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Sickle Cell Trait, Rhabdomyolysis, and Mortality among U.S. Army Soldiers

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Abstract

Background—Studies have suggested that sickle cell trait elevates the risks of exertional rhabdomyolysis and death. We conducted a study of sickle cell trait in relation to these outcomes, controlling for known risk factors for exertional rhabdomyolysis, in a large population of active persons who had undergone laboratory tests for hemoglobin AS (HbAS) and who were subject to exertional-injury precautions.

Methods—We used Cox proportional-hazards models to test whether the risks of exertional rhabdomyolysis and death varied according to sickle cell trait status among 47,944 black soldiers who had undergone testing for HbAS and who were on active duty in the U.S. Army between January 2011 and December 2014. We used the Stanford Military Data Repository, which contains comprehensive medical and administrative data on all active-duty soldiers.

Results—There was no significant difference in the risk of death among soldiers with sickle cell trait, as compared with those without the trait (hazard ratio, 0.99; 95% confidence interval [CI], 0.46 to 2.13; P = 0.97), but the trait was associated with a significantly higher adjusted risk of exertional rhabdomyolysis (hazard ratio, 1.54; 95% CI, 1.12 to 2.12; P = 0.008). This effect was similar in magnitude to that associated with tobacco use, as compared with no use (hazard ratio, 1.54; 95% CI, 1.23 to 1.94; P<0.001), and to that associated with having a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 30.0 or more, as compared with a BMI of less than 25.0 (hazard ratio, 1.39; 95% CI, 1.04 to 1.86; P = 0.03). The effect was less than that associated with recent use of a statin, as compared with no use (hazard

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ratio, 2.89; 95% CI, 1.51 to 5.55; P = 0.001), or an antipsychotic agent (hazard ratio, 3.02; 95% CI, 1.34 to 6.82; P = 0.008).

Conclusions—Sickle cell trait was not associated with a higher risk of death than absence of the trait, but it was associated with a significantly higher risk of exertional rhabdomyolysis. (Funded by the National Heart, Lung, and Blood Institute and the Uniformed Services University of the Health Sciences.)

Exertional rhabdomyolysis is characterized by the severe breakdown of skeletal-muscle tissue that is precipitated by strenuous physical exertion, leading to systemic manifestations that typically include myoglobinuria. This syndrome has received considerable attention because of high-profile deaths involving exertional rhabdomyolysis in athletes and military personnel.[1-10] A number of such cases have been attributed to sickle cell trait,[11-15] a condition in which persons are heterozygous for the sickle cell mutation in the beta-globin gene. The beta-globin protein forms part of the tetrameric hemoglobin complex; heterozygous persons have wild-type hemoglobin A as well as hemoglobin S, hence the term hemoglobin AS (HbAS). Sickle cell trait is most prevalent among persons with African ancestry. An estimated 7.3% of blacks, 0.7% of Hispanics, and 1.6% of U.S. residents overall have sickle cell trait.[16]

Two previous population-based studies of sickle cell trait and adverse outcomes showed substantially higher risks (by a factor of 20 to 30) of sudden, unexplained deaths among black military recruits[15] and of exertion-related deaths among black football players participating on National Collegiate Athletic Association (NCAA) Division 1 teams.[17] However, these studies did not include the sickle cell trait status of the total population studied or the longitudinal capture of participants' health histories. The need for population-based research on the effect of sickle cell trait in highly physically active groups that have been tested for HbAS has long been expressed,[18,19] but such research has not been conducted because of the lack of suitable databases.

Consequently, many organizations proceed with caution regarding the potential for exertion-related events among persons with sickle cell trait who are exposed to demanding physical training (e.g., military service members and athletes). The NCAA and the U.S. Air Force and Navy use universal screening for sickle cell trait.[19] However, concerns have been raised by the American Society of Hematology and other professional organizations about the possibility of stigmatization and discrimination resulting from the mandated screening for sickle cell trait.[20-23] These concerns warrant consideration, especially given the absence of published evidence that such screening is effective in preventing exertion-related events.

The U.S. Army has primarily used screening for sickle cell trait in situations of combat deployment and specific occupational specialties involving high altitude.[24] At present, there is no special recognition or handling of soldiers with sickle cell trait before or during physical activity. Instead, the Army uses universal precautions to reduce the risks of dehydration and heat-induced and exercise-induced illness among all its soldiers (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[24,25] Such measures have been shown to be effective in reducing the rates of exercise-related death, regardless of status with respect to sickle cell trait.[26]

We conducted an analysis involving HbAS-tested soldiers who served between 2011 and 2014 to quantify the associations between sickle cell trait and mortality and between sickle cell trait and the risk of exertional rhabdomyolysis in the context of mandated exertional-injury precautions. Because sickle cell trait is most prevalent among persons with African ancestry, this analysis focused on black soldiers.

Methods

Study Design

We conducted a retrospective cohort study using the Stanford Military Data Repository (SMDR). The SMDR comprises all digitally recorded health encounters (inpatient and outpatient; within military facilities or purchased from civilian institutions) for all active-duty soldiers in the U.S. Army. These health-encounter data have been combined with administrative, health-related, physical-performance, and mortality data from distinct official sources (Table 1). All the data were deidentified for research purposes by the Army Office of the Surgeon General. This study was approved by the institutional review board at Stanford University and by the Human Research Protection Office of the Assistant Secretary of Defense for Health Affairs and the Defense Health Agency.

Study Population

Eligible participants were black soldiers who served on active duty in the U.S. Army for any part of the study observation period (January 2011 through December 2014) and who had undergone testing for HbAS before or during this period. We obtained test results directly from laboratory findings in the electronic health records for the participants. Persons who reported their race as “black or African American” were identified from official personnel records. Soldiers from the National Guard and the Army Reserve were not included in the database. The resulting population consisted of 47,944 persons. Universal precautions, including primary and secondary prevention measures, were used throughout the Army during this time (Table S1 in the Supplementary Appendix).[24,25]

Study Outcomes

Exertional rhabdomyolysis and death were the main outcomes of interest. We initially identified the first occurrence of exertional rhabdomyolysis by the assignment of the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) code for rhabdomyolysis (728.88) or myoglobinuria (791.3). These diagnoses originated from data in the patients' electronic health records, which include information on inpatient or outpatient care that was delivered inside or outside the military health system.

To ensure that events during the study period most likely constituted rhabdomyolysis with an exertional cause, we excluded cases that were due to a drug-toxicity event or to tissue trauma. ICD-9-CM codes for diagnoses of toxic events or of trauma to an extremity or the torso (injury and poisoning codes 800–999) that were recorded on the day of the rhabdomyolysis event, up to 2 days before, and up to 7 days afterward served as the primary exclusion criteria. However, we retained the following conditions in this code range that could plausibly occur in conjunction with an exertional event or were unlikely to

independently precipitate nonexertional rhabdomyolysis: sprains and strains of joints and adjacent muscles (ICD-9-CM codes 840–848), superficial injuries (910–919), contusion of the eye and ocular adnexa (921), effects of a foreign body entering an orifice (930–939), effects of heat and light (992), effects of air pressure (993), effects of thirst (994.3), exhaustion due to exposure (994.4), exhaustion due to excessive exertion (994.5), motion sickness (994.6), adult emotional or psychological abuse (995.82), and adult sexual abuse (995.83).

An additional criterion that we used to rule out cases that were likely to be nonexertional cases was the presence of North Atlantic Treaty Organization (NATO) standardized agreement (STANAG) codes, which may indicate a specific traumatic or toxicity-related reason for military health care. However, events with the following specific codes were retained as being possibly related to exertional events: athletics and sports including physical training (STANAG codes 200–249) and specified environmental factors, including in natural and artificial environments (STANAG codes 800–899).

Deaths were determined with the use of data from the Defense Manpower Data Center, which maintains official records of deaths among soldiers. Deaths were coded in the original data as battle-related or non–battle-related. We modeled against three mortality outcomes: overall mortality, battle-related mortality, and non–battle-related mortality.

Independent Variables

The main independent predictor of interest, sickle cell trait, was a binary variable that was based on laboratory-confirmed tests of the hemoglobin AS phenotype. We controlled for sex and age. A high level of physical fitness, as indicated by a score of 270 or more on the most recent Army Physical Fitness Test (with scores ranging from 0 to 300, and higher scores indicating better fitness) was included to control for physical conditioning.[27]

The analysis included the participants' most recent body-mass index category according to standard classifications.[28] Participants with a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 25.0 to 29.9 were categorized as overweight, and those with a BMI of 30.0 or more were categorized as obese. All other participants were included in the reference group, which consisted mainly of persons with normal BMI (18.5 to <25.0); fewer than 2% of the study participants were underweight (BMI, <18.5) or had missing data for BMI.

We also included any self-reported tobacco use during the previous 6 months as a predictor for each participant, and this information was updated monthly during each participant's time at risk. In addition, three binary covariates indicated the presence of at least one dispensed prescription in either the observed or the previous month for statins, antipsychotic agents, or stimulants, given their previously reported associations with rhabdomyolysis.[29,30] These factors were also updated throughout each participant's time at risk.

Statistical Analysis

The observational unit for the longitudinal-panel data set was the person-month. For new soldiers, the time at risk for exertional rhabdomyolysis began at the initial entry to military

service during the study period, given that a history of exertional rhabdomyolysis disqualifies a person from induction into the armed forces.[24]

The time at risk for exertional rhabdomyolysis for those soldiers who had entered the Army before January 2011 began at the earliest annual physical examination without a diagnosis of exertional rhabdomyolysis. Among experienced soldiers with no record of physical examinations, time at risk began in June 2011, the sixth observed month. Soldiers were excluded if exertional rhabdomyolysis or any notations of duty restrictions that were due to exertion-related problems occurred during that initial 6-month period. After the time at risk began, data from participants with an outcome during the study were censored at the time of the event. Otherwise, data were censored either at the participants' exit from the study population due to the end of military service or at the end of the observation period in the study.

We used a multivariable Cox proportional-hazards regression model to estimate adjusted hazard ratios for each covariate. Two sensitivity analyses were performed. In the first, we included an interaction term to test whether the association between sickle cell trait and exertional rhabdomyolysis varied between new soldiers and those who were more experienced. In the second, we tested whether the inclusion of duration of service affected the association between sickle cell trait and exertional rhabdomyolysis. All the statistical analyses were conducted with the use of Stata software, version 13 (StataCorp).

Results

Associations of Sex and Age with Exertional Rhabdomyolysis

We observed 391 exertional rhabdomyolysis events during the 1.61 million person-months contributed by the 47,944 participants (Table 2). Women were at substantially lower risk for exertional rhabdomyolysis than were men (hazard ratio, 0.51; 95% confidence interval [CI], 0.38 to 0.67; P<0.001) (Table 3). We observed a progressive increase in risk that was associated with increasing age, including a 57% higher risk among soldiers 36 years of age or older than among those in the lowest age category (hazard ratio, 1.57; 95% CI, 1.06 to 2.32; P = 0.02).

Associations of Modifiable Risk Factors with Exertional Rhabdomyolysis

With regard to modifiable risk factors, we observed that the risk of exertional rhabdomyolysis was significantly higher among obese persons than among persons with in the reference BMI category (hazard ratio, 1.39; 95% CI, 1.04 to 1.86; P = 0.03) (Table 3). Similarly, a report of tobacco use in the previous 6 months was associated with a risk of exertional rhabdomyolysis that was 54% higher than that associated with no tobacco use (hazard ratio, 1.54; 95% CI, 1.23 to 1.94; P<0.001). Recent use of an antipsychotic medication was associated with a tripling of the risk of exertional rhabdomyolysis, as compared with no use of antipsychotic medication (hazard ratio, 3.02; 95% CI, 1.34 to 6.82; P = 0.008). Recent statin use was associated with a near-tripling of the risk of exertional rhabdomyolysis, as compared with no statin use (hazard ratio, 2.89; 95% CI, 1.51 to 5.55; P = 0.001).

Association of Sickle Cell Trait with Exertional Rhabdomyolysis

Participants with sickle cell trait made up 7.4% of the study population and were broadly similar to participants without sickle cell trait in terms of demographic characteristics and health predictors (Table 2). The presence of sickle cell trait was associated with an adjusted risk of exertional rhabdomyolysis that was 54% higher than that associated with the absence of the trait (hazard ratio, 1.54; 95% CI, 1.12 to 2.12; P = 0.008) (Table 3).

Association of Sickle Cell Trait with Death

We observed 96 deaths from all causes among the study participants (Table 2). There was no significant difference in the risk of death among soldiers with sickle cell trait, as compared with those without the trait (hazard ratio, 0.99; 95% CI, 0.46 to 2.13, P = 0.97) (Table 4). Nearly identical hazard ratios were observed for battle-related deaths and non–battle-related deaths. Seven deaths occurred among participants with sickle cell trait, one of which was classified as battle-related. A review of the records for the six participants with sickle cell trait who died from non–battle-related causes indicated diverse medical histories, including cancer, substance abuse, mental disorders, heart disease, and postoperative complications. One death was observed among the soldiers who had exertional rhabdomyolysis; this death occurred in a participant without sickle cell trait.

Discussion

In this population-based study involving black soldiers who had undergone testing for HbAS and were subject to exertional-injury precautions, sickle cell trait was not associated with a higher overall risk of death, although it was associated with a significantly higher adjusted risk of exertional rhabdomyolysis. Other factors were of similar or greater concern in the assessments of the risk of exertional rhabdomyolysis. For example, obesity and tobacco use were each associated with a significantly higher risk of exertional rhabdomyolysis, and the magnitude of the risk was similar to that associated with the presence of sickle cell trait. A recent prescription of an antipsychotic or statin medication was associated with an approximate tripling of the risk of exertional rhabdomyolysis in this study population, as compared with no use of the specified medications.

These findings are compelling because case reports dominate the relevant literature and emphasize the presence of sickle cell trait as a risk factor for adverse outcomes, including exertional rhabdomyolysis and sudden death.[9,11-13,31-35] A large, longitudinal study involving a population fully tested for HbAS that has formally investigated the relationship between the presence of sickle cell trait and exertional rhabdomyolysis or death while also examining other known, major risk factors such as use of medications has been lacking.

One strength of our study is that the hemoglobin type of each participant in the analytic study population was confirmed by laboratory results rather than by self-report or medical history. The inclusion in our analysis of only participants with verified laboratory results enabled the accurate estimation of the risks of exertional rhabdomyolysis and death among persons with sickle cell trait and among those without sickle cell trait. By contrast, other population-based studies of sickle cell trait in relation to sudden, nontraumatic, or exertion-

related death attempted to assess the hemoglobin types only of participants with the outcome event with certainty.[15,17,36,37] Among participants in these studies without the outcomes of interest (i.e., sudden, nontraumatic, or exertion-related death), inferences about the expected proportion with sickle cell trait were made from population average values.

Additional strengths of our study were the inclusion of a very large number of black soldiers, precision with regard to the nature of the exertional rhabdomyolysis outcome, and the ability to control for a wide range of confounders. Finally, our data reflect recent conditions in the U.S. Army, which has used universal precautions to mitigate heat- and exertion-related injuries since at least 2003.[24,25]

Men in the SMDR study population were found to have an adjusted risk of exertional rhabdomyolysis that was twice as high as that among women, a result that was similar to the findings of a recent report involving the total military population.[38] In contrast to the findings of that report, however, the risk of exertional rhabdomyolysis increased with increasing age in our study population. This difference probably reflects the adjustments we made for other demographic, military, and health-related factors, some of which may be associated with both age and the risk of exertional rhabdomyolysis.

One plausible concern about this study was that participants with sickle cell trait who were prone to exertional rhabdomyolysis might have been medically discharged, which would have produced a selection bias effect. However, a sensitivity analysis showed no significant difference in the association between sickle cell trait and exertional rhabdomyolysis between new soldiers and those who were more experienced. An additional sensitivity analysis, including duration of service in the model to control for potential attrition-related selection effects, showed no resulting differences in the effect sizes for exertional rhabdomyolysis or death in the association with sickle cell trait. Finally, the age and rank distributions of participants with sickle cell trait and those without the trait were very similar (Table 2), which argues against any generalized selection effect.

The study has several limitations. First, not all black soldiers in the total Army population were tested for sickle cell trait. Testing in the Army takes place for diverse reasons. For example, in military-unit-readiness processing, hundreds or thousands of persons are tested at once. Testing also occurs at certain physical examinations as mandated by regulation, in addition to occurring because of sporadic clinical indications. Our analyses indicate that testing has not occurred differentially on the basis of either demographic characteristics or health-related factors (data not shown). Thus, there is no reason to expect systematic differences in the association between the presence of sickle cell trait and exertional rhabdomyolysis among persons who have been tested and those who have not been tested.

An additional limitation derives from the possibility that some soldiers in the study population may have had an exertional rhabdomyolysis event before January 2011. However, the eligibility criteria and careful selection of the start time for risk calculations were aimed at mitigating that concern. It is also possible that some cases of exertional rhabdomyolysis during the study observation period were not included in the soldier's electronic health record. However, the seriousness of the condition and the fact that the electronic health data

included care in military and civilian institutions reduce the probability of this scenario. We acknowledge the general limitations of ICD-9-CM coding, which may be subject to clinician error and bias. We were not able to perform chart audits to examine coding fidelity. Finally, we did not explore the potential for alcohol use or other toxic events to compound an effect of sickle cell trait on the risk of exertional rhabdomyolysis or death.

In conclusion, we conducted a population-based, longitudinal study of sickle cell trait in relation to the risks of exertional rhabdomyolysis and death in a population that is known to engage consistently in regular and strenuous exercise while protected by exertional-injury precautions. It is not clear to what extent the precautionary measures might have influenced the occurrence of exertional rhabdomyolysis events. A significantly higher risk of exertional rhabdomyolysis was identified among black U.S. Army soldiers with sickle cell trait than among those without the trait. Similarly elevated risks of exertional rhabdomyolysis were observed in association with tobacco use and obesity, and stronger effects were observed in association with recent use of statins or antipsychotic agents. Mortality — overall, battle-related, or non–battle-related — was not higher among participants with sickle cell trait than among those without the trait.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Sources and Types of Data in the Stanford Military Data Repository Used in the Study

Defense Manpower Data Center
Active Duty File: Demographic and military service data
Transactions File: Mortality data
Medical Data Repository
Combined Ambulatory/Professional Encounter Record: Outpatient care in military facilities
Standardized Inpatient Data Record: Inpatient care in military facilities
Tricare Encounter Data, Non-Institutional: Outpatient care in civilian facilities
Tricare Encounter Data, Institutional: Inpatient care in civilian facilities
Pharmacy Detail Transaction Service: Prescription medication information
Clinical Data Repository Laboratory: Sickle cell phenotype testing results
Clinical Data Repository Vitals: Height and weight readings taken in military facilities
Medical Operational Data System
Periodic Health Assessment: Annual health surveys and associated medical screenings
eProfile: Permanent and temporary duty restrictions assigned by medical providers
Digital Training Management System
Height and Weight File: Heights and weights measured approximately every 6 mo to assess body composition
Army Physical Fitness Test: Scores and other details from physical performance evaluations conducted every 6 mo

Table 2

Characteristics of Black U.S. Army Soldiers Tested for Sickle Cell Trait Who Were on Active Duty between January 2011 and December 2014*

Characteristic	Sickle Cell Trait (N = 3564)	No Sickle Cell Trait (N = 44,380)
Male sex — no. (%)	2488 (69.8)	31,822 (71.7)
Age — yr	30.7±7.8	30.5±7.6
Military pay-grade category — no. (%)		
Private, E1–E3	529 (14.8)	6,238 (14.1)
Specialist or corporal, E4	1121 (31.5)	13,389 (30.2)
Junior sergeant, E5–E6	1132 (31.8)	14,039 (31.6)
Senior sergeant, E7–E9	424 (11.9)	5,433 (12.2)
Warrant officer, W1–W5	73 (2.0)	1,071 (2.4)
Junior officer, O1–O3	176 (4.9)	2,896 (6.5)
Senior officer, O4–O10	109 (3.1)	1,314 (3.0)
Health-related factors		
BMI	26.8±3.8	26.8±3.7
APFT score ≥270 — no. (%)†	620 (17.4)	9,333 (21.0)
Tobacco use in previous 6 mo — no. (%)	788 (22.1)	9,909 (22.3)
Prescription medication in previous 2 mo — no. (%)		
Statin	43 (1.2)	569 (1.3)
Antipsychotic agent	29 (0.8)	442 (1.0)
Stimulant	9 (0.3)	189 (0.4)
Exertional rhabdomyolysis — no. (%)	42 (1.2)	349 (0.8)
Death — no. (%)		
Any cause	7 (0.2)	89 (0.2)
Battle-related	1 (<0.1)	13 (<0.1)
Non–battle-related	6 (0.2)	76 (0.2)

*Plus–minus values are means ±SD. The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters. All values that could vary over time were the values that were known for each participant in the last observed month before data censoring.

†Scores on the Army Physical Fitness Test (APFT) range from 0 to 300, with higher scores indicating better physical performance. A minimum score of 180 is ordinarily required to pass. Soldiers who have a score of 90 or greater in each of the three fitness categories (push-ups, sit-ups, and cardiovascular endurance) are awarded recognition for high fitness.[25]

Table 3
Risk of Exertional Rhabdomyolysis among Black U.S. Army Soldiers

Characteristic	Hazard Ratio (95% CI)	P Value
Sickle cell trait		
Negative	Reference	
Positive	1.54 (1.12–2.12)	0.008
Sex		
Male	Reference	
Female	0.51 (0.38–0.67)	<0.001
Age category		
17–23 yr	Reference	
24–28 yr	1.10 (0.80–1.49)	0.56
29–35 yr	1.27 (0.91–1.77)	0.16
≥36 yr	1.57 (1.06–2.32)	0.02
Modified BMI category *		
<25.0	Reference	
25.0–29.9	1.21 (0.95–1.54)	0.13
≥30.0	1.39 (1.04–1.86)	0.03
APFT score		
<270 or no score	Reference	
≥270	1.13 (0.87–1.47)	0.37
Tobacco use in previous 6 mo		
No	Reference	
Yes	1.54 (1.23–1.94)	<0.001
Statin prescription in previous 2 mo		
No	Reference	
Yes	2.89 (1.51–5.55)	0.001
Antipsychotic-agent prescription in previous 2 mo		
No	Reference	
Yes	3.02 (1.34–6.82)	0.008
Stimulant prescription in previous 2 mo		
No	Reference	
Yes	1.63 (0.41–6.59)	0.49

* Modified BMI indicates that all participants with a BMI of 25 or less (normal and underweight) were included with those with unknown BMI to create the reference category.

Table 4

Association between Sickle Cell Trait and Death among Black U.S. Army Soldiers*

Outcome	Hazard Ratio (95% CI)	P Value
Death from any cause	0.99 (0.46–2.13)	0.97
Battle-related death	0.96 (0.13–7.37)	0.97
Non–battle-related death	0.99 (0.43–2.27)	0.98

*All models were adjusted for sex, age, rank, modified BMI, APFT score, selected prescribed medications (statin, antipsychotic agent, or stimulant), and tobacco use.