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Clinical Outcomes Associated With Sickle Cell Trait:

A Systematic Review

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Abstract

Background: Although sickle cell trait (SCT) is largely a benign carrier state, it may increase risk for certain clinical outcomes.

Purpose: To evaluate associations between SCT and clinical outcomes in children and adults.

Data Sources: English-language searches of PubMed, CINAHL, the Cochrane Library, Current Contents Connect, Scopus, and Embase (1 January 1970 to 30 June 2018) and bibliographies of review articles.

Study Selection: Observational controlled studies (published in English) in children or adults that examined an association between SCT and any of 24 clinical outcomes specified a priori in the following 6 categories: exertion-related injury; renal, vascular, pediatric, and surgery- or trauma-related out- comes; and overall mortality.

Data Extraction: A single reviewer extracted study data, which was checked by another; 2 reviewers independently assessed study quality; and strength of evidence was assessed by consensus.

Data Synthesis: Of 7083 screened studies, 41 met inclusion criteria. High-strength evidence supported a positive association between SCT and risk for pulmonary embolism, proteinuria, and chronic kidney disease. Moderate-strength evidence supported a positive association between SCT and exertional rhabdomyolysis and a null association between SCT and deep venous thrombosis, heart failure or cardiomyopathy, stroke, and pediatric height or weight. Absolute risks for

thromboembolism and rhabdomyolysis were small. For the remaining 15 clinical outcomes, data were insufficient or strength of evidence was low.

Limitation: Publication bias was possible, and high-quality evidence was scant.

Conclusion: Sickle cell trait is a risk factor for a few adverse health outcomes, such as pulmonary embolism, kidney disease, and exertional rhabdomyolysis, but does not seem to be associated with such complications as heart failure and stroke. Insufficient data or low-strength evidence exists for most speculated complications of SCT.

Sickle cell trait (SCT), defined as the heterozygous inheritance for sickle hemoglobin, has evolutionarily persisted throughout the world because of its strong protective effect against severe and cerebral malaria (1). In the United States, 2.5 million to 3 million persons live with SCT, including an estimated 6% to 9% of the African American population and 0.01% to 0.07% of the remaining population, primarily those of Arab, Southeast Asian, Hispanic, or Mediterranean descent (2, 3). Worldwide, SCT affects an estimated 300 million persons, with a prevalence ranging from 2% to 30% in more than 40 countries (4, 5). This high prevalence means that SCT has considerable implications in reproductive counseling because carriers can have homozygous or compound heterozygous offspring with sickle cell disease (3, 5).

Although SCT is generally an asymptomatic carrier state and most carriers never have complications, numerous studies have reported potential clinical manifestations (6). The Sickle Cell Disease Association of America, the Department of Health and Human Services Secretary's Advisory Committee on Heritable Disorders in Newborns and Children, and the American Society of Hematology have called for research to generate high-quality data that scientifically clarify the health outcomes associated with SCT (3, 7–9). Because newborn screening for sickle hemoglobin is mandated in several countries, including the United States (10), health care providers, patients, and families also seek quality information about clinical risk.

The purpose of this study was to evaluate associations between SCT and adverse clinical outcomes (exertion-related injury; renal, vascular, pediatric, and surgery- or trauma-related outcomes; and overall mortality) in children and adults.

Methods

Data Sources and Searches

We followed standard procedures for systematic reviews and reported results according to PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines. A medical librarian experienced in systematic reviews developed search strategies to identify studies published in English that reported an association between SCT and any clinical outcome. The following databases were searched from 1 January 1970 to 30 June 2018: PubMed, CINAHL, the Cochrane Library, Current Contents Connect, Scopus, and Embase (the Supplement, gives terms used in the PubMed search). We also examined bibliographies of review articles.

Study Selection

Studies were selected using an iterative process. Two members of the expert working group (EWG), which included hematologists and sickle cell experts, screened each title and abstract and excluded articles on the basis of predefined criteria. We excluded non–English-language research articles; research articles that reported exclusively on in vitro cells, nonhuman animals, or patients with sickle cell disease; those that solely examined physiologic mechanisms or laboratory variables, had no information on clinical outcomes, or solely reported outcomes related to malaria or pregnancy; and prevalence studies, case reports, case series, meeting abstracts, editorials, commentaries, and review articles.

Two EWG members then reviewed the full text of the remaining articles to identify those reporting any of 24 clinical outcomes deemed relevant for this systematic review. These outcomes were chosen before the search by consensus agreement of the EWG to include outcomes with strong effects on policy and clinical practice (Supplement Table 1). Outcomes were organized into 6 categories. At this stage, studies were excluded if they did not use a valid method for genotyping for all included study participants, did not have a non-SCT comparison group, or did not list separate outcomes for SCT carriers and noncarriers. Valid genotyping methods were hemoglobin electrophoresis, isoelectric focusing, high-performance liquid chromatography, and direct DNA genotyping with or without imputation for SCT. Studies using the International Classification of Diseases (ICD) code for SCT or sickle solubility without confirmatory methods for quantifying sickle hemoglobin were not included. For all screening stages, the 2 EWG members assessed articles independently and resolved differences by discussion.

Data Extraction and Quality Assessment

An EWG member extracted relevant data using a standardized abstraction form, which captured basic citation information, characteristics of study populations, details of study methodology, and pertinent results. For articles that included 2 or more clinical outcomes relevant to the systematic review, results for each outcome were abstracted separately. We calculated the unadjusted odds ratio (OR) and 95% CI for each outcome based on prevalence described in the text. We also recorded the adjusted or unadjusted risk measure (OR, risk ratio, or hazard ratio [HR]) reported for each outcome. For articles that measured only a risk difference, the reported statistical associations were recorded. Extractions were checked by a second reviewer.

The quality of each article was assessed using rubrics tailored for this review by Abt Associates with input from the EWG. These rubrics were modeled after the Agency for Healthcare Research and Quality's Evidence-based Practice Centers methodology (Supplement Table 2) (11). For study-level grading, each relevant outcome from included studies was assessed separately. Studies were rated as high quality if they involved a population-based observational cohort, included a direct measure of the relevant outcome and adjustment for relevant confounders, and had precise findings and no suspected bias. Studies rated as high quality were adjusted for age and sex (at a minimum) and for additional outcome-specific confounders that had been determined by discussion as necessary. Any study with suspected bias was automatically rated as very low quality. Two

members of the EWG who were not authors on the included studies independently rated quality, and differences were resolved through discussion.

Data Synthesis and Analysis

We categorized the 24 outcomes into 6 areas (exertion-related injury; renal, vascular, pediatric, and surgery- or trauma-related outcomes; and overall mortality) and assessed the strength of evidence for each outcome. Strength of evidence was defined by using rubrics tailored for this review by Abt Associates with input from the EWG (Supplement Table 3). These rubrics were modeled after the Agency for Healthcare Research and Quality's Evidence-based Practice Centers methodology (12). By consensus agreement, the EWG determined strength of evidence separately for each outcome on the basis of the number, design, and rating of relevant studies and the consistency in direction and association estimate of their findings. Outcome data from studies rated as very low quality were not included in the strength-of-evidence assessment. Members with a potential conflict of interest for any given outcome did not participate in the grading.

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Results

We screened 7083 records (after removing duplicates) and excluded 6905 after title and abstract review. Of 178 full-text articles reviewed, 41 met eligibility criteria (Figure). Most were population-based cohort studies ($n = 16$) or case–control studies ($n = 16$). Twenty-six involved adults only, 12 involved children only, and 3 involved both adults and children. Supplement Tables 4 and 5 summarize the characteristics, findings, and quality assessments for each individual study, by clinical outcome. Strength-of-evidence ratings for each outcome are shown in the Table.

Exertion-Related Injury

We evaluated 3 exertion-related outcomes and found 2 studies that addressed sudden death (13, 14), 2 that addressed rhabdomyolysis (14, 15), and none that examined splenic infarction. The studies addressing sudden death were of moderate quality. One (13), published in 1987, evaluated the relative risk for death among 466,300 African American recruits in the U.S. military using prevalence controls and found a 15-fold (95% CI, 6- to 38-fold) increased risk for death among recruits with SCT versus those without. This relative risk was based on small absolute numbers of deaths per group: 10 (0.0002%) among SCT noncarriers and 13 (0.03%) among persons with SCT. The analysis did not include adjustment for potential confounders. The second study (14) examined risk for death by SCT status among 47,944 African American soldiers who were on active duty in the U.S. Army between 2011 and 2014, a period in which the Army used universal precautions to reduce risks for dehydration and heat- and exercise-induced illness. Six of the 3564 soldiers

with SCT died of nonbattle causes (0.2%). No association between SCT status and non–battle-related death was found in a model adjusted for multiple variables, including sex, age, rank, body mass index, and tobacco status.

Both studies of rhabdomyolysis suggested that SCT is associated with increased risk for exertional rhabdomyolysis. A moderate-quality study (14) involving 47 944 active-duty military personnel found that diagnoses based on ICD, Ninth Revision, codes for exertional rhabdomyolysis occurred in 1.2% of soldiers with SCT and 0.8% of those without. The adjusted HR estimate for increased risk for rhabdomyolysis with SCT was 1.54 (CI, 1.12 to 2.12). The other study (15)—a small case–control study that did not adjust for potential confounders—was of low quality and showed an increased prevalence of SCT among persons with exertional rhabdomyolysis who were referred for genetic polymorphism testing or muscle biopsy compared with healthy active-duty or civilian participants in exercise training.

Renal Outcomes

We evaluated studies pertaining to the following 6 kidney outcomes: hematuria, papillary necrosis, proteinuria, chronic kidney disease (CKD), end-stage renal disease (ESRD), and renal medullary carcinoma. A single cohort study of moderate quality (16) involving 23,192 hospitalized African American adults found an increased prevalence of hematuria according to ICD, Eighth Revision (ICD-8), codes among patients with SCT versus those without (2.5% vs. 1.3%), which is consistent with a 1.98-fold (CI, 1.52- to 2.62-fold) relative risk for hematuria in SCT carriers.

Of 6 studies that evaluated proteinuria, 1 was rated as high quality (17), 2 as moderate quality (18, 19), and 3 as low quality (20 –22). The high-quality study (17) evaluated albuminuria in 6432 African American adults from 4 population cohorts. It found a 1.86-fold (CI, 1.49- to 2.31-fold) increased risk for baseline albuminuria among persons with SCT versus those without (31.8% vs. 19.6%). The other studies in adults showed a consistent direction of increased risk for proteinuria with SCT.

Two high-quality studies (17, 23) and 2 low-quality studies (24, 25) evaluated CKD. The first high-quality study (17) assessed prevalent CKD in 15,969 self-identified African Americans in 5 population-based cohorts. Creatinine-based CKD was found in 19.2% of participants with SCT, compared with 13.5% without. The meta-analyzed increased risk was 1.57 (CI, 1.34 to 1.84). This study also evaluated incident CKD among 9156 persons with follow-up creatinine measurements and found a 1.79-fold (CI, 1.45- to 2.20-fold) increased risk for CKD among SCT carriers. The second high-quality study (23) found a 1.89-fold (CI, 1.59- to 2.23-fold) increased risk for CKD by estimated glomerular filtration rate and albuminuria criteria among a large population cohort of 9909 African American adults.

Five studies evaluated dialysis-dependent ESRD. One was rated as high quality (23), 2 as moderate quality (17, 26), and 2 as very low quality (not included in strength-of-evidence ratings) (27, 28). The high-quality study (23) was a longitudinal study of 9909 African American adults. It found an increased risk for incident ESRD in SCT carriers compared with noncarriers, with an HR of 2.03 (CI, 1.44 to 2.84). Analyses were adjusted for age, sex,

smoking, diabetes, hypertension, and *APOL1* genotype. A similar study (17) in 11,263 African Americans in 2 U.S. population cohorts did not find an association between SCT and ESRD (HR, 1.02 [CI, 0.59 to 1.76]). We rated this study as moderate rather than high quality because of imprecision and an upper CI bound compatible with increased risk. Finally, a moderate-quality case–control study (26) involving 3258 African Americans with ESRD related to hypertension or diabetes found no statistically significant association between SCT and diabetic or nondiabetic ESRD. No included studies evaluated papillary necrosis or renal medullary carcinoma.

Vascular Outcomes

We evaluated the following 9 vascular-related outcomes: venous thromboembolism (VTE), pulmonary embolism (PE), deep venous thrombosis (DVT), hypertension, myocardial infarction, heart failure or cardiomyopathy, stroke, retinopathy, and diabetic vasculopathy.

For the venous outcomes, we evaluated VTE, PE, and DVT separately. Two studies addressed overall VTE (including PE and DVT). One was rated as high quality and the other as moderate quality (29, 30). The high-quality study (29) was a longitudinal cohort study involving 4016 African Americans that found a VTE incidence of 9.0% in SCT carriers and 5.9% in noncarriers, resulting in a 1.60-fold (CI, 1.05- to 2.45-fold) increased risk for incident VTE events after adjustment for age, sex, and ancestry. This risk estimate attenuated to 1.50-fold (CI, 0.96- to 2.36-fold) with additional adjustment for hormone replacement therapy, body mass index, diabetes, and estimated glomerular filtration rate. The moderate-quality study (30)—a case–control study that evaluated 1062 African American adults—found a similar adjusted risk for VTE (OR, 1.8 [CI, 1.1 to 2.28]). Both studies also evaluated PE and DVT separately.

Three studies evaluated PE. One was graded as high quality (29) and 2 as moderate quality (16, 30). A subset analysis of the high-quality study (29) showed a 5.2% versus 2.5% prevalence of PE with or without DVT in persons with versus without SCT, corresponding to an HR of 2.24 (CI, 1.28 to 3.95). A subset analysis of 1 of the moderate-quality studies (30) also showed increased risk for PE without diagnosed DVT among SCT carriers (OR, 3.9 [CI, 2.2 to 6.9]) and a similar increased odds for PE with or without diagnosed DVT. The third study (16) of 23 192 hospitalized African American adults similarly suggested increased risk for PE with SCT (OR, 1.46 [CI, 1.14 to 1.89]).

Three studies evaluated DVT. Two were rated as moderate quality (29, 30) and 1 as low quality (31). The moderate-quality studies suggested no increased risk for isolated DVT among SCT carriers.

Five studies evaluated hypertension. Two were rated as moderate quality and 3 as low quality (18, 20, 21, 32, 33). The largest, a longitudinal study by Liem and colleagues (32) of 1590 African American adults, did not show an association between SCT and incident hypertension.

A single moderate-quality study (16) that evaluated risk for ICD-8 – coded myocardial infarction among 23 192 hospitalized adults found no statistically significant association

between SCT and myocardial infarction. Two studies (18, 34), 1 of which was of moderate quality, evaluated heart failure or cardiomyopathy. The moderate-quality study (34) involved 15 364 African American adults from 4 longitudinal, population-based cohort studies; it found no statistically significant association between SCT and adjudicated incident heart failure.

One high-quality and 1 moderate-quality study assessed stroke. The high-quality study (35) evaluated validated hospitalizations for incident stroke among 3497 self-identified African Americans. The incidence of stroke was 13.0% among persons with SCT compared with 11.4% among non–SCT carriers, corresponding to an HR of 1.4 (CI, 1.0 to 2.0). The moderate-quality study (36) included 4 population-based cohorts and found no association between SCT and ischemic stroke.

Three studies investigated retinopathy. Two were rated as low quality (18, 21) and 1 as very low quality (37). The studies had inconsistent effect sizes. Only a single low-quality study (16) evaluated SCT's association with diabetic vascular complications among hospitalized adults; it found no association.

Pediatric Outcomes

Height or weight was investigated in 8 studies involving children or adolescents. We rated 1 as moderate quality (38), 6 as low quality (39–44), and 1 as very low quality (not included in strength-of-evidence ratings) (45). The moderate- and low-quality studies involved various populations and included persons from Jamaica, Dominica, India, Brazil, Nigeria, and the United States. None found an association between SCT and continuous measures of height and weight.

A single low-quality study (46) evaluated risk for sudden infant death syndrome and found no association with SCT.

Surgery- or Trauma-Related Outcomes

The same 3 studies evaluated surgical complications and surgical length of stay. One (16) was rated as moderate quality for both outcomes, whereas 2 (47, 48) were rated as low quality. None found statistically significant differences in the number of surgical outcomes or length of stay between patients with and without SCT.

A single moderate-quality study (49) evaluated traumatic hyphema complications and found an increased prevalence of secondary hemorrhage after blunt eye trauma among African American children with and without SCT (64.3% vs. 0%).

Overall Mortality

Five studies assessed overall mortality. Three were graded as low quality (16, 50, 51) and 2 as very low quality (52, 53). None found an association between SCT and mortality.

Strength-of-Evidence Assessments

High-strength evidence suggests that SCT is a risk factor for VTE, PE, proteinuria, and CKD (Table). Moderate-strength evidence suggests that SCT is associated with exertional

rhabdomyolysis and that SCT is not a risk factor for DVT, stroke, heart failure, or low pediatric height or weight.

Discussion

The clinical consequences of SCT have long been the subject of controversy, from screening policies authorized by the government in the 1970s to the more recent mandate for screening of Division I to III athletes by the National Collegiate Athletic Association initiated in 2010 to 2012 (3, 54–56). These programs sparked speculation about adverse health outcomes related to SCT, which highlighted the need for a broad, evidence-based reevaluation of SCT. Our systematic review found insufficient or low-strength evidence for most speculated complications. We found high-strength evidence that SCT is a risk factor for VTE, PE, proteinuria, and CKD and moderate-strength evidence that it is associated with extreme exertion-related rhabdomyolysis. We also found moderate-strength evidence for a null association between SCT and risk for DVT, stroke, heart failure, and low pediatric height or weight.

Although exertion-related sudden death in persons with SCT, particularly in the military and athletics, has received considerable attention in the media and medical literature (8, 54, 57, 58), results varied among the few studies we found that evaluated this outcome. An early study from the 1980s (13) showed low absolute risk—but increased relative risk—for sudden death among military recruits with SCT, but the study was limited by its prevalence control design and lack of adjustment for confounders. No increased risk for sudden death was found in a more contemporary cohort of Army soldiers on active duty between 2011 and 2014 that was followed after the Army's adoption of universal precautions (acclimitization, hydration, and optimization of activity duration and recovery) (14). Studies that rigorously evaluated the risk for exertional death in athletics were lacking altogether. Although we rated the strength of evidence for exertion-related sudden death as low, we note that SCT may be associated with a small absolute risk for this outcome in extreme exertion-related conditions, such as are possible in military or highly strenuous athletic training. We do concur with the American Society of Hematology statement recommending against routine SCT screening in athletics and supporting the consistent use of universal precautions to mitigate exertion-related risk in all persons, regardless of SCT status (9). Similarly, although we found moderate-strength evidence that SCT is a risk factor for exertional rhabdomyolysis, we note that the absolute risk for this outcome is small, that it likely occurs only in high-intensity training settings, and that additional genetic and environmental factors probably modify the risk.

In addition, we found that although SCT is generally believed to be a risk factor for the rare complications of altitude-related splenic infarction, renal medullary carcinoma, and papillary necrosis (6), evidence was insufficient to assess degree of risk. We believe that the number of anecdotal reports and case series for these rare outcomes suggests a likely association with low absolute risk that warrants further study with appropriate control groups.

Venous and renal complications had the strongest body of evidence for an association with SCT. Several experimental studies have shown elevated procoagulant markers in persons

with SCT, providing biological plausibility for increased VTE risk (59–62). Our systematic review shows high-strength evidence for SCT's association with PE with and without DVT but moderate-strength evidence for no increased risk for isolated DVT in SCT carriers. The cause of this paradoxical observation is unknown but may be an increased risk for clot embolization in SCT (29). Nonetheless, the magnitude of increased risk for VTE and PE among SCT carriers compared with noncarriers seems to be about 1.5 to 2, a level similar to that found in low-risk thrombophilia, such as heterozygous prothrombin gene mutation or factor V Leiden; therefore, routine testing for SCT in VTE is not warranted. Future studies are needed to clarify modifiers of risk and rate of VTE recurrence in SCT.

Renal manifestations are among the most common outcomes attributed to SCT. In terms of chronic renal impairment, we found that SCT is a risk factor for both proteinuria and CKD. Prior injection radiographs have shown renal medullary vascular disruption in persons with SCT compared with those with normal hemoglobin, suggesting that chronic pathologic changes in SCT do occur (63). However, whether carriers are at risk for progression to ESRD is unknown.

Our systematic review has several strengths. Our literature searches of multiple databases identified no similar systematic reviews. We evaluated evidence for many complications that experts had considered to be relevant and to have strong implications for policy and clinical practice. We included only studies with accurate genotypic methods in our final review.

A major limitation of our review is the possibility of negative publication bias. Studies reporting positive (that is, statistically significant) results are overall more likely to be published than those with nonsignificant results. However, we did find some studies with null findings, especially in the category of growth in children. Other limitations include an overall lack of high-quality data and our exclusion of case reports and case series that may have provided additional understanding of SCT and clinical complications.

Around the world, millions of persons with SCT live without complications. In this systematic review, we found low-strength evidence or insufficient data for associations between SCT and most clinical outcomes. Several outcomes do have high- or moderate-strength evidence for a positive or null association with SCT. Future rigorous studies are needed to address potential complications of SCT and to determine modifiers of risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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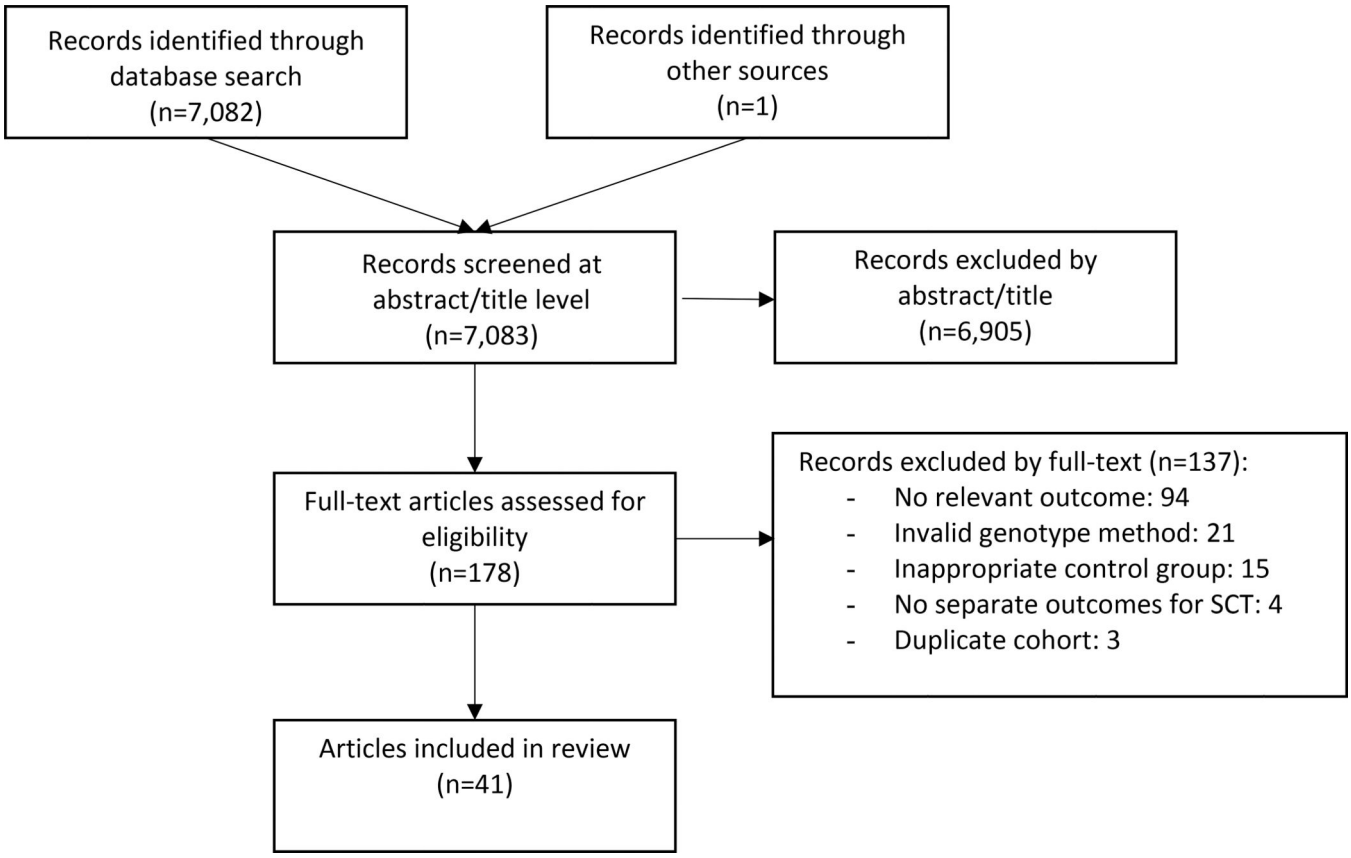

Figure.
Evidence search and selection.

Table.

Summary of the Evidence in SCT

Outcome	Strength of Evidence	Direction of Association With SCT*	Basis for Grade/Body of Evidence Limitations	Comments
Exertion-related				
Sudden death	Low	NA	2 moderate-quality studies with large sample sizes; largely discordant effect estimates	2 large military studies done in different eras, with very discordant effect estimates; early study with prevalence controls and no adjustment for confounders; no direct comparison of effect before and after universal precautions were used†
Exertional rhabdomyolysis	Moderate	Positive	2 studies (1 moderate quality with a large sample size); consistent positive effect direction	Small but significant increase in risk observed in a large modern military study with adjustment for most relevant confounders; consistent effect direction in the small study; no information on degree of exertion or environmental conditions
Splenic infarction	No evidence	NA	No studies included	None
Renal				
Hematuria	Low	NA	Single moderate-quality study with a large sample size and positive effect estimate	Measure of events by ICD-8 code only; no control for confounders; no validating study
Papillary necrosis	No evidence	NA	No studies included	None
Proteinuria	High	Positive	6 studies (1 high-quality multicohort study and 2 moderate-quality studies); consistent positive effect estimate	Large multicohort study with consistent effect estimates among included cohorts and adjustment for appropriate confounders; additional small validating studies
CKD	High	Positive	4 studies (2 high quality, including 1 multicohort); consistent positive effect estimates	2 large cohort studies with consistent effect estimates among included cohorts (for the multicohort study) and among studies, with adjustment for appropriate confounders
ESRD	Low	NA	5 studies (1 high quality, 2 moderate quality, and 2 very low quality); inconsistent effect estimates	3 well-performed studies with discordant effect estimates, with discordance even among prospective population-based cohort studies
Renal medullary carcinoma	No evidence	NA	No studies included	None
Vascular				
VTE	High	Positive	2 studies (1 high quality and 1 moderate quality); consistent positive effect estimates	Well-performed studies with consistent effect estimates and adjustment for appropriate confounders
PE	High	Positive	3 studies (1 high quality and 2 moderate quality); consistent positive effect estimates	Well-performed studies (2 subgroup analyses of VTE studies) with consistent effect estimates and adjustment for appropriate confounders
DVT	Moderate	Null	3 studies (2 moderate quality, large sample size); consistent null effect	Well-performed studies (2 subgroup analyses of VTE studies) with consistent null effect; sample size probably sufficient
Hypertension	Low	NA	5 studies (1 moderate quality and 1 very low quality); inconsistent effect estimates and direction	1 large study with null effect but inconsistent effect estimates among smaller studies; definitions of outcome differed

Outcome	Strength of Evidence	Direction of Association With SCT*	Basis for Grade/Body of Evidence Limitations	Comments
MI	Low	NA	Single moderate-quality study with large sample size and null effect	Measure of events by ICD-8 code only; no control for confounders; no validating study
Heart failure/cardiomyopathy	Moderate	Null	2 studies (1 moderate quality, multicohort, large sample size); consistent null effect	1 large multicohort study with largely consistent null effect among included cohorts and adjustment for relevant confounders; sample size probably sufficient
Stroke	Moderate	Null	2 studies (both high quality and 1 multicohort); the multicohort study had a null effect, and the other had a borderline positive effect estimate	Single-cohort study with borderline effect estimate; 1 large multicohort study with largely consistent null effect among included cohorts and adjustment for relevant confounders; sample size probably sufficient
Retinopathy	Low	NA	3 studies (1 very low quality); inconsistent effect estimates	Low-quality studies
Diabetic vasculopathy	Low	NA	Single study with null effect	Measure of events by ICD-8 code only; no control for confounders; no validating study
Pediatric				
Height/weight	Moderate	Null	8 studies (1 moderate quality with a large sample size); consistent null effect	1 study with a large sample size with appropriate age/sex stratification and null effect; consistent null effect among the many remaining studies; continuous height/weight variable; sample size probably sufficient
SIDS	Low	NA	Single low-quality study with null effect	Single low-quality study
Surgery-/trauma-related				
Surgical complications	Low	NA	Heterogeneous studies; null effect	Definitions of outcome differed
Surgical length of stay	Low	NA	Heterogeneous studies; null effect	Definitions of outcome differed
Complications of traumatic hyphema	Low	NA	Single small study with positive effect estimate	Small sample size; no validating study
Overall mortality				
Mortality	Low	NA	5 studies (3 low quality and 2 very low quality); null effect	Low-quality studies; most studies did not directly address mortality

CKD = chronic kidney disease; DVT = deep venous thrombosis; ESRD = end-stage renal disease; ICD-8 = International Classification of Diseases, Eighth Revision; MI = myocardial infarction; NA = not applicable; PE = pulmonary embolism; SCT = sickle cell trait; SIDS = sudden infant death syndrome; VTE = venous thromboembolism.

*For moderate or high strength-of-evidence ratings only.

†*Universal precautions* refers to such measures as acclimatization, hydration, and optimization of activity duration/recovery.