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Physical Impairment and Function in Children and Adolescents with Sickle Cell Disease: A Systematic Review

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Abstract

Objective: To examine the factors that underlie physical impairments and function is needed to develop targeted rehabilitation interventions. Thus, the purpose of this systematic review was to examine physical impairments and physical function in children and adolescents with sickle cell disease (SCD).

Data Sources: PubMed, Embase (embase.com), CINAHL (EBSCO), the Cochrane Central Register of Controlled Trials (Wiley), and Dissertations and Theses (ProQuest) were searched from January 1, 1990 to September 25, 2020. References retrieved were required to include a term for sickle cell disease and a term for physical impairments or physical function. Results were limited to articles with children and adolescents and in the English language.

Study Selection: A total of 3,054 non-duplicate articles were independently screened by two reviewers, resulting in 240 articles for full-text review. The full-text review, performed by two independent reviewers, resulted in 67 articles.

Data Extraction: Data was extracted from each full text to a custom Excel document by a single reviewer and was verified by a secondary reviewer.

Data Synthesis: The studies identified in this systematic review offer evidence that children and adolescents with SCD demonstrate physical impairments and physical function limitations compared to controls as noted by varying percentages in deficits up to 19–58% in muscle and bone

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7.Conflict of interests

The authors have no conflicts of interest to declare.

composition/symptoms, muscle strength, cardiopulmonary function, motor performance, physical activity, and physical function domains of quality of life questionnaires.

Conclusions: Children and adolescents with SCD present with physical impairments and physical function limitations. Scientists and clinicians should consider developing collaborative standards to define and objectively measure physical impairment and function in this population to comprehensively examine the underlying factors that contribute to physical impairments and function.

Keywords

sickle cell disease; physical impairment; physical function; pediatric; child; adolescent

Sickle cell disease (SCD) is the most common serious genetically-inherited condition identified by newborn screening in the United States with a rate of one in every 350 African American newborns, an estimated 2,000 children per year.[1,2] Over the first six months to 12 months of life, fetal hemoglobin transitions to adult hemoglobin S or C in infants with SCD leading to polymerization of abnormal hemoglobins and abnormally shaped red blood cells. These changes result in the conditions of hemoglobin SS disease (HbSS) or hemoglobin SC disease (HbSC) SCD, or sickle cell beta null ($HbS\beta^0$) or beta plus ($HbS\beta^+$) thalassemia. The sickled-form of hemoglobin causes improper blood flow and transportation of oxygen, known as sickle cell anemia. The sickle-shaped cells lack the flexibility needed to transverse circulation, are fragile, have a shortened life span, and have increased adhesiveness to vascular endothelium. This cascade causes vaso-occlusion in small blood vessels and local ischemia resulting in painful episodes, known as vaso-occlusive crises. Vaso-occlusive crises and anemia can lead to chronic damage to organs and tissues and an inflammatory cascade, causing further tissue damage of the bones (avascular necrosis and osteomyelitis), muscle (myonecrosis), brain (cerebral infarction), and lungs (acute chest syndrome, pulmonary hypertension, and chronic lung disease).[2–4] In combination, these factors can affect physical function such as walking, running, and jumping, thus limiting participation in school, play, and sports activities.[5–10]

SCD affects many body systems including physical impairments of the neuromuscular (pain, muscle tone, balance), musculoskeletal (strength, range of motion), and cardiopulmonary (endurance, energy expenditure) systems. Physical impairments can lead to deficits in physical function. Physical function is defined as, “the ability to perform the basic actions that are essential for maintaining independence and carrying out more complex activities.”[11] In children and adolescents with SCD, an increase in episodes and intensity of pain is associated with decreased physical function.[12] Decreased physical function is associated with an increased number of missed days of school and parental missed days of work.[13,14] Therefore, it is important to understand how SCD affects physical impairments and changes in physical function.

Evidence supports underlying factors contribute to physical impairments and function. Muscle extensibility, muscle size, and neuromuscular activation contribute to muscle strength and physical function in children and adolescents with differing health conditions. In children and adolescents with lower-extremity bone cancer, hemophilia, and cerebral

palsy, impairments in muscle extensibility and muscle size were correlated with muscle strength and physical function as measured by the Timed Up and Go, Timed Up and Down Stairs, 9-minute run-walk tests, Gross Motor Function Measure and gait characteristics.[15–18] In children without health conditions, neuromuscular activation influences early stages of strength development, which is important for physical function such as running and jumping.[19–21]

It is important to understand how SCD affects physical impairments and changes in physical function and to understand the factors that underlie physical impairments and function. Thus, the purpose of this systematic review was to identify literature published between 1990 and 2020 to examine physical impairments and physical function in children and adolescents with SCD to provide a basis for the development of targeted rehabilitation interventions for children and adolescents with SCD.

2. Methods

The systematic review procedures were guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and are registered in the PROSPERO (CRD42020220176). This review is exploratory; therefore, studies were not excluded based on quality.

2.1. Search Methods

Searches were run and constructed by a medical librarian (AGS) in PubMed, Embase (embase.com), CINAHL (EBSCO), the Cochrane Central Register of Controlled Trials (Wiley), and Dissertations and Theses (ProQuest). Each search was customized for the database and contained both keywords and controlled vocabulary. References retrieved were required to include a term for sickle cell disease and a term for physical impairments or physical function. The complete search algorithm is provided in Appendix 1. Search strategies included limits to studies with children and adolescents as subjects, in the English language, and published since 1990. This date range was selected due to the paucity of published articles prior to 1990. A total of 3,054 references were retrieved on September 25, 2020.

2.2. Inclusion criteria and study characteristics

Articles were included if the studies measured physical impairment, physical function, and/or quality of life measurements that include measurements of physical impairment and/or physical function. Studies had to be in the English language and published since 1990. The study population was children and adolescents with sickle cell disease between birth and 21 years of age. Studies with the following research design were included: (1) observational studies, (2) cross-sectional studies, (3) randomized experimental studies, (4) quasi-experimental studies, (5) case reports, (6) mix-methods, and (7) retrospective case studies.

2.3. Exclusion criteria

Studies were excluded if the study participants had underlying neurological disorders not related to the sickle cell disease diagnosis and if the participants had undergone a stem cell transplant. Studies reporting only pain and no other measures of physical impairment or limitation were excluded. Manuscripts with the following study design were excluded: (1) meta-analyses, (2) umbrella reviews, (3) systematic reviews, (4) narrative reviews, (5) position papers, (6) scoping reviews, (7) white paper/editorials, and (8) qualitative studies.

2.4. Article selection and data extraction

Titles and abstracts screening and full-text reviews were performed by two independent reviewers using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). If the two independent reviews did not agree, a third independent reviewer served as a tiebreaker. Data were extracted from each full text to a custom Microsoft Excel spreadsheet (Microsoft Corporation, Redmond, WA, USA) by a single reviewer and were verified by a secondary reviewer. Extraction data points included article information (author, title, year), study design, study objective, participant diagnoses, inclusion/exclusion criteria, number of participants, participant age range, outcome measures and data, and the comparison group. Clear protocol and instructions were provided for all steps of screening, selection, and extraction.

3. Results

The search strategy resulted in 3,054 non-duplicate articles; 67 studies were included in the synthesis. The PRISMA flow diagram is outlined in Figure 1. Of the excluded studies, the most common study designs were narrative reviews and position papers. The resultant 67 studies included 50 cross-sectional observational studies, 12 longitudinal studies, three case studies, one mixed-methods study, and one quasi-experimental study related to physical impairment and physical function outcomes.

Of the three case studies, two explored the range of motion of the hip before and after casting and surgical management for a dislocated hip replacement and a slipped capital femoral epiphysis, respectively.[22,23] The third case study described a differential diagnosis of autoimmune rheumatic disorders in SCD.[24] These case studies represent unique diagnoses and therefore were not discussed in this review. Seven studies included health-related quality of life surveys but did not report results related to specific physical impairments or limitations.[14,25–30] Therefore, these seven studies will not be discussed any further.

The remaining 57 studies had components related to physical impairments and physical function limitations. Of the 57 studies, one study included interventions specifically targeting physical impairments and physical function limitations.[31] Only baseline data is reported for longitudinal studies.

3.1. Body Structure and Function Impairments

3.1.1. Muscle and Bone Composition/Symptoms—Changes in muscle and bone composition in children with SCD were described in two studies[32,33] and musculoskeletal symptoms were reported in three studies.[10,34] Children with SCD, compared to children without SCD, presented with a reduction of lean muscle mass (5 to 18%), bone density (3 to 6%), bone mineral content (7%), and bone area (6%).[32,33,35] Musculoskeletal symptoms of joint stiffness (16% to 19%), decreased flexibility, and muscle tenderness (8%) were reported by children and adolescents with SCD (Table 1).[10,34–36]

3.1.2. Muscle Strength—Children and adolescents with SCD present with impaired muscle strength. Muscle strength was an outcome measure in eight studies (Table 2).[10,35,37–42] Compared to controls, children and adolescents with SCD presented with a significant reduction in maximal handgrip strength (4 to 43%), vertical jump peak power (24 to 29%), jump height (10 to 23%), ankle plantarflexion torque (17 to 37%), and back strength (7 to 25%).[10,35,38–40] Generalized weakness was reported in 14 to 88% of children and adolescents with SCD.[41,42]

3.1.3. Cardiopulmonary Function—Ten studies included outcomes of cardiopulmonary function (Table 3).[8,9,31,33,43–48] Children and adolescents with SCD presented with impaired cardiopulmonary function at rest, during maximal and submaximal cardiopulmonary testing, and these impairments may be amenable to exercise intervention. Compared to healthy controls, children and adolescents with SCD presented with impaired resting cardiopulmonary function. The cardiopulmonary function was measured during rest and/or exercise through vital signs (heart rate, respiratory rate, blood pressure, pulse oximetry), and blood and gas properties. Children and adolescents with SCD presented with higher resting heart rate and metabolic rate, and impaired adjusted resting energy expenditure and activity-related energy expenditure.[33,43,44,48] Pulmonary blood flow and stroke volume were consistently greater in children and adolescents with SCD compared to controls at rest, during exercise, and during recovery.[45] Arteriovenous oxygen was consistently one-third lower in SCD compared to controls.[45] However, no ventilatory differences were detected.[45]

During maximal and submaximal cardiopulmonary testing, children and adolescents with SCD performed poorer than controls. During maximal cardiopulmonary exercise testing, using cycle ergometer, children and adolescents with SCD demonstrated reduced total exercise time (28%), peak work rate (29%), weight-adjusted peak VO_2 max (27%), and ventilatory threshold (23%) and efficiency (9%) compared to controls.[46,47] Impaired gas exchange and impaired oxygen uptake and delivery compared to controls were also observed.[46,47] After the 6-minute walk test (6MWT), children with SCD reported higher rates of perceived exertion (4.1 out of 10) as compared to controls (1.2).[9] Children with HbSS/HbSβ^0 presented with decreased pulse oximetry and increased respiratory rate compared to children with HbSC/HbSβ^+.[8]

A single intervention study by Liem et al. (2017) explored a 12-week individualized cardiovascular exercise training program for adolescents with SCD. The adolescents were

prescribed three exercise sessions per week for 12 weeks on a stationary bicycle at the participant's home.[31] The training protocol was progressed throughout the duration of the intervention by increasing goals for target heart rate and duration of exercise.[31] Participants demonstrated an increased mean peak rate of oxygen consumption (VO_2) and peak workload after the first seven weeks of training.[31] However, there was no significant improvement in exercise parameters, including maximal VO_2, peak workload, and ventilatory threshold, at the end of the training program.[31] In this study, 77% of the subjects completed 89% of prescribed sessions without exercise-related adverse events.[31]

3.2. Physical Function

3.2.1. Motor Performance—Gross motor and fine motor performance were measured in 17 studies (Table 4).[5,6,51–57,7–10,37,39,49,50] The results of these studies suggest children and adolescents with SCD may present with deficits in motor performance.

In three studies, infants' and toddlers' gross motor performance was measured by the Bayley Scale of Infant Development.[49,50,52] Drazen et al. (2016) reported, as compared to a normative population, infants and toddlers with SCD present with below-average performance in fine motor (31.7%) and gross motor (32.6%) performance. However, Armstrong et al. (2013) and Glass et al. (2013) reported on average, infants and toddlers with SCD did not present with motor delay. One study in children with SCD using the Vineland Adaptative Behavior Scale (VABS) motor scale, reported lower age-adjusted motor scores at 32–40 months of age compared to 12–18 months of age.[55]

Two studies reported motor performance using the Bruininks-Oseretsky Test of Motor Proficiency (BOT) Short Form to quantify motor proficiency with baseline scores in children and adolescents with SCD.[37,39] The mean BOT score in children and adolescents with SCD was reported as 62 to 67 out of 88 compared to 62 in controls.[37,39] Burkhardt (2017) and Newby et al. (2018) explored fine motor performance in children with SCD. Burkhardt et al. (2017) found children and adolescents with SCD presented with impaired fine motor function, whereas Newby et al. (2018) reported children with SCD performed average for fine motor dexterity.[51,54]

Motor performance was reported to be impaired in children and adolescents with SCD performing tasks required for participation in school, play, and sports activities. While performing the 6MWT, children and adolescents with SCD performed below norm-referenced distances (72 to 83% of predicted distance).[5–9] Children with SCD had poorer performance on the 20-yard swim, 40-yard swim, 100-yard "potato race", and jump height compared to age- and sex-matched controls.[10,53] Zempky et al. (2013, 2014) measured physical function via Functional Independence Measure (FIM) with baseline motor scores of 54 to 57 out of 91 in children and adolescents with SCD during vaso-occlusive pain episodes. During hospitalizations, children and adolescents with SCD demonstrated improvements in physical function from initial FIM scores at admission to before discharge.[56]

3.2.2 Physical Activity—In four studies, physical activity was used as an outcome measure (Table 5).[44,48,58,59] Physical activity has been defined as bodily movements

produced by skeletal muscles that require energy expenditure.[60] Physical activity was measured using accelerometers, heart rate monitors, metabolic parameters, or surveys. Children and adolescents with SCD present with decreased amount and level of physical activity by 24 to 58% and spend more time at lower physical activity intensities with mean physical activity at light intensity.[44,48,58,59]

3.3 Health-related Quality of Life: Physical Function

Of the resultant studies, 28 analyzed reported health-related quality of life questionnaires with domains of physical function or mobility (Table 6).[7,9,64–73,12,74–81,13,39,57,59,61–63] These questionnaires included: the Patient-Reported Outcome Measurement Information System (PROMIS), Pediatric Quality of Life Inventory (PedsQL), Functional Disability Inventory (FDI), Child Health Questionnaire (CHQ), Physical Activity Questionnaire for Older Children and Adolescents (PAQ-C), Barthel Index for Activities of Daily Living (Barthel Index), 36-Item Short Form Health Survey (SF-36), Child Activities Limitations Interview (CALI), EUROQOL, Youth Acute Pain Functional Ability Questionnaire (YAPFAQ), National Health and Nutrition Survey (NHANES), International Physical Activity Questionnaire (IPAQ), Child Physical Activity Questionnaire, and a self-designed questionnaire. Physical function using questionnaires were used to assess differences between children and adolescents with SCD compared to controls (healthy or with the sickle-cell trait), to assess differences between SCD groups with medical or symptomatic conditions, and to provide objective measurements at baseline for SCD samples.

Compared to controls, children and adolescents with SCD present with a significant deficit of physical function (17%; SF-36), physical activity (49–51%; PAQ-C, NHANES, IPAQ), physical function (39 to 55%; PedsQL), and physical functioning (17%) and physical role impact (19%; CHQ).[7,9,59,61,67,68,70,80] Children and adolescents with SCD presented with poorer upper extremity function by 9% and lower extremity function by 8% as measured by the PROMIS compared to controls.[39] Children and adolescents without health conditions reported “no problems” with mobility, however, 24% of children and adolescents with SCD reported “problems on some days” with mobility as measured by the EUROQOL.[39,72] As compared to normative samples, children and adolescents with SCD presented within the normative range for the CHQ and PROMIS measures of mobility and upper extremity dexterity.[12,62,79] Children and adolescents with SCD reported lower levels of physical activity on the IPAQ and NHANES compared to controls.[7,80] Although most studies did not explore relationships between age and physical function, PedsQL data from Menenez et al. (2008)[68] suggest that younger children (5–7 years of age) report less percentage of physical function deficits compared to controls (39%) than older children (8–12 years of age; 49%) and adolescents (13–18 years of age; 55%).

Seven studies assessed differences in self-reported physical function between SCD groups with medical or symptomatic conditions including migraine/headaches, hip dysfunction, pain patterns, and those receiving and not receiving hydroxyurea. Palermo et al. (2005) studied children and adolescents with SCD who presented migraine ± aura, tension headache, or no headache. This study reported a significant difference in functional disability, as measured by the FDI, between migraine and tension headache, and migraine

and no headache groups.[81] Malheiros et al. (2015) compared children and adolescents with and without hip dysfunction using the Barthel Index and PedsQL. Those with hip dysfunction reported significantly lower physical activity compared to those without hip dysfunction, but no differences were noted in activities of daily living.[66] Sil et al. (2016, 2020) compared children and adolescents with SCD with varying frequencies of pain. This study identified significantly lower functional disability scores on the FDI in those with no pain compared to episodic pain, and no pain compared to chronic pain.[73,74] Using the PROMIS measure, Singh et al. (2019, 2020) assessed physical activity and strength impact in children and adolescents with SCD who received or did not receive pain medication in the prior week, and varying levels of pain. Pain medication status and pain level did not affect physical activity, but those who received pain medicine in the past week and those with higher pain scores reported lower strength impact scores.[75,76] Thornburg et al. (2011) reported significantly higher physical function as measured by the PedsQL in children and adolescents with SCD on hydroxyurea compared to those not on hydroxyurea.

The remaining 10 articles including health-related quality of life questionnaires related to physical function reported raw baseline values for the FDI, YAPFAQ, PedsQL, CALI, CHQ, Child Physical Activity Questionnaire, and a self-made questionnaire.[13,57,62–65,69,71,77,78]

4. Discussion

The studies identified in this systematic review offer emerging evidence that children and adolescents with SCD demonstrate physical impairments and physical function limitations related to muscle and bone composition/symptoms, muscle strength, cardiopulmonary function, motor performance, physical activity, and physical function domains of quality of life questionnaires. The manuscripts included utilized a variety of outcomes and procedures to measure physical impairment and physical function. Objective measurements of physical impairments and function were used in 47% of the studies. Subjective child and/or parent proxy reports were used in 47% of the studies. A combination of both objective and subjective measurements of physical impairment and physical function were used in 5.3% of the studies.

The body structure and function impairments identified in this review begin in childhood and progress well into adulthood including muscle and bone composition and cardiopulmonary function. Young adult women (mean age of 31 years) with SCD demonstrate a high mean percentage of fat, low fat-free mass, and low bone mineral density despite average weight and bone mass indexes.[82] Similarly, low bone mineral density is prevalent in 80% of young adults with SCD (mean age of 36 years), where the lumbar spine is the most common site.[83] This high incidence of low bone mineral density may be attributed to the failure of children and adolescents with SCD to obtain optimal peak bone mass during growth.[83,84] Factors including female sex, older age, higher body mass index, and lower hemoglobin levels demonstrated relationships with lower fitness levels as measured by maximal treadmill exercise testing in a large sample of adults (mean age of 43 years) with SCD from the Cooperative Study of Sickle Cell Disease.[85] Therefore, the early identification of physical impairments and initiation of targeted interventions in

individuals with SCD during childhood and adolescence may have the potential to influence the physical impairment and function into adulthood.

Few published studies focus on factors that influence physical function besides pain in children and adolescents with SCD.[21,86,87] Although pain impacts physical function,[56] other factors such as changes in muscle force production and muscle power can affect physical function in children.[21,87] In SCD, muscle hypoxia affects muscle remodeling, which could lead to impaired force production.[4] Muscle performance capacity can be quantified through measurements of peak muscle force or joint torque.[88] Factors contributing to muscle force production include not only muscle size (muscle thickness, cross-sectional area, volume), but also neuromuscular activation (amplitude of activation, rate of activation, rate force development) as measured by electromyography and dynamometry. Muscle size is associated with the ability to produce maximal strength.[89] Measurements of neuromuscular activation, such as the rate of muscle activation, can be measured through electromyography and may be critical in not only the ability to produce maximal strength but also the quick and coordinated movements required in many physical function activities.[20,21] In populations other than SCD, relationships between underlying factors and physical function are well-studied. For example, in children and adolescents with childhood cancer undergoing treatment for acute lymphoblastic leukemia, strength was significantly associated with physical function.[90,91] The Timed Up and Go test was correlated with knee extension strength, and the Timed Up and Down Stairs and the 9-Minute Run-Walk tests were correlated with ankle dorsiflexion strength.[90,91] Interventions focusing on muscle force production in healthy children and adolescents improve performance in physical function activities, such as running, jumping, and throwing.[92,93] Thus, further exploration of strength and the underlying factors are warranted in children and adolescents of SCD.

This systematic review did not identify any published articles related to balance function in children and adolescents with SCD, even though balance deficits can occur due to impaired perfusion to the brain and downstream dysfunction in the neuromuscular system.[94] Silva et al. (2018) identified deficits in balance in adults with SCD without known neurological involvement compared with healthy controls.[94] Deficits in balance in children and adolescents are measured through static, dynamic, transfer, and mobility testing.[95] Balance assessment can be performed through timing tasks (single leg stance, timed up and go), performing standardized testing (BOT-2 balance subscale, Berg Balance Scale), or using specialized force plates to measure a child or adolescent's center of pressure during tasks (limits of stability, Modified Clinical Test of Sensory Interaction in Balance).[95,96] In children and adolescents, deficits in balance have been associated with impaired physical function.[97] Therefore, the underlying factors that contribute to balance need to be thoroughly examined in children and adolescents with SCD to assist in the development of targeted intervention programs aimed to improve physical function.

There are very few rehabilitation intervention studies in children and adolescents with SCD. One intervention study was identified through this systematic review. Besides the one pediatric study included in our review,[31] we identified a manuscript published outside of this systematic review's date range. Alcorn et al. (1984)[98] explored the range of motion, gait, and length of hospitalization in children and adolescents with SCD hospitalized for

painful vaso-occlusive crises. The intervention included heat fluidotherapy twice daily, initiated on hospital day two. Once ambulatory, the children and adolescents participated in moderate strength and endurance exercise in 10-to-30 minutes durations that included recreational gymnastics, stationary bike riding, and games.[98] The authors concluded exercise and heat therapy may contribute to a reduction in the length of hospitalization in children and adolescents with SCD and painful vaso-occlusive crises.[98] Both the Liem et al. (2017) and Alcorn et al. (1984) studies demonstrate children and adolescents can improve with a focused intervention program. There is a significant need for further study for rehabilitation interventions targeting physical impairment and physical function in children and adolescents with SCD.

Many of the studies identified in this systematic review included questionnaires as the main measure of physical function. Questionnaires offer a reliable and valid method for obtaining subjective information regarding physical function. However, children and adolescents often report higher physical function compared to their caregiver's reports.[13,62,65,69,71] Although questionnaires have practical and clinical utility, using questionnaires only without an objective assessment measure of physical impairment and function may not provide the comprehensive picture required for measuring change over time in response to a targeted intervention. Objective measures provide specific information about a participant's body structure function and physical function that can be directly compared to controls and used to measure change over time. Discrepancies between subjective and objective measurements favor the use of objective measurements or a combination of these two types of measurement methods for children and adolescents.[99,100] Therefore, the results from this systematic review support the utility of both methods of measurement when examining physical impairments and physical function in children and adolescents with SCD.

Disease-modifying medical management, such as hydroxyurea, shows promise in the reduction of physical symptoms and serious medical complications of SCD,[101] thus may also demonstrate a role in the reduction of physical impairments and improvements in physical function. Hydroxyurea is an antimetabolite medication, which has the capacity to increase fetal hemoglobin production thus decreasing the likelihood of red blood cell sickling.[101] Wali & Moheeb (2011)[35] report that hydroxyurea not only increased hemoglobin concentrations in adolescents with SCD but also improved physical fitness, as measured by mean heart rate and non-fatigued time on a treadmill test. The physical fitness of these children and adolescents with SCD after taking hydroxyurea for a minimum of two years was more similar to controls compared to their non-medicated baseline.[35] Thornburg et al. (2011)[77] studied the health-related quality of life in children and adolescents with SCD receiving hydroxyurea compared to those not receiving hydroxyurea. After adjusted for age, sex, and SCD genotype and disease severity, children and adolescents receiving hydroxyurea reported greater PedsQL total and physical functioning scores compared to their non-medicated peers.[77] The use of hydroxyurea also benefits other areas of health-related quality of life including social function, pain recall, general health perception.[102] According to Badawy et al. (2017), higher levels of adherence in taking hydroxyurea suggest a better health-related quality of life in adolescents and young adults with SCD.[103] Further studies are needed to explore the potential effects of hydroxyurea therapy on physical impairments and function in children and adolescents with SCD.

The findings of this systematic review, with a detailed search strategy across multiple search engines, highlight the breadth of physical impairments and physical function limitations experienced by children and adolescents with SCD. This review identified that many previous studies have relied heavily on health-related quality of life questionnaires and identified gaps in evidence including skeletal muscle properties and performance, gross motor performance, and balance. Additionally, the relationships between physical impairments and gross motor performance have not been explored. These findings can help to provide a basis for clinical practice, and future research exploring objective measurement of physical impairments and function in this unique population. With an increased understanding of how SCD and its management affects physical impairments and function, clinicians and rehabilitation scientists can explore the effects of targeted interventions to mitigate these adverse effects. This review has also identified the need for rehabilitation scientists and clinicians to develop collaborative standards to define and objectively measure changes in physical impairment and function to allow for data analysis of larger samples of children and adolescents with SCD.

4.1. Study Limitations

This systematic review explored manuscripts related to physical impairments and physical function in children and adolescents with SCD published since 1990. Although the search strategy was comprehensive, we were able to identify an intervention study outside the date range for this systematic review search. Therefore, a larger search range may have improved capturing the full breadth of literature for this specific population. The systematic search strategy of this review excluded grey literature and manuscripts not published in the English language. This review was exploratory, and due to the heterogeneity of study designs, participant characteristics, and outcome measurements across studies, a meta-analysis was not performed.

5. Conclusions

This systematic review identified 57 articles supporting that children and adolescents with SCD present with physical impairments and physical function limitations. Further research is needed to comprehensively examine the underlying factors that contribute to physical impairments and function in children and adolescents with SCD. Further studies exploring the factors contributing to physical impairments and physical function in children and adolescents with SCD will support the development of targeted intervention programs that aim to improve physical performance. Additionally, rehabilitation scientists and clinicians should consider developing collaborative standards to define and objectively measure changes in physical impairment and function experienced by children and adolescents with SCD.

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Appendix 1.: Search Strategies

[Limits: publication date: 1990-present, English language]

PubMed

("anemia, sickle cell"[mesh] OR sickle cell[tiab] OR sickle anemia[tiab] OR sickle anaemia[tiab] OR hemoglobin S disease[tiab] OR haemoglobin S disease[tiab] OR hemoglobin SS[tiab] OR haemoglobin SS[tiab] OR hemoglobin SC[tiab] OR haemoglobin SC[tiab] OR hemoglobin SD[tiab] OR haemoglobin SD[tiab] OR SCA[tiab] OR sicklemia[tiab] OR sicklaemia[tiab] OR sickling[tiab] OR drepanocyt*[tiab])

AND

(muscle tone[tiab] OR spasticity[tiab] OR hemiparesis[tiab] OR haemiparesis[tiab] OR ataxi*[tiab] OR proprioception[tiab] OR kinesthesi*[tiab] OR kinaesthesi*[tiab]OR static balance[tiab] OR dynamic balance[tiab] OR sitting balance[tiab] OR standing balance[tiab] OR range of motion[tiab] OR flexibility[tiab] OR extensibility[tiab] OR contracture[tiab] OR gait[tiab] OR muscle strength[tiab] OR weakness[tiab] OR muscle force[tiab] OR torque[tiab] OR musc* power[tiab] OR functional strength[tiab] OR muscle activation[tiab] OR neuromuscular activation[tiab] OR electromyography[tiab] OR muscle size[tiab] OR muscle architecture[tiab] OR posture[tiab] OR scoliosis[tiab] OR lordosis[tiab] OR kyphosis[tiab] OR physical function*[tiab] OR motor function*[tiab] OR muscle function*[tiab] OR gross motor[tiab] OR fine motor[tiab] OR motor performance[tiab] OR physical performance[tiab] OR sports[tiab] OR physical activity[tiab] OR endurance[tiab] OR fatigue[tiab] OR fitness[tiab] OR exercise capacity[tiab] OR functional capacity[tiab] OR exertion[tiab] OR developmental delay*[tiab] OR neurodevelopmental delay*[tiab] OR functional status[tiab] OR functional disability[tiab] OR motor deficit*[tiab] OR physical deficit*[tiab] OR exercise tolerance[tiab] OR "exercise tolerance"[mesh] OR "exercise test"[mesh] OR "motor activity"[mesh] OR "musculoskeletal physiological phenomena"[mesh] OR "muscle spasticity"[mesh] OR "paresis"[mesh] OR "proprioception"[mesh] OR "muscle weakness"[mesh] OR "scoliosis"[mesh] OR "lordosis"[mesh] OR "kyphosis"[mesh] OR "motor skills"[mesh])

NOT

(adult[mesh] NOT (adolescent[mesh] OR child[mesh] OR infant[mesh]))

Embase (embase.com)

('sickle cell anemia'/exp OR 'sickle cell':ab,ti OR 'sickle anemia':ab,ti OR 'sickle anaemia':ab,ti OR 'hemoglobin S disease':ab,ti OR 'haemoglobin S disease':ab,ti OR 'hemoglobin SS':ab,ti OR 'haemoglobin SS':ab,ti OR 'hemoglobin SC':ab,ti OR 'haemoglobin SC':ab,ti OR 'hemoglobin SD':ab,ti OR 'haemoglobin SD':ab,ti OR SCA:ab,ti OR sicklemia:ab,ti OR sicklaemia:ab,ti OR sickling:ab,ti OR drepanocyt*:ab,ti)

AND

('muscle tone':ab,ti OR spasticity:ab,ti OR hemiparesis:ab,ti OR haemiparesis:ab,ti OR ataxi*:ab,ti OR proprioception:ab,ti OR kinesthesi*:ab,ti OR kinaesthesi*:ab,ti OR 'static balance':ab,ti OR 'dynamic balance':ab,ti OR 'sitting balance':ab,ti OR 'standing balance':ab,ti OR 'range of motion':ab,ti OR flexibility:ab,ti OR extensibility:ab,ti OR contracture:ab,ti OR gait:ab,ti OR 'muscle strength':ab,ti OR weakness:ab,ti OR 'muscle force':ab,ti OR torque:ab,ti OR 'musc* power':ab,ti OR 'functional strength':ab,ti OR 'muscle activation':ab,ti OR 'neuromuscular activation':ab,ti OR electromyography:ab,ti OR 'muscle size':ab,ti OR 'muscle architecture':ab,ti OR posture:ab,ti OR scoliosis:ab,ti OR lordosis:ab,ti OR kyphosis:ab,ti OR 'physical function*':ab,ti OR 'motor function*':ab,ti OR 'muscle function*':ab,ti OR 'gross motor':ab,ti OR 'fine motor':ab,ti OR 'motor performance':ab,ti OR 'physical performance':ab,ti OR sports:ab,ti OR 'physical activity':ab,ti OR endurance:ab,ti OR fatigue:ab,ti OR fitness:ab,ti OR 'exercise capacity':ab,ti OR 'functional capacity':ab,ti OR exertion:ab,ti OR 'developmental delay*':ab,ti OR 'neurodevelopmental delay*':ab,ti OR 'functional status':ab,ti OR 'functional disability':ab,ti OR 'motor deficit*':ab,ti OR 'physical deficit*':ab,ti OR 'exercise tolerance':ab,ti OR 'muscle characteristics and function'/exp OR spasticity/de OR hemiparesis/de OR 'motor dysfunction'/exp OR proprioception/de OR kinesthesia/de OR 'body equilibrium'/de OR 'range of motion'/de OR 'muscle strength'/de OR scoliosis/de OR lordosis/de OR kyphosis/exp OR 'physical activity'/exp OR 'physical capacity'/exp OR 'physical performance'/exp OR endurance/de OR fitness/de OR exercise/exp OR 'functional status'/de OR 'exercise test'/exp OR 'motor activity'/exp)

NOT

(([adult]/lim OR [aged]/lim) NOT ([newborn]/lim OR [infant]/lim OR [child]/lim OR [adolescent]/lim))

NOT

[conference abstract]/lim

CINAHL (EBSCO)

(TI ("sickle cell" OR "sickle anemia" OR "sickle anaemia" OR "hemoglobin S disease" OR "haemoglobin S disease" OR "hemoglobin SS" OR "haemoglobin SS" OR "hemoglobin SC" OR "haemoglobin SC" OR "hemoglobin SD" OR "haemoglobin SD" OR SCA OR sicklemia OR sicklaemia OR sickling OR drepanocyt*) OR AB ("sickle cell" OR "sickle anemia" OR "sickle anaemia" OR "hemoglobin S disease" OR "haemoglobin S disease" OR "hemoglobin SS" OR "haemoglobin SS" OR "hemoglobin SC" OR "haemoglobin SC" OR "hemoglobin SD" OR "haemoglobin SD" OR SCA OR sicklemia OR sicklaemia OR sickling OR drepanocyt*) OR (MH "anemia, sickle cell+"))

AND

(TI ("muscle tone" OR spasticity OR hemiparesis OR haemiparesis OR ataxi* OR proprioception OR kinesthesi* OR kinaesthesi* OR "static balance" OR "dynamic balance" OR "sitting balance" OR "standing balance" OR "range of motion" OR flexibility OR

extensibility OR contracture OR gait OR “muscle strength” OR weakness OR “muscle force” OR torque OR “musc* power” OR “functional strength” OR “muscle activation” OR “neuromuscular activation” OR electromyography OR “muscle size” OR “muscle architecture” OR posture OR scoliosis OR lordosis OR kyphosis OR “physical function*” OR “motor function*” OR “muscle function*” OR “gross motor” OR “fine motor” OR “motor performance” OR “physical performance” OR sports OR “physical activity” OR endurance OR fatigue OR fitness OR “exercise capacity” OR “functional capacity” OR exertion OR “developmental delay*” OR “neurodevelopmental delay*” OR “functional status” OR “functional disability” OR “motor deficit*” OR “physical deficit*” OR “exercise tolerance”)) OR (AB (“muscle tone” OR spasticity OR hemiparesis OR haemiparesis OR ataxi* OR proprioception OR kinesthesi* OR kinaesthesi* OR “static balance” OR “dynamic balance” OR “sitting balance” OR “standing balance” OR “range of motion” OR flexibility OR extensibility OR contracture OR gait OR “muscle strength” OR weakness OR “muscle force” OR torque OR “musc* power” OR “functional strength” OR “muscle activation” OR “neuromuscular activation” OR electromyography OR “muscle size” OR “muscle architecture” OR posture OR scoliosis OR lordosis OR kyphosis OR “physical function*” OR “motor function*” OR “muscle function*” OR “gross motor” OR “fine motor” OR “motor performance” OR “physical performance” OR sports OR “physical activity” OR endurance OR fatigue OR fitness OR “exercise capacity” OR “functional capacity” OR exertion OR “developmental delay*” OR “neurodevelopmental delay*” OR “functional status” OR “functional disability” OR “motor deficit*” OR “physical deficit*” OR “exercise tolerance”))

NOT

((MH “adult+”) NOT (MH “adolescence+” OR MH “child+”))

Cochrane Central Register of Controlled Trials (Wiley)

(“sickle cell” OR “sickle anemia” OR “sickle anaemia” OR “hemoglobin S disease” OR “haemoglobin S disease” OR “hemoglobin SS” OR “haemoglobin SS” OR “hemoglobin SC” OR “haemoglobin SC” OR “hemoglobin SD” OR “haemoglobin SD” OR SCA OR sicklemia OR sicklaemia OR sickling OR drepanocyt*):ti,ab,kw

AND

(“muscle tone” OR spasticity OR hemiparesis OR haemiparesis OR ataxi* OR proprioception OR kinesthesi* OR kinaesthesi* OR “static balance” OR “dynamic balance” OR “sitting balance” OR “standing balance” OR “range of motion” OR flexibility OR extensibility OR contracture OR gait OR “muscle strength” OR weakness OR “muscle force” OR torque OR “musc* power” OR “functional strength” OR “muscle activation” OR “neuromuscular activation” OR electromyography OR “muscle size” OR “muscle architecture” OR posture OR scoliosis OR lordosis OR kyphosis OR “physical function*” OR “motor function*” OR “muscle function*” OR “gross motor” OR “fine motor” OR “motor performance” OR “physical performance” OR sports OR “physical activity” OR endurance OR fatigue OR fitness OR “exercise capacity” OR “functional capacity” OR

exertion OR “developmental delay*” OR “neurodevelopmental delay*” OR “functional status” OR “functional disability” OR “motor deficit*” OR “physical deficit*” OR “exercise tolerance”):ti,ab,kw

Dissertations and Theses (ProQuest)

AB,TI(“sickle cell” OR “sickle anemia” OR “sickle anaemia” OR “hemoglobin S disease” OR “haemoglobin S disease” OR “hemoglobin SS” OR “haemoglobin SS” OR “hemoglobin SC” OR “haemoglobin SC” OR “hemoglobin SD” OR “haemoglobin SD” OR SCA OR sicklemia OR sicklaemia OR sickling OR drepanocyt*)

AND

AB,TI(“muscle tone” OR spasticity OR hemiparesis OR haemiparesis OR ataxi* OR proprioception OR kinesthesi* OR kinaesthesi* OR “static balance” OR “dynamic balance” OR “sitting balance” OR “standing balance” OR “range of motion” OR flexibility OR extensibility OR contracture OR gait OR “muscle strength” OR weakness OR “muscle force” OR torque OR “musc* power” OR “functional strength” OR “muscle activation” OR “neuromuscular activation” OR electromyography OR “muscle size” OR “muscle architecture” OR posture OR scoliosis OR lordosis OR kyphosis OR “physical function*” OR “motor function*” OR “muscle function*” OR “gross motor” OR “fine motor” OR “motor performance” OR “physical performance” OR sports OR “physical activity” OR endurance OR fatigue OR fitness OR “exercise capacity” OR “functional capacity” OR exertion OR “developmental delay*” OR “neurodevelopmental delay*” OR “functional status” OR “functional disability” OR “motor deficit*” OR “physical deficit*” OR “exercise tolerance”)

List of abbreviations:

6MWT	6-minute walk test
Barthel Index	The Barthel Index for Activities of Daily Living
BOT	Bruininks-Oseretsky Test of Motor Proficiency
CALI	Child Activities Limitations Interview
CHQ	Child Health Questionnaire
FDI	Functional Disability Inventory
FIM	Functional Independence Measure
HbSC	hemoglobin SC disease
HbSS	hemoglobin SS disease
HbSβ^+	sickle cell beta plus thalassemia
HbSβ^0	sickle cell beta null thalassemia

IPAQ	International physical activity questionnaire
NHANES	National Health and Nutrition Examination Survey
PAQ-C	Physical Activity Questionnaire for Older Children and Adolescents
PedsQL	Pediatric Quality of Life Inventory
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROMIS	Patient-Reported Outcome Measurement Information System
SCD	Sickle cell disease
SF-36	36-Item Short Form Health Survey
VO_2	Rate of oxygen consumption
YAPFAQ	Youth Acute Pain Functional Ability Questionnaire

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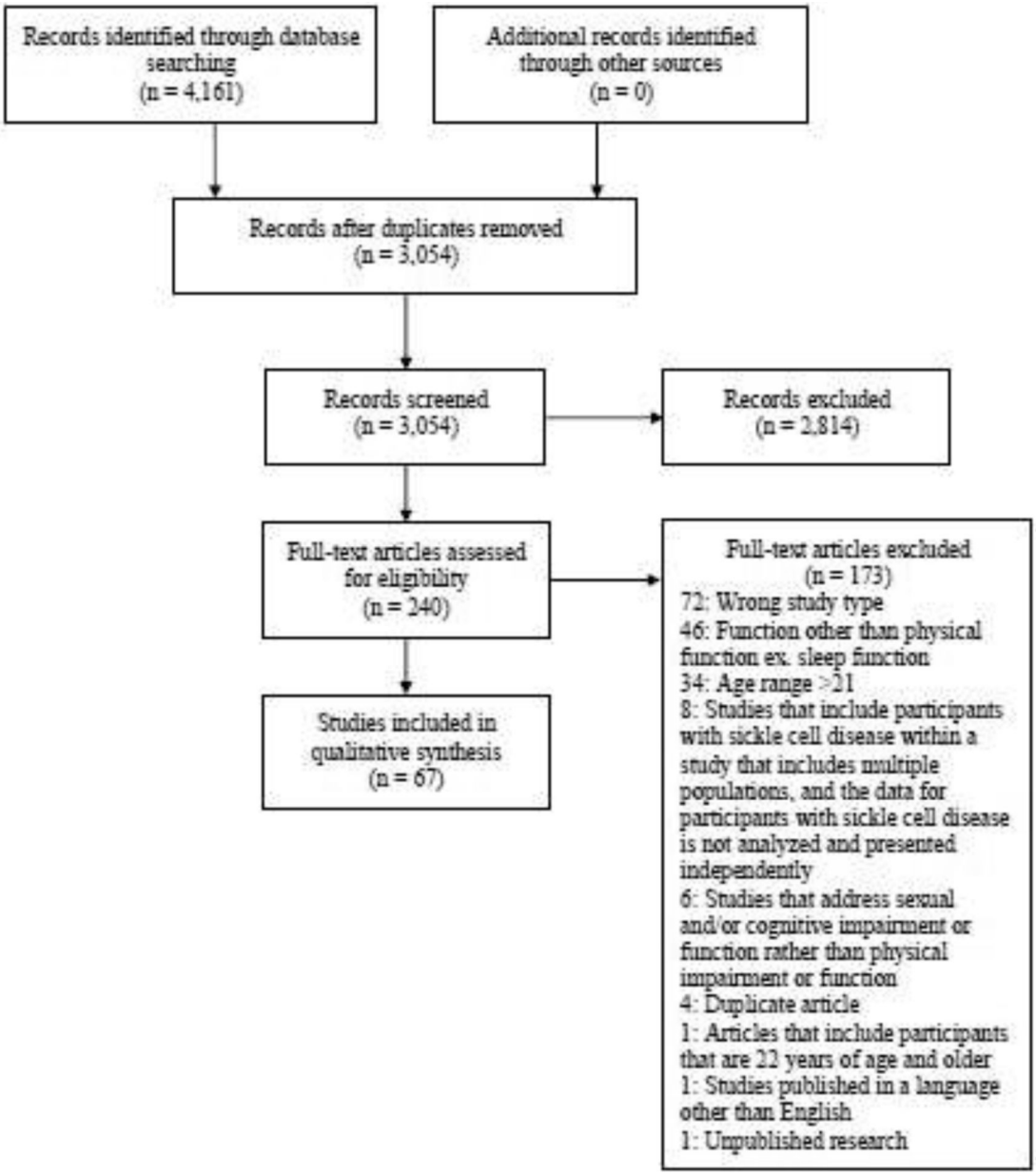

Figure 1.

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Chart

Table 1.

Muscle and Bone Composition/Symptoms

Study	N	Age range/ mean	Diagnoses	Non-SCD Control	Relevant Outcome Measures	Findings Related to Physical Impairments and Function
Buison et al. 2005[32]	90	4–19 years/ 10.7 ± 4.2 years	HbSS	Yes	• Lean body mass • Relative bone age • DEXA scan • Whole-body bone mineral content (WBBMC) • Whole-body bone area (WBBA)	• SCD with reduced adjusted lean muscle mass compared to controls ratio = 0.95, $p < 0.01$ • Bone age (8.0 ± 3.4 years) • Relative bone age (−0.6 ± 1.3 years) • WBBMC ratio = 0.93; $p < 0.01$ • WBBA ratio = 0.94; $p < 0.001$
Jacob et al. 2013[34]	76	10–17 years/ 13.0 ± 1.9 years	HbSS HbSC	No	• e-Diary of symptoms	• Stiffness in joints (15.8%) • Muscle tenderness (8.4%)
Moheeb et al. 2007[10]	141	9–12 years/ 10.1 ± 0.076 years *	HbSS	Yes	• Flexibility	• SCD decreased flexibility compared to controls (SCD: −3.4 ± 1.0 cm *; controls: −0.9 ± 0.6 cm *); $p < 0.05$
Rhodes et al. 2009[33]	64	10–13 years/ 11.29 ± 11.2 (male) 11.70 ± 1.62 (female)	SCA	Yes	• Bone mineral density	• Bone mineral density (g/ cm^3) lower in SCA males compared to controls (0.93 ± 0.05 vs. 0.99 ± 0.06), but not females (0.96 ± 1.33 vs. 0.99 ± 0.07)
Wali & Moheeb 2011[35]	93	10.4–14.6 years/12.81 ± 0.136 years *	SCA	Yes	• Flexibility • Lean body mass	• Lower flexibility in SCD group compared to controls (0.66 ± 0.54 * vs. 1.34 ± 0.63 *; $p < 0.05$) • Lower lean body mass in SCD group compared to controls (SCD: 20.2 ± 0.84 *; controls: 24.5 ± 0.89 *); $p < 0.05$

Abbreviations: N = number of participants with sickle cell disease; SCA = Sickle Cell Anemia; SCD = Sickle Cell Disease; DEXA= dual energy X-ray absorptiometry. Results are reported as mean ± standard deviation, except where noted otherwise.

*Standard Error.

Table 2.

Muscle Strength

Study	N	Age range/ mean	Diagnoses	Non-SCD Control	Relevant Outcome Measures	Findings Related to Physical Impairments and Function
Brownell et al. 2020[37]	22	9–19 years/ 13.8 ± 3.3 years	HbSS	No	• Maximum left and right handgrip force • Knee extension and flexion maximal torque • Jump height • Jump peak power	• Right handgrip (23.2 ± 10.3 kg) • Left handgrip (22.5 ± 11.0 kg) • Knee extension (55.2 ± 30.8 ft/ lb). • Knee flexion (22.4 ± 13.9 ft/lb) • Jump height (33.2 ± 9.9 cm) • Jump peak power (1705 ± 894 W)
Dougherty et al. 2011[40]	35	5–13 years/9 ± 2.2 years	HbSS	Yes	• Handgrip force • Vertical squat jump peak power	• Participants with SCD had significantly lower dominant hand maximal handgrip force and jump peak power than the controls • Dominant handgrip force (SCD: 12.7 ± 3.3; controls: 15.2 ± 5.1 kg); $p < 0.008$ • Jump peak power (SCD: 882 ± 298; controls: 1167 ± 384 W); $p < 0.001$
Dougherty et al. 2018[38]	21	5–17 years/11 ± 4 years	HbSS	Yes	• Maximal handgrip force • Ankle plantarflexion maximal torque • Vertical squat jump peak power	• Significantly lower handgrip force, ankle plantarflexion torque at two angles, and jump peak power in participants with SCD compared to controls • Maximum handgrip strength lower in participants with SCD ($p<0.01$) • Ankle plantarflexion torque at two angles lower in participants with SCD ($p<0.05$) • Jump peak power lower in participants with SCD ($p<0.04$)
Dougherty et al. 2020[39]	21	5–20 years/11 ± 4 years	HbSS	Yes	• Maximal handgrip force • Plantarflexion and dorsifleixion maximal torque • Knee extension torque • Jump height • Vertical squat jump peak power	• Significantly lower handgrip force, ankle plantarflexion torque at 10° and 20°, and jump peak power in participants with SCD compared to controls • Dominant handgrip force (SCD: 15.6 ± 8.6 kg; controls: 27.6 ± 9.6 kg); $p < 0.05$ • Ankle plantarflexion torque: – −10° (SCD: 44.7 ± 22.2 Nm; controls: 53.6 ± 36.9 Nm); NS – 0° (SCD: 39.0 ± 20.0 Nm; controls: 50.0 ± 31.0 Nm); NS

Study	N	Age range/ mean	Diagnoses	Non-SCD Control	Relevant Outcome Measures	Findings Related to Physical Impairments and Function
						– 10° (SCD: 27.3 ± 17.1 Nm; controls: 42.2 ± 24.7 Nm), $p < 0.05$ – 20° (SCD: 21.2 ± 11.8 Nm; controls: 33.5 ± 19.5 Nm); $p < 0.05$ • Ankle dorsiflexion torque; NS: – −10° (SCD: 9.8 ± 5.7 Nm; controls: 12.5 ± 6.9 Nm) – 0° (SCD: 12.3 ± 7.3Nm; controls: 15.7 ± 10.7 Nm) – 10° (SCD: 13.3 ± 8.3 Nm; controls: 16.9 ± 12.1Nm) – 20° (SCD: 14.9 ± 9.3 Nm; controls: 18.1 ± 13.4 Nm) • Knee extension peak torque (SCD: 49.6 ± 27.6 Nm; controls: 65.8 ± 44.1 Nm); NS • Knee flexion torque (SCD: 22.4 ± 13.3 Nm; controls: 23.3 ± 17.7 Nm); NS • Jump height (SCD: 25.2 ± 5.2 cm; controls: 28.0 ± 8.3 cm); NS • Jump peak power (SCD: 1054.3 ± 477.8 W; controls: 1487.6 ± 811.1 W); NS
Jacob et al. 2012[41]	31	10–17 yers	HbSS, HbSC	No	• e-Diary created for the study	• 14.3% of participants with SCD reported general weakness
Moheeb et al. 2007[10]	50	9–12 years/ 10.1 ± 0.076* years	HbSS	Yes	• Handgrip force • Back and leg muscle force • Vertical jump height	• Participants with SCD had significantly lower handgrip strength, leg and back muscle force, and vertical jump height compared to controls • Right handgrip force (SCD: 13.1 ± 0.5* kg; controls: 17.0 ± 0.9* kg); $p < 0.001$ • Left handgrip force (SCD: 12.6 ± 0.5* kg; controls: 14.9 ± 0.7* kg); $p < 0.001$ • Leg muscle force (SCD: 23.3 ± 0.7* kg; controls: 28.1 ± 1.4* kg); $p < 0.001$ • Back muscle strength (SCD: 23.3 ± 0.7* kg; controls: 30.9 ± 1.4* kg); $p < 0.001$

Study	N	Age range/ mean	Diagnoses	Non-SCD Control	Relevant Outcome Measures	Findings Related to Physical Impairments and Function
						• Jump height (SCD: 17.7 ± 0.8 * cm; controls: 23.1 ± 0.8 * cm); $p < 0.001$
Patra et al. 2013[42]	330	9 months-14 years/7.60 (males) 9.22 (females)	SCA	Yes	• Symptom list	• Generalized weakness reported in 87.7% (SCA) vs. 60% (controls)
Wali & Moheeb 2011[35]	93	10.4–14.6 years/12.81 ± 0.136 * years	SCA	Yes	• Handgrip strength • Leg and back muscle strength	• Participants with SCD on hydroxyurea had significantly lower right handgrip and leg muscle strength compared to controls
						• Right handgrip [a] (SCD: 16.02 ± 0.254 *; controls: 18.23 ± 0.192 *); $p < 0.05$
						• Left handgrip [a] (SCD: 15.42 ± 0.231 *; controls: 16.02 ± 0.255 *); NS
						• Leg strength [a] (SCD: 29.45 ± 0.544 *; controls: 33.24 ± 0.437 *); $p < 0.05$
						• Back strength [a] (SCD: 30.2 ± 1.2 *; controls: 32.6 ± 1.3 *); NS

Abbreviations: N = number of participants with sickle cell disease; NS = not significant; SCA = Sickle Cell Anemia; SCD = Sickle Cell Disease. Results are reported as mean ± standard deviation, except where noted otherwise.

* Standard error.

[a] Unknown units of measure.

Table 3.

Cardiopulmonary Function

Study	N	Age range/ mean	Diagnoses	Non-SCD Control	Relevant Outcome Measures	Findings Related to Physical Impairments and Function
Barden et al. 2000[43]	36	5–18 years/ 11.3 ± 3.8 years	HbSS	Yes	• Resting energy expenditure (REE) • Activity-related energy expenditure (AEE)	• Participants with SCD had significantly higher adjusted REE and lower AEE compared to controls • Adjusted REE (SCD: 1303 ± 325 kcal/d; controls: 1172 ± 28 kcal/d); p = 0.001 • AEE (SCD: 455 ± 68 kcal/d; controls: 723 ± 97 kcal/d); p = 0.029. • No significant differences in REE or adjusted AEE
Buchowski et al. 2002[44]	28	14–18 years/ 15.6 ± 1.5 years	SCA	Yes	• Accelerometer • Resting energy expenditure (REE) • Physical activity-related energy expenditure (PAEE)	• Participants with SCD had significantly higher REE (difference 216 kcal × day^{-1}; p < 0.000) and lower adjusted PAEE (difference 629 kcal × day^{-1}; p = 0.003) compared to controls
Chaudry et al. 2013[45]	50	10–18 years/ 14.1 ± 2.4 years (male) 14.2 ± 2.5 years (female)	HbSS HbSC	Yes	• Incremental ergometer cardiopulmon ary exercise testing (CPET)	• Participants with SCD had greater pulmonary blood flow by 15% to 20%, greater corrected diffusing capacity of the lungs for carbon monoxide by 7% to 10%, and less arteriovenous oxygen content by about one-third compared to controls • There were no ventilatory differences between participants with SCD and control subjects
Hostyn, et al. 2013[8]	46	6–18 years/ 9.15 ± 3.06 years	HbSS HbSC HbSβ^0 HbSβ$^+$	No	• 6-minute walk test (6MWT) • Vital signs	• Heart rate (baseline: 91.93 ± 13.0 bpm; end of test: 102.76 ± 20.3 bpm; 10 minutes after test: 91.17 ± 12.1 bpm); p < 0.001 • Respiratory rate (baseline: 21.67 ± 4.4 rpm; end of test: 26.17 ± 5.0 rpm; 10 minutes after test: 21.26 ± 4.2 rpm); p < 0.001 • Systolic blood pressure (baseline: 99.37 ± 11.6 mmHg; end of test: 103.22 ± 15.4 mmHg; 10 minutes after test: 97.96 ± 11.6 mmHg); p = 0.003 • Diastolic blood pressure (baseline: 59.26 ± 10.0 mmHg; end of test: 62.35 ± 10.2 mmHg; 10 minutes after test: 56.46 ± 7.9 mmHg); p < 0.001
Liem et al. 2015[46,47]	60	8–21 years/ 15.1 ± 3.4 years	HbSS HbSβ^0	Yes	• Incremental ergometer cardiopulmonary	• Participants with SCD had significantly lower total exercise time, achieved significantly lower peak work rate and

Study	N	Age range/ mean	Diagnoses	Non-SCD Control	Relevant Outcome Measures	Findings Related to Physical Impairments and Function
					exercise testing (CPET)	weight-adjusted peak VO_2, reduced ventilatory threshold, lower heartrate reserve, slower and reduced oxygen uptake and reduced oxygen update efficiency, and reduced ventilatory efficiency compared to controls • Total exercise time (SCD: 5.6 ± 1.3; controls: 7.8 ± 2.0 min); $p < 0.001$ • Peak work rate (SCD: 108 ± 37 W; controls: 153 ± 49 W); $p < 0.001$ • Weight-adjusted peak VO_2 (SCD: 26.9 ± 6.9 mL/kg/min; controls: 37.0 ± 9.2 ml/kg/min); $p < 0.001$ • Ventilatory threshold (SCD: 1.0 ± 0.3 L/min; controls: 1.3 ± 0.03 L/min); $p < 0.001$ • No significant difference in peak heartrate ($p = 0.32$) • Heartrate reserve (SCD: 99 ± 14 bpm; controls: 109 ± 15 bpm); $p = 0.005$ • Slower and reduced oxygen uptake and reduced oxygen update efficiency noted by: – lower $\Delta VO_2/\Delta$ work rate (SCD: 9 ± 2 mL/min/watt; controls: 12 ± 2 mL/min/watt); $p < 0.001$ – higher $\Delta V_E/\Delta VO_2$ (SCD: 42 ± 8; controls: 32 ± 5); $p < 0.001$ – lower $\Delta VCO_2/\Delta$ heart rate (SCD: 12 ± 4 mL/beats; controls: 32 ± 5 ml/bears); $p < 0.001$ • Reduced ventilatory efficiency evidenced by higher ΔV_E / ΔVCO_2 (SCD: 30.3 ± 3.7; controls: 27.3 ± 2.5); $p < 0.001$
Liem et al. 2017[31]	10	13–21 years/ 14.4 ± 2.5 years	HbSS HbSβ^0	No	• Incremental ergometer cardiopulmary exercise testing (CPET)	• Intervention = 12-week individualized exercise program 3x/week on stationary bike – 10–30 minutes per session (weeks 1–6) – 30 minutes per session (weeks 7–12) – weekly heart rate target 50–100% maximal heart rate (weeks 1–6) and

Study	N	Age range/ mean	Diagnoses	Non-SCD Control	Relevant Outcome Measures	Findings Related to Physical Impairments and Function
						100% maximal heart rate (weeks 7–12) • First half (7 weeks) – mean peak Vo_2 increased (baseline: 28.5 ± 5.6 ml/kg/min; week 7: 30.8 ± 5.6 ml/kg/min); p = 0.01 – peak workload improved (baseline: 103 ± 20 W; week 7: 111 ± 26 W); p = 0.03 • No significant change from baseline to final (week 12) for peak Vo_2 (p = 0.39), peak workload (p = 0.39), ventilatory threshold (p = 0.93), peak heart rate (p = 0.46), $\Delta V_E / \Delta VCO_2$ (0.07), $\Delta VO_2/\Delta$ work rate (p = 0.19), and $\Delta VCO_2/\Delta$ heart rate
Melo et al. 2017[9]	57	6–18 years/ 11.9 ± 3.5 years	HbSS	Yes	• 6-minute walk test (6MWT) • Borg scale of the perceived rate of exertion	• Participants with SCD reported higher Borg score after 6MWT compared to controls (SCD: 4.1 ± 1.4; controls: 1.17 ± 1.1); p < 0.001
Rhodes et al. 2009[33]	64	10–13 years/ 11.29 ± 11.2 years (male) 11.70 ± 1.62 years (female)	SCA	Yes	• Resting energy expenditure (REE)	• Participants with SCD had higher REE compared to controls (SCD: 44.48–45.92 ± 2.45–5.39 kcal/kg fat free mass/day; controls: 53.45–57.03 ± 53.45–5.94 kcal/kg fat free mass/day); p < 0.05
Singhal et al. 1997[48]	16	16.1–20.1 years/ 18.0 ± 1.1 years	SCD	Yes	• Heart rate monitor	• Participants with SCD had higher resting heart rate, higher flex heart rate, and lower resting metabolic rate compared to controls • Resting heart rate (SCD: 52.4 ± 8.6 bpm; controls: 34.2 ± 8.0 bpm); p < 0.001 • Flex heart rate (SCD: 71.6 ± 10.8%; controls: 88.8 ± 10.9%); p < 0.001 • Resting metabolic rate (SCD: 6.3 ± 0.5 MJ/d; controls: 7.0 ± 0.9 MJ/d); p = 0.018

Abbreviations: N = number of participants with sickle cell disease; SCA = Sickle Cell Anemia; SCD = Sickle Cell Disease; bpm = beats per minute; rpm = respirations per minute. Results are reported as mean ± standard deviation, except where noted otherwise.

Table 4.

Motor Performance

Study	N	Age range/ mean	Diagnoses	Non-SCD Control	Relevant Outcome Measures	Findings Related to Physical Impairments and Function
Armstrong et al. 2013[56]	193	7–18 months/ 12.7 ± 2.7mo	HbSS HbSβ^0	No	• Bayley Scale of Infant Development, 2nd edition (BSID-II) – Psychomotor Development Index (PDI) • Vineland Adaptive Behavior Scales (VABS)	• Participants with SCD presented with scores within the average range for BSID-II, PDI, and VABS motor skills • BSID-II, PDI (5.7% ≤ 70 or < 10th percentile; 7.7% 70–84 or 10th −29th percentile; 86.5% ≥ 85 or ≥ 30th percentile • VABS Motor Skills (0% ≤ 70 or < 10th percentile; 1.6% 70–84 or 10th −29th percentile; 98% ≥ 85 or ≥ 30th percentile
Brousse et al. 2020[5]	51	5–17 years/ 11.9 ± 3.8 years	HbSS HbSβ^0	No	• 6-minute walk test (6MWT)	• 6MWT distance (531–593 ± 38–76 m) • Percentage of expected 6MWT distance (72–76 ± 7–10%)
Brownell et al. 2020[37]	22	9–12 years/ 13.8 ± 3.3 years	HbSS	No	• Jump Height • Bruininks-Oseretsky Test of Motor Performance, 2nd edition (BOT-2)	• Jump Height (33.2 ± 9.9 cm) • BOT-2 total score (67.4 ± 6.1)
Burkhardt et al. 2017[49]	32	7–17.25 years/ 11.14 ± 4.48 years	HbSS HbSC HbSβ^0	Yes	• WACOM fine motor-digital writing tablet	• Participants with SCD performed worse on the WACOM writing tablet task for frequency, automatization, velocity, and variability. • WACOM frequency z-score (SCD: −0.95 ± 1.49); p ≤ 0.001 • WACOM automatization z-score (SCD: 0.57 ± 1.62); p ≤ 0.02 • WACOM velocity z-score (SCD: 0.70 ± 2.09); p ≤ 0.02 • WACOM variability z-score (SCD: 0.53 ± 1.30); p ≤ 0.02 • WACOM pressure z-score (SCD: 0.15 ± 0.96); NS
Dedeken et al. 2014[6]	46	6.1–19.7 years/12 years	HbSS HbSC HbSβ^0 HbSβ$^+$	No	• 6-minute walk test (6MWT)	• 6MWT distance (551 ± 92 m) • 6MWT distance % of predicted: – Silent infarct (74.9%)

Study	N	Age range/ mean	Diagnoses	Non-SCD Control	Relevant Outcome Measures	Findings Related to Physical Impairments and Function
						– No silent infarct (86.0%) – All (83.2 ± 12.1%)
Dougherty et al. 2020[39]	21	5–20 years/11 ± 4 years	HbSS	Yes	• Maximal jump height • Bruininks-Oseretsky Test of Motor Performance (BOT)	• Jump height (SCD: 25.2 ± 5.2 cm; controls: 28.0 ± 8.3 cm) • BOTMP total score (SCD: 61.5 ± 14.0; controls: 62.3 ± 15.2)
Drazen et al. 2015[50]	43	1–34 months/ 8.8 ± 7.5 months	HbSS HbSC HbSβ^0 HbSβ$^+$ SPFH	No	• Bayley Scale of Infant Development, 3rd edition (BSID-III)	• BSID-III, fine motor ($p < 0.001$): mean 8.0 ± 2.6, Scores of ≤ 7 (31.7%) • BSID-III, gross motor ($p = 0.009$): mean 8.7 ± 2.9; Scores of ≤ 7 (32.6%)
Glass et al. 2013[57]	80	Mean: 20.5 months	HbSS HbSC	No	• Bayley Scales of Infant Development, 2nd edition (BSID-II)	• Participants with SCD overall, on average, presented with no motor delay. • Bayley Motor Index: 89.1 ± 14.4
Hostyn et al. 2013[8]	46	6–18 years/ 9.15 ± 3.06 years	HbSS HbSC HbSβ^0 HbSβ$^+$	No	• 6-minute walk test (6MWT)	• 6MWT distance: – All (480.89 ± 68.70 m) – HbSS/HbSβ^0 thalassemia (459.30 ± 57.19 m) – HbSC/HbSβ$^+$ thalassemia (502.39 ± 73.6 m)
Melo et al. 2017[9]	57	6–18 years/ 11.9 ± 3.5 years	HbSS	Yes	• 6-minute walk test (6MWT)	• 6MWT distance (SCD: 500.6 ± 88.7; controls: 536.3 ± 94); $p = 0.09$, NS
Millis et al. 1994[51] †	30	Only 10-year olds	HbSS	Yes	• Swimming tests (20 yard and 40 yard) • Potato race (100 yard)	• Participants with SCD had decreased performance on 20-yard swim, 40-yd swim, and 100-yard potato race • 20-yard swim (SCD: 23.1 ± 0.6 * sec; controls: 8.9 ± 0.5 * sec †); $p < 0.05$ • 40-yard swim (SCD: 46.7 ± 1.0 * sec; controls: 22.9 ± 0.7 * sec †); $p < 0.05$ • 100-yard potato race (SCD: 29.9 ± 0.7 sec; controls: 21.4 ± 0.5 * sec); $p < 0.05$

Study	N	Age range/ mean	Diagnoses	Non-SCD Control	Relevant Outcome Measures	Findings Related to Physical Impairments and Function
						• % time difference: – 20-yard swim (160 ± 16 *%) – 40-yard swim (104 ± 28 *%) – 100-yard potato race (40 ± 58 *%)
Möckesch et al. 2017[7]	46	10–16 years/15 ± 2.4 years (HbSS) 15.1 ± 2.6 years (HbSC)	HbSS, HbSC	No	• 6-minute walk test (6MWT)	• 6MWT distance: 78% of participants with SCD (HbSS: 79%, HbSC: 77%) performed an abnormal (<80% of normative value indicates abnormal) 6MWT compared to age-standardized predicted distance • No difference between 6MWT distance between HbSC and HbSS.
Moheeb et al. 2007[10]	50	9–12 years/ 10.1 ± 0.076 years	HbSS	Yes	• Vertical jump height	• Participants with SCD had lower jump height compared to controls • Jump height (SCD: 17.7 ± 0.8 * cm; controls: 23.1 ± 0.8 * cm); $p < 0.001$
Newby et al. 2018[52]	67	5–18 years/ 11.36 ± 3.51 years	HbSS HbSC HbSβ^0 HbSβ$^+$	Yes	• Grooved Pegboard Test	• Participants with SCD performed Grooved Pegboard fine motor dexterity test within the average range (SCD: 89.62 ± 3.08; controls: 92.08 ± 3.56); NS
Schatz & Roberts 2007[53]	61	12–18 & 32–40 months/ 14.8 ± 2.6 & 37.3 ± 3.4 months (HbSS/ HbSβ^0); 15.9 ± 2.1 & 36.1 ± 2.5 months (HbSC/ HbSβ$^+$)	HbSS HbSC HbSβ^0 HbSβ$^+$	No	• Denver-II – fine motor scale • Vineland Adaptive Behavior Scales (VABS) – motor domain	• Denver II- fine motor developmental quotient: – HbSS/HbSβ^0 12–18 months (98.7 ± 19.0) – HbSC/HbSβ$^+$ 12–18 months (86.4 ± 13.3) – HbSS/HbSβ^0 32–40 months (85.8 ± 13.8) – HbSC/HbSβ$^+$ 32–40 months (83.2 ± 14.0) • VABS motor standard score: – HbSS/HbSβ^0 12–18 months (100.0 ± 5.9)

Study	N	Age range/ mean	Diagnoses	Non-SCD Control	Relevant Outcome Measures	Findings Related to Physical Impairments and Function
						– HbSC/HbSβ$^+$ 12–18 months (101.1 ± 4.3) – HbSS/HbSβ^0 32–40 months (88.9 ± 10.7) – HbSC/HbSβ$^+$ 32–40 months (86.6 ± 14.9)
Zempsky et al. 2013[54]	25	7–21 years/ 16.6 ± 2.4 years	HbSS HbSC HbSβ$^+$	No	• Functional Independence Measure (FIM)	• FIM motor score significantly improved during hospitalization for participants with SCD • FIM motor (first day of hospitalization: 54.1 ± 11.8; last day of hospitalization: 65.8 ± 12.4); $p < 0.001$
Zempsky et al. 2014[55]	159	7.26–21.82 years/ 15.73 ± 3.63 years	HbSS HbSC HbSβ^0 HbSβ$^+$	No	• Functional Independence Measure (FIM)	• Mean FIM 56.65 ± 15.23

Abbreviations: N = number of participants with sickle cell disease; NS = not significant; SCD = Sickle Cell Disease; SPFH = S persistent fetal hemoglobin. Results are reported as mean ± standard deviation, except where noted otherwise.

*Standard error.

†The unusually fast reported times for 20- and 40-yard swim for control sample were unable to be validated due to unsuccessful attempts to contact the corresponding author.

Table 5.

Physical Activity

Study	N	Age range/ mean	Diagnoses	Non-SCD Control	Relevant Outcome Measures	Related to Physical Impairments and Function
Buchowski et al. 2002[44]	28	14–18 years/ 15.6 ± 1.5 years	SCA	Yes	• Accelerometer	• Participants with SCD had decreased physical activity level compared to controls • Physical activity level (SCD: 1.32 ± 0.10; controls: 1.48 ± 0.12); p = 0.001 • Adjusted physical activity level (SCD: 1.32 ± 0.10; controls: 1.41 ± 0.01); p = 0.040
Karlson et al. 2017[58]	30	8–18 years/ 13.9 ± 2.9 years	HbSS HbSC HbSβ^0 HbSβ$^+$	No	• Actiwatch 2 – movement counts	• Mean physical activity was light intensity 97.7% of days (386 ± 143 counts/min • Overall peak physical activity (2820 ± 1118 counts/min) – Moderate (42.4% of days) – Vigorous (57.4% of days) • Children with SCD presented with decreased peak physical on pain days compared with non-pain days
Melo et al. 2018[59]	50	6–18 years/ 12.02 ± 3.63 years	HbSS	Yes	• Accelerometer	• Participants with SCD presented with lower physical activity compared to controls • Decreased vector magnitude counts (SCD: 3967142 ± 1743719; controls: 5194904 ± 2098832); p < 0.01 • Decreased vector magnitude count per minute (SCD: 764 ± 297; controls: 1096 ± 1096); p < 0.01 • Less vigorous physical activity minutes per day (SCD: 3.6 ± 4.1; controls: 7.8 ± 7.4); p < 0.01 • Less moderate physical activity minutes per day (SCD: 19.2 ± 11.9; controls: 27.1 ± 13.8); p < 0.01) • Lower MET (SCD: 1.71 ± 0.4; controls: 1.87 ± 0.39); p = 0.04 • Fewer total steps (SCD: 51010 ± 19600; controls: 59105 ± 22650); p = 0.04 • Lower total energy expenditure (SCD: 1015 ± 516 Kcal; controls: 2404 ± 1308 Kcal); p < 0.01

Study	N	Age range/ mean	Diagnoses	Non-SCD Control	Relevant Outcome Measures	Related to Physical Impairments and Function
Singhal et al. 1997[48]	16	16.1–20.1 years/ 18.0 ± 1.1 years	SCD	Yes	• Heart rate monitor	• Participants with SCD had decreased physical activity compared to controls • More low activity (SCD: 3.6 ± 1.2 mJ; controls: 4.8 ± 1.5 mJ); p = 0.033 • Less high activity (SCD: 10.2 ± 5.8 mJ; controls: 5.7 ± 3.4 mJ); p = 0.022 • Lower total daily energy expenditure (SCD: 13.8+/−4.9 MJ/d; controls: 0.5+/−2.2 MJ/d); p=0.034 • Decreased physical activity as measured by the ratio of total daily energy expenditure to resting metabolic rate (SCD: 2.2 ± 0.8; controls: 1.5 ± 0.3; p = 0.006) and total energy expenditure minus resting metabolic rate (SCD: 7.5 ± 4.9 MJ/d; controls: 3.5 ± 2.2 MJ/d; p = 0.01)

Abbreviations: N = number of participants with sickle cell disease; SCA = Sickle Cell Anemia; SCD = Sickle Cell Disease; MET = metabolic equivalent of task. Results are reported as mean ± standard deviation, except where noted otherwise.

Table 6.

Health-related Quality of Life: Physical Function

Study	N	Age range/ mean	Diagnoses	Non-SCD Control	Relevant Outcome Measures	Findings Related to Physical Impairments and Function
Adeyemo et al. 2015[79]	80	15–18 years/16 ± 1.5 years	HbSS HbSC	Yes	• SF-36	• Participants with SCD report lower physical function and physical role compared to controls • Physical function (SCD: 69.0 ± 23.2; controls: 83.0 ± 20.7); p = 0.002 • Role physical (SCD: 61.4 ± 28.5; controls: 74.2 ± 23.9); p = 0.02
Barakat et al. 2008[80]	42	12–18 years/15 ± 1.82 years	HbSS	No	• CHQ	• Participants with SCD scored within the normative range for physical functioning • Participants with SCD reported higher physical function compared to caregivers (p = 0.009)
Dampier et al. 2010[13]	1,772	2–18 years/9.6 ± 4.7 years	HbSS HbSC HbSβ$^+$ HbSβ^0	No	• PedsQL	• Physical functioning – Child (72.28 ± 16.02) • Parent (71.13 ± 22.97)
Dampier et al. 2016[12]	121	8–17 years/ 12.5 ± 3.1 years	HbSS HbSC	Yes	• PROMIS	• Participants with SCD had similar scores compared to the mean of a reference sample (children with and without health conditions) • Pain interference (56.1 ± 1.2) • Mobility (48.2 ± 0.9) • Upper dexterity (50.0 ± 0.9)
Dampier et al. 2016[76]	235	8–17 years/ 12.5 ± 2.8 years	HbSS HbSC HbSβ$^+$ HbSβ^0	Yes	• PROMIS	• Participants with SCD had similar scores compared to the mean of a reference sample (children with and without health conditions) • Pain interference (48.7 ± 13.6) • Mobility (50.6 ± 8.3) • Upper dexterity (50.6 ± 7.5)
Dougherty et al. 2020[39]	21	5–20 years/11 ± 4 years	HbSS	Yes	• PROMIS	• Participants with SCD reported similar physical function (upper and mobility), and pain impact scores compared to controls • Physical function upper (SCD: 45.9 ± 10.9; controls: 50.6 ± 8.8); NS • Physical function mobility (SCD: 53.1 ± 6.2; controls: 57. 8 ± 3.3); NS

Study	N	Age range/ mean	Diagnoses	Non-SCD Control	Relevant Outcome Measures	Findings Related to Physical Impairments and Function
						• Pain impact (SCD: 54.4 ± 13.3; controls: 48.6 ± 8.7); NS
Hoff et al. 2006[81]	56	8–17 years/ 12.14 ± 2.46 years	HbSS HbSC HbSβ+	No	• FDI	• FDI (10.99 ± 10.67)
Hussein et al. 2019[61]	100	6–12 years/ 8.90 ± 2.06	SCA	No	• Self-made questionnaire	• Activities and motor (transferring): – Poor (13.0%), – Moderate (55.0%) – Good (32.0%) • Play activities: – Poor (11.0%) – Moderate (53.0%) – Good (23.0%)
Kambasu et al. 2019[62]	140	8–17 years/ 14.25 years	HbSS	NO	• PedsQL	• Physical function – Child (57.5 ± 20.3) – Caregiver (52.8 ± 22.1) • Participants with SCD reported higher physical function compared to caregivers ($p < 0.001$)
Karlson et al. 2020[75]	206	8–17 years/ 11.72 ± 4.42 years	HbSS HbSC	No	• Child Physical Activity Questionnaire	• Reported days of physical activity (30 minutes) per week: – Child: ♦ 0 days (10.88%) ♦ 1–2 days (23.13%) ♦ 3–5 days (43.54%) ♦ 6–7 days (22.45%) – Caregiver: ♦ 0 days (3.66%) ♦ 1–2 days (21.95%) ♦ 3–5 days (40.24%) ♦ 6–7 days (34.15%) • No significant difference between child and caregiver report

Study	N	Age range/ mean	Diagnoses	Non-SCD Control	Relevant Outcome Measures	Findings Related to Physical Impairments and Function
Malheiros et al. 2015[63]	71	8–21 years/ 12.19 ± 3.2 years	SCA with and without hip dysfunction	No	• PedsQL • Barthel Index	• PedsQL activities score – All (68.60 ± 18.73) – With hip dysfunction (58.78 ± 14.3) – Without dysfunction (71.68 ± 18.72) – A significant difference between groups with and without hip dysfunction (p = 0.011) • Barthel Index – All (98.24 ± 3.51) – With hip dysfunction (98.24 ± 3.51) – Without hip dysfunction 98.15 ± 3.51) – No significant difference between groups with and without hip dysfunction (p = 0.925)
Matos et al. 2018[64]	24	8–18 years/ 11.1 ± 3.9 years	SCA	Yes	• PedsQL	• Participants with SCA and avascular necrosis presented with decreased PedsQL physical function compared to the group without necrosis (SCD: 65.1 ± 19.3; controls: 87.5 ± 6.9); p = 0.005 • No significant difference between SCD and Perthes disease groups
Melo et al. 2017[9]	57	6–18 years/ 11.9 ± 3.5 years	HbSS	Yes	• PAQ-C – Brazilian version	• Participants with SCD presented with lower PAQ-C scores compared to controls • Total score (SCD: 1.64 ± 0.39; controls: 3.2 ± 0.38); p < 0.001 • Spare time activity (SCD: 0.77 ± 0.37; controls: 2.37 ± 0.55); p < 0.001 • Activity during physical education classes (SCD: 1.77 ± 0.68; controls: 3.2 ± 0.55); p < 0.001 • Lunch-time activity (SCD: 1.4 ± 0.53; controls: 3.1 ± 0.72); p < 0.001 • After school activity (SCD: 1.77 ± 0.92; controls: 3.0 ± 0.61); p < 0.001 • Evening activity (SCD: 1.63 ± 0.77; controls: 3.22 ± 0.77); p < 0.001

Study	N	Age range/ mean	Diagnoses	Non-SCD Control	Relevant Outcome Measures		Findings Related to Physical Impairments and Function
							• Weekend activity (SCD: 2 ± 0.75; controls: 3.44 ± 0.77); p < 0.001 • Activity frequency in the last 7 days (SCD: 2.26 ± 0.76; controls: 3.43 ± 0.62); p < 0.001 • Activity during each day last week (SCD: 1.63 ± 0.53; controls: 3.21 ± 0.50); p < 0.001
Melo et al. 2018[59]	50	6–18 years/ 12.02 ± 3.63 years	HbSS	Yes	• PAQ-C – Brazilian version		• Participants with SCD presented with lower PAQ-C scores compared to controls • Total score (SCD: 1.65 ± 0.41; controls: 3.39 ± 0.38); p < 0.01 • Spare time activity (SCD: 0.75 ± 0.31; controls: 2.48 ± 0.61); p < 0.01 • Activity during physical education classes (SCD: 1.74 ± 0.62; controls: 3.36 ± 0.65); p < 0.01 • Break-time activity (SCD: 1.61 ± 0.69; controls: 3.36 ± 0.65); p < 0.01 • Lunch-time activity (SCD: 1.42 ± 0.53; controls: 3.32 ± 0.71); p < 0.01 • After school activity (SCD: 1.85 ± 0.98; controls: 3.38 ± 0.56); p < 0.01 • Evening activity (SCD: 1.77 ± 0.84; SCD: 3.58 ± 0.73); p < 0.01 • Weekend activity (SCD: 2.08 ± 0.75; controls: 3.63 ± 0.78); p < 0 01 • Activity frequency in the last 7 days (SCD: 2.26 ± 0.76; controls: 3.43 ± 0.62); p < 0.001 • Activity during each day last week (SCD: 1.62 ± 0.53; controls: 3.37 ± 0.58); p < 0.01
Menezes et al. 2008[65]	100	5–18 years	HbSS HbSC HbSβ$^+$	Yes	• PedsQL		• Participants with SCD presented with lower PedsQL physical function and compared to controls – 5–7 years (SCD: 56.16 ± 12.33; controls: 91.81 ± 9.36); p < 0.0001 – 8–12 years (SCD: 48.37 ± 13.77; controls: 94.10 ± 6.64); p < 0.0001 – 13–18 years (SCD: 42.86 ± 13.77;

Study	N	Age range/ mean	Diagnoses	Non-SCD Control	Relevant Outcome Measures	Findings Related to Physical Impairments and Function
						controls: 94.55 ± 6.31); p < 0.0001
Möckesch et al. 2017[7]	46	10–16 years/15 ± 2.4 (HbSS) 15.1 ± 2.6 (HbSC)	HbSS HbSC	Yes	• IPAQ – adapted for adolescents	• Participants with SCD reported decreased daily expenditure related to moderate and intense physical activity compared to controls (p = 0.02)
Omwanghe et al. 2017[77]	100	6–12th graders	SCD	Yes	• NHANES – Physical Activity Questionnaire	• A lower proportion of participants with SCD reported: – Less time spent in sustained physical activity (60 minutes or more) on any given day of the week ♦ Vigorous physical activity (SCD: 24%; controls: 43%); p = 0.01 ♦ Moderate-to-vigorous physical activity (SCD: 17%; controls: 23%); p < 0.01 • A greater proportion of participants with SCD reported: – At least 10 minutes of moderate-to-vigorous activity (SCD: 67%; controls: 42%); p < 0.01 – The number of days spent in moderate-to-vigorous physical activity was higher in SCD (2.3 vs. 1.4 days per week; p < 0.01 • Similar portions of participants with SCD reported: – At least 10 continuous minutes of vigorous physical activity in a typical week (SCD: 66%; controls: 65%); p = 0.91 – The number of days per week in vigorous physical activity (SCD: 2.8

Study	N	Age range/ mean	Diagnoses	Non-SCD Control	Relevant Outcome Measures	Findings Related to Physical Impairments and Function
						days; controls: 2.5 days); p = 0.44
Oliver-Carpenter et al. 2011[66]	47	6–18 years/ 11.93 ± 3.8 years	HbSS HbSC HbSβ+ HbSβ0	Yes	• FDI	• Participants with SCD reported higher functional disability compared to caregiver-report (child: 19.2 ± 15.2; parent: 10.6 ± 14.5); p < 0.05
Palermo et al. 2002[67]	58	5–18 years/ 10.97 ± 3.41	HbSS HbSC HbSβ+	Yes	• CHQ – Parent-form (PF50)	• Caregivers of children and adolescents with SCD reported lower scores on CHQ-PF50 physical functioning, role impact-physical, and physical health scales compared to controls • Physical functioning (SCD: 78.7 ± 11.4; controls: 94.5 ± 8.6); p = 0.0001 • Role impact - physical (SCD: 80.2 ± 13.8; controls: 98.6 ± 4.6); p = 0.0001 • Physical health summary score (SCD: 39.4 ± 6.4; controls: 54.9 ± 3.2); p < 0.0001
Palermo et al. 2005[78]	42	9–17 years/ 13.36 ± 1.34 years	HbSS HbSC HbSβ+	No	• FDI	• A significant difference in functional disability between migraine and tension and migraine and no headache groups • FDI score – Migraine ± aura (15.81 ± 4.69) – Tension headache (7.14 ± 4.89) – No headache (4.71 ± 3.58)
Panepinto et al. 2005[68]	99	5–8 years/ 10.67 ± 3.71 years	HbSS HbSC HbSβ+ HbSβ0 HbS tacoma	No	• CHQ – Child form (CF87) – Parent form (PF28)	• Participants with SCD reported higher physical function compared to caregiver-report (child: 75.22; caregiver: 58.82); p < 0.005
Patel & Pathan 2005[69]	25	8–18 years/ 11.2 ± 1.7 years	SCA	Yes	• EUROQOL	• Mobility: – No problem (SCD: 76%; controls: 100%) – Problem on some days (SCD: 24%; controls: 0%) – Unable to do on most days (SCD: 0%; controls 0%)

Study	N	Age range/ mean	Diagnoses	Non-SCD Control	Relevant Outcome Measures	Findings Related to Physical Impairments and Function
Sil et al. 2016[70]	100	8–18 years/ 13.54 ± 2.7 years	HbSS HbSC HbSβ$^+$ HbSβ^0	No	• FDI	• A significant difference in reported functional disability between no pain and episodic pain, and no pain and chronic pain. • FDI – No pain (6.70 ± 0.67) – Episodic pain (14.33 ± 11.02) – Chronic pain (20.58 ± 11.09)
Sil et al. 2020[71]	42	8–18 years/ 14.95 years	HbSS HbSC HbSβ$^+$ HbSβ^0	No	• FDI	• FDI – Asymptomatic and episodic pain (10.15 ± 12.69) – Chronic pain (24.53 ± 12.87)
Singh et al. 2020[72]	67	8–18 years/ 10.7 ± 3.6 years	HbSS HbSC HbSβ$^+$ HbSβ^0 Other	No	• PROMIS from Pediatric-25 profile	• Physical activity – ED visit: 48.1 ± 6.8 – 7–10 days: 44.3 ± 10.2 – 1–3 months: 44.2 ± 6.6 • Physical strength impact – ED visit: 34.8 ± 4.1 – 7–10 days: 38.9 ± 9.4 – 1–3 months: 40.3 ± 9.0 • Physical function mobility – ED visit: 41.0 ± 9.1 – 7–10 days: 43.7 ± 10.2 – 1–3 months: 49.6 ± 9.4
Singh et al. 2019[73]	164	5–17 years/10 ± 4 years	HbSS HbSC HbSβ^0 Other	No	• PROMIS	• Physical activity – All (49 ± 7.6) – No pain medication in the prior week (48.6 ± 7.8) – Pain medication in the prior week (50.2 ± 6.8) – Pain intensity 0–3 (49.4 ± 8.4) – Pain intensity 4–6 (47.9 ± 7.6) – Pain intensity 7–10 (49 ± 5.6)

Study	N	Age range/ mean	Diagnoses	Non-SCD Control	Relevant Outcome Measures	Findings Related to Physical Impairments and Function
						– No significant difference between pain medication in the prior week or pain intensity groups
						• Strength impact
						– All (39.7 ± 8.1)
						– No pain medication in the prior week (40.4 ± 8.6)
						– Pain medication in the prior week (36.9 ± 5.0)
						– Pain intensity 0–3 (41.6 ± 8.6)
						– Pain intensity 4–6 (39.9 ± 8.1)
						– Pain intensity 7–10 (36.2 ± 5.7)
						– Significant difference between medication in prior week ($p = 0.02$) and pain intensity ($p = 0.01$) groups
Thornburg et al. 2011[74]	191	2–18 years/ 10.4 ± 4.7 years	HbSS HbSC HbSβ+ HbSβ0 HbSOArab HbSGPhil-adelphia	No	• PedsQL	• Physical functioning – child-report
						– Hydroxyurea (79.7† [IQR 62.5–90.6])
						– No Hydroxyurea (71.4† [IQR 58.6–81.2]
						– $p = 0.01$
						• Physical Function – caregiver-report
						– Hydroxyurea (75† [IQR 53.9–8.75])
						– No Hydroxyurea (71.9† [IQR 53.2–90.6])
						– $p = 0.05$
Zempsky et al. 2014[55]	159	7.2621.82 years/ 15.73 ± 3.63 years	HbSS HbSC HbSβ+ HbSβ0	No	• YAPFAQ • CALI • FIM	• YAPFAQ (17.56 ± 11.95) • CALI (23.96 ± 17.56) • FIM (56.65 ± 15.23)

Abbreviations: N = number of participants with sickle cell disease; NS = not significant; SCA = Sickle Cell Anemia; SCD = Sickle Cell Disease; Barthel Index = The Barthel Index for Activities of Daily Living; CALI = Child Activities Limitations Interview; CHQ = Child Health Questionnaire; FDI = Functional Disability Index; FIM = Functional Independence Measure; IPAQ = International physical activity questionnaire; NHANES = National Health and Nutrition Examination Survey; PAQ-C = Physical Activity Questionnaire for Older Children; PedsQL = Pediatric Quality of Life Inventory; PROMIS = Patient-Reported Outcomes Measurement Information System; SF-36 = 36-Item Short Form Health Survey; YAPFAQ = Youth Acute Pain Functional Ability Questionnaire. Results are reported as mean ± standard deviation, except where noted otherwise.

*Standard error.

†Median (Interquartile range [IQR]).