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Research Article

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ABSTRACT

Objectives: SCD is a rare, inherited blood disorder causing acute and chronic complications that affect physical, psychological, and social well-being. This study examines SCD patient characteristics using a biopsychosocial model integrating biological, quality-of-life (QoL), and social factors across life stages.

Methods: This observational study, conducted between November 2022 and July 2024 at a tertiary care hospital in Northern Italy, included patients aged 4-25 years with confirmed SCD. Participants underwent cognitive and QoL assessments; genotype, hospital visits, treatments, and socio-demographic data were collected. Wechsler scales assessed intellectual abilities; PROMIS questionnaires measured QoL. Analyses were performed with SPSS.

Results: Eighty-nine patients were enrolled. Profiles showed age-related clinical, cognitive, and psychosocial variations. Around 45% reported anxiety and depression, and 50% experienced social isolation and pain interference. Adolescents and young adults (12-25 years) exhibited higher psychological vulnerability—depression, pain interference, and fatigue—than younger groups ($P<.007$). Cognitive performance was below normative means, particularly in executive functions ($P = .039$). Working memory and processing speed were most affected, declining with age. Significant differences emerged in Verbal Comprehension [$F(3,82) = 6.473$, $P < .001$] and Perceptual Reasoning [$F(3,82) = 2.987$, $P = .036$], with poorer outcomes in older participants. Visuospatial skills were relatively preserved but declined in young adults.

Conclusions: Age-specific risk patterns highlight the need for developmentally tailored, multidisciplinary care. Early detection of cognitive and emotional vulnerabilities, together with preventive strategies, may reduce long-term complications and improve QoL. However, the cross-sectional design of the study limits causal inferences. Overall, findings support holistic care models addressing medical, cognitive, psychological, and social dimensions of SCD.

KEYWORDS: SCD, bio-psycho-social model, cognitive assessments, quality of life

LAY SUMMARY

This study examines SCD using a comprehensive approach that considers biological, quality-of-life, and social factors across different age groups. Researchers assessed 89 SCD patients aged 4-25 at a hospital in Northern Italy, evaluating their cognitive abilities, quality of life, and medical history. Key findings reveal that nearly half of the patients reported symptoms of anxiety, depression, social isolation, and pain interference, with adolescents and young adults (12-25 years) showing more psychological vulnerability than younger patients. Cognitive performance was below average, especially in executive functions, working memory, and processing speed, which worsened with age. Verbal Comprehension and Perceptual Reasoning were poorer in older participants, compared to the younger groups. These results emphasize the need for age-specific, multidisciplinary care in SCD. Early detection of cognitive and emotional issues, combined with preventive strategies, may help reduce long-term complications and improve quality of life. The study supports a holistic care approach addressing medical, cognitive, psychological, and social aspects of SCD.

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INTRODUCTION

SCD is an inherited hemoglobinopathy caused by a point mutation in the beta-globin gene. This mutation results in the production of an abnormal hemoglobin variant known as hemoglobin S. Under low oxygen conditions, hemoglobin S can polymerize, causing red blood cells to adopt the characteristic sickle shape. The disease is characterized by a complex pathophysiology, including chronic hemolytic anemia, vasculopathy, and vaso-occlusion, associated with sudden, acute, and often severe complications, leading to hospitalizations of varying duration and, in some cases, life-threatening outcomes.[1,2] The most common acute complications of SCD include vaso-occlusive crises, acute chest syndrome, and central nervous system events such as stroke and silent cerebral infarcts,[3-8] which in turn lead to neurocognitive deficits.[9]

In Italy, the SCD genotype is predominantly observed in individuals of African descent, but it is also found among individuals from southern Italy, the Middle East, and South Asia.[10] The chronic nature of SCD affects patients' lives across multiple dimensions, extending far beyond individuals' physical health. Moreover, Socio-economic factors such as lower parents' education, family income or limited community resources may contribute to some of the psychological and physical consequences of the disease.[11-14] Recurrent crises and hospitalizations significantly impact patients' education and employment, often resulting in frequent absences from school or work. These challenges are further accompanied by potential psychological distress, stemming from physical pain and the uncertainty of disease manifestations. Patients with SCD face, indeed, not only the daily burden of living with the disease but also with its several unpredictable complications.[15]

Neurocognitive deficits are among the most frequently reported complications of SCD.[9,12] Studies examining medical and cognitive factors have revealed that strokes (11%) and silent cerebral infarctions (17%-35%) are associated with a higher risk of cognitive impairments.[8,12,16] Following cerebrovascular events or abnormal brain development due to anemia, approximately 40% of individuals with SCD experience neurocognitive impairments, including slower processing speeds, reduced working memory, and executive dysfunction.[12,17-19] Notably, individuals with lower IQs are more vulnerable to cognitive decline and behavioral difficulties.[18,20,21] In synthesis, genetic, physical, psychological, and socio-economic factors collectively contribute to the development and impact of SCD on individuals.

Given the complexity and multifactorial nature of SCD manifestations, the biopsychosocial model provides an ideal framework for analyzing the disease's impact. Unlike the biomedical model, which attributes the etiology of pathology solely to physio-chemical processes, the biopsychosocial model proposes that health and illness result from the interaction of biological, psychological, and social factors.[22,23]

Although SCD has been described in the literature from various perspectives, relatively few studies have investigated the interconnected relationships among its biological, social, and psychological factors within a biopsychosocial framework across the lifespan. To date, the biopsychosocial model has primarily been applied to examine specific SCD symptoms, for example pain interference within particular target groups, such as children or adults[24,25] or to investigate neuropsychological functioning at specific ages.[14] Moreover, research on SCD has primarily focused on examining the relationships between only 2 or 3 aspects of patients' lives. For instance, Essien et al.[26] found that psychological distress increases with higher hospitalization rates, particularly during adolescence. Similarly, Dairi et al.[27] highlighted the impact of social determinants of health, such as low income and limited education, in exacerbating psychological distress of SCD patients. These studies underline the fragmentation in the application of the bio-psycho-social model in the study of SDC up until now, which has been limited in scope. None of these studies have comprehensively addressed the interplay of biological, psychological, and social factors across different age groups.

This cross-sectional study explores the complex interplay of bio-psycho-social factors in individuals with SCD across different age groups, providing insights that may inform future longitudinal research on how SCD's impact potentially varies throughout development. Building on prior research[28,29] and grounded in the biopsychosocial theory,[30] the present study seeks to categorize the specific and multidimensional determinants of quality of life for children, adolescents, and young adults (AYAs) with SCD within a biopsychosocial framework. The data are derived from a cross-sectional cohort of 89 patients referred to the Sickle Cell Center of the Azienda Ospedale-Università di Padova, a national reference center for sickle cell anemia. This preliminary descriptive study will provide a foundation for prospectively designing comprehensive bio-psycho-social interventions and therapeutic pathways tailored to the patient's developmental phase. The data analysis was structured into 3 exploratory phases: first, an analysis of the general characteristics of the target population was conducted, second, the evolution of patients' clinical profiles and quality of life across different developmental stages was examined; finally, the pattern of associations between different set of factors—medical/clinical factors, perceived quality of life, cognitive abilities, and socio-demographic factors—was explored.

MATERIALS AND METHODS

Participants selection: inclusion/exclusion criteria

The selection of medical, psychological, cognitive, and social variables for inclusion in the biopsychosocial analysis was based on a comprehensive review of the literature and meta-analyses conducted by Prussien.[12,20,31] These variables were prospectively collected as part of the ongoing Natural History Study at the Center, initiated in 2007.

Participant inclusion criteria: having a confirmed diagnosis of SCD; being at least 4 years old; being sufficiently fluent in Italian (defined as at least 2 years of exposure to the Italian language to avoid bias in cognitive evaluations due to insufficient language comprehension); and being in a stable clinical condition (ie, at least 4 weeks post-acute event). Participation required informed consent from adult participants or from parents/legal guardians for minors. Exclusion criteria encompassed a diagnosis of cognitive impairment not directly attributable to SCD or its complications, as well as insufficient compliance with the study criteria (defined as fewer than 2 visits to the reference center during the study period).

For the present study, recent data collected between November 2022 and July 2024 at the Sickle Cell Center of the Azienda Ospedale-Università di Padova, a university teaching hospital in northeastern Italy, were analyzed. Eligible children and adolescents/young adults (AYAs) with a diagnosis of SCD were approached by the researcher during routine visits and the purpose of the study was explained. After obtaining informed consent cognitive and psychological assessments were integrated into participants' routine care.

Data collected for the study

Data collected for the study included: clinical data, such as patients' genotype and clinical history, socio-demographic data, such as education level and the presence of government subsidies; health-related quality of life data, such as fatigue and psychological information; and cognitive data, related to the patient's neurocognitive profile.

Clinical data

Clinical variables considered in this study included: patient genotypes, history of emergency room visits and of hospital admissions (including duration and number), pharmacological treatments (eg, hydroxyurea-HU) or combined HU treatments (eg, chronic transfusions, or participation in clinical trials), and the number of routine follow-up visits that disrupted the patients' daily routines (eg, school or work). The data were retrieved from the SCD Natural History database and regarded the time of the study.

Socio-demographics data

To evaluate socio-demographic status, a questionnaire adapted from Anderson et al.[32] and Khan et al.[33] was administered. The questionnaire was completed by patients 18 years of age and older, while for minors, it was completed by their parents or legal guardians acting as proxies for their children. It took approximately 10 minutes to complete (Table S1). Data were collected on the family's education level and employment status. Access to state welfare benefits was investigated through the presence of a civil disability certificate, a document that certifies the degree of disability necessary to access a range of economic and welfare benefits such as disability pensions, healthcare exemptions, and other economic support measures provided by Italian legislation; and/or specific benefits provided by Law 104/99, which recognizes rights and benefits for individuals with disabilities, including work permits, tax benefits, and educational assistance (Article 39, paragraph 1 of Law 448/2001; Article 3, paragraph 131 of Law 350 of December 24, 2003; Article 3, paragraph 3 of Law 104/92).

Health-related quality of life data

Quality of life assessment was conducted using the PROMIS self-report questionnaires. The PROMIS Pediatric Profile 49 v2.0 was used for pediatric self-assessment in participants aged 8 to 18 years, and it addressed 7 domains: physical mobility, anxiety, depressive symptoms, fatigue, peer relationships, pain interference, and pain intensity (PROMIS Manual). The PROMIS Adult Profile 57 v2.1 was used for adults and included 8 domains: physical mobility, anxiety, depressive symptoms, fatigue, sleep disturbances, social role participation, pain interference, and pain intensity. Each questionnaire was administered in the presence of a researcher to clarify any questions.

Cognitive data

The assessment of intellectual functions was conducted using the 10 main subtests of the Wechsler scales.[34-36] The evaluation involved a session with each patient, typically lasting 60-90 minutes. To prevent fatigue and maintain focus, some patients' assessments were divided into multiple shorter sessions conducted over a period of a few weeks.

The Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (WPPSI-IV), was employed to assess the child group (ages 4:0 to 7:7 years). For each participant, the 6 primary indices were calculated: Verbal Comprehension (VCI) Visual Spatial (VSI) Fluid Reasoning (FRI), Working Memory (WMI), and Processing Speed (PSI) and Full Scale Intelligence Quotient (FSIQ).[36]

For children and adolescents aged 7:8 to 16:11 years, the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV), was utilized. For each participant, the 5 primary indices were calculated: Verbal Comprehension (VCI), Perceptual Reasoning (PRI), Working Memory (WMI), Processing Speed (PSI) and Full Scale Intelligence Quotient (FSIQ).[34] The WISC-IV was used in this study rather than the more recent WISC-V due to the unavailability of the Italian version of the WISC-V during the data collection period.

For participants over 18 years old, the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV), was used. For each participant, the 5 primary indices were calculated: Verbal Comprehension (VCI), Perceptual Reasoning (PRI), Working Memory (WMI), Processing Speed (PSI) and Full Scale Intelligence Quotient (FSIQ).[35]

The comparison of indices across the 3 Wechsler scales was conducted aligning the indices that measure the same psychometric constructs.[37,38] The division into age groups was determined based on the boundaries of the Wechsler scales, with the transition from childhood to adolescence set at 12 years, aligning with studies on preadolescence.[39,40]

Statistical data analyses

Statistical analyses were conducted with the IBM SPSS Statistics 23® (Version 25).[41] Descriptive statistics were used to explore data distribution and pattern. Preliminary analyses involved zero-order correlations, to examine the association between clinical, socio-demographic, quality of life, and cognitive factors. Finally, between-group comparison analyses were conducted to explore differences between age-groups using Chi-square test, ANOVA, and Kruskal-Wallis tests, depending on the scales of the variables and normality of distribution. Based on ANOVAs, pairwise group comparisons were run by Student's *t* tests.

The study protocol has been approved by the local ethics committee (approval 3068P). This study was performed in accordance with the ethical principles established by the Declaration of Helsinki and with the regulations of the European General Data Protection Regulation (GDPR) and informed consent was collected by caregivers of patients or adult patients.

RESULTS

Descriptive analysis

Socio-demographics and clinical data: descriptive analyses

Out of the 129 patients, 40 patients were not eligible (see below the reasons). Eighty-nine patients were approached to perform the cognitive and psychological evaluation and all accepted (100%). All 89 completed the cognitive assessments, while 60 completed both cognitive and psychological evaluations, representing a 67% completion rate for the full assessment battery.

The division of groups by age was defined based on the ranges of the Wechsler scales: WPPSI-V up to 7 years old, WISC-IV up to 17 years old, and WAIS-IV for those over 18 years old. Additionally, the group that was administered the WISC-IV was further divided into 2 subgroups, as described by Erikson[39] and Bottesi,[40] to distinguish between pre-adolescents and adolescents.

The questionnaire for collecting socio-demographic information was completed by adult patients or by the caregivers of minor patients. Table 1 presents the descriptive statistics of the population for demographic and clinical factors in the total sample and by age group. The participant group consisted of a similar number of men and women, with most individuals having a severe genotype, either homozygous (SS) or Sbeta°. More than half of the sample was taking hydroxyurea. Additionally, the means and ranges of emergency room visits (with or without hospitalization) and hospital admissions are provided, showing the variability in hospital entries (visits and admissions). Overall, the number of hospitalizations was higher in the group aged over 18 years and lower in the 8-11-year age group.

Table 2 presents the distribution of social factors for the total sample and across different age groups. The data indicate that less than 20% of participants come from single-parent households, with years of education ranging from preschool to university level. Additionally, the prevalence of disability certification exceeds that of benefits granted under Law 104 and school support services.

Health-related quality of life: descriptive statistics

The PROMIS questionnaire was fully administered to 60 patients, but it was not administered to the 16 children in the 4-7-year-old group, and 3 additional evaluations were excluded due to incompleteness.

Overall, 16.9% of the total participants completed the adult version of PROMIS (PROMIS-57), while 73.2% received the PROMIS Pediatric Profile 49 v2.0. In Table S1, the mean scores (and standard deviation) for each age group, as well as for the entire sample are presented. Table 3 reports the severity percentages, based on the PROMIS calibration, for each domain of the PROMIS questionnaire.[42] The data show that approximately 45% of patients present anxious and depressive symptoms, perception of fatigue, while 40% present pain interference and approximately 50% report social isolation. Additionally, the AYA population (age groups 12-17 and >18) exhibits greater vulnerability in perceived quality of life compared to younger age groups (7-11 years).

Cognitive data: descriptive statistics

The Wechsler scales were administered to 85 participants. Table S2 presents the average scores (SD) for each age group and for the total sample.

Figure 1 shows the distribution of the 5 main indices based on the scores obtained by the participants. The data generally indicates a performance below the average (=100). In particular, the boxplot that describes the best trend is that of visuo-perceptual abilities. The areas in which the participants show the greatest difficulties are working memory (WMI) and processing speed (PRI) that refer to the Executive Functions domain. Although in this domain several children show a performance below 85 IQ, on average their performance remains

Table 1. Descriptive statistics of demographic, medical factors for the entire population and by age group.

	Total ***N* = 89**	**Age 4-7** ***N* = 16**	**Age 8-11** ***N* = 30**	**Age 12-17** ***N* = 26**	**Age >18** ***N* = 17**
Age mean (SD)	12.39 (5.64)	6.00 (0.89)	9.03 (1.54)	14.19 (1.92)	21.59 (2.69)
Months mean (SD)	152.63 (69.12)	73.94 (10.21)	111.07 (18.84)	175.62 (23.19)	264.88 (31.85)
Male Sex (%)	43 (48.3%)	8 (50%)	13 (43.3%)	13 (50%)	9 (52.9%)
Family's origin (%)					
Geographic Europe	8 (9%)	2 (12.5%)	2 (7.2%)	2 (7.7%)	2 (11.8%)
North Africa	1 (1.1%)	0	0	0	1 (5.9%)
Central Africa	7 (7.9%)	0	3 (10%)	2 (7.7%)	2 (11.8%)
Occidental Africa	71 (79.8%)	14 (87.6%)	25 (83.3%)	22 (84.5%)	10 (58.8%)
North America	1 (1.1%)	0	0	0	1 (5.9%)
Central America	1 (1.1%)	0	0	0	1 (5.9%)
Born in Italy (%)	64 (71.9%)	12 (75%)	23 (76.7%)	20 (76.9%)	9 (52.9%)
Genotype severe (%)	78 (87.6%)	15 (93.8%)	26 (86.7%)	21 (80.8%)	16 (94.1%)
Hydroxyurea (%)	75 (84.3%)	13 (81.3%)	28 (93.3%)	21 (80.8%)	13 (76.5%)
Combination therapy with HU (%)	20 (22.5%)	1 (25%)	1 (3.3%)	6 (23.1%)	9 (52.9%)
Number of ambulatory visits (days)	2-27	5-23	2-14	2-27	3-22
Mean of ambulatory visits (SD)	10.84 (5.60)	11.06 (4.67)	8.17 (2.64)	11.58 (6.72)	14.24 (6.15)
Number of ER accesses (days)	0-11	0-5	0-9	0-8	0-11
Mean of ER accesses (SD)	1.36 (2.10)	1.19 (1.56)	1.43 (2.11)	1.12 (1.73)	1.76 (2.99)
Length of stay of admission (days)	0-17	0-17	0-10	0-10	0-14
Mean of length of stay of admissions (SD)	3.23 (3.83)	3.53 (4.91)	2.62 (2.87)	3.08 (3.28)	4.27 (4.92)

The percentage data describe the presence of the variable. All the clinical, psychosocial and cognitive variables refer to the period from November 2022 to July 2024.
Abbreviations: SD = standard deviation; ER = emergency room.

Table 2. Social factors for the entire population and by age group.

	Total $N = 89$	Age 4-7 $N = 16$	Age 8-11 $N = 30$	Age 12-17 $N = 26$	Age >18 $N = 17$
Single-parent family (%)	15 (16.9%)	1 (6.3%)	2 (6.7%)	2 (7.7%)	10 (58.8%)
School years (SD)	6.38 (4.77)	0.50 (0.730)	3.53 (1.55)	8.85 (2.22)	13.18 (1.98)
Disability certificate (%)	56 (62.9%)	10 (62.5%)	15 (50%)	22 (84.6%)	13 (76.5%)
Presence of Law 104/99 (%)	27 (30.3%)	2 (12.5%)	6 (20%)	11 (42.3%)	8 (47.1%)
School support (%)	23 (25.8%)	0.0%	7 (23.3%)	10 (38.5%)	6 (35.3%)
Extracurriculars activities (%)	31 (34.8%)	1 (6.3%)	10 (33.3%)	13 (50.0%)	7 (41.2%)

The percentage data describe the presence of the variable within the total sample.
Abbreviation: SD = standard deviation

Table 3. Percentage scores for normal, mild, moderate, and severe difficulties reported at PROMIS Pediatric-49 and PROMIS-57 questionnaires.

	Total $N = 60$	Age 8-11 $N = 21$	Age 12-17 $N = 23$	Age >18 $N = 16$
% **Anxiety**				
Absent	55%	57.1%	47.8%	62.5%
Mild	11.7%	14.3%	13%	6.3%
Moderate	26.7%	19%	34.8%	25%
Severe	6.7%	9.5%	4.3%	6.3%
% **Depression**				
Absent	55%	42.9%	65.2%	56.3%
Mild	18.3%	28.6%	17.4%	6.3%
Moderate	18.3%	19%	8.7%	31.3%
Severe	8.3%	9.5%	8.7%	6.3%
% **Pain interference**				
Absent	60%	66.7%	56.5%	56.3%
Mild	16.7%	9.5%	30.4%	6.3%
Moderate	18.3%	19%	8.7%	31.3%
Severe	5%	4.8%	4.3%	6.3%
% **Fatigue**				
Absent	56.7%	52.4%	65.2%	50%
Mild	16.7%	28.6%	8.7%	12.5%
Moderate	20%	14.3%	17.4%	31.3%
Severe	6.7%	4.8%	8.7%	6.3%
% **Social isolation**				
Absent	51.7%	57.1%	47.8%	50%
Mild	20%	14.3%	21.7%	25%
Moderate	25%	23.8%	26.1%	25%
Severe	3.3%	4.8%	4.3%	0%

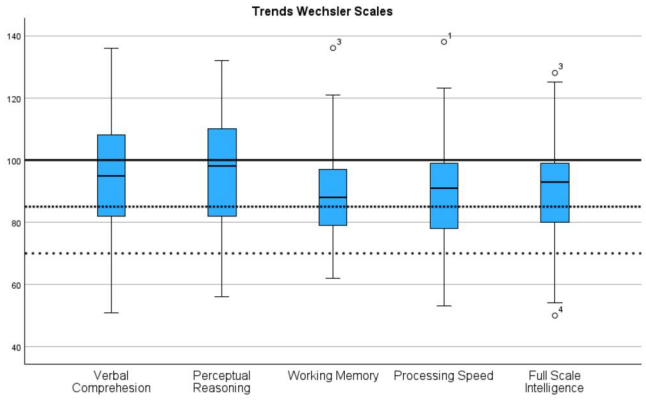

Figure 1. Distribution of scores on the 5 Wechsler scales. The solid line represents the normal score (100). Scores between the 2 dashed lines indicate scores within the lower normal range (85-70), while scores below the second dashed line represent levels of intellectual disability (<70).

within 1.5 standard deviation, indicating a performance in the lower normal range.[34-36]

Correlation analysis: association between clinical, socio-demographic, quality of life indexes and cognitive factors (total sample)

Differences between participants were examined based on clinical, socio-demographic, quality-of-life (QoL), and cognitive characteristics. Independent samples *t*-tests were conducted when at least one variable was dichotomous, whereas Pearson's correlation coefficients were calculated for relationships involving continuous variables.

Exploratory correlation analysis was conducted on the total sample, as shown in Tables S3-S5.

Table 4 shows the correlations with age. Significant correlations between age and clinical, social, quality of life, and cognitive variables, support the importance of exploring differences between age groups or developmental phases.

These findings indicate that older participants reported greater psychological burden and impairments in verbal and working memory skills, more frequent clinical monitoring, and greater access to state support.

Overall correlations between clinical, socio-demographic, quality of life measures and cognitive

Healthcare utilization and clinical indicators. Sex was associated with significant differences in healthcare use. Male participants showed a higher number of ambulatory visits ($t(88) = -20.75$, $P < .001$, $d = -2.20$), more frequent Emergency Room access ($t(88) = -17.19$, $P < .001$, $d = -1.82$), and length of hospital stay of admissions ($t(88) = -6.61$, $P < .001$, $d = -0.70$). In addition, disability certification was more common among males ($t(88) = 3.57$, $P < .001$, $d = 0.38$).

Being born in Italy was associated with greater healthcare utilization, including more ambulatory visits ($t(88) = -20.82$, $P < .001$, $d = -2.21$), more Emergency Room access ($t(88) = -17.98$, $P < .001$, $d \approx -1.89$), and longer hospitalization duration ($t(88) = -7.28$, $P < .001$, $d = -0.78$).

Participants with homozygous genotype presented a more severe clinical profile, with significantly higher rates of healthcare use (eg, ambulatory visits: $t(88) = -20.80$, $P < .001$, $d = -2.21$) and longer length of stay ($t(88) = -7.35$, $P < .001$, $d = -0.78$).

Use of hydroxyurea, both as monotherapy and in combination therapy, was associated with greater clinical severity and more intensive healthcare utilization (eg, ambulatory visits:

Table 4. Correlations of the variables with age.

Continuous variables			
	Pearson correlation	***P*-value**	**N**
Clinical factors			
Ambulatory visits	.303	.004	89
Quality of life measures			
Anxiety	.262	.043	60
Depression Symptom	.351	.006	60
Pain Interference	.443	<.001	60
Fatigue	.352	.006	60
Cognitive factors			
VCI	−.234	.031	85
WMI	−.300	.005	85
Dichotomous variables			
	T-test di Student	***P*-value; *d* Cohen**	**gl**
Clinical factors			
Genotype homozygous	20.803	<.001; 2.207	88
Hydroxyurea	20.701	<.001; 2.194	88
Combination therapy with HU	20.849	<.001; 2.210	88
Social factors			
Disability certificate	20.792	<.001; 2.204	88
Presence of Law 104/99	20.832	<.001; 2.208	88
School support	20.840	<.001; 2.209	88
Extracurriculars activities	20.824	<.001; 2.207	88

Analyses between age (in month) and continuous variables were conducted using Pearson's correlation, while analyses between age and dichotomous variables were performed using Student's *t*-test.

$t(88) = -20.70$, $P < .001$, $d = -2.19$), indicating that treatment was preferentially administered in more severe cases.

The presence of a disability certificate and eligibility for Italian Law 104/99 support were both strongly associated with increased healthcare utilization and greater clinical burden (eg, disability certification: $t(88) = -17.56$, $P < .001$, $d = -1.86$).

Psychological outcomes. Significant differences were also observed in psychological functioning and cognitive performance. Participants with more severe clinical characteristics (eg, homozygous genotype) reported higher levels of: anxiety (eg, $t(59) = -27.52$, $P < .001$, $d = -3.55$); depressive symptoms ($t(59) = -26.60$, $P < .001$, $d = -3.43$); pain interference ($t(59) = -28.07$, $P < .001$, $d = -3.62$); fatigue ($t(59) = -24.65$, $P < .001$, $d = -3.18$); social isolation ($t(59) = -36.53$, $P < .001$, $d = -4.72$) (Table S3-S5).

Taken together, these findings suggest that clinical severity is associated not only with increased healthcare needs and physical burden but also with heightened psychological distress and reduced cognitive functioning.

Strong positive correlations emerged among all psychological symptom dimensions: anxiety and depressive symptoms: $r = .820$, $P < .001$; anxiety and pain interference: $r = .652$, $P < .001$; fatigue and depressive symptoms: $r = .741$, $P < .001$; fatigue and pain interference: $r = .725$, $P < .001$.

These results indicate that emotional distress, pain perception, and fatigue tend to co-occur, reflecting a shared underlying psychosocial burden.

Social isolation showed no statistically significant associations with healthcare utilization or psychological distress (all $P > .05$), although the direction of correlations suggested that greater isolation may correspond to higher symptom burden. These trends did not reach significance, possibly due to reduced sample size ($N = 60$).

Cognitive outcomes. Moreover, cognitive indices assessed through standardized measures were substantially lower in these groups, with very large effect sizes: VCI and severe genotype (eg, $t(85) = -45.28$, $P < .001$, $d = -4.88$); WMI and severe genotype ($t(84) = -54.25$, $P < .001$, $d = -5.89$); PSI and combined therapy with hydroxyurea ($t(84) = -50.09$, $P < .001$, $d = -5.44$); FSIQ and severe genotype ($t(84) = -52.42$, $P < .001$, $d = -5.69$). Cognitive indices were generally not significantly associated with healthcare utilization or psychological symptoms. Only 2 small but meaningful negative correlations emerged: PRI and number of outpatient visits: $r = -.219$, $P = .044$; WMI and number of outpatient visits: $r = -.300$, $P = .005$.

These findings suggest that greater clinical management needs are associated with lower performance in perceptual reasoning and working memory, although the effect sizes were modest.

No significant correlations were found between cognitive indices and anxiety, depression, pain interference, fatigue, or social isolation (all $P > .05$).

Between group comparisons: analyses of variance between age-groups

Analyses were conducted using Chi-square or ANOVA to describe the differences between the 4 age groups (4-7 years, 8-11 years, 12-17 years, and >18 years). The results were further explored through pairwise comparisons; The full set of analyses is presented in Tables S6-S11.

Clinical measures. The analyses showed a significant difference between groups in the amount of ambulatory visits [F(3,

88) =2761.798, $P = .003$, $\eta^2 = -.003$] and in the use of a combination of therapy with hydroxyurea [$\chi^2(3) = 15.430$, $P = .001$]. Pairwise Student's *t*-test (Tables S6-S11) and Fisher's Exact Tests, for dichotomous variables, reveal that the 8-11-year-old group has fewer ambulatory visits ($P < .050$ for all comparisons) and fewer therapies combined with hydroxyurea ($P < .060$ for all comparisons), compared to the other groups.

Socio-demographic measures. Chi-square tests showed a significant difference in Law 104/99 certificate [$\chi^2(3) = 7.938$, $P = .047$], disability certificate [$\chi^2(3) = 13.161$, $P = .004$], school support [$\chi^2(3) = 8.627$, $P = .035$] and extracurricular activities [$\chi^2(3) = 8.725$, $P = 0.033$]. It emerged that the 4-7-year group had lower state support (presence of Law 104, Disability and School support), while with age, social benefits tended to improve, as shown in Figure 2. This phenomenon may stem from different reasons: challenges in identifying impairment in preschool children, bureaucratic and linguistic difficulties, particularly for foreign families facing obstacles in accessing subsidies. Additionally, the complex and lengthy process of obtaining social benefits delays access to services. Finally, parents of young children may not fully perceive the issues related to the illness, focusing instead on other needs of the child.

Health-related quality of life. Since data were normal and homoscedastic, ANOVAs were performed, and Student's *t*-tests were conducted for pairwise comparisons between 2 groups (Tables S6-S11). The results showed significant differences between age-groups in depressive symptoms [F(2, 57) =4428, $P = .016$, $\eta^2 = -.134$], investigating group differences, we found a significant difference between the 8-11 group and the >18 group ($t(35) = -2.896$, $P = .006$, $d = 13.246$), suggesting that depressive symptoms increased with age. Pain interference also showed significant differences between age groups [$F(2, 57) = 6.517$, $P = .003$, $\eta^2 = -.186$], which were significant between the 8-11 Group and the >18 Group ($t(35) = -3.716$, $P < .001$, $d = 11.161$), and between the 12-17 and >18 age groups ($t(37) = -2.143$, $P = .039$, $d = 10.307$), indicating that Pain Interference increased with age.

Significant between-group differences are also found for Fatigue [$F(2, 57) = 4.428$, $P = .016$, $\eta^2 = -.134$], between the 8-11 year Group and the >18 year Group ($t(37) = -3.302$, $P = .002$, $d = 12.395$) and between the 12-17 and >18 age groups ($t(37) = -2.008$, $P = .052$, $d = 14.351$). The analyses suggest that as patients age, they are more psychologically vulnerable and perceive more the severity of the clinical condition, particularly in relation to pain and fatigue. This is likely due to both a greater awareness of their own experience and an intensification of the symptoms. Figure 3 shows the increasing scores on the 3 scales of the PROMIS questionnaire, which are statistically significant.

Cognitive variables. In this case, as the data were normally distributed and homoscedastic, ANOVAs were used, and post-hoc comparisons were conducted using Bonferroni correction to compare scores between age groups. Unlike the findings from the zero-order correlation analyses (reported above), where age was significantly correlated with the Verbal Comprehension Index (VCI) and the Working Memory Index (WMI), the age-group analyses revealed significant differences between age groups in Verbal Comprehension Index (VCI) [$F(3, 82) = 6.473$, $P < .001$, $\eta^2 = .191$] and Perceptual Reasoning Index (PRI) [$F(3, 82) = 2.987$, $P = .036$, $\eta^2 = .100$]. Specifically, for VCI, the youngest group (ages 4-7) demonstrated lower performance compared to the 8-11 group ($t(42) = -2995$, $P = .005$, $d = 17.244$) and the 12-17 group ($t(39) = -4.456$, $P < .001$, $d = 17.265$). For the PRI, the 8-11 age group had a higher score than the >18 group ($t(2.796$, $P = .008$, $d = 16.154$). Student's *t*-tests revealed that

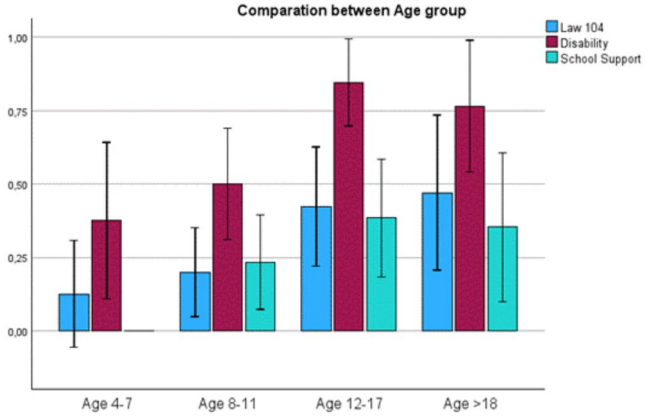

Figure 2. Frequency of Law 104/99, Disability Certificate and School Support by age group.

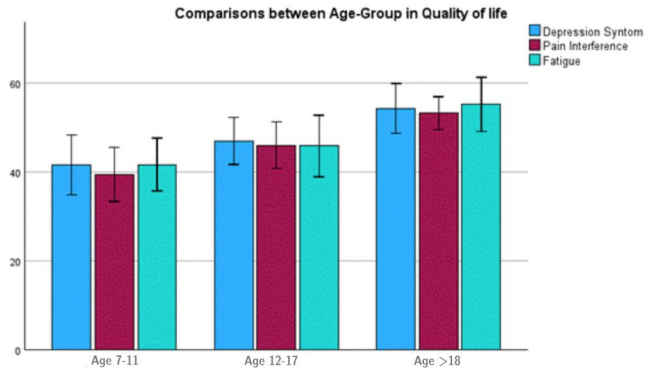

Figure 3. Scores by group for Depressive Symptom, Pain Interference and Fatigue.

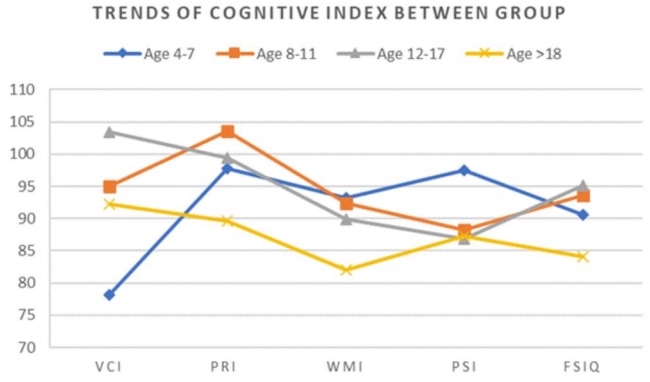

Figure 4. Participant's scores across the 5 Wechsler scales. The normative mean of Wechsler scales is 100 and SD is 15; lower scores indicate a decline in cognitive performance, with scores below 70 falling within the range of intellectual disability.

the oldest age group (>18 years) had significantly lower scores on the PRI, WMI, and FSIQ scales (Tables S6-S11), suggesting a possible decline in cognitive performance with increasing age, as shown in Figure 4.

DISCUSSION

Interpretation of findings

This study, founded on the biopsychosocial model and prior meta-analytic studies by Prussien et al.,[12,20,31] identifies significant age-related variations in the cognitive, clinical, and QoL profile of patients with SCD. The findings confirm that age is a crucial variable in SCD, with clinical, quality of life, and social factors dynamically evolving across different life stages.

In general, the results underscore the multifactorial and age-dependent nature of SCD, in line with the biopsychosocial model, emphasizing the importance of personalized management strategies for each life stage. As age increases, patients tend to make greater use of disease-modifying therapies, reflecting both growing clinical severities, alongside an intensification of negative symptoms related to quality of life and cognitive deficits, particularly in visuospatial abilities and working memory. The progression of verbal abilities, in contrast to the typical developmental trajectory,[43] demonstrates that patients, starting from the age of 8, exhibit better verbal performance compared to the young adult group. While the younger group shows poor verbal skills, likely due to limited exposure to the Italian language, which is primarily acquired at school. In this sample, children aged 8 to 11 exhibit the best health conditions in terms of biological factors and quality of life, but not in social aspects. Delaying access to social and healthcare support until the overt effects of the disease emerge may represent a limitation of the healthcare system. Early identification of cognitive and psychological challenges, combined with targeted interventions, is important for optimizing outcomes in patients with SCD.

The innovation of this study lies in the application of the bio-psycho-social model for a systematic comparison across multiple age groups, which enabled the identification of specific age-related characteristics. The exploratory analysis supports the findings of foundational studies[20,21,26] on the significant influence of psychological, cognitive, and social factors in shaping the experiences of individuals with SCD.

Previous research has primarily focused on 2 age-group comparisons or isolated cognitive domains, overlooking the dynamic interplay between age, cognition, and psychosocial factors in a developmental perspective. Although recent studies such as Ford[44] and Walker,[45] argue that cognitive deficits worsen with age, with significant declines in processing speed observed in adults, Alpakra[46] and other studies, did not confirm this hypothesis. This study emphasizes the importance of early identification of cognitive decline, demonstrating that signs of cognitive deficits can emerge as early as childhood or adolescence in these patients, highlighting the need for early interventions. Moreover, with increasing age, cognitive changes are observed, not only in processing speed as Walker[45] reported. In future studies, it will be crucial to assess a further element, the role of "silent strokes," identified by Vichinsky[18] as a key factor contributing to cognitive decline in adults with SCD.

Detailed analysis of the age groups' cognitive profiles revealed different patterns across cognitive domains: younger children (4-7 years) experienced delays in language development, which can be attributed to socio-linguistic background and limited exposure to the Italian language, which is also correlated with reduced school attendance. Adolescents and preadolescents (8-17 years) displayed comparatively better linguistic skills and relatively stable cognitive performance, whereas young adults showed signs of a relative cognitive decline, consistent with theories of early-onset cognitive deterioration in this population. In particular, working memory has been identified as a cognitive index of disease worsening. This is confirmed by the existing literature on SCD, reporting that individuals with this condition face executive and cognitive challenges, with one-third of the patients recording an intelligence quotient below average.[11,12,17,18] Patients with lower scores tend to receive more intensive support, both state-provided and medical perspective, often involving combined therapies alongside HU. Perceptual Reasoning abilities (PRI) remained relatively preserved and actually appear to be the most resilient functions in SCD, although they also tended to decline in the young adult group. Processing speed (PSI), in contrast, emerged as the most impaired cognitive domain across all age groups,[12,17] indicating again a greater vulnerability in executive functioning of patients with SCD.

Moving to QoL factors, the data collected through the PROMIS questionnaires indicated that adolescents and young adults face the most frequent challenges, marking this period as particularly critical. However, the potential absence of 19 QoL questionnaires across age groups may have introduced a bias affecting the generalizability of the data. Furthermore, it remains unclear whether this is due to the developmental phase per se, for instance the greater need of social relations which conflict with hospitalizations and the care routines, or to the increased severity of the health condition, which shows a deteriorating trend. Adolescence and young adulthood are shaped by the interplay of family education and puberty-related factors, such as evolving social roles and risk/protective dynamics. Moreover, with age, patients become more aware and better understand the consequences of the disease, leading to an increased perception of its impact on their quality of life. Although public health initiatives like the Millennium Development Goals and the Leadership in Adolescent Health program[47] have made so far limited progress, recent reviews[48] demonstrate the effectiveness of group interventions in yielding social and medical benefits.[49-51] Such programs may be coupled with individualized interventions, since in other chronic diseases individualized psychological support seems also very effective.[52,53]

An additional note relates to socio-demographic and social factors. SCD is classified as a rare disease in Italy, granting patients access to welfare benefits under regulations such as Law 448/2001 and Law 104/92. However, some patients are from immigrant backgrounds and unfamiliar to the Italian health-care and social assistance system, encountering administrative challenges that can be further exacerbated by limited proficiency in Italian, potentially affecting access to services and benefits. In many cases, support is provided only after

disease progression, following a predominantly reactive and bio-medical model.[52]

Simplifying administrative procedures and providing direct assistance to families could facilitate access to benefits, as suggested by the discrepancy between the prevalence of disability (62.9%) and recognition of severity under Law 104 (30.3%). Educational support is also important to ensure continuity during school absences and addressing cognitive difficulties. Providing schools with detailed information on the cognitive abilities of children with SCD can help tailor educational programs and environments, promoting more effective learning.[54,55]

Through a multidisciplinary approach, involving healthcare professionals across diverse fields, the analysis reported in this article allows it to go beyond the purely medical dimensions of SCD to include social, quality of life, and cognitive aspects, as recommended by the AIEOP Guidelines.[2]

Limitations

While this study provided a comprehensive picture of the bio-psycho-social profile of a moderately large sample of patients with SCD, we must also acknowledge several limitations: a moderate sample size, heterogeneity among participant groups, and incomplete patient-reported data, specifically regarding self-reported PROMIS questionnaires across age groups. Moreover, the database did not provide data on socio-economic status (SES). In Italy, the systematic collection of SES indicators at the clinical level is not standard practice and is left to the discretion of individual clinical teams. This makes it challenging to assess the influence of socioeconomic factors on disease progression or access to health and social services. The absence of these data therefore represents a limitation in fully understanding the social determinants of health in the studied population. Variability in participants' linguistic competencies may have influenced the results, despite our attempt to follow rigorous exclusion criteria. Additionally, while PROMIS questionnaires offer flexibility across age groups, they focus on state-related constructs and self-reports, which, on the one hand, may limit generalizability and, on the other, may reduce reliability. Finally, given the cross-sectional design of the study, causal inferences cannot be drawn from the observed associations.

Future directions

Future studies should integrate standard cognitive assessment (through Wechsler scales) and self-report measures with more subtle neuropsychological and neuroimaging tools to gain a deeper understanding of the cognitive characteristics of patients with SCD.

CONCLUSIONS

The study highlights the importance of a personalized and age-related approach in managing SCD, confirming that the SCD-relevant biological, cognitive, quality of life, and social factors significantly change across life stages. Age emerges as a crucial variable in identifying the most critical manifestations of the disease and early markers of cognitive decline, which may support timely and targeted interventions for each age group.

In particular, adolescence and young adulthood represent critical periods for addressing the psychological correlates of SCD, where family and social support play a pivotal role. From a social perspective, challenges in accessing welfare benefits are evident, especially for children and younger patients and families of immigrant backgrounds. Reforming welfare policies to adopt a proactive approach, including direct assistance in navigating bureaucratic processes, could significantly improve patients' quality of life and reduce social inequalities.

Finally, this study distinguishes itself through its multidisciplinary approach, which allows for consideration of the biological, quality of life, and social dimensions of SCD, providing a comprehensive understanding of the condition. However, certain limitations remain, including the small sample size and the need for more specific neuropsychological tools, suggesting the need for further research with larger and more diverse samples.

In general, the findings underscore the importance of intervention strategies rooted in the biopsychosocial model, capable of proactively addressing the cognitive, psychological, and social challenges faced by patients with SCD. These strategies can reduce the risk of future complications and promote a better quality of life throughout their lifespan.

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AUTHOR CONTRIBUTIONS

Drs Raffaella Colombatti and Barbara Arfè contributed equally to this work.

Maria Elisa delle Fave (Conceptualization, Data curation, Formal analysis, Methodology, Writing—original draft, Writing—review &hx0026; editing), Veronica Marchiori (Data curation, Methodology), Giulia Reggiani (Methodology, Resources), Maria Paola Boaro (Methodology, Resources), Jackeline Elizabeth Maran (Methodology, Resources), Ilaria Baido (Resources), Desirè Fantasia (Investigation, Methodology, Resources), Elisabetta Mezzalira (Visualization, Writing—review & editing), Raffaella Colombatti (Conceptualization, Methodology, Project administration, Supervision, Writing—review & editing), and Barbara Arfè (Conceptualization, Formal analysis, Methodology, Project administration, Writing—review & editing)

SUPPLEMENTARY MATERIAL

Supplementary material is available at *Journal of Sickle Cell Disease* online.

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CONFLICTS OF INTEREST

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DATA AVAILABILITY

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical Committee of the Province of Padova, first approval study 3068P March 2014.

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