Study challenges view that sickle cell trait increases mortality risk

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Health experts have long believed that sickle cell gene variants, which occur in about 1 in 13 African-Americans, increase the risk of premature death, even when people carry only a single copy of the variant. But health records of nearly 50,000 active-duty U.S. Army soldiers between 2011 and 2014 shows that's not the case, according to a study led by researchers at the Stanford University School of Medicine.

People who carry two copies of the sickle cell gene variant have sickle cell disease, which brings a drastically shortened life span of only 40 to 60 years, as well as lifelong bouts of intense pain.

In contrast, those carrying just one copy of the gene variant have what's called sickle cell trait. Earlier studies have suggested that the health consequences of sickle cell trait might be dire, including higher mortality from a potentially fatal condition called exertional rhabdomyolysis. ER, which occurs when molecules from the breakdown of muscles end up in the kidneys, has been known to fell football players, often when they are practicing too hard in the hot sun without drinking enough water. (ER is distinct from heat exhaustion, however.) Likewise, ER is a risk for soldiers on active duty.

Yet, in the first-ever longitudinal cohort study of sickle cell trait—which included African-American soldiers of all ages—researchers have found they suffered no increase in mortality. Lianne Kurina, PhD, an associate professor of medicine at Stanford, and a team of medical researchers found that having sickle cell trait does not increase the risk of death. A

paper describing their findings will be published Aug. 3 in *The New England Journal of Medicine*. Kurina is senior author. D. Alan Nelson, PhD, PA-C, a postdoctoral scholar at Stanford and former Army medical officer, is the lead author.

Inconclusive studies

Case reports suggesting a connection between sickle cell trait and deaths of individual patients have dominated the medical literature, according to the new study. A paper published in 1987 reported a 2,800 percent increase in the risk of exertion-induced sudden deaths among African-American military recruits thought to have sickle cell trait. But the actual sickle cell status of every individual was not known.

Despite relatively weak evidence, Kurina said, it's been assumed that sickle cell trait increases the risk of death, of exertional rhabdomyolysis and of heat stroke. This assumption has led to mandated screening by organizations such as the Air Force, the Navy and the NCAA. But the American Society for Hematology and other organizations have argued that screening programs raise questions about job discrimination. The Army typically screens only before combat deployment and high-altitude activities, the study said.

For the study, the researchers reviewed the health records of 47,944 African-American soldiers who served on active duty between 2011 and 2014 and for whom sickle cell status was known. The researchers got the health records from the Stanford Military Data Repository data set, which Nelson and Kurina created. The repository includes all digitally recorded health encounters at military medical facilities or civilian institutions, general health information and official records of physical performance and mortality of all active-duty U.S. Army soldiers. The data in the repository are de-identified to protect privacy.

Kurina and her colleagues found that the risk of exertional rhabdomyolysis was only 54 percent higher among African-American soldiers with sickle cell trait than among those without it. A 54 percent increase might sound like a lot, but it's far less than the 300 percent increase caused by some ordinary prescription drugs. And smoking, obesity and increasing age each incur a heightened risk of ER that is about the same as sickle cell trait, the study showed.

Why the difference?

A major reason for the difference between the current study and previous ones, Kurina said, may be better safety for active-duty soldiers. As of 2003, soldiers who are engaged in strenuous exercise are required to drink plenty of fluids, build up to strenuous exercise gradually and take regular rests when it's hot. All of these measures are known to reduce exercise-related fatality rates, regardless of whether individuals have sickle cell trait, the study said.

"Another critical difference between our study and the earlier, population-based studies is that in our study, we knew the sickle cell status of everyone in the population," said Kurina. She and her team looked only at soldiers whose sickle cell status was confirmed by blood tests taken during their years of service, instead of from self-reported sickle cell status or past medical history, as had been done in the other studies.

"The most important thing to come out of this study is the really reassuring news that under conditions of universal precautions against dehydration and overheating, we don't see an elevation in the risk of mortality in people with sickle cell trait," said Kurina. It happens, she noted, that the lead author of the 1987 paper went on to propose and validate the measures adopted by the Army to mitigate dehydration and overheating.

The study's results call into question the need to screen service members with sickle cell trait, especially with better safety precautions during intense exertion, Kurina said.

Big data at Stanford

The work is an example of Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill, and could not have been done without the Stanford Military Data Repository.

Kurina said she values collaborating with the military on health research. "In each of these projects," she said, "it's critical to be able to have these really productive partnerships with military partners." That said, she said she'd like to see the work repeated and confirmed in a civilian population.

Researchers from the Army, the University of Texas and the Army-Baylor University Graduate Program in Health and Business Administration contributed to the study.

Provided by Stanford University Medical Center

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