Tables

Table S1. Baseline demographics and DXA results of the Hb SS/Hb Sβ^0-thalassemia subgroup in SCCRIP BMD cohort						
	All (n=196)		Female (n=93)		Male (n=103)	
	School age	Adolescent	School age	Adolescent	School age	Adolescent
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Variables	60 (30.6)	136 (69.4)	26 (28.0)	67 (72.0)	34(33.0)	69 (67.0)
Age at DXA (years)						
Mean (SD)	7.2 (1.20)*	14.7 (2.17)*	7.1 (0.92)*	14.7 (2.17)*	7.3 (1.38)*	14.7 (2.19)*
Hydroxyurea use						
No	12 (20.0)	24 (17.7)	5 (19.2)	10 (14.9)	7 (20.6)	14 (20.3)
Yes	48 (80.0)	112 (82.3)	21 (80.8)	57 (85.1)	27 (79.4)	55 (79.7)
Chronic RBC transfusions						
No	59 (98.3)	130 (95.6)	26 (100)	63 (94.0)	33 (97.1)	67 (97.1)
Yes	1 (1.7)	6 (4.4)	0 (0)	4 (6.0)	1 (2.9)	2 (2.9)
Height (cm)						
Mean (SD)	121.5 (9.38)*	159.4 (12.29)*	119.7 (4.18)*	157.8 (9.11)*	122.8 (10.48)*	161.1 (14.63)*
Height-for-age Z-scores						
Mean (SD)	-0.23 (0.92)	-0.28 (1.1)	-0.37 (0.75)	-0.15 (1.09)	-0.12 (1.03)	-0.41 (1.11)
TBLH BMD (g/cm2)						
Mean (SD)	0.57 (0.07)*	0.83 (0.11)*	0.56 (0.06)*	0.83 (0.08)*	0.58 (0.08)*	0.83 (0.13)*
TBLH aBMD Z-score						
Normal	44 (73.3)	77 (56.6)	19 (73.1)	42 (62.3)	25 (73.5)	35 (50.7)
Low	16 (26.7)	59 (43.4)	7 (26.9)	25 (37.3)	9 (26.5)	34 (49.3)
TBLH aBMD Z-score						
Mean (SD)	-1.4 (0.86)*	-1.9 (1.19)*	-1.3 (0.89)*	-1.8 (1.11)*	-1.47 (0.85)*	-2.0 (1.25)*
TBLH Ht-aBMD Z-score						
Normal	56 (93.3)*	95 (69.9)*	24 (92.3)	50 (74.6)	32 (94.1)*	45 (65.2)*
Low	4 (6.7)*	43 (30.2)*	2 (7.7)	18 (25.4)	2 (5.9)*	24 (34.8)*
TBLH Ht-aBMD Z-score						
Mean (SD)	-0.97 (0.61)*	-1.62 (0.98)*	-0.90 (0.65)*	-1.57 (0.94)*	-1.02 (0.58)*	-1.66 (1.02)*
DXA Dual-energy X-ray absorptiometry; SCCRIP Sickle Cell Clinical Research and Intervention Program; BMD Bone mineral density; RBC Red blood cell; Chronic RBC transfusions ≥ 4 RBC transfusions per year						
TBLH Total body less head; aBMD Areal bone mineral density; Ht-aBMD Height-adjusted areal bone mineral density *p<0.05 school age versus adolescent values						

Table S2. Clinical characteristics of the Hb SS/Hb Sβ^0-thalassemia subgroup in SCCRIP BMD Cohort						
	All (n=196)		**Female (n=93)**		**Male (n=103)**	
	Normal BMD n(%)	**Low BMD, n(%)**	**Normal BMD, n(%)**	**Low BMD, n(%)**	**Normal BMD, n(%)**	**Low BMD, n(%)**
Variables	**151(77.0)**	**45(23.0)**	**74 (79.6)**	**19 (20.4)**	**77 (74.8)**	**26 (25.2)**
Age at DXA (years)						
Mean (SD)	11.8 (4.06)*	14.4 (2.91)*	12.1 (4.06)	14.2 (2.98)	11.5 (4.05)*	14.5(2.90)*
Age category						
School age	55 (37.1)*	4 (8.9)*	24 (32.4)	2 (10.5)	32 (41.6)*	2 (7.7)*
Adolescent	95 (62.9)*	41 (91.1)*	50 (67.6)	17 (89.5)	45 (58.4)*	24 (92.3)*
VOE per year (total)						
Mean (SD)	0.36 (0.50)*	0.26 (0.52)*	0.32 (0.43)	0.35 (0.66)	0.40 (0.55)	0.20 (0.39)
VOE per year (2 years to DXA)						
Mean (SD)	0.89 (2.64)	0.89 (2.28)	0.77 (1.88)	0.74 (1.37)	1.01 (3.22)	1.00 (2.79)
VOE total (categorical)						
< 5 times	60 (39.7)*	26 (57.8)*	25 (33.8)*	12 (63.2)*	35 (45.5)	14 (53.9)
5-10 times	50 (33.1)*	10 (22.2)*	33 (45.6)*	2 (10.5)*	17 (22.1)	8 (30.8)
> 10 times	41 (27.2)*	9 (2.0)*	16 (21.6)*	5 (26.3)*	25 (32.5)	4 (15.4)
Hydroxyurea use						
No	29 (19.2)	7 (15.6)	12 (16.2)	3 (15.8)	17 (22.1)	4 (15.4)
Yes	121 (80.8)	38 (84.4)	62 (83.8)	16 (84.2)	60 (77.9)	22 (84.6)
Hydroxyurea duration						
< 5 years	92 (60.9)	23 (51.1)	45 (60.8)	10 (52.6)	47 (61.0)	13 (50.0)
5-10 years	22 (14.6)	7 (15.6)	9 (12.2)	2 (10.5)	13 (16.9)	5 (19.2)
> 10 years	37 (24.5)	15 (33.3)	20 (27.0)	7 (36.8)	17 (22.1)	8 (30.8)
Hydroxyurea duration (years)						
Mean (SD)	4.48 (4.21)	4.98 (4.33)	4.47 (4.17)	4.71 (3.83)	4.50 (4.27)	5.17 (4.73)
Chronic RBC transfusions						
No	146 (96.7)	43 (95.6)	71 (96.0)	18 (94.7)	75 (97.4)	25 (96.2)
Yes	5 (3.3)	2 (4.4)	3 (4.0)	1 (5.3)	2 (2.6)	1 (3.8)
Chronic pain						

No	147 (97.3)	41 (91.1)	73 (98.7)	19 (100.0)	74 (961)	22 (84.6)
Yes	4 (2.7)	4 (8.9)	1 (1.3)	0 (0)	3 (3.9)	4 (15.4)
Hip osteonecrosis						
No	146 (96.7)*	40 (88.9)*	74 (100.0)	19 (100)	72 (93.5)	21 (80.8)
Yes	5 (3.3)*	5 (11.1)*	0 (0)	0 (0)	5 (6.5)	5 (19.2)
Vitamin D status						
Normal	45 (31.3)	9 (22.5)	21(30.0)	2 (10.5)	24 (32.4)	7 (33.3)
Insufficient	50 (34.7)	17 (42.5)	28 (40.0)	7 (36.8)	22 (29.7)	10 (47.6)
Deficient	49 (34.0)	14 (35.0)	21 (30.0)	10 (52.6)	28 (37.8)	4 (19.1)

BMD Bone mineral density; SCD Sickle cell disease; VOE Vasoocclusive episode; RBC Red blood cell; Chronic RBC transfusions $\geq$ 4 times/year; Vitamin D status (normal > 30 ng/ml, insufficient 20-30 ng/ml, deficient < 20 ng/ml);

*$p < 0.05$ in normal vs. low BMD per variable

Table S3. Laboratory parameters of the Hb SS/Hb Sβ^0-thalassemia subgroup in SCCRIP BMD cohort						
	All (n=196)		**Female (n=93)**		**Male (n=103)**	
	Normal BMD (n=151)	**Low BMD (n=45)**	**Normal BMD (n=74)**	**Low BMD (n=19)**	**Normal BMD (n=77)**	**Low BMD (n=26)**
Variables	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
WBC (x10^3 mm^3)	10.1 (4.26)	9.9 (3.52)	9.5 (4.12)	9.9 (4.42)	10.6 (4.35)	9.9 (2.74)
Hemoglobin (g/dL)	9.3 (1.31)	9.1 (1.03)	9.2 (1.16)	9.0 (0.94)	9.4 (1.43)	9.1 (1.12)
Platelets (mm^3)	389 (183.7)	419 (184.8)	361(174.9)	435(203.5)	416 (189.1)	407 (172.6)
LDH (units/L)	489 (178.4)	451 (152.4)	448 (149.8)	415 (136.1)	528 (195.1)	478 (160.7)
Total bilirubin (mg/dL)	2.3 (1.38)*	2.8 (1.66)*	2.2 (1.12)	2.8 (1.82)	2.4 (1.59)	2.8 (1.58)
Indirect bilirubin (mg/dL)	2.3 (1.30)*	2.8 (1.51)*	2.2 (0.98)*	3.0 (1.59)*	2.4 (1.53)	2.7(1.48)
Fetal hemoglobin (%)	18.4 (9.8)*	14.7 (7.32)*	18.5 (9.93)*	13.7 (6.79)*	18.3 (9.74)	15.4 (7.80)
Albumin (g/dL)	4.5 (0.28)	4.4 (0.29)	4.5 (0.29)	4.4 (0.27)	4.5 (0.26)	4.4 (0.31)
ALP (units/L)	153.3 (58.38)	139.0 (59.41)	137.7 (56.11)	121.5 (63.12)	168.0 (57.02)	152.6 (53.8)
AST/SGOT (units/L)	39.3 (16.39)	37.3(12.25)	36.4 (16.45)	34.0 (11.09)	42.1 (15.94)	40.0 (12.72)
Calcium (mg/dL)	9.5 (0.38)*	9.3 (0.31)*	9.4 (0.39)	9.4 (0.31)	9.5 (0.37)*	9.3 (0.30)*
Creatinine (mg/dL)	0.44 (0.13)	0.46 (0.11)	0.43 (0.12)	0.46 (0.10)	0.45 (0.14)	0.47 (0.12)
BUN (mg/dL)	7.4 (2.74)	6.9 (1.96)	7.1 (2.26)	6.5 (2.20)	7.7 (3.11)	7.1 (1.77)

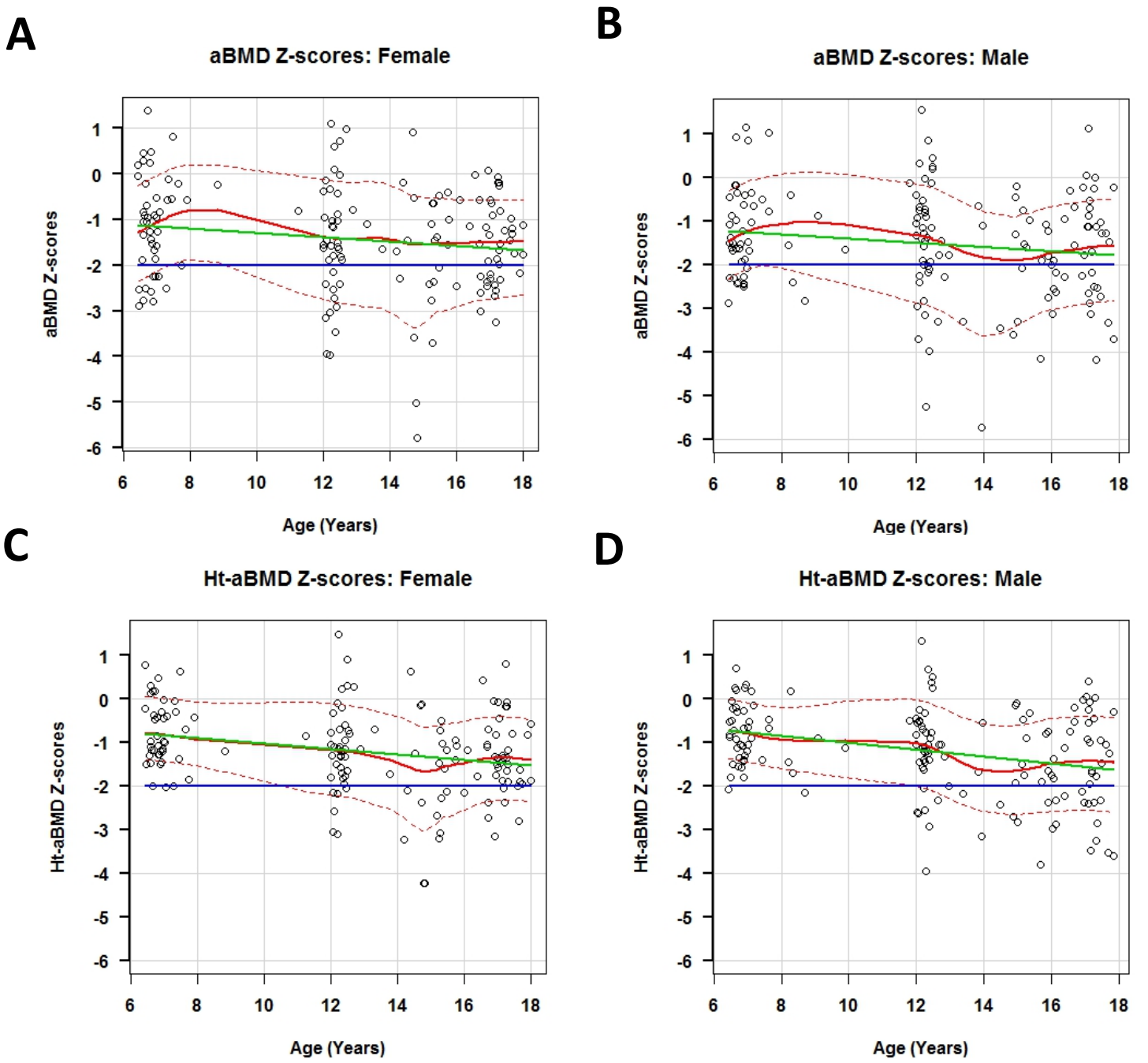
Vitamin D (ng/ml)	25.6 (12.5)	22.9 (9.0)	26.0 (12.55)*	19.1 (8.87)*	25.2 (12.54)	26.4 (7.77)
SCCRIP Sickle Cell Clinical Research and Intervention Program; BMD Bone mineral density; WBC White blood cell; ALP Alkaline phosphatase; AST Aspartate aminotransferase; SGOT Serum glutamic-oxaloacetic transaminase; BUN Blood urea nitrogen;						
*$p < 0.05$ in normal versus low BMD per variable						

Table S4: Univariate logistic regression of clinical and laboratory correlates in SCCRIP cohort				
	Total cohort (n=308)		**Hb SS/Sβ^0-thalassemia subset (n=196)**	
Variables	**Odds ratio (95% CI)**	***p*-value**	**Odds ratio (95% CI)**	***p*-value**
SCD genotype		0.000385		
Hb SC	0.18(0.0617-0.5126)	0.0014		
Hb Sß+ thalassemia	1.07(0.4312-2.6788)	0.88		
Hb SS/Sß0 thalassemia (ref)				
Gender		0.38		0.40
Male	1.30 (0.73-2.33)		1.33 (0.68-2.61)	
Female (ref)				
Age (years)	1.20 (1.10-1.31)	4.4×10^{-5}	1.21 (1.09-1.34)	2.2×10^{-4}
Age category		1.6×10^{-4}		0.00096
Adolescent	7.57 (2.65-21.61)		6.15 (2.09-18.07)	
School age (ref)				
Hydroxyurea use		0.041		0.53
Yes	1.93 (1.03-3.63)		1.33 (0.54-3.28)	
No (ref)				
Hydroxyurea duration		0.11		0.44
5-10 years	2.01 (1.00-4.03)	0.049	1.64 (0.77-3.48)	0.2
>= 10 years	1.75 (0.69-4.42)	0.24	1.29 (0.49-3.38)	0.61
<5 years (ref)				
Hydroxyurea duration (years)	1.07 (1.00-1.14)	0.058	1.03 (0.95-1.11)	0.47
Chronic pain		0.027		0.078
Yes	3.99 (1.17-13.57)		3.61 (0.87-15.06)	
No (ref)				
Hip osteonecrosis		0.0068		0.048
Yes	4.32 (1.50-12.47)		3.68 (1.01-13.32)	
No (ref)				
Chronic RBC transfusions		0.054		0.71
Yes	3.77 (0.98-14.52)		1.37 (0.26-7.30)	
No				
Hemoglobin (mg/dL)	0.76 (0.63-0.93)	0.0065	0.85 (0.64-1.12)	0.24
Total bilirubin (mg/dL)	1.37 (1.13-1.67)	0.0015	1.24 (1.00-1.54)	0.049
Indirect bilirubin (mg/dL)	1.34 (1.06-1.69)	0.014	1.29 (1.01-1.65)	0.042

Table S4: Univariate logistic regression of clinical and laboratory correlates in SCCRIP cohort				
	Total cohort (n=308)		**Hb SS/Sβ^0-thalassemia subset (n=196)**	
Fetal hemoglobin (%)	0.98 (0.94-1.01)	0.18	0.95 (0.91-1.00)	0.032
Calcium (mg/dL)	0.37 (0.15-0.88)	0.025	0.32 (0.12-0.86)	0.024
Vitamin D status		0.2392		0.5042
Deficient	1.86 (0.79-4.40)	0.15	1.4 (0.55-3.55)	0.48
Insufficient	1.91 (0.83-4.39)	0.13	1.7 (0.69-4.193	0.25
Normal (ref)				
BMD Bone mineral density; SCCRIP Sickle Cell Clinical Research and Intervention Program; SCD Sickle Cell Disease; RBC Red blood cell (chronic transfusions ≥4 per year)				

Figure

Total body less head areal bone mineral density Z-scores (aBMD Z-scores) versus chronological age (years) for females (panel A) and males (Panel B), compared with height-adjusted total body less head aBMD Z-scores (Ht-aBMD Z-scores) versus chronological age (years) for females (panel C) and males (Panel D) in the Sickle Cell Clinical Research Program (SCCRIP) pediatric cohort. Low bone density is defined as aBMD Z-scores or Ht-aBMD Z-scores ≤ -2 (blue horizontal line)


A
aBMD Z-scores: Female
aBMD Z-scores
Age (Years)
B
aBMD Z-scores: Male
aBMD Z-scores
Age (Years)
C
Ht-aBMD Z-scores: Female
Ht-aBMD Z-scores
Age (Years)
D
Ht-aBMD Z-scores: Male
Ht-aBMD Z-scores
Age (Years)

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