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Alzheimer's Disease prevalence, costs, and prevention for military personnel and veterans☆

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Abstract By 2050, more than 13 million Americans of all ages are estimated to be living with Alzheimer's disease (AD), and the aggregate costs of care will swell to approximately $1.2 trillion. The rapidly climbing number of those affected with AD includes a growing population of aging military veterans affected who may have an added risk for the disease as a consequence of traumatic brain injury, posttraumatic stress disorder, and/or service-related injuries. The increasing number of individuals, the long duration of disability, and the rising cost of care for AD and other dementia to our society are important public health challenges facing many older adults. These challenges are further compounded by a burgeoning military veteran population that is much younger, with an increased risk of AD and other dementia, and who may experience decades-long periods of disability and care. This outlook underscores the critical need for investments in research at the federal and international levels to accelerate the pace of progress in developing breakthrough discoveries that will change the trajectory of AD and related dementia.

Keywords: Alzheimer's disease; Military medicine; Traumatic brain injury; Posttraumatic stress disorder; Healthcare costs

1. Introduction

Alzheimer's disease (AD) affects more than 5 million Americans of all ages, and this number is projected to nearly triple to more than 13 million by 2050 [1]. The prevalence among US veterans is 563,786 individuals, similar to the overall population, and is likewise expected to increase dramatically in the coming decades [2–5]. Yet, there are concerns that the number of at-risk veterans extends beyond the issues of population aging. Notably, the prevalence of dementia in veterans is predicted to rise as a result of an increasing incidence of traumatic brain injury (TBI) and posttraumatic stress disorder (PTSD) [2].

Since March 2003, more than 2.3 million soldiers were deployed to the Iraq-Afghanistan war zones [3], and among these service members, nearly 300,000 veterans between 2000 and 2013 have been diagnosed with TBI [4] and more than 83,000 with newly diagnosed PTSD [5]. As a result of greatly improved military health and battlefield survival from these signature acute injuries, there is now a paradox that veterans will be at a greater risk of developing chronic neurodegenerative diseases such as AD and dementia [2].

2. Costs of dementia care

The aggregate cost of care for older adult individuals affected by AD and other dementia is estimated to be approximately $203 billion in direct and indirect expenses [6]. Medicare and Medicaid cover approximately 70% of these costs, but out-of-pocket expenses account for $34 billion or 17% of this total. Moreover, in 2008, the total per-person payments from all sources of health care and

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long-term care, including private insurance and out-of-pocket payments, were three times greater for Medicare beneficiaries with a form of dementia than for other Medicare beneficiaries when matched for age [7].

These costs reflect that people living with AD and other dementia have more than three times the number of hospital stays per year than other individuals of the same or similar age [7]. Furthermore, they reflect the high costs associated with long-term care services. For example, in 2012, the national average cost for a private room in a nursing home was $90,520 per year and the average cost of an adult day center was $70 per day [8]. These figures do not take into account the number of or the dollar value of hours of unpaid care provided by nonprofessional and family caregivers. In 2012, the total value of unpaid care provided by such individuals was approximately $216 billion [6].

Dementia care is expensive today, and such related expenditures are projected to increase dramatically. It is estimated that aggregate payments for health care, long-term care, and hospice will increase from the current $203 billion to $1.2 trillion by 2050 [6]. However, what remains unknown is how these costs will be affected by present and future veterans who may be diagnosed with neurodegenerative illnesses at an earlier than expected time points, possibly in their fifth or even fourth decade of life.

Veterans with dementia incur elevated health-care costs. They are more likely to require hospitalization and their hospital stays tend to be substantially longer than those without dementia [5]. In addition, possible risk factors for dementia such as TBI and PTSD are also linked to substantially increased health-care expenses. For example, one study found that the median annual health-care costs for veterans diagnosed with TBI are four times higher than those for veterans without TBI and are even higher for veterans experiencing both TBI and PTSD or pain [9]. Psychiatric visits are also much more common among veterans with dementia [2].

The annual cost of informal care provided to elderly community-dwelling individuals with dementia, including veterans, averaged approximately $18,385 per individual according to a study conducted in 1998 [10]. These informal costs, as well as the costs associated with nursing home and home health care, are expected to increase dramatically for veterans in the coming decade in line with expected increases in the general population [11]. It is unknown if veterans today or in the future will experience increased care-related costs due to battle-related injuries (e.g., TBI and PTSD) or whether the Veterans Health Administration system will enable better care management for concomitant diseases described in greater detail in Section 3.

3. Are veterans at an increased risk of AD?

Military personnel and veterans are subject to the same risk factors of AD as the general population, in addition to potential exposure to other factors that may further increase their risk. In the general population, there are hints in literature of possible factors that increase an individual's risk of AD, including age, family history, and heart health. These factors are outlined in greater detail in the following paragraph. More research into how these factors may affect veterans or military personnel is needed.

Age is the greatest risk factor for AD, with the incidence of AD dementia doubling every 5 to 6 years after the age of 65 years [12]. Genetic factors may also increase the risk of developing AD. The apolipoprotein E ε4 (*APOE* ε4) allele is the strongest genetic predictor of risk for AD. Individuals who inherit two copies of this allele have a 12- to 15-fold increased risk of developing AD and an earlier age of onset than individuals with other allelic forms of the *APOE* gene [13]. Furthermore, TBI recovery and outcomes have been connected to the possible genetic areas of interest, including *APOE* ε4 (described previously). TBI in the presence of *APOE* ε4 allele is associated with poorer health outcomes in adults and is linked to increased mortality after ischemic stroke and cardiopulmonary arrest [14,15]. Other genes have also been linked to an increased risk of disease, including genes involved in the processing of the AD precursor protein and pathways involved in the immune response and inflammation, lipid transport, synaptic function, and other important physiologic processes that are involved in AD pathogenesis [16]. The influence of genetics is also reflected in the fact that individuals with a parent or sibling with AD are more likely to develop AD than those who do not have a first-degree relative with AD [17].

Cardiovascular risk factors also raise the risk of dementia. For example, in a study of 678 Catholic nuns, stroke emerged as the greatest risk factor for subsequent dementia [18], and other studies have linked an increase in dementia incidence to hypertension [19], diabetes and insulin resistance [20], obesity [21], and atherosclerosis [22].

Depression has also shown to increase the risk of dementia [23], as do TBI and PTSD [2]. In addition, lifestyle factors including physical activity, smoking, diet, level of education, and social and cognitive engagement and sociodemographic factors such as race, gender, and socioeconomic status may potentially be related to an increased risk of dementia [24,25]. These factors impact the general population; research regarding how these factors may impact veterans and military personnel specifically is needed to understand the potential risk to these groups.

In addition to the factors described in the above sections, veterans may be at an increased risk for AD because of both the demographics of the veteran population, compared with the general population, and the risks related to combat injuries. Veterans are, on average, older than nonveterans [26]. In Veterans aged 30 to 64 years, there is a higher proportion of African-Americans compared to the overall US population (16% -17% African American veterans compared with 13% in the US population), and the incidence of AD in African-Americans is about twice that of Caucasian individuals [27]. Veterans may also be affected by socioeconomic factors such as lower incomes or unemployment [28].

In addition, the stress on soldiers deployed in the 21st century wars includes more frequent and longer deployments and increased exposure to hostile forces, suicide bombs, and injured civilians, which may also link to an increased risk of AD and related dementia [29].

Combat-related injuries include an increased incidence of TBI and PTSD. TBI and PTSD are often referred to as "invisible wounds of war" because those affected may appear uninjured [30]. Research about these combat injuries goes back at least to the First World War in which soldiers exposed to trench warfare experienced symptoms then described as "shell shock" or battle fatigue [27]. Both TBI and PTSD have also been linked to an increased risk of AD and related dementia, although the exact mechanisms of this connection are unknown [31].

3.1. TBI—potential risk factor

TBI is the most frequent cause of death and disability among Americans under the age of 35 years, most frequently as a result of automobile accidents, falls, and sports-related injuries [28]. It occurs when an external force to the head causes injury and results in an alteration or loss of consciousness. Those with moderate and severe, but not mild, head injuries have a two- to fourfold increased risk of AD and other dementias in late life [32].

The association of TBI with dementia has been reported in both veteran and nonveteran populations. In the 1920s, dementia pugilistica, now referred to as chronic traumatic encephalopathy (CTE), was seen in boxers [33] and is identified today in correlation to other sport activities including American football, hockey, and other contact sports. Sports-related TBI, particularly concussion, is a frequent occurrence with 1.6 to 3.8 million affected annually in the United States [34–36]. In military and veteran populations, the widespread use of improvised explosive devices in Iraq and Afghanistan reportedly produced up to 23% confirmed cases of TBI in one brigade combat team of nearly 4000 soldiers [35]. This increase is further supported by estimates from the Defense and Veterans Brain Injury Center that 22% of all combat wounds from the wars in Afghanistan and Iraq are brain injuries compared with 12% of combat wounds that occurred in Vietnam.

Multiple concussions or even a single moderate-to-severe TBI can predispose individuals to develop a pathologically distinct form of tauopathy-related dementia at an early age [37]. Tauopathies are neurodegenerative diseases, such as AD, characterized by neurofibrillary tangles comprised of filamentous tau protein. In the early stages of CTE, large deposits of phosphorylated tau (phospho-tau) are seen, particularly in the frontal cortex. This pattern of phospho-tau deposition is different from the pattern seen in AD. The link between phospho-tau deposition in individuals with TBI and neurodegenerative pathology is not well understood; however, TBI could conceivably prompt multiple molecular pathways that result in the overproduction and aggregation of numerous key proteins that form the pathologic accumulations seen in neurodegenerative diseases [38]. Clinically, CTE may cause alterations in an individual's behavior/mood and/or an individual's cognition [39].

3.2. PTSD—potential risk factor

PTSD is a distinct psychological condition that often co-occurs with TBI but may also occur in the absence of a brain injury in response to emotionally upsetting events. The prevalence of PTSD in veterans is much higher than that seen in the general population (13%–31% in veterans compared with 7% in the US general population) [40], and those with PTSD are also at nearly twice the risk of developing dementia [41,42].

The underlying mechanisms involved in PTSD are believed to include changes in synaptic connectivity associated with learning and alterations of central and peripheral hormones [43]. Veterans with PTSD have been shown to have reduced hippocampal volume, correlating with impaired memory [44]. Interestingly, PTSD is also associated with a greater risk of other comorbid conditions that have been independently linked to an increased risk of dementia. For example, a meta-analysis found that 52% of individuals with PTSD also had co-occurring major depressive disorder, with higher rates among those with PTSD resulting from military service [45]. Veterans with depression and dysthymia are at twice the risk of developing dementia compared with those without depression and dysthymia [46]. Another study of veterans found that those with PTSD had a 59% increased risk of coronary atherosclerosis as measured by coronary artery calcification [47]. PTSD also has been linked to a significant increased risk of prediabetes and type 2 diabetes (odds ratio, 3.56) [48]. Greater understanding of how PTSD may contribute to an increased risk of AD, as well as the comorbid conditions, is needed.

4. Possible prevention of AD

To date, there is no treatment that stops or slows the progression of AD. However, there are numerous clinical studies underway to develop and test therapies that may inhibit or decelerate the progression of AD in individuals exhibiting the early stages of the disease. One example is the Dominantly Inherited Alzheimer's Network Trial. This study is enrolling adult children of individuals who have rare genetic mutations in the genes for the amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*), or presenilin 2 (*PSEN2*), all of which cause early-onset autosomal-dominant AD [49]. Other studies aimed at stopping or slowing the progression of AD in its early stages among individuals at a potential increased risk (based on genetics or altered biological markers associated with AD) have also recently begun enrolling volunteers. These include the Alzheimer's Prevention Initiative studies [50], Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) study [51], and TOMMORROW trial in AD [52]. These efforts are vital

to advancing innovative models of trial design, participant selection, and moving the field to a new era of improved treatments to stop or slow disease progression.

5. Responding to a growing crisis in the military

The links between risks factors, such as TBI and PTSD, and AD are critical to the mental health of the US military population. The military has responded to this growing threat in multiple ways. The Militarily-Relevant, Peer Reviewed Alzheimer's Disease Program (MRPRA) was created through the Telemedicine & Advanced Technology Research Center (TATRC) [53]. The mission of the MRPRA is to build an integrated program devoted to understanding the association between TBI and AD and to reduce the burden on those affected by TBI AD symptoms, especially in the military community. In its first years, the program focused on imaging, genomics, and proteomics, enhancing quality of life and tau pathology. Another project, the Vietnam Veterans Alzheimer's Disease Neuroimaging Initiative Project funded by the Department of Defense (DoD-ADNI) has been added to the overall Alzheimer's Disease Neuroimaging Initiative (ADNI) project in an effort to determine the effects of TBI and PTSD on AD. By assessing Vietnam War veterans between the ages of 60 and 80 years, this study is attempting to use neuroimaging and other biomarkers to establish biological connections between TBI, PTSD, and AD. For example, a set of various proteins synthesized within neurons is presently being assessed as potential biomarkers, including glial fibrillary acidic protein, neuron-specific enolase, myelin basic protein, and S100B [54]. These ongoing studies may be able to identify whether changes in these markers are able to function as diagnostic and prognostic tools and predictors of adverse secondary effects that may assist in the diagnosis and management of TBI.

6. Next steps

This review summarizes the current knowledge of military-related costs, prevalence, and risks related to AD and dementia and outlines ongoing efforts to increase our understanding of AD in military-relevant populations (e.g., DoD-ADNI). Continued funding of the MRPRA through TATRC will help us understand the basis for the relationships that research has suggested and clarify the extent to which military risk factors increase the risk of AD and related dementia. In times of fiscal austerity, funding models are increasingly incorporating partnership models to fund longitudinal studies in older individuals that will provide the necessary information for how and when dementia develops as we age. The ADNI-DoD project is one example that encourages the sharing of data and findings with the global research community. This example sets the stage for leveraging existing research explorations for further study and highlights the need to study longitudinal change in populations with potentially increased risk such as military personnel and/or veterans to ascertain the degree of risk. To this end, the Global Alzheimer's Association Interactive Network connects international data sets through a federated network, allowing researchers around the globe to query data to drive hypotheses, generate validation samples, and integrate complex computer modeling of disease-disease or disease-risk interactions. Collaborations across funding organizations may create opportunities to explore including integrated analysis across the ADNI-DoD and ADNI along with other TBI or PTSD and AD data sets, as well as bridge longitudinal data sets associated with different neurologic diseases such as Parkinson's disease and AD (e.g., Biomarkers Across Neurodegenerative Diseases funding announcement; alz.org/BAND).

Our understanding of the molecular mechanisms driving the association of TBI and PTSD with AD is limited, and more research is needed to elucidate these connections. This knowledge will not only add to our understanding of the pathogenic mechanisms that underlie neurodegeneration in general but will also further aid in efforts to discover and validate biomarkers that may better predict neurodegeneration after either TBI or PTSD and to the development of a measure to capture TBI exposure upon the initial injury. Broader efforts in the AD research community will inform our understanding of the linkage between TBI and PTSD with AD; however, funding mechanisms to enable such explorations are important both to leverage existing data sets and to integrate these with the ongoing and novel data collection efforts.

There are clear gaps in our knowledge regarding dementia-related health expenditures for veterans and the population of current military personnel and veterans who may be at a greater risk for developing AD and related dementia in the future. Addressing these knowledge gaps at all levels (molecular to economic) is essential for the growing number of veterans who may develop dementia as a result of military exposures. Moreover, the knowledge gained will have ramifications throughout the society by improving our understanding of the factors that contribute to an increased incidence of dementia in an aging population.

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