

# DEFENSE HEALTH RESEARCH PROGRAMS

Relevance to National Security and Military Families

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the 1990s, the number of people in the UK who are aged 65 and over has increased from 10.5 million to 13.5 million, and the number of people aged 75 and over has increased from 4.5 million to 6.5 million (Office for National Statistics 2000).

There is a growing awareness of the need to address the needs of older people, and the need to ensure that the health care system is able to meet the needs of older people. The Department of Health (2000) has published a strategy for older people, which sets out the government's commitment to older people and the need to ensure that the health care system is able to meet the needs of older people.

The strategy for older people is based on the following principles: (1) to ensure that older people are able to live independently and actively; (2) to ensure that older people are able to access the health care services that they need; (3) to ensure that older people are able to participate in the decisions that affect their lives; and (4) to ensure that older people are able to live in their own homes and communities.

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## INTRODUCTION

Seventy years ago, baseball legend Lou Gehrig gave his name to a mysterious and rare disease called amyotrophic lateral sclerosis (ALS). He stood on the field at Yankee Stadium on July 4, 1939, and delivered one of the most memorable speeches in American history, announcing to the world, "Today I consider myself the luckiest man on the face of this earth." Lou Gehrig was an American hero.

Today, we know that besides being a hero, Gehrig had something else in common with the men and women serving in the armed forces of our country – his disease, ALS.

Existing evidence supports the conclusion that people who have served in the military are at a greater risk of developing ALS and dying from the disease than those with no history of military service. As outlined in this paper, study after study continues to demonstrate this to be true: if you serve in the military, regardless of the branch of service, regardless whether you served in the Persian Gulf War, Vietnam, Korea, or World War II, and regardless whether you served during a time of peace or a time of war, you are at a greater risk of developing ALS than if you had not served in the military. The questions we are asking today are these: why is there a greater risk of ALS with military service, and what are we, as a nation, going to do about it?

It is the goal of The ALS Association that this paper raise awareness of the important work that so far has been done on the relationship between ALS and military service. In this effort, we hope to impress upon the Congress, the Administration, and the American public the seriousness of this issue and the need to act now.

As we work to address the risk of ALS associated with military service, we must not lose sight of the fact that ALS is a disease that impacts both the veteran and non-veteran communities. Therefore, research into ALS and the military should be broad-based and should not be conducted at the expense of other important research into ALS. This disease knows no boundaries; research into the many potential causes and treatments for ALS will benefit veterans and non-veterans alike.

The Association and our more than 40 Chapters and affiliates across the country advocate for increased funding for ALS research and public policies that respond to the needs of people with ALS, as well as vital state and federal resources that are needed to immediately assist patients and families affected by this horrible disease. The ALS Association and our local Chapters are a central resource for information, assistance, and support for people with ALS and their families.

By committing the resources necessary to better understand the apparent link between ALS and military service, we can take action to help ensure that our military men and women, today and in the future, are at no greater risk of ALS than other Americans and that their medical and caregiving needs are met. A concerted national effort to understand this connection may also yield important clues about ALS, what causes the disease and how it may be prevented, treated and, ultimately, cured – advances that truly will benefit us all.

## ABOUT ALS

ALS was first identified as a disease in 1869. Although much more is known about the disease today, we still do not know how it can be prevented, effectively treated, or cured. Nerve cells, or motor neurons, reach from the brain to the spinal cord and from the spinal cord to muscles throughout the body. It is through these neurons that we are able to control all muscle movement, whether it be moving our arms and legs, opening and closing our eyelids, or simply breathing. ALS attacks these neurons and, as the disease progresses, these neurons cease functioning and die. ALS patients gradually lose the ability to initiate and control muscle movement and ultimately succumb to total paralysis in the later stages of the disease. Early in the disease, ALS patients retain mental acuteness,



aware of the limits ALS has imposed on their lives. However, as the disease progresses many ALS patients will succumb to cognitive decline and develop psychological and behavioral symptoms.<sup>1</sup> Furthermore, it is now clear that frontotemporal dementia (FTD), a condition characterized by progressive degeneration of the temporal and frontal lobes of the brain resulting in permanent changes in personality, behavior, and emotion, is part of the same neurodegenerative disease spectrum as ALS.<sup>2,3</sup> Therefore, the number of people suffering with ALS and related FTDs is greater than previously recognized.

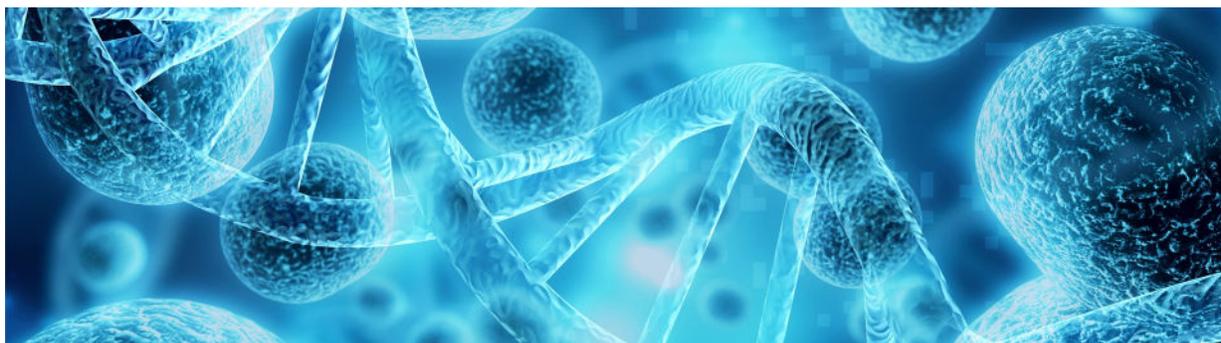
The prognosis for a person diagnosed with ALS in 2018 is largely the same as it was for a person diagnosed with the disease in 1869: death in an average of two to five years. Only three drugs, Rilutek (riluzole), Nuedexta, and Radicava (edaravone), are approved for the treatment of ALS. Riluzole is a glutamate antagonist and was approved by the FDA in 1995 to extend life or the time to mechanical ventilation for people with ALS. Unfortunately, riluzole has shown only limited effects, prolonging life by just a few months, and there is no evidence that it exerts a therapeutic effect on motor function. Nuedexta, a combination of dextromethorphan and quinidine, is used as an adjunct medication in the management of ALS symptoms. Nuedexta was approved by the FDA in 2010 to treat pseudobulbar affect, an emotional dysfunction common in ALS patients characterized by unpredictable and sudden laughing or crying. Interestingly, in addition to improvements related to pseudobulbar affect, Nuedexta has also been shown to improve speech, swallowing, and saliva control in ALS patients. In 2017, Edaravone was approved by the

<sup>1</sup>Wicks P, Albert SM. 2018. It's time to stop saying "the mind is unaffected" in ALS. *Neurology* 91(15):679-681.

<sup>2</sup>Renton AE, Majounie E, Waite A, et al. 2011. A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. *Neuron* 72(2):257-268.

<sup>3</sup>Daoud H, Suhail H, Sabbagh M, et al. 2012. C9orf72 hexanucleotide repeat expansions as the causative mutation for chromosome 9p21-linked amyotrophic lateral sclerosis and frontotemporal dementia. *Arch Neurol* 69(9):1159-1163.

FDA to treat ALS based on clinical trial data showing the drug helped slow the progression of functional loss in ALS patients. Edaravone is thought to confer its protective benefits via its role as an antioxidant, but the mechanism of action is still unclear. However, like Riluzole, Edaravone does not reverse motor neuron death and does little to treat the underlying cause of ALS.



The incidence rate (i.e., number of newly diagnosed cases) is generally higher in white males and increases with age. However, it is important to note that while ALS is a rare disease, the prevalence (number of cases of disease existing in a population) continues to increase: in 2002 there was a prevalence of 3.7/100,000 (95% CI 3.66–3.80), 4.4/100,000 in 2003 (95% CI 4.34–4.50), 4.8/100,000 in 2004 (95% CI 4.76–4.91) and 5.0/100,000 in 2013 and 2014 (95% CI 4.9–5.1).<sup>4,5</sup> Experts predict that ALS prevalence will continue to increase over the next several decades due to the increased numbers of older adults, more sophisticated diagnostic tools, and better healthcare records.<sup>6</sup>

Researchers believe that 5%-10% of all ALS cases are hereditary, meaning “caused by genetic factors that are passed from parents to their children.” The other 90%-95% of cases of ALS are termed “sporadic” or “non-familial”. The research community has identified the genes associated with familial ALS in ~70% of cases. Approximately 12% of sporadic cases have also been associated with a genetic cause.<sup>7</sup> For the remaining cases of sporadic ALS, a variety of factors from excessive physical activity to toxic exposures have been investigated and continue to be investigated. Gender, smoking, increased physical activity, trauma/physical injury, and certain chemicals (e.g., lead, solvents, diesel exhaust, pesticides) have all been recognized as potential risk factors for the development of sporadic ALS. Unfortunately, a complete analysis of risk factors is not feasible since ALS is a rare disease and it is difficult to generalize findings from individual studies. Additionally, there are shortcomings with retrospective data collection that often relies on patient-based recall methods. Despite the limitations of identifying definitive ALS risk factors, mounting lines of evidence suggest onset and progression of ALS are a complex interaction between environmental and genetic factors such as a genetic predisposition with an environmental trigger.

<sup>4</sup> Mehta P, Kaye W, Bryan L, et al. 2016. Prevalence of Amyotrophic Lateral Sclerosis — United States, 2012–2013. *MMWR Surveill Summ* 65(No. SS-8):1–12.

<sup>5</sup> Mehta P, Kaye W, Raymond J, et al. 2018. Prevalence of Amyotrophic Lateral Sclerosis — United States, 2014. *MMWR Morb Mortal Wkly Rep* 67:216–218.

<sup>6</sup> Arthur KC, Calvo A, Price TR, et al. 2016. Projected increase in amyotrophic lateral sclerosis from 2015 to 2040. *Nat Commun* 7:12408.

<sup>7</sup> Chia R, Chiò A, Traynor BJ. 2018 Novel genes associated with amyotrophic lateral sclerosis: diagnostic and clinical implications. *Lancet Neurol* (1):94–102.

Several occupations have been identified as having a close association with the development of ALS including construction work, precision-tool manufacturing, veterinary medicine, medical work, athletic activity, power-plant operation, and military employment.<sup>8,9,10</sup> Recently published results from a Danish cohort indicate occupations with exposures to toxicants such as lead and diesel exhaust, in combination with strenuous physical activity, increase the odds of ALS in men to 1.21;<sup>11</sup> however, the 95% confidence interval varied by occupational group. The men in the Danish study were classified as construction, agriculture, hunting, forestry, or fishing workers. Other populations that engage in intense physical activity, such as collegiate- or professional-level athletes, may also be associated with ALS risk; however, studies into those cohorts need to be performed to clarify any true association. Military service also requires intense physical exertion, and members of the armed forces are frequently exposed to diesel exhaust (through the use of engines and heavy machinery) and are more likely than their civilian counterparts to come into contact with certain substances thought to be linked to ALS, such as lead, formaldehyde, hydrocarbons, and chlorinated solvents.<sup>12,13,14</sup> Additionally, smoking and use of smokeless tobacco are prevalent in the military and these are thought to be risk factors. Compounding effects of physical traumas or traumatic brain injuries (TBIs) occurring earlier in life<sup>15</sup> have also been suggested as playing a role in the higher incidence of ALS reported in military personnel. However, greater than 80% of military TBIs are diagnosed in the non-deployed setting and occur in civilian settings, suggesting that if TBI or repetitive head injury were a driving force, we should also see a spike of ALS in populations engaged in intense employment, such as wrestlers, horseback riders, lacrosse players, and soccer players, and not just military personnel. It is clear that multi-factorial issues must be considered when attempting to define ALS risk in the military, particularly until subgroup analyses are performed or we have information on other populations that equate them to military personnel. Despite not knowing what increases risk in military populations, reports continue to show that if you serve, your chances of developing ALS are greater than those of the general population.



<sup>8</sup> Al-Chalabi A, Hardiman O. 2013. The epidemiology of ALS: a conspiracy of genes, environment and time. *Nat Rev Neurol* 9:617–628.

<sup>9</sup> Fang F, Quinlan P, Ye W, et al. 2009. Workplace exposures and the risk of amyotrophic lateral sclerosis. *Environ Health Perspect* 117(9):1387-1392.

<sup>10</sup> Peters TL, Kamel F, Lundholm C, et al. 2016. Occupational exposures and the risk of amyotrophic lateral sclerosis. *Occup Environ Med* 74(2):87-92.

<sup>11</sup> Dickerson AS, Hansen J, Kioumourtoglou M, et al. 2018. Study of occupation and amyotrophic lateral sclerosis in a Danish cohort *Occup Environ Med* 75:630-638.

<sup>12</sup> <https://www.cdc.gov/niosh/topics/lead/jobs.html>

<sup>13</sup> Seals RM, Kioumourtoglou MA, Gredal O, et al. 2017. Occupational formaldehyde and amyotrophic lateral sclerosis. *Eur J Epidemiol* 32(10):893-899.

<sup>14</sup> Bello A, Woskie SR, Gore R, et al. 2017. Retrospective Assessment of Occupational Exposures for the GENEVA Study of ALS among Military Veterans. *Ann Work Expo Health* 61(3):299-301.

<sup>15</sup> Seals RM, Hansen J, Gredal O, et al. 2016. Physical Trauma and Amyotrophic Lateral Sclerosis: A Population-Based Study Using Danish National Registries. *Am J Epidemiol* 183(4):294-301.

## ALS AND MILITARY SERVICE: REPORTS PUBLISHED IN THE EARLY 1990'S TO 2008

Shortly after the 1990-91 Persian Gulf War, studies were conducted in response to reports that ALS was occurring in Gulf War veterans at an unexpected rate, particularly in young veterans who were not yet of the age at which ALS is more common. One study was led by Ronnie D. Horner, Ph.D., of the National Institute of Neurological Disorders and Stroke at the National Institutes of Health (NIH), and was funded by the Department of Veterans Affairs (VA) and the Department of Defense. The study, "Occurrence of amyotrophic lateral sclerosis among Gulf War veterans,"<sup>16</sup> was published in the September 23, 2003 issue of *Neurology*, the scientific journal of the American Academy of Neurology. The study sought to identify all of the cases of ALS that occurred in the military after the start of the Gulf War and determine whether Gulf War veterans have an elevated rate of the disease. After examining a total study population of nearly 2.5 million military personnel who were on active duty during the war, researchers found that those serving in the Gulf were nearly twice as likely to develop ALS as those not serving in the Gulf. The study found an increased risk of ALS among all branches of the military, although Army and Air Force personnel experienced the greatest risk.

Another study, "Excess incidence of ALS in young Gulf War veterans,"<sup>17</sup> also published in the September 23, 2003 edition of *Neurology*, was conducted by Robert Haley, M.D., of the University of Texas Southwestern Medical Center at Dallas and was funded by a grant from the Perot Foundation. The study examined ALS in Gulf War veterans ages 45 and younger and found that ALS occurred in these veterans at more than twice the rate as in the general population. During eight postwar years, 20 ALS cases were confirmed in approximately 690,000 Gulf War veterans, and 17 were diagnosed before age 45. Half of Desert Storm veterans diagnosed with ALS were younger than 25, and 98% were younger than 55. In young veterans, the observed incidence increased from 1 to 5 cases/year. The observed incidence of ALS in young Gulf War veterans exceeded the expected value, suggesting a war-related environmental trigger. As these veterans continue to age and reach the ages more commonly associated with ALS, the rate of the disease may continue to increase in this population.



### INSTITUTE OF MEDICINE (IOM) REPORT

*According to an IOM report published in 2006, "[T]he implication is that military service in general – not confined to exposures specific to the Gulf War – is related to the development of ALS. The findings, if validated in other studies, suggest that exposures during military services, even among those with no wartime service, might be responsible."*

<sup>16</sup> Horner RD, Kamins KG, Feussner JR, et al. 2003. Occurrence of amyotrophic lateral sclerosis among Gulf War veterans. *Neurology* 61(6):742-749.

<sup>17</sup> Haley RW. 2003. Excess incidence of ALS in young Gulf War veterans. *Neurology* 61(6):750-756.

The VA is currently conducting a large-scale health survey of veterans, the Million Veteran Program, which may provide data addressing this possibility.

The studies used different methods to examine the issue, yet they produced similar conclusions: Gulf War veterans were approximately twice as likely to develop ALS as veterans who had not served in the Gulf War. Following publication of these studies, the VA established a registry to identify cases of ALS in military veterans, regardless of the era in which they served. From 2003 to 2007, the registry enrolled 2,121 veterans with ALS and collected more than 1,200 DNA samples. The registry identified veterans with ALS who served in every era dating from before World War II and included veterans who served in the military



since the start of the current conflict in Iraq. The VA stopped enrollment in the registry at the end of 2007. However, the registry continues to supply data for research, including the Genes and Environmental Exposures in Veterans with ALS study (GENEVA), an NIH-funded case-control study evaluating the

joint effects of genetic susceptibility and environmental exposures to the risk of sporadic ALS. The VA also established in 2006 a national ALS brain bank, the VA Biorepository Brain Bank (VABBB), which continues to follow and obtain postmortem brain and spinal cord donations from past VA Registry and other veterans with ALS to support research. In 2008, Congress mandated a National ALS Registry, subsuming the 2003-2007 VA registry, which was launched by the U.S. Centers for Disease Control and Prevention (CDC) in 2010.

In 2005, in response to studies linking ALS and service in the Gulf War, researchers at Harvard University's School of Public Health sought to assess the relationship between military service and ALS mortality in different time periods.<sup>18</sup> The results of these retrospective studies demonstrated that men who had served in the military and were born between 1915-1939, had higher ALS mortality rates than those men who did not in serve in the military. The authors noted that the increase in ALS mortality was largely independent of both the length of military service and era of service (i.e., World War II, Korea, or Vietnam). Since fewer than 2% of the cohort in this 2005 study were Gulf War veterans, the authors suggest that the link between ALS and military service during the Gulf War may be extended to other military conflicts and is not specific to the Gulf War.

Examination of additional ALS cohorts has generated similar conclusions about an association with

<sup>18</sup>Weisskopf MG, O'Reilly EJ, McCullough ML, et al. 2005. Prospective study of military service and mortality from ALS. *Neurology* 64(1):32-7.

military service, including the ALS Patient Care Database (ALS C.A.R.E) from 1996-2005. ALS C.A.R.E. was the first large-scale effort to track the disease course and outcomes of patients with ALS. The project enrolled 6,000-plus patients from more than 300 clinical sites in the United States. Long-term follow-up was conducted through clinical assessments, patient self-reported questionnaires, and caregiver assessments. Findings reported in a 2009<sup>19</sup> publication showed that for male patients in the database over 60 years of age, veterans were more numerous than non-veterans (66% vs 34%;  $p < 0.001$ ). In addition, compared to non-veterans, male veterans with ALS exhibited a greater prevalence of deafness ( $p < 0.0001$ ) and diseases of the bones and joints ( $p = 0.002$ ), but had a similar incidence of lung disease, diabetes mellitus, and depression. These findings further prompted interest in study of veterans and ALS.



Based on the accumulating evidence that ALS was occurring in veterans at an unexpected and accelerated rate, the VA in 2006 requested that the National Academies of Science, Engineering, and Medicine conduct an independent assessment of the relationship between military service and the development of ALS. The National Academies assigned the task to the Institute of Medicine (IOM) (now known as the National Academy of Medicine), which advises the federal

government on public health issues and healthcare policy. The IOM appointed an expert committee to evaluate the existing scientific literature on ALS in the veteran population, and in November 2006 issued the finding that the existing evidence does in fact support an increased risk of ALS in veterans.<sup>20</sup> The IOM noted that the Harvard study on retrospective cohorts from all eras of service had provided some of the strongest evidence to show the connection between ALS and the military. The committee called for new, high-quality studies to further investigate the connection between ALS and military service and to examine those aspects of military service that contribute to disease etiology.

In 2008, two years after the IOM report, the VA implemented regulations to establish a presumption of service connection for ALS. Under the regulation, the VA presumes that the development of ALS was incurred or aggravated by a veteran's service in the military. As a result, veterans with ALS are eligible for full service-connected benefits. Unlike other presumptions, which generally are limited to a specific era (e.g., the Gulf War) or exposure (e.g., Agent Orange), the presumption for ALS is broad, among the most comprehensive that the VA has ever issued. It applies to veterans diagnosed with ALS at any time following service in the military and is not limited to where or when a veteran served.

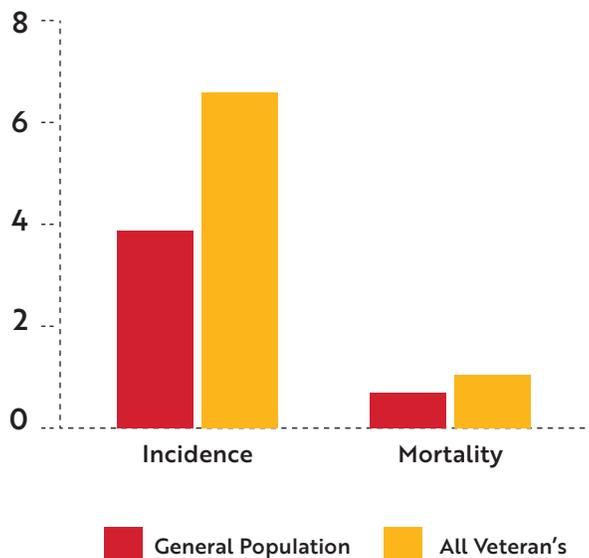
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<sup>19</sup> Miller RG, Anderson F, Brooks BR, et al. 2009. Outcomes research in amyotrophic lateral sclerosis: lessons learned from the amyotrophic lateral sclerosis clinical assessment, research, and education database. *Ann Neurol* 65 Suppl 1:S24-8

<sup>20</sup> Institute of Medicine. 2006. *Amyotrophic Lateral Sclerosis in Veterans: Review of the Scientific Literature*. Washington, DC: The National Academies Press. <https://doi.org/10.17226/11757>

## ALS AND MILITARY SERVICE: REPORTS PUBLISHED IN 2008 TO 2016

Additional studies conducted by epidemiologists at Harvard’s School of Public Health published in 2009<sup>21</sup> and 2015<sup>22</sup> further reported evidence for a nearly 60% greater risk of ALS in men with a history of military service in the last century.



### ALS INCIDENCE AND MORTALITY

in the veteran population compared  
to the U.S. general population  
adapted from Weisskopf et al. 2015  
*Epidemiology* 26(6):831-838.

The studies assessed the relationship between military service and mortality from ALS. They examined men who served in the military in different time periods, from 1910-1982, as well as different branches of the service, by looking at those who participated in the Cancer Prevention Study II cohort of the American Cancer Society, which comprises over 500,000 men. The study, conducted in 2009, examined data accrued from 1989 through 2004 and confirmed the earlier 2005 findings of an increased risk of ALS in all veterans. Both studies found that the risk of ALS was similar for those serving in World War II, Korea, and Vietnam. One of the important aspects of these studies is that researchers did not have data on deployment during wartime. Therefore, it is possible that the risk of ALS could have been greater for men who served during wartime had the study not mixed those who served during a period of war and those who did not. The lower risk of ALS, 1.6 times versus 2 times in the Gulf War studies, is consistent with this explanation.

<sup>21</sup>Weisskopf MG, Morozova N, O’Reilly EJ, et al. 2009. Prospective study of chemical exposures and amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry* 80(5):558-561.

<sup>22</sup>Weisskopf MG, Cudkovic ME, Johnson N. 2015. Military service and amyotrophic lateral sclerosis in a population-based cohort. *Epidemiology* 26(6):831-838.

In 2016, a meta-analysis was conducted using eight case-control studies and three cohort studies to further elucidate the relationship between military service and ALS. The authors examined over 1,200 studies in their initial query and excluded all but nine articles for their meta-analysis. Most of the studies were excluded due to the specific inclusion criteria. Either the studies focused on disorders other than motor neuron disease, the studies were not cohort or case-control studies, or the study did not involve military service. Overall, the meta-analysis indicated that risk of ALS was significantly increased in military personnel when compared to non-military personnel (pooled OR = 1.29, 95% CI: 1.08–1.54, by random-effects model),<sup>23</sup> which strongly supported a positive relationship between military service and the risk of ALS. The meta-analysis also conducted subgroup and sensitivity analysis, and the results further supported the overall conclusion: military service increases the risk of ALS.



Epidemiologists are discovering that cohorts with specific toxic exposures, such as veterans with known exposure to burning agents during their military service<sup>24</sup>, appear to be at an increased risk of ALS. Other recent large population-based case-control studies, such as one conducted in Denmark, found employment by the military was associated with 1.3-fold increased rate of ALS.<sup>25</sup> This study is particularly important because it is the largest analysis to date on the ALS/military link and it is also the first study conducted outside the U.S. in a population representative sample. Taken together, these large epidemiological studies strongly support a positive association between ALS and military service and illuminate the need for further studies that will help to identify the factors that influence the risk of ALS in military populations.

Published reports have discussed the potential for an association of TBI and ALS. Active duty and reserve service members are at increased risk for sustaining a TBI compared to their civilian peers. The Defense and Veterans Brain Injury Center (DVBIC) is part of the U.S. Military Health System and is the traumatic

<sup>23</sup> Tai H, Cui L, Shen D, et al. 2017. Military service and the risk of amyotrophic lateral sclerosis: A meta-analysis. *J Clin Neurosci* 45:337-342.

<sup>24</sup> Beard JD, Engel LS, Richardson DB, et al. 2017. Military service, deployments, and exposures in relation to amyotrophic lateral sclerosis survival. *PLoS ONE* 12(10): e0185751.

<sup>25</sup> Seals RM, Kioumourtzoglou MA, Hansen J, et al. 2016. Amyotrophic lateral sclerosis and the military: A population-based study in the Danish registries. *Epidemiology* 27(2):188-193.

brain injury center of excellence for the Defense Health Agency. The DVBIC has published several information papers “to provide clarification on general topics of interest related to traumatic brain injury (TBI) research.” In a research review of ALS and TBI conducted by DVBIC and published in early 2018, 12 studies and one meta-analysis relating to ALS and TBI were summarized, and evidence of a link was formally assessed. The authors found that the strongest evidence for an association between ALS and TBI was if the TBI occurred within a year of the ALS diagnosis. The DVBIC research review also stated that, in six of



the ten civilian studies that were reviewed, there was “at least some increase of risk of ALS associated with TBI history” while the remaining four civilian studies found no association between TBI and later diagnosis of ALS. In four of the six civilian studies that linked TBI and ALS, the association was determined to be dependent on the number of TBIs as well as the proximity of the TBI to the date of the ALS diagnosis. Specifically, multiple TBIs and shortened duration between the TBI and ALS diagnosis were found to be more closely associated with the risk of developing ALS. The DVBIC authors further stated that analyses of the risk factors associated with ALS are difficult to assess due to the rarity of the illness. Ultimately, the DVBIC authors found the results inconclusive. They reported that the links and associations noted in the studies they considered did not provide strong enough evidence to establish causality between TBI and an ALS diagnosis. Other more common risk factors facing military personnel, such as smoking, use of smokeless tobacco, and stress and sleep issues are important factors that need to be considered in future research. Additionally, subgroup analyses for military occupational specialty, frequency, duration, duty station, or specific incidents may be appropriate to broaden the horizons of multi-factorial causes in military populations.

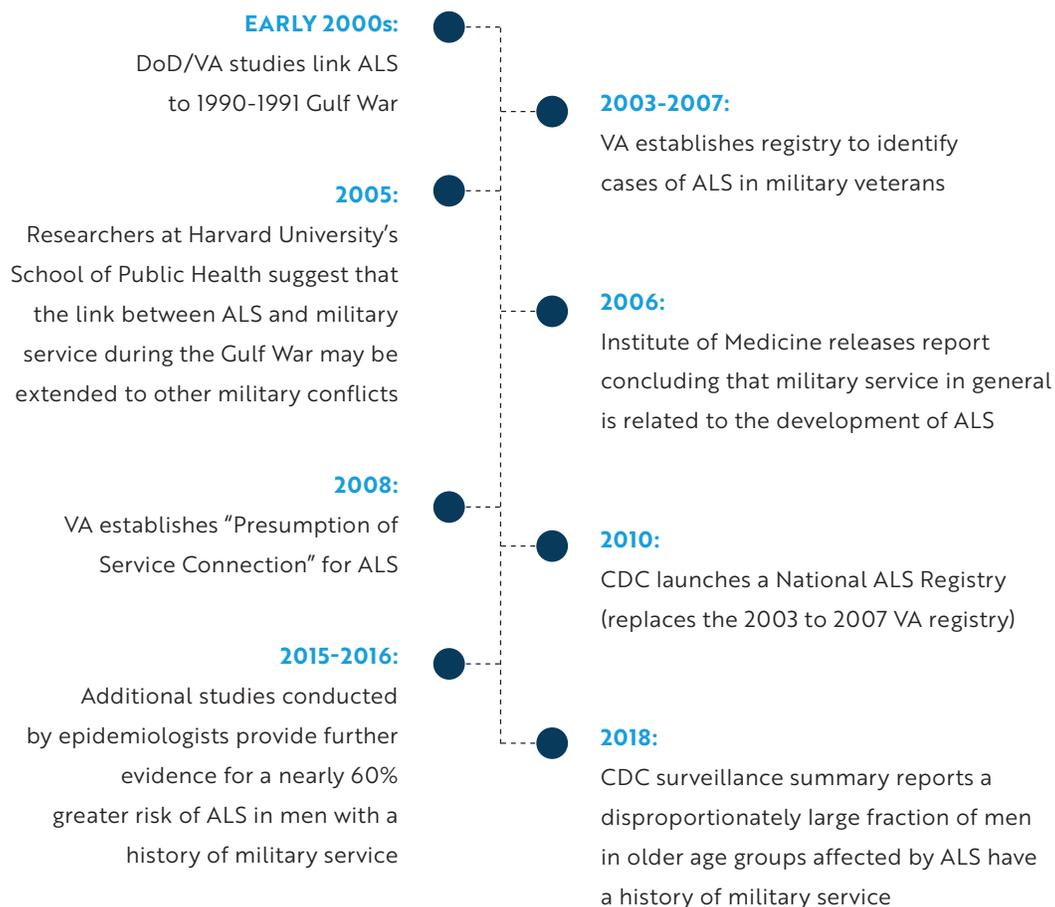
Recently, researchers from the VA published the results of studies examining data and tissues from subjects with confirmed ALS from the VA Biorepository Brain Bank.<sup>26</sup> The researchers were interested in examining possible links between ALS and chronic traumatic encephalopathy (CTE), a neurodegenerative disorder linked to repetitive head impacts. Of 155 subjects examined, nine (5.8%) were found to have both ALS and CTE. This is similar to the rate of CTE comorbidity in other neurodegenerative cohorts. Subjects with ALS and CTE comorbidity were more likely to have a history of brain injury or repetitive head injury and were more likely to have ALS with bulbar onset and mood and emotional changes and exhibit more severe pathology related to the tau protein.

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<sup>26</sup> Walt GS, Burris HM, Brady CB, et al. 2018. Chronic traumatic encephalopathy within an amyotrophic lateral sclerosis brain bank cohort. *J Neuropathol Exp Neurol* 77(12):1091-1100.

Reports on data findings from the CDC’s National ALS Registry have also reaffirmed that military service is a risk factor. In the surveillance summary published in 2014,<sup>27</sup> of 12,187 U.S. persons meeting the case definition for ALS from national administrative healthcare records and via self-report, the percentage of those who reported service in the military was 23.5%. Given that the U.S. veteran population is less than 10% of the total adult population, this fraction of ALS patients reporting military service would appear to be a disproportionately large fraction of the ALS population. Another CDC report published in 2018, using national administrative healthcare data as a case-finding method for prevalence, further demonstrated that a disproportionately large fraction of men in older age groups affected by ALS have a history of military service.<sup>28</sup>

### TIMELINE OF REPORTS LINKING ALS TO MILITARY SERVICE



<sup>27</sup> Mehta P, Kaye W, Raymond J, et al. 2018. Prevalence of amyotrophic lateral sclerosis — United States, 2014. *MMWR Morb Mortal Wkly Rep* 67:216–218.

<sup>28</sup> Nelson LM, Topol B, Kaye W, et al. 2018. Estimation of the prevalence of amyotrophic lateral sclerosis in the United States using national administrative healthcare data from 2002 to 2004 and capture-recapture methodology. *Neuroepidemiology* 51(3-4):149-157.

## VETERAN'S HEALTH ADMINISTRATION (VHA) HEALTHCARE DATA

Currently, there are 48 VA Medical Centers across the U.S. that specialize in ALS treatment. VA healthcare delivers patient-centric care with support to caregivers. In 2009, a national task group called for the establishment of ALS interdisciplinary care teams to meet VA's obligation to these service-connected veterans.

According to the VHA Amyotrophic Lateral Sclerosis System of Care Procedures Handbook 1101.07, issued in 2014, approximately 3,600 veterans living with ALS received care from VHA between 2005 and 2009. In 2018, a new search of the VHA patient database identified a roughly 30% increase in the average number of veterans currently living with ALS.<sup>29</sup> Of those, 96% were white males with an average age of 68. The designation of ALS as a presumptively compensable illness for veterans in 2008 is likely a contributing factor to the increase in patient numbers. Given the aging veteran population, it is unknown how many new patients will come to the VHA for care.



## CONCLUSIONS

Since 2001, ALS has taken the lives of more veterans than the wars in Iraq and Afghanistan combined. Although many questions remain unanswered, scientific evidence strongly demonstrates that military service increases a person's risk of ALS. Additional studies are needed to find factors that may be influencing this risk and to investigate how these factors can be translated into preventative and/or treatment strategies. As we work to address the risk of ALS in military veterans, we must bear in mind that resources also are needed to care for and serve those living with the disease today – to help improve quality of life, to provide access to necessary medical care, and to assist people with ALS in meeting the day-to-day challenges the disease has imposed on their lives.

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<sup>29</sup> Personal communication, VA Healthcare System



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