was commensurate with an established prevalence in over 73,000 Veterans between the ages of 50 and 79 (55%; Lederle et al., 1997) and alcohol use disorder (3%) was commensurate with data from other Veterans (4%; Chwastiak, Rosenheck, Desai, & Kazis, 2010). Prevalence for both current smoking (4%) and hypercholesterolemia (16%) in the current study were less than the prevalence in Veterans (19% for current smoking and 52% for hypercholesterolemia; Lederle et al., 1997). Mean pulse pressure (62 mm Hg) was higher than that of almost 200,000 Veterans between 45 and 57 years of age (47.28 mm Hg; Domanski et al., 2002) but in the same range as 7,983 men and women over 55 years old (Mattace-Raso et al., 2006).

Descriptive statistics for variables retained in the composite dementia risk score are shown in Table 3. Only age was statistically significant between those with and without dementia ($p < .01$) and alcohol use disorder diagnosis was marginally significant ($p = .08$). All other variables, although not significant between the two groups, were trending upward for dementia, such that those with a dementia diagnosis had a higher mean or percentage even though it was not statistically higher.

Composite Dementia Risk Score

In order to compute the composite risk score, the variables in the risk score were first placed in a multivariate logistic regression model with bias-corrected bootstrapping. The omnibus test was marginally significant, $\chi^2 = 11.95$, $p = .06$. Alcohol use disorder diagnosis was the only significant risk factor in the multivariate model, $B = 1.91$, $\text{Exp}(B) = 6.75$, $p = .02$, and age was marginally significant, $B = 0.24$, $\text{Exp}(B) = 1.27$, $p = .07$. Table 1 shows the results from the logistic regression stratified by variations in the risk factors that were changed into point values. Based on the regression coefficients from the multiple logistic regression for the composite risk score, the points above the reference values ranged from 1 to 5, with age greater than 68 and pulse pressure greater than 66 leading to a score of 5 points each. The odds ratios for each risk factor were all over 1.00 and ranged from 1.26 (63-66 years old) to 6.63 (alcohol use disorder); however, there was a large degree of variability in the 95% confidence intervals, as shown in Table 1.

The final variables retained in the composite dementia risk score are shown in Table 1, along with the calculation values for the points associated in the risk score. Statistics for the maximum-likelihood logistic regression analysis are shown in Table 4. The omnibus test was significant at the .05 level ($p = .02$). The composite dementia risk score showed a 19% increase in the likelihood of a dementia diagnosis for each 1-point increase in the risk score. The 95% CI for this increase was between 2% and 38% for each 1-point increase in the composite risk score. In order to better account for the imbalanced outcome variable, an exact logistic regression analysis was also computed using Fisher's scoring for the optimization technique. Results from this model can be seen in Table 5. The association between composite dementia risk score and dementia diagnosis using exact logistic regression was significant at the .0001 level. Similar to

the maximum-likelihood model, the composite dementia risk score showed a 19% increase in the likelihood of a dementia diagnosis for each 1-point increase in the risk score. The range of the 95% CI was improved using the exact logistic regression model, as an increased risk of dementia between 12% and 27% was predicted for each 1-point increase in the composite risk score. The bootstrapped sample was similar to the maximum-likelihood model and the omnibus test was significant at the .05 level, $B=.17$, $SE=.08$, $Wald=5.15$, $p=.02$, $Exp(B)=1.187$, 95% $CI=[1.02-1.38]$.

The composite dementia risk score was then analyzed by survival analysis using the Cox Proportional Hazards regression model in order to account for time in the prediction of dementia 10 years later. Results from the cox proportional hazards regression model are shown in Table 6. The overall model was significant at the .01 level and the hazard ratio for dementia using the composite dementia risk score was 1.29, indicating that for each 1-point increase in the composite dementia risk score, Veterans were 29% more at risk for developing dementia. The 95% CI for the hazard ratio was between 9% and 53%. As with logistic regression, the exact conditional analysis was used in the Cox Proportional Hazards regression as well. Using the exact method, the model was significant at the .0001 level and again the 95% CI range was tightened, indicating increased precision. The exact method revealed a 10% increase in 10-year-dementia-risk for each 1 point increase in the risk score, with the 95% CI ranging from 5% to 16%.

The mean composite risk score was 5.87 and it ranged from 0 to 17. The mode was 6, accounting for 12% of all scores, and 99% of the scores were less than 13. Using the Kaplan-Meier estimator, the baseline survival was set at .995 for the mean of the risk score. This baseline hazard was used to calculate the overall risk of dementia based on the composite risk score.

Table 7 shows the final composite risk score calculation sheet and risk estimates based on the score. The predicted risk of dementia based on the composite risk score total ranged from 0.05% (0) to greater than 25% (15 through 17). As recommended by Sullivan and colleagues (2004), risk values that corresponded to a considerably low number of individuals were cut off to avoid overestimation bias. The risk score was cut off at 15, such that scores greater than or equal to 15 corresponded to 25% risk. A risk score total less than 10 corresponded to less than 5% risk of developing dementia in 10 years.

As performed by Kivipelto and colleagues (2006), the risk score was split into tertiles to compare risk factors for each risk level, as shown in Table 8. Scores less than or equal to nine were classified as low risk, scores between 10 and 12 were classified as medium risk, and scores greater than or equal to 13 were classified as high risk. Only two variables—age and alcohol use disorder—were statistically significant when compared using one-way ANOVA. All variables, including age and alcohol use disorder, showed increasing trends with dementia risk groups, such that the mean or percent diagnosed in each variable was smallest in the low risk group and highest in the high risk group, as shown in Table 8. Of particular note, 92% of Veterans who were categorized in the high risk group had a hypertension diagnosis.

Predictive accuracy of the composite risk score is shown using the ROC curve in Figure 2. The AUC for the curve was 0.7811, which is classified as “good” for a disease of multifactorial origins such as dementia (Kivipelto et al., 2006). Using an optimal cutoff score of 8, the sensitivity for the composite risk score was 50% and the specificity was 80%. The overall accuracy was 79%. Positive predictive value was calculated as 50% and negative predictive value was 80%.

Exploratory Analyses

Oversampling using SMOTE.

As an exploratory analysis, the SMOTE technique was used to oversample the minority class (dementia cases) in order to allow for the usual asymptotic assumptions of logistic regression and reduce bias caused by imbalanced data. This procedure uses statistical estimates based on the sample in order to derive values that would likely exist if the sample were balanced. Recall that in the original sample, there were only 16 cases of dementia. Using the SMOTE procedure, 192 cases were classified as positive for dementia while 2,286 cases were classified as negative; the oversampling of the minority class provided a more accurate balance between the dementia and not dementia groups, as 7% of cases were derived to be classified as “dementia,” which is consistent with the estimated prevalence for this group (Wray et al., 2013). These new oversampled values were analyzed using 10-fold cross validation to determine the predictive validity of the composite dementia risk score. As shown in Figure 3, the SMOTE procedure produced a ROC curve that was well into the “good” category, with an AUC of 0.85. The sensitivity of the model using SMOTE was 86% and the specificity was 96%. The negative predictive value was 93% and the positive predictive value was 92%.

Framingham General Cardiovascular Risk Score.

Modified versions of the Framingham General Cardiovascular Risk Score (D’Agostino et al., 2008) as shown in Table 9. Because of their age, the lowest General Cardiovascular Risk score that a Veteran from the current study could have was 8. The mean cardiovascular risk score was 16, although these values may not be directly commensurate with the original risk values because of the alternations necessary to produce the score using data from the current study. That said, the mean cardiovascular risk score, using the guidelines from the D’Agostino et al. (2008)

study, correspond to over a 30% risk of CVD in the next 10 years. Using exact logistic regression, the model using the general cardiovascular risk score was significant at the .0001 level, $B=.21$, $SE = .04$, $Wald = 29.94$, $Exp(B) = 1.23$, $95\% CI = [1.14 - 1.32]$. These results indicate that for every increase of one point in the Framingham General Cardiovascular Risk score in this sample, risk of dementia increases by approximately 23%. The ROC curve for the general cardiovascular risk score is provided in Figure 4; the AUC for this model was lower than that of the dementia risk score and was .720, which is still considered “good” for predicting a disease of multifactorial origins (Kivipelto et al., 2006).

Discussion

Without interventions to prevent or delay the onset of dementia, the Alzheimer’s Association (2014) estimates that the rate of dementia diagnoses will triple by 2050. After the age of 65, the likelihood of developing Alzheimer’s disease doubles every five years and the risk reaches nearly 50 percent after the age of 85 (Alzheimer’s Association, 2014). While currently 6th on the list of causes of death in the United States, some researchers estimate that Alzheimer’s disease may contribute to close to as many deaths as heart disease or cancer in the coming years (James et al., 2014). These are astonishing numbers by themselves; these numbers do not account for other types of dementia, such as vascular dementia, and do not factor in the magnitude of increased risk based on risk factors. As shown in Figure 1, a substantial proportion of Veterans will reach the prime age for developing dementia in the coming years and interventions to prevent or delay the onset are important now. The current study provides a preliminary analysis of a composite dementia risk score based on modifiable and routinely collected variables that achieved moderate success; the AUC for the ROC curve in this study was in the “good” range and was similar to that from Kivipelto and colleagues (2006). The Kivipelto

et al. (2006) risk score used a combination of age, sex, SBP, BMI, total cholesterol, physical activity in one model and those same factors with ApoE4 added in another model to achieve AUCs of .769 and .776, respectively. The composite dementia risk score in the current study achieved an AUC of .781, which was in the same range as the Kivipelto et al. (2006) study and can be classified as “good.”

The sensitivity for the composite dementia risk score in this study was 50% and the specificity was 80%, meaning that classification of a dementia diagnosis based on a “high” dementia risk score was accurate 50% of the time while classification of no dementia based on a “low” dementia risk score was accurate 80% of the time. The current model also showed 79% accuracy. Ideally, a screening measure should have both high sensitivity and specificity (Feigelson, Criqui, Fronek, Langer, & Molgaard, 1994). The Kivipelto et al. (2006) risk score had a sensitivity of 77%, a specificity of 63%, and an overall accuracy of 64%. Their risk score has a strength in that it has much higher sensitivity than the current risk score, allowing it to better predict dementia risk; however, the current dementia risk score had higher specificity and accuracy than the Kivipelto et al. (2006) risk score. These results imply that there are strengths and weaknesses to each risk score, but that the current risk score is promising as a preliminary predictor of dementia risk. It is important not to overdiagnose dementia due to the potential psychological, social, and occupations impacts of receiving a diagnosis (Aminzadeh, Byszewski, Molnar, & Eisner, 2007), so this risk score errs on the side of caution. Still, the risk score from the current study is of similar quality to other composite dementia risk scores (viz. Kivipelto et al., 2006) and are composed of completely modifiable and routinely collected health factors.

As compared to other dementia risk scores, the composite score predicting risk for dementia in 10 years from this study has many strengths. Composite risk in itself is a strength of

this study. Risk prevention is steadily becoming more frequently based on the interaction between various risk factors as opposed to a simple cause and effect model (Pronk et al., 2004). The composite risk score in the current study not only allows for these risk factors to vary together in a statistical sense, but also factors in the possibility of an additive effect of multiple risk factors occurring at the same time. Another strength of the current dementia risk score is that it is based on variables that are modifiable and routinely gathered in the primary care setting. Interventions are likely to have more effect if they are based on modifiable factors that can be changed in the future (McMahon et al., 2006). The Kivipelto and colleagues (2006) risk score contains mostly modifiable risk factors aside from sex and ApoE4 status. A dementia risk score that is based purely on modifiable risk factors, such as the one in this study, offers the individual an opportunity to work to reduce those risk factors. For example, an individual with high cholesterol, high blood pressure, and an alcohol use disorder could learn that they can reduce their risk for dementia if they take positive steps to reduce those risk factors. Interventions based on lifestyle changes have shown success in the VA population previously (Burke, Dunbar-Jacob, & Hill, 1997; Chapman et al., 2013). In the current study, age is considered a modifiable risk factor to place importance on early intervention. As opposed to a later age in which the risk factors have had more time to cause biological changes that increase risk for dementia, an intervention with a younger individual may help to offset these changes; however, data for this type of conclusion cannot be made by the current study, but could be a fruitful area of future research. In addition, the knowledge that a patient could gain from a modifiable dementia risk score before the onset of dementia could improve their self-efficacy and motivation for change, as the Health Belief Model suggests that an increase in perceived threat and a decrease in the

perceived barriers could provide such an increase in the efficacious deployment of life style changes.

The dementia risk score from this study is based on risk factors that are routinely gathered in the primary care setting. In general, risk scores have the most impact on treatment when they are based on factors that are easily measurable in the setting in which they are applied (Koopman & Mainous, 2008). In this case, a dementia risk score that is intended to be used in the primary care setting, in addition to including factors that are modifiable, includes information that is routinely collected at every primary care visit. If the results of this preliminary study are replicated with additional populations of Veterans and non-Veterans, primary care physicians could use a gross cutoff score (e.g., 8 for male Veterans if current findings are replicated) to indicate binary risk (viz., high versus low) for dementia risk, similar to the method used in the mini-mental state exam (Folstein, Robins, & Helzer, 1983). The universal collection of data used in the dementia risk score from the current study, once further validated, would optimize the introduction of such a risk score into primary care because it could be easily calculated by the EMR.

Finally, Veterans present a substantial portion of the United States population (Martinez & Bingham, 2011) and, as such, targeting this group could have many public health applications. Furthermore, just as Veterans have been shown to be less healthy than non-Veterans (Agha et al., 2000), they generally have more substantial risk factors for dementia. Not only is the Veteran population likely more at risk for dementia than non-Veterans, but they are rapidly aging as a whole, as shown in Figure 1. Thus, a risk score that was created using health information from Veterans that can be applied to Veterans may more accurately predict dementia in this population than one that was validated on a different population. By the same token, however, the

extrapolation of these results to non-Veteran samples should be done with care for the same reason (Agha et al., 2000). Nevertheless, additional research is warranted to examine the extent to which the reported findings are unique to Veterans or are equivalent to those obtained in the general population. As said earlier, this area of research is in its nascent stages for both Veterans and non-Veterans, and the preliminary findings of this study support continued research in this important public health concern.

Exploratory Analyses

As shown in Figure 4, a modified version of the Framingham General Cardiovascular Disease Risk Score (D'Agostino et al., 2008) also showed promising results in its ability to predict dementia. This makes intuitive sense, in that many of the risk factors in the risk score are shared with those in the current model. In addition, this provides further evidence that composite risk scores based on cardiovascular variables can be important indicators of dementia risk because a previously validated risk score (viz. Framingham General Cardiovascular Disease Risk Score) shows similar results to the composite risk score in the current study.

Limitations

While there are strengths of the dementia risk score in the current study, there are also limitations that should be considered.

Limitations of the sample.

This study is retrospective in nature and utilized data from EMRs in the VA database. While it was necessary to perform this study in a retroactive way, because there has not been a previously validated measure of dementia risk in Veterans, the conclusions from this data would likely be stronger in a prospective analysis. Furthermore, 503 Veterans from the current study died before the follow-up period 10 years later; this is a limitation that is often confronted when

studying risk in older individuals (e.g., Kivipelto et al., 2006; Reijmer et al., 2011). A period of 10 years was used in this study to limit survival bias, though attrition due to death is almost definite when studying large numbers of older adults. It is possible that the 503 Veterans who died before the follow-up period had higher risk factors for dementia and would have developed it had they lived longer, which may have altered the sensitivity and specificity of the risk score (Kivipelto et al., 2006). Another important limitation from this sample, although relatively common in Veteran samples, was that it was purely male. This limitation limits the generalizability of these findings to the female population. Future validation of this score should include a sample with enough women to be representative of that subsection of the population.

The current study was not the initial objective in the data collection for the outcome variable in this study; as previously stated, the current study was derived from the Wray et al. (2013) study that investigated a method to identify undiagnosed dementia Veterans. Thus, some of the data that would have been applicable for the current study was not available. The most apparent problem with this sample was that Veterans who developed dementia after FY00 and before FY98 were not included in the current study due to the original focus on undiagnosed dementia in the Wray et al. (2013) study. Furthermore, because this sample was based on historical information from the EMR, information used in the risk score may not have been as accurate as a prospective study would allow. For example, the use of diagnoses based on encounters, while helpful in determining diagnostic status for this study, has flaws in that 1) only the two primary diagnoses for each encounter were available, and 2) diagnoses may have not been accurate in that those with a diagnosis may not have been diagnosed in their medical record. While most of the variables used in this study were commensurate with what would be expected for this population, current smoking and hypercholesterolemia may have not been fully

representative of the Veterans sample as a whole. In addition, diabetes diagnosis, although similar in prevalence to the VA population, led to extremely large error rates and confidence intervals. Because diabetes in particular has shown strong associations with dementia previously (Carvalho, Katz, Dutta, Katakam, Moreira, & Busija, 2014; Wang et al., 2014), it should not necessarily be dismissed as a risk factor for dementia in future work. Similarly, it is possible that “depression” was too nonspecific to lead to an identifiable pattern of risk, possibly because of the mixed etiology of the diagnoses. The inclusion of a continuous variable to measure depression severity, such as the PHQ-9 (Kroenke, Spitzer, & Williams, 2001), may improve this outcome, as would a continuous measure of mental status such as a MOCA (Nasreddine et al., 2005) or MMSE (Folstein, Robins, & Helzer, 1983) score. Because high cholesterol and BMI are thought to measure the same general concept and have been interchangeable in composite risk scores previously (e.g., D’Agostino et al., 2008), hypercholesterolemia was retained in the current study because it was more predictive than BMI. The pitfalls of BMI have been previously shown (e.g., Livingston, 2012) and other measurements such as waist-hip or waist-height ratio have been suggested as more effective measurements (Lee, Huxley, Wildman, & Woodward, 2008; Kivipelto et al., 2006; Sayeed et al., 2003).

Statistical limitations.

The imbalanced outcome based on dementia diagnosis was another limitation in the current study. There were only 16 cases of dementia out of 2,238 Veterans in this study, which was commensurate with that used in the Wray et al. (2013) study. In the Kivipelto et al. (2006) study, 61 individuals had dementia and 1,348 individuals did not. While the difference between the number of individuals with and without dementia was larger than the Kivipelto et al. (2006) study (i.e. the positive versus negative dementia cases was more imbalanced), similar results

emerged from the current study. Furthermore, one difficulty with secondary analysis in studying risk is the need to force a restricted age range. As can be seen in numerous studies (e.g. Jousilahti et al., 1999; Wray et al., 2013), risk factors tend to vary by age, so there may not necessarily be a linear relationship between the composite risk score in the current study and age. Therefore, further validation using a younger sample is warranted in order to be able to apply the current risk score to a younger population.

Both conservative and optimistic strategies were used in this study to examine the variability of the findings that could have been biased due to the imbalanced outcome variable. The results from the exact logistic regression analysis were generally similar to the maximum-likelihood models but the exact logistic regression results narrowed the confidence interval range, making the predictions more precise. Still, the fact that the results did not drastically change using exact logistic regression, which is a known method to handle imbalanced data, shows that the results from the current study show promise for the future. In the more optimistic approach using the SMOTE method, in which values for the dementia diagnoses were oversampled to offset the large-scale difference, the AUC further improved to .85, as shown in Figure 3, and the sensitivity drastically improved from 50% to 86%. If a value of this caliber can be further validated with a larger sample, the risk score from the current study that is based solely on modifiable, routinely gathered information will be more accurate and precise than any other composite dementia risk score.

Implications of the results

The current study offers a composite risk score for dementia in 10 years based on only modifiable and routinely gathered variables. While, as described above, this method is important as an intervention because it offers information regarding the ability to modify one's risk, it is

limited in that some nonmodifiable risk factors, such as family history of dementia, are some of the most predictive (Duara et al., 1996; Jayadev et al., 2008). Further, it is both a strength and a weakness that the current study was analyzed specifically on Veterans; on one hand, it offers for more accurate prediction in Veterans, but on the other hand application of the results from the current study are not necessarily directly transferable to the general population. Furthermore, it is also of note that the current dementia risk score was only validated for male Veterans, so it cannot be applied to female Veterans until further research is completed. Future research may address the distinction between genders as well as the distinctions between Veterans and the general population with regard to dementia risk. While the focus of the current study was on modifiable risk factors that enable a Veteran to reduce their risk over time, this may not necessarily reverse damage that has already occurred. In this sense, the most promising effects of this type of intervention may be in increased longevity rather than reversal of damage. Finally, the distribution of risk factors in the population has changed since 1998 when the predictive data was taken in this study. For example, blood pressure and cholesterol and become lower while obesity is on the rise (Kivipelto et al., 2006). For this reason, it is possible that the distribution of risk factors in 1998 was not the same as it was in 2008, which may have impacted on the results and may limit the predictive validity of this type of risk score in the future.

Ideally, this risk score would be scaled back even further to be applicable to even younger individuals, as their risk factors are generally less developed at earlier ages (Jousilahti et al., 1999). Increased dementia risk factors at midlife have been shown to be related to increased severity of dementia later in life (e.g., Debette et al., 2011; Freitag et al., 2006) and there is evidence that early treatment of risk factors such as high cholesterol and blood pressure at midlife can reduce the risk of developing dementia in the future (Wilson, Ritchie, Peters &

Ritchie, 2011). Similarly, this type of risk score may be utilized as more of a dichotomous risk indicator in the way that a MMSE (Folstein, Robins, & Helzer, 1983). It should be reiterated, however, that the results from the current study require further validation due to the fairly small number of dementia diagnoses in the sample. As previously stated, the current study is preliminary in nature, though the results are promising for a dementia risk score of this type to be fully validated in this population.

Conclusions

The current study produced a composite risk score that predicted dementia in Veterans 10 years later using solely modifiable and routinely gathered information from the EMR that had good predictive validity, especially for a disease of multifactorial origins such as dementia. This risk score is the first composite dementia risk score created for Veterans and provides optimism for future research in this area. The results from this study add to the previous study by Wray and colleagues (2013) by providing some evidence that risk factors for dementia are more specific earlier in life and become less specific later in life, as evidenced by Wray and colleagues (2013). As this was a preliminary investigation to determine the utility of such a risk score in Veterans, it was not without limitations; however, the statistical models used in this study for the main analysis are all convergent on the conclusion that a single composite score based on cardiovascular risk factors can predict the risk of dementia 10 years later. Once further validated, this type of risk score could be seamlessly introduced into the primary care setting where the information to create this score is already available. This type of intervention would be a considerable step forward in the prevention or delay of dementia onset in a rapidly aging Veteran population.

Appendix A

ICD-9 codes used for diagnosis

General Diagnosis	ICD-9 Diagnostic Code	Specific Diagnosis
Hypertension	401.0	Hypertension, malignant
	401.9	Hypertension, unspecified
	405.11	Hypertension, renovascular, benign
	405.01	Hypertension, renovascular, malignant
Hypercholesterolemia	272.0	Hypercholesterolemia, pure
	272.2	Hyperlipidemia, mixed
Alcohol Use Disorder	303	Alcohol dependence syndrome
	303.0	Acute alcoholic intoxication
	303.00	Acute alcoholic intoxication in alcoholism, unspecified
	303.01	Acute alcoholic intoxication in alcoholism, continuous
	303.02	Acute alcoholic intoxication in alcoholism, episodic
	303.03	Acute alcoholic intoxication in alcoholism, in remission
	303.9	Other and unspecified alcohol dependence
	303.90	Other and unspecified alcohol dependence, unspecified
	303.91	Other and unspecified alcohol dependence, continuous
	303.92	Other and unspecified alcohol dependence, episodic
	303.93	Other and unspecified alcohol dependence, in remission
305.00	Alcohol Abuse, Unspecified	
Diabetes (type II)	250	Diabetes mellitus
	250.00	Diabetes mellitus without mention of complication, type II or unspecified type, not stated as uncontrolled
	250.02	Diabetes mellitus without mention of complication, type II or unspecified type, uncontrolled
	250.10	Diabetes with ketoacidosis, type II or unspecified type, not stated as

	uncontrolled
250.12	Diabetes with ketoacidosis, type II or unspecified type, uncontrolled
250.20	Diabetes with hyperosmolarity, type II or unspecified type, not stated as uncontrolled
250.22	Diabetes with hyperosmolarity, type II or unspecified type, uncontrolled
250.3	Diabetes with other coma
250.30	Diabetes with other coma, type II or unspecified type, not stated as uncontrolled
250.32	Diabetes with other coma, type II or unspecified type, uncontrolled
250.4	Diabetes with renal manifestations
250.40	Diabetes with renal manifestations, type II or unspecified type, not stated as uncontrolled
250.42	Diabetes with renal manifestations, type II or unspecified type, uncontrolled
250.5	Diabetes with ophthalmic manifestations
250.50	Diabetes with ophthalmic manifestations, type II or unspecified type, not stated as
250.52	Diabetes with ophthalmic manifestations, type II or unspecified type, uncontrolled
250.6	Diabetes with neurological manifestations
250.60	Diabetes with neurological manifestations, type II or unspecified type, not stated as uncontrolled
250.62	Diabetes with neurological manifestations, type II or unspecified type, uncontrolled
250.7	Diabetes with peripheral circulatory disorders
250.70	Diabetes with peripheral circulatory disorders, type II or unspecified type, not stated as uncontrolled
250.72	Diabetes with peripheral circulatory disorders, type II or unspecified type, uncontrolled
250.9	Diabetes with unspecified

		complication
	250.90	Diabetes with unspecified complication, type II or unspecified type, not stated as uncontrolled
	250.92	Diabetes with unspecified complication, type II or unspecified type, uncontrolled
<hr/>		
	290	Dementia
	290.0	Senile dementia, uncomplicated
	290.1*	Presenile dementia
Dementia	290.2*	Senile dementia with delusional or depressive features
	290.3	Senile dementia with delirium
	290.4*	Vascular dementia
	290.8	Other specified senile psychotic conditions
	290.9	Unspecified senile psychotic condition
<hr/>		
	296.2	Major Depressive Disorder, Single Episode
	296.3	Major Depressive Disorder, Recurrent Episode
Depression	296.9*	Unspecified episodic mood disorder
	300.4	Dysthymic Disorder
	309.0	Adjustment Disorder with depressed mood
	309.1	Prolonged depressive reaction
	311	Depressive disorder, NOS

Note. * = all subsidiary diagnoses

Appendix B

Formulae and meanings for validity classifications

	Formula	Meaning
Odds Ratio	$\frac{TP * TN}{FP * FN}$	Probability that a positive classification will lead to a diagnosis compared to the probability of a diagnosis occurring if classified as negative
Hazard Ratio	$\frac{P}{1 - P}$	Probability that a patient classified as high risk will develop a diagnosis faster than one classified as low risk
Sensitivity (Recall)	$\frac{TP}{TP + FN}$	How good is the test at correctly selecting positives?
Specificity	$\frac{TN}{TN + FP}$	How good is the test at avoiding false alarms?
Precision	$\frac{TP}{TP + FP}$	How accurate is a classification of positive risk?

Note. TP = True Positives, TN = True Negatives, FP = False Positives, FN = False Negatives, P = Probability of a given hazard. All formulae above are referenced from Liu, Berry, Dawson, and Pearson (2005) aside from Hazard Ratio, which is referenced from Spruance, Reid, Grace, and Samore (2004).

Appendix C

Mathematic procedures used in the weighting process for exact logistic regression

The weights are produced by the following equation: $\omega_i = \omega_1 y_i + \omega_0 (1 - y_i)$, where $\omega_1 = \frac{\tau}{\bar{y}}$

and $\omega_0 = \frac{(1 - \tau)}{1 - \bar{y}}$. This formula was used with 0.001 for \bar{y} and 0.07 for τ in order to create weights for the sample to correct for the discrepancy between the observed and population rates of dementia.

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DEMENTIA RISK SCORE FOR VETERANS

Table 1

Logistic regression model for dementia risk in 10 years

Risk Factor	Categories	W_{ij}	W_{ij}-W_{REF}	Bi	OR (95% CI)	Points
Age	<63	62 (REF)				0
	63-66	64.5	2.5	0.298	1.26 (0.78, 20.31)	2
	66-68	67	5	0.298	3.87 (0.43, 35.15)	3
	>68	69.5	7.5	0.298	4.49 (0.53, 38.03)	5
Hypercholesterolemia Diagnosis	No	0 (REF)	0			0
	Yes	1	1	0.530	1.77 (0.46, 6.77)	1
Current Smoking	No	0 (REF)	0			0
	Yes	1	1	0.688	1.71 (0.21, 14.08)	2
Pulse Pressure	<55	45 (REF)		0.028		0
	55-66	60.5	15.5	0.028	1.71 (0.31, 9.47)	3
	>66	82	37	0.028	2.58 (0.51, 13.11)	5
Alcohol Use Disorder	No	0 (REF)				0
	Yes	1	1	1.854	6.63 (1.36, 32.06)	4
Hypertension Diagnosis	No	0 (REF)				0
	Yes	1	1	0.439	1.58 (0.47, 5.36)	1

Note. Odds ratios for continuous predictors (age and pulse pressure) were calculated from a separate logistic regression model as categorical variables reflecting the above categories.

DEMENTIA RISK SCORE FOR VETERANS

Table 2

Descriptive Statistics for Risk Factors in the Dataset

	Valid	Mean	SD	Minimum	Maximum
Age (years)	1818	66.01	2.80	58.15	70.84
Body Mass Index (kg/m ²)	1338	29.77	5.11	16.95	47.76
Systolic Blood Pressure (mm Hg)	1966	140.41	15.72	100	201
Diastolic Blood Pressure (mm Hg)	1968	78.75	8.83	49	110
Pulse Pressure (mm Hg)	1966	61.64	13.48	22	129
Follow-Up (years)	1992	8.97	0.91	7	12
	Valid	Percent			
Diabetes	2254	9.50			
Depression	2254	7.80			
Hypercholesterolemia	2254	15.30			
Hypertension	2254	49.70			
Alcohol Use Disorder	2254	3.00			
Current Smoking	2254	4.40			

Note. Age refers to age at the most recent encounter in FY98 through FY00, BMI, SBP, and DBP are based off of averages of values available between FY98 and FY00 (if necessary), Pulse Pressure is defined as the difference between SBP and DBP, Follow-Up refers to the difference between the most recent encounter in FY08-FY09 and the most recent encounter in FY98-FY00, diagnoses are based on ICD-9 codes from the electronic medical records.

Table 3

Descriptive Statistics for the Composite Risk Score, Stratified by Dementia Diagnosis

	Non-Demented (n=2238)	Demented (n=16)	<i>p</i>
Age, years (SD)	66.00 (2.8)	67.68 (2.2)	.007
Hypercholesterolemia Diagnosis, n (%)	342 (15%)	3 (19%)	.725
Current Smoking, n (%)	98 (4%)	1 (6%)	.514
Hypertension Diagnosis, n (%)	1109 (50%)	11 (69%)	.140
Pulse Pressure, mm Hg (SD)	61.61 (13.5)	65.31 (16.2)	.357
Alcohol Use Disorder Diagnosis, n (%)	65 (3%)	2 (13%)	.080

Note. Independent Samples t-tests were used for continuous variables and χ^2 tests (Fisher's exact tests) were used for categorical variables. Results were computed using bias corrected accelerated bootstrapping to account for sample size differences. Veterans with missing data were excluded from the corresponding analyses: Age (432), Pulse Pressure (288).

Table 4

Logistic Regression Analysis for the Composite Dementia Risk Score

Independent Variable	B	SE	Wald	Sig	Exp(B)	95% CI
Composite Risk Score	.17	.08	5.15	.035	1.187	1.02 - 1.38

Status	Freq.
Dementia	16
No Dementia	2238

Note. Exp(B) is the exponentiated log odds and represents the odds ratio. Analyses were bootstrapped using Bias Corrected Accelerated Bootstrapping with 1000 samples to reduce the potential for overfitting.

Table 5

Exact Logistic Regression Analysis for the Composite Dementia Risk Score

Independent Variable	B	SE	Wald	Sig	Exp(B)	95% CI
Composite Risk Score	.18	.03	32.96	<.0001	1.19	1.12 – 1.27

Status	Freq.
Dementia	96
No Dementia	13684

Note. Exp(B) is the exponentiated log odds and represents the odds ratio. Fisher's scoring was used as the optimization technique.

Table 6

Cox Proportional Hazards Results for the Composite Dementia Risk Score

Maximum Likelihood						
Independent Variable	B	SE	Wald	Sig	Exp(B)	95% CI
Composite Risk Score	.26	.09	8.4	.004	1.29	1.09 – 1.53

Exact Conditional Analysis						
Independent Variable	B	SE	Wald	Sig	Exp(B)	95% CI
Composite Risk Score	.0959	.026	13.87	<.0001	1.101	1.045 – 1.158

Note. Exp(B) refers to the hazard ratio. Mean composite risk score was 5.874. Maximum likelihood model was bootstrapped using Bias Corrected Accelerated Bootstrapping with 1000 samples to reduce the potential for overfitting.

DEMENTIA RISK SCORE FOR VETERANS

Table 7.

Composite Dementia Risk Score Calculation Sheet

Risk Factor	Categories	Points	Risk Score	% Risk of Dementia in next 10 years
Age	<63	0	0	0.05%
	63-66	2	1	0.08%
	66-68	3	2	0.13%
	>68	5	3	0.20%
Hypercholesterolemia Diagnosis	No	0	4	0.31%
	Yes	1	5	0.48%
Current Smoking	No	0	6	0.76%
	Yes	2	7	1.19%
Hypertension Diagnosis	No	0	8	1.86%
	Yes	1	9	2.89%
Pulse Pressure	<55	0	10	4.50%
	55-66	3	11	6.97%
	>66	5	12	10.71%
Alcohol Use Disorder Diagnosis	No	0	13	16.28%
	Yes	4	14	24.32%
Total Dementia Risk Score			15	>25%
			16	>25%
			17	>25%

Table 8

Composite Risk Score Descriptive Statistics, Stratified by Tertile

	Low Risk Profile (0 – 9)	Medium Risk Profile (10 - 12)	High Risk Profile (13 - 17)	<i>p</i>
Age, years (SD)	65.5 (2.7)	68.6 (1.6)	69.0 (1.0)	.038
Hypercholesterolemia Diagnosis, n (%)	275 (14%)	63 (23%)	7 (28%)	.718
Current Smoking, n (%)	60 (3%)	27 (10%)	12 (48%)	.721
Hypertension Diagnosis, n (%)	930 (47%)	167 (62%)	23 (92%)	.123
Pulse Pressure, mm Hg (SD)	59.2 (12.3)	75.4 (11.6)	75.4 (10.2)	.290
Alcohol Use Disorder Diagnosis, n (%)	28 (1%)	26 (10%)	13 (52%)	.024
10-year risk for Dementia	0.48%	6.97%	>25%	

Note. Significance testing was calculated via separate one-way ANOVAs for each risk factor using Bias Corrected Accelerated Bootstrapping with 1000 samples. 10-year risk for dementia for each level of risk is calculated by the median risk level for each factor.

Table 9

Modified Dementia Risk Score based on Framingham General Cardiovascular Risk Score

Risk Factor	Categories	Points	Risk Score	10-year risk for CVD
Age	55-59	10	8	9.5%
	60-64	11	9	11.2%
	65-69	13	10	13.3%
	70-74	14	11	15.7%
	75+	15	12	18.5%
Diabetes	No	0	13	21.7%
	Yes	3	14	25.4%
Total Cholesterol	Low	0	15	29.6%
	High	3	16	Above 30%
Smoking	No	0	17	Above 30%
	Yes	4	18	Above 30%
SBP Not Treated	< 120	-2	19	Above 30%
	120-129	0	20	Above 30%
	130-139	1	21	Above 30%
	140-159	2	22	Above 30%
	≥ 160	3	23	Above 30%
SBP Treated	< 120	0	24	Above 30%
	120-129	2	25	Above 30%
	130-139	3	26	Above 30%
	140-159	4	27	Above 30%
	≥ 160	5		
Total				

Note. Based on the General Cardiovascular disease risk score by D’Agostino et al., 2008. SBP = Systolic blood pressure; systolic blood pressure was characterized as “treated” if the individual had a concurrent ICD-9 diagnosis of hypertension and was considered “untreated” if they did not. High and low values for total cholesterol were assigned based on an ICD-9 diagnosis of hypercholesterolemia. The highest possible percent risk for this score in the D’Agostino et al (2008) study was 30%.

DEMENTIA RISK SCORE FOR VETERANS

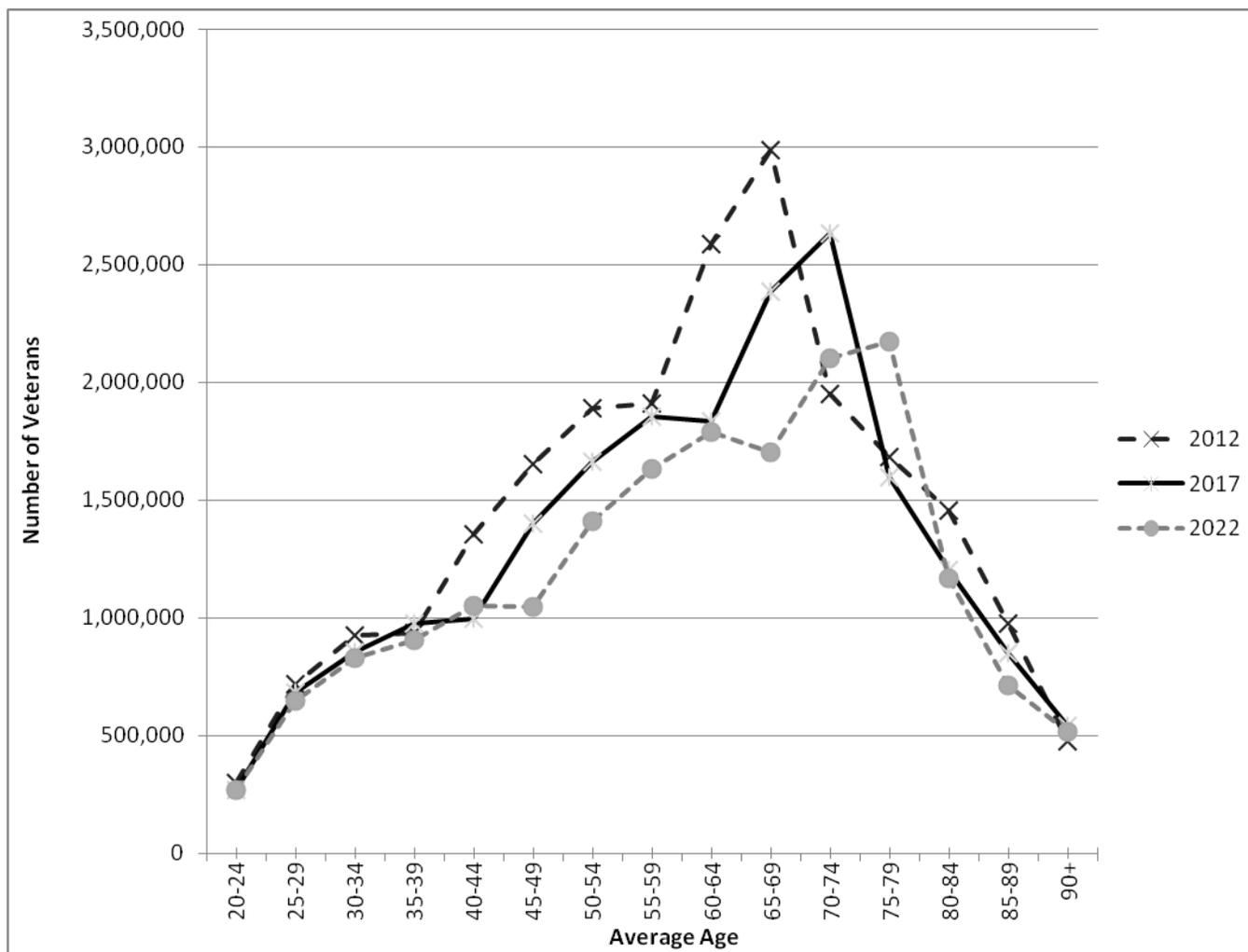


Figure 1. The projected population of United States Veterans stratified by age group in 2012, 2017, and 2022 (Department of Veteran Affairs, 2010).

DEMENTIA RISK SCORE FOR VETERANS

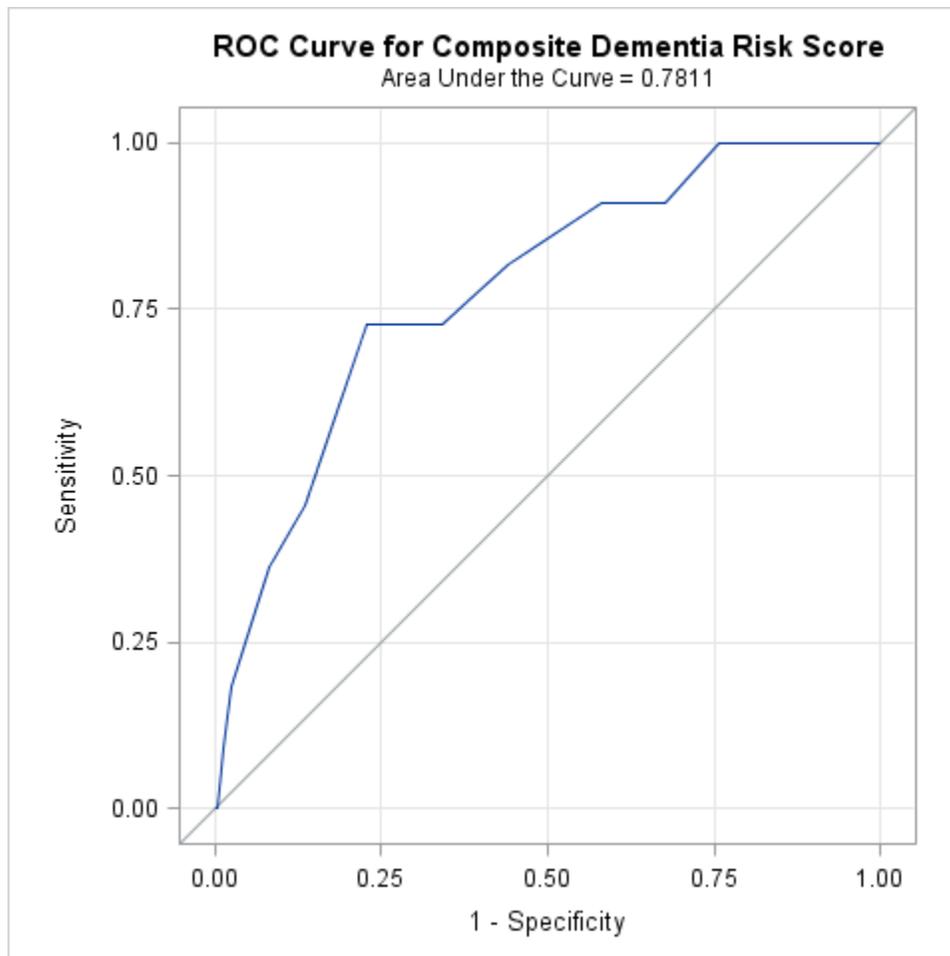


Figure 2. Receiver Operating Characteristic (ROC) Curve for the composite dementia risk score.

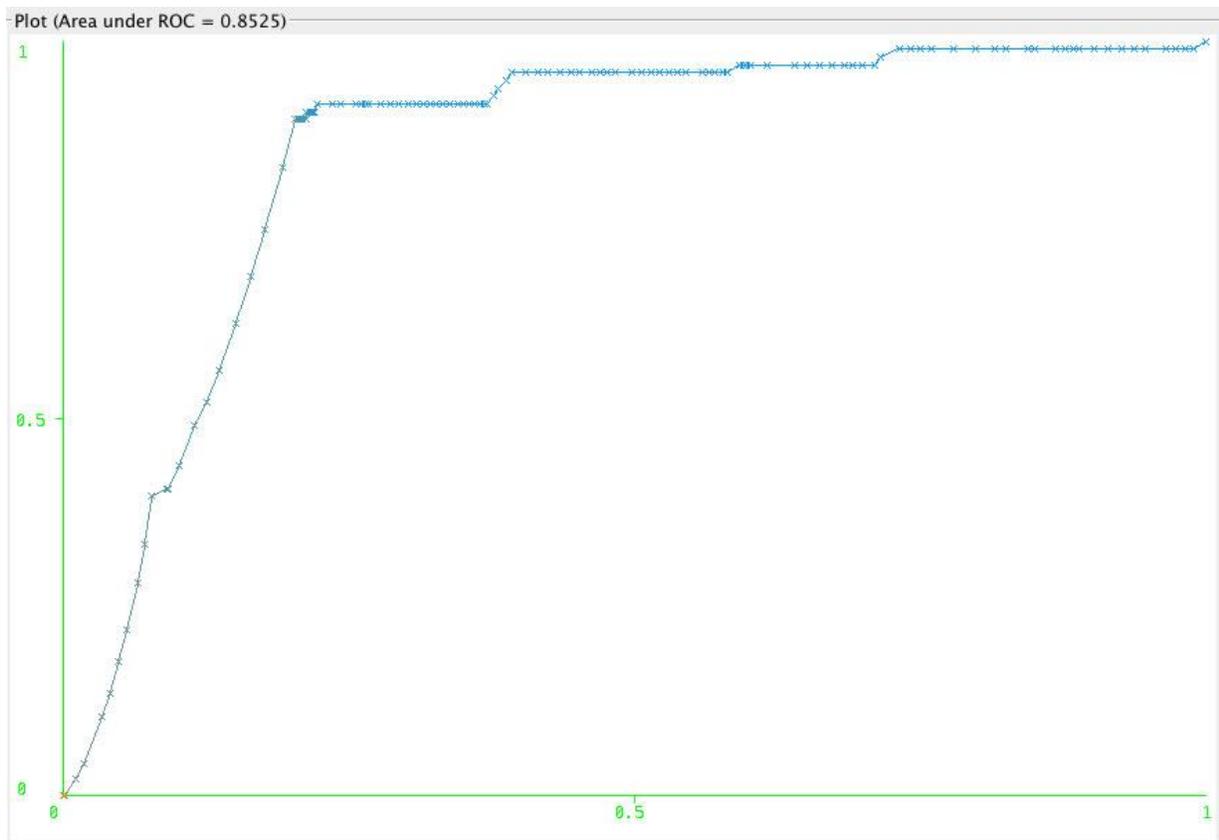


Figure 3. Receiver Operating Characteristic (ROC) Curve for the composite dementia risk score using the SMOTE procedure

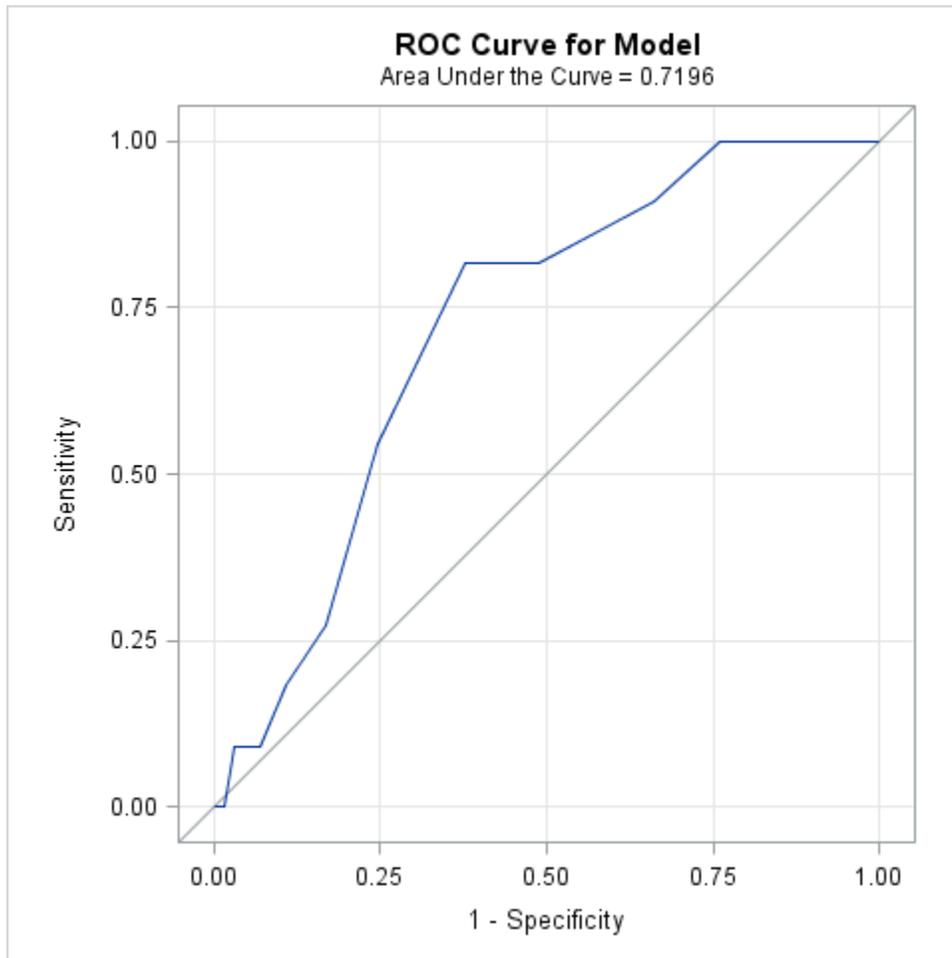


Figure 4. Exploratory Receiver Operating Characteristic (ROC) Curve for the Framingham 10-year Composite Cardiovascular risk score.

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EDUCATION

Ph.D.	2014	Syracuse University Syracuse, NY Clinical Psychology <u>Advisor:</u> Randall Jorgensen, Ph.D. <u>Dissertation:</u> Detection of Dementia Risk in Primary Care: Preliminary Investigation of a Composite Dementia Risk Score in Veterans
M.S.	2012	Syracuse University Syracuse, NY Clinical Psychology <u>Thesis:</u> Feedback, task demand, and cognitive test performance in college students
B.S.	2008	University of Rochester Rochester, NY <u>Major:</u> Neuroscience <u>Minor:</u> Spanish

CLINICAL TRAINING

Postdoctoral Fellowship	2014-2016	The Johns Hopkins University School of Medicine Baltimore, MD Clinical Neuropsychology
Predocotrinal Internship	2013-2014	SUNY Upstate Medical University Syracuse, NY Clinical Psychology, Adult Track