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Natick, Massachusetts

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A POPULATION-BASED INVESTIGATION OF HEALTH OUTCOMES IN ACTIVE DUTY ARMY SERVICE MEMBERS BEFORE AND AFTER REQUIREMENT FOR FULL-TIME WEAR OF PERMETHRIN-TREATED UNIFORMS (USARIEM #17-22H; MRDC #M-10683)

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United States Army
Medical Research & Development Command

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14. ABSTRACT

The purpose of the research study titled, "A Population-based Investigation of Health Outcomes in Active Duty Army Service Members Before and After Requirement for Full-time Wear of Permethrin-treated Uniforms," was to examine longer-term health effects (24 months) of wearing permethrin-treated uniforms and evaluate the impact of physical workload on permethrin exposure and health conditions. The study utilized electronic medical encounter data from USARIEM's Soldier Performance, Health and Readiness (SPHERE) data repository (formerly known as the Total Army Injury and Health Outcome Database (TAIHOD) repository), under research protocol #17-22H/M-10683, to investigate the hypothesized relationship between permethrin exposure and increased longer-term (over a 2 year period) risk of select health outcomes (primarily dermatological, neurological, and renal) among the US Army Active Duty (AAD) population.

To address the study's research hypotheses, multivariate Poisson regression analyses were conducted to compare outcomes among a group of Soldiers who entered military service between 1 July and 21 December 2010 (n=21,182), which was prior to the required

15. SUBJECT TERMS

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TABLE OF CONTENTS

LIST OF TABLES

BACKGROUND

Permethrin is a common synthetic pyrethroid insecticide used widely in agriculture and found in household products such as Raid®, as well as scabies and lice-treatment medications. Permethrin is approved for use in insecticide-treated clothing, both commercial and military (22). As the US military deploys personnel to many insect-infested areas around the world and often on short notice, traditional ground spraying and pesticide application programs are neither realistic nor feasible. Thus, current methods that incorporate permethrin directly into clothing worn by the Soldier post-tailoring, support an efficient personal protection system.

The U.S. Army Research Institute of Environmental Medicine (USARIEM) established a research program, starting in 2007, to provide evidence-based guidance on aspects of operational exposure dosimetry as it pertains to neurological and physical health risk[1]. This program has addressed known and emerging military-relevant occupational neurotoxicant exposures, such as permethrin. Several USARIEM studies[2] have examined real-life operational conditions and their effect on permethrin exposure following short-term (days, weeks) wear of permethrin-treated military uniforms (such as Army Combat Uniforms (ACU)-Permethrin (ACU-P)). This report describes findings from a study that examined electronic medical records to determine the occurrence of health conditions associated with longer-term (two years) permethrin exposure among U.S. Active Duty Army Soldiers wearing factory-permethrin-treated uniforms compared to Soldiers who entered military service before wearing of these treated uniforms was required.

[1] The first study examined the role of uniform wear-time duration on permethrin absorption (USARIEM #H06-15; Proctor et al, 2014).

[2] One study examined the role of high temperature and humidity environments on permethrin exposure (USARIEM #14-27H/MOMRP-funded project #17330) while wearing ACU-P (Proctor et al. 2019; Maule et al., 2020). The second study examined the role of body composition and of physical workload on permethrin exposure (USARIEM #14-29H/DHP JPC5-funded #W81XWH-14-2-0130) while wearing permethrin-treated military uniforms (Proctor et al., 2018; Scarpaci et al., 2020). No obvious significant acute or short-term health effects were found to be related to permethrin exposure in these studies.

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EXECUTIVE SUMMARY

The purpose of the research study titled, "A Population-based Investigation of Health Outcomes in Active Duty Army Service Members Before and After Requirement for Full-time Wear of Permethrin-treated Uniforms,"[3] was to examine longer-term health effects (24 months) of wearing permethrin-treated uniforms and evaluate the impact of physical workload on permethrin exposure and health conditions. The study utilized electronic medical encounter data from USARIEM's Soldier Performance, Health and Readiness (SPHERE) data repository (formerly known as the Total Army Injury and Health Outcome Database (TAIHOD) repository), under research protocol #17-22H/M-10683, to investigate the hypothesized relationship between permethrin exposure and increased longer-term (over a 2 year period) risk of select health outcomes (primarily dermatological, neurological, and renal) among the US Army Active Duty (AAD) population.

To address the study's research hypotheses, multivariate Poisson regression analyses were conducted to compare outcomes among a group of Soldiers who entered military service between 1 July and 31 December 2010 (n=21,182), which was prior to the required routine wear of permethrin-treated uniforms, to outcomes recorded among a group of Soldiers who entered the service between 1 July and 31 December 2013 (n=29,556), after routine issuing of permethrin-treated uniforms was required.

No significant adverse health outcomes were observed among those Soldiers who entered the service in 2013 and wore permethrin-treated uniforms regularly compared to those Soldiers who entered the service in 2010, prior to the requirement to wear permethrin treated uniforms. Significant differences in risk for certain medical health outcomes were found when comparing the two cohorts. However, those in the 2010 cohort (prior to permethrin wear) demonstrated higher risk. In exploratory analyses, no significant difference between the two cohort groups in terms of risk of the vector-borne disease, Lyme Disease, was demonstrated, although these analyses were not adequately powered to fully draw definitive conclusions.

In summary, these findings suggest there is currently no increased longer-term (~24 months) exposure risk of select medical outcomes related to wear of permethrin-treated uniforms.

[3] USARIEM Protocol #17-22H/M10683 (MOMRP project #19840) A Population-based Investigation of Health Outcomes in Active Duty Army Service Members Before and After Requirement for Full-time Wear of Permethrin-treated Uniforms (PI: Proctor; MOMRP Core intramural funding-Task Area F; 2017-2018).

INTRODUCTION

Permethrin is a common synthetic pyrethroid insecticide used widely in agriculture and found in household products such as Raid®, as well as scabies and lice-treatment medications. Permethrin is also approved for use in insecticide-treated clothing, for both commercial and military purposes (22).

In humans, the main adverse effects reported following acute exposure to permethrin are skin irritation and prickliness, itching, and tingling of the skin (paresthesia). Additional symptoms such as headaches, dizziness, and nausea have been reported following occupational pyrethroid exposure (8,9) lasting anywhere from 30 minutes to 32 hours after exposure, depending on the pyrethroid compound. Acute poisoning from a pyrethroid targets the central nervous system and produces symptoms of incoordination, ataxia, hyperactivity, and convulsions usually within 2 hours of exposure. Such poisoning may ultimately result in paralysis and death (14).

Effects of long term exposure have been less studied, and only in occupational cohorts of farmers and pesticide applicators. Associated health effects of permethrin from these studies include rhinitis, non-atopic asthma, cardiovascular disease, multiple myeloma, end-stage renal disease and sperm aneuploidy (1,5,11,12,19,21,24,25). Some of these associations were discovered among small samples and therefore may not provide a complete picture nor a true association between exposure and outcome.

Since 2013, all US Army personnel regardless of deployment status, military job or location have been required to wear permethrin treated uniforms, a standard-issue uniform garment that is impregnated with permethrin post-tailoring. These treated uniforms are part of the Army's pest management and personal protection directives against biting insects and associated vector-borne diseases, such as malaria and leishmaniasis (23). As the US military deploys personnel to many insect-infested areas around the world and often on short notice, traditional ground spraying and pesticide application programs became impractical. Thus, permethrin incorporation directly into clothing worn by the Soldier was mandated to support an efficient and reliable personal protection system.

Military personnel have been observed to have considerably higher levels of permethrin exposure as measured by urinary biomarkers (13,15) as result of wearing permethrin-treated clothing, compared to the general population (6,7). Given the duration of time that Soldiers are required to wear pesticide-treated uniforms, it is important to consider the possible health effects associated with longer-term exposure to permethrin in this population.

Additional factors are known to affect permethrin absorption, including environmental temperature conditions and workload (18). The effect of climate on permethrin has been studied previously, demonstrating higher exposure to permethrin (as measured by urinary biomarkers) under conditions of extreme temperature and combined high temperature and humidity (13,17) compared to more ambient conditions. Workload, as measured by direct energy expenditure, also has been associated with

higher permethrin biomarker levels in some studies (16,18), but not others (20). However, the effect of workload, determined on the basis of military occupational specialty (MOS) codes, and the potential relationship with health outcomes, has not been evaluated in military personnel.

The purpose of this study was to examine longer-term (up to ~2 years) health outcomes of wearing permethrin-treated uniforms and to evaluate the potential role pertaining to the impact of physical workload on permethrin exposure and possible health conditions. We hypothesized that persons new to the Army since the requirement for full-time wear of permethrin-treated uniforms in 2013 (referred to as the 2013 cohort below) compared to Soldiers who entered the service in 2010 (referred to as the 2010 cohort below) before the requirement was put in place, would have a higher incidence of health outcomes associated with permethrin exposure over a 2-year period (mid-2013 to mid-2015 and mid-2010 to mid-2012, respectively). Based on the literature, we investigated the incidence of dermal, neurological, circulatory, and renal conditions between the two groups.

Additionally, we examined whether occupational physical workload would modify the relationship between permethrin exposure and adverse health conditions, hypothesizing that a higher level of physical workload activities (determined based on MOS codes) would be associated with higher risk of specific diagnoses (as a result of higher exposures).

Based on some literature describing associations between permethrin exposure and multiple myeloma, male fertility, and reproductive outcomes, we explored whether a higher incidence in these outcomes was observed in the 2013 compared to the 2010 cohort as secondary exploratory hypotheses. Also, we examined if there was evidence that wearing permethrin treated uniforms was protective of US vector-borne diseases (e.g., Lyme Disease, West Nile virus).

METHODS

The study protocol was reviewed and approved by the Institutional Review Board at the U.S. Army Research Institute of Environmental Medicine and the U.S. Army Medical Research and Development Command. The investigators adhered to the policies for protection of human subjects as prescribed in Army Regulation 70-25, and the research was conducted in adherence with the provisions of 32 CFR Part 219.

STUDY POPULATION

This analytic study utilized data from the Soldier Performance and Health Readiness (SPHERE) data repository (formerly known as the Total Army Injury and Health Outcome Database (TAIHOD)), managed and housed with the Military Performance Division at USARIEM (2,3). The SPHERE is a data repository containing

medical encounter and military tracking information on all US Active Duty Army (AAD) personnel. Personnel information including demographic and occupational characteristics on study subjects were extracted from the DoD Defense Manpower Data Center. Information on inpatient and ambulatory/outpatient medical encounter information was extracted from the Military Health System Data Repository.

The target study cohort included all Army enlisted Active Duty Soldiers new to the service between 1 July 2013 and 31 December 2013 (N=33,070) and a comparison group of enlisted AAD Soldiers new to the service between 1 July 2010 and 31 December 2010 (N=33,121).

EXPOSURE DEFINITION

Permethrin

Due to the nature of this study, exposure to permethrin via permethrin-treated uniforms was not directly measured. However, since 2013, U.S. Army has required all new, unwashed uniform permethrin concentrations to be within a minimum of 0.095 mg/cm^2 and maximum of 0.135 mg/cm^2 and this treatment has been demonstrated to provide 99-100% bite protection up to 50 launderings (which is considered the life of the Army uniform). Prior to 2013, Soldiers in deployment status used alternate methods of treating their own uniforms with permethrin (such as spray on applications). Hence, Soldiers who deployed in the 2010- 2012 or 2013-2015 timeframes were excluded from these analyses (see further description below under Statistical Analyses). All subjects within the 2013 cohort were classified as exposed to permethrin, and all within the 2010 cohort were classified as unexposed to permethrin.

OUTCOME DEFINITION

From the literature, health outcomes associated with long-term permethrin exposure have the potential to include conditions affecting the renal, neurological, dermatological, and circulatory systems of the body. Illnesses of interest in this study were determined by International Classification of Diseases (ICD) codes (Table 1). Secondary outcomes of interest included male infertility measures, myeloma and U.S. vector-borne illnesses of interest.

Table 1. ICD-9 codes and ICD-10 equivalents for primary outcomes of interest

ICD9-CM Codes	Diagnosis	ICD10 Codes
PRIMARY OUTCOMES OF INTEREST		
RENAL		
276	Fluid/electrolyte disorders	E86, E87
276.0	*Hyperosmolality*	E87.0
276.1	*Hyposmolality*	E87.1
276.2	*Acidosis*	E87.2
276.3	*Alkalosis*	E87.3
276.4	*Mixed acid-base balance disorder*	E87.4
276.5	*Volume depletion disorder*	E86
276.50	*Volume depletion nos*	E86.9

276.51	*Dehydration*	E86.0
276.52	*Hypovolemia*	E86.1
276.7	*Hyperpotassemia*	E87.5
276.8	*Hypopotassemia*	E87.6
276.9	*Electrolyte/fluid disorder nec*	E87.8
580-589	Nephritis, nephrotic syndrome and nephrosis	N00-N08, N10-N16, N17-N19
NEUROLOGICAL		
331	Other cerebral degenerations	G31, G32
332	Parkinson's	G20
333	Abnormal movement disorders	G25, G26
337	Disorders of autonomic nervous system	G90
338	Pain, not elsewhere classified	G89
339	Other headache syndromes	G44
341	Other demyelinating diseases of CNS	G61, G65
351	Inflammatory and toxic neuropathy	G35-G37
DERMATOLOGICAL		
692	Contact dermatitis and other eczema	L23-L25
680-688	Infections of skin and subcutaneous tissue	L00-L08
690-698 (except 692)	Other inflammatory conditions of skin and subcutaneous tissue	L20-L22, L26-L30
CIRCULATORY		
401-405	Hypertensive disease	I10-I15
410	Acute myocardial infarction	I21-I22
430-438	Cerebrovascular disease	I60-I69
SELECTED SECONDARY OUTCOMES OF INTEREST		
606	Male infertility	N46
606.0	*Azoospermia*	N46.0
606.1	*Oligospermia*	N46.1
606.8	*Male infertility NEC*	N46.8
606.9	*Male infertility NOS*	N46.9
203	Multiple myeloma et al	C90.0
203.0	*Multiple myeloma*	
203.00	*Multiple myeloma w/o remission*	C90.00
203.01	*Multiple myeloma w/ remission*	C90.01
203.02	*Multiple myeloma in relapse*	C90.02
US VECTOR-BORNE DISEASES		
062.2	Eastern equine encephalitis	A83.2
066.4	West Nile virus	A92.3
082.0	Spotted fevers	A77
082.4	Ehrlichiosis	A77.4
088.81	Lyme disease	A69.2
088.82	Babesiosis	A60.0

Workload

Each MOS in the Army is associated with a physical demands rating, which corresponds with the physical work requirements of the job (10). For each month of military service, activity levels were recorded based on MOS via a 5-point scale (Table 2). The average of the monthly scores over the 2-year study period served as each participants' workload for this analysis.

Table 2. MOS Physical Demands Classifications

Physical Demands Classification	Description/definitions	2010 Cohort (n=21,182)	2013 Cohort (n=29,556)
Light	Lift, on an occasional basis, a maximum of 20 pounds with frequent or constant lifting of 10 pounds	176 (0.83%)	393 (1.33%)
Medium	Lift, on an occasional basis, a maximum of 50 pounds with frequent or constant lifting of 25 pounds	848 (4.00%)	1,360 (4.60%)
Moderately Heavy	Lift, on an occasional basis, a maximum of 80 pounds with frequent or constant lifting of 40 pounds	2,216 (10.46%)	3,591 (12.15%)
Heavy	Lift, on an occasional basis, a maximum of 100 pounds with frequent or constant lifting of 50 pounds	4,254 (20.08%)	6,326 (21.40%)
Very Heavy	Lift, on an occasional basis, over 100 pounds with frequent or constant lifting in excess of 50 pounds	9,212 (43.49%)	13,500 (45.68%)
Not Applicable	No physical demands requirement listed.	287 (1.35%)	201 (0.68%)

STATISTICAL ANALYSES

Analyses excluded persons who deployed during the July through December time point (N=10,761 from the 2010 cohort; N=2,027 from the 2013 cohort) and those ranked as Officers or Warrant Officers (N=1,178 from the 2010 cohort; N=1,487 from the 2013 cohort). Descriptive statistics were computed for each of the study cohorts: i) Soldiers who entered the service between 1 July and 31 December 2010 (n=21,182) prior to the required routine wear of permethrin-treated uniforms and ii) Soldiers who entered the service between 1 July and 31 December 2013 (n=29,556).

To address the primary study and exploratory hypotheses, generalized linear models for a Poisson distribution were performed to analyze diagnosis risk ratios among the two study cohorts for each of the health outcomes. Logistic regression models were used to calculate odds ratios among the two study cohorts for each of the health outcomes. An interaction term (workload*cohort) was added to the respective models to examine the effect that job-specific workload had on the relationship between uniform and health outcomes. Persons in jobs for which no physical demand requirements were defined were not included in the workload analysis; a total of 5,566 persons were

excluded from the workload analysis (3,113 from the 2010 cohort; 2,453 from the 2013 cohort).

All models were adjusted by age, sex and race/ethnicity. All analyses were conducted using SAS software (version 9.4; SAS Institute, Inc. Cary, NC).

RESULTS

Among Enlisted Soldiers in this study, roughly 80% were male and 55-60% were identified as white (Table 3).

Table 3. Demographic characteristics of the study cohorts

		2010 Cohort (n=21,182)	2013 Cohort (n=29,556)
Age		21.45 ± 4.31	20.26 ± 3.13
Sex	Male	16,804 (79.33%)	24,558 (83.09%)
	Female	4,378 (20.67%)	4,998 (16.91%)
Ethnicity	White	13,081 (61.76%)	16,405 (55.50%)
	Black	4,488 (21.19%)	7,103 (24.03%)
	Hispanic	2,458 (11.60%)	4,185 (14.16%)
	Native American Indian/Alaskan	174 (0.82%)	243 (0.82%)
	Asian/Pacific Islander	926 (4.37%)	1,616 (5.47%)
	Other	55 (0.26%)	4 (0.01%)
Height (inches)		68.63 ± 3.50	68.32 ± 3.35
Weight (pounds)		165.90 ± 30.97	162.55 ± 29.25

The frequency of persons with documented diagnoses by cohort are presented in Table 4 with the unadjusted and adjusted risk ratios for each diagnosis calculated from the generalized linear models.

Table 4. Diagnosis incidence and results of the unadjusted and adjusted Poisson and logistic regression models, using the 2010 cohort as the reference

	2010 Cohort (n=21,182)	2013 Cohort (n=29,556)	Unadjusted RR/OR (95% CI) χ^2, p-value	Adjusted RR/OR (95% CI) χ^2, p-value
RENAL			**0.785 (0.72, 0.85) 33.25, p<.0001**	**0.793 (0.73, 0.86) 29.83, p<.0001**
Fluid/electrolyte disorders*	1,223 (5.77%)	1,027 (3.47%)	0.587 (0.54, 0.64) 150.77, p<.0001	0.596 (0.55, 0.65) 137.74, p<.0001
Hyperosmolality	◆	◆	1.746 (0.37, 8.30) 0.46, p=0.499	1.508 (0.28, 8.08) 0.23, p=0.632
Hyposmolality	◆	◆	0.614 (0.28, 1.37) 1.42, p=0.233	0.60 (0.27, 1.35) 1.52, p=0.217
Acidosis	◆	◆	0.915 (0.30, 2.83) 0.02, p=0.877	0.903 (0.27, 3.02) 0.03, p=0.868
Alkalosis	◆	◆	0.608 (0.08, 4.69) 0.22, p=0.636	0.608 (0.08, 4.69) 0.23, p=0.633
Mixed acid-base balance disorder	0 (0.0%)	0 (0.0%)	--	--
Volume depletion disorder*	1,128 (5.33%)	928 (3.14%)	0.576 (0.53, 0.63) 148.25, p<.0001	0.584 (0.53, 0.64) 136.03, p<.0001
Volume depletion – not otherwise specified*	173 (0.82%)	119 (0.40%)	0.592 (0.54, 0.65) 115.23, p<.0001	0.492 (0.39, 0.62) 34.34, p<.0001
Dehydration*	949 (4.48%)	798 (2.70%)	0.793 (0.72, 0.87) 24.00, p<.0001	0.601 (0.55, 0.66) 104.60, p<.0001
Hypovolemia	10 (0.05%)	11 (0.04%)	1.198 (0.41, 3.53) 0.11, p=0.745	1.217 (0.40, 3.71) 0.12, p=0.730
Hyperpotassemia	◆	◆	3.00 (0.59, 15.18) 1.64, p=0.201	3.496 (0.55, 22.18) 1.76, p=0.184
Hypopotassemia	55 (0.26%)	70 (0.24%)	1.03 (0.72, 1.49) 0.03, p=0.854	1.051 (0.73, 1.52) 0.07, p=0.793

Electrolyte/fluid disorder – not elsewhere classified	◆	◆	0.289 (0.06, 1.50) 2.07, p=0.150	0.288 (0.06, 1.50) 2.19, p=0.139
Nephritis, nephrotic syndrome and nephrosis	27 (0.13%)	46 (0.16%)	0.908 (0.57, 1.45) 0.16, p=0.685	0.912 (0.56, 1.49) 0.13, p=0.714
NEUROLOGICAL			**0.960 (0.89, 1.04) 1.07, p=0.302**	**0.956 (0.88, 1.03) 1.24, p=0.266**
Other cerebral degenerations	◆	◆	0.191 (0.03, 1.26) 2.79, p=0.100	0.191 (0.03,1.26) 2.96, p=0.086
Parkinson's	0 (0.0%)	0 (0.0%)	…	…
Abnormal movement disorders	34 (0.16%)	44 (0.15%)	1.052 (0.64, 1.73) 0.04, p=0.841	1.007 (0.61, 1.67) 0.00, p=0.979
Disorders of autonomic nervous system	◆	◆	0.807 (0.27, 2.39) 0.15, p=0.697	0.915 (0.32, 2.66) 0.03, p=0.870
Pain - not elsewhere classified*	639 (3.02%)	862 (2.92%)	0.966 (0.87, 1.07) 0.43, p=0.510	1.056 (0.95, 1.17) 0.997, p=0.318
Other headache symptoms*	436 (2.06%)	608 (2.06%)	0.999 (0.88, 1.13) 0.00, p=0.992	1.034 (0.91, 1.17) 0.27, p=0.606
Other demyelinating diseases of CNS	◆	◆	3.47 (0.33, 36.51) 1.00, p=0.318	3.470 (0.33, 36.51) 1.07, p=0.300
Inflammatory and toxic neuropathy	15 (0.07%)	12 (0.04%)	0.946 (0.38, 2.36) 0.01, p=0.906)	1.050 (0.39, 2.83) 0.01, p=0.923
DERMATOLOGICAL			**0.905 (0.87, 0.95) 19.88, p<.0001**	**0.905 (0.86, 0.95) 19.16, p<.0001**
Contact dermatitis and other eczema*	1,479 (6.98%)	1,893 (6.40%)	0.912 (0.85, 0.98) 6.63, p=0.010	0.945 (0.88, 1.02) 2.37, p=0.123
Infections of skin and subcutaneous tissue*	1,879 (8.87%)	2,182 (7.38%)	0.819 (0.77, 0.87) 37.02, p<.0001	0.846 (0.79, 0.90) 24.87, p<.0001
Other inflammatory conditions of skin and subcutaneous tissue*	437 (2.06%)	506 (1.71%)	0.827 (0.73, 0.94) 8.31, p=0.004	0.861 (0.75, 0.98) 4.97, p=0.026

CIRCULATORY			**0.940 (0.79, 1.12) 0.50, p=0.48**	**0.973 (0.81, 1.16) 0.09, p=0.760**
Hypertensive disease*	263 (1.24%)	240 (0.81%)	0.651 (0.55, 0.78) 22.86, p<.0001	0.767 (0.64, 0.92) 8.02, p=0.005
Acute myocardial infarction[1]	◆	◆	--	--
Cerebrovascular disease	12 (0.06%)	26 (0.09%)	1.85 (0.86, 3.96) 2.64, p=0.104	1.844 (0.86, 3.96) 2.47, p=0.116
SELECTED SECONDARY OUTCOMES OF INTEREST				
Male infertility	32 (0.15%)	50 (0.17%)	0.910 (0.60, 1.39) 0.19, p=0.663	0.887 (0.56, 1.39) 0.27, p=0.603
Azoospermia	◆	◆		…
Oligospermia	◆	◆	0.440 (0.08, 2.36) 0.90, p=0.343	0.44 (0.08, 2.34) 0.93, p=0.335
Male infertility – not elsewhere classified	--	--	NA	NA
Male infertility – not otherwise specified	28 (0.13%)	44 (0.15%)	0.949 (0.61, 1.48) 0.05, p=0.818	0.928 (0.57, 1.51) 0.09, p=0.764
Multiple myeloma et al	0 (0.0%)	0 (0.0%)	--	--
Multiple myeloma	0 (0.0%)	0 (0.0%)	--	--
Multiple myeloma without remission	0 (0.0%)	0 (0.0%)	--	--
Multiple myeloma with remission	0 (0.0%)	0 (0.0%)	--	--
Multiple myeloma in relapse	0 (0.0%)	0 (0.0%)	--	--
US VECTOR-BORNE DISEASES				
Eastern equine encephalitis	0 (0.0%)	0 (0.0%)	--	--
West Nile virus	--	--	NA	NA
Spotted fevers	0 (0.0%)	0 (0.0%)	--	--
Ehrlichiosis	--	--	NA	NA

Lyme disease	◆	◆	1.669 (0.35, 8.00) 0.43, p=0.514	2.045 (0.25, 16.62) 0.45, p=0.503
Babesiosis	0 (0.0%)	0 (0.0%)	--	--

All models were adjusted by age, sex and race/ethnicity.
*Denotes outcomes analyzed using a logistic regression model rather than a Poisson regression model.
◆Denotes incidence counts <10 in one or both groups, data are not presented.
--Denotes outcomes in which OR/RR were not able to be computed.
NA Denotes outcomes in which OR/RR are not able to be computed due to low incidence counts.
[1]An unadjusted zero-inflated Poisson regression model was run to evaluate for differences in cases of acute myocardial infarction. There was no significant difference between groups (χ^2=0.00; p=0.9614).

Significant differences in risk between the cohorts were noted for the renal and dermatological systems, as well as a few of the primary diagnoses of interest including fluid/electrolyte disorder, volume depletion disorder, dehydration, and infections of skin and subcutaneous tissue. However, for each of these outcomes, the comparison 2010 Cohort was at higher risk for these medical conditions compared to the 2013 Cohort wearing permethrin-treated uniforms. No significant differences in risk between the groups were observed for the secondary diagnoses of interest.

Results of the models including workload as a covariate also demonstrated significant effects of permethrin exposure (cohort) on health outcomes for the renal (OR (95% CI): 0.607 (0.558, 0.661), p<.0001) and dermatological (OR (95% CI): 0.873 (0.832, 0.916), p<.0001) systems, fluid/electrolyte disorders (OR (95%CI): 0.596 (0.546, 0.650), p<.0001), volume depletion disorders (0.585 (0.533, 0.641), p<.0001), dehydration (0.605 (0.548, 0.668) p<.0001), infections of skin and subcutaneous tissue (0.848 (0.793, 0.907) p<.0001), and hypertensive disease (0.774 (0.641, 0.934) p=0.0076). However, for each of these outcomes, as was observed in the main effect analyses presented above, the comparison 2010 Cohort was at higher risk. There was no significant interaction effect observed between workload and study cohort (Table 5).

Table 5. Results of the adjusted Poisson and logistic regression models including workload as a covariate and as an interaction term with study cohort, using the 2010 cohort as the reference

	Workload* Cohort Interaction χ^2, p-value
RENAL	
Fluid/Electrolyte Disorders*	1.78, p=0.182
Hyperosmolality	--
Hyposmolality	2.34, p=0.126
Acidosis	1.60, p=0.206
Alkalosis	--
Mixed acid-base balance disorder	--
Volume depletion disorder*	2.60, p=0.107
Volume depletion – not otherwise specified*	0.42, p=0.516
Dehydration*	2.51, p=0.113
Hypovolemia	1.41, p=0.235
Hyperpotassemia	0.74, p=0.391
Hypopotassemia	0.01, p=0.929
Electrolyte/fluid disorder – not elsewhere classified	--
Nephritis, nephrotic syndrome and nephrosis	0.48, p=0.488
NEUROLOGICAL	
Other cerebral degenerations	--
Parkinson’s	--
Abnormal movement disorders	0.20, p=0.652

Disorders of autonomic nervous system	0.00, p=0.981
Pain - not elsewhere classified*	0.14, p=0.712
Other headache symptoms*	5.74, p=0.017
Other demyelinating diseases of CNS	--
Inflammatory and toxic neuropathy	0.00, p=0.961
DERMATOLOGICAL	
Contact dermatitis and other eczema*	0.24, p=0.626
Infections of skin and subcutaneous tissue*	0.61, p=0.434
Other inflammatory conditions of skin and subcutaneous tissue*	2.41, p=0.120
CIRCULATORY	
Hypertensive disease*	0.73, p=0.394
Acute myocardial infarction	--
Cerebrovascular disease	0.06, p=0.813
SECONDARY OUTCOMES OF INTEREST	
Male infertility	0.11, p=0.735
Azoospermia	--
Oligospermia	--
Male infertility – not elsewhere classified	--
Male infertility – not otherwise specified	0.01, p=0.927
Multiple myeloma et al	--
Multiple myeloma	--
Multiple myeloma without remission	--
Multiple myeloma with remission	--
Multiple myeloma in relapse	--
US VECTOR-BORNE DISEASES	
Eastern equine encephalitis	--
West Nile virus	--
Spotted fevers	--
Ehrlichiosis	--
Lyme disease	--
Babesiosis	--

*Denotes outcomes analyzed using a logistic regression model rather than a Poisson regression model.

DISCUSSION

In this study, no significant increased longer-term exposure risks were observed for select medical outcomes related to the wearing of permethrin-treated uniforms over a 24 month period at the start of one's military service. This Army population study allows for adequate power to examine most of the broad body system outcome categories of interest.

In terms of limitations, the rates of some of the specific conditions within the body system outcomes of interest were quite low, and even in this population study, the ability to observe significant group differences was hindered, especially when evaluating the risk impact on vector-borne diseases. However, this Army population study allows for adequate power to examine most of the broad body system outcome categories of interest. In addition, given the nature of this study, direct measurement of permethrin exposure was not possible, thus there exists the potential for misclassification of exposure. Instead, we compared two cohort groups based on the assumption that those entering the service before permethrin-treated uniforms were required (in the 2010-2012 period) would not have had exposure to permethrin on a regular basis. It is possible that some persons in the non-treated uniform group may have worn commercially available treated clothing or physically and directly treated their military uniform with permethrin and as such may have had some level of permethrin exposure. But, by excluding persons who deployed from the analysis group, the likelihood of persons directly treating uniforms is minimized. Another limitation of the present study was the limited time frame in which health outcomes were ascertained. It is possible that wearing of treated uniforms over longer periods of time (> 24 months) and following those health outcomes that may take longer to emerge (later in life or with aging) may produce different results.

CONCLUSIONS

Findings from this study suggest that wearing of permethrin treated uniforms over a period of 24 months at the start of military service are not associated with increased risk of select medical conditions.

RECOMMENDATIONS

While no significant risk of adverse medical conditions was found to be associated with permethrin exposure in this population study as a result of wearing treated uniforms among young Soldiers starting their military service and the rates of certain outcomes were quite low, continued monitoring of the rates of all-cause mortality and specific medical morbidities over time may still be prudent. As has been demonstrated in several recent studies, although the estimated dose of permethrin does not exceed recommended dose levels, the levels of permethrin exposure experienced by wearing of treated clothing are considerably higher than general population levels (7), and there is only minimal research examining the longer-term (over many years) impacts of health for chronic, low dose exposure to many occupational chemicals.

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