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# Occupational exposure to complex mixtures in the United States military

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BOSTON UNIVERSITY  
SCHOOL OF PUBLIC HEALTH

Dissertation

**OCCUPATIONAL EXPOSURE TO COMPLEX MIXTURES  
IN THE UNITED STATES MILITARY**

by

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Submitted in partial fulfillment of the  
requirements for the degree of  
Doctor of Philosophy

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## **DEDICATION**

Dedicated to David Maule

He believes I can “change the world” and empowers me to believe the same.

## **ACKNOWLEDGMENTS**

I would like to thank my committee, Bobbie White, Mike McClean, and Kim Sullivan.

First, I must thank Bobbie, who as my advisor, provided wonderful guidance, was generous with her time, and shared with me her expert knowledge on the subject of Gulf War Illness. I am extremely lucky for the opportunity to have her as my mentor. Thank you to Mike McClean and Kim Sullivan for their knowledge, mentorship, and thoughtful reviews of my work. Special thanks must go to Mike for setting me down the Environmental Health road many years ago as a Master's student.

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All my love and thanks goes to my family. I am here because of your love, support, and never-ending belief in me.

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# **OCCUPATIONAL EXPOSURE TO COMPLEX MIXTURES**

## **IN THE UNITED STATES MILITARY**

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### **ABSTRACT**

**Background:** Military personnel are occupationally exposed to chemical mixtures at domestic locations and in theater.

At military bases, a chemical hazard of concern is JP-8 jet fuel, the largest chemical exposure in the United States Air Force (USAF). We examined blood concentrations of JP-8 constituents as biomarkers of exposure and determined if workday exposure is associated with diminished balance control.

Veterans of the 1990–1991 Gulf War (GW) were exposed to mixtures of chemicals in theater and about a third of GW veterans developed GW illness (GWI) on return from deployment. We identified health symptom profiles in the GWI literature and examined longitudinal exposure-symptom relationships in a subset of GW veterans.

**Methods:** In USAF personnel, personal air, urine, and blood samples were analyzed for components of JP-8. Separate multivariate linear regression analyses were conducted to examine relationships between personal air and post-shift blood volatile organic compounds (VOCs) and between JP-8 exposure and postural sway.

Meta-analytic techniques were conducted to determine pooled prevalence and

combined odds ratios of symptoms comparing GW and GW-era control veterans.

Repeated logistic regression models stratified by sex examined the association of GW exposures and symptoms.

**Results:** Blood VOC concentrations were higher among participants with work-shift JP-8 exposure and breathing zone total hydrocarbons significantly predicted VOC blood levels. Postural sway outcomes were associated with personal variables and task difficulty but not JP-8 exposure.

GW veterans had higher odds of reporting all analyzed symptoms compared to GW-era controls, with 20% excess prevalence for fatigue, memory problems, and joint pain. Men had more significant associations between GW exposures and symptoms compared to women. Specific exposures were significantly associated with higher symptom reporting over time.

**Conclusion:** In USAF personnel, blood VOC concentrations reflected work-shift exposure to jet fuel, supporting their use as biomarkers of JP-8 exposure. Work-shift exposure to JP-8 did not diminish balance control.

Health symptoms evaluated through meta-analysis with the largest summary odds ratios were consistent with the symptom clusters reported in case definitions of GWI. The associations between GW exposure and longitudinal symptom reporting differed between men and women.

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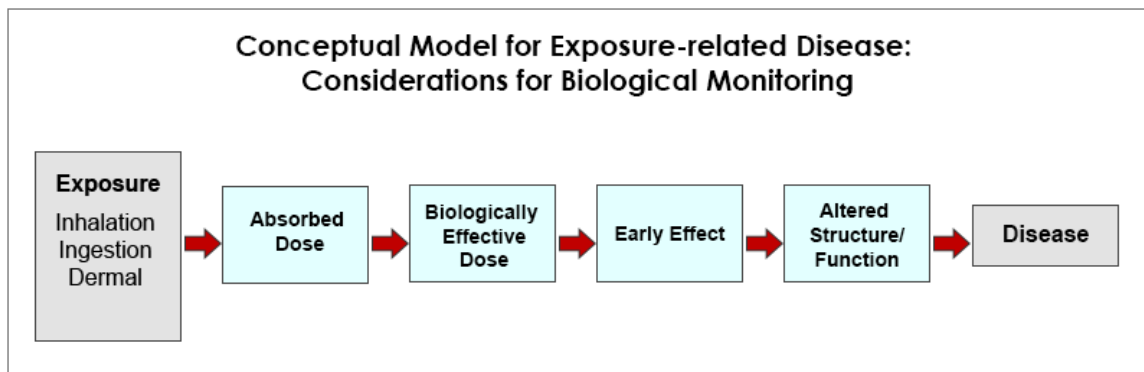
## **CHAPTER ONE. INTRODUCTION**

Over 2.4 million people serve in the United States Armed Forces, including Active Duty Armed Forces, Coast Guard, and DoD Ready Reserve (Office of the Deputy Assistant Secretary of Defense for Military Community and Family 2016). These individuals represent an occupational group distinct from the civilian workforce both during their time in the service and as veterans following their separation from the military. First, personnel in the US Armed Forces are, on average, younger than the civilian workforce and more physically fit than their civilian counterparts because of regular physical training and combat readiness requirements (Proctor 2008; Sulsky 2003). One-half of the Active Duty enlisted personnel and one-third of Reserve personnel are younger than 25 years old (Office of the Deputy Assistant Secretary of Defense for Military Community and Family 2016), while just 15% of civilian workforce in 2016 is younger than 24 (Bureau of Labor Statistics 2016). Second, an analysis comparing military occupational specialty codes to department of labor statistics showed that approximately 30% of military jobs do not have a civilian counterpart, leading to unique occupational health and safety needs for military occupations (Sulsky 2003). Finally, the life-cycle of a military career is often a combination of garrison and deployment stations, each with its own mission requirements and potential hazards (Gaydos 2011; Proctor 2008).

This research focuses on two groups of military personnel who experienced exposure to complex mixtures of chemicals, one during occupational activities in garrison

and the other in a deployment zone. In *Chapters 2* and *3*, we use a standard exposure-related disease framework to explore methods for characterizing exposure to JP-8 and nervous system effects of JP-8 in a group of United States Air Force (USAF) jet fuel workers from the Occupational JP-8 Exposure Neuroepidemiology Study (OJENES) (Figure 1.1). Following this traditional framework is more challenging in a deployment zone where standard occupational health and monitoring procedures are not always possible. In the third and fourth studies, we focus on veterans of the 1990–1991 Gulf War (GW). The research and medical communities have identified health problems that emerged after return from deployment, requiring retrospective identification of relevant exposures and causal links. In *Chapters 4* and *5*, we investigate symptom profiles and exposure-related health complaints among GW veterans exposed to complex mixtures of chemicals and other hazards during deployment.

Figure 1.1



Source: [http://sphweb.bumc.bu.edu/otlt/mph-modules/exposureassessment/exposureassessment\\_print.html](http://sphweb.bumc.bu.edu/otlt/mph-modules/exposureassessment/exposureassessment_print.html)

### *JP-8 exposures and their effects*

Jet propulsion fuel-8 is the only fuel used in the US Air Force and widely used in

the other branches of the US Armed Forces and NATO militaries (NRC 2003). It is a kerosene-based fuel with over 200 aliphatic and aromatic hydrocarbons and can be used to fuel ground vehicles, generators, heaters, and other fuel-driven equipment (NRC 2003). For military aircraft, specific performance objectives are met by enhancing the base JP-8 formula with additives, including corrosion inhibitors, static inhibitors, biocides, and thermal stability improvers (ATSDR 2017; Ritchie et al. 2003). JP-8 is a complex mixture and there is no current standard industrial hygiene method for quantifying occupational jet fuel exposure. Previous studies have used several different techniques to measure exposure to components of JP-8 as surrogate measures of jet fuel exposure, including total hydrocarbons (THC) and volatile organic compounds (VOCs) (*e.g.*, naphthalene, benzene, toluene, and xylenes) in personal breathing zone, dermal skin samples, and exhaled breath, in addition to the urinary biomarkers 1- and 2-naphthol, which are metabolites of the parent compound naphthalene (Chao et al. 2005; Chao et al. 2006; Egeghy et al. 2003; Merchant-Borna et al. 2012; Puhala et al. 1997; Rodrigues et al. 2014; Serdar et al. 2003; Serdar et al. 2004; Smith et al. 2010; Smith et al. 2012; Tu et al. 2004). VOCs measured in blood provide an estimate of total absorbed dose and a more biologically relevant measure of VOCs that could reach target organs; however, very few studies have utilized this biomarker (Blount 2006; Kirman 2012).

The OJENES study recruited 74 Active Duty personnel from three USAF bases based on job activities with a range of potential occupational jet fuel exposure. Personnel categorized as low JP-8 exposed worked in administrative office jobs, and high JP-8 exposed personnel worked in aircraft and fuel cell maintenance and fuel handling. Over

the course of a work shift, JP-8 exposure was assessed by self-reported jet fuel contact and by measuring components of JP-8 in personal air, urine and blood samples. Blood samples from 69 OJENES participants were analyzed for toluene, ethylbenzene, *m/p*-xylene, and *o*-xylene . The research summarized in *Chapter 2* aimed to characterize blood biomarkers of JP-8 exposure and to establish the validity of blood VOCs as indicators of exposure to jet fuel. To address these aims, we compared VOC blood levels in USAF personnel with and without self-reported JP-8 contact. We used multiple linear regression models to examine the relationship between VOC levels in blood and a well-characterized JP-8 exposure measure, personal breathing zone levels of total hydrocarbons in air (Maule et al. 2016).

Components of JP-8 are known to be neurotoxic, though the mechanisms of toxicity of VOC constituents in JP-8 depend on their specific structures and the exposure dose (White and Proctor 1997). Due to the possible neurotoxicity of JP-8 components, central (CNS) and peripheral nervous system (PNS) effects of exposure are a concern. As a benchmark for protection of personnel health, the USAF adopted the 2013 American Conference of Governmental Industrial Hygienists (ACGIH) threshold level value set over an 8-hour time weighted average (TWA) of 200 mg/m<sup>3</sup> for jet fuel in air (ATSDR 2017).

Balance control involves functional aspects of both the CNS and PNS and has been evaluated using posturography, a technique for measuring postural sway, in many occupational settings where workers are exposed to organic solvents (Hegeman et al.

2007; Kuo et al. 1996; Kurikawa et al. 2002; Vouriot et al. 2005; Yokoyama et al. 1997). Less efficient balance, or increased postural sway, has been noted in adhesive manufacturing, shipbuilding, and sewage treatment workers (Herpin et al. 2009; Ledin et al. 1989; Kuo et al. 1996). In two previous studies of USAF jet fuel workers, as exposure to personal air levels of JP-8 constituents (*e.g.*, benzene, xylenes, naphthalene) increased, postural sway during the most difficult balance task (*i.e.*, standing on two legs with eyes closed on a foam support) was significantly increased, indicating dysfunction among JP-8 exposed USAF personnel (Bhattacharya 2001; Smith et al. 1997).

Thirty-seven OJENES participants, whose JP-8 exposure was categorized as high or low based on job activities, completed four balance tasks before and after a work shift. The high exposure group was comprised of 23 personnel and the low group of 14 personnel. Diminished balance control was quantified for each of the balance tasks by increased sway area and increased sway velocity. JP-8 exposure was measured using THC and naphthalene levels in personal breathing zone air and urinary 1- and 2-naphthol concentrations. The research in *Chapter 3* aimed to determine the relationship between acute JP-8 exposure and postural sway performance at the end of a work shift. We compared sway area and velocity measurements from four balance tasks in the high and low JP-8 exposed USAF personnel. Multiple linear regression models were used to evaluate the association between JP-8 exposure (*i.e.*, THC and naphthalene levels in personal air and urinary naphthol concentrations) and postural sway (Maule et al. 2013).

### *Health effects of service in the 1991 Gulf War*

Beginning in 1990 through early 1991, approximately 700,000 US troops were deployed to the Persian Gulf in support of Operations Desert Shield and Desert Storm, collectively known as the Gulf War (GW) (RAC-GWVI 2008). These two operations resulted in a 6-week intensive air-strike in the region and a four-day ground war. During the GW, women were 7% of the deployed force, the largest group of women to deploy to a war-zone up to that time (Coughlin 2016).

There were fewer combat casualties and fatalities among American military personnel during the course of these two operations compared to previous wars and the most recent conflicts in Iraq and Afghanistan. However, during their GW deployment, US troops were exposed to a combination environmental and physical hazards, including petrochemicals, oil well fire smoke, depleted uranium, pesticides, pharmaceuticals agents and chemical warfare agents (RAC-GWVI 2008).

Exposure to raw petrochemicals was widespread because it was used as a sand suppressant during the high wind season, and petrochemicals were used to fuel aircraft, ground vehicles and other equipment including tent heaters. The tent heaters were often unvented, exposing troops to high levels of fuel combustion products in their living quarters (RAC-GWVI 2008). In February 1991, as the Iraqi Army retreated from Kuwait, Iraqi troops set fire to over 600 Kuwaiti oil wells. The last oil well fire was extinguished on November 6, 1991 (Smith et al. 2002). Large smoke plumes from these fires contained particulates and gases exposing military personnel to a mixture of carbon dioxide, carbon

monoxide, sulfur dioxide, nitrogen oxides, volatile organic compounds, ozone, polycyclic aromatic hydrocarbons, heavy metals, and soot (Kelsall et al 2004a; Petrucci et al. 1999; Spektor 1998). Troops stationed in Kuwait and Saudi Arabia were exposed to these toxicants. During the GW, the US used depleted uranium (DU) ordinance and armor-plating for the first time, and US troops were often unaware that they were handling DU munitions (RAC-GWVI 2008). There was also widespread use of pesticides in the desert environment during the GW to control insects carrying vector-borne illnesses such as sand flies, sand fleas and mosquitoes. Organophosphate and carbamate pesticides were used in area spraying or fogging to protect living and eating quarters as well as work spaces, while permethrin and DEET were issued for personal use (Fricker et al. 2000; Winkenwerder 2003). DEET was applied directly to the skin and permethrin was applied to uniforms, bedding, and bed nets. Finally, several prophylactic pharmaceuticals were given to US and other allied troops during GW deployment, including anthrax and botulinum toxin vaccines and pyridostigmine bromide (PB pills), which were given for the first time in a military operation in the hopes that they would protect troops from chemical warfare agents (RAC-GWVI 2008). No accurate records were kept that would identify which troops received the anthrax vaccine, and PB pills were distributed without tracking their use by individual soldiers.

Prior to and during the GW, it was known that the Iraqi Army had chemical weapons. Troops were given devices that were designed to detect the presence of chemical warfare agents, and there were widespread reports of chemical alerts/alarms sounding in theater. However, only one incident of chemical warfare exposure of US

troops has been confirmed by the Department of Defense (DoD). This incident occurred following the ceasefire agreement at the end of February 1991, at which time US military personnel moved into the Khamisiyah area of southeastern Iraq (Winkenwerder 2002a). The operational goal was to destroy munitions and weapons being held at an Iraqi storage facility in Khamisiyah. Demolition of the facility, which contained thousands of munitions and chemical warfare agents, occurred in March and April 1991. In June 1996, the DoD publicly announced that chemical weapons were stored at the Khamisiyah facility, and during the demolition of the facility, sarin and cyclosarin nerve gas agents were released into the environment, resulting in exposure for approximately 100,000 US troops.

Shortly after returning from deployment, GW veterans began to report persistent health problems. These reports were seen in troops across all US service components, service branches, and unit locations in the Persian Gulf theater and were also documented in troops from allied militaries that deployed to the Gulf as part of the coalition of 30 countries engaged in the conflict against Iraq. These included the United Kingdom, Canada, Australia, France, and Denmark (Cherry et al. 2001a; Doebbeling et al. 2000; Fukuda et al. 1998; Goss Gilroy Inc. 1998; Gray et al. 2002; Ishoy et al. 1999; Kang et al. 2000; Kelsall et al. 2004b; Proctor et al. 1998; Salamon et al. 2006; Steele 2000; Unwin et al. 1999; Unwin et al. 2002). In research attempts to understand the patterns and etiologies of the chronic health symptoms reported by GW veterans, researchers spent many years identifying GW veteran symptom profiles and defining the illness through self-report and medical evaluations. The most commonly reported symptoms include a

combination of cognitive dysfunction, chronic headaches, widespread pain, unexplained fatigue, chronic diarrhea, skin rashes and respiratory problems (Fukuda et al. 1998; IOM 2014; RAC-GWVI 2008; RAC-GWVI 2014; Steele 2000). A combination of these symptoms in an individual veteran can be used to diagnose GW illness (GWI), a disorder prevalent in 25–32% of GW veterans (Fukuda et al. 1998; RAC-GWVI 2008; RAC-GWVI 2014; Steele 2000; IOM 2014). The two most widely accepted case definitions are the Centers for Disease Control (CDC) chronic multisymptom illness (CMI) and the Kansas case definition (Fukuda et al. 1998; IOM 2014; Steele 2000). According to the CDC CMI case definition, a veteran is diagnosed with GWI if s/he reports one or more symptoms that last for at least six months in two of three categories: fatigue, pain, and mood/cognition (Fukuda et al. 1998). Depending on the population studied, the case definition includes between 29–60% of the GW veteran population (Fukuda et al. 1998; IOM 2014). The Kansas definition requires moderate levels of self-reported symptoms in three out of six categories: fatigue/sleep, pain, neurological/cognition/mood, gastrointestinal, respiratory and skin (Steele 2000). In the study that established the Kansas criteria, the prevalence of GWI was 34%; however, veterans with certain medical or psychiatric conditions were excluded from the diagnosis (IOM 2014; Steele 2000). The Haley criteria are a third set of symptoms that have been used to define GWI in research (Haley et al. 1997). The criteria were devised by assessing a specific military unit of US Navy Seabees and include three syndromes that are based on factor analysis of symptoms reported by study participants: impaired cognition (Syndrome 1), confusion/ataxia (Syndrome 2), and neuropathic pain (Syndrome 3). The Seabee Unit

showed a 20% prevalence of GWI (Haley et al. 1997). Uncertainty remains about the sensitivity and specificity of these case definitions because of differences in the study populations and the methods used to ask about health outcomes.

The research in *Chapter 4* aimed to identify the symptoms most commonly reported in the GWI literature by deployed GW veterans and the non-deployed controls used in each study. To address this aim, we evaluated published data on self-reported symptoms using meta-analytic techniques to pool data from 18 unique veteran populations. Our goal was to determine the excess prevalence and the combined odds ratios of individual symptoms among deployed GW veterans compared to their controls. A secondary aim of our study was to examine differences in pooled symptom reporting between population-based and military-unit based GW cohorts. Some military-units in the GW theater experienced specific deployment exposures (*e.g.*, forward-deployed personnel, US Navy Seabees) (Haley et al. 1997; Haley and Tuite 2013; Ismail et al. 2000; Spencer et al. 2001; Steele et al. 2012). To examine the differences in GW exposures experienced by some military-units compared to the whole population of deployed GW veterans and its effect on symptom reporting, we re-evaluated symptoms using a meta-analysis stratified by the study sampling strategy (population-based versus military-unit).

Researchers have focused on chemical, pharmaceutical, climatic, stress and other theater-specific exposures as the cause of GWI and as predictors of other objective measures of health outcomes in GW veterans. The challenge in this field of research is

that records of exposures to individual hazards and objective measurements of environmental and pharmaceutical exposures present in the GW theater are almost non-existent. Using historical data and modeling techniques, exposure models have been developed for oil well fire smoke plumes and for sarin/cyclosarin exposure following the demolition of the Khamisiyah munitions facility. For oil well fire smoke exposure models, the US Army Center for Health Promotion and Preventive Medicine combined troop location data with a National Oceanic and Atmospheric Administration model that spatially and temporally predicted oil fire smoke using satellite imagery, ground station air-monitoring data, oil well emission rates, and Kuwaiti crude oil composition data (Cowan et al. 2002; Smith et al. 2002). In 2000, the DoD and the CIA modeled sarin/cyclosarin exposure at Khamisiyah to determine which US troops who had been exposed to nerve gas agents there (Winkenwerder 2002a; Winkenwerder 2002b). The exposure plume was modeled for four days (March 10–13, 1991) using available global and regional meteorological data; estimates of atmospheric transport, diffusion, and removal; and estimates of the types and numbers of sarin/cyclosarin-containing weapons present at the bunker. The exposure models determined the geographic areas surrounding the Khamisiyah demolition in which sarin/cyclosarin was likely present at levels above the general population limit ( $GPL=0.01296 \text{ mg min/m}^3 \text{ per day}$ ) each day for a 4-day exposure period. The GPL was set by the US Army and the CDC and represents the maximum exposure where no adverse health effects would be expected for an individual exposed to sarin 24-hours a day over 70 years (CDC 1988; McNamara and Leitnaker 1971). Exposure models were combined with troop location data using a database of GW

unit locations to determine which US troops were in the modeled exposure plume area.

Due to lack of objective modeling data, most of the epidemiological research on effects of GW theater exposures has, by necessity, relied heavily on self-reported exposures to evaluate relationships between specific exposures and health effects. Review of the literature suggests that exposures to pesticides and consumption of PB pills have consistently been linked to the diagnosis of GWI in health outcome studies (RAC-GWVI 2008; RAC-GWVI 2014; Steele et al. 2012, White et al. 2016). In cross-sectional studies, GW veterans with self-reported exposure to pesticides and PB pills were also more likely than unexposed veterans to report specific symptoms such as cognitive dysfunction, depressive symptomatology and neurological complaints; similar complaints were also seen in GW veterans reporting exposure to smoke from oil well fires, debris from SCUD missiles, and chemical weapon alerts (The Iowa Persian Gulf Study Group 1997; Kelsall et al. 2005; Proctor et al. 1998; Steele et al. 2012; White et al. 2001). Among GW veterans exposed to oil well fire and tent heater emissions, pulmonary symptoms were more likely to be reported compared to unexposed GW veterans (Cowan et al. 2002; Petrucci et al. 1999; Proctor et al. 1998). GW exposures have been linked to objectively measured health outcomes as well. Exposure to smoke from oil well fires has been linked to respiratory disease and increased mortality from brain cancer. (Cowan et al. 2002; Barth et al. 2009; Kelsall et al. 2004a). GW veterans with sarin exposure have been found to show significant differences in brain structure (Chao et al. 2011; Heaton et al. 2007), demonstrate cognitive dysfunction (Chao et al. 2010; Proctor et al. 2006; Toomey et al. 2009) and have increased mortality due to brain cancer (Barth et al. 2009;

Bullman et al. 2005) compared to unexposed veterans who were deployed to the Gulf theater.

The Fort Devens Cohort is a population of former US Army Active, Reserve, and National Guard GW veterans who have been followed prospectively through a series of surveys since immediately after their return from deployment to the Persian Gulf in 1991 (Wolfe et al. 1998; Proctor et al. 1998; White et al. 2001; Wolfe et al. 2002; Proctor et al. 2006; Heaton et al. 2006). Follow-up questionnaires were distributed from Winter 1992–Spring 1993 (Follow-up 1), Spring 1994–Fall 1996 (Follow-up 2), and Spring 1997–Spring 1998 (Follow-up 3). A subset of the Fort Devens Cohort (n=117) completed health symptom questionnaires on all three follow-up surveys. Participants self-reported whether they thought they had heard chemical weapons alerts, took PB pills, and/or had been exposed to exhaust from tent heaters, pesticides, smoke from oil well fires, debris from SCUD missiles at Follow-up 2. Information from the DoD regarding which cohort members had been notified of sarin nerve gas exposure based on the 2000 DoD/CIA plume model was also available to us. The research in *Chapter 5* aimed to examine the relationship between modeled and self-reported GW deployment exposures and health symptoms, with a particular focus on sex differences, using longitudinal data from the three health symptom surveys conducted over a 7-year follow-up period. We used repeated logistic regression models stratified by sex to determine associations between individual GW exposures and health symptoms over time.

## **CHAPTER TWO. VOLATILE ORGANIC COMPOUNDS IN BLOOD AS BIOMARKERS OF EXPOSURE TO JP-8 JET FUEL AMONG US AIR FORCE PERSONNEL**

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The views expressed are those of the authors and do not reflect the official policy of the U.S. Department of the Army or the U.S. Department of Defense. The findings and conclusions of this paper are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

## ABSTRACT

**Objective:** This study aimed to evaluate blood VOC levels as biomarkers of occupational JP-8 exposure while controlling for smoking.

**Methods:** Among 69 Air Force personnel, post-shift blood samples were analyzed for components of JP-8, including ethylbenzene, toluene, *o*-xylene, and *m/p*-xylene, and for the smoking biomarker, 2,5-dimethylfuran. JP-8 exposure was characterized based on self-report and measured work shift levels of total hydrocarbons in personal air. Multivariate regression was used to evaluate the relationship between JP-8 exposure and post-shift blood VOCs while controlling for potential confounding from smoking.

**Results:** Blood VOC concentrations were higher among USAF personnel who reported JP-8 exposure and work shift smoking. Breathing zone total hydrocarbons was a significant predictor of VOC blood levels, after controlling for smoking.

**Conclusions:** These findings support the use of blood VOCs as a biomarker of occupational JP-8 exposure.

## INTRODUCTION

Jet propulsion fuel 8 (JP-8) is a complex, kerosene-based chemical mixture composed of more than 200 aliphatic and aromatic hydrocarbons (NRC 2003). More than five billion gallons of JP-8 are used every year by U.S. and North Atlantic Treaty Organization (NATO) militaries for fueling aircraft, ground vehicles, and support

equipment, making it potentially the single largest source of chemical exposure for military personnel. Personal exposure assessment has proved challenging because of the complex composition of JP-8, and has focused on using surrogate measures of exposure including self-reported exposure and biomarkers of exposure (Chao et al. 2005; Chao et al. 2006; Merchant-Borna et al. 2012; Pleil et al. 2000; Puhala et al. 1997; Rodrigues et al. 2014; Serdar et al. 2003; Serdar et al. 2004; Smith et al. 2010; Smith et al. 2012; Tu et al. 2004). These studies have shown a wide range in the levels of exposure to JP-8 among U.S. Air Force (USAF) personnel, with the highest occurring among those who report routine occupational exposure to jet fuel.

Self-reported exposure to JP-8 was found to be associated with total hydrocarbons (THCs) in personal breathing zone air samples (Merchant-Borna et al. 2012; Smith et al. 2010). Similarly, previous studies have demonstrated that THCs in personal air samples were associated with other biomarkers of JP-8 exposure, including levels of volatile organic compounds (VOCs) in exhaled breath and 1- and 2-naphthols in urine (Chao et al. 2006; Pleil et al. 2000; Rodrigues et al. 2014; Serdar et al. 2003; Serdar et al. 2004; Smith et al. 2012; Tu et al. 2004). Although these exposure assessment methods are noninvasive, certain methods only monitor a single route of exposure, and differences among individuals and dynamic environmental factors only permit approximating body burden of VOCs and their metabolites.

The National Health and Nutrition Examination Survey (NHANES) monitors levels of VOCs in blood collected from a representative sample of the U.S. population (Chambers et al. 2011; Kirman et al. 2012). Measuring VOC exposure levels in blood is

important because it provides an estimate of total absorbed dose from multiple routes of exposure (*i.e.*, dermal, inhalation) and a biologically relevant measure of VOCs that potentially can reach target organs such as the brain, liver, and kidneys (Kirman et al. 2012). Most half-lives for VOCs in blood are bi-phasic and on the time course of hours; however, half-life increases in repeated exposure scenarios such as occupational exposure (Ashley et al. 1996a). To date, no studies have characterized blood VOCs in USAF personnel with occupational exposure to jet fuel or assessed their relationship with personal measures of JP-8 exposure (*e.g.*, THC in personal air samples).

Certain VOCs that make up fuel such as JP-8 are also abundant in cigarette smoke, gasoline and other organic solvents, which also can affect levels of VOCs in blood (Ashley et al. 1994; Chambers et al. 2008; Chambers et al. 2011; Polzin et al. 2007). In a U.S. Department of Defense health behavior study, approximately one-third of U.S. service members reported any cigarette use in the past month (Bray et al. 2010). In many of the studies examining USAF personnel JP-8 exposure, smoking also has been significantly associated with measured levels of JP-8 constituents in personal air and urine biomarkers, confounding the association between JP-8 exposure and blood VOC levels in active duty military personnel exposed to JP-8 (Chao et al. 2006; Rodrigues et al. 2014; Serdar et al. 2003; Serdar et al. 2004; Smith et al. 2012).

The overall goal of this study was to evaluate VOCs in blood as a biomarker for characterizing exposure to JP-8. Specifically, the objectives were to characterize VOCs in blood among a population of USAF personnel exposed to JP-8, evaluate self-reported

work shift JP-8 exposure and measured personal exposure to THC as predictors of VOCs in blood, while for controlling for the effect of smoking on VOC levels in blood.

## **METHODS**

We recruited 74 active duty personnel who served at least six months in the USAF from three bases according to their Air Force Specialty Code (AFSC) and current job tasks (i.e., administrative, aircraft structural maintenance, fuel systems maintenance) such that some participants were expected to have higher exposure to JP-8 and other participants were expected to have lower exposure to JP-8. Persons with a self-reported history of loss of consciousness >20 min or known neurological or psychological disorder(s) were excluded from the study. The parent study included a six-day protocol designed to assess JP-8 exposure and central nervous system functioning in active duty USAF personnel (Proctor et al. 2011). Blood samples were only collected at the end of shift on day 5 (Thursday) of the week-long sampling investigation and were available for 69 of the 74 participants. Accordingly, this investigation focuses on the 69 workers who provided a blood sample on day 5. The study protocol was approved by institutional review boards at the U.S. Army Research Institute of Environmental Medicine, USAF Research Laboratory at Wright Patterson Air Force Base and Boston University, and was in compliance with human subjects review procedure at the Centers for Disease Control and Prevention. Written informed consent was obtained from all participants.

### *Personal air samples*

Personal air samples were collected and extracted in accordance with National Institute for Occupational Safety and Health Method 1550 for THC (NIOSH 1994). Methods for personal air sampling and laboratory analysis are described in detail by Merchant-Borna *et al.* (2012) and Smith *et al.* (2010). In brief, participants wore a battery operated personal air sampling pump (Casella Apex Pro IS; Casella USA, Amherst, NH) that was attached to a two-section (100/50 mg) coconut shell charcoal tube (Anasorb; SKC Inc., Eight Four, PA, USA) clipped to the lapel of each subject near their breathing zone (flow rate = 0.2 l/min). The personal air-sampling pump was turned off and sealed during breaks from job tasks when the participant left the work area (*e.g.*, during lunch and cigarette breaks), and when participants were required to put on respirators to perform certain job tasks. Samples were analyzed for THC at the Organic Chemistry Analytical Laboratory (Harvard School of Public Health, Boston, MA) using gas chromatography with flame ionization detection (NIOSH 1994). THC concentrations determined to be below the limit of detection (LOD), calculated as three times the standard deviation of the field blanks, were replaced with a value of half the LOD. Air concentrations of THC are reported as eight-hour (8-h) time-weighted averages (TWAs) in  $\text{mg}/\text{m}^3$  to account for difference in work shift length.

A data logger (HOBO; Onset Computer Corporation, Bourne, MA, USA) was attached to each worker to obtain air temperature and relative humidity measurements in 15-min intervals through the duration of each work shift. Air temperature and relative humidity measurements were averaged across an 8-h work shift.

### *Blood VOCs*

After the same work shift in which air samples were collected, a trained phlebotomist obtained a blood sample ( $\leq 20$  ml total) from each worker. Samples were collected in specially prepared BD Vacutainer tubes (Becton, Dickinson and Company, Franklin Lakes, NJ, USA) and sent to the Centers for Disease Control and Prevention laboratory for analysis. Using automated solid-phase microextraction coupled with capillary gas chromatography and quadrupole mass spectrometry, blood samples were analyzed for trace level amounts of the following 11 VOCs: *n*-hexane, *n*-heptane, *n*-octane, benzene, 1,4-dichlorobenzene, ethylbenzene, methyl tert-butyl ether, styrene, toluene, *o*-xylene, and *m/p*-xylene (Chambers et al. 2006; Chambers et al. 2008). Blood samples were also analyzed for 2,5-dimethylfuran, a highly specific combustion biomarker of cigarette smoke exposure for daily smokers or nonsmokers exposed to environmental tobacco smoke (ETS), using the same method (Ashley et al. 1996b; Chambers et al. 2011). Concentrations of blood analytes are reported in  $\mu\text{g/l}$ .

### *Questionnaires*

Participants completed a baseline questionnaire providing information about demographics and smoking, as well as occupational, military, and health history. Before starting the work shift, participants completed a brief questionnaire asking about chemical exposures from the previous evening and the morning. The pre-shift survey asked “Since we last saw you have you been to the gas station and filled up your car (self-service)?” (yes/no).

At the end of the work shift, participants completed another brief questionnaire which included a section for participants whose “job involved direct exposure to JP-8 during the work shift.” If participants completed this section, this was considered self-reported work shift JP-8 exposure. The post-shift questionnaire also asked about contact with other solvents and chemicals, use of protective equipment, and tobacco use during the work shift. On this survey, participants were asked to report if they had worked with gasoline, cutting or lubricating oils, coolants or antifreeze, degreasers or other cleaners, organic solvents, mineral spirits, and/or epoxy or adhesives (yes/no). The questionnaire also asked, “How many cigarettes have you had during today’s work shift?” Response options included “none,” “quarter-pack,” “half-pack,” “1 pack,” “1+ to 2 packs,” and “2+ packs.” Because of the lack of diversity in responses and the small number who smoked a half pack or more, we lacked statistical power for an analysis of the influence of fractional pack. Of the 23 persons who reported smoking during their work shift, 20 indicated that they had smoked a quarter-pack and three indicated they had smoked a half-pack of cigarettes during the work shift. Responses were dichotomized according to yes/no responses for smoking during the work shift for the data analysis.

### *Data analysis*

Statistical analyses focused on five VOCs that were detected above the LOD in  $\geq 50\%$  of the blood samples for both self-reported exposure groups: 2,5-dimethylfuran, ethylbenzene, toluene, *o*-xylene, and *m/p*-xylene. Blood VOC concentrations below the analytical LOD were replaced with a calculated value of the LOD/SQRT(2). Distribution

of personal air and blood concentrations were right-skewed, so the data were transformed with the natural log function before statistical analyses. THC<sub>s</sub> in personal air and VOC<sub>s</sub> in blood were analyzed using descriptive statistics, and Student's *t*-test compared mean concentrations between workers who reported JP-8 exposure and those who reported no exposure. Blood VOC<sub>s</sub> also were compared between USAF personnel who smoked during the work shift and those who did not using the same method.

Air concentrations were natural log-transformed to reduce skewness for the correlation analysis and blood concentrations were natural log-transformed for both correlation and regression analyses. Pearson correlations were used to estimate the strength of the relationship between THC concentrations in air and VOC concentrations in blood. Multiple linear regression models examined the association between blood VOC levels and two surrogate measures of JP-8 exposure: categorical self-reported work shift jet fuel exposure (yes/no) and 8-h TWA THC (mg/m<sup>3</sup>). To control for cigarette smoking, two variables were considered in separate models: categorical self-reported cigarette smoking during the work shift (yes/no) and 2,5-dimethylfuran in blood (μg/l). USAF base and relative humidity were included as covariates in all models. A model was fit for each of the VOC<sub>s</sub> measured in blood.

Mean air temperature, self-service at a gas station, age and body mass index of participant were also considered as possible covariates. These covariates were not significant predictors of blood VOC<sub>s</sub> in either regression model and were not included in the final models. We considered conducting a post-hoc analysis to include exposure to other chemicals endorsed on the post-shift survey as possible covariates in our regression

models. However, the sample size was small for those reporting the additional exposures ( $n \leq 5$ ) and therefore not performed. All statistical analyses were conducted using SAS statistical software version 9.2 (SAS Institute, Cary, NC, USA).

## RESULTS

Table 2.1 shows demographics for the 69 study participants. On average, the USAF personnel participating in this study were 25.3 years old and had spent 5.3 years in the USAF. The majority of participants were white males in the lower enlisted ranks. Significantly more males than females reported work shift JP-8 exposure. Significantly more JP-8 exposed individuals reported smoking during the work shift ( $\chi^2 = 5.71$  (1 df),  $P = 0.02$ ). Work shift exposure to JP-8 did not differ by other demographic factors.

Table 2.2 shows post-shift VOC concentrations in blood by self-reported JP-8 exposure and shift cigarette smoking. 2,5-dimethylfuran, a biomarker for cigarette smoking, was detected in 91% of the samples for persons who reported smoking during the work shift. The geometric mean (GM) concentrations of 2,5-dimethylfuran ( $P < 0.0001$ ), toluene ( $P = 0.0001$ ), *o*-xylene ( $P = 0.005$ ), and *m/p*-xylene ( $P = 0.0006$ ) in blood were significantly higher among participants who reported smoking during the work shift. Similarly, the GM concentrations of toluene ( $P = 0.003$ ), *o*-xylene ( $P = 0.0003$ ), and *m/p*-xylene ( $P < 0.0001$ ) in blood were significantly higher among participants who reported exposure to JP-8.

Concentrations of THC in personal air samples were significantly higher among participants who self-reported jet fuel exposure (GM = 4.40 mg/m<sup>3</sup>) than among those

who did not ( $GM = 0.46 \text{ mg/m}^3$ ) ( $P < 0.0001$ ). In this sample of workers, personal air THC concentrations were strongly correlated with blood levels of *o*-xylene ( $r = 0.7$ ) and *m/p*-xylene ( $r = 0.7$ ), moderately correlated with blood concentrations of toluene ( $r = 0.5$ ), and weakly correlated with ethylbenzene ( $r = 0.3$ ) (Figure 2.1). When participants smoked, they removed their personal air-sampling pumps. Consequently, the correlations between 8-h TWA THC levels and blood levels of 2,5-dimethylfuran were negligible ( $r = 0.2$ ).

Table 2.3 presents regression models evaluating predictors of ethylbenzene, toluene, *o*-xylene, and *m/p*-xylene in blood. Model 1 examined self-reported work shift exposure to JP-8 as a predictor of the individual blood VOCs, while controlling for self-reported shift cigarette smoking, USAF base (Base A [reference], Base B, or Base C), and mean relative humidity. Work shift jet fuel exposure was a significant predictor for *o*-xylene, and *m/p*-xylene in blood. There was a positive association between work shift JP-8 exposure and ethylbenzene and toluene, but the association did not reach statistical significance. Smoking during the shift was a significant predictor for all analyzed blood VOCs, and participants at USAF Base B had significantly higher blood VOC concentrations compared with participants from the other USAF bases (Table 2.3, Model 1).

Model 2 was used to evaluate THC in personal air samples as a predictor of individual blood VOCs, while controlling for cigarette smoking using the blood biomarker 2,5-dimethylfuran, USAF base, and mean relative humidity (Table 2.3). THC in personal air was a significant predictor for ethylbenzene, toluene, *o*-xylene, and *m/p*-

xylene in blood. The measure of cigarette smoking, blood levels of 2,5-dimethylfuran, remained significant in all models, with the exception of *o*-xylene. Model 2 explained a larger portion of the variance in the blood VOCs than did Model 1, with adjusted R<sup>2</sup> values ranging from 63% (toluene) to 82% (ethylbenzene).

To further evaluate confounding from cigarette smoking, Model 2 was re-run only among USAF personnel who did not smoke during the work shift (n = 46), and 2,5-dimethylfuran was excluded as a covariate (data not shown). For each of the JP-8 components, parameter estimates for 8-h TWA THC and adjusted R<sup>2</sup> were consistent with results in Table 2.3.

## DISCUSSION

VOCs in blood can serve as biomarkers of JP-8 exposure over a work shift in USAF personnel. Specifically, of the VOCs measured, *o*-xylene and *m/p*-xylene appear to be the most appropriate blood biomarkers of JP-8 exposure. This is based on their strong correlations with THC in personal air, and results of the regression model which indicated that THC concentration was a significant predictor of *o*-xylene and *m/p*-xylene. Also, results showed that self-reported work shift jet fuel exposure was a good predictor of *o*-xylene and *m/p*-xylene. Because the half-life of VOCs in blood is on the time course of several hours, we used an exposure measure self-reported during the same work shift as the collection of the blood sample. THC concentration in the personal breathing zone measured over a work shift was a better predictor of ethylbenzene and toluene than self-reported exposure, potentially indicating another source of VOC exposure other than jet

fuel.

We explored the role of several potential confounders, particularly cigarette smoke. Significantly more individuals exposed to JP-8 during the day 5 work shift also smoked during that shift. We used two different variables to control for the effect of smoking on VOC levels in blood: self-reported smoking during the work shift and concentration of 2,5-dimethylfuran in blood. Self-reported smoking during the work shift corresponded well with smoking biomarker 2,5-dimethylfuran. Among the 23 participants who smoked during their work shift, 21 (91%) had detectable levels of 2,5-dimethylfuran and 20 (87%) had a blood concentration of 2,5-dimethylfuran  $\geq 0.014 \mu\text{g/l}$ , the CDC cut-off for classifying a daily smoker smoking the equivalent of one cigarette per day (Chambers et al. 2011). Blood levels of 2,5-dimethylfuran can be affected by several factors not captured by our questionnaires, including environmental tobacco smoke (ETS), brand style of cigarette, time since last cigarette, and cigarettes smoked per day. In our study, cigarette usage was categorized to the nearest fractional pack, rather than cigarettes per day, to simplify the estimation of cigarettes smoked during shift by participants and to utilize an inherent categorization established by smokers. Information regarding brand and style of cigarette smoked or exact time since the previous cigarette was not obtained.

The USAF base at which personnel worked was also a significant predictor of VOCs in blood. Participating personnel at USAF Base B had significantly higher levels of all the analyzed blood VOCs compared with those at other USAF base locations. There could be multiple factors contributing to the differences in VOC exposure by

location. First, JP-8 composition can vary based on batch and can also be altered based on performance needs and type of aircraft maintained at a particular location (Ritchie et al. 2003). Second, exposure could be affected by specific job task being performed and differences in use of personal protective equipment (PPE) (e.g., tasks requiring respirators). Certain tasks may require the use of other solvents and chemicals. We could not analyze exposure to other chemicals because of small sample size endorsing their use during the work shift ( $n \leq 5$ ). Lastly, personal air levels of THC capture occupational exposure to VOCs via inhalation; however, air sampling pumps were turned off while respirators were in use. Respirator use decreases inhalation exposure, but past studies have found that dermal exposure can also be an important route of VOC exposure (Chao et al. 2005; Kim et al. 2006). Blood biomarkers can provide a measure for both inhalation and dermal exposure.

## **CONCLUSION**

This study demonstrates that VOCs in blood reflect occupational exposure to JP-8 during a work shift. USAF personnel who reported occupational exposure to JP-8 had higher concentrations of blood VOCs than did personnel who did not report occupational contact with JP-8. Higher concentrations of THC in personal air samples were significantly associated with higher levels of VOCs in blood, even after controlling for smoking and other potential confounders. Although more invasive, detection of VOCs in blood offers an estimate of absorbed dose from multiple routes of exposure and a direct measure of body burden compared to detection of these compounds in personal breathing

zone samples. These observations support the use of blood VOCs as a biomarker of occupational exposure to fuels such as JP-8.

**Table 2.1.** Demographics of participating US Air Force (USAF) personnel tested for volatile organic compounds in blood (n = 69)

<b>Continuous variables</b>	<b>Mean (Standard deviation)</b>	<b>Range</b>
Age, years	25.3 (6.0)	18.6–43.0
Body mass index	26.1 (3.4)	17.8–34.4
Years active USAF service	5.31 (5.2)	0.5–20.0
<b>Categorical variables</b>	<b>No.</b>	<b>(%)</b>
Cigarette(s) smoked during shift		
Yes	23	(33.3)
No	46	(66.7)
Day 5 work shift jet fuel exposure		
Yes	37	(53.6)
No	32	(46.4)
USAF base		
Base A	20	(29.0)
Base B	17	(24.6)
Base C	32	(46.4)
Rank		
Airmen (lower enlisted ranks)	45	(65.2)
Non-commissioned officers (higher enlisted ranks)	24	(34.8)
Sex		
Male	58	(84.1)
Female	11	(15.9)
Ethnicity		
White	49	(71.0)
Nonwhite	20	(29.0)

**Table 2.2.** Volatile organic compound (VOC) blood concentrations for sampled US Air Force (USAF) personnel (n = 69)

Analyte (µg/l)	LOD	Cigarette(s) smoked during shift						Day 5 work shift JP-8 exposure					
		Yes (n = 23)			No (n = 46)			Yes (n = 37)			No (n = 32)		
		% Detect	GM (GSD)	Range	% Detect	GM (GSD)	Range	% Detect	GM (GSD)	Range	% Detect	GM (GSD)	Range
2,5-dimethylfuran	0.0112	91	0.04 (2.6)	<LOD– 0.2	7	0.01 (1.6)	<LOD– 0.06	46	0.02 (2.8)	<LOD– 0.26	22	0.01 (2.5)	<LOD– 0.15
Octane	0.1	30	0.11 (2.1)	<LOD– 0.55	11	0.08 (1.5)	<LOD– 0.44	30	0.10 (2.0)	<LOD– 0.55	3	0.10 (1.1)	<LOD– 0.15
Isopropylbenzene	0.04	30	0.04 (1.8)	<LOD– 0.22	11	0.03 (1.5)	<LOD– 0.13	30	0.04 (1.8)	<LOD– 0.22	3	0.03 (1.2)	<LOD– 0.08
Benzene	0.024	96	0.11 (2.1)	<LOD– 0.41	22	0.02 (1.9)	<LOD– 0.12	65	0.05 (2.7)	<LOD– 0.41	25	0.03 (2.3)	<LOD– 0.25
Ethylbenzene	0.024	96	0.19 (3.8)	<LOD– 1.65	70	0.11 (5.1)	<LOD– 1.81	86	0.17 (4.8)	<LOD– 1.81	69	0.10 (4.4)	<LOD– 1.21
Toluene	0.025	96	0.33 (2.6)	0.02– 1.15	91	0.09 (3.6)	<LOD– 2.76	97	0.22 (3.4)	<LOD– 2.76	88	0.09 (3.4)	<LOD– 0.68
<i>o</i> -xylene	0.024	96	0.11 (3.0)	<LOD– 1.16	80	0.05 (2.7)	<LOD– 0.63	92	0.10 (3.4)	<LOD– 1.16	78	0.04 (2.0)	<LOD– 0.30
<i>m</i> -/ <i>p</i> -xylene	0.0335	96	0.35 (3.0)	0.02–3.1	94	0.13 (3.0)	<LOD– 1.62	100	0.30 (3.3)	0.05– 3.11	88	0.10 (2.4)	<LOD– 0.80

Definitions: GM = geometric mean; GSD = geometric standard deviation; JP-8 = jet propulsion fuel 8; LOD = limit of detection; ND = not detected.

**Table 2.3.** Models\* evaluating predictors of volatile organic compound (VOC) blood levels in sampled US Air Force (USAF) personnel (n = 69)

Model/Variables	Ethylbenzene (µg/l)**		Toluene (µg/l)**		o-xylene (µg/l)**		m-/p-xylene (µg/l)**	
	β (SE)	P-value	β (SE)	P-value	β (SE)	P-value	β (SE)	P-value
<b>Model 1</b>								
Intercept	-4.28 (0.42)	<0.0001	-3.83 (0.49)	<0.0001	-5.18 (0.41)	<0.0001	-4.40 (0.42)	<0.0001
JP-8 exposure (yes/no)	0.31 (0.22)	0.16	0.43 (0.26)	0.10	0.52 (0.22)	0.02	0.58 (0.22)	0.01
Shift cigarette smoking (yes/no)	0.43 (0.21)	0.05	1.13 (0.25)	<0.0001	0.48 (0.21)	0.03	0.73 (0.21)	0.001
USAF base A	Ref		Ref		Ref		Ref	
USAF base B	3.44 (0.26)	<0.0001	1.65 (0.31)	<0.0001	1.45 (0.25)	<0.0001	1.59 (0.26)	<0.0001
USAF base C	-0.05 (0.58)	0.93	-0.97 (0.68)	0.16	-0.41 (0.57)	0.47	-1.04 (0.59)	0.08
Mean relative humidity	0.03 (0.02)	0.09	0.03 (0.02)	0.09	0.04 (0.02)	0.006	0.05 (0.02)	0.001
<b>Summary Adjusted R<sup>2</sup></b>	<b>0.74</b>		<b>0.50</b>		<b>0.51</b>		<b>0.55</b>	
<b>Model 2</b>								
Intercept	-3.57 (0.37)	<0.0001	-3.24 (0.45)	<0.0001	-4.26 (0.34)	<0.0001	-3.54 (0.38)	<0.0001
8-h TWA THC (mg/m <sup>3</sup> )	0.04 (0.01)	<0.0001	0.03 (0.01)	<0.0001	0.04 (0.01)	<0.0001	0.04 (0.01)	<0.0001
2,5-dimethylfuran (µg/L)	3.76 (1.78)	0.04	13.32 (2.17)	<0.0001	0.45 (1.67)	0.79	4.65 (1.86)	0.02
USAF base A	Ref		Ref		Ref		Ref	
USAF base B	3.36 (0.22)	<0.0001	1.55 (0.26)	<0.0001	1.38 (0.20)	<0.0001	1.50 (0.23)	<0.0001
USAF base C	0.44 (0.46)	0.34	-0.77 (0.56)	0.17	0.12 (0.43)	0.79	-0.64 (0.48)	0.19
Mean relative humidity	0.003 (0.01)	0.81	0.02 (0.02)	0.13	0.02 (0.01)	0.13	0.03 (0.01)	0.03
<b>Summary Adjusted R<sup>2</sup></b>	<b>0.82</b>		<b>0.63</b>		<b>0.69</b>		<b>0.67</b>	

Abbreviations: JP-8 = jet propulsion fuel 8; Ref = referent; SE = standard error; THC = total hydrocarbons; TWA = time-weighted average.

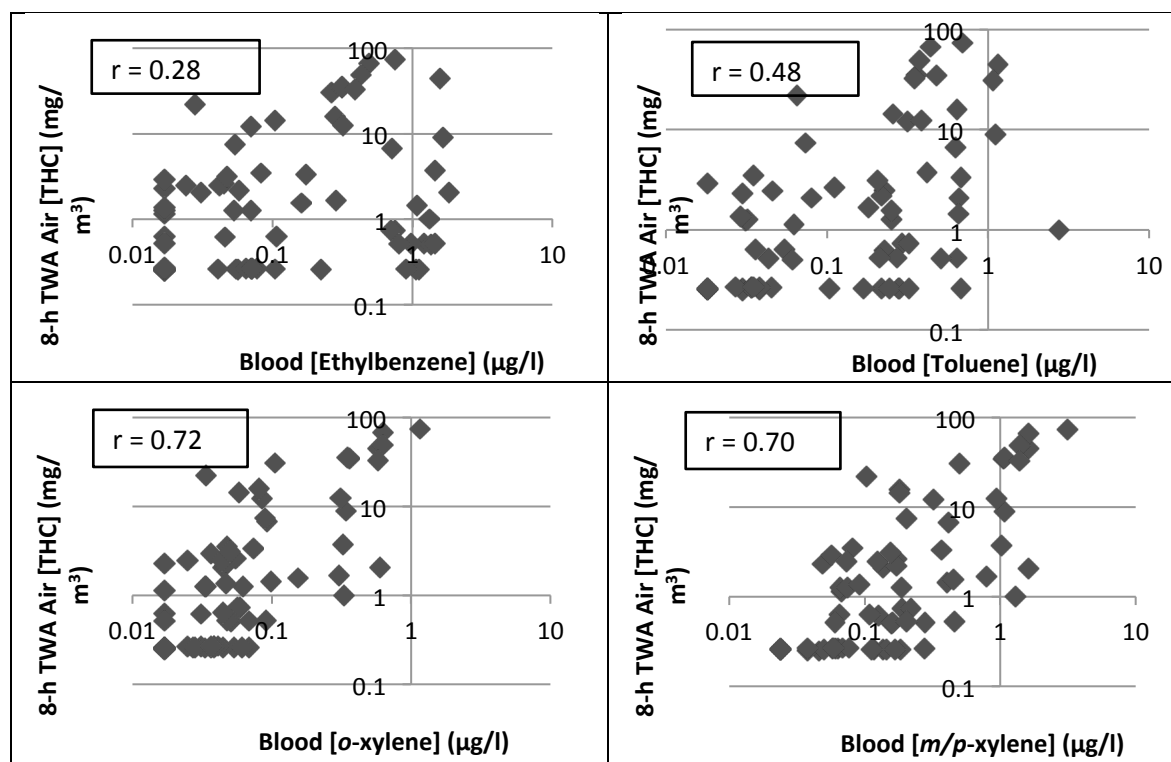
\* Multiple linear regression

\*\* Natural log-transformed.

Model 1: With self-reported cigarette use (shift cigarette smoking (yes/no)) and Day 5 JP-8 exposure (yes/no)

Model 2: With measured JP-8 (8-h TWA THC (mg/m<sup>3</sup>)) and cigarette smoke exposure (2,5-dimethylfuran (µg/L))

**Figure 2.1.** Correlation on log-scale between concentrations of personal air total hydrocarbons and blood volatile organic compounds in sampled US Air Force personnel (n = 69)



Definitions: r = Pearson's correlation coefficient; THC = total hydrocarbons; TWA = time-weighted average.

## **CHAPTER THREE. POSTURAL SWAY AND EXPOSURE TO JET FUEL 8 AMONG US AIR FORCE PERSONNEL**

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## ABSTRACT

**Objective:** To determine whether acute jet propulsion fuel 8 (JP-8) exposure is associated with balance task measurements in JP-8 exposed Air Force personnel.

**Methods:** As part of a larger neuroepidemiology study, balance tasks were completed by JP-8 exposed individuals (n=37). Acute JP-8 exposure was measured using personal breathing zone levels and urinary biomarkers. Multivariate linear regression analyses were conducted to examine the relationship between workday JP-8 exposure and postural sway.

**Results:** Balance control decreased as the balance task became more challenging. Workday exposure to JP-8, either measured by personal air or urinary metabolite levels, was not significantly related to postural sway. Increases in workday postural sway were associated with demographic variables, including younger age, being a current smoker, and higher body mass index.

**Conclusions:** Results suggest that acute workday JP-8 exposure does not significantly contribute to diminished balance control.

## INTRODUCTION

Jet-propulsion fuel 8 (JP-8) is currently the exclusive jet fuel used by the United States Air Force (USAF) for the fueling of its aircraft, ground vehicles and support equipment and is widely used in other branches of the US Armed Forces and NATO

country militaries (NRC 2003). JP-8, which replaced JP-4 as the primary propulsion fuel, is a kerosene-based fuel that contains a mixture of over 200 aliphatic and aromatic hydrocarbons (NRC 2003; Smith et al. 1997). The percent volume of hydrocarbons, including naphthalene, toluene, and benzene, present in a JP-8 fuel supply can vary and depends on the fuel manufacturer, fuel lot, and performance objectives (Ritchie et al. 2003). The USAF and other militaries consume an estimated 5 billion gallons of JP-8 every year, making JP-8 the single largest chemical exposure in the USAF (Carlton and Smith 2000; Ritchie et al. 2003).

Because of its widespread use, all Air Force (AF) personnel may be exposed to JP-8 through inhalation of fuel combustion exhaust (Ritchie et al. 2003). However, personnel working in aircraft fuel-cell maintenance, fuels-specialty, and fuels-transportation shops are also likely to be exposed to raw fuel and vapor phase via dermal contact, inhalation, and incidental ingestion (NRC 2003; Ritchie et al. 2003). There is a large body of research characterizing JP-8 exposure among AF personnel and several techniques have been employed to determine these exposure levels. These methods include the measurement of exposure through breathing zone samples, dermal skin samples, analysis of exhaled breath, and urinary biomarkers (Carlton and Smith 2000; Chao et al. 2005; Chao et al. 2006; Pleil et al. 2000; Puhala et al. 1997; Serdar et al. 2003; Serdar et al. 2004; Smith et al. 2010; Smith et al. 2012; Tu et al. 2004). Urinary biomarkers may provide a surrogate measure for combined dermal and inhalation JP-8 exposure using aromatic hydrocarbons that are readily absorbed into the bloodstream and metabolized (Chao et al. 2006; Serdar et al. 2003; Serdar et al. 2004). Studies have shown

that levels of naphthalene metabolites (1- and 2-naphthol) in urine samples are significantly associated with both dermal and breathing zone sample measurements and may be a valid biomarker for total absorbed dose (Chao et al. 2006). In addition, study results have demonstrated that urinary 1- and 2-naphthol concentrations significantly correspond with *a priori* classification of low, moderate, and high occupational exposure categories (Serdar et al. 2003; Serdar et al. 2004; Smith et al. 2012).

A smaller number of studies have examined potential neurological health effects of JP-8 exposure. Dizziness, headache, nausea, fatigue, slurred speech, mental confusion and staggered gait are all symptoms noted after acute JP-8 exposure (Carlton and Smith 2000; Smith et al. 1997). Similar acute symptoms have been documented among individuals who have been exposed to solvents contained in JP-8 (Herpin et al. 2009; Hodgkinson and Prasher 2006; Kraut et al. 1988; Vouriot et al. 2005). Research has also demonstrated that individuals who are chronically exposed to organic solvents (*e.g.*, *n*-hexane, and toluene) show neuropsychological and neurophysiological changes over longer periods of time (Kuriwaka et al. 2002; Taylor 1985; White and Proctor 1997; Xiao and Levin 2000). Posturography, a technique for measuring postural sway, has been utilized as a non-invasive way to measure neurotoxic effects of chemicals and solvents on the functional aspects of the central nervous system (CNS). Balance control involves both the CNS and the peripheral nervous system, and postural sway measurement quantifies the displacement of the body's center of mass during balance control tasks (Hegeman et al. 2007; Kuo et al. 1996). Less efficient balance, or increased postural sway, has been noted in workers in many occupational settings involving solvent exposure: adhesive

manufacturers, serigraphy plant, leather factory, shipbuilding, shipyard, and sewage treatment workers (Herpin et al. 2009; Kuo et al. 1996; Kuriwaka et al. 2002; Ledin et al. 1989; Vouriot et al. 2005; Yokoyama et al. 1997). Two studies to date have used posturography to examine the possible neurotoxic effects of JP-8 exposure in AF personnel (Bhattacharya 2001; Smith et al. 1997). Marginally significant differences in postural sway on specific balance tasks were observed for JP-8 exposed personnel, demonstrating some functional changes in those chronically exposed to JP-8 compared to non-military, healthy controls (Smith et al. 1997).

The primary aim of this study was to characterize the relationship between acute JP-8 exposure and postural sway among a group of AF personnel with varying levels of exposure to JP-8 based on job task activities. JP-8 exposure was evaluated using both personal breathing zone air levels (naphthalene and total hydrocarbon) and urinary biomarkers of exposure (1- and 2-naphthol). We hypothesized that decreased balance control, quantified by increased postural sway measurements, would be associated with higher acute JP-8 exposure.

## **METHODS**

### *Subjects*

A group of male and female Active Duty AF personnel (n=37) participated in a postural sway evaluation. These individuals were a part of a larger neuroepidemiology study (n=74) in which participants were invited to participate based on the degree to

which they were exposed to JP-8 during their current job tasks (Proctor et al. 2011). The evaluation of balance control included 23 persons working in current jobs with higher levels of JP-8 exposure and 14 persons from jobs involving little to no exposure to JP-8. Each participant completed a questionnaire to ascertain demographic information (*e.g.*, age, gender, education level), work history (*e.g.*, current job, length of AF service) and other lifestyle and physical characteristics (*e.g.*, smoking history, use of alcohol, height, weight).

#### *Assessment of Postural Sway*

The Sway Star<sup>TM</sup> Balance System was used for the postural sway evaluation. The Sway Star<sup>TM</sup> Balance System consists of a belt mounted device that rests against the subject's lower back and contains two digitally based angular velocity transducers that measure pitch (anterior/posterior movement) and roll (lateral movement). Measurements of angular velocity were collected and calculated as described by Gill et al. (2001). The postural sway evaluation protocol involved four stance tasks: (1) standing on two legs with eyes open (EO), (2) standing on two legs eyes closed (EC), (3) standing on two legs with eyes open on foam support (FO), and (4) standing on two legs with eyes closed on foam support (FC). The tasks conducted without the foam support took place on a smooth bare surface. The foam support surface was 10 cm thick and 40 cm wide by 50 cm long. All tasks were completed without footwear.

The postural sway evaluation occurred pre-shift and post-shift. The participants

performed two trials of each of the four stance tasks, for a total of 8 consecutively recorded trials, at both the pre- and post-shift data collection periods. The Sway Star™ software computed the total angular area (TAA:  $\text{deg}^2$ ), which is the total area encompassed by both pitch and roll movements of an individual over a complete trial, and the mean path velocity (MPV:  $\text{deg/s}$ ), which is the mean velocity of both pitch and roll movements over each completed trial. During the balance control evaluation trials, individual movements over a larger total area and with a faster velocity (higher values for TAA and MPV, respectively) were generally considered indicative of reduced balance control.

Before starting the series of stance tasks participants were instructed to stand in a normal, comfortable position with their arms at their sides. The location of their feet was marked with tape so that they stood in approximately the same position for all of the trials. During the pre-shift data collection period, before each new stance task, participants completed a practice run to become accustomed to the length of the trial and the task. Balance data for each pre- and post-shift trial were recorded for 30 seconds. A spotter watched the participants throughout all trials for loss of balance defined as the participant falling or stepping off the foot tape markings. Additionally, an investigator monitored the participants for any voluntary movements, such as hand movements, and noted them in a study log. If voluntary movements were excessive (*e.g.*, sneezing), recorded data from that trial was excluded from analysis.

### *JP-8 Exposure Measures*

Breathing zone sampling was conducted using a Casella Apex Pro IS (Casella USA, Amherst, NH) personal air sampling pump worn by participants conducting work tasks throughout an entire work-shift. The personal air sampling pump was turned off during breaks from job tasks in which the participant left the work area (*e.g.*, lunch, cigarette break). Personal air sampling and analytical methods have been described in Merchant-Borna *et al.* (2012). Work-shift breathing zone samples were collected on four consecutive workdays, including the same day as the postural sway evaluation. Air samples were collected and extracted in accordance with OSHA Method 35 for naphthalene and NIOSH Methods 1550 for THC (NIOSH 1994; OSHA 1982). Breathing zone samples were analyzed using gas chromatography mass spectrometry (GC/MS) in selective ion monitoring (SIM) mode for naphthalene and THC. Samples determined to be below the limit of detection (LOD – calculated as 3 times the standard deviation of the field blanks) were replaced with a value half the LOD. Air concentrations are presented as mg/m<sup>3</sup> for THC and as µg/m<sup>3</sup> for naphthalene.

In addition, pre- and post-shift urine samples were collected on the same day as the postural sway evaluation. Samples were collected in 15-mL polyethylene cups and stored frozen until sent to the Center for Disease Control laboratory for analysis. Urine samples were analyzed for urinary metabolites of naphthalene (1- and 2-naphthol), using gas chromatography/mass spectrometry and for creatinine levels (Smith et al. 2012). Samples determined to be below the limit of detection (LOD – calculated as 3 times the

standard deviation of the field blanks) were noted as <LOD. No samples in this subgroup analysis were <LOD.

### *Data Analysis*

For analyses of the postural sway data, the duration of each trial was truncated from 30 seconds to 20 seconds. Five seconds from the beginning and end of the data recording were not included in the analyses to ensure stability of data (Gill et al. 2001). The average TAA and MPV for the two trials were used in the analysis. In cases where a trial was excluded (n=3) from the analysis due to excessive movement (*e.g.*, sneezing), data from the non-excluded trial from the same subject was used in the place of an averaged measurement. Analyses were performed for the EO task which is best utilized as a screening for gross balance problems and for the three balance task scenarios that are most sensitive to subtle balance deficits (*i.e.* EC, FO, FC) (Allum et al. 2001; Allum and Carpenter 2005). No participants lost their balance during any of the study trials.

For analyses examining the relationship between acute JP-8 exposure and balance, the 8-hour time-weighted averages (8-hr TWA) for breathing zone air samples on the day of balance testing were determined. Urinary biomarkers of exposure were used as an additional measure of acute JP-8 exposure. Data analyses were conducted separately, using both creatinine-adjusted and unadjusted naphthol levels, but since differences in results were minimal, we have only reported the creatinine-adjusted urinary 1- and 2-naphthol ( $\mu\text{g/g}$  creatinine).

Demographic data of the *a priori* high and low exposure groups were compared using Student t test for continuous variables or chi-square statistics for categorical variables. A comparison of means was used to compare the mean postural sway variables from this study with age-matched, non-clinical reference values embedded in the Sway Star<sup>TM</sup> software (Allum and Honegger 2009; Gill et al. 2001).

Multiple linear regression analyses were used to examine potential associations between JP-8 exposure and postural sway outcomes. Post-shift TAA and MPV were the dependent variables of interest to quantify postural sway. Postural sway variables were natural log transformed to reduce skewness for regression analyses. For each independent exposure variables of interest, three separate models were run for each of the dependent variables (TAA and MPV) reflecting the four stance tasks (EO, EC, FO, and FC). In those models examining acute breathing zone exposure, the independent variables were 8-hr TWA THC and 8-hr TWA naphthalene (each examined in separate models). In models examining urinary biomarker of exposure, the independent variables were post-shift 1-naphthol and 2-naphthol (examined in separate models).

Covariates considered included age (continuous), current smoking status (yes/no), and body mass index (BMI – kg/m<sup>2</sup>) computed based on self-reported height and weight information. In all models, the pre-shift postural sway variables were included to account for pre-shift performance levels. In all models, the exposure measure was forced to remain in the model in a regression step following the stepwise entry of the covariates (p-value  $\leq 0.15$  for inclusion and p-value  $\geq 0.20$  for exclusion).

Three sets of post hoc analyses were conducted. First, we evaluated the influence of age on balance performance. Specifically, t-tests were conducted to determine if individuals aged 25 or younger presented a different pattern of postural sway performance compared to individuals older than 25. We also examined the role of current alcohol use (yes/no) on the regression results. Additionally, to examine whether long-term or chronic exposure to JP-8 was a significant predictor of balance performance, years of AF service was included in the regression models. Since age was highly correlated with years of AF service ( $r = 0.91$ ), age was omitted as a covariate for these latter post hoc analyses.

A Bonferroni correction was used to account for multiple comparisons (4 models for each postural sway outcome), with a p-value  $\leq 0.013$  indicating significant results in the multiple linear regression models. SPSS Statistics Version 19.0 software (IBM SPSS Statistics 19, IBM Corporation, Somers, NY) was used for all data analyses.

## **RESULTS**

Participant characteristics of those in the neuroepidemiology study and balance study subgroup are presented in Table 3.1. As in the overall study, those in the balance study subgroup ranged in age from 18.6 to 43 years. Also, the majority of participants were in the lower enlisted ranks, white (Caucasian) and married. There were significantly more males in the high JP-8 exposure group compared to the low JP-8 exposure group (100% vs. 71.4%;  $p=0.015$ ). Compared with the larger neuroepidemiology study group,

the balance study participants were slightly older, had more years of active AF service, and included a higher proportion of individuals with a history of previous overseas deployment.

In general, increased sway, quantified by increases in both MPV and TAA, was observed as the support-surface changed (no foam versus foam) and as the stance task became more challenging (Table 3.2). This trend was observed during pre-shift and post-shift task performance. Among both the *a priori* high and low exposure groups, the largest sway values were observed during the eyes closed on foam (FC) support stance task. Results from the comparison of overall study postural sway data with reference norms from Sway Star<sup>TM</sup> found that regardless of exposure group, the AF personnel performed better, sometimes significantly so, in each stance task at both pre- and post-shift testing points (Table 3.2). AF personnel demonstrated similar performance compared to reference MPV and TAA values on the eyes closed (EC) stance task. However, their performance on the more challenging tasks (eyes open on foam (FO) and eyes closed on foam (FC)) was significantly better than those from the reference population. No significant differences between the *a priori* exposure groups were observed for either the pre-shift MPV or TAA postural sway measurements or post-shift postural sway measurements (Table 3.2).

Work-shift breathing zone air samples were significantly higher among the *a priori* high exposure group compared to the low exposure group for both THC (geometric mean (GM)<sub>high</sub> = 4.4 mg/m<sup>3</sup>, GM<sub>low</sub> = 0.9 mg/m<sup>3</sup>, p = 0.023) and naphthalene (GM<sub>high</sub> =

4.8  $\mu\text{g}/\text{m}^3$ ,  $\text{GM}_{\text{low}} = 0.7 \mu\text{g}/\text{m}^3$ ,  $p = 0.008$ ). Creatinine-adjusted urinary naphthol levels increased in both *a priori* exposure groups during the work-shift (Figure 3.1). In both exposure groups, pre-shift measured levels of 2-naphthol ( $\text{GM}_{\text{high}} = 3.27 \mu\text{g}/\text{g}$  creatinine,  $\text{GM}_{\text{low}} = 4.33 \mu\text{g}/\text{g}$  creatinine,  $p = 0.21$ ) were higher than pre-shift measured levels of 1-naphthol ( $\text{GM}_{\text{high}} = 2.91 \mu\text{g}/\text{g}$  creatinine,  $\text{GM}_{\text{low}} = 1.47 \mu\text{g}/\text{g}$  creatinine,  $p = 0.14$ ). The same trend was observed for post-shift levels of 1-naphthol ( $\text{GM}_{\text{high}} = 4.04 \mu\text{g}/\text{g}$  creatinine,  $\text{GM}_{\text{low}} = 2.44 \mu\text{g}/\text{g}$  creatinine,  $p = 0.25$ ) and 2-naphthol ( $\text{GM}_{\text{high}} = 4.25 \mu\text{g}/\text{g}$  creatinine,  $\text{GM}_{\text{low}} = 4.45 \mu\text{g}/\text{g}$  creatinine,  $p = 0.73$ ).

In regression analyses, acute JP-8 exposure, as measured by 8hr TWA THC personal breathing zone air samples, was not significantly associated with increased sway velocity (MPV) or increased angular area (TAA) (Table 3.3). Though 8hr TWA THC was not a significant predictor, the multivariate models that included the combination of acute THC exposure, pre-shift balance performance, and demographic covariates accounted for 45.2 – 65.9% of the variance in post-shift MPV and 39.3 – 62.2% of variance in post-shift TAA. The pre-shift measures of these balance outcomes were significant predictors in each MPV and TAA model run for each balance task. Younger age was a significant predictor of balance control in FC task models. In all cases, higher  $r^2$  values were observed in the models where MPV was the outcome of interest compared to models where TAA was the outcome of interest. Similar results were observed for 8hr TWA naphthalene (Table 3.4). Naphthalene 8hr-TWA exposure measure was not significantly associated with increased postural sway (MPV or TAA), and no additional variance in postural sway performance was explained by this exposure measure

compared to that with THC exposure.

Biomarkers of acute JP-8 exposure, quantified by creatinine adjusted 1-naphthol and 2-naphthol levels, were not significantly associated with either MPV or TAA (Tables 3.5 and 3.6). In models with 1-naphthol as the exposure measure, the strongest predictor for the post-shift measurements of MPV and TAA for all four of the balance tasks was the pre-shift measurement of MPV or TAA (Table 3.5). All models were significant with the combination of variables included and accounted for 40–60% of the variance in the balance outcomes (MPV  $R^2 = 0.529 - 0.678$ ; TAA  $R^2 = 0.449 - 0.607$ ; Table 3.5). Similar results were seen when creatinine adjusted 2-naphthol was entered into the model as the exposure covariate (Table 3.6). Models were all significant, with a range of MPV  $R^2 = 0.521 - 0.672$  and TAA  $R^2 = 0.426 - 0.608$ . Again, the highest  $R^2$  values were observed in the MPV regression models. Pre-shift measures of MPV and TAA remained the most significant predictor of post-shift outcomes in all four balance tasks, and age was a significant negative predictor in the FC task models.

In the post hoc analyses, although there was a somewhat wider variance in both sway area and velocity outcomes among those aged 25 years or younger compared to those older than 25 years, particularly on the eyes closed on foam task, no statistically significant differences were observed for any of the balance measures. Recent alcohol use was not found to be a significant predictor of MPV or TAA. Similar to the findings observed for age, years of AF service was a significant negative predictor of MPV and TAA in the most difficult balance task, FC.

## DISCUSSION

In this study, no significant associations between balance performance and workday exposure to JP-8 using either work-shift breathing zone area levels of THC and naphthalene or urinary 1- and 2-naphthol were observed. We did observe that as the difficulty of the balance task increased (comparing EO to EC to FO to FC tasks) postural sway performances were adversely influenced, as observed by increased (wider) sway areas (TAA) with accompanying faster sway velocities (MPV).

In a sample of AF personnel, Bhattacharya (2001) observed a significant association between acute, passive naphthalene exposure and increased sway. However, this association was only seen during the EC balance task, and JP-8 exposure estimated from area measurements rather than a personal measure of JP-8 exposure. Our findings do coincide with the results of acute JP-8 exposure models reported by Smith *et al.* (1997). Using 8-hour personal breathing zone samples of benzene, toluene, and xylene as the measurement of acute JP-8 exposure, Smith *et al.* (1997) found no significant relationship between acute JP-8 exposure and postural sway performance. In terms of covariates, Smith *et al.* (1997) found age and weight to height ratio contributed significantly to increased postural sway measurements. While we observed similar results with BMI, in several of our regression models (particularly on FC tasks) age was negatively associated with post-shift balance performance. The commonly reported relationships between age and balance performance indicate postural control decreases in older individuals and remains steady in young and middle aged populations (age range 25

– 65) (Gill et al. 2001; Hegeman et al. 2007). Approximately half of our study population was aged 25 or younger, and it has been observed that postural sway is increased in those in the 5 – 25 year old range (Hegeman et al. 2007). Presumably, as a result of our young, healthy, and physically active study population, we surmise that the negative associations we observe between age and balance performance measures in this study are most likely due to the generally young age and healthy fitness level of our study population and do not demonstrate a practical or clinical difference related to age.

All personal exposure levels for THC were below the ACGIH threshold limit value for jet fuels ( $200 \text{ mg/m}^3$ ) which also serves as the occupational exposure limit for the USAF (Smith et al. 2010). The absence of a significant relationship between the acute exposure measure and post-shift balance performance could be related to lower observed JP-8 exposure concentrations in our AF population compared to previously published studies of AF personnel (Merchant-Borna et al. 2012). Carlton and Smith (2000) reported full-shift mean THC levels of  $14.2 \text{ mg/m}^3$  and Puhala *et al.* (1997) reported full-shift mean naphthalene levels of  $10 \text{ mg/m}^3$ . These full-shift mean levels are higher than levels found in our *a priori* high exposure category. Chao *et al.* (2006) reported post-shift levels of unadjusted 1-naphthol and 2-naphthol at 28 ng/ml and 38 ng/ml, respectively. These reported post-shift levels of both urinary naphthols were 4–5 times higher than levels found in our high JP-8 exposed group (unadjusted 1-naphthol = 7.7 ng/ml and 2-naphthol = 8.1 ng/ml). Similarly, Serdar *et al.* (2003), reported 1- and 2-naphthol geometric means for low, moderate, and high exposed JP-8 smokers and nonsmokers. The pre- and post-shift levels measured in our AF personnel population were either similar or lower than

those reported by Serdar *et al.* (2003). In this study, compared to earlier studies, the lower observed exposure levels may be related to a lack of handling fire-suppressant foam required for certain aircraft, which often becomes saturated with JP-8 (Smith et al. 2012).

A larger percentage of smokers in the low exposure group and the relationship between cigarette smoke and urinary naphthols may explain why our low exposed group had slightly higher levels of 2-naphthol compared to the high exposed group (Figure 3.1). Serdar *et al.* (2004) reported different rates of naphthol production in smokers and nonsmokers depending on JP-8 exposure level. Among individuals exposed to low levels of JP-8, smokers had a higher rate of 2-naphthol production compared to nonsmokers. The rate of 2-naphthol production was lower in high exposed individuals and did not vary by smoking status (Serdar et al. 2004). These results suggest different metabolic pathways for absorbed naphthalene depending on the primary source, cigarette smoke versus JP-8, of naphthalene.

In addition to relatively low exposure levels observed in this study, the modest sample size, while adequate to enable identification of clinically-relevant (15–25%) differences, may have further limited the ability to detect sub-clinical differences in postural sway outcomes associated with low-level JP-8 exposure.

This study had several notable strengths. First, in contrast with other studies that have examined neurological health effects of JP-8 exposure in the military our study participants were all Active Duty AF personnel (Smith et al. 1997). Therefore, with the exception of their level of JP-8 exposure, *a priori* low and high JP-8 exposure groups

were similar on demographic and non-exposure work experience variables. An unexposed healthy comparison group from the general (non-military) population does not necessarily provide an adequate comparison with regards to important demographic and non-exposure military work experience variables. Second, the ability to include measurement of personal JP-8 exposure using both individual breathing zone samples and urinary biomarkers provided a more complete objective documentation of individual JP-8 exposure than reliance on self-reported JP-8 exposure or job task categories (Merchant-Borna et al. 2012). Moreover, the use of the Sway Star™ instrumentation allowed for non-invasive but objective measurement of postural sway control. Also, because we measured postural sway at two time points (pre- and post-shift) we were able to control for pre-shift postural sway performance. In terms of study design, we observed minimal differences in descriptive characteristics between participants in the higher and lower exposure groups, thus confounding and misclassification of exposure and outcome status are not major concerns for the study (Proctor et al. 2011).

## CONCLUSION

This study was designed to focus on measurement of acute workday and workweek JP-8 exposure, which we found had no significant relationship with post-shift balance performance. In contrast to our study, Smith *et al.* (1997) did demonstrate a significant relationship between an estimated cumulative JP-8 exposure and increased postural sway in a group of AF personnel that were both older (35 years compared to 27

years old in this study) and with more years of service (12 years compared to 7 years in this study). This finding may support a continued interest in studying chronic occupational exposure to JP-8 and its relationship to balance and other neurological outcomes.

**Table 3.1.** Participant Demographics and Pre-shift Measurements

<b>Variable</b> <b>Mean (SD)</b> <b>[Range]</b>	<b>Overall</b> <b>Study</b> <b>Group</b> <b>(n=74)</b>		<b>Balance</b> <b>Study</b> <b>Subgroup</b> <b>(n=37)</b>	<b>High</b> <b>exposure+</b> <b>(n=23)</b>	<b>Low</b> <b>exposure+</b> <b>(n=14)</b>
<b>Age</b>	25.8 (6.3) [18.6–43.0]		26.8 (6.7) [18.6–43.0]	26.9 (6.8) [18.6–40.8]	26.6 (6.9) [19.4–43.0]
<b>Education</b>	12.5 (1.4) [12–20]		12.5 (1.0) [12–16]	12.5 (1.0) [12–16]	12.5 (0.9) [12–14]
<b>Years Active AF Service</b>	5.8 (5.4) [0.5–20.0]		6.6 (5.6) [0.5–20.0]	6.5 (5.5) [0.5–17.0]	6.8 (6.0) [0.8–20.0]
<b>BMI</b>	26.2 (3.5) [17.8–34.4]		25.6 (3.2) [21.5–34.4]	26.4 (3.2) [21.5–34.4]	24.4 (3.0) [21.7–31.1]
<b>N (%)</b>					
<b>Rank</b>					
<b>E2 – E4</b>	45 (60.8)		19 (51.4)	12 (52.2)	7 (50.0)
<b>E5 – E8</b>	29 (39.2)		19 (48.6)	11 (47.8)	7 (50.0)
<b>Ethnicity</b>					
<b>White (Caucasian)</b>	53 (71.6)		27 (73.0)	17 (73.9)	10 (71.4)
<b>Non-White</b>	21 (28.4)		10 (27.0)	6 (26.1)	4 (28.6)
<b>Male</b>	62 (83.8)		33 (89.2)	23 (100.0)	10 (71.4)*
<b>Married</b>	40 (54.1)		21 (56.8)	13 (56.5)	8 (57.1)
<b>Deployed overseas &gt; 30 days</b>	39 (52.7)		24 (64.9)	15 (65.2)	9 (64.3)
<b>Currently Smoke</b>	32 (43.2)		18 (48.6)	11 (47.8)	7 (50.0)
<b>Currently drink alcohol</b>	51 (68.9)		28 (75.7)	18 (78.3)	10 (71.4)

+ High and low exposure groups from *a priori* categorizations based on job-type activities

\*p<0.05 (Comparison between high and low exposure groups in the balance study)

**Table 3.2.** Summary of postural sway variables

	Eyes Open (EO) Mean (SD)			Eyes Open on Foam (FO) Mean (SD)		
Exposure	High (n=23)	Low (n=14)	Overall (n=37)	High (n=23)	Low (n=14)	Overall (n=37)
MPV(deg/s)						
Pre-shift	0.376(0.21)	0.365(0.13)	0.372(0.18)	0.427(0.20)	0.467(0.18)	0.442(0.19)
Post-shift	0.351(0.13)	0.370(0.11)	<b>0.358 (0.12)</b>	0.398(0.17)	0.437(0.16)	<b>0.413(0.16)*</b>
TAA (deg <sup>2</sup> )						
Pre-shift	0.339(0.53)	0.224(0.20)	0.295(0.44)	0.453(0.42)	0.312(0.20)	0.400(0.36)
Post-shift	0.236(0.20)	0.235(0.17)	<b>0.236(0.19)*</b>	0.362(0.30)	0.327(0.15)	<b>0.349(0.25)*</b>
	Eyes Closed (EC) Mean (SD)			EC on Foam (FC) Mean (SD)		
Exposure	High (n=23)	Low (n=14)	Overall (n=37)	High (n=23)	Low (n=14)	Overall (n=37)
MPV(deg/s)						
Pre-shift	0.413(0.16)	0.418(0.12)	0.415(0.15)	0.526(0.18)	0.603(0.27)	0.555(0.22)
Post-shift	0.420(0.18)	0.419(0.15)	<b>0.420(0.17)</b>	0.535(0.17)	0.583(0.21)	<b>0.553(0.18)*</b>
TAA (deg <sup>2</sup> )						
Pre-shift	0.290(0.20)	0.273(0.18)	0.284(0.19)	0.542(0.35)	0.564(0.40)	0.550(0.36)
Post-shift	0.354(0.26)	0.274(0.15)	<b>0.324(0.23)*</b>	0.713(0.42)	0.675(0.62)	<b>0.700(0.50)*</b>

[SwayStar™ reference values: MPV/EO=0.385(0.10); MPV/EC=0.444(0.13); MPV/FO=0.624(0.19); MPV/FC=0.845(0.31); TAA/EO=0.386(0.31); TAA/EC=0.486(0.43); TAA/FO=0.995(1.0); TAA/FC=1.76(1.2). MPV, mean path velocity; TAA, total angular area]

**Bolded text** - SwayStar™ reference values were compared to overall post-shift postural sway performance (\*p<0.05)

**Table 3.3.** Regression Model with 8hr TWA Total Hydrocarbons (THC) as Exposure Measure (n=37)

Dependent Variable	Eyes Open (EO)	Eyes Closed (EC)	Eyes Open on Foam (FO)	EC on Foam (FC)
<b>Post-shift MPV(deg/s)+</b>	<b>β† (95%CI)</b>	<b>β (95%CI)</b>	<b>β (95%CI)</b>	<b>β (95%CI)</b>
Intercept	-0.307 (-0.646, 0.032)	-0.788 (-1.49, -0.084)	-0.451 (-0.679, -0.221)	0.328 (-0.007, 0.663)
8hr TWA THC (mg/m <sup>3</sup> )	-0.002 (-0.006, 0.003)	0.002 (-0.004, 0.007)	0.001 (-0.005, 0.007)	-0.001 (-0.006, 0.003)
Pre-shift MPV (deg/s)	0.500 (0.335, 0.665)*	0.655 (0.408, 0.902)*	0.556 (0.339, 0.773)*	0.600 (0.402, 0.798)*
Current Smoker	0.236 (0.097, 0.375)*	0.200 (0.032, 0.367)	-	-
BMI	-	0.028 (0.000, 0.055)	-	-
Age	-0.012 (-0.023, -0.002)	-0.013 (-0.027, 0.000)	-	-0.021 (-0.032, -0.011)*
<b>Model R<sup>2</sup></b>	<b>0.659</b>	<b>0.614</b>	<b>0.452</b>	<b>0.603</b>
<b>Post-shift TAA(deg<sup>2</sup>)+</b>				
Intercept	0.238 (-0.480, 0.955)	-0.549 (-1.05, -0.050)	0.259 (-0.562, 1.08)	0.964 (0.121, 1.8)
8hr TWA THC (mg/m <sup>3</sup> )	-0.006 (-0.016, 0.004)	0.002 (-0.010, 0.015)	-0.008 (-0.020, 0.004)	-0.004 (-0.017, 0.008)
Pre-shift TAA (deg <sup>2</sup> )	0.602 (0.414, 0.790)*	0.685 (0.388, 0.982)*	0.468 (0.253, 0.682)*	0.525 (0.232, 0.818)*
Current Smoker	-	0.343 (-0.039, 0.725)	-	-
BMI	-	-	-	-
Age	-0.033 (-0.056, -0.010)*	-	-0.033 (-0.060, -0.005)	-0.041 (-0.069, -0.012)*
<b>Model R<sup>2</sup></b>	<b>0.622</b>	<b>0.436</b>	<b>0.446</b>	<b>0.393</b>

+Dependent variables are natural log transformed.

† Unstandardized β coefficient

\* p&lt;0.017

[In all models, the exposure measure was forced to remain in the model in a regression step following the stepwise entry of the covariates (p-value ≤ 0.15 for inclusion and p-value ≥ 0.20 for exclusion). 8hr TWA, 8-hour time-weighted average; MPV, mean path velocity; TAA, total angular area]

**Table 3.4.** Regression Model with 8hr TWA Naphthalene (NAP) as Exposure Measure (n=37)

Dependent Variable	Eyes Open (EO)	Eyes Closed (EC)	Eyes Open on Foam (FO)	EC on Foam (FC)
<b>Post-shift MPV(deg/s)+</b>	<b>β (95%CI)</b>	<b>β (95%CI)</b>	<b>β (95%CI)</b>	<b>β (95%CI)</b>
Intercept	-0.303 (-0.633, 0.027)	-0.747 (-1.6, -0.034)	-0.445 (-0.666, -0.225)	0.328 (0.000, 0.656)
8hr TWA NAP (μg/m <sup>3</sup> )	-0.004 (-0.011, 0.003)	0.003 (-0.005, 0.012)	0.000 (-0.009, 0.010)	-0.003 (-0.010, 0.004)
Pre-shift MPV (deg/s)	0.494 (0.331, 0.657)*	0.666 (0.418, 0.915)*	0.559 (0.344, 0.775)*	0.596 (0.399, 0.793)*
Current Smoker	0.237 (0.103, 0.372)*	0.201 (0.036, 0.365)	-	-
BMI	-	0.026 (-0.002, 0.055)	-	-
Age	-0.013 (-0.023, -0.003)	-0.013 (-0.027, 0.000)	-	-0.021 (-0.031, -0.011)*
<b>Model r<sup>2</sup></b>	<b>0.667</b>	<b>0.616</b>	<b>0.451</b>	<b>0.606</b>
<b>Post-shift TAA(deg<sup>2</sup>)+</b>				
Intercept	0.207 (-0.496, 0.910)	-0.554 (-1.05, -0.059)	0.220 (-0.581, 1.02)	0.932 (0.097, 1.77)
8hr TWA NAP (μg/m <sup>3</sup> )	-0.009 (-0.025, 0.007)	0.007 (-0.012, -0.026)	-0.012 (-0.031, 0.006)	-0.005 (-0.024, 0.014)
Pre-shift TAA (deg <sup>2</sup> )	0.594 (0.407, 0.781)*	0.693 (0.396, 0.989)*	0.452 (0.239, 0.664)*	0.524 (0.230, 0.818)*
Current Smoker	-	0.338 (0.245, 1.85)	-	-
BMI	-	-	-	-
Age	-0.032 (-0.056, -0.009)*	-	-0.032 (-0.059, -0.005)	-0.040 (-0.068, -0.012)*
<b>Model r<sup>2</sup></b>	<b>0.622</b>	<b>0.442</b>	<b>0.448</b>	<b>0.389</b>

+Dependent variables are natural log transformed.

‡ Unstandardized β coefficient

\* p<0.017

[In all models, the exposure measure was forced to remain in the model in a regression step following the stepwise entry of the covariates (p-value ≤ 0.15 for inclusion and p-value ≥ 0.20 for exclusion). 8hr TWA, 8-hour time-weighted average; MPV, mean path velocity; TAA, total angular area]

**Table 3.5.** Regression Model with 1-Naphthol (1-NAP) as Exposure Measure (n=37)

<b>Dependent Variable</b>	<b>Eyes Open (EO)</b>	<b>Eyes Closed (EC)</b>	<b>Eyes Open on Foam (FO)</b>	<b>EC on Foam (FC)</b>
<b>Post-shift MPV(deg/s)+</b> Intercept 1-NAP (mg/g creatinine) Pre-shift MPV (deg/s) Current Smoker BMI Age	<b>β (95%CI)</b> -0.272 (-0.615, 0.071) -0.004 (-0.011, 0.003) 0.514 (0.343, 0.686)* 0.231 (0.095, 0.368)* - -0.013 (-0.023, -0.002)	<b>β (95%CI)</b> -0.394 (-0.685, -0.103) 0.000 (-0.009, 0.008) 0.681 (0.411, 0.952)* 0.202 (0.025, 0.379) - -	<b>β (95%CI)</b> -0.433 (-0.661, -0.206) -0.001 (-0.010, 0.008) 0.567 (0.345, 0.788)* - - -	<b>β (95%CI)</b> 0.311 (-0.022, 0.644) -0.001 (-0.008, 0.006) 0.593 (0.385, 0.800)* - - -0.021 (-0.031, -0.010)*
<b>Model r<sup>2</sup></b>	<b>0.663</b>	<b>0.517</b>	<b>0.451</b>	<b>0.599</b>
<b>Post-shift TAA(deg<sup>2</sup>)+</b> Intercept 1-NAP (mg/g creatinine) Pre-shift TAA (deg <sup>2</sup> ) Current Smoker BMI Age	0.147 (-0.593, 0.886) -0.002 (-0.017, 0.014) 0.590 (0.391, 0.789)* - - -0.032 (-0.056, -0.007)*	-0.544 (-1.07, -0.039) 0.005 (-0.013, 0.023) 0.688 (0.386, 0.990)* 0.345 (-0.036, 0.727) - -	0.085 (-0.749, 0.918) -0.001 (-0.019, 0.017) 0.450 (0.222, 0.678)* - - -0.030 (-0.019, 0.017)	0.899 (0.045, 1.75) -0.003 (-0.022, 0.015) 0.523 (0.221, 0.825)* - - -0.039 (-0.068, -0.010)*
<b>Model r<sup>2</sup></b>	<b>0.606</b>	<b>0.438</b>	<b>0.415</b>	<b>0.385</b>

+Dependent variables are natural log transformed.

‡ Unstandardized β coefficient

\* p<0.017

[In all models, the exposure measure was forced to remain in the model in a regression step following the stepwise entry of the covariates (p-value ≤ 0.15 for inclusion and p-value ≥ 0.20 for exclusion). 8hr TWA, 8-hour time-weighted average; MPV, mean path velocity; TAA, total angular area]

**Table 3.6.** Regression Model with 2-Naphthol (2-NAP) as Exposure Measure (n=37)

<b>Dependent Variable</b>	<b>Eyes Open (EO)</b>	<b>Eyes Closed (EC)</b>	<b>Eyes Open on Foam (FO)</b>	<b>EC on Foam (FC)</b>
<b>Post-shift MPV(deg/s)+</b>	<b>β (95%CI)</b>	<b>β (95%CI)</b>	<b>β (95%CI)</b>	<b>β (95%CI)</b>
Intercept	-0.261 (-0.604, 0.081)	-0.386 (-0.678, -0.093)	-0.413 (-0.644, -0.182)	0.326 (-0.010, 0.662)
2-NAP (mg/g creatinine)	-0.007 (-0.017, 0.003)	-0.002 (-0.015, 0.011)	-0.005 (-0.018, 0.009)	-0.003 (-0.014, 0.007)
Pre-shift MPV (deg/s)	0.501 (0.334, 0.667)*	0.679 (0.409, 0.949)	0.565 (0.345, 0.785)*	0.586 (0.379, 0.793)*
Current Smoker	0.232 (0.097, 0.367)*	0.205 (0.029, 0.382)	-	-
BMI	-	-	-	-
Age	-0.013 (-0.023, -0.003)	-	-	-0.021 (-0.032, -0.011)*
<b>Model r<sup>2</sup></b>	<b>0.668</b>	<b>0.519</b>	<b>0.458</b>	<b>0.603</b>
<b>Post-shift TAA(deg<sup>2</sup>)+</b>				
Intercept	0.194 (-0.553, 0.940)	-0.533 (-1.06, -0.010)	0.128 (-0.719, 0.974)	0.906 (0.037, 1.78)
2-NAP (mg/g creatinine)	-0.007 (-0.031, 0.017)	-0.001 (-0.029, 0.028)	-0.006 (-0.035, 0.022)	-0.005 (-0.034, 0.024)
Pre-shift TAA (deg <sup>2</sup> )	0.589 (0.394, 0.784)*	0.684 (0.380, 0.989)*	0.441 (0.210, 0.672)*	0.520 (0.214, 0.825)*
Current Smoker	-	0.360 (-0.022, 0.743)	-	-
BMI	-	-	-	-
Age	-0.032 (-0.057, -0.008)*	-	-0.030 (-0.059, -0.002)	-0.039 (-0.068, -0.010)*
<b>Model r<sup>2</sup></b>	<b>0.610</b>	<b>0.433</b>	<b>0.418</b>	<b>0.385</b>

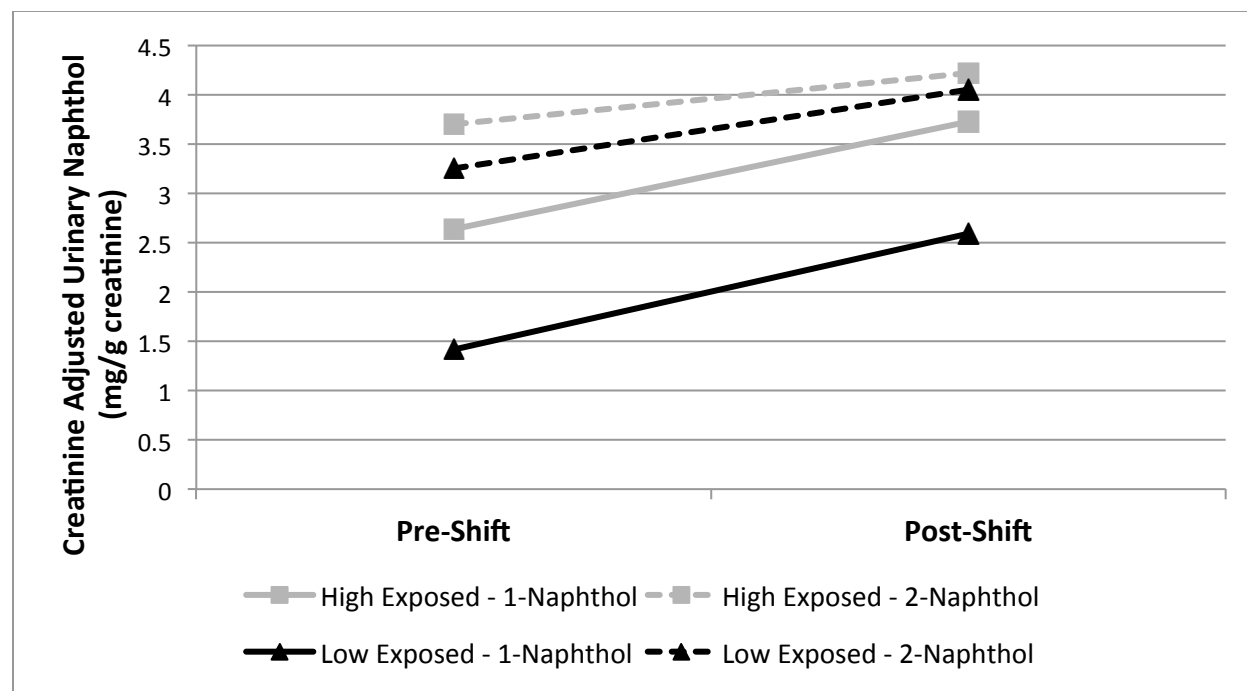
+Dependent variables are natural log transformed.

‡ Unstandardized β coefficient

\* p<0.017

[In all models, the exposure measure was forced to remain in the model in a regression step following the stepwise entry of the covariates (p-value ≤ 0.15 for inclusion and p-value ≥ 0.20 for exclusion). 8hr TWA, 8-hour time-weighted average; MPV, mean path velocity; TAA, total angular area]

**Figure 3.1.** Creatinine Adjusted Urinary Biomarkers during Work-shift



## **CHAPTER FOUR. A META-ANALYSIS OF SELF-REPORTED HEALTH SYMPTOMS IN 1990–1991 GULF WAR AND GULF WAR-ERA VETERANS**

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## **ABSTRACT**

**Objectives:** Across diverse groups of Gulf War (GW) veterans reports of pain, cognitive dysfunction, fatigue, and gastrointestinal issues are common. GW illness (GWI) is a condition resulting from GW service in veterans who report critical numbers of these symptoms. This study integrated the GW literature using meta-analytic methods to characterize the most significant symptoms occurring among GW veterans and to better understand the spectrum of GWI.

**Design:** Meta-analysis

**Primary measures:** Data were extracted from published studies to determine pooled prevalence and combined odds ratios of health symptoms comparing deployed GW and GW-era control veterans.

**Results:** GW veterans had higher odds of reporting all 56 analyzed symptoms compared to GW-era control veterans, with the largest excess prevalence reported for fatigue, memory problems, difficulty concentrating, forgetfulness, and joint pain. Odds of reporting irritability, feeling detached, muscle weakness, diarrhea, and rash were more than 3 times higher among GW veterans compared to GW-era controls.

**Conclusions:** Mood-cognition, fatigue, musculoskeletal, gastrointestinal and dermatological symptom domains are critical when assessing GW veteran health status and GWI.

**Keywords:** meta-analysis, Gulf War veterans, health symptoms, deployment health, Gulf War Illness

## INTRODUCTION

From 1990 through early 1991, approximately 700,000 troops from the United States (US), along with military personnel from over 30 coalition countries, were deployed to the Persian Gulf in support of Operation Desert Shield and Operation Desert Storm, collectively known as the Gulf War (GW) (RAC-GWVI 2008). After returning from the Persian Gulf, US GW veterans reported greater deployment-related health problems when compared with veterans of the same era who did not deploy to the Gulf or who were deployed elsewhere (e.g. Bosnia, Germany) (CDC 1995; Doebbeling et al. 2000; Fukuda et al. 1998; Gray et al. 2002; Iannacchione et al. 2011; The Iowa Persian Gulf Study Group 1997; Kang et al. 2000; Knoke et al. 2000; Proctor et al. 1998; Shapiro et al. 2002; Sostek et al. 1996; Steele 2000; Stretch et al. 1995). Similar reports of increased ill health were seen in GW veterans from other countries, including the United Kingdom (UK), Australia, Denmark, Canada, and France (Cherry et al. 2001a; Goss Gilroy Inc. 1998; Ishoy et al. 1999; Kelsall et al. 2004b; Murphy et al. 2006; Salamon et al. 2006; Simmons et al. 2004; Unwin et al. 1999; Unwin et al. 2002). Research indicates that these excess health symptoms in GW veterans, known as Gulf War Illness (GWI), have remained chronic with no improvement over time (Dursa et al. 2016; Hotopf et al. 2003; Ozakinci et al. 2006; Proctor et al. 1998; Wolfe et al. 2002).

GWI is prevalent in 25–32% of US and UK GW veterans and is characterized in individual veterans by one or more of the following symptoms: chronic pain, fatigue, cognitive dysfunction, gastrointestinal complaints, respiratory symptoms, and skin rashes (Fukuda et al. 1998; IOM 2014; RAC-GWVI 2008; RAC-GWVI 2014; Steele 2000).

Although some critics have claimed that GWI is not a unique syndrome, this central group of symptoms has consistently been used to determine case criteria for the illness (Doebbeling et al. 2000; Ismail et al. 1999). Two case definitions for GWI have received endorsement for use by the Institute of Medicine, the Centers for Disease Control and Prevention (CDC) chronic multisymptom illness (CMI) and the Kansas GWI definition (Fukuda et al. 1998; IOM 2014; Steele 2000). According to the CDC CMI case definition, a veteran is diagnosed with GWI if s/he reports one or more symptoms that last for at least six months in two of three categories: fatigue, musculoskeletal pain, and mood/cognition (Fukuda et al. 1998). The Kansas definition requires moderate levels of self-reported symptoms in at least three out of six symptom categories: fatigue/sleep, pain, neurological/cognitive/mood, respiratory, gastrointestinal and skin (Steele 2000). A third set of symptoms used to define GWI are the Haley criteria (Haley et al. 1997). These include three syndromes characterized by different symptom clusters. Syndrome 1 (Impaired cognition) requires reported attention, memory, sleep and depression symptoms. Syndrome 2 (Confusion/ataxia) requires reported problems with thinking and balance symptoms. Syndrome 3 (Neuropathic pain) requires self-reported joint and muscle pain (Haley et al. 1997).

Uncertainty remains about the sensitivity and specificity of these case definitions. The Kansas definition is associated with a more consistent rate of GWI across multiple GW populations (34% prevalence in GW veterans) but excludes veterans with certain concomitant medical or psychiatric conditions who may also have GWI (IOM 2014; Steele 2000; Steele et al. 2012; White et al. 2016). In contrast, depending on the

population studied, the CDC case definition includes between 29–60% of GW veterans and is considered the most inclusive but the least specific of the case criteria (IOM 2014). Finally, the Haley criteria provide a more restrictive characterization of GWI (Haley and Tuite 2013). The syndromes were originally devised by assessing a specific military unit of US Navy Seabees who showed a 20% rate of GWI (Haley et al. 1997). More current estimates in a larger population-based cohort showed that the combined Haley syndromes include about 14% of GW veterans (Iannacchione et al. 2011).

The epidemiological literature on health symptoms among GW veterans has identified environmental exposures unique to deployment to the Persian Gulf as etiologic agents in the development of specific health outcomes and the occurrence of GWI (RAC-GWVI 2008; RAC-GWVI 2014; White et al. 2016). Exposures that have been linked to health effects in this veteran population include oil well fires, pesticides, pyridostigmine bromide pills, and chemical nerve gas agents, with pesticides and pyridostigmine bromide exposures most consistently linked to GWI (Haley et al. 1997; Kelsall et al. 2004b; Proctor et al. 1998; RAC-GWVI 2008; Shapiro et al. 2002; Steele et al. 2012; Unwin et al. 1999; Wolfe et al. 2002). However, deployment experiences and exposures were not uniform across all troops deployed to the GW (Ismail et al. 2000; Spencer et al. 2001). Some studies have utilized unit-level characteristics as surrogates of deployment exposures and found that illness rates in GW veterans were associated with deployment location and time frame of deployment (i.e., Operation Desert Shield, Operation Desert Storm) (Gray et al. 2002; The Iowa Persian Gulf Study Group 1997; Ismail et al. 2000; Nisenbaum et al. 2000; Steele 2000; Steele et al. 2012).

Collectively, prior studies have used several analytical techniques in separate cohorts to identify symptom prevalence rates and a common complex of symptoms among different groups of GW veterans including cluster analysis, correlation analysis, and factor analysis (Cherry et al. 2001a; Doebbeling et al. 2000; Everitt et al. 2002; Forbes et al. 2004; Fukuda et al. 1998; Haley et al. 1997; Hallman et al. 2003; Kang et al. 2002; Knoke et al. 2000; Nisenbaum et al. 2004; Shapiro et al. 2002; Steele 2000). Some GW researchers have suggested that development of a new case definition using the data now available on the disorder could provide greater clarity and lead to better comparability of studies in GWI research (IOM 2014; RAC-GWVI 2014).

The present study is the first, to our knowledge, to pool published health symptom data from different populations of GW veterans and their controls. It uses meta-analytic statistical methods to: (1) determine the combined total and excess prevalence of individual self-reported symptoms, (2) identify symptoms most commonly reported in the GWI literature, and (3) examine the differences in symptom reporting between population-based GW cohort studies and GW cohorts recruited from specific military units.

## **METHODS**

### *Data search*

Two members of the research team (ALM, MKY) used the literature search strategy in Figure 4.1 to identify studies examining self-reported health symptoms in deployed GW veterans and a relevant veteran comparison group (defined below in Step

3). This process was performed in duplicate to ensure that all relevant, peer-reviewed GW health symptom studies were identified and reviewed for possible inclusion.

Step 1, a Medline and Google Scholar database search was filtered for papers published between January 1990 and May 2015, and “Human Subjects” and “English” language studies. Following the database search, study titles, abstracts, and full manuscripts were reviewed for eligibility criteria using a 4-step process. Exclusion criteria included the following: (1) the study population included veterans of other wars or civilians in conflict zones; (2) the study data were collected in-theater; (3) duplicate titles were found or the paper was an editorial commentary.

Step 2, studies were eliminated if the study’s outcome of interest was not health symptoms or health status. From Step 2 forward, if it was unclear whether the study met the inclusion/exclusion criteria by reviewing the study title and abstract, full articles were reviewed.

In Step 3, studies were removed if the investigation: (1) had no relevant veteran comparison group; (2) was a follow-up survey to an original cohort; (3) did not include self-reported health symptoms/conditions. A relevant comparison group was defined as non-deployed veterans or veterans who deployed to areas other than the Gulf (*e.g.*, Germany, Bosnia) serving in the military during the 1990–1991 GW period; referred to as “GW-era controls” throughout the rest of the manuscript.

In Step 4, studies were eliminated for (1) overlapping GW veteran populations; (2) no usable data.

### *Data extraction*

When studies were found to have used survey results from the same veteran population (*e.g.*, survey data completed by 4 Air Force units were published by both CDC MMWR (1995) and Fukuda *et al.* (1998)), the prevalence data were extracted from the paper that presented results for the greatest number of self-reported health symptoms. If different symptoms were reported in the second paper from the same veteran population, those specific symptoms were extracted from the second paper. One of the eligibility criteria for Step 4 was the availability of usable data. If manuscripts published descriptive statistics other than symptom frequency (*e.g.*, mean symptom severity score, factor loading score), the corresponding author was contacted with a request for frequency data. If a follow-up request went unanswered, the study was eliminated.

The symptom checklists and wording of specific symptoms differed between studies. To determine which health symptoms matched across studies, members of the study team (ALM, PAJ, KAS, MHK) completed a qualitative comparison. For example, the Knoke *et al.* (2000) health symptom checklist includes “chest pains” while Simmons *et al.* (2004) used “chest pains and tightness”, and a consensus was reached that these symptoms were comparable and both included in analysis of “chest pain.” Once the final list of health symptoms that matched across studies was determined, the quantitative data were extracted if the symptom was reported in three or more studies. We extracted total *n*, symptomatic *n*, frequency, standard error, and unadjusted odds ratio for both the deployed GW veteran and GW-era controls. If any of the statistics listed above were not included, they were calculated using data that could be extracted.

### *Data analysis*

To calculate the pooled prevalence rate of each symptom in both the deployed GW veteran and GW-era controls, each symptom frequency from the individual studies was transformed using an arcsin transformation (Barendregt et al. 2013). To account for heterogeneity between studies, a random-effects maximum likelihood model was used to calculate the summary arcsin transformed proportion. The pooled transformed prevalence and its 95% confidence limits were back-transformed to a proportion using equations published in Barendregt *et al.* (2013). Excess prevalence was calculated for each symptom by subtracting the pooled transformed prevalence of the GW-era controls from the pooled transformed prevalence of the deployed GW veterans group.

For each health symptom, a summary odds ratio was estimated using a random-effects binomial-normal model. This two-level model accounts for the binomial distribution of proportions and the normal distribution of the study specific odds ratios around the summary odds ratio ( $\mu$ ) with a variance term,  $\tau^2$  (Nyaga et al. 2014). The starting values for  $\mu$  and  $\tau^2$  were set using the summary log odds estimate from the fixed-effects model and the variance term from the maximum likelihood random-effects model, respectively (Nyaga et al. 2014). Additionally, an offset term ( $\log n_{\text{GW veterans}}/n_{\text{GW-Era veterans}}$ ) was included to account for different sample sizes of GW veterans and GW-era controls.

### *Confounding and bias assessment*

In a meta-analysis, study characteristics are explored as potential confounders

since individual level data are not available. We explored each study's participant cohort sampling strategy as a possible confounder. Studies either had participants who were recruited from specific military unit cohorts or participants who were sampled from a population-based cohort of deployed GW and GW-era controls. We performed a stratified analysis to explore the effect of participant cohort sampling strategy on the symptom odds ratios. If the symptom was reported by three or more studies in each stratum, the summary odds ratio was estimated for each stratum using the binomial-normal model described above.

To assess publication bias on the summary odds ratios, we used a method described in Levy *et al.* (2001). For the studies that did not report an odds ratio for a health symptom, the odds ratio for that health symptom was assigned the null ( $OR = 1.0$ ) and the standard error was assumed to be the same as the minimum standard error amongst the reported studies. The summary odds ratio was estimated using a maximum likelihood random-effects model. We could not use the binomial-normal model for the bias assessment because it relies on counts rather than odds ratios for the binomial level of the model and for the offset term. Although these models yield slightly different results for summary odds ratio estimates, they provide comparable estimates of the standard errors.

## **RESULTS**

The literature search identified 37 peer-reviewed studies examining self-reported health symptoms in deployed GW veterans and GW-era control veterans. Fifteen of these

studies were excluded because their study populations overlapped with another identified study and reported no additional health symptoms that were different from the study with an overlapping population. Of the remaining papers, we extracted primary data directly from 19 of the studies. We contacted the authors of three additional papers to obtain primary data and received data for two of these studies (Cherry et al. 2001a; Iannacchione et al. 2011). We did not receive primary data for the third study, which was not included in the analysis (Pierce 1997). Table 4.1 gives an overview of the final studies used in the meta-analysis, which include data from over 129,000 deployed GW veterans and GW-era controls from four different countries, all branches of the military, and both Active Duty and Reserve components of the US military. Eleven of the studies sampled participants from specific military units (*e.g.*, US Navy Seabees) and 15 were population-based studies (Table 4.1).

A total of 56 distinct health symptoms were reported in three or more studies and included in the meta-analysis. Table 4.2 shows the pooled prevalence of each symptom in GW veterans and GW-era control veterans. The combined data from these studies show that GW veterans have a higher reported frequency of each of these symptoms compared to GW-era controls (Table 4.2). The excess prevalence was largest for some of the mood-cognition symptoms (memory problems: excess prevalence (EP) = 24.2%; forgetfulness: EP = 20.4%; difficulty concentrating: EP = 20.1%); pain (joint pain: EP = 20.2%) and fatigue (fatigue: EP = 24.9%).

Table 4.3 presents the results of the summary odds ratios of reporting symptoms in GW veterans compared to GW-era controls veterans. Of the 56 symptoms, the most

data were available for the analysis of headaches, joint pain, diarrhea/loose stools, fatigue, feeling depressed, irritability, rash, and unrefreshing sleep. GW veterans had significantly higher odds of reporting all the analyzed symptoms. The odds of reporting mood-cognition (feeling detached: OR = 3.59; irritability: OR = 3.21), musculoskeletal (muscle weakness/loss of strength: OR = 3.19), gastrointestinal (diarrhea/loose stools: OR = 3.24), and dermatological (rash: OR = 3.18) symptoms were over three times higher in GW veterans compared to GW-era controls.

The bias assessment demonstrates that GW veterans continue to have higher odds of reporting all the analyzed symptoms compared to GW-era control veterans, and the majority of the odds ratios shown in Table 4.3 remain significant after assigning the missing studies an OR=1 and the minimum standard error of the reported studies. However, the summary measure of effect for loss of balance/coordination, feeling detached, lacking energy, joint swelling, flatulence or burping, vomiting, itching, sweating, pain during intercourse, asthma, bleeding gums, lump in throat, swollen glands, and weight gain were no longer significant (*i.e.*, 95% CI for the OR included null) when accounting for possible publication bias (Table 4.3).

In the meta-analysis stratified by sampling strategy (military unit versus population based studies), a total of 19 distinct health symptoms were reported in three or more studies in both strata and were included in the analysis. The results of the stratified meta-analysis show that odds ratios move further from the null compared to the unadjusted meta-analysis in studies with participants recruited from specific military units, for all but 2 of the 19 analyzed outcomes (Table 4.4). For self-reported dizziness,

irritability, fatigue, and several musculoskeletal, gastrointestinal, and dermatological symptoms, the adjusted OR is more than a 10% change away from the null compared to the unadjusted symptom OR (Table 4.4).

## **DISCUSSION**

Using meta-analytic models, we combined data from 21 studies reporting on health symptoms endorsed by over 129,000 deployed GW veterans and GW-era control veterans. These 21 studies represented GW veterans from 18 unique veteran populations, four different countries, and all branches of the military. Results of the meta-analysis showed GW veterans reported all the analyzed symptoms more frequently than GW-era controls, indicating that the health problems associated with GW deployment include widespread, multiple body symptoms. The largest differences in symptom reporting (i.e., 20–24% excess prevalence) between the two veteran groups were for the mood-cognition, pain, and fatigue symptoms. Furthermore, the odds of GW veterans' reporting several mood-cognition, musculoskeletal, gastrointestinal, and dermatological symptoms were more than three times higher than GW-era controls. Additionally, in the unadjusted meta-analysis, the group of symptoms with the highest combined prevalence (fatigue, memory problems, forgetful, joint pain) and the largest summary odds ratios (irritability, feeling detached, muscle weakness, diarrhea, and rash) are consistent with the cluster of symptoms reported by GW veterans with GWI (Fukuda et al. 1998; Haley et al. 1997; Steele 2000). Although it was not possible in this meta-analysis to compare overlapping symptom reporting at the individual level across studies, Smith *et al.* (2013) recently

reported that nearly half of all respondents in their population-weighted sample endorsed symptoms in all three CDC criteria categories (fatigue, mood-cognition, musculoskeletal), with 96% of GWI cases reporting mood-cognition symptoms.

We also characterized studies based on their cohort sampling strategy and performed a stratified meta-analysis comparing population based studies to military-unit based studies, using military-unit as a surrogate for deployment exposures. The stratified analysis showed evidence of confounding by sampling strategy. In studies where participants were sampled from specific military units, the adjusted summary odds ratios were higher compared to the unadjusted summary odds ratios. These results agree with previous studies that found GW veteran health problems were associated with deployment/operational time frame and location and may be reflective of specific deployment exposures experienced by different military-units in the GW theater (Gray et al. 2002; Haley et al. 1997; Haley and Tuite 2013; Ismail et al. 2000; Nisenbaum et al. 2000; Spencer et al. 2001; Steele 2000; Steele et al. 2012). In our stratified analysis, several of the symptoms with higher adjusted odds ratios in the military-unit cohort studies have been associated with GW exposures in previous research. For example, in the Fort Devens cohort, Proctor *et al.* (1998) found that musculoskeletal symptom reporting was associated with pesticide and chemical warfare agent exposure, while neurological and psychological symptoms were linked to self-reported exposure to debris from SCUDS and chemical warfare agents. Similarly, McCauley *et al.* (2001) found that self-reported exposure to chemical warfare agents was associated with fatigue and gastrointestinal symptoms, and Cherry *et al.* (2001b) found that exposure to pesticides

was related to neurological, dermatological and musculoskeletal symptoms.

A major strength of this meta-analysis is the method used to estimate the summary measures of effect. The binomial-normal model is recommended for rare events, which made the analysis of some of the lesser reported health symptoms more robust. Moreover, both the Freeman-Tukey transformation of proportions and the binomial-normal model are designed to analyze binary outcomes and take into account the non-normal distribution of the prevalence and odds ratio effect estimate, in contrast to the fixed-effects of maximum likelihood random-effects model, which assumes normal distributions and is the traditional meta-analytic approach.

As mentioned previously, a limitation of a meta-analysis is the lack of individual level data. Consequently, we were not able to assess the effect of some covariates relevant to health symptom reporting (e.g., PTSD and specific deployment exposures). While some of the primary studies published adjusted odds ratios, we extracted or calculated unadjusted odds ratios in this meta-analysis because effect measures were not adjusted for the same covariates across all studies (Gray et al. 2002; The Iowa Persian Gulf Study Group 1997; Kelsall et al. 2004b; Murphy et al. 2006; Proctor et al. 1998; Simmons et al. 2004; Steele 2000; Unwin et al. 1999; Unwin et al. 2002). This limits comparability of the combined study data and increases the heterogeneity across studies.

Another limitation of the meta-analytic approach is the effect of publication bias on results. Publication bias occurs when studies with positive findings are more likely to be published than studies with null and/or negative findings. In this analysis we were limited to peer-reviewed, published literature on GWI and then further limited by the

number of health symptoms reported by each study. To address the latter issue, we performed a bias analysis where individual study odds ratios were assigned the null value for a symptom that was unreported. The meta-analysis was re-run with the null odds ratios, and 42 out of the 56 summary odds ratios remained significant (Table 4.3), demonstrating that the significant associations between GW veteran status and self-reported health symptoms cannot be attributed solely to publication bias. Lastly, studies were evaluated using a hypothesis validity checklist outlined by Wampold *et al.* (1990), however, we used other methods to assess the risk of bias on our results.

## **CONCLUSION**

Results of this meta-analysis of 21 health symptom studies provides the first comprehensive reference of pooled health symptom data from 129,000 deployed GW and GW-era control veterans representing four different countries and all branches of the military. The excess prevalence and odds ratios found in this meta-analysis indicate that the mood-cognition, fatigue, musculoskeletal, gastrointestinal, and dermatological symptom domains should be considered in attempts to derive a new consensus case definition of GWI. They should also continue to be utilized in symptom surveys when assessing GW veterans for illness biomarkers or treatment trial efficacy (IOM 2014; RAC-GWVI 2008; RAC-GWVI 2014). The stratified analysis demonstrated important differences by study sampling strategy, with higher symptoms odds ratios in studies of specific military-unit cohorts, potentially reflecting symptoms that are associated with specific deployment-related exposures that warrant further study.

## **DATA SHARING STATEMENT**

All of the data, with the exception of Iannacchione *et al.* (2011) and Cherry *et al.* (2001a), was extracted from published, peer-reviewed journal articles. Corresponding authors from Iannacchione *et al.* (2011) and Cherry *et al.* (2001a) were contacted for the primary data relevant to this meta-analysis.

**TABLE 4.1.** Overview of 21 peer-reviewed studies used in health symptom meta-analysis

Author	Year Published	GWV (N)	NGV (N)	Sampling Strategy	Country	Date of Collection
CDC MMWR – Unit A*	1995	313	364	Military unit	US	January – March 1995
CDC MMWR – Unit B*	1995	119	421	Military unit	US	January – March 1995
CDC MMWR – Unit C*	1995	262	581	Military unit	US	January – March 1995
CDC MMWR – Unit D*	1995	470	1397	Military unit	US	January – March 1995
Cherry	2001	8014	3900	Population	UK	December 1997 – September 1999
Doebbeling†	2000	1896	1799	Population	US	September 1995 – May 1996
Fukuda*	1998	1163	2538	Military unit	US	January – March 1995
Gray	2002	3831	3104	Military unit	US	May 1997 – July 1999
Iannacchione	2011	6480	1522	Population	US	May 2007 – April 2009
Iowa – Active Duty†	1997	985	968	Population	US	September 1995 – May 1996
Iowa – NG/Reserve†	1997	911	831	Population	US	September 1995 – May 1996
Ishoy	1999	686	231	Population	Denmark	January 1997 – January 1998
Kang	2000	11441	9476	Population	US	1995 – No end date mentioned
Kelsall	2004b	1430	1533	Population	Australia	August 2000 – April 2002
Knoke	2000	524	935	Military unit	US	Late 1994 – early 1995
Murphy	2006	149	622	Population	UK	2002 – 2003
Nisenbaum‡	2004	3454	2577	Population	UK	November 1997 – November 1998
Proctor#	1998	186	48	Military unit	US	Spring 1994 – Fall 1996
Shapiro	2002	610	516	Population	US	October 1998 – April 1999
Simmons	2004	23358	17730	Population	UK	August 1998 – March 2001
Sostek	1996	57	44	Military unit	US	1994 – No end date mentioned but published Dec 1996
Steele	2000	1435	409	Population	US	February – August 1998
Stretch – Active Duty	1995	715	1576	Military unit	US	No mention but published in 1995
Stretch – Reserves	1995	766	948	Military unit	US	No mention but published in 1995

Unwin – Male <sup>‡</sup>	1999	3284	2408	Population	UK	August 1997 – November 1998
Unwin – Female <sup>‡</sup>	2002	236	192	Population	UK	August 1997 – November 1998

GWV: deployed Gulf War veterans; NGV: Gulf War era control veterans; CDC MMWR: Centers for Disease Control and Prevention Morbidity and Mortality Weekly Report; US: United States; UK: United Kingdom; NG: National Guard

\* Overlapping populations; for Fukuda (1998) only used symptoms that were not reported in CDC MMWR (1995)

† Overlapping populations, for Doebbeling (2000) only used symptoms that were not reported in Iowa (1997)

# NGV group for Proctor (1998) was GW-Era personnel deployed to Germany; all other control groups were non-deployed GW-Era veterans

‡ Overlapping populations, for Nisenbaum (2004) only used symptoms that were not reported in Unwin (1999, 2002)

**TABLE 4.2.** Frequency of self-reported symptoms in Gulf War veteran (GWV) and Gulf War era control veteran (NGV) populations

Self-reported symptom	GWV Frequency (%) (95% CI)	NGV Frequency (%) (95% CI)	Excess Prevalence
Fatigue	41.3 (32.3, 50.6)	16.4 (10.3, 23.4)	24.9
Memory problems	39.8 (31.0, 49.0)	15.6 (9.1, 23.5)	24.2
Forgetful	35.2 (29.5, 40.8)	14.7 (7.6, 23.5)	20.4
Joint pain	35.1 (29.5, 40.8)	14.9 (11.4, 18.8)	20.2
Difficulty concentrating	33.7 (27.2, 40.4)	13.6 (9.2, 18.7)	20.1
Unrefreshing sleep	43.3 (33.4, 53.4)	23.4 (14.6, 33.6)	19.8
Lacking energy	47.0 (36.9, 57.2)	27.4 (18.6, 37.1)	19.6
Irritability	31.2 (22.4, 40.8)	11.6 (6.1, 18.6)	19.6
Difficulty sleeping, falling or staying asleep	38.9 (33.5, 44.5)	20.9 (15.4, 26.9)	18.0
Joint stiffness	31.3 (28.1, 34.7)	14.0 (9.7, 18.9)	17.4
Feeling detached	24.1 (18.5, 30.1)	6.7 (3.4, 11.0)	17.4
Sleepiness	29.7 (17.1, 44.0)	12.4 (4.0, 24.1)	17.3
Headaches	43.4 (35.5, 51.4)	26.2 (18.9, 34.2)	17.2
Rash	24.8 (20.3, 29.6)	8.1 (5.2, 11.6)	16.7
Sinus congestion	40.4 (35.4, 45.6)	25.1 (20.6, 30.0)	15.3
Diarrhea/loose stools	21.8 (15.6, 28.8)	6.7 (4.2, 9.8)	15.1
Flatulence or burping	44.6 (32.6, 56.9)	30.1 (16.5, 45.6)	14.5
Recurrent headaches	25.5 (19.7, 31.8)	11.0 (6.1, 17.1)	14.5
Itching	29.7 (17.1, 44.1)	15.5 (7.2, 26.1)	14.3
Trouble finding words	23.4 (15.9, 31.8)	9.2 (4.1, 16.0)	14.2
Muscle aches/pain	25.1 (19.7, 33.3)	11.7 (6.5, 18.1)	13.4
Bleeding gums	17.4 (4.3, 35.7)	5.7 (0.0, 17.2)	11.7
Ringing in ears	26.8 (21.1, 32.9)	15.2 (10.3, 21.0)	11.6
Dizziness	19.8 (15.4, 24.6)	8.2 (5.6, 11.3)	11.6
Night sweats	15.7 (10.9, 21.3)	4.4 (2.4, 6.8)	11.4
Weight gain	20.3 (16.2, 24.8)	9.0 (7.6, 10.5)	11.3
Numbness and tingling in body parts	20.7 (13.0, 29.5)	9.4 (5.6, 11.3)	11.2
Sweating	28.8 (15.8, 43.8)	17.7 (8.4, 29.4)	11.1

**TABLE 4.2 (continued).** Frequency of self-reported symptoms in Gulf War veteran (GWV) and Gulf War era control veteran (NGV) populations

Self-reported symptom	GWV Frequency (%) (95% CI)	NGV Frequency (%) (95% CI)	Excess Prevalence
Abdominal pain and cramps	19.7 (14.0, 26.1)	8.9 (5.7, 12.8)	10.8
Back pain	36.2 (30.1, 42.6)	25.5 (18.3, 33.5)	10.7
Loss of appetite	15.5 (6.3, 27.6)	5.1 (1.8, 9.7)	10.5
Muscle weakness/loss of strength	15.1 (10.3, 20.6)	4.7 (2.8, 7.2)	10.3
Coughing	19.8 (14.1, 26.2)	9.7 (6.3, 13.7)	10.1
Feeling depressed	18.1 (13.5, 23.1)	8.0 (5.6, 10.8)	10.0
Shortness of breath	15.2 (11.3, 19.5)	5.4 (3.3, 7.9)	9.8
Chest pain	17.1 (9.3, 26.7)	7.4 (3.4, 12.7)	9.7
Loss of balance/coordination	17.0 (10.1, 25.2)	7.5 (3.8, 12.2)	9.6
Sore throat	21.1 (15.0, 28.0)	11.7 (7.2, 17.1)	9.5
Wheezing	18.3 (9.7, 28.8)	9.2 (3.9, 16.3)	9.1
Nausea	15.4 (11.4, 20.0)	6.7 (3.6, 10.5)	8.8
Nightmares	13.1 (6.1, 22.1)	4.7 (1.2, 10.1)	8.4
Feeling anxious/anxiety	12.2 (5.3, 21.3)	4.3 (1.0, 9.5)	7.9
Irregular heart beat	17.8 (5.9, 33.6)	10.0 (3.1, 19.7)	7.8
Loss of interest in sex	14.0 (4.6, 26.9)	6.4 (1.4, 14.1)	7.6
Hair loss	12.6 (6.9, 19.7)	5.0 (1.8, 9.6)	7.6
Chemical sensitivity	14.7 (8.2, 22.7)	7.2 (3.4, 12.3)	7.5
Tremors and/or shaking in body parts	11.0 (10.6, 11.4)	4.0 (3.7, 4.4)	6.9
Joint swelling	11.0 (5.4, 18.2)	4.6 (1.3, 9.5)	6.4
Constipation	10.8 (7.4, 14.8)	4.9 (2.5, 8.0)	6.0
Swollen glands	10.7 (5.5, 17.3)	5.0 (2.0, 9.2)	5.7
Fever	9.7 (4.5, 16.4)	4.2 (1.4, 8.1)	5.5
Lump in throat	7.8 (7.0, 8.6)	3.2 (2.7, 3.8)	4.6
Rapid/racing heart beat	12.4 (7.0, 19.1)	8.1 (6.9, 9.4)	4.3
Vomiting	7.1 (4.2, 10.8)	3.0 (0.7, 6.6)	4.2
Asthma	5.0 (3.2, 7.1)	3.5 (2.4, 4.9)	1.4
Pain during intercourse	2.7 (1.4, 4.3)	1.9 (1.6, 2.1)	0.8

**TABLE 4.3.** Meta-analysis of self-reported health symptoms in Gulf War veterans compared to Gulf War era controls

Full unadjusted meta-analysis results			
Symptom	# of studies in analysis	OR	95% CI
<b>Neurological</b>			
Tremors and/or shaking in body parts	4	2.68	(2.53, 2.84)
Dizziness	10	2.34	(2.06, 2.67)
Recurrent Headache	4	2.34	(1.74, 3.15)
Numbness and tingling in body parts	8	2.32	(1.96, 2.74)
Loss of balance/coordination	3	2.18	(1.83, 2.59)*
Headaches	18	1.78	(1.49, 2.12)
<b>Mood-Cognition</b>			
Feeling detached	3	3.59	(1.83, 7.03)*
Irritability	14	3.21	(2.28, 4.52)
Nightmares	5	2.92	(1.98, 4.30)
Feeling anxious/anxiety	8	2.68	(2.10, 3.43)
Memory Problems	7	2.63	(2.10, 3.30)
Trouble finding words	7	2.62	(1.92, 3.57)
Forgetful	6	2.52	(1.80, 3.52)
Difficulty concentrating	11	2.47	(2.06, 2.96)
Feeling depressed	14	2.26	(1.88, 2.71)
<b>Sleep, Fatigue</b>			
Fatigue	15	2.74	(2.11, 3.57)
Sleepiness	5	2.49	(1.79, 3.48)
Difficulty sleeping, falling or staying asleep	11	1.91	(1.67, 2.19)
Unrefreshing sleep	12	1.91	(1.59, 2.30)
Lacking energy	3	1.73	(1.52, 1.97)*
<b>Musculoskeletal</b>			
Muscle weakness/loss of strength	5	3.19	(2.73, 3.74)
Joint pain	17	2.36	(1.99, 2.80)
Muscle aches/pain	13	2.36	(1.91, 2.92)
Joint swelling	3	2.35	(1.67, 3.30)*
Joint stiffness	10	2.28	(1.79, 2.90)
Back pain	9	1.47	(1.27, 1.70)
<b>Gastrointestinal</b>			
Diarrhea/loose stools	15	3.24	(2.51, 4.17)
Loss of appetite	5	2.58	(1.90, 3.51)
Constipation	6	2.20	(1.77, 2.74)
Nausea	6	2.20	(1.61, 3.02)
Abdominal pain and cramps	11	2.08	(1.79, 2.42)
Vomiting	5	1.60	(1.45, 1.76)*
Flatulence or burping	4	1.45	(1.15, 1.84)*

OR: Odds ratio, CI: confidence interval

\*OR no longer significant in bias analysis; 95% CI contains null using minimum standard error

**TABLE 4.3 (continued).** Meta-analysis of self-reported health symptoms in Gulf War veterans compared to Gulf War era controls

<b>Full unadjusted meta-analysis results</b>			
<b>Symptom</b>	<b># of studies in analysis</b>	<b>OR</b>	<b>95% CI</b>
<b>Dermatological</b>			
Rash	14	3.18	(2.47, 4.09)
Hair loss	9	2.60	(1.85, 3.67)
Itching	3	1.90	(1.59, 2.27)*
Sweating	3	1.67	(1.34, 2.07)*
<b>Cardiac</b>			
Chest pain	7	2.24	(1.92, 2.61)
Rapid/racing heart beat	3	2.04	(1.97, 2.11)
Irregular heart beat	3	1.78	(1.70, 1.87)
<b>Genitourinary</b>			
Pain during intercourse	3	2.39	(2.12, 2.70)*
Loss of interest in sex	5	2.34	(1.80, 3.05)
<b>Pulmonary</b>			
Shortness of breath	6	2.81	(2.35, 3.35)
Coughing	11	2.02	(1.72, 2.38)
Wheezing	5	1.92	(1.66, 2.22)
Sinus congestion	9	1.63	(1.46, 1.81)
Asthma	7	1.38	(1.20, 1.58)*
<b>Miscellaneous</b>			
Night sweats	5	3.42	(2.73, 4.29)
Bleeding gums	4	2.99	(1.73, 5.17)*
Fever	6	2.30	(1.75, 3.03)
Lump in throat	3	2.26	(1.62, 3.17)*
Weight gain	3	2.16	(1.93, 2.41)*
Swollen glands	4	1.98	(1.68, 2.34)*
Chemical sensitivity	4	1.95	(1.60, 2.38)
Sore throat	10	1.82	(1.56, 2.12)
Ringing in ears	6	1.69	(1.42, 2.01)

OR: Odds ratio, CI: confidence interval

\*OR no longer significant in bias analysis; 95% CI contains null using minimum standard error

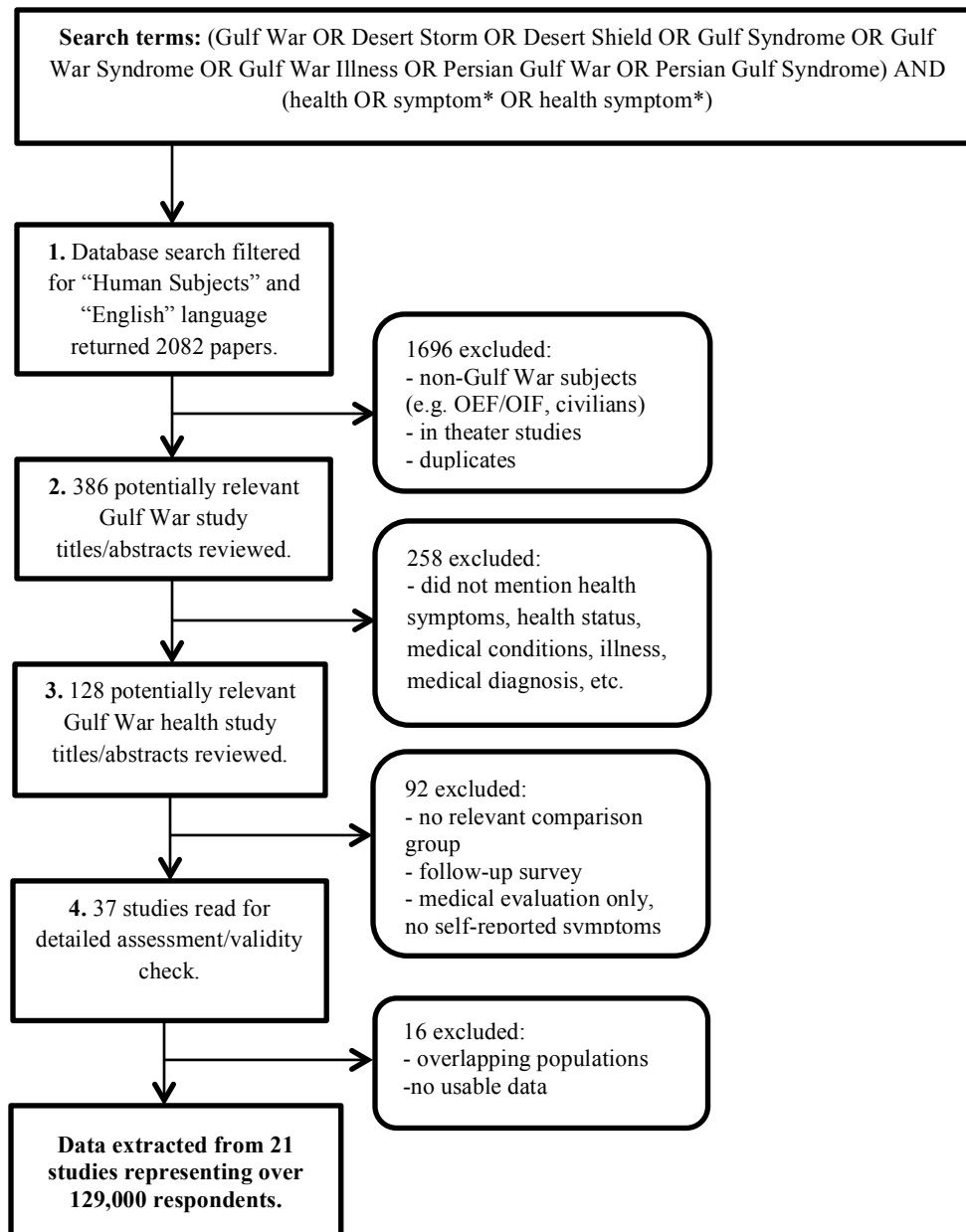
**TABLE 4.4.** Meta-analysis of self-reported health symptoms in Gulf War veterans compared to Gulf War era controls stratified by cohort sampling strategy

Symptom	Military unit studies			Population based studies		
	# of studies in analysis	OR	(95% CI)	# of studies in analysis	OR	(95% CI)
<b>Neurological</b>						
Dizziness	3	2.96 <sup>#</sup>	(2.27, 3.86)	7	2.21	(1.82, 2.68)
Headaches	10	1.72	(1.44, 2.05)	8	1.82	(1.34, 2.47)
<b>Neuropsychological, Psychological</b>						
Irritability	6	3.56 <sup>#</sup>	(2.48, 5.10)	8	2.93	(1.67, 5.14)
Feeling depressed	7	2.32	(1.86, 2.89)	7	2.22	(1.70, 2.89)
<b>Sleep, Fatigue</b>						
Fatigue	8	3.11 <sup>#</sup>	(2.36, 4.10)	8	2.33*	(1.53, 3.55)
Difficulty sleeping, falling or staying asleep	3	2.08	(1.71, 2.54)	8	1.86	(1.57, 2.19)
<b>Musculoskeletal</b>						
Joint stiffness	5	3.00 <sup>#</sup>	(2.74, 3.29)	5	1.69*	(1.32, 2.17)
Joint pain	8	2.99 <sup>#</sup>	(2.49, 3.60)	8	1.88*	(1.57, 2.24)
Muscle aches/pain	8	2.87 <sup>#</sup>	(2.27, 3.63)	8	2.09*	(1.59, 2.75)
Back pain	5	1.64 <sup>#</sup>	(1.32, 2.06)	5	1.37	(1.15, 1.63)
<b>Gastrointestinal</b>						
Diarrhea/loose stools	8	4.42 <sup>#</sup>	(3.27, 5.99)	8	2.49*	(1.91, 3.25)
Constipation	3	2.98 <sup>#</sup>	(2.44, 3.63)	3	1.79*	(1.57, 2.03)
Abdominal pain and cramps	5	2.15	(1.83, 2.52)	5	2.05	(1.66, 2.54)
<b>Dermatological</b>						
Rash	5	3.93 <sup>#</sup>	(3.18, 4.86)	5	2.21*	(1.53, 3.20)
Hair loss	6	3.84 <sup>#</sup>	(3.35, 4.41)	6	2.20*	(1.50, 3.24)
<b>Cardiac</b>						
Chest pain	4	2.39	(1.86, 3.06)	4	2.06	(1.77, 2.41)
<b>Pulmonary</b>						
Coughing	5	2.10	(1.69, 2.61)	5	1.95	(1.54, 2.46)
Sinus congestion	3	1.61	(1.42, 1.82)	3	1.71	(1.34, 2.18)
<b>Miscellaneous</b>						
Sore throat	5	2.04 <sup>#</sup>	(1.71, 2.43)	5	1.55*	(1.29, 1.86)

\*greater than 10% change towards the null (OR=1.0)

<sup>#</sup> greater than 10% change away from the null (OR=1.0)

**Figure 4.1.** Meta-analysis literature search strategy



(Note: \* syntax indicates that all variations of the word were searched by the databases, e.g., symptom\* searched for symptoms, symptomatology, etc.)

## **CHAPTER FIVE. HEALTH SYMPTOMS ASSOCIATED WITH GULF WAR-SPECIFIC EXPOSURES IN MALE AND FEMALE VETERANS: A LONGITUDINAL ASSESSMENT**

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## **ABSTRACT**

**Background:** 1990–1991 Gulf War (GW) veterans encountered a combination of hazardous exposures during their deployment to the Persian Gulf theater that have been linked to several adverse health outcomes, including Gulf War Illness (GWI). Using a subset of the Fort Devens cohort, this study examines the relationship between GW-specific exposures and health symptoms reported over a follow-up period of seven years and the sex differences between the exposure-symptom associations.

**Methods:** Fifty-nine men and 58 women reported health symptoms on three surveys. Repeated logistic regression models stratified by sex were used to examine the association of GW-specific exposures and health symptoms over time.

**Results:** Men and women endorsed GW hazards at a high frequency. Men exposed to debris from SCUD missiles had increased odds of reporting feeling anxious (OR=2.62), trouble sleeping (OR=2.64), dizziness (OR=2.41), and muscle twitching (OR=5.02) compared to unexposed men. Among men, self-reported exposure to tent heaters, pesticides, and chemical alarms were also associated with significantly higher odds of reporting symptoms. Women exposed to debris from SCUD missiles had higher odds of reporting crying easily (OR=4.32), feeling anxious (OR=3.05), trouble sleeping (OR=2.74), lacking energy (OR=2.94), and shortness of breath (OR=4.29) compared to unexposed women. Among women, self-reported exposure to tent heaters and chemical alarms were also significantly associated with symptom reporting.

**Conclusions:** In men and women, specific GW exposures were associated with significantly higher odds of symptom reporting. The differences between men and women in the profile of symptoms associated with the same GW exposures highlight the need for more deployment health research focusing on sex-specific issues.

## INTRODUCTION

US military personnel deployed to the Persian Gulf in support of the 1990–1991 Gulf War (GW) were exposed to many unique environmental hazards in theater, including petrochemicals, debris from SCUD missiles, oil well fire smoke, depleted uranium, pesticides, pharmaceutical agents (e.g., anti-nerve gas pyridostigmine bromide (PB) pills) and chemical warfare agents (e.g., sarin and cyclosarin nerve gas). Several of these chemicals are neurotoxic, belonging to a class of chemicals known as acetylcholinesterase inhibitors (AChEi). AChEi's inhibit the breakdown of acetylcholine (ACh) by inactivating the AChE enzyme, leading to build-up of ACh in the synapse (Grob and Harvey 1958; McDonough and Shih 1997). This causes overstimulation of muscarinic and nicotinic cholinergic receptors in organs and muscles containing these receptors which can lead to cognitive, muscle, and sleep dysfunction (Golomb 2008; National Academies of Sciences, Engineering, and Medicine 2016). Because cholinergic receptors are present outside of the central nervous system (CNS), hazardous chemicals that inactivate AChE can disrupt the autonomic nervous system and alter innate immune function, activating microglia and astrocytes in the brain and leading to enhanced expression of cytokines and chemokines and to chronic neuroinflammation (Abou-Donia

et al. 2016; Banks and Lein 2015; Golomb 2008; Milligan and Watkins 2009; Morris et al. 2015; O'Callaghan et al. 2015; Parihar et al. 2013; White et al. 2016).

Studies have used the DoD sarin plume model and/or troop proximity to Khamisiyah, Iraq, to estimate sarin/cyclosarin exposure following demolition of an arms depot at that location. Exposed GW veterans were more likely to report problems with numbness and tingling, difficulty sleeping, fatigue, depression, and changes in cognition (McCauley et al. 2001; Proctor et al. 2006; Shapiro et al. 2002; White et al. 2016).

The cross-sectional epidemiological literature suggests that GW veterans who self-report exposure to smoke from oil well fires, hearing chemical weapon alerts, use of PB pills, pesticide exposure, and debris from SCUD missiles were more likely to report cognitive dysfunction (e.g., changes in memory), depressive symptoms, and neurological complaints (e.g., headaches) compared to unexposed GW veterans (The Iowa Persian Gulf Study Group 1997; Kelsall et al. 2005; Proctor et al. 1998; Steele et al. 2012; White et al. 2001). Pulmonary symptoms (asthma, cough and shortness of breath) were more likely to be reported among GW veterans exposed to emissions from oil well fires and tent heaters compared to unexposed GW veterans (Petrucelli et al. 1999; Cowan et al. 2002; Proctor et al. 1998). In addition to their links to individual health symptoms, consuming PB pills and exposure to pesticides have been consistently implicated as causal factors of Gulf War Illness (GWI), a disorder that affects approximately 30% of GW veterans and is characterized by a combination symptoms that include: fatigue, cognitive dysfunction, musculoskeletal pain, gastrointestinal complaints, respiratory

symptoms and skin rashes (Fukuda et al. 1998; RAC-GWVI 2008; RAC-GWVI 2014; Steele 2000; White et al. 2016).

Prospective, longitudinal GW cohort studies provide evidence that the health problems experienced by returning GW veterans persist many years after deployment to the Gulf. Most investigations have found that the number and severity of symptoms remained stable over follow-up periods of varying lengths (4–18 years), indicating neither improvement nor progression of symptoms (Brewer et al. 2008; Dursa et al. 2016; Gwini et al. 2016; Hotopf et al. 2003; Kang et al. 2009; Li et al. 2011; Ozakinci et al. 2006). However, few longitudinal studies have examined the relationship over time between GW exposures and health symptoms and disorders. In a follow-up survey of UK GW veterans, Hotopf *et al.* (2004) found that self-reported exposure to smoke from oil well fires and hearing chemical weapons alarms were significantly associated with continuing complaints of fatigue. This follow-up study concluded that GW exposures were important risk factors for the onset of illness; however, the severity of initial symptoms, rather than exposures, was the most important risk factor for the persistence of symptoms over a 4-year period (Unwin et al. 1999; Hotopf et al. 2004).

The Fort Devens cohort is a population of former US Army Active, Reserve, and National Guard GW veterans who have been followed prospectively through a series of surveys since their return from deployment in the Persian Gulf in 1991 (Heaton et al. 2006; Proctor et al. 1998; Proctor et al. 2006; White et al. 2001; Wolfe et al. 1998; Wolfe et al. 2002; Yee et al. 2016). In cross-sectional analyses, Fort Devens cohort members

who reported exposure to debris from SCUDs and chemical warfare agents were more likely to endorse neurological and cognition-mood symptoms (Proctor et al. 1998). In the same study, individuals who reported pesticide use and chemical warfare agent exposure were more likely to report musculoskeletal symptoms; a similar relationship was found between tent heater exposure and cardiac/pulmonary symptoms (Proctor et al. 1998). At a later follow-up, individuals with self-reported exposure to smoke from oil well fires, tent heater emissions, and consuming PB pills had significantly higher odds of chronic multi-symptom illness (CMI), which is a commonly used definition for GWI (Wolfe et al. 2002; Fukuda et al. 1998).

There is some evidence that women are at higher risk for deployment-related illness or more severe illness than their male counterparts, but many GW studies have been underpowered to look at sex-specific deployment issues because only 7% of GW veterans are women (Coughlin 2016; Fukuda et al. 1998; Pierce 1997; Smylie et al. 2013; Spencer et al. 2001; Steele 2000; Wolfe et al. 1998).

The present study examined data from a subset of the Fort Devens cohort that was over-sampled for women so that sex-specific health issues could be better assessed (Proctor et al. 1998). Using longitudinal data from three health symptom surveys over a 7-year period, our study further examined the relationship between modeled and self-reported GW deployment exposures and health symptoms over time, with a particular focus on sex differences.

## METHODS

### *Participants and Surveys*

In the spring of 1991 (Baseline), Active Duty, Reserve, and National Guard Army personnel who returned from a deployment to the Persian Gulf through Fort Devens, MA, were recruited to participate in a survey to assess participants' demographics, psychological health, and combat exposure. Follow-up questionnaires were designed to assess long-term health and psychological and functional well-being, as well as Gulf-specific environmental and combat exposures (Proctor et al. 1998; Wolfe et al. 1998; Wolfe et al. 2002). Figure 5.1 illustrates the overall timeline of the Fort Devens cohort study. The sample at Follow-up 2 was much smaller because in depth in-person interviews and neuropsychological testing were completed. The Follow-up 2 study sample was oversampled for women; the full sampling strategy is outlined in Proctor *et al.* (1998). The current study uses the subset of Fort Devens cohort participants who completed Health Symptom Checklists at the three follow-up time points, there are a total of 117 participants for the current study (59 men and 58 women).

The health symptom checklist allowed participants to report whether they had experienced specific health symptoms from a pre-set list that was originally adapted from Bartone *et al.* (1989). Over the course of the Fort Devens cohort surveys, two different health symptom checklists were included in the survey questionnaires. At Follow-up 1, a 20-item Health Symptom Checklist asked participants to indicate the frequency of 20 symptoms over the past 4 weeks using a Likert-scale rating (0=none; 1=a little; 2=often;

3=very often) (Wolfe, 1998). Each response was dichotomized for the analysis; endorsing 0 (none) was coded as 0=non-endorsement and checking 1 (a little), 2 (often) or 3 (very often) was coded as 1=endorsement of the health symptom. At Follow-ups 2 and 3, the questionnaire included a 52-item Expanded Health Checklist (Proctor et al. 1998; Wolfe et al. 2002). Respondents were asked to indicate the frequency with which they experienced each health symptom over the past 30 days using a Likert-scale rating (0=no symptom; 1=rarely (1–2 times in all); 2=some (1–2 times/week); 3=often (several times/week); 4=very often (almost every day)). Each response was again dichotomized so that checking 0 (no symptom) was considered non-endorsement (coded as 0) and other responses were considered as endorsing the symptom (coded as 1).

Based on the epidemiological literature examining GW exposures and reported health symptoms, we chose symptoms from the 20-item and 52-item Health Symptom Checklists that could be characterized as belonging to one of the following categories: mood-cognition, fatigue, neurological or physical symptoms. A total of 12 symptoms fit these categories and were included on all 3 follow-up surveys: difficulty concentrating, feeling depressed, crying easily, feeling anxious, trouble sleeping, lack of energy, dizziness, headache, muscle twitching/trembling, rapid heart rate, rash, and shortness of breath.

### *Gulf War Exposure Characterization*

Participants were asked about environmental and combat exposures specific to GW deployment on the Follow-up 2 and 3 survey questionnaires. To minimize the length of

time between deployment and recall, exposures self-reported on the Follow-up 2 surveys were used in the present study's models analyzing the relationship between GW-specific exposures and self-reported health symptoms. Exposures self-reported at Follow-up 3 were used to determine the test-retest reliability of exposure recall. Participants were asked to recall consumption of PB pills and hearing formal chemical weapons alerts in a dichotomous, yes or no response. They were also asked whether they had experienced exposure to smoke from tent heaters or oil well fires, pesticides, and debris from SCUD missiles according to these categories: 'not exposed', 'exposed but did not feel ill', 'exposed and felt ill'. Answers for these four GW-specific exposures were dichotomized to 0=not exposed and 1=exposed but did not feel ill or exposed and felt ill.

Sarin nerve gas exposure was determined by exposure estimates from the 2000 CIA/DoD exposure plume model developed by the Directorate of Health Risk Management, US Army Center for Health Promotion and Preventive Medicine to determine US troops who had been exposed to sarin and cyclosarin nerve gas as a result of the destruction of the Khamisiyah munitions facility in March 1991 (Winkenwerder 2002a; Winkenwerder 2002b). Exposure models were combined with troop location data using a database of GW unit locations to determine which US troops were located in the modeled exposure plume. The identified individuals were notified about their possible exposure by mail. A list of which cohort members received notifications was provided by the DoD.

### *Data Analysis*

Preliminary analyses demonstrated that the relationships between GW-specific exposures and health symptoms differed by sex in our dataset; therefore, we conducted stratified analyses to evaluate sex as an effect modifier. Study sample demographic characteristics were determined at each follow-up time point, along with the reporting frequency of GW-specific exposures and health symptoms. Kappa coefficients were calculated to estimate the level of agreement between Follow-up 2 and Follow-up 3 exposure responses.

Repeated logistic regression models were used to determine the unique associations between GW-specific exposures and health symptoms, controlling for age at deployment and military status during deployment, comparing Active Duty (reference) versus Army Reserve/National Guard. To evaluate the effect of time on health symptom reporting, we used dates of survey completion to determine the amount of time in years since the Baseline Survey was completed immediately upon return from the Persian Gulf. Odds ratios (OR) and 95% confidence intervals (CI) were calculated from the logistic regression models. To examine the effect of PTSD on the results, a sensitivity analysis was conducted in which individuals with a missing baseline PTSD scale score ( $n = 2$ , 1 male and 1 female) or a Mississippi PTSD scale score greater than the clinical cutoff ( $>85$ ) were excluded from the sex strata ( $n = 8$ , 2 males and 6 females). All analyses were performed using SAS 9.3/9.4 (SAS, Cary, NC).

## RESULTS

Table 5.1 shows the demographic characteristics of the men and women in our study sample compared to the full Fort Devens cohort. Compared to their male counterparts, women in our study sample were younger, less likely to be white, more likely to be Active Duty, and more often have a high score on the Mississippi PTSD scale at the Baseline Survey.

On average, the number of years since deployment for the first follow-up survey was 1.26 years ( $sd = 0.3$  years) and 3.99 years ( $sd = 0.8$  years) and 5.94 years ( $sd = 0.2$  years), for Follow-ups 2 and 3, respectively. The time since deployment did not differ significantly between the men and women in our study sample for any of the follow-up periods. Table 5.2 shows the differences between symptom reporting in males and females at each time point. Generally, women reported symptoms at a higher frequency than men, with the one exception that men had higher reports of trouble sleeping than women. Trends of symptom reporting over time were examined in the repeated logistic regression models, but in both men and women the frequency of symptom reporting most often remained stable or decreased over time.

Twenty-five men (42.4%) from the study sample were notified that they had likely exposure to sarin nerve gas based on modeled estimates of the Khamisiyah detonation. Of the GW exposures examined in this analysis, the most frequent self-reported GW exposure among men was smoke from oil well fires ( $n = 52$ , 88.1%), followed by hearing chemical alerts ( $n = 40$ , 67.8%), tent heaters ( $n = 34$ , 57.6%), taking

PB pills (n = 28, 47.5%), debris from SCUDs (n = 26, 44.1%), and pesticide use (n = 23, 38.9%). Twenty-seven women (46.6%) from the study sample were notified that they had likely exposure to sarin nerve gas based on modeled estimates of the Khamisiyah demolition. The most commonly self-reported GW exposure among women was hearing chemical alerts (n = 52, 89.7%), followed closely by smoke from oil well fires (n = 48, 82.8%) and tent heaters (n = 43, 74.1%). Thirty-nine (67.2%) women self-reported consuming PB pills, thirty-two (55.2%) reported exposure to debris from SCUD missiles, and twenty-nine (50.0%) reported pesticide use.

Comparing Follow-up 2 and 3 responses, consumption of PB pills was recalled with a high level of agreement,  $\kappa = 0.73$  for males and  $\kappa = 0.82$  for females, and hearing chemical weapons alerts was also recalled with high reliability,  $\kappa = 0.65$  for males and  $\kappa = 0.70$  for females. Exposure to smoke from tent heaters was recalled with moderate agreement,  $\kappa = 0.50$  for males and  $\kappa = 0.55$  for females.

#### *Longitudinal associations between GW exposure and health*

Table 5.3a shows the relationship between GW exposures and the mood-cognition and fatigue symptoms that were asked on all three health symptom surveys. Among male participants, those reporting exposure to tent heaters, pesticides, PB pills, and debris from SCUD missiles had higher odds of reporting each of the mood-cognition and fatigue symptoms. Compared to unexposed individuals, tent heater exposure was significantly associated with feeling depressed (OR = 3.28, 95% CI: 1.41, 7.59), anxious (OR = 2.39,

95% CI: 1.08, 5.32), and having trouble sleeping (OR = 4.81, 95% CI: 1.97, 11.78).

Exposure to debris from SCUD missiles was significantly associated with higher odds of reporting feeling anxious (OR = 2.62, 95% CI: 1.17, 5.86) and having trouble sleeping (OR = 2.64, 95% CI: 1.10, 6.35) compared to unexposed individuals.

Among women, debris from SCUD missiles was the only exposure consistently associated with higher odds of reporting each mood-cognition and fatigue symptom (Table 5.3a). Compared to unexposed women, women reporting exposure to debris from SCUD missiles had significantly higher odds of reporting crying easily (OR = 4.32, 95% CI: 1.90, 9.84), feeling anxious (OR = 3.05, 95% CI: 1.30, 7.15), trouble sleeping (OR = 2.74, 95% CI: 1.28, 5.86), and lack of energy (OR = 2.94, 95% CI: 1.21, 7.18).

In women, an increase in the number of years since deployment was associated with significantly lower symptom reporting in some cases (Table 5.3a). In the models of exposure to sarin based on the DoD model and of self-reported exposures to tent heaters, hearing chemical alerts, and smoke from oil well fires, odds of reporting feeling depressed significantly decreased as the number of years from deployment increased. Similarly, models investigating exposure to sarin based on the DoD model and self-reported exposures to tent heaters, pesticides, hearing chemical alerts, smoke from oil well fires, and debris from SCUD missiles, showed that the odds of reporting feeling anxious significantly decreased as the number of years from deployment increased.

The relationship between GW exposures and neurological and other physical symptoms are shown in Table 5.3b. Men reporting exposure to tent heaters, pesticides,

hearing chemical alerts, and debris from SCUD missiles had higher odds of endorsing each of these symptoms on the three symptom surveys. Compared to unexposed men, those reporting exposure to tent heaters had significantly higher odds of reporting headaches (OR = 3.19, 95% CI: 1.39, 7.29), muscle twitching and/or trembling (OR = 8.54, 95% CI: 3.06, 23.85), and skin rashes (OR = 3.16, 95% CI: 1.07, 9.28). Men reporting pesticide exposure had significantly higher odds of endorsing headaches (OR = 2.67, 95% CI: 1.11, 6.42) and muscle twitching and/or trembling (OR = 4.36, 95% CI: 1.68, 11.30) compared to unexposed men. Significantly higher odds of muscle twitching and/or trembling (OR = 3.88, 95% CI: 1.2, 11.41) and skin rash (OR = 3.42, 95% CI: 1.04, 11.19) were seen among men who reported hearing chemical alerts compared to unexposed men. Men who endorsed being exposed to debris from SCUD missiles had significantly higher odds of reporting dizziness (OR = 2.41, 95% CI: 1.03, 5.66) and muscle twitching and/or trembling (OR = 5.02, 95% CI: 2.05, 12.31) compared to the unexposed men.

For the models in Table 5.3b, there were some significant associations between the length of time since deployment and symptom reporting among men. In the models using the DoD-determined sarin exposure and those examining self-reported exposures to tent heaters, hearing chemical alerts, smoke from oil well fires, and debris from SCUD missiles, odds of reporting headaches significantly decreased as the years from deployment increased. The opposite effect was seen for time since deployment and self-reported muscle twitching/trembling and skin rash. Among men with DoD-reported sarin exposure and those with self-reported exposures to tent heaters, pesticides, hearing

chemical alerts, taking PB pills, smoke from oil well fires, and debris from SCUD missiles, odds of reporting rashes significantly increased as time since deployment increased. With the exception of the model investigating consumption of PB pills, increased time since deployment was significantly associated with increased reporting of muscle twitching/trembling for the self-reported GW exposure models.

Among women, there were fewer GW exposures that were consistently associated with higher odds of symptom reporting. Women reporting exposure to tent heaters and debris from SCUD missiles had higher odds of reporting each of the neurological and physical symptoms, but only one of those associations reached the level of significance (Table 5.3b). Compared to unexposed women, women who reported exposure to debris from SCUD missiles had significantly higher odds of reporting shortness of breath (OR = 4.29, 95% CI: 1.54, 11.96).

Among women, the direction of the significant associations between years since deployment and symptom reporting varied between the exposure-symptom models. In the models testing the association between sarin exposure based on the DoD model and self-reported exposures to tent heaters, pesticides, hearing chemical alerts, taking PB pills, smoke from oil well fires, and debris from SCUD missiles, odds of reporting headaches significantly decreased as the years from deployment increased (Table 5.3b). But among women in the model investigating sarin exposure based on the DoD model, odds of reporting dizziness significantly increased as the years from deployment increased.

### *Sensitivity Analysis Removing Participants with Baseline PTSD*

Three males were removed from the primary analysis omitting persons with PTSD, 1 male with missing PTSD data and 2 with a score greater than 85 on the Mississippi PTSD scale score on the Baseline Survey. Among men, the results of the exposure-symptom relationships noted above remained mostly unchanged. The relationships between self-reported tent heater exposure and feeling anxious and between self-reported pesticide exposure and headache were no longer significant. Seven females were removed from this analysis, 1 female with missing PTSD data and 6 with a score greater than 85 on the Mississippi PTSD scale score on the Baseline Survey. Among women, the significant association seen between DoD-modeled sarin exposure and the mood/fatigue symptoms was no longer significant. The relationships between hearing chemical alerts and crying easily, debris from SCUD missiles and feeling anxious, and debris from SCUD missiles and shortness of breath were also no longer significant.

## **DISCUSSION**

In a longitudinal analysis stratified by sex, several self-reported GW-specific exposures (tent heater exhaust, pesticide use, hearing chemical alerts, and debris from SCUD missiles), were significantly associated with higher symptom reporting. However, the most noteworthy results were the differences in exposure-symptom relationships between the sexes. We found a larger number of significant associations between GW exposures and health symptom reporting in men compared to their female counterparts.

Among men, self-reported exposure to tent heaters and exposure to debris from SCUD missiles were the GW hazards most frequently associated with significantly higher odds of health symptoms in each of the categories of interest: feeling depressed, anxious, trouble sleeping, headache, muscle twitching/trembling, and rash. In men, self-reported exposure to pesticides and hearing chemical alerts were also significantly associated with higher odds of reporting of dizziness, headache, muscle twitching/trembling, and rash. These results are similar to associations found in previous cross-sectional studies of GW veterans, and to chronic symptoms associated with organophosphate pesticide exposure in agricultural workers and pesticide applicators (Cherry et al. 2001b; Hanssen et al. 2015; The Iowa Persian Gulf Study Group 1997; Kamel et al. 2005; Kamel et al. 2007; Kelsall et al. 2005; McCauley et al 2001; Payán-Rentería et al. 2012; Proctor et al. 1998; Steele et al. 2012). Furthermore, the significant findings among men correspond with symptom clusters from the most widely accepted case definitions of GWI: mood-cognition, fatigue, neurological and dermatological (Fukuda et al. 1998; IOM 2014; Steele 2000).

In this study, women endorsed deployment exposures and symptoms, sometimes with greater frequency than their male counterparts, but we did not see as many significant exposure-symptom relationships, suggesting that there might be other factors influencing their self-perceived health. Of the covariates explored in this analysis, women in the Reserve/National Guard and women who were older when they deployed had higher odds of reporting symptoms. This contrasts with the findings of Pierce *et al.* (1997), who showed Active Duty US Air Force (USAF) women reported more general

health problems than women in the USAF Reserve. In that study and a study of female GW veterans in the UK, headache, fatigue, trouble sleeping, depression, and irritability were reported with the highest frequency (Pierce 1997; Unwin et al. 2002). Neither study looked at the relationship between health symptoms and deployment exposures. Although women were only 7% of the deployed force during the GW, they constituted the largest group of women deployed to a war-zone at that time; therefore, these results highlight the importance of continuing to look at sex-specific issues in deployment health research (Coughlin 2016; Smylie et al. 2013).

Some of the exposures assessed on the survey questionnaires were reported by most participants, with only 7 men and 10 women reporting no exposure to smoke from oil well fires and only 6 women reporting hearing no formal chemical alerts. The skewed distribution of exposure resulted in a limited number of unexposed, symptom-positive subjects. Without an adequate representation of each exposure-symptom combination, the results for the logistic regression models become less reliable. Indeed, among male participants we had 2 models that failed to converge, the model analyzing the association between smoke from oil fires and rapid heart rate and the model analyzing the association between smoke from oil fires and shortness of breath. In cross-sectional analyses these exposures have been linked to cognitive dysfunction, depressive symptoms, neurological complaints, and pulmonary issues; unfortunately we did not have sufficient power to assess the longitudinal effects associated with exposure to smoke from oil well fires and hearing chemical alerts.

Previous research indicates that symptom reporting remains relatively stable in GW veterans over time. However, in this stratified, longitudinal analysis, there were some significant associations between time since deployment and symptom trajectories. In both men and women, across all exposure models, we found a decrease in odds of reporting headache over time. Among females, there was also a decrease in the reporting of feeling depressed and anxious over time. Lastly, in men, we saw increasing odds of reporting muscle twitching/trembling and rash as time from deployment increased. The changes in symptom trajectories over the 7-year follow-up period could indicate emerging symptoms as time since deployment increases; on the other hand, it could indicate differences in the ability of the medical community to treat certain symptoms that are commonly experienced by GW veterans. There is another Fort Devens cohort follow-up survey underway (data collection ends in 2017); this will enable us to examine a much longer symptom trajectory.

### *Limitations and Strengths*

Our study sample is a small subset of the full Fort Devens cohort; however, to analyze this sample longitudinally we limited our study sample to Fort Devens cohort members who had completed health symptom surveys on three follow-up survey questionnaires. This may limit the generalizability of our results to the greater Fort Devens cohort and the population of GW veterans as a whole.

We tested many exposure-symptom relationships, so it is possible that some of

the significant associations we found are due to chance. However, using an alpha level of 0.05, we would expect approximately 5% of our significant associations could be by chance alone (approximately 4 exposure-symptom relationships per sex strata). In both the male and female groups, the number of significant exposure-symptoms relationships was greater than what we would expect by chance, giving us confidence in results which demonstrate that some GW-specific exposures are significantly related to health symptom reporting in this sample of GW veterans.

An important challenge to studying the effects of GW exposures on veteran health is a lack of records or measurements quantifying chemical exposures during deployment. For this study, we relied mostly on self-reported exposures. To determine the effect of possible recall bias on our results we calculated a kappa statistic, a measure of agreement, for exposures that were self-reported at Follow-up 2 and 3. Similar levels of agreement were found in other GW cohort studies, mean  $\kappa$  for GW exposures = 0.74 (Gray et al. 2002);  $\kappa$ (consuming PB pills) = 0.86 (McCauley et al. 1999);  $\kappa$ (chemical weapons alarms) = 0.64 (McCauley et al. 1999);  $\kappa$ (chemical weapons alarms) = 0.49 (Wessely et al. 2003). The high but not perfect level of agreement of exposure recall between follow-up surveys indicates that while exposure misclassification likely exists in this study, the magnitude of the exposure misclassification would not change the significant results found in this study.

Selection bias, in which individuals with more health problems are more likely to remain in the study than healthy individuals, can affect the results of longitudinal studies.

At Follow-up 1, individuals were flagged as high or low symptom reporters and the study sample at that time point was randomized to yield a balance of high symptom reporters and low symptom reporters. Using this flag variable, we determined that the balance of high and low symptom reporters remained steady for our study sample, so we can be confident that our results are not due to sicker individuals from the cohort participating in the surveys at a higher rate than healthy individuals. We also saw relatively few changes to our results when removing individuals with PTSD from the primary analysis. These results add to the literature demonstrating that GW veteran ill health is being driven by specific exposures encountered in the Gulf region and not psychological conditions. We did see more results change in the sensitivity analysis in our female participants; however, these changes could be due to small sample size and removing additional participants decreases the precision of exposure-symptom associations.

## **CONCLUSION**

In this longitudinal analysis, results showed higher odds of symptom reporting associated with specific deployed-related exposures in a group of male and female GW veterans. Understanding sex-specific symptom trajectories and the relationship between GW exposures and outcomes is critical as the research focus shifts to developing effective treatments for persistent health issues experienced by GW veterans.

**Table 5.1.** Demographics of study sample (n=117) compared to full Fort Devens cohort (n=2949)

	Full Fort Devens cohort (n=2949)	Male Study Sample (n=59)	Female Study Sample (n=58)
Age	30.2 (8.4) [18–65]	35.5 (10.0) [20–56]	30.2 (7.9) [19–55]
Mississippi PTSD scale-score	61.9 (13.4) [35–131]	61.5 (11.0) [42–95]	67.6 (16.1) [45–116]
n (%) Caucasian	2702 (91.6%)	58 (98.3%)	51 (87.9%)
n (%) Active Duty	823 (27.9%)	4 (6.8%)	8 (13.8%)
n (%) above clinical cutoff on Mississippi scale-score	116 (3.9%)	2 (3.4%)	6 (10.3%)

**Table 5.2.** Symptom frequencies at follow-up surveys: mood-cognition and fatigue symptoms

	Follow-up 1		Follow-up 2		Follow-up 3	
	Male	Female	Male	Female	Male	Female
Difficulty concentrating						
Yes	27 (45.8%)	33 (56.9%)	30 (50.8%)	37 (64.8%)	22 (37.3%)	22 (37.9%)
No	32 (54.2%)	25 (43.1%)	26 (44.1%)	17 (28.8%)	36 (61.0%)	36 (62.1%)
Missing	0	0	3 (5.1%)	4	1 (1.7%)	0
Feeling depressed						
Yes	27 (45.8%)	29 (50.0%)	20 (33.9%)	27 (46.6%)	19 (32.2%)	22 (37.9%)
No	32 (54.2%)	29 (50.0%)	38 (64.4%)	31 (53.4%)	38 (64.4%)	36 (62.1%)
Missing	0	0	1 (1.7%)	0	2 (3.4%)	0
Cry easily						
Yes	8 (13.6%)	28 (48.3%)	8 (13.6%)	25 (43.1%)	11 (18.6%)	21 (36.2%)
No	51 (86.4%)	30 (51.7%)	50 (84.7%)	32 (55.2%)	45 (76.3%)	36 (62.1%)
Missing	0	0	1 (1.7%)	1 (1.7%)	3 (5.1%)	1 (1.7%)
Feeling anxious						
Yes	26 (44.1%)	35 (60.3%)	20 (33.9%)	27 (46.6%)	18 (30.5%)	21 (36.2%)
No	32 (54.2%)	23 (39.7%)	39 (66.1%)	31 (53.5%)	40 (67.8%)	37 (63.8%)
Missing	1 (1.7%)	0	0	0	1 (1.7%)	0
Trouble sleeping						
Yes	28 (47.5%)	26 (44.8%)	36 (61.0%)	31 (53.4%)	29 (49.2%)	26 (44.8%)
No	31 (52.5%)	32 (55.2%)	23 (39.0%)	26 (44.8%)	29 (49.2%)	32 (55.2%)
Missing	0	0	0	1 (1.7%)	1 (1.7%)	0
Lack of energy						
Yes	30 (50.9%)	35 (60.3%)	29 (49.2%)	41 (70.7%)	28 (47.5%)	37 (63.8%)
No	29 (49.1%)	23 (39.7%)	29 (49.2%)	16 (27.6%)	30 (50.8%)	21 (36.2%)
Missing	0	0	1 (1.7%)	1 (1.7%)	1 (1.7%)	0

**Table 5.2 (continued).** Symptom frequencies at follow-up surveys: neurological and physical symptoms

	Follow-up 1		Follow-up 2		Follow-up 3	
	Male	Female	Male	Female	Male	Female
Dizziness						
Yes	10 (17.0%)	12 (20.7%)	14 (23.7%)	26 (44.8%)	10 (17.0%)	20 (34.5%)
No	49 (83.0%)	46 (79.3%)	43 (72.9%)	31 (53.4%)	48 (81.3%)	38 (65.5%)
Missing	0	0	2 (3.4%)	1 (1.7%)	1 (1.7%)	0
Headache						
Yes	37(62.7%)	44 (75.9%)	33 (55.9%)	49 (84.5%)	28 (47.5%)	28 (48.3%)
No	22 (37.3%)	14 (24.1%)	26 (44.1%)	9 (15.5%)	31 (52.5%)	30 (51.7%)
Missing	0	0	0	0	0	0
Muscle twitching/trembling						
Yes	14 (23.7%)	17 (29.3%)	13 (22.0%)	23 (39.7%)	21 (35.6%)	20 (34.5%)
No	45 (76.3%)	41 (70.7%)	43 (72.9%)	35 (60.3%)	37 (62.7%)	38 (65.5%)
Missing	0	0	3 (5.1%)	0	1 (1.7%)	0
Rapid heart rate						
Yes	10 (17.0%)	16 (27.6%)	8 (13.6%)	14 (24.1%)	7 (11.9%)	11 (19.0%)
No	49 (83.0%)	41 (70.7%)	51 (86.4%)	43 (74.1%)	52 (88.1%)	47 (81.0%)
Missing	0	1 (1.7%)	0	1 (1.7%)	0	0
Rash						
Yes	11 (18.6%)	17 (29.3%)	16 (27.1%)	17 (29.3%)	20 (33.9%)	22 (37.9%)
No	48 (81.4%)	41 (70.7%)	42 (71.2%)	41 (70.7%)	38 (64.4%)	36 (62.1%)
Missing	0	0	1 (1.7%)	0	1 (1.7%)	0
Shortness of breath						
Yes	12 (20.3%)	16 (27.6%)	11 (18.6%)	16 (27.6%)	15 (25.4%)	15 (25.9%)
No	47 (79.7%)	41 (70.7%)	48 (81.4%)	42 (72.4%)	43 (72.9%)	43 (74.1%)
Missing	0	1 (1.7%)	0	0	1 (1.7%)	0

**Table 5.3a.** Longitudinal associations between GW exposure and health: mood-cognition and fatigue symptoms

	<b>Difficulty concentrating</b>	<b>Feeling depressed</b>	<b>Cry easily</b>
<b>Model 1 – sarin nerve gas exposed (modeled)</b>			
Males Exposed	-0.45 (-1.2, 0.3)	-0.42 (-1.2, 0.4)	0.35 (-0.7, 1.4)
Years from deployment	-0.07 (-0.19, 0.1)	-0.11 (-0.3, 0.03)	0.12 (-0.1, 0.3)
Females Exposed	-0.43 (-1.3, 0.4)	<b>-1.33 (-2.2, -0.4)*</b>	-0.21 (-1.0, 0.6)
Years from deployment	-0.10 (-0.2, 0.05)	<b>-0.15 (-0.3, -0.005)*</b>	-0.09 (-0.2, 0.05)
<b>Model 2 – tent heater (self-reported)</b>			
Males Exposed	0.44 (-0.3, 1.2)	<b>1.19 (-0.4, 2.0)*</b>	0.50 (-0.6, 1.6)
Years from deployment	-0.06 (-0.2, 0.1)	-0.11 (-0.3, 0.04)	0.12 (-0.1, 0.3)
Females Exposed	0.61 (-0.2, 1.5)	0.44 (-0.6, 1.5)	<b>1.46 (0.4, 2.5)*</b>
Years from deployment	-0.11 (-0.3, 0.03)	<b>-0.15 (-0.3, -0.02)*</b>	-0.10 (-0.3, 0.1)
<b>Model 3 – pesticides (self-reported)</b>			
Males Exposed	0.31 (-0.4, 1.1)	0.41 (-0.4, 1.2)	0.65 (-0.4, 1.7)
Years from deployment	-0.07 (-0.2, 0.1)	-0.10 (-0.3, 0.04)	0.09 (-0.1, 0.3)
Females Exposed	0.69 (-0.1, 1.5)	-0.05 (-0.9, 0.8)	0.68 (-0.2, 1.5)
Years from deployment	-0.11 (-0.3, 0.03)	-0.12 (-0.3, 0.02)	-0.11 (-0.3, 0.05)
<b>Model 4 – hearing chemical alerts (self-reported)</b>			
Males Exposed	0.30 (-0.5, 1.1)	-0.55 (-1.5, 0.4)	0.30 (-1.1, 1.7)
Years from deployment	-0.07 (-0.2, 0.1)	-0.11 (-0.3, 0.03)	0.12 (-0.1, 0.3)
Females Exposed	-0.40 (-1.8, 1.0)	-0.62 (-1.9, 0.6)	<b>1.48 (0.1, 2.8)*</b>
Years from deployment	-0.10 (-0.2, 0.04)	-0.15 (-0.3, -0.02)	-0.10 (-0.2, 0.05)
<b>Model 5 – consuming PB pills (self-reported)</b>			
Males Exposed	0.42 (-0.4, 1.3)	0.25 (-0.7, 1.2)	0.02 (-1.2, 1.2)
Years from deployment	-0.09 (-0.2, 0.04)	-0.14 (-0.3, 0.01)	0.08 (-0.1, 0.3)
Females Exposed	0.45 (0.6, 1.5)	-0.23 (-1.2, 0.8)	0.84 (-0.02, 1.7)
Years from deployment	-0.13 (-0.3, 0.02)	<b>-0.18 (-0.3, -0.03)*</b>	-0.15 (-0.3, 0.01)
<b>Model 6 – Smoke from oil well fires (self-reported)</b>			
Males Exposed	-0.14 (-1.3, 1.0)	-0.14 (-1.2, 0.9)	1.39 (-0.7, 3.5)
Years from deployment	-0.05 (-0.2, 0.1)	-0.09 (-0.2, 0.1)	0.12 (-0.1, 0.3)
Females Exposed	0.32 (-0.8, 1.4)	-1.17 (-2.6, 0.2)	-0.48 (-1.5, 0.5)
Years from deployment	-0.11 (-0.2, 0.03)	<b>-0.15 (-0.3, -0.01)*</b>	-0.09 (-0.2, 0.05)
<b>Model 7 – Debris from SCUDs (self-reported)</b>			
Males Exposed	0.35 (-0.4, 1.1)	0.54 (-0.3, 1.4)	0.55 (-0.5, 1.6)
Years from deployment	-0.08 (-0.2, 0.1)	-0.12 (-0.3, 0.02)	0.12 (-0.1, 0.3)
Females Exposed	0.62 (-0.2, 1.5)	0.82 (-0.1, 1.7)	<b>1.46 (0.6, 2.3)*</b>
Years from deployment	-0.11 (-0.3, 0.04)	-0.13 (-0.3, 0.01)	-0.13 (-0.3, 0.04)

Note: Unexposed (reference); models adjusted for baseline age (continuous), baseline military status (0=Active Duty, 1=Reserve/Guard)

\*  $p < 0.05$

**Table 5.3a (continued).** Longitudinal associations between GW exposure and health: mood-cognition and fatigue symptoms

	Anxious	Trouble sleeping	Lack of energy
<b>Model 1 – sarin nerve gas exposed (modeled)</b>			
Males Exposed	-0.33 (-1.1, 0.5)	-0.31 (-1.2, 0.5)	-0.40 (-1.2, 0.4)
Years from deployment	-0.11 (-0.3, 0.04)	0.03 (-0.1, 0.1)	-0.03 (-0.1, 0.1)
Females Exposed	-0.62 (-1.5, 0.3)	<b>-0.98 (-1.8, -0.2)*</b>	<b>-1.02 (-2.0, -0.1)*</b>
Years from deployment	<b>-0.20 (-0.3, -0.1)*</b>	-0.0004 (-0.1, 0.1)	0.03 (-0.1, 0.2)
<b>Model 2 – tent heater (self-reported)</b>			
Males Exposed	<b>0.87 (0.1, 1.7)*</b>	<b>1.57 (0.7, 2.5)*</b>	0.76 (-0.1, 1.6)
Years from deployment	-0.12 (-0.3, 0.04)	0.03 (-0.1, 0.2)	-0.03 (-0.1, 0.1)
Females Exposed	0.70 (-0.3, 1.7)	0.75 (-0.1, 1.6)	-0.15 (-1.2, 0.9)
Years from deployment	<b>-0.21 (-0.4, -0.1)*</b>	0.002 (-0.1, 0.1)	0.02 (-0.1, 0.2)
<b>Model 3 – pesticides (self-reported)</b>			
Males Exposed	0.71 (-0.1, 1.6)	0.86 (-0.1, 1.8)	0.27 (-0.6, 1.2)
Years from deployment	-0.10 (-0.3, 0.1)	0.03 (-0.1, 0.1)	-0.04 (-0.2, 0.1)
Females Exposed	0.14 (-0.7, 1.0)	-0.02 (-0.8, 0.7)	0.48 (-0.4, 1.4)
Years from deployment	-0.22 (-0.3, -0.1)	0.002 (-0.1, 0.1)	0.01 (-0.1, 0.2)
<b>Model 4 – hearing chemical alerts (self-reported)</b>			
Males Exposed	-0.09 (-1.0, 0.8)	0.25 (-0.7, 1.2)	0.41 (-0.5, 1.3)
Years from deployment	-0.11 (-0.3, 0.03)	0.03 (-0.1, 0.1)	-0.03 (-0.1, 0.1)
Females Exposed	-0.09 (-1.1, 0.9)	-0.04 (-1.4, 1.3)	<b>-2.31 (-4.2, -0.4)*</b>
Years from deployment	<b>-0.20 (-0.3, -0.1)*</b>	0.001 (-0.1, 0.1)	0.02 (-0.1, 0.2)
<b>Model 5 – consuming PB pills (self-reported)</b>			
Males Exposed	0.22 (-0.7, 1.1)	0.23 (-0.7, 1.2)	0.38 (-0.5, 1.3)
Years from deployment	-0.14 (-0.3, 0.02)	-0.005 (-0.1, 0.1)	-0.02 (-0.1, 0.1)
Females Exposed	0.41 (-0.4, 1.3)	0.36 (-0.6, 1.3)	-0.05 (-1.2, 1.1)
Years from deployment	<b>-0.22 (-0.4, -0.1)*</b>	0.01 (-0.1, 0.1)	0.01 (-0.1, 0.2)
<b>Model 6 – Smoke from oil well fires (self-reported)</b>			
Males Exposed	-0.21 (-1.3, 0.9)	-0.18 (-1.4, 1.0)	-0.81 (-1.9, 0.3)
Years from deployment	-0.10 (-0.3, 0.1)	0.03 (-0.1, 0.1)	-0.03 (-0.1, 0.1)
Females Exposed	-0.42 (-1.6, 0.7)	-0.41 (-1.4, 0.6)	0.71 (-0.4, 1.8)
Years from deployment	<b>-0.20 (-0.3, -0.1)*</b>	-0.002 (-0.1, 0.1)	0.02 (-0.1, 0.2)
<b>Model 7 – Debris from SCUDs (self-reported)</b>			
Males Exposed	<b>0.96 (0.2, 1.8)*</b>	<b>0.97 (0.1, 1.9)*</b>	0.50 (-0.3, 1.4)
Years from deployment	-0.13 (-0.3, 0.03)	0.005 (-0.1, 0.1)	-0.02 (-0.1, 0.1)
Females Exposed	<b>1.11 (0.3, 2.0)*</b>	<b>1.01 (0.3, 1.8)*</b>	<b>1.08 (0.2, 2.0)*</b>
Years from deployment	<b>-0.25 (-0.4, -0.1)*</b>	0.02 (-0.1, 0.2)	0.02 (-0.1, 0.2)

Note: Unexposed (reference); models adjusted for baseline age (continuous), baseline military status (0=Active Duty, 1=Reserve/Guard)

\*  $p < 0.05$

**Table 5.3b.** Longitudinal associations between GW exposure and health: neurological and physical symptoms

	<b>Dizziness</b>	<b>Headache</b>	<b>Muscle twitching/ trembling</b>
<b>Model 1 – Sarin nerve gas (modeled)</b>			
Males Exposed	-0.24 (-1.2, 0.7)	-0.31 (-1.1, 0.5)	0.46 (-0.4, 1.3)
Years from deployment	0.01 (-0.2, 0.2)	<b>-0.13 (-0.2, -0.02)*</b>	<b>0.15 (0.02, 0.3)*</b>
Females Exposed	-0.86 (-1.8, 0.1)	-0.59 (-1.5, 0.3)	-0.95 (-1.9, 0.04)
Years from deployment	<b>0.18 (0.01, 0.4)*</b>	<b>-0.26 (-0.4, -0.1)*</b>	0.06 (-0.1, 0.2)
<b>Model 2 – tent heater (self-reported)</b>			
Males Exposed	0.89 (-0.03, 1.8)	<b>1.16 (0.3, 2.0)*</b>	<b>2.15 (1.1, 3.2)*</b>
Years from deployment	0.02 (-0.2, 0.2)	<b>-0.15 (-0.3, -0.02)*</b>	<b>0.17 (0.02, 0.3)*</b>
Females Exposed	0.47 (-0.7, 1.6)	0.18 (-0.8, 1.1)	0.57 (-0.5, 1.6)
Years from deployment	0.09 (-0.1, 0.3)	<b>-0.26 (-0.4, -0.1)*</b>	0.06 (-0.1, 0.2)
<b>Model 3 – pesticides (self-reported)</b>			
Males Exposed	0.63 (-0.2, 1.5)	<b>0.98 (0.1, 1.9)*</b>	<b>1.47 (0.5, 2.4)*</b>
Years from deployment	0.03 (-0.2, 0.2)	-0.12 (-0.2, 0.01)	<b>0.18 (0.04, 0.3)*</b>
Females Exposed	0.82 (-0.1, 1.7)	-0.04 (-0.9, 0.8)	0.95 (0.03, 1.9)
Years from deployment	0.11 (-0.1, 0.3)	<b>-0.25 (-0.4, -0.1)*</b>	0.10 (-0.1, 0.3)
<b>Model 4 – hearing chemical alerts (self-reported)</b>			
Males Exposed	0.52 (-0.5, 1.5)	0.38 (-0.6, 1.4)	<b>1.36 (0.3, 2.4)*</b>
Years from deployment	0.01 (-0.2, 0.2)	<b>-0.13 (-0.3, -0.02)*</b>	<b>0.16 (0.03, 0.3)*</b>
Females Exposed	-1.13 (-2.6, 0.4)	-1.23 (-2.7, 0.2)	-1.22 (-2.6, 0.2)
Years from deployment	0.09 (-0.1, 0.3)	<b>-0.27 (-0.4, -0.1)*</b>	0.06 (-0.1, 0.2)
<b>Model 5 – consuming PB pills (self-reported)</b>			
Males Exposed	0.66 (-0.5, 1.8)	0.12 (-0.8, 1.1)	0.96 (-0.02, 1.9)
Years from deployment	0.03 (-0.2, 0.2)	-0.11 (-0.2, 0.004)	0.12 (-0.02, 0.3)
Females Exposed	-0.34 (-1.4, 0.8)	-0.46 (-1.5, 0.6)	0.37 (-0.8, 1.6)
Years from deployment	0.04 (-0.1, 0.2)	-0.24 (-0.4, -0.1)	0.08 (-0.1, 0.2)
<b>Model 6 – Smoke from oil well fires (self-reported)</b>			
Males Exposed	1.33 (-0.8, 3.4)	0.72 (-0.6, 2.1)	0.98 (-0.2, 2.2)
Years from deployment	0.02 (-0.2, 0.2)	<b>-0.14 (-0.3, -0.02)*</b>	<b>0.16 (0.03, 0.3)*</b>
Females Exposed	0.14 (-0.9, 1.2)	-0.38 (-1.5, 0.7)	0.64 (-0.3, 1.6)
Years from deployment	0.09 (-0.1, 0.3)	<b>-0.27 (-0.4, -0.1)*</b>	0.06 (-0.1, 0.2)
<b>Model 7 – Debris from SCUDs (self-reported)</b>			
Males Exposed	<b>0.88 (0.03, 1.7)*</b>	0.48 (-0.4, 1.3)	<b>1.61 (0.7, 2.5)*</b>
Years from deployment	0.02 (-0.2, 0.2)	<b>-0.14 (-0.3, -0.01)*</b>	<b>0.17 (0.02, 0.3)*</b>
Females Exposed	0.75 (-0.2, 1.7)	0.68 (-0.1, 1.5)	0.58 (-0.4, 1.6)
Years from deployment	0.09 (-0.1, 0.3)	<b>-0.27 (-0.5, -0.1)*</b>	0.10 (-0.1, 0.3)

Note: Unexposed (reference); models adjusted for baseline age (continuous), baseline military status (0=Active Duty, 1=Reserve/Guard)

\* **p<0.05**

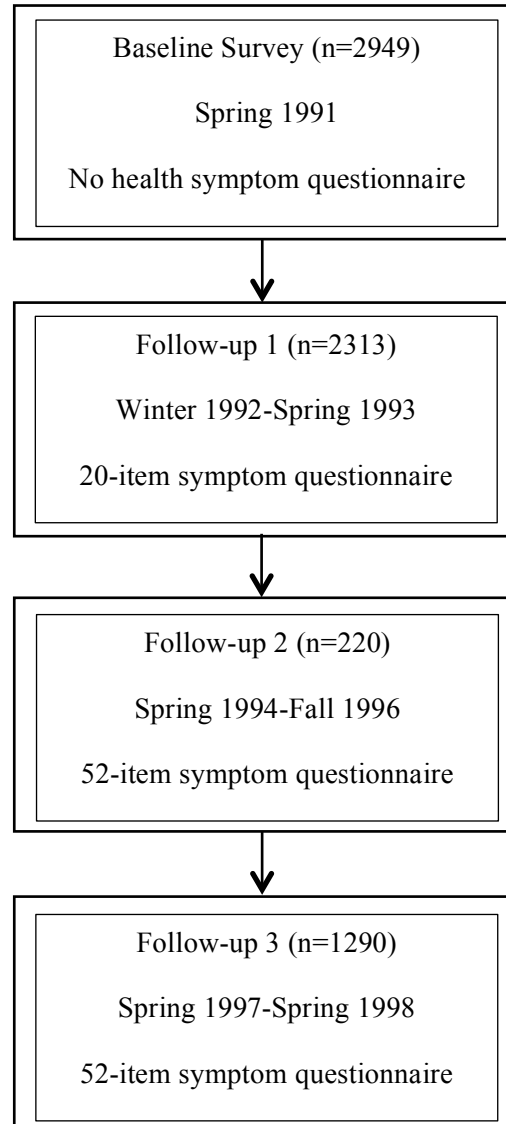
**Table 5.3b (continued).** Longitudinal associations between GW exposure and health: neurological and physical symptoms

	<b>Rapid heart rate</b>	<b>Rash</b>	<b>Shortness of breath</b>
<b>Model 1 – Sarin nerve gas (modeled)</b>			
Males Exposed	0.39 (-0.6, 1.4)	-0.26 (-1.2, 0.7)	-0.37 (-1.4, 0.7)
Years from deployment	-0.08 (-0.3, 0.1)	<b>0.18 (0.05, 0.3)*</b>	0.08 (-0.1, 0.2)
Females Exposed	-0.44 (-1.5, 0.6)	-0.75 (-1.6, 0.1)	-0.17 (-1.1, 0.8)
Years from deployment	-0.07 (-0.2, 0.1)	0.11 (-0.1, 0.3)	-0.01 (-0.2, 0.1)
<b>Model 2 – tent heater (self-reported)</b>			
Males Exposed	1.06 (-0.04, 2.2)	<b>1.15 (0.1, 2.2)*</b>	1.19 (-0.1, 2.4)
Years from deployment	-0.08 (-0.3, 0.1)	<b>0.19 (0.05, 0.3)*</b>	0.07 (-0.1, 0.2)
Females Exposed	1.23 (-0.4, 2.8)	0.25 (-0.8, 1.3)	0.90 (-0.4, 2.2)
Years from deployment	-0.07 (-0.2, 0.1)	0.10 (-0.1, 0.3)	-0.02 (-0.2, 0.1)
<b>Model 3 – pesticides (self-reported)</b>			
Males Exposed	0.78 (-0.2, 1.8)	0.95 (-0.1, 2.0)	0.95 (-0.1, 2.0)
Years from deployment	-0.08 (-0.3, 0.1)	<b>0.17 (0.03, 0.3)*</b>	0.08 (-0.1, 0.2)
Females Exposed	0.88 (-0.2, 2.0)	0.16 (-0.02, 0.3)	0.85 (-0.1, 1.8)
Years from deployment	-0.04 (-0.2, 0.1)	0.14 (-0.02, 0.3)	0.02 (-0.2, 0.2)
<b>Model 4 – hearing chemical alerts (self-reported)</b>			
Males Exposed	0.43 (-0.7, 1.5)	<b>1.23 (0.04, 2.4)*</b>	0.63 (-0.6, 1.8)
Years from deployment	-0.08 (-0.3, 0.1)	<b>0.19 (0.05, 0.3)*</b>	0.08 (-0.1, 0.2)
Females Exposed	0.02 (-1.7, 1.7)	-0.68 (-1.9, 0.5)	-0.79 (-2.0, 0.4)
Years from deployment	-0.07 (-0.2, 0.1)	0.11 (-0.1, 0.3)	-0.01 (-0.2, 0.1)
<b>Model 5 – consuming PB pills (self-reported)</b>			
Males Exposed	0.36 (-0.8, 1.6)	-0.43 (-1.5, 0.6)	0.38 (-0.8, 1.6)
Years from deployment	-0.07 (-0.3, 0.2)	<b>0.18 (0.04, 0.3)*</b>	0.04 (-0.1, 0.2)
Females Exposed	0.30 (-0.9, 1.5)	-0.28 (-1.2, 0.7)	-0.004 (-1.0, 1.0)
Years from deployment	-0.12 (-0.3, 0.05)	0.07 (-0.1, 0.2)	-0.01 (-0.2, 0.2)
<b>Model 6 – Smoke from oil well fires (self-reported)</b>			
Males Exposed	-----	1.36 (-0.9, 3.6)	-----
Years from deployment		<b>0.20 (0.1, 0.3)*</b>	
Females Exposed	0.14 (-0.9, 1.1)	0.02 (-1.1, 1.1)	0.65 (-0.5, 1.8)
Years from deployment	-0.07 (-0.2, 0.1)	0.10 (-0.1, 0.3)	-0.02 (-0.2, 0.1)
<b>Model 7 – Debris from SCUDs (self-reported)</b>			
Males Exposed	0.80 (-0.2, 1.8)	0.89 (-0.1, 1.9)	0.36 (-0.7, 1.4)
Years from deployment	-0.07 (-0.3, 0.1)	<b>0.19 (0.04, 0.3)*</b>	0.09 (-0.04, 0.2)
Females Exposed	0.73 (-0.4, 1.8)	0.57 (-0.4, 1.5)	<b>1.01 (0.3, 1.8)*</b>
Years from deployment	-0.05 (-0.2, 0.1)	0.13 (-0.03, 0.3)	0.005 (-0.2, 0.2)

Note: Unexposed (reference); models adjusted for baseline age (continuous), baseline military status (0=Active Duty, 1=Reserve/Guard)

\*  $p < 0.05$

**Figure 5.1.** Fort Devens cohort survey timeline



## CHAPTER SIX. CONCLUSION

The research summarized in this dissertation explores occupational exposures in two distinct groups of military personnel, Air Force personnel with exposure to toxicants found in jet fuel and Gulf War (GW) veterans, some of whom experienced ill health and/or a syndrome known as GW illness (GWI) following their deployment in 1990–1991. In the first two studies that are summarized here, we assessed USAF personnel exposed to JP-8 jet fuel in garrison using a standard, explicit exposure-related disease conceptual model. The next two investigations evaluated GW veterans exposed to a mixture of chemicals in operational theater. Given the challenges of health research among military personnel who become ill after return from active duty in a combat theater, the use of retrospective research methods were required for this effort.

The investigation summarized in *Chapter 2* addressed the validity of biomarkers of JP-8 exposure. The results showed that VOCs in blood can serve as biomarkers to assess exposure to JP-8, a complex mixture of aliphatic and aromatic hydrocarbons (Maule et al. 2016). These results follow on evidence of other investigators that VOC levels measured in the personal breathing zone, exhaled breath, and urine are higher in USAF personnel self-reporting occupational exposure to JP-8 (Egeghy et al. 2003; Merchant-Borna et al. 2012; Pleil et al. 2000; Puhala et al. 1997; Smith et al. 2010; Smith et al. 2012; Tu et al. 2004). Our study adds to that literature by providing evidence that USAF personnel self-reporting occupational exposure to JP-8 also have higher VOC concentrations in blood. Of the VOCs examined in that study, we concluded that the

xylenes (o-xylene, m/p-xylene) are the most appropriate biomarkers of occupational JP-8 exposure. Levels of THC measured in personal breathing zone air correlated best with xylenes and in regression models significantly predicted VOCs in blood. To most accurately assess the contribution of occupational JP-8 exposure to absorbed VOC dose, we controlled for the effect of cigarette smoking using blood levels of the biomarker 2,5-dimethylfuran and for USAF base of the military personnel participants to control for differences in JP-8 composition, job tasks, and environmental conditions. Although collecting blood is more invasive for participants than collecting urine samples or air samples around the breathing zone, this approach directly quantifies the concentration of JP-8 constituents in blood that could reach target tissues (*e.g.*, brain, liver, adipose tissue) while also representing cumulative exposure from multiple sources and routes (*i.e.*, dermal, inhalation).

*Chapter 3* describes research that addresses the relationship between occupational JP-8 exposure and potential adverse effects on nervous system function in the same group of USAF personnel that participated in the *Chapter 2* work (Maule et al. 2013). Components of JP-8 are neurotoxic and previous studies provided inconsistent evidence concerning whether JP-8 exposure is associated with diminished balance control, a measure of nervous system function, following work-shift exposures (Bhattacharya 2001; Smith et al. 1997; White and Proctor 1997). In our study, the postural sway evaluation included four balance tasks performed before and after the work shift: (1) standing with eyes open, (2) standing with eyes closed, (3) standing on foam support with eyes open, and (4) standing on foam support with eyes closed. Diminished balance control was

quantified as increases in postural sway velocity (*i.e.*, faster movements) and postural sway area (*i.e.*, larger movements) during in each of the four balance tasks (Gill et al. 2001; Hegeman et al. 2007). Participants' pre- and post-shift postural sway measurements increased as the balance task grew more difficult (*i.e.*, removal of visual stimuli and addition of uneven standing surface). Work shift JP-8 exposure, quantified by breathing zone levels of THC and naphthalene and urinary naphthol concentrations, was not associated with diminished balance control on any of the balance tasks. Results suggested that pre-shift balance performance and age were the most significant predictors of post-shift postural sway measurements. We concluded that short-term exposure to JP-8 during the work-shift did not impair postural sway performance.

*Chapter 4* describes work exploring the symptoms of ill health reported by military personnel following deployment to the Persian Gulf during the 1990–1991 GW. The existing literature on this military population has concluded that multiple symptoms of ill health were experienced by about 25–30% of GW veterans, a phenomenon that is known as GWI (RAC-GWVI 2008; RAC-GWVI 2014). To better understand the health complaints of GW veterans who were deployed to the Gulf theater, the aim of this work was to characterize the most significant symptoms occurring after deployment. We used meta-analytic techniques to integrate health symptom data contained in the literature from 18 distinct veteran populations, representing over 129,000 deployed GW veterans and GW-era veterans who were not deployed or who were deployed to areas other than the Gulf (*e.g.*, Bosnia or Germany). The sample included veterans from the GW-era in all branches of the US and allied militaries and from four different countries (CDC MMWR

1995; Cherry et al. 2001; Doebbeling et al. 2000; Fukuda et al. 1998; Gray et al. 2002; Iannacchione et al. 2011; Iowa Study Group 1997; Ishoy et al. 1999; Kang et al. 2000; Kelsall et al. 2004b; Knoke et al. 2000; Murphy et al. 2006; Nisenbaum et al. 2004; Proctor et al. 1998; Shapiro et al. 2002; Sostek et al. 1996; Steele 2000; Stretch et al. 1995; Unwin et al. 1999; Unwin et al. 2002). Deployed GW veterans had higher odds of reporting all of the analyzed health symptoms compared to GW-era control veterans, even after controlling for the effects of publication bias on the results. For several mood-cognition, musculoskeletal, gastrointestinal, and dermatological symptoms, the odds were more than three times higher for deployed GW veterans compared to controls. These findings suggest that symptoms assessing these particular domains are especially critical when assessing GW veteran health status and for diagnosing GWI. A secondary analysis revealed important differences in symptom reporting by study sampling strategy. Studies of specific military-unit cohorts showed higher odds ratios for symptoms compared to population-based studies. It is possible the high likelihood of symptom occurrence is related to specific exposures experienced by different military-units in the GW theater; however, we did not have access to individual level health outcome or exposure data to explore this hypothesis.

*Chapter 5* describes an investigation that employed a subset of the Fort Devens cohort, a population of former US Army Active, Reserve, and National Guard GW veterans who have been followed prospectively through a series of surveys since their return from deployment in the GW in 1991. This work assessed the longitudinal relationship between GW-specific exposures and health symptoms. Our results were

similar to those described in prior research on GW veterans, showing significant associations between self-reported exposures and experiences (tent heater exhaust, pesticide use, hearing chemical alerts, and debris from SCUD missiles) and reports of greater numbers of symptoms. In addition, our results indicated that there were gender-specific differences in the relationships between predictor variables and symptom reporting. Among men compared to women, the results indicated a larger number of significant associations between specific self-reported GW exposures and mood-cognition, fatigue, neurological, and physical symptoms. The data from female veterans revealed that demographic variables were the most significant indicators of health symptom reporting. Women who were older when they deployed and those serving in the Army Reserves/National Guard had increased odds of symptom reporting. These results highlight the importance of understanding sex-specific symptom trajectories and relationships between GW exposures and outcomes.

### *Research Limitations*

The research limitations specific to each study were outlined in *Chapters 2–5* and will be summarized here.

JP-8 is a mixture of 200 aliphatic and aromatic hydrocarbons. At this time there is no standard industrial hygiene method for measuring occupational exposure to JP-8 limiting researchers' ability to measure occupational exposure to jet fuel and total absorbed dose attributable to occupational exposure to jet fuel. Exposure assessment

studies, including our examination of VOC concentrations in blood, measure constituents of JP-8 as surrogates of occupational JP-8 exposure. The BTEX (*i.e.*, benzene, toluene, ethylbenzene, xylenes) concentration in breath samples taken from JP-8 exposed USAF personnel ranged from 14–50% of the total JP-8 fingerprint, so researchers are using measurements of these constituents in air, breath, skin, urine and blood to approximate total absorbed dose of JP-8 (Pleil 2001).

The JP-8 constituents we evaluated to determine occupational exposure to jet fuel are abundant in other products, including gasoline and cigarette smoke (Ashley et al. 1994; Chambers et al. 2011; NRC 2003; Polzin et al. 2007). Non-occupational exposure to components found in JP-8 and occupational exposure to other chemicals and solvents can affect levels of VOCs measured in blood and urine. First, we used two different approaches to control for potential confounding by cigarette smoke in our jet fuel studies. In the research summarized in *Chapter 2*, we controlled for 2,5-dimethylfuran, a biomarker of daily cigarette smoking in blood, to control for the effect of smoking on VOC levels in blood (Ashley et al. 1996; Chamber et al. 2011). For the work in *Chapter 3*, we controlled for current smoking using a binary categorical variable (current smoker – yes/no). Separately, we characterized self-service at a gas station and other occupational exposures to chemicals (*e.g.*, organic solvents, cutting or lubricating oils, coolants or anti-freeze, and/or degreasers). However, because the sample size was small for those reporting these additional exposures, we were unable to control for them in our statistical models. These exposures could be explored in a larger study.

The research examining the relationship between occupational JP-8 exposure and diminished balance control was powered to detect clinically relevant changes in postural sway measurements (*i.e.*, 15–25% change in performance); however, our study had limited power to detect subclinical decrements in performance. Our study was also limited in its ability to assess the health impact of chronic occupational JP-8 exposure in jet fuel workers because it examined only an 8-hour period of exposure (Maule et al. 2013). In our study, USAF personnel with high JP-8 exposure had worked, on average, for 6.5 years in the AF (range 0.5–17 years). In another study investigating postural sway in USAF personnel, workers exposed to jet fuel had worked an average of 12.0 years in the AF (range 0.8–30 years) (Smith et al. 1997). Smith *et al.* (1997) estimated cumulative exposure to JP-8 using work shift levels of JP-8 constituents measured in personal air and the length of each participant’s USAF career. Using the same postural sway evaluation as the study in *Chapter 3*, Smith *et al.* (1997) found a significant association between increased cumulative benzene and xylene levels and diminished balance control. These results support a need to study long-term occupational JP-8 exposure and potential adverse effects on nervous system function.

In the third and fourth studies, which focused on veterans of the 1990–1991 GW, different forms of selection bias were a potential concern. Publication bias and non-reporting bias is a limitation of conducting a meta-analysis on data published in peer-reviewed literature. Publication bias arises when studies with null or negative findings are less likely to be published than studies with positive findings. Non-reporting bias occurs when researchers include only positive or significant findings in their studies, omitting

null or negative findings. To address this issue in the meta-analysis summarized in *Chapter 4*, we used a method described in Levy *et al.* (2001), assigning studies with missing symptom data a null finding. The impact of selection bias on the results of the 7-year longitudinal assessment described in *Chapter 5* was also a concern. The results can be affected when individuals with more health problems are more likely to remain in the study than healthy individuals. At the first follow-up, participants in the Fort Devens Cohort were flagged as high- or low-symptom reporters based on the number of symptoms endorsed on the 20-item Health Symptom Checklist. The proportion of high and low symptom reporters did not change over the three follow-up periods, indicating that healthier individuals were participating at the same rate as sick individuals.

A major limitation of researching exposure-related disease in GW veterans results from a lack of record-keeping, environmental monitoring, and personal exposure measurements during the operations in the Persian Gulf region leading to potential exposure misclassification. GW researchers have relied heavily of retrospective self-reported exposure measures, which can be subject to recall bias, to examine causal links between deployment exposures and adverse health effects. In *Chapter 5*, we discussed the evidence of a moderate to good reliability of self-reported exposures on survey questionnaires at two different time points in our study sample and several other GW cohort studies. Results of two studies evaluating exposure recall in GW veterans showed that recall reliability did not differ between symptomatic and non-symptomatic GW veterans (McCauley, 1999; Brewer, 2008). This suggests that non-differential exposure misclassification would likely result from any exposure recall bias.

### *Public Health Impact*

The measured levels of VOCs in blood in *Chapter 2* provide evidence of occupational exposure to JP-8 despite the use of protective equipment (e.g., gloves, coveralls, booties, and respirators). The evidence of occupational exposure even with these personal protective measures suggests that other strategies could be employed to further limit occupational exposure. For example, an individual entering a fuel cell for inspection or maintenance is required to wear a respirator, but his/her attendant standing directly at the opening of the fuel cell does not wear a respirator (Pleil et al. 2000). During fuel cell inspection/maintenance, area monitoring has shown that the highest levels of THC in air are inside the fuel cell, with the second highest air levels measured directly outside the fuel tank undergoing maintenance (Pleil et al. 2000). Occupational exposure to JP-8 may be further decreased if the attendant is also required to wear a respirator during inspection and maintenance activities.

Our investigation of JP-8 exposure and health outcome research in a military population can also have direct applications to the civilian workforce. The commercial airline and civil aviation equivalents to JP-8 are Jet-A and Jet-A1, which have the same base formula as JP-8 without the military performance additives (Ritchie et al. 2003). In the US, the commercial consumption of jet fuel is expected to grow over the course of the next several decades. According to the Department of Energy, approximately 1.43 million barrels of jet fuel was consumed in the US on a daily basis. That number is expected to increase to 1.52 million barrels per day in 2020, 1.60 million barrels per day

in 2030, and 1.66 million barrels per day by 2040 (ATSDR 2017). Jet fuel will continue to be an occupational exposure that impacts a large number of workers. According to the latest estimate used by the Agency for Toxicology and Disease Registry in their toxicological profile of jet fuels, including JP-8, over 1 million military and civilian workers are occupationally exposed to jet fuel on a yearly basis (ATSDR 2017).

Unfortunately, some of the chemical hazards (*e.g.*, chemical warfare agents and oil well fire smoke) associated with health problems experienced by GW veterans following their deployment to the Persian Gulf are now present in theater in current conflicts in Iraq and Syria. In addition to health concerns for local populations, there are US troops currently stationed in both of those countries. The international community widely accepts that Syrian forces have used chemical warfare agents (*i.e.*, sarin and chlorine gas) in several attacks of rebel forces and civilian populations (Fields 2017; Loveluck 2017; Pita and Domingo 2014; Zarocostas 2017). In Iraq, Iraqi forces are fighting ISIS for control of the city of Mosul. During the summer of 2016, to create defensive barriers, ISIS fighters set fires to oil wells located south of Mosul. These fires, as well as a sulfur plant fire started in October 2016, have significantly affected the air quality in the area around Mosul (Malsin 2016). US troops stationed 50 miles south of Mosul at Camp Swift and Qayyarah Airfield as part of Combined Joint Task Force Operation Inherent Resolve have at certain points limited outdoor activity and worn personal protective equipment due to poor air quality (CJTF-OIR 2016). The results from the exposure-symptom associations explored in *Chapter 5* can inform likely health outcomes among US troops and civilian populations encountering chemical hazards

similar to those experienced by troops during the 1990–1991 GW.

We recognize that environmental and occupational exposure assessment and monitoring is often not feasible in an operational or combat setting. The physical hazards of combat, battle injuries that threaten lives, and the completion of combat mission objectives will continue to be the top priority for US Armed Forces in deployment zones (Proctor 2008; Richards 2011). However, the evidence of chronic and persistent health effects experienced by GW veterans suggest that the research and medical community needs to continue to find ways to rapidly identify adverse health outcomes and their etiology post-deployment. When possible the Department of Defense should make efforts to implement environmental and occupational monitoring programs in the battlefield and should use this information to rapidly address health issues that arise in theater and once troops have returned from deployment.

### *Future Research Directions*

The current American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit value (TLV) for jet fuel vapor is 200 mg/m<sup>3</sup>, based on a measure of total hydrocarbons in personal air over an average of 8-hours (ATSDR 2017). The occupational TLV is based on a measure that only captures inhalation exposure despite evidence that dermal contact is an important exposure route. In the 2017 Toxicological Profile of Jet Fuels, the ATSDR stated it could not set or recommend an occupational exposure limit because of lack of data. Future research could continue to

expand work on biomarkers of JP-8 exposure that capture dermal exposure so that an occupational exposure limit can be established. Furthermore, efforts could be made to use multiple biomarkers of exposure to characterize JP-8. Researchers are using several different statistical methods to study exposure to mixtures and their possible health effects (Taylor et al. 2016).

While the focus of those studying the health of GW veterans and GWI is shifting to finding effective treatments for GWI and other GW-related health problems, epidemiology will continue to play a role in studying the long-term health of GW veterans. In 2014, the Fort Devens Cohort Study commenced data collection for a fifth follow-up survey. Data collection will end later this year. The survey asks questions about demographic and health information; military service and civilian work history; and occupational and non-occupational chemical exposures. A 34-item health symptom survey is included. Adding this health symptom information to the data evaluated in Chapter 5 will help characterize GW veteran health more than 20-years after deployment and will allow us to analyze a 20-year health symptom trajectory in relation to different GW and post-GW experiences.

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## CURRICULUM VITAE

