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Exercise Capacity and Clinical Outcomes in Adults Followed in the Cooperative Study for Sickle Cell Disease (CSSCD)

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Abstract

Objectives: To determine factors associated with exercise capacity in adults with sickle cell disease (SCD) and its relationship to hospitalizations and mortality.

Methods: A total of 223 participants in the Cooperative Study of Sickle Cell Disease (CSSCD) (64% female, 70% hemoglobin SS/Sβ^0 thalassemia, mean age 43.3 ± 7.5 years) underwent maximal exercise testing using a treadmill protocol with a mean duration of 11.6 ± 5.2 minutes.

Results: Female sex (β = −3.34, 95% CI [–1.80, −4.88], $p < 0.001$), older age (β = −0.14, 95% CI [–0.24, −0.04], $p = 0.005$), higher body mass index (β = −0.23, 95% CI [–0.37, −0.10]; $p = 0.001$) and lower hemoglobin (β = 0.56, 95% CI [0.08, 1.04], $p = 0.02$) were independently associated with lower fitness, while there was a trend with abnormal pulmonary function testing (β = −1.42, 95% CI [–2.92, 0.07]; $p = 0.06$). Lower percent predicted forced expiratory volume in 1 second (FEV_1) was independently associated with lower fitness (β = 0.08, 95% CI [0.03, 0.13], $p = 0.001$). Genotype and hospitalization rates for pain and acute chest syndrome (ACS) prior to testing were not associated with exercise capacity. Baseline exercise capacity predicted neither future pain or ACS nor survival in our cohort. Adults with SCD tolerated maximal exercise testing.

Conclusions: Prospective studies are needed to further evaluate the impact of regular exercise and improved fitness on clinical outcomes and mortality in SCD.

Keywords

Sickle cell disease; exercise capacity; fitness; pain; acute chest syndrome; mortality

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Introduction

Sickle cell disease (SCD) is a common, potentially life-threating inherited hemoglobin disorder affecting approximately 100,000 individuals in the United States.[1] Complications of SCD range from intermittent debilitating pain episodes, acute chest syndrome (ACS), chronic hemolytic anemia, cardiopulmonary disease, and stroke to long-term end organ damage.[2] As such, these complications lead to substantial declines in patients' health-related quality of life across the lifespan.[3–6] In particular, overall physical functioning and exercise capacity are significantly reduced among individuals with SCD.[7–12] Chronic anemia and cardiopulmonary disease may contribute to this impact of SCD on exercise capacity.

Various clinical and laboratory factors have been associated with increased morbidity and early mortality in patients with SCD, including renal failure,[13,14] pulmonary hypertension,[15,16] low forced expiratory volume in 1 second (FEV_1),[17] history of smoking, ACS, asthma and/or wheezing,[14,18–21] seizures,[14] high white cell count (WBC), low fetal hemoglobin (HbF),[14] and laboratory markers suggestive of severe hemolysis.[22–24] Exercise capacity, also referred to as cardiopulmonary fitness in the epidemiology literature, represents one of the most important predictors of all cause mortality in the general adult population as well as among adults with chronic medical conditions.[25–31] Fitness may play an important independent protective role through its influence on various risk factors of cardiovascular disease such as hypertension, diabetes, and hypercholesterolemia, the development of which could explain the relationship between mortality and low fitness.[32–36] While earlier studies have underscored the contribution of fitness to clinical outcomes, including disease-related morbidity and mortality, in the general population, no studies have investigated this relationship in SCD.

The objectives of this secondary analysis were to: 1) determine the factors associated with baseline exercise capacity in a cohort of adults with SCD, and 2) evaluate the relationship of exercise capacity to hospitalization for pain and ACS and overall mortality. We hypothesized that clinical factors such as age, sex, hemoglobin, SCD genotype and cardiopulmonary disease significantly affect exercise capacity, and that reduced exercise capacity is a predictor of more frequent hospitalizations for pain and ACS and higher mortality in adults with SCD.

Methods

Patient population

A cohort was constructed using data from the Cooperative Study of Sickle Cell Disease (CSSCD), a prospective cohort study designed to investigate the natural history of SCD. The CSSCD cohort has been previously described.[37] Data from participants enrolled in the Phase 2A continuation study were used for this analysis. The Phase 2A continuation study was designed to examine the progression of organ damage in adult CSSCD participants born before January 1, 1956, enrolled between March 1979 and May 1981, at 11 of the original 23 participating centers. Participants in Phase 2A underwent annual physical exams and completed exercise and pulmonary function testing at Phase 2A enrollment and exit visits. Excluded from this study were participants who did not complete exercise testing (N=75) for

reasons that were not reported, had exercise data that did not pass quality control for the CSSCD dataset (N=25), had missing laboratory and/or pulmonary function measurements (N=9), had contraindications for exercise testing (N=10), and had missing data related to exercise duration (N=17) (Figure 1).

Mortality and follow-up time

Date and cause of death were recorded during Phase 2A follow-up; however, autopsy information was not routinely available. Follow-up time was computed as the time between the completion of the first exercise test and death, recorded date of final disposition, or September 30, 1993 (the date of the end of Phase 2A data collection), whichever came first.

Pain and acute chest syndrome hospitalization rates

Vaso-occlusive pain events were defined as previously described (events lasting at least two hours that resulted in a healthcare provider visit and that could not be explained by any other reason than SCD).[38] ACS events were also defined as previously described (a new radiodensity on chest imaging with or without respiratory symptoms accompanied by fever).[39] Rates were defined as the number of events occurring during the follow-up period divided by the total follow-up time.

Measures of exercise capacity

Data from the first exercise test upon enrollment in Phase 2A were used for this study. Test data were reviewed centrally for quality. Participants underwent a maximal treadmill test using a modified Balke protocol, which consisted of 10 stages of exercise lasting 2 minutes each. Treadmill speed was kept constant at 2 mph. Incline was initially set at 0% followed by a 2.5% increase at each stage. Breath-by-breath gas exchange data were not measured during exercise. Test termination occurred at either volitional exhaustion or the discretion of the physician supervising the test for medical reasons. Exercise capacity in this analysis was defined by total number of minutes spent on the treadmill. Although maximal oxygen consumption (VO_2max) is considered the gold standard for defining exercise capacity, treadmill duration is considered an acceptable surrogate and is commonly adopted in other published epidemiological studies of fitness in which direct gas exchange is not performed during exercise testing.[29,40–43] Additionally, peak METS reported in the CSSCD were calculated using the equation METS = VO_2max/3.5 mL/kg/min, in which VO_2max was estimated through previously published prediction equations.[44,45]

Other predictors

Other predictors of mortality, pain and ACS rates, and/or exercise capacity included age, genotype, baseline hemoglobin, baseline WBC, hydroxyurea and/or chronic transfusion use, and retrospective pain and acute chest syndrome rates. Age was defined as the age at time of exercise testing. Genotype was determined by cellulose acetate hemoglobin electrophoresis and quantitative chromatography at the Centers for Disease Control and Prevention. Baseline hemoglobin and WBC were defined using data from steady-state laboratory evaluation closest to the date of exercise testing. Hydroxyurea and chronic transfusion use were collected in the clinical record. Retrospective pain and acute chest syndrome rates were

defined using follow-up data collected during Phase 1 of CSSCD and calculated over the three years prior to exercise testing. Tricuspid regurgitant jet velocity (TRJV) data on echocardiography were not included in our analysis due to a large number of missing values and the inability to confirm standardized procedures for their measurements in the CSSCD.

Data from the pulmonary function testing (PFT) completed closest to the exercise testing date were also used for this study. Test data were reviewed centrally for quality. Percent predicted values for FEV_1, Forced Vital Capacity (FVC), and the ratio of FEV_1/FVC were calculated using the Global Lung Initiative 2012 regression equations.[46] Percent predicted values were classified as below the lower limit of normal if they were below the 5th percentile for age, sex, race, and height.[46] Percent predicted values for Total Lung Capacity (TLC) were obtained using previously-published prediction equations[46,47] and were adjusted by 12%[48] to account for the effect of race. A percent predicted TLC value less than 80% was considered abnormal. Participants were categorized as having normal, obstructive, restrictive, or mixed pulmonary function patterns using predicted FEV_1, FVC, FEV_1/FVC, and TLC criteria previously published by the American Thoracic Society/European Respiratory Society.[49]

Statistical analysis

Standard descriptive analysis was performed for categorical data using Pearson's chi-square test or Fisher's exact test, where appropriate. Continuous data that were normally distributed were analyzed using t-tests or ANOVA; data with a non-normal distribution were analyzed with the Mann Whitney Wilcoxon, Wilcoxon signed ranks, or Kruskal-Wallis tests. Tobit regression was used to evaluate factors associated with exercise capacity (treadmill duration). Negative binomial regression was used to evaluate factors associated with prospective rates of ACS and pain to end of follow-up. Kaplan-Meier product estimation and Cox proportional hazards regression were used to evaluate factors associated with survival to the end of follow-up. In all regression models, variables were entered in one step. Post-estimation analysis was performed to check model assumptions and potentially influential observations. Analyses were performed using IBM SPSS Statistics (Version 23, Armonk, NY: IBM Corp.) or Stata Statistical Software (Release 14, College Station, TX: StataCorp LP).

Results

Participant characteristics

A total of 223 African-American adults with SCD completed at least 1 exercise test and were followed for an average of 3.1±0.5 years. Participants (64% female, 70% with hemoglobin SS or S/β^0 thalassemia, mean age 43.3±7.5 years) had mean hemoglobin of 9.1 ± 2.2 g/dl. In the CSSCD Phase 2A study cohort, the baseline clinical characteristics of adult African-American participants with SCD who completed exercise testing (N=223) compared with those who did not (N=136) are shown in Table 1. Characteristics were not significantly different between groups except that participants who completed exercise testing had longer duration of follow up, lower annual rate of pain episodes and lower mortality, when compared with those who did not.

Exercise capacity in the CSSCD cohort

Participants lasted a mean of 11.6 ± 5.2 minutes on the treadmill with 87% completing ≥ 3 stages but only 17% reaching stage 9 or 10. Participants' exercise data are summarized in Table 2. Of the 223 eligible participants who completed first exercise testing, only 100 (45%) completed a second exercise test, which occurred a mean of 2.2 ± 0.5 years after the first. Exercise data were not significantly different between exercise tests (Table 2). However, more participants reported dyspnea during the second test.

We categorized exercise capacity as low, medium and high based on tertiles of treadmill duration with an average of 5.7 ± 1.9 minutes in the low tertile, 11.8 ± 1.6 minutes in the intermediate tertile, and 18.1 ± 2.1 minutes in the high tertile (Table 3). Across tertiles of exercise capacity, participants in the high tertile were more likely to be males (% males 60 vs. 29 vs. 23%, $p < 0.001$), of younger age (mean age 41.3 vs. 43.1 vs. 45.2 years old, $p = 0.007$) and to have higher baseline hemoglobin (mean hemoglobin 9.8 vs. 9.0 vs. 8.5 g/dl, $p = 0.003$), when compared to those in the intermediate and low tertiles. Moreover, participants in the low tertile were more likely to have abnormal PFT results (% abnormal PFT 58 vs. 35 vs. 39%, $p = 0.008$) or lower FEV_1 (mean FEV_1 % predicted 74.7 vs. 81.9 vs. 85.8% predicted, $p = 0.002$), when compared to participants in the high and intermediate tertiles. Pain or ACS hospitalization rates during the 3 years prior to exercise testing were not significantly different across high, intermediate and low tertiles of exercise capacity.

Predictors of baseline exercise capacity

In a multivariable tobit regression model, female sex ($\beta = -3.34$, 95% CI [–1.80, −4.88]; $p < 0.001$), older age at the time of exercise testing ($\beta = -0.14$, 95% CI [–0.24, −0.04]; $p = 0.005$), higher body mass index (BMI) at study entry ($\beta = -0.23$, 95% CI [–0.37, −0.10]; $p = 0.001$), and lower hemoglobin ($\beta = 0.56$, 95% CI [0.08, 1.04]; $p = 0.02$) were independently associated with lower baseline exercise capacity (i.e. shorter duration on treadmill), with abnormal PFT trending toward significance in its association with lower exercise capacity ($\beta = -1.42$, 95% CI [–2.92, 0.07]; $p = 0.06$) (Table 4). Lower percent predicted FEV_1, however, was independently associated with lower exercise capacity ($\beta = 0.08$, 95% CI [0.03, 0.13], $p = 0.001$) if used instead of abnormal PFT in an alternative model (supplemental Table 1). Genotype (HbSS or HbS/β^0 thalassemia) and hospitalization rates for pain and ACS prior to exercise testing were not significantly associated with exercise capacity.

Relationship of exercise capacity to prospective pain or acute chest syndrome and mortality

In a negative binomial regression model, we found that exercise capacity did not predict future pain (incidence rate ratio (IRR) = 1.0; 95% CI [0.91, 1.10]; $p = 0.92$) or ACS episodes (IRR = 0.95; 95% CI [0.85, 1.07]; $p = 0.41$) after adjustment for age, sex, genotype and hemoglobin (Table 5). Using the same model, only pain (IRR = 3.29; 95% CI [2.56, 4.23]; $p < 0.001$) and ACS hospitalization rates (IRR = 31.60; 95% CI [4.68, 213.48]; $p < 0.001$) prior to exercise testing predicted future pain or ACS episodes.

Death was reported in only 9 out of 191 participants (4.7%) in our cohort, all of whom had either hemoglobin SS or S/β^0 thalassemia. Survival was not significantly different across

tertiles of exercise capacity (Supplemental Figure 1). Using a Cox regression model, exercise capacity did not predict survival in our cohort (hazard ratio (HR) = 0.98; 95% CI [0.85, 1.13]; $p = 0.82$). Similarly, age at exercise testing and abnormal PFT were not predictors of mortality. However, male sex (HR = 6.5; 95% CI [1.2, 33.9]; $p = 0.02$) and lower hemoglobin (HR = 0.55; 95% CI [0.37, 0.84]; $p = 0.005$) were independent predictors of mortality (Table 6).

Discussion

This retrospective analysis from the CSSCD represents the largest study to date of exercise capacity in adults with SCD. Few adults with SCD in the CSSCD could complete all 10 stages of a standard Balke treadmill exercise test. We found that lower exercise capacity in adults with SCD is independently associated with female sex, older age, higher BMI and lower Hb. Although the least fit participants were more likely to have lung disease on PFT both by conventional ATS classification and by FEV_1 alone, only the association between percent predicted FEV_1 and exercise capacity was significant in our multivariable model. Moreover, we found that baseline exercise capacity neither was associated with nor predicted pain and ACS hospitalizations by either retrospective or prospective analysis, respectively. Baseline exercise capacity in adults with SCD in this study also did not predict future mortality.

Few studies in the literature have directly examined exercise capacity in the adult SCD population through formal exercise testing.[8,12,50–54] Compared to that in our study, sample sizes in previously published studies have been relatively small. A major challenge to comparing the results from our study to data in other studies is the variability among studies in exercise testing protocols. These differences pertain to required effort (maximal versus submaximal), type of machine (cycle versus treadmill) and whether or not breath-by-breath, gas exchange was directly measured. In contrast to ours, other studies have focused on using gas exchange data to characterize cardiopulmonary responses during exercise challenge or on examining the relationship between fitness and specific cardiopulmonary complications such as pulmonary hypertension.[50,52] Although breath-by-breath gas exchange was not employed as part of the exercise testing performed in the CSSCD study, the Balke treadmill protocol is commonly used in large-scale epidemiology studies of fitness in the general population.[55–57] Importantly, our study supports the safety of maximal exercise testing using a protocol such as the Balke treadmill test in adults with SCD.

It was not surprising that exercise capacity was low among participants in the CSSCD cohort. Differences in exercise protocols and measurements used to define exercise capacity and fitness across the literature make it difficult to directly compare exercise capacity measured in the CSSCD to that reported in other studies. Whether we use estimated VO_2 max derived from treadmill duration or METS calculated from VO_2 max to define exercise capacity, exercise capacity in the CSSCD cohort was lower compared to levels reported in the literature for the general black population, for which fitness is already known to be lower compared to other race groups.[58] Mean estimated VO_2 max, for example, in the CSSCD participants was lower than that measured even for the lowest fitness group in NHANES study.[59]

We found that male sex, lower age, higher Hb and lower BMI were associated with better exercise capacity in participants in the CSSCD. Although this finding is not surprising given that these variables are known to be associated with fitness in the general population as well as in children and adolescents with sickle cell anemia, it further elucidates the contributions to exercise capacity in adults with SCD, for whom very little is currently known.[9,41,60–62]. We also found that having had an abnormal PFT in the CSSCD was associated with decreased exercise capacity on bivariate analysis and trended toward significance in our multivariable model. This finding is supported by the known relationship between reduced fitness and poor lung function in other disease populations such as COPD or conditions associated with restrictive lung disease.[63–67] In our analysis, we were not able to specifically examine the effect of restrictive versus obstructive lung disease on exercise capacity given the number of participants in the CSSCD with mixed patterns on PFT. Nonetheless, our finding that lower FEV_1 itself is independently associated with lower exercise capacity in adults with SCD warrants further investigation since greater annual declines in FEV_1 has also been associated with greater reductions in fitness among young adults in the general population.[68]

Our results did not support our hypothesis of an association between exercise capacity and overall mortality. This is in contrast to studies that suggest cardiopulmonary fitness is an important predictor of all-cause mortality in the general population as well as in other chronic conditions.[29,69–71] However, the small number of deaths in the CSSCD cohort and relative short follow-up may have affected our ability to discern a relationship. The group of SCD patients that made it into adulthood during this era or was able to complete maximal exercise testing may also have been inherently healthier. Although most clinical and laboratory characteristics were not different in patients who did versus did not undergo exercise testing, pain hospitalization rates and mortality were higher in patients who did not complete baseline exercise testing. Nonetheless, it was still valuable to examine the relationship between mortality and exercise capacity despite the possibility for a sampling bias that resulted in a “healthier” group of patients completing exercise testing. More feasible strategies may be needed in SCD to measure exercise capacity such as 6-minute walk distance or submaximal exercise testing, which may improve our ability to evaluate the relationship between exercise capacity and mortality. Finally, low exercise capacity in SCD is multifactorial in etiology and despite the known impact of cardiopulmonary complications on exercise capacity in SCD, mortality may be more directly associated with these complications or other pathophysiologic sequelae themselves rather than with reduced exercise capacity.

It was surprising that we did not find a relationship between exercise capacity and traditional indices of disease severity such as hospitalization for pain and ACS. This suggests that reduced exercise capacity in SCD could be more a function of physiologic derangements in exercise responses and less a function of absolute reductions in physical activity or increase in sedentary behavior, which might be expected of higher hospitalization rates for disease-related complications. Similar to other aspects of our analysis, existing studies that have examined this relationship in SCD are limited by variability in their approach to measuring exercise capacity and physical functioning as well as by their chosen outcomes of disease severity. In studies focusing on exercise capacity, reduced exercise capacity by 6-minute

walk distance or exercise testing in SCD has been associated with complications such as elevated TRJV, recurrent ACS or silent stroke.[10,50,72] In studies that focus instead on general physical functioning, poor self-reported physical functioning on HRQOL assessments is associated with increased pain.[3,73]

The retrospective nature of our analysis may have impacted our interpretation of the exercise test results. In the CSSCD, exercise testing was terminated by volitional exhaustion rather than using more objective criteria to assess maximal effort such as serum lactate or respiratory exchange ratio. However, maximal heart rates recorded for subjects at the end of exercise testing were on average about 85% of predicted maximal heart rates, which supports the maximal nature of testing in the CCSCD. Although quality control of exercise testing in the CSSCD could not be fully assessed, rigor could in part be assumed given the study's adoption of the modified Balke protocol, a well accepted and validated exercise test, as well as the completeness of the data elements collected during testing. Since breath-by-breath gas exchange data were not collected during exercise testing in the CSSCD study, we could not directly measure VO_2 or analyze specific parameters that allow for a deeper understanding of the cardiopulmonary response to exercise. Nonetheless, we used treadmill duration as a surrogate for exercise capacity and fitness in our study, which represents a common approach used in several other landmark epidemiological studies of fitness.[29,40–43] Finally, given the high degree of missing exercise data from the 2nd tests originally planned for this cohort, we could not assess change in fitness, which compared to baseline fitness may represent a more important risk predictor for mortality in SCD.

Several other limitations of our study warrant discussion. Participants enrolled in the CSSCD may not accurately reflect a contemporary cohort of adults with SCD given the inception date of the CSSCD, thus reducing the overall generalizability of our findings. The ability to reach adulthood in this era while living with SCD may have introduced a selection or survival bias toward the healthiest adults enrolled in the CSSCD. Moreover, a large number of participants did not undergo exercise testing, and we were unable to determine if more severe disease precluded some participants from undergoing exercise testing. Still, our cohort was large enough to include some deaths and more importantly, allowed us to examine other surrogates of disease severity such as pain and ACS hospitalizations. Another limitation of this study was our exclusion of TRJV, a known predictor of mortality in SCD, due to the large number of patients for whom TRJV was unquantifiable. The inability to differentiate unquantifiable from missing values due to technical challenges may explain why TRJV data has been omitted from published studies of CSSCD data to date. We did not look for other evidence of cardiac disease on echocardiography given that measurements required to diagnose diastolic dysfunction, for example, are also prone to technical error and assessing the quality of these measurements was beyond the scope of our analysis. Finally, although elevated N-terminal pro brain natriuretic peptide level may be a surrogate marker for pulmonary vascular disease, these data were not publically available through the NHLBI's BioLink dataset for the CSSCD study.

In conclusion, data from this study corroborate findings from other studies that have demonstrated poor exercise capacity in adults with SCD. Our results suggest that maximal exercise testing in adults with SCD is feasible and safe. Besides other known risk factors,

having an abnormal PFT or low percent-predicted FEV_1 may be associated with reduced exercise capacity in SCD. Hospitalization for pain or ACS, however, was not associated with reduced fitness levels. Given its utility as a prognostic biomarker in other populations, future prospective studies are warranted to further study exercise capacity and cardiopulmonary fitness, as well as change in fitness over time, and their relationship to disease severity and mortality in SCD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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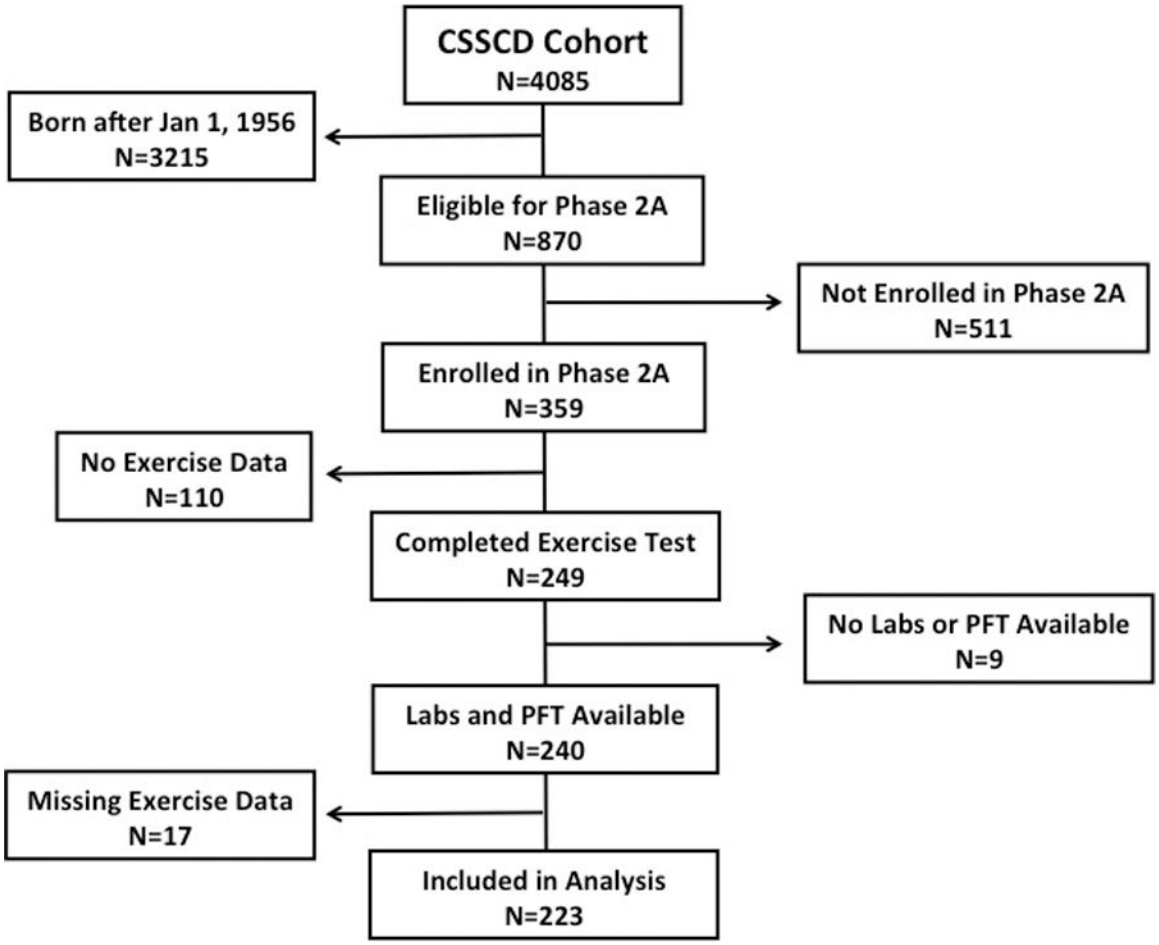

Figure 1.
Flow diagram of study participants enrolled in the CSSCD and their eligibility for inclusion in the analysis.

Table 1.

Characteristics of participants in the CSSCD who completed or did not complete baseline exercise testing

Variable	Exercise test		No exercise test		*p* value
	N	Values	N	Values	
Male, number (%)	223	80 (35.9)	136	51 (37.5)	0.756
SS or $S\beta^0$ thalassemia, number (%)	221	154 (69.7)	136	101 (74.3)	0.352
Obstructive lung disease, number (%)	219	25 (11.4)	99	8 (8.1)	0.373
Restrictive lung disease, number (%)	220	38 (17.3)	99	22 (22.2)	0.295
Chronic transfusions, number (%)	222	10 (4.5)	134	6 (4.5)	0.991
Hydroxyurea, number (%)	227	5 (2.2)	136	3 (2.2)	0.990
Mortality, number died (%)	223	9 (4.0)	136	24 (17.6)	**0.001**
Age[^], (yrs), mean±SD	223	42.5 ±7.4	136	44.0 ±8.3	0.071
Follow-up (yrs), mean±SD	223	3.1 ±0.5	136	2.8 ±0.8	**0.001**[†]
BMI[^], mean±SD	220	24.2 ±5.7	132	23.7 ±5.3	0.418
ACS hospitalization rate[*], mean±SD	223	0.04 ±0.13	136	0.05 ±0.16	0.630[†]
Pain hospitalization rate[*], mean±SD	223	0.31 ±1.11	136	0.64 ±1.56	**0.001**[†]
WBCs, ($x10^3$/ml), mean±SD	223	10.8 ±3.8	128	11.2 ±4.2	0.476
Haemoglobin, (g/dL), mean±SD	223	9.1 ±2.2	128	8.8 ±2.2	0.210
Platelet count, ($x10^3$/ml), mean±SD	218	366.0 ±125.6	123	345.9 ±139.1	0.174

ACS: acute chest syndrome; BMI: body mass index; SD: standard deviation; WBCs: white blood cells

[^]Age and BMI at phase 2A study entry

[*]Events per patient/year

[†]Mann-Whitney U test

Table 2.

Summary of exercise data for participants in the CSSCD who completed one or two exercise tests

Variable	N	All participants	Participants with two exercise tests			
			N	First test	Second test	*p* value
Duration on treadmill (minutes), mean±SD	223	11.6 ±5.2	100	12.1 ±5.0	12.2 ±4.7	0.764#
Peak incline, mean±SD	208	12.1 ±6.2	79	12.3 ±5.5	12.4 ±5.9	0.882
METS, mean±SD	223	5.9 ±1.7	79	5.9 ±1.5	5.9 ±1.6	0.873
Baseline, mean±SD						
HR (bpm)	223	77.1 ±14.2	97	75.6 ±14.0	78.2 ±14.8	0.05
Systolic BP (mm Hg)	221	119.0 ±17.1	97	114.9 ±14.3	120.4±16.3	**0.002**
End of study, mean±SD						
HR (bpm)	220	151.8 ±21.2	90	153.2 ±23.8	149.5 ±18.9	0.111
Systolic BP (mm Hg)	211	163.4 ±30.2	80	157.2 ±25.8	162.3 ±23.9	0.123
RPE	213	8.3 ±2.2	95	8.5 ±2.0	8.1 ±2.9	0.403#
Stage completed, number (%)						
0	223	5 (2.2)	99	1 (1.0)	1 (1.0)	0.784#
1 − 2	223	25 (11.2)	99	8 (8.1)	9 (9.1)	
3 − 4	223	51 (22.9)	99	25 (25.3)	22 (22.2)	
5 − 6	223	56 (25.1)	99	28 (28.3)	33 (33.3)	
7 − 8	223	48 (21.5)	99	19 (19.2)	16 (16.2)	
9 − 10	223	38 (17.0)	99	18 (18.2)	18 (18.2)	
Symptoms, number (%)						
Chest pain	223	6 (2.7)	99	5 (5.1)	5 (5.1)	1.00#
Dyspnea	223	69 (30.9)	99	28 (28.3)	41 (41.4)	**0.016**#
Dizziness	223	13 (5.8)	99	8 (8.1)	6 (6.1)	0.564#

BP: blood pressure; HR: heart rate; METS; Metabolic Equivalent of Task; RPE: Rated Perceived Exertion; SD: standard deviation

#Wilcoxon signed ranks test

Table 3.

Factors associated with exercise capacity among participants in the CSSCD

Variable	N	Low Fitness Tertile (N=74)	Intermediate Fitness Tertile (N=84)	High Fitness Tertile (N=65)	*p* value*
Age (years), mean±SD	223	45.2 ±8.2	43.1 ±7.5	41.3 ±6.0	**0.007**
SS or S/β^0 thalassemia, number (%)	222	58 (79.5)	55 (66.3)	41 (63.1)	0.078
Male sex, number (%)	223	17 (23)	24 (28.6)	39 (60)	< **0.001**
Baseline haemoglobin (g/dL), mean±SD	223	8.5 ±2.1	9.0 ±2.1	9.8 ±2.2	**0.003**
Baseline WBC (x10^3/ml), mean±SD	223	11.5 ±4.3	10.6 ±3.4	10.3 ±3.5	0.139
BMI at fitness test, mean±SD	194	25.1 ±7.1	25.2 ±5.8	23.3 ±4.6	0.111
Duration on treadmill (min), mean±SD	223	5.7 ±1.9	11.8 ±1.6	18.1 ±2.1	< **0.001**
Peak incline, mean±SD	208	5.4 ±2.6	12.5 ±2.2	19.8 ±2.8	< **0.001**
METS, mean±SD	208	4.0 ±0.7	6.0 ±0.6	8.0 ±0.8	< **0.001**
Abnormal PFT, number (%)	220	42 (58.3)	29 (34.9)	25 (38.5)	**0.008**
Pain hospitalization rate, 3 year retrospective, mean ±SD	223	0.38 ±0.00	0.33 ±0.00	0.31 ±0.00	0.630#
ACS hospitalization rate, 3 year retrospective, mean ±SD	223	0.03 ±0.00	0.06 ±0.00	0.03 ±0.00	0.426#

ACS: acute chest syndrome; BMI: body mass index; METS: Metabolic Equivalent of Task; PFT: pulmonary function test; SD: standard deviation; WBCs: white blood cells

^Exercise capacity defined by the duration on treadmill in minutes

*ANOVA for comparing means and chi-square test for comparing percentages, unless otherwise noted

#Kruskal-Wallis test

Table 4.

Multivariable tobit regression model for factors associated with fitness (N=215)

	β Coefficient (95% CI)	**SE**	***p* value**
Gender (female)	−3.34 (−1.80, −4.88)	0.78	< **0.001**
Genotype (SS or S/β^0 thalassemia)	−1.78 (−4.23, 0.66)	1.24	0.152
Age (years)	−0.14 (−0.24, −0.04)	0.05	**0.005**
Haemoglobin (g/dL)	0.56 (0.08, 1.04)	0.24	**0.023**
Abnormal PFT	−1.42 (−2.92, 0.07)	0.76	0.061
BMI at study entry	−0.23 (−0.37, −0.09)	0.07	**0.001**
Pain hospitalization rate	0.22 (−0.48, 0.92)	0.36	0.538
ACS hospitalization rate	−0.99 (–6.73, 4.76)	2.91	0.735

ACS: acute chest syndrome; BMI: body mass index; CI: confidence interval; PFT: pulmonary function test; SE: standard error

^ Fitness defined by the duration on treadmill in minutes

Table 5.

Multivariable negative binomial regression model for predicting pain and ACS hospitalizations (N=187)

	Prospective ACS Rate			Prospective Pain Rate		
	IRR	**95% CI**	***p* value**	**IRR**	**95% CI**	***p* value**
Gender (male)	1.80	0.66, 4.90	0.25	0.78	0.33, 1.85	0.58
Genotype (SS or S/β^0 thalassemia)	1.86	0.36, 9.62	0.46	2.74	0.76, 9.95	0.13
Age at exercise test (years)	0.99	0.90, 1.08	0.78	0.96	0.88, 1.03	0.24
Haemoglobin (g/dL)	1.21	0.90, 1.64	0.21	1.02	0.78, 1.33	0.9
Retrospective 3 year ACS hospitalization rate	31.60	4.68, 213.48	< **0.001**	N/A	N/A	N/A
Retrospective 3 year pain hospitalization rate	N/A	N/A	N/A	3.29	2.56, 4.23	< **0.001**
Exercise capacity[^]	0.95	0.85, 1.07	0.41	1.00	0.91, 1.10	0.92
Abnormal pulmonary function test	1.54	0.56, 4.23	0.41	1.28	0.56, 2.92	0.55

ACS: acute chest syndrome; CI: confidence interval; IRR: Incidence Rate Ratio; N/A: not applicable

[#]Prospective hospitalization rates for pain and ACS were calculated using events after exercise testing with ≥ 6 month follow up

[^]Exercise capacity defined by the duration on treadmill in minutes

Table 6.

Cox regression model for survival and predictors of mortality (N=176)

	Hazard Ratio (95% CI)	***p* value**
Gender (male)	6.47 (1.24, 33.88)	**0.02**
Age (years)	1.06 (0.97, 1.16)	0.22
Haemoglobin (g/dL)	0.55 (0.37, 0.84)	**0.005**
Exercise capacity[^]	0.98 (0.85, 1.13)	0.82
Abnormal pulmonary function test	1.04 (0.22, 4.86)	0.96

CI: confidence interval

[^] Exercise capacity defined by the duration on treadmill in minutes

Note: Sickle cell genotype (SS or S/β^0 thalassemia) is not included in the model because patients with non-SS or S/β^0 thalassemia had no deaths, and so the model does not converge to a stable solution.