Risk of Exertional Heat Illnesses Associated with Sickle Cell Trait in U.S. Military

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ABSTRACT Introduction: A number of studies have found an association between sickle cell trait (SCT) and exertional heat illnesses (EHIs) including heat stroke, a potentially fatal condition. The strength of this association varied across studies, limiting the ability to quantify potential benefits of SCT-screening policies for competitive athletics and military service members. We determined the relative rate and attributable risk of developing EHI associated with being SCT positive and the EHI health care utilization. Methods: We conducted a retrospective cohort study among U. S. enlisted, active duty service members during 1992–2012 from the Department of Defense Military Healthcare System databases. All 15,081 SCT-positive individuals and a sample of 60,320 from those considered SCT negative were followed through 2013 for EHI outcomes ranging from mild heat illness to heat stroke. Results: The adjusted hazard ratio for EHI in SCT-positive compared with SCT-negative individuals was 1.24 (95% confidence interval 1.06, 1.45). Risk factors for EHI included age over 30 yr at enlistment, female gender, Marine Corps, combat occupations, and enlistment between April and June. An estimated 216 Department of Defense enlistees (95% confidence interval: 147, 370) would need to be screened to identify and potentially prevent one case of EHI. The attributable risk of EHI due to SCT was 33% (95% confidence interval 19, 45%). Conclusion: Our findings suggest that SCT screening will identify approximately a third of SCT individuals at risk for EHI, but does not provide definitive evidence for universal compared with selective (e.g., occupational based) in military enlistees. A cost-effectiveness analysis is needed for policy makers to assess the overall value of universal SCT screening to prevent morbidity and mortality in both the military and the collegiate athletic populations.

INTRODUCTION

Despite decades of investigation and discussion, the risk of exertional heat-related illness (EHI) or death among individuals with sickle cell trait (SCT) remains a significant and controversial issue for the Department of Defense (DoD) and for organized athletic programs including the National Collegiate Athletic Association (NCAA).[1–4]

EHIs comprise a spectrum of unintentional injuries typically associated with intense training or sporting activities. EHIs include heat cramps, syncope, exhaustion, exertional rhabdomyolysis, exercise-associated collapse, and the most severe form, exertional heat stroke, resulting from an individual's inability to maintain thermoregulation.[5,6] The incidence of EHIs increases with elevated ambient temperatures, high humidity, exercise duration, and intensity. Personal risk factors for developing an EHI include age, genetics, acclimatization, acute illnesses and chronic conditions, use of medications and supplements, as well as heavy clothing and equipment.[7] The Centers for Disease Control and Prevention estimated that U.S. emergency departments treated 5,946 cases of sports-related heat injuries annually between 2001 and 2009. Of these EHI cases, 36.6% were aged 15–19 yr and 72.5% were males.[8]

Individuals serving in the military and athletes experience higher rates of EHIs than others in the general population. EHIs are a significant threat to military readiness[9] and have potential long-term health and career implications for affected SMs and athletes.[10] EHIs in the military are considered occupationally related and rates within the military are often compared with those within young athletic populations.[5] In 2016, the U.S. Military experienced an overall EHI incidence rate of 1.96 per 1,000 person-years, and from 2012 to 2016, the heat stroke incidence rate ranged from approximately 24 to 32 per 100,000 person-years.[11] The estimated rate for high school athletes was 1.6 per 100,000 athlete exposures, although not comparable with military person-years. High school athletes playing football had the highest rates and more deaths occurred during the period of 2005–2009 than in any other 5-yr interval over the previous 35 years.[12] The Centers for Disease Control and Prevention analyzed 2001–2009 data from the National Electronic Injury Surveillance System – All Injury Program and estimated an

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annual rate of 2.0 emergency departments visits per 100,000 population for a heat illness sustained while participating in a sport or recreational activity.[8]

The deleterious health risks to those individuals homozygous for hemoglobin S (Hb SS) having sickle cell disease are well known.[13] Less well understood at either the population or the individual patient level is whether there are associated health effects for the estimated four million individuals[14] in the United States heterozygous (Hb AS) with SCT. Long considered a benign condition by the general medical community, more recent case reports, case–control, and cohort studies are linking SCT with deleterious health outcomes.[2,15–17]

A 2009 review of published reports[18] described negative health-related associations and risks among those with SCT as compared with SCT-negative individuals. Primarily observational studies, these reports estimated a significantly increased risk (23.5- to 40-fold) of exercise-related injuries and sudden (non-traumatic) death among SCT-positive military service members (SMs) as compared with SCT-negative SMs.[19,20] A similar increased risk of sudden death has also been described among SCT-positive college football players as compared with SCT-negative players (37-fold).[21] A recent study of Black soldiers serving in the US Army between 2011 and 2014 found an increased rate of exertional rhabdomyolysis, but no difference in the death rates for those who had tested positive for SCT compared with others.[2] Because universal screening for SCT is not mandated in the Army, the authors have acknowledged that during the time period of that study,[2] Blacks who were ill may have been more likely to have been tested for SCT, thus artificially associating positive SCT with medical conditions and medication usage.

Periodic re-analysis of U.S. Military surveillance data including illness, injuries, and death has led to a dynamic and varied policy on both SCT testing and occupational restrictions for SCT-positive SMs. SCT-specific testing was initiated in 1969 by all service branches for incoming recruits, and SCT-positive SMs were restricted from occupations exposed to high-altitude and/or hyperbaric conditions (flying, diving, parachute, and special operations). The Army discontinued universal SCT-screening procedures in 1991 and implemented prevention policies to mitigate environmental and occupational conditions to prevent heat and exertion injuries for all soldiers.[3,22,23] The U.S. Navy and Air Force continue universal screening of all recruits. The length and rigor of basic training varies by service as do the countermeasure policies to prevent heat injuries and the way SCT-positive trainees are publicly identified (i.e., arm band, and dog tag).[23]

Recent efforts to reduce physical harm among athletes competing under the authority of the NCAA has resulted in a decision to institute a policy where athletes entering Division 1 institutions must be tested for SCT, show proof of testing, or sign a waiver releasing their institution and the NCAA from liability.[24] The current NCAA policy has generated controversy and concern from professional and advocacy groups, geneticists, and ethicists on the utility of the testing, ability to reduce injury, and potential to harm.[25] Screening for SCT is a controversial issue. Knowledge of one's own SCT status might enable one to take preventive action against EHI, thus reducing the incidence of EHI. However, other's knowledge of someone's SCT status might result in restrictions or limitations in an effort to reduce outcomes such as EHI. The objective of our study is to estimate the burden of EHI in terms of incidence and health care utilization associated with SCT in enlisted SMs.

METHODS

Study Subjects

We conducted a retrospective cohort study among U.S. SMs who were enlisted and active duty from 1992 to 2012 using the existing DoD Military Healthcare System databases. Reserve component SMs were excluded because of incomplete capture of medical encounters during breaks in active duty service. Officers were excluded because the variety in sources of commissioning and differences in the length, vigor, and risk of EHI compared with enlisted initial entry training. Eligible SCT-positive participants were identified in the following two ways: (1) medical encounter SCT diagnosis (ICD-9-CM 282.5) in ambulatory or hospitalized encounter records from 1992 to 2012 and provided by Armed Forces Health Surveillance Center or (2) documentation of a positive laboratory SCT test result in the existing Military Health System HL-7 laboratory database available only from 2006 to 2012 provided by the Navy and Marine Corps Public Health Center. A stratified random sample of active duty SMs during the same time period with no documentation of SCT-positive diagnosis identified the SCT-negative participants. Four SCT-negative subjects were selected for every SCT-positive subject within matched strata of gender, racial ethnic group (non-Hispanic White, non-Hispanic Black, Hispanic, non-Hispanic, other/unknown), service branch, as well as quarter and year of enlistment to maximize power to detect associations in subgroup analyses. Demographic data provided by Armed Forces Health Surveillance Center on SCT-positive and SCT-negative individuals included quarter of enlistment (due to the historical seasonal variation in EHI rates that are higher in summer), age at enlistment, gender, race/ethnicity, country of origin, home of record by region, location of enlistment (basic training site) by region, DoD military occupation categories that are utilized by all U.S. Military services (i.e., Army, Navy, Marine Corps, Air Force, and Coast Guard), and date of discharge. All study subjects were followed for diagnoses with ICD-9-CM codes of 992.0–992.9 and 728.88 (rhabdomyolysis) present in inpatient and/or outpatient medical encounter records between January 1, 1992, and December 31, 2013, and were identified as EHI positive. Ultimately, rhabdomyolysis cases were excluded from the overall category of EHI because the ICD-9 coding does not identify if the diagnosis was related specifically to exertional and/or heat exposure versus other causes. The hypothesis was that universal enlistee screening for SCT in the Navy, Marine Corps, and Air Force reduces the incidence of EHI compared with selective screening based on military occupation in the Army.

Statistical Analysis

We conducted descriptive analyses of demographic variable distributions for the entire cohort and those with EHI by exposure status (SCT positive versus negative). Trends in EHI prevalent cases (including incident and recurrent or follow-up medical encounters) across time intervals (1992–1994, 1995–1999, 2000–2004, 2005–2009, and 2009–2012) were graphically depicted by SCT status for all subjects and for non-Hispanic Blacks alone. EHI frequency and rate per subject of all visits for any ICD-9-CM medical encounter codes associated with EHI in any diagnostic field were calculated by SCT status. Median and interquartile range (25–75%) of time in service from enlistment until first EHI diagnosis was compared between SCT-positive and SCT-negative individuals. We tested the differences in the median time to EHI event using the Wilcoxon rank sum (for comparisons of only two groups) or Kruskal–Wallis tests (for comparisons of more than two groups) as appropriate. We estimated the burden of EHI by examining the severity and health care utilization by SCT status. We categorized EHI into mild heat illness, heat exhaustion, and heat stroke based on ICD-9 codes to assess the proportion of each category among SCT-positive and SCT-negative individuals. If an individual suffered an EHI in more than one category, only the most severe category of EHI was used. The distribution of the total number of EHI visits per subject among SCT-positive and SCT-negative individuals were calculated to estimate the difference in health care utilization by SCT status. Time to event or survival analysis with Cox proportional hazards models estimated unadjusted and adjusted hazard ratios (HRs) and are interpreted similarly to a relative risk with 95% confidence intervals (CIs). The Cox proportional hazards models allowed us to assess the association between SCT status and time from enlistment to first EHI. The following potential confounders were considered for inclusion in our multivariable model: racial/ethnic group, gender, age, service branch, occupation, home region, quarter-year of enlistment, and enlistment region. The EHI incidence densities (per 1,000 person-years) were evaluated by SCT status and service. The number needed to be screened (NNS) for SCT to potentially prevent a case of EHI was calculated to better inform the SCT enlistment-screening policy debate by taking the inverse of the absolute EHI risk reduction between SCT-positive and SCT-negative subjects. The NNS to identify and potentially prevent one case of EHI and the attributable risk percentage (AR%) of EHI related to SCT was calculated using the following formula: (Relative Risk−1)/Relative Risk where the relative risk is approximated by the HR. A *p*-value of <0.05 was considered statistically significant. All analyses were conducted using SAS (Version 9.3, Cary, NC).

The Uniformed Services University of the Health Sciences Institutional Review Board approved this protocol. The study was funded through an Interagency Agreement with the National Heart, Lung, and Blood Institute.

RESULTS

Table I compares the distribution of selected demographic characteristics and DoD military occupational categories in subjects, who are either negative or positive for SCT, the subjects who had a medical encounter (i.e., inpatient and/or outpatient) for EHI, and the rate of all EHI visits per 1000 subjects. The distribution of EHI visits was similar for both matched (i.e., age, gender, race, and service) and unmatched (i.e., home region, quarter of enlistment, enlistment region, and occupation at discharge) variables by SCT status.

Over 95% of EHI visits were from outpatient encounters without a significant difference between SCT-positive or SCT-negative subjects (separate results not shown). The EHI rate was generally higher in SCT-positive than in SCT-negative subjects for each demographic characteristic and occupational category. EHI rates in SCT-positive subjects were highest for non-Hispanic Blacks, females, age over 30 years at enlistment, home region in the North, Marine Corps SMs, armor/motor/transport occupations, enlistment from April to June, and enlistment region in the southeast.

Figure 1 plots the prevalence of EHI (inpatient or outpatient) for all services combined by year and SCT status, irrespective of whether it was the subjects' initial or recurrent medical encounter. Subjects may be counted in multiple years if they had EHI medical encounters in more than 1 year. The EHI prevalence increased over time in both groups but was higher in SCT-positive subjects (mean 1.7% versus 0.5% per year). Similar findings were observed when subjects were restricted to non-Hispanic Blacks (results not shown).

The frequency of the highest severity EHI for inpatient EHI and outpatient EHI visits was evaluated by subject and SCT status. Heat stroke was more common for SCT-positive (7.3%) versus SCT-negative (4.8%) subjects. Among those with any inpatient diagnostic code for EHI, heat exhaustion was more common in SCT-negative (25.0%) than in SCT-positive (19.2%) subjects. The incidence of all EHI encounters in subjects with a rhabdomyolysis diagnosis was greater in SCT-positive (10.0%) compared with SCT-negative (6.6%) subjects, but the difference was not significant (odds ratio = 1.48, 95% CI 0.89, 2.42, results not shown).

The highest severity of EHI was examined by comparing the frequency and proportion of subjects with mild EHI, heat exhaustion, and heat stroke. SCT-positive and SCT-negative subjects had similar distribution of severity of EHI (Fig. 2, $p = 0.57$). The utilization of health care for EHI was compared by plotting the total number of EHI health care encounters per subject as a percentage of all EHI encounters by SCT

TABLE I. Selected Characteristics of Subjects with EHI Inpatient and/or Outpatient Records by SCT-Negative Versus SCT-Positive Status in the U.S. Military, 1992–2012

	SCT Negative			SCT Positive		
Patient Characteristics, *n* (%)	Total, $N = 60,320$	EHI, $N = 577$	EHI Rate/1,000	Total, $N = 15,081$	EHI, $N = 214$	EHI Rate/1000
Race						
Non-Hispanic White	2,711 (4.5)	19 (3.3)	7.01	677 (4.5)	9 (4.2)	13.29
Non-Hispanic Black	49,118 (81.4)	488 (84.6)	9.94	12,281 (81.4)	177 (82.7)	14.41
Non-Hispanic other	3,444 (5.7)	32 (5.6)	9.29	860 (5.7)	10 (4.7)	11.63
Hispanic	5,047 (8.4)	38 (6.6)	7.53	1,263 (8.4)	18 (8.4)	14.25
Gender						
Male	40,304 (66.8)	314 (54.4)	7.79	10,077 (66.8)	140 (65.4)	13.89
Female	20,016 (33.2)	263 (45.6)	13.14	5,004 (33.2)	74 (34.6)	14.79
Age at enlistment						
18–19	33,190 (55.0)	305 (52.9)	9.19	8,064 (53.5)	116 (54.2)	14.38
20–24	21,979 (36.4)	211 (36.5)	9.60	5,580 (37.0)	77 (36.0)	13.80
25–29	3,955 (6.6)	40 (6.9)	10.11	1,077 (7.1)	14 (6.5)	13.00
30+	1,196 (2.0)	21 (3.6)	17.56	360 (2.4)	7 (3.3)	19.44
Home region[a]						
Southeast	18,736 (31.5)	186 (32.5)	9.93	5,180 (34.6)	85 (39.9)	16.41
Central	7,975 (13.4)	62 (10.8)	7.77	1,695 (11.3)	8 (3.8)	4.72
Southwest	8,310 (14.0)	73 (12.8)	8.78	1,935 (12.9)	26 (12.2)	13.44
Northeast	5,780 (9.7)	61 (0.7)	10.55	1,843 (12.3)	30 (14.1)	16.28
Mid-Atlantic	6,146 (10.4)	67 (11.7)	10.90	1,653 (11.1)	25 (11.7)	15.12
North	7,038 (11.9)	79 (13.8)	11.22	1,562 (10.4)	30 (14.1)	19.21
West	5,411 (9.1)	44 (7.7)	8.13	1,091 (7.3)	9 (4.3)	8.25
Service						
Army	13,152 (21.8)	236 (40.9)	17.94	3,277 (21.7)	93 (43.5)	28.38
Air Force	13,944 (23.1)	143 (24.8)	10.26	3,488 (23.1)	34 (15.9)	9.75
Marines	3,944 (6.5)	91 (15.8)	23.07	989 (6.6)	33 (15.4)	33.37
Navy	29,280 (48.5)	107 (18.5)	3.65	7,327 (48.6)	54 (25.2)	7.37
Occupation at separation						
Combat[b]	2,701 (4.5)	19 (3.3)	7.03	549 (3.6)	7 (3.3)	12.75
Armor/motor transport	3,621 (6.0)	36 (6.2)	9.94	906 (6.0)	14 (6.5)	15.45
Repair/engineer	17,034 (28.2)	51 (8.8)	2.99	4,241 (28.1)	15 (7.0)	3.54
Communication/intelligence	15,335 (25.4)	81 (14.0)	5.28	4,246 (28.2)	33 (15.4)	7.77
Health care	5,121 (8.5)	25 (4.3)	4.88	1,350 (9.0)	7 (3.3)	5.19
Other	16,508 (27.4)	365 (63.3)	22.11	3,789 (25.1)	138 (64.5)	36.42
Quarter of enlistment year						
January to March	15,050 (25.0)	139 (24.1)	9.24	3,775 (25.0)	47 (22.0)	12.45
April to June	14,810 (24.6)	162 (28.1)	10.94	3,741 (24.8)	75 (35.1)	20.05
July to September	18,450 (30.6)	185 (32.1)	10.03	4,534 (30.1)	60 (28.0)	13.23
October to December	12,010 (19.9)	91 (15.8)	7.58	3,031 (20.1)	32 (15.0)	10.56
Enlistment region[c]						
Southeast	12,047 (20.3)	243 (43.0)	20.17	3,201 (21.5)	96 (46.4)	29.99
Southwest	15,072 (25.4)	163 (28.9)	10.81	3,781 (25.4)	39 (18.8)	10.31
Midwest	28,504 (48.0)	105 (18.6)	3.68	7,189 (48.3)	52 (25.1)	7.23
West	3,804 (6.4)	54 (9.6)	14.20	706 (4.8)	20 (9.7)	28.33

[a]1,046 records missing from total.
[b]Includes infantry, cavalry and field artillery.
[c]1,097 records missing from total.

status (Fig. 3). SCT-positive subjects had a slightly higher proportion of multiple visits for EHI with approximately 43% of SCT-positive compared with 30% of SCT-negative subjects with two or more visits for EHI ($p < 0.01$). Similar findings were observed when subjects were restricted to non-Hispanic Blacks (results not shown).

The median time from enlistment to first EHI diagnosis (inpatient or outpatient) was compared between the SCT status groups, by other characteristics. Among SCT-positive and SCT-negative subjects, the Marines had the shortest time (0.4 and 0.3 years, respectively) and the Navy had the longest (2.0 and 1.9 years, respectively). SCT-positive subjects had a longer median time from enlistment to EHI compared with SCT-negative subjects for those in the Army (1.4 versus 0.8 years, $p < 0.01$), females (1.9 versus 0.8 years, $p < 0.01$), non-Hispanic Blacks (1.8 versus 1.0 years, $p < 0.01$), and 18- to 19-yr-old enlistees (1.8 versus 1.0 years, $p < 0.01$) compared with negative subjects.

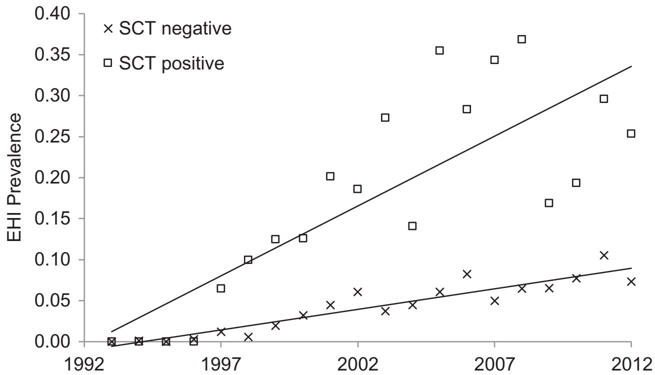

FIGURE 1. EHI prevalence by year, stratified by SCT-positive versus SCT-negative subjects.

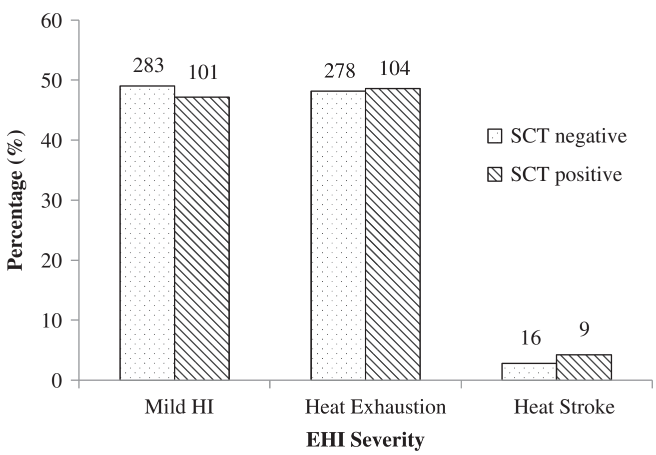

FIGURE 2. Distribution (frequency and percentage) of EHI subjects by severity: mild heat illness (HI), heat exhaustion, and heat stroke by SCT-positive versus SCT-negative subjects ($p = 0.57$).

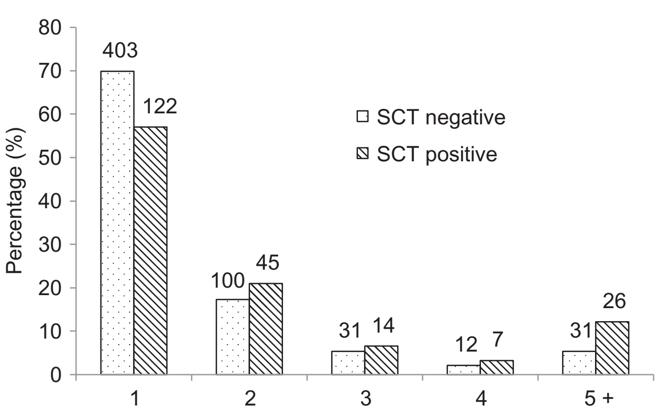

FIGURE 3. Distribution of the total number of EHI visits per study subject (expressed as a percentage) by SCT-positive versus SCT-negative subjects ($p < 0.01$).

The crude and adjusted relative rates (HR) of developing an EHI (either inpatient or outpatient) for SCT-positive compared with SCT-negative subjects were 1.33 (95% CI 1.13, 1.55) and 1.24 (95% CI 1.06, 1.45), respectively (Table II). Other factors related to an increased rate of an EHI included female; age over 30 years at enlistment, in the Marines compared with the Army, either combat (includes infantry), health care workers or other occupations compared with repair, engineer, armor, motor, communications, or intelligence occupations; and enlistment in April to June compared with July to September. Subjects in the Navy and Air Force and enlistment in October to December were protected from developing EHI compared with those in the Army and July to September, respectively, after adjusting for the other covariates including SCT status.

The incidence rate of EHI was 48% higher among those who were SCT positives versus negatives overall (14.2 versus 9.6 per 1,000 persons, respectively) and this pattern held for all branches of the services except for the Air Force (Table III). The Marines had the highest EHI rates for both SCT-positive and SCT-negative subjects (33.4 and 23.1 per 1,000 persons, respectively). The NNS for SCT to identify and potentially prevent one case of EHI overall was 216 (95% CI 147, 370) and ranged from 96 in the Army to 269 in the Navy. The overall AR% was 33% (95% CI 19, 45%) and ranged from 37% in the Army to 50% in the Navy. Similar results for incidence density, NNS, and AR% were observed when the analysis was restricted to non-Hispanic Blacks.

TABLE II. Association Between an EHI (Inpatient and/or Outpatient) Incidence and SCT-Negative Versus SCT-Positive Status

	Adjusted HR[a] (95% CI)
SCT	
Negative	Reference
Positive	1.24 (1.06–1.45)
Age	
18–19	Reference
20–24	1.05 (0.90, 1.22)
25–29	1.00 (0.75–1.34)
30+	1.57 (1.07–2.33)
Gender	
Male	Reference
Female	1.36 (1.17–1.59)
Service	
Army	Reference
Navy	0.25 (0.21–0.30)
Marines	1.51 (1.22–1.88)
Air Force	0.49 (0.41–0.59)
Occupation	
Repair/engineer	Reference
Armor/motor transport	0.80 (0.52–1.23)
Communication/intelligence	1.21 (0.98–1.48)
Combat	1.57 (1.15–2.13)
Health care	1.42 (1.08–1.87)
Other	1.62 (1.31–2.00)
Quarter of enlistment year	
July to September	Reference
January to March	0.95 (0.78–1.15)
April to June	1.29 (1.08–1.55)
October to December	0.80 (0.64–0.99)

EHI, exertional heat illnesses; HR, adjusted relative rates; NNS, number needed to be screened; SCT, sickle cell trait.
[a]Adjusted HRs are adjusted for all of the above covariates.

TABLE III. Incidence of EHI, Number of SMs NNS for SCT, and the AR of EHI Due to SCT-Negative (−) Versus SCT-Positive (+) Status

	EHI Incidence in SCT, per 1,000 Persons/yr	EHI Incidence in SCT+, per 1,000 Persons/yr	NNS	NNS 95% CI	AR%	AR% 95% CI
All races	9.6	14.2	216	(147, 370)	0.33	(0.19, 0.45)
Army	17.9	28.4	96	(58, 213)	0.37	(0.17, 0.55)
Navy	3.7	7.4	269	(166, 556)	0.50	(0.27, 0.73)
Air Force	10.3	9.7	*		*	
Marine	23.1	33.4	**		**	
Black only	9.9	14.4	223	(144, 435)	0.31	(0.16, 0.45)
Army	18.2	28.3	99	(58, 250)	0.36	(0.15, 0.56)
Navy	3.8	7.3	285	(161, 714)	0.48	(0.22, 0.75)
Air Force	10.2	9.5	*		*	
Marine	25.6	36.9	**		**	

EHI, exertional heat illnesses; NNS, number needed to be screened; SCT, sickle cell trait.
*Air Force NNT and AR% for all races and Black only are not reported because the AR is less than zero.
**Marine Corps NNT and AR% for all and Black only not reported because the sample size of MC subjects (with and without SCT) and the number of MC EHI events are very small resulting in imprecise 95% CI estimates.

DISCUSSION

This study is the first cohort study linked to a longitudinal electronic health record designed to estimate the rate of EHI associated with SCT status. We found an approximately 24% increase in the risk of any EHI in SCT-positive compared with SCT-negative U.S. Military enlistees, although the proportion of heat stroke was similar in both groups. Additional risk factors for any EHI included older age at enlistment, female, Marine Corps branch of service, combat and health care occupations, and enlistment between April and June, whereas Navy, Air Force, and enlistment between October and December were protective. The frequency of EHI increased over the study period and increased faster in SCT-positive compared with SCT-negative SMs. An unanticipated finding was that EHI severity and specifically the proportion of EHI diagnoses due to heat stroke were not significantly different by SCT status, potentially due to better compliance in EHI countermeasures in SCT SMs. We speculate that the longer median time from enlistment to EHI in SCT-positive compare with SCT-negative subjects in the Army, females, non-Hispanic Blacks, and 18- to 19-yr-old enlistees may be due to greater compliance to heat illness countermeasures during the risk period of initial entry training. SCT-positive SMs with an EHI had a higher health care utilization perhaps due to clinicians' awareness of their SCT status as a potential risk factor for EHI resulting in closer monitoring of their condition. The number of enlistees needed to screen for SCT to identify and potentially prevent a case of EHI was approximately 200 and approximately a third of EHI cases in enlisted personnel was attributable to SCT status. These estimates were not higher for African Americans, or for the Army that does not perform universal SCT screening.

Our findings are generally consistent with the previous military and NCAA athlete literature of an increased risk of EHI in SCT individuals. SCT status has also been associated with a significant ($p < 0.05$) increased risk of exertional related rhabdomyolysis in military populations (relative risk [RR] 16.7,[19] HR 1.54[2]) and sudden death (RR 23.5 in the military[19] and 15 in NCAA athletes[21]), although neither outcome not included in the spectrum of EHI in our study, and none of these studies employed a large cohort study design with up to 21 years of follow-up for outcomes. The pathophysiology of the association of SCT with EHI and exercise collapse associated with sickle cell trait (ECAST) is not fully known but a common element includes deoxygenation of hemoglobin S in erythrocytes.[26] Intensive exercise is known to induce metabolic acidosis and a small percentage of irreversibly sickled cells, which can potentially cause vaso-occlusion.[27] Regular physical activity has been shown to affect markers of oxidative stress, nitric oxide metabolism, and endothelial adhesion in SCT-positive individuals compared with controls. The clinical significance of these findings is unknown. The relative contributions of SCT-related genetic and environmental factors including physical activity on the risk of EHI and ECAST is also not known.

The strength of this study was that it included a large cohort of 15,081 enlisted SMs with SCT followed longitudinally for EHI for 1–21 years of service, which provided adequate power to study associations for a variety of subpopulations and risk factors and EHI outcomes that included mild, heat exhaustion, and heat stroke. Several weaknesses exist in this study. EHI outcomes were based on ICD-9 codes without clinical validation. Potentially, clinicians may be more inclined to diagnose EHI in SMs known to be SCT positive, which would bias results away from the null. Misclassification of true SCT positive as negative may occur due to lack of universal screening in Army, which would also bias the association toward the null. No ICD-9 code exists for ECAST, so we could not study that outcome. Our sample size was underpowered to study associations of SCT status with rhabdomyolysis and exercise-related sudden death. The generalizability of results to NCAA and even more so the U.S. young adult population is limited in part to the medical and other requirements for military service but may also be generalizable to the pre-employment evaluation of a variety of physically demanding and heat-exposed occupations such as law enforcement, fire and rescue, agriculture, and construction-employing young adults.

CONCLUSION

The findings of this study contribute to the evidence base for DoD and by extrapolation to other organizations regarding the decision to institute universal screening for SCT status before beginning sustained and strenuous exertional activities. Our findings suggest that SCT screening will identify approximately 33% of the rate for EHI in SCT individuals but does not provide sufficient evidence for universal compared with selective (e.g., occupational based) screening in military enlistees. Neither does it suggest specific interventions to mitigate EHI risk such as disqualifying SCT positive from enlistment for combat occupations or SCT positive targeted EHI countermeasures. Future research will quantify the rate of chronic diseases such as venous thrombosis and renal diseases associated with SCT. Research is needed to elucidate the biological pathway by which SCT is associated with EHI and other health outcomes such as rhabdomyolysis, ECAST, and potentially exertional related sudden death. Additionally, a cost-effectiveness analysis is needed by SCT screening policy makers to assess the overall value of universal SCT screening to prevent morbidity and mortality.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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