

Draft 2014 RAC–GWVI Report

Review of Epidemiology Research and Recommendations



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Epidemiologic Research Overview and Update

- ▶ Extensive body of epidemiologic studies prior to 2008 report; Committee drew conclusions from existing studies, recommended research to address high priority issues
- ▶ More limited epidemiologic research since 2008; many issues remain unaddressed
- ▶ 2014 draft findings and recommendations: Updates what we have learned from epi studies since 2008, recommends priority research that is needed, methodological improvements

Epidemiologic Research 2008 Report: Major Findings/Issues

- ▶ Multiple large studies of diverse Gulf War veteran populations
- ▶ Gulf War Illness (GWI) --“umbrella” term for chronic symptomatic condition (variously defined) associated with military service in 1990-91 Gulf War
- ▶ GWI most prevalent condition in GW veterans--affects at least 25%. Not explained by stress or established med/psych dx. Longitudinal studies indicate little improvement over time. Treatments urgently needed.

GWI symptom domains consistent across GW populations; different approaches for using symptom “groupings” to define GWI (6 case defs, 4 other approaches reviewed)



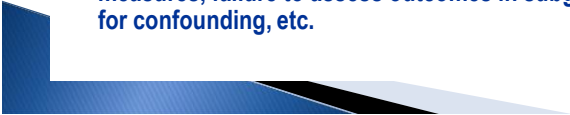
Epidemiologic Research 2008 Report: Major Findings/Issues

- ▶ Mortality. No overall increase in disease-related mortality. GW veterans in modeled Khamisiyah exposure area had sign. increased brain cancer mortality compared to other GW veterans
- ▶ Diagnosed diseases. Little research or systematic data to determine if GW vets have excess rates of most medical conditions of concern.
 - Studies indicate ALS rate sign. higher than in other veterans
 - Possible increase in asthma for greatest oil fire exposed.
 - Increase in dx CFS (maybe FM)
 - Psych conditions affected GW vets at higher rates than nondeployed, but much lower rates than after other conflicts (e.g. PTSD prev. = 3-6%)


Several GW surveys indicated sign. increase in vet-reported medical diagnoses: migraines, gastrointestinal conditions, respiratory conditions, skin conditions



Epidemiologic Research Major Findings/Issues as of 2008 Report

- ▶ Hospitalizations – limited differences between GW, nondeployed veterans
 - ▶ Health of family members
 - Reproductive outcomes. Inadequate data on birth defects in children of GWV, indications of higher rates overall than nondeployed, increased congenital heart defects in children of GW vets, increased miscarriages among GW vets.
 - Other family members. One study showed minimal health difference in spouses of GWV. Data on health of GW veterans' children collected by VA but never published.
 - ▶ Serious methodological issues in GW epidemiologic research: lack of research guidelines and standards, inconsistent health and outcomes measures, failure to assess outcomes in subgroups of interest, little control for confounding, etc.
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Epidemiologic Research Major Findings/Issues as of 2008

- ▶ Recommendations: regular longitudinal assessment of veterans to assess GWI over time
 - ▶ Determine if GW veterans affected by excess rates of dx medical conditions, with focus on neurological conditions, cancers
 - ▶ Regular monitoring of overall and disease-specific mortality (5 year intervals)
 - ▶ Further evaluation of birth defect findings; publish available data on family health
 - ▶ Recs for improved methods in GW epidemiologic research
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Epidemiologic Research 2014 Update: Overview

- ▶ Much less published GW epidemiologic research since 2008
Highlights:
 - 2009 VA study of neurological mortality; papers from 2005 longitudinal survey
 - national GW survey from VA UTSW contract, several smaller studies
- ▶ Additional major GW epi studies now underway:
 - 2 large studies funded by DOD (Boston/Fort Devens, Baylor nat'l survey)
 - VA longitudinal survey of GW era veterans (target n = 30,000)
- ▶ IOM 2010 Report: called for improved monitoring of GW veterans over time, improved research effort overall
- ▶ VA Gulf War Strategic Planning process: plans for improved surveillance of health outcomes, and for establishing expert-consensus case definition for GWI
- ▶ Table: Additional insights re: Prevalence of Gulf War illness

Population-Based Prevalence Estimates: Chronic Symptomatic Illness in 1990-1991 Gulf War Veterans and Nondeployed Era Veterans

Study	Gulf War Veterans Assessed	Year(s) of Assessment	Case Definition Used	Prevalence in Gulf War Veterans	Prevalence in Nondeployed Veterans	Excess Illness in Gulf War Veterans
Prevalence estimates published before 2008						
Fukuda 1998 (Fukuda et al., 1998)	1,155 Air Force veterans	1995	CMI	45%	15%	30%
Proctor 2001 (Proctor et al., 2001)	180 New England Army veterans	1994-1996	CMI (modified)	65%	33%	32%
Unwin 1999 (Unwin et al., 1999)	4,428 U.K. male veterans	1998	CMI (modified)	62%	36%	26%
Unwin 2002 (Unwin et al., 2002)	226 U.K. female veterans	1998	CMI (modified)	64%	35%	29%
Steele 2000 (Steele et al., 2002)	1,548 Kansas veterans	1998	Kansas GWI CMI	34% 47%	8% 20%	26% 27%
Blanchard 2006 (Blanchard et al., 2006)	1,035 U.S. veterans	1999-2001	CMI (modified) ¹	29%	16%	13%
Prevalence estimates published since 2008						
King 2008	357 U.S. veterans	2001	CMI	54%	not evaluated	-
Kang 2009 (Kang et al., 2009)	6,111 U.S. veterans	2005	VA-defined multisymptom illness ²	37%	12%	25%
Kelsall 2009 (Kelsall et al., 2009)	1,381 Australian veterans	2000-2002	Australian factor definition	26%	16%	10%
Iannacchione 2011 (Iannacchione et al., 2011)	5,699	2007-2009	Haley factor definition (3 syndromes combined)	14%	4%	10%
Steele 2012 (Steele et al., 2012)	646 Kansas City area veterans	2000	CMI	45%	not evaluated	-
Smith 2012 (Smith et al., 2012)	317 U.S. veterans	2001	CMI	50%* 34%*	not evaluated	-

Epidemiologic Research 2014 Update: Research Findings


- ▶ Overall, all population-based studies conducted since the Gulf War have continued to identify a significant excess rate of chronic symptomatic illness, variously defined, in 1990-1991 Gulf War veterans. The majority of studies, overall, suggest a GWI prevalence in the 25-30% range.
- ▶ Prognosis for veterans with Gulf War illness. Little additional information on the long-term prognosis of Gulf War illness has become available since 2008. Prior data suggest that there is little to no improvement in the health of ill Gulf War veterans over time. The effect that aging will have on this vulnerable population remains unclear.
- ▶ General health among Gulf War veterans. Studies published since 2008 have continued to document poorer general health status and greater disability among Gulf War veterans. Despite the extensive number of studies conducted with Gulf War veterans in the 23 years since Desert Storm, medical surveillance in this population remains woefully inadequate.

Epidemiologic Research 2014 Update: Research Findings


- ▶ Medical conditions in Gulf War veterans. Very little research has yet been conducted to determine rates at which Gulf War veterans have been affected by medical conditions of possible concern. As a result, it is not currently known if Gulf War veterans have experienced excess rates of most medical conditions. Disorders of concern reviewed in this report include the following:
 - Neurological disorders. Although ALS and other neurological conditions are a prominent concern for Gulf War veterans, very little research is available that identifies rates of most neurological disorders in this population. Rates of multiple sclerosis, Parkinson's disease, and other neurological diseases are currently unknown; there is particular concern regarding these conditions as the Gulf War veteran population ages.
 - Cancer. Since 2008, research using state cancer registries suggested increased rate of lung cancer in GW veterans. Brain cancer mortality also appears to be increased in subgroup of GW veterans with greatest exposure to Khamisiyah fallout and oil fire smoke.

In general, rates of most medical conditions remains unknown and understudied.

Epidemiologic Research 2014 Update: Research Findings

- ▶ **Sleep dysfunction.** A single study published since 2008 identified sleep abnormalities in a group of Gulf War veterans compared to obesity matched controls. Sleep disturbance is an extremely common symptom in veterans with GWI and C-PAP treatment has shown some promise in a small treatment trial (see Treatment Research section).
 - ▶ **Multisymptom conditions.** Chronic Fatigue Syndrome, Fibromyalgia, Multiple Chemical Sensitivity. These disorders share similar symptoms with Gulf War illness, but few Gulf war illness patients meet criteria for them. Gulf War illness is a distinct syndrome and Gulf War veterans who meet criteria for these disorders often differ significantly from non-veteran populations. It may be necessary to consider Gulf War veterans who do and do not meet criteria for these disorders separately in research studies of GW veterans, including treatment research.
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Epidemiologic Research 2014 Update: Research Findings

- ▶ **Psychiatric disorders.** Studies on psychiatric morbidity in deployed Gulf War veterans since 2008 continue to show that combat and other wartime stressors are associated with PTSD, anxiety, depression and alcohol abuse but do not predict or explain Gulf War illness.
 - ▶ **Birth defects.** No definitive new information is available on risk of birth defects in offspring of Gulf War veterans. It is important that birth outcomes be assessed in children of veteran subgroups of interest (e.g. exposure, location, illness subgroups)
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Epidemiologic Research 2014 Update: Research Findings

- ▶ **Mortality.** Lack of current information on overall and disease-specific mortality among U.S. Gulf War veterans is an important issue. No comprehensive information has been published on the mortality experience of U.S. Gulf War era veterans after the year 2000. The 13 years for which no mortality figures are available represent more than half of the 23 years since Desert Storm.

Mortality information from the last decade is particularly crucial for understanding the health consequences of the Gulf War, given the latency periods often associated with chronic diseases of interest. Despite specific recommendations, over many years, from both the current Committee and Institute of Medicine panels, federal research efforts to monitor the mortality experience of 1990-1991 Gulf War veterans remains seriously inadequate.



Epidemiologic Research 2014 Update:

- Methodological issues**
- ▶ Collecting data on Gulf War illness has been hampered by a number of methodological issues relating to case definitions, concurrent disorders and conditions in ill veterans, multiple exposures, subject recruitment, subject follow up and survey tools. For example, as raised in both the 2004 and 2008 Committee reports, it is important to assess health outcomes in identifiable Gulf War veteran subgroups, as opposed to grouping all veterans with heterogeneous exposures and experiences together. Whether these groupings are based on exposure, unit membership, symptom profiles, deployment location or a combination of factors, comparisons of subgroups with healthy controls will be more informative than assessing deployed veterans as a single group.



Epidemiologic Research 2014 Update:

Case definitions.

Case definitions currently include the Haley syndrome criteria, the Fukuda et al chronic multisymptom illness (CMI), criteria, the Kansas GWI definition and other adaptations of these approaches to defining Gulf War illness. Each of these definitions has advantages and drawbacks. The Haley syndromes are quite narrow and underestimate the occurrence of the disorder, but may allow highly specific characterization of veterans who meet criteria for a syndrome; the mild form of CMI is very broad and over inclusive, resulting in high prevalence rates even in control populations but is inclusive in terms of a range of ill health in Gulf War veterans, and the Kansas criteria predict Gulf War illness at rates that appear to be consistent with those seen across multiple Gulf War populations but exclude veterans with some concurrent medical disorders who may also have Gulf War illness.

Many research papers and proposals do not clearly define the criteria used for identifying veterans with Gulf War illness at all, an even greater problem. A VA Strategic Planning Group identified a process for a consensus case definition using input from experts on Gulf War illness and case definition methodology (see Appendix X), but this process was never initiated. VA has authorized the Institute of Medicine to develop a case definition, but the charge to the IOM is seen by the Committee as being seriously flawed. In the absence of a consensus case definition 22 years after the appearance of this condition, it is quite difficult to compare research findings in epidemiological, pathobiological or treatment research approaches to Gulf war illness.

Epidemiologic Research 2014 Update:

- ▶ **Surveillance.** Relatively little data are available that provide a clear understanding of the impact of Gulf War service on the current health of Gulf War veterans. This includes data on the clinical course and prognosis of veterans with Gulf War illness, rates of other medical conditions, and the mortality profile of Gulf War veterans, many years after the war. Some of these issues are addressed in the VA longitudinal survey currently underway, but the survey instrument does not allow identification of veterans with Gulf War illness and other outcomes of interest, despite urging from the RAC and despite recommendations in the 2010 IOM report for improved surveillance of this population.

Information about Gulf War illness prevalence and prognosis as well as other medical disorders is key to healthcare planning for this population.

Epidemiologic Research Recommendations

Case definition of Gulf War illness. Differences in GWI prevalence reported among the studies reviewed in this section provide a clear illustration of the importance of a consistent and widely accepted case definition for Gulf War illness research. The Committee recommends the following approaches to the development of such a definition.

1. VA should implement the steps outlined in the draft strategic plan (see Appendix) for developing an evidence based, expert consensus-driven case definition for Gulf War illness. This effort should involve representatives from other federal agencies sponsoring research in Gulf War veterans, a broad spectrum of scientists conducting research in Gulf War veterans, clinicians knowledgeable about the problem, and Gulf War veterans.
2. VA should cancel the current IOM assignment to develop a Gulf War illness case definition, since it will not be developed using an evidence-based process that includes analytic assessment of data available to evaluate and optimize the definition. The IOM panel charged to develop this case definition does not include adequate representation by scientists with expertise in Gulf War illness research and methods for developing case definitions based on symptom profiles.

Epidemiologic Research Recommendations

Case Definition (cont.)

3. VA should adopt the name *Gulf War illness* for the symptomatic condition associated with military service in the 1990-1991 Gulf War.

Epidemiologic Research Recommendations

Surveillance. Ongoing monitoring and surveillance of the Gulf War veteran population is critical as this group of veterans ages. A plan for such monitoring was included in the plan proposed by a VA Strategic Planning group composed of representatives from RAC, VA and DoD (see Appendix). Such surveillance must include the following elements:

1. Ongoing assessment of Gulf War illness and its impact on the health and lives of Gulf War veterans.
2. Systematic assessment of overall and disease-specific mortality in Gulf War veterans overall, and in specific subgroups of interest . Reports on the results of these assessments should be published at a minimum of 5-year intervals.



Epidemiologic Research Recommendations

Surveillance (cont.)

3. Use of VA's longitudinal survey to assess rates of physician-diagnosed medical conditions in Gulf War and era veterans. Survey data can be used to flag conditions of possible importance and followed up with more in-depth study.
4. Use of VA's longitudinal survey to assess rates of health problems and birth defects in children of Gulf War era veterans. Survey data can be used to flag condition of possible concern and followed up with more in-depth study. It is also important that VA publish results from studies of children conducted over 10 years ago.
5. Evaluation of health outcomes in Gulf War veterans in subgroups of potential importance—defined by suspected or documented exposures in theater, geographical locations in the Gulf War theater or other predictors.



Epidemiologic Research Recommendations

Improved methodology in Gulf War epidemiologic research. It is important that VA work with CDMRP to establish guidelines for improved methodology in Gulf War research that can be included in requests for proposals and subject to research application reviews. Such guidelines should include the following:

1. Systematic methods for assessing symptoms and other health outcomes in Gulf War veterans.
 2. Evaluation of health outcomes in Gulf War veteran subgroups of importance—for example, subgroups defined by relevant exposure history or location in theater.
 3. Consideration of subpopulations with multiple health outcomes.
 4. In evaluating risk factors for Gulf War illness and other health outcomes, use of analytic methods that adequately control for confounding effects of additional exposures and etiologic factors that may be associated both with the exposures and outcomes of interest as well as consideration of the effects of mixed exposures.
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