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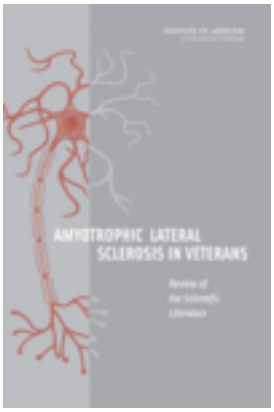


## Amyotrophic Lateral Sclerosis in Veterans: Review of the Scientific Literature

Committee on the Review of the Scientific Literature on Amyotrophic Lateral Sclerosis in Veterans

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# SUMMARY

Amyotrophic lateral sclerosis (ALS) is a progressive and nearly always fatal disease that affects a person's nervous system. It is sometimes referred to as Lou Gehrig's disease, after the famous baseball player who died from it. When a person develops ALS, nerve cells in the brain and spinal cord degenerate. The degeneration prevents communication between the nervous system and the voluntary muscles of the body, and the breakdown in communication leads to muscle paralysis. Eventually, the muscles responsible for breathing are affected, and respiration fails. There is no effective treatment for ALS.

ALS affects 20,000-30,000 men and women in the United States at any given time. It occurs in people of all races and ethnic backgrounds. About 5-10% of ALS cases are inherited; the cause of the remaining 90-95% of cases is not known.

Four recent epidemiologic studies have reported an association between development of ALS and prior service in the US military. Three of those studies[1] evaluated veterans of the 1991 Persian Gulf War; the fourth[2] evaluated veterans who served in the military in the period 1910-1982. Because of the findings of

[1] Haley RW. 2003. Excess incidence of ALS in young Gulf War veterans. *Neurology* 61(6):750-756; Horner RD, Kamins KG, Feussner JR, Grambow SC, Hoff-Lindquist J, Harati Y, Mitsumoto H, Pascuzzi R, Spencer PS, Tim R, Howard D, Smith TC, Ryan MA, Coffman CJ, Kasarskis EJ. 2003. Occurrence of amyotrophic lateral sclerosis among Gulf War veterans. *Neurology* 61(6):742-749; Smith TC, Gray GC, Knoke JD. 2000. Is systemic lupus erythematosus, amyotrophic lateral sclerosis, or fibromyalgia associated with Persian Gulf War service? An examination of Department of Defense hospitalization data. *American Journal of Epidemiology* 151(11):1053-1059.

[2] Weisskopf MG, O'Reilly EJ, McCullough ML, Calle EE, Thun MJ, Cudkowicz M, Ascherio A. 2005. Prospective study of military service and mortality from ALS. *Neurology* 64(1):32-37.

those studies, the Department of Veterans Affairs (VA) asked the National Academies to conduct an independent assessment of the potential relationship between military service and the later development of ALS. The population of interest to VA encompasses all veterans, not only veterans who served in a specific deployment (for example, veterans of the Gulf War). The National Academies assigned the project to the Institute of Medicine (IOM), which appointed a committee and charged it with evaluating the scientific literature on ALS in veterans. In addition, if an association were found to exist between military service and the later development of ALS, the committee might make recommendations that would help to identify risk factors for ALS that are relevant to military service.

In 2001, Secretary of Veterans Affairs Anthony J. Principi made a policy decision to provide disability compensation to Gulf War veterans who served in the Southwest Asia Theater of Operations during the period August 2, 1990-July 31, 1991, and who later developed ALS. Other US veterans with ALS do not receive disability compensation for their illness.

## METHODOLOGY

The committee began its work by identifying the medical and scientific literature on ALS. PubMed, a database created and managed by the National Library of Medicine, was searched for studies on ALS in the veteran population. The articles relevant to the committee's task were identified, and copies were obtained. Next, the committee assessed the studies for methodologic rigor and for evidence of association between service in the military and development of ALS. For information on possible ALS risk factors, PubMed was searched for studies on ALS in nonveteran populations and review articles on ALS (including articles on studies conducted in laboratory animals).

The committee framed its conclusion on the basis of categories that qualitatively rank the strength of the evidence of an association (described in Box S-1). The categories are adapted from the system of the International Agency for Research on Cancer for evaluating evidence of the carcinogenicity of various

agents, and they have been used by many previous IOM committees.

## CONCLUSION

The committee identified one high-quality cohort study[3] that adequately controlled for confounding factors and reported a relationship between serving in the military and later development of ALS. Results of three other studies supported the association. One of the three[4] was generally well conducted, but it was limited by the potential for underascertainment of cases in the comparison group. The other two[5] had several methodologic limitations that made them less valuable for the committee's evaluation. Another study[6] did not report an association between military service and ALS; it also had methodologic limitations.

**On the basis of its evaluation of the literature, the committee concludes that there is limited and suggestive evidence of an association between military service and later development of ALS.**

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[3] Weisskopf MG, O'Reilly EJ, McCullough ML, Calle EE, Thun MJ, Cudkowicz M, Ascherio A. 2005. Prospective study of military service and mortality from ALS. *Neurology* 64(1):32-37.

[4] Horner RD, Kamins KG, Feussner JR, Grambow SC, Hoff-Lindquist J, Harati Y, Mitsumoto H, Pascuzzi R, Spencer PS, Tim R, Howard D, Smith TC, Ryan MA, Coffman CJ, Kasarskis EJ. 2003. Occurrence of amyotrophic lateral sclerosis among Gulf War veterans. *Neurology* 61(6):742-749; Coffman CJ, Horner RD, Grambow SC, Lindquist J. 2005. Estimating the occurrence of amyotrophic lateral sclerosis among Gulf War (1990-1991) veterans using capture-recapture methods. *Neuroepidemiology* 24(3):141-150.

[5] Haley RW. 2003. Excess incidence of ALS in young Gulf War veterans. *Neurology* 61(6):750-756; Smith TC, Gray GC, Knoke JD. 2000. Is systemic lupus erythematosus, amyotrophic lateral sclerosis, or fibromyalgia associated with Persian Gulf War service? An examination of Department of Defense hospitalization data. *American Journal of Epidemiology* 151(11):1053-1059.

[6] Kang HK, Bullman TA. 2001. Mortality among US veterans of the Persian Gulf War: 7-year follow-up. *American Journal of Epidemiology* 154(5):399-405.

## RECOMMENDATIONS

The committee developed recommendations to assist VA in gathering information on ALS in the veteran population so that it might be able to determine more definitively whether there is an association between military service and ALS. The committee also provided guidance for further study of risk factors that are most relevant to military service. The committee recommends the following:

- Explore the use of existing cohort studies designed for other outcomes and ongoing or completed high quality case-control studies of ALS for their suitability to assess the relationship between ALS and military service.
- Identify all putative ALS risk factors relevant to military service and conduct systematic reviews of the literature on them.
- Conduct further corroborative or exploratory studies to elucidate ALS risk factors relevant to military service.

**BOX S-1 Categories of Strength of Association**

**Sufficient Evidence of a Causal Relationship**

This category would indicate that evidence is sufficient to conclude that there is a causal relationship between military service and ALS in humans. The evidence must be supported by experimental data and fulfill the guidelines for sufficient evidence of an association (below). The evidence must be biologically plausible and satisfy several of the guidelines used to assess causality, such as strength of association, dose-response relationship, consistency of association, and temporal relationship.

**Sufficient Evidence of an Association**

This category would indicate that evidence is sufficient to conclude that there is a positive association, that is, a consistent positive association has been observed between military service and ALS in human studies in which chance and bias, including confounding factors, could be ruled out with reasonable confidence. For example, several high-quality studies had reported consistent positive associations, and the studies were sufficiently free of bias, including adequate control for confounding factors.

**Limited and Suggestive Evidence of an Association**

This category would indicate that evidence is suggestive of an association between military service and ALS in humans, but the body of evidence is limited by the inability to rule out chance and bias, including confounding factors, with confidence. For example, at least one high-quality study had reported a positive association that was sufficiently free of bias, including adequate control for confounding factors. Other corroborating studies might provide support for the association, but they were not sufficiently free of bias, including confounding factors. Alternatively, several studies of lower quality might show consistent positive associations, and the results were probably not due to bias, including confounding factors.

**Inadequate or Insufficient Evidence to Determine Whether an Association Exists**

This category would indicate that evidence is of insufficient quantity, quality, or consistency to permit a conclusion regarding the existence of an association between military service and ALS in humans.

**Limited and Suggestive Evidence of No Association**

This category would indicate that evidence is consistent in not showing a positive association between military service and ALS in humans after exposure of any magnitude. A conclusion of no association is inevitably limited to the conditions, magnitudes of exposure, and length of observation in the available studies. The possibility of a very small increase in risk after exposure cannot be excluded.

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**Committee on the Review of the Scientific Literature on Amyotrophic Lateral Sclerosis in Veterans**

**Board on Population Health and Public Health Practice**

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

*"Knowing is not enough; we must apply.*
*Willing is not enough; we must do."*
—Goethe

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# REVIEWERS

This report has been reviewed in draft form by persons chosen for their diverse perspectives and technical expertise in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards of objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following for their review of this report:

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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. The review of this report was overseen by **Elena Nightingale**, Scholar-in-Residence, Institute of Medicine. Appointed by the National Research Council, she was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the author committee and the institution.

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