Bulletin of Faculty of Physical Therapy

ORIGINAL RESEARCH ARTICLE

Open Access

# Associations between disease severity, depression, health-related quality of life, and physical activity in adults with sickle cell disease

Adekola B. Ademoyegun[1,4*], Mutiu A. Adeyemo[2], Babatunde Y. Adewuyi[1], Adebukola G. Ibitoye[1], Olalekan I. Akerele[3], Taofeek O. Awotidebe[4] and Chidozie E. Mbada[5]

## Abstract

**Background** Individuals with sickle cell disease (SCD) are faced with a plethora of challenges that affect their quality of life, mood, and physical and social participation. Physical activity (PA) is known to reduce inflammatory activity and enhance psychosocial health in individuals with chronic illnesses; however, there exist controversies on the role of PA in disease severity (DS), depression, and health-related quality of life (HRQoL) in SCD.

**Objective** This study aimed to assess the role of PA in the level of DS, depression, and HRQoL in SCD and investigate mediation models among DS, depression, HRQoL, and PA in adults with SCD.

**Methods** A total of 385 patients with SCD (mean age 35.45 ± 12.01 years; 51.70% female) attending hematology clinics in two Nigerian tertiary hospitals participated in this cross-sectional study. Data on DS, depression, HRQoL, and PA were assessed through modified disease severity scoring protocol, patient health questionnaire-9, 12-item short-form health survey, and international physical activity questionnaire short-form, respectively. Multiple hierarchical regression and mediation analyses were applied.

**Results** The findings show that 53.5% are physically inactive, and PA accounts for 27.50%, 18.40%, 38.80%, and 8.50% of the variance observed in DS, depression, and physical component summary (PCS-12) and mental component summary (MCS-12) of HRQoL, respectively. There was a significant mediating role of DS in the relationship between PA and depression (β = −0.0026; LLCI −0.0031; ULCI −0.0022), PCS-12 (β = 0.0019; LLCI 0.0013; ULCI 0.0024), and MCS-12 (β = 0.0009; LLCI 0.0001; ULCI 0.0018). The relationship between DS and depression was mediated only through PCS-12 (β = 0.2975; LLCI 0.1825; ULCI 0.4066). Similarly, only PCS-12 significantly mediated the relationship between PA and depression (β = −0.0021; LLCI −0.0026; ULCI −0.0017).

**Conclusion** Individuals with SCD with high levels of PA have low levels of DS and symptoms of depression and reported better HRQoL. Furthermore, patients with better HRQoL, especially physical health showed low depressive symptoms in adults with SCD. Clinicians and policymakers should consider incorporating PA assessments and interventions into the care of patients with SCD. The formulation of specific PA guidelines for patients with SCD is also warranted.

**Keywords** Sickle cell anemia, Depression, Physical activity, Disease severity, Quality of life

*Correspondence:
Adekola B. Ademoyegun
aademoyegun@gmail.com
Full list of author information is available at the end of the article

## Introduction

Sickle cell disease (SCD) is an inherited disorder that limits the ability of hemoglobin in red blood cells (RBCs) to carry oxygen [1, 2]. SCD arises from a single mutation of glutamic acid by valine at the sixth position of the beta globin resulting in a genetic haemoglobinopathy haemoglobin S (HbS) [1, 2]. Under low or absence of oxygen saturation, the HbS polymerizes changing the shape of RBCs from normal to sickle-shaped. The sickle-shaped RBCs are fragile, carry little oxygen, and cannot easily circulate within small blood vessels leading to hemolysis and recurrent vaso-occlusion [2]. SCD, being one of the most common genetic hematological ailments globally [2], affects people of different age groups and is reported to be more prevalent in Sub-Saharan Africa compared to other climes [3–6]. Nigeria has been reported to have the largest burden of SCD in the world [7, 8] as it is estimated that about 3–5% of the Nigerian population of over 200 million people are affected by SCD [8].

The hemolytic anemia or vascular obstruction impairing the normal distribution of tissue oxygen supply forms the basis of disease severity (DS) observed in patients with SCD. The DS is reflected in clinical complications experienced by patients with SCD including acute chest syndrome, pulmonary hypertension, heart failure, stroke, pain in bones, muscles, and joints, etc. [2, 9, 10], while many of the patients suffer from psychosocial problems [6, 11]. Reports have shown that depression is a common psychological problem suffered by people with chronic disease [11, 12]. The high prevalence of depression among individuals with SCD is associated with the rate of the vaso-occlusive crisis (VOC) crisis [13]. Other factors related to depression in SCD patients include social support, age, gender, income, and educational status [14–16].

As observed in other chronic diseases wherein symptoms of depression hurt disease progression [17], individuals with SCD complicated with depressive symptoms have more medical problems, increased hospitalization, and a higher rate of VOC compared to SCD patients without major depressive symptoms [18–21]. It appears then that DS contributes majorly to the negative mental health experienced by patients with SCD [6, 22] and their low health-related quality of life (HRQoL) [1, 6, 16, 22–24]. According to the literature, the HRQoL of patients with SCD is poor [18, 25]. Furthermore, evidence suggests a bidirectional relationship between depression and HRQoL among patients with SCD [18]. Depression and HRQoL in SCD are predicted by similar factors, including DS [14–16, 18–21, 23, 24]. Meanwhile, DS is reported to directly affect the HRQoL in patients with SCD including sociability, employment, family cohesion, and functional capacity [1]. Thus, the high prevalence of depression in SCD may be precipitated by the low HRQoL occasioned by DS.

One of the pathological bases or associated factors for some of the clinical manifestations seen in patients with SCD is intense physical effort or activity [2, 9]. It is believed that physical efforts trigger metabolic changes, increase dehydration and demand for oxygen leading to tissue hypoxia, and accentuate or precipitate VOC events [26]. Specifically, engaging in walking, climbing stairs/ramps, or performing any vigorous activities induces dyspnea among SCD patients [27]. Therefore, clinicians often ask patients with SCD to refrain from physical efforts [1], while others give contradictory messages on physical activity (PA) to patients with SCD [28]. Thus, the apathy among patients with SCD to engage in PA is due to fear [29]. However, clinicians are beginning to recommend physical exercise as a non-pharmacologic therapy in ameliorating SCD complications [30]. Some studies have proven the benefits of aerobic and resistance exercise in SCD [31, 32], however, these interventions may not be suitable and feasible for all patients with SCD [26].

Preliminary results indicate that PA positively modulates DS in sickle cell trait and models by lowering blood viscosity [33, 34] and improving vascular function and inflammation, and as a result reduces the risk of VOC [1, 35–37]. Karlson et al. reveal that contrary to physiological theory-based hypotheses, lower PA was associated with greater pain in children with SCD [38]. Although PA is one of the non-pharmacological methods that could be employed in addressing SCD, however, there is limited evidence on the impact of PA on SCD. Patients with SCD who engage in regular PA may have less DS and depression, and better HRQoL. Furthermore, since PA is known to help modulate some VOC in SCD, patients with adequate PA may have low depressive symptoms and better HRQoL through a reduction in DS.

Meanwhile, results have shown that PA may help in improving depressive symptoms and HRQoL among patients with or without chronic illnesses [39, 40], and preliminary data suggest HRQoL may mediate the association between PA and depression in chronic illness [40]. However, the mechanisms by which PA affects depression and HRQoL are said to be different [39] and it is yet to be fully explored in patients with SCD. Therefore, there is a need to understand the effect of PA on HRQoL predicting the depressive symptoms of patients with SCD. Furthermore, the association of DS with depression and HRQoL, and between depression and HRQoL have been studied in SCD. However, the potential mediating role of HRQoL between DS and depression is yet to be explored in SCD. It is possible that the negative direct impacts of SCD on the HRQoL precipitate or worsen the depressive symptoms of patients with SCD. Thus, there

is a need to evaluate the mechanisms by which HRQoL relates to depression in patients with SCD.

The hypothetical model of the influence of PA on disease severity, depression, and HRQoL is shown in Fig. 1. The research questions are the following: (1) do PA levels affect DS, depression, and HRQoL in adults with SCD, and (2) what are the underlying mechanisms among PA, depression, and HRQoL in adults with SCD? Thus, it is hypothesized in this study that (i) the level of DS, depression, and HRQoL in patients with SCD would be associated with PA, (ii) the effect of PA on depression and HRQoL in patients with SCD would be mediated through DS, (iii) the effect of DS on depressive symptoms would be mediated through HRQoL, and (iv) the effect of PA on depressive symptoms would be mediated through HRQoL.

## Methods

### Participants

The participants in this cross-sectional observational study were patients with SCD undergoing medical treatment at the Haematology clinics of the Osun State University Teaching Hospital, and State Specialist Hospital, Osogbo, Nigeria between November 2021 and February 2023. Patients who were 18 years and older, who could comprehend words and follow simple instructions were included. However, patients currently with or just recovering from VOC and those with a physical disability (e.g., amputation, stroke) that may hamper PA were excluded. Physical disability was assessed with a checklist and from patients' case files. With a 95% confidence interval, 0.05 precision level, and 30.5% prevalence of depression in SCD in Nigeria [41], an estimate of 382 samples was required using Kasiulevicius et al. [42] sample size formula ($N=Z^2\ p\ (1-p)/e^2$) on an epidemiological survey. Furthermore, a G*Power calculation showed that a minimum of 184 samples are required for a linear regression model involving 12 predictors at 95% power, 0.05 error of probability, and medium (0.15) effect size [43]. In all, a total of 385 patients with complete data were involved in this study. This study followed the Declaration of Helsinki and strictly adhered to the ethics committee's approval. The ethical approval was obtained from the Research Ethics Committee of the Osun State University Teaching Hospital, Osogbo, Nigeria with protocol number UTH/EC/2021/11/544. In addition, written informed consent was obtained from all the participants.

### Measures

The 12-item short-form health survey (SF12) was used to assess the HRQoL of the participants. The 8 subscales of assessment in SF-12 including role limitation physical (RP), physical functioning (PF), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role limitation emotional (RE) and mental health (MH) were derived and linearly transformed into 0–100 scale, while the SF-12 scales were combined and normalized to derive mental component summary (MCS) and physical component summary (PCS) scores with higher scores indicating better mental and physical health [44]. SF-12 has been found valid and reliable when compared with the longer SF-36 [45], has been proven valid among individuals of

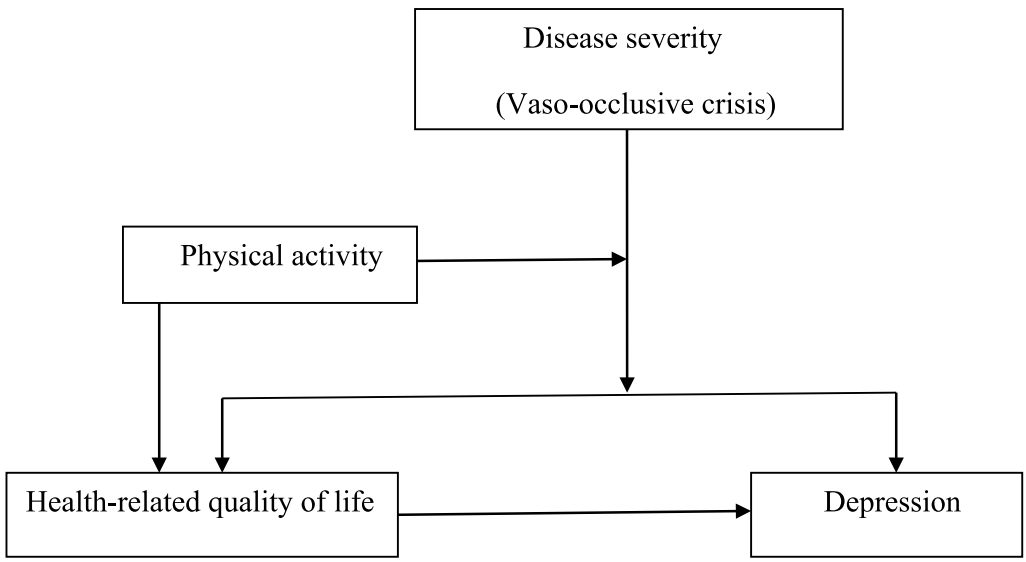


**Fig. 1** The hypothetical influence of physical activity on disease severity, depression, and health-related quality of life in adults with sickle cell disease

different socio-economic and cultural backgrounds [46], and patients with similar genetic blood disorders [47], and has been employed previously among adults with SCD [48]. The concurrent validity, convergent validity, and internal consistency of the Yoruba-Nigerian version of SF-12 have been established as acceptable [49]. The Cronbach's α for SF-12 in the present study was 0.807.

The International Physical Activity Questionnaire short form (IPAQ-SF) was used to assess the PA of the participants. The IPAQ-SF assesses the number of days and minutes or hours of PA in the past week in terms of vigorous, moderate, and walking activities and was converted to Metabolic Equivalent of Tasks (METs) scores using the IPAQ-SF scoring protocol by multiplying the total minutes and days of engaging in PA in the past week with the MET for each of vigorous (MET = 8.0), moderate (MET = 4.0), and walking (MET = 3.3) activities [50–52]. Subsequently, the total METs were obtained by adding the MET values of the three domains of IPAQ-SF. The total MET scores were used to categorize the PA of the participants into physically inactive (< 600 MET-min per week) and active (≥ 600 MET-min per week) [49–51]. In this study, the IPAQ-SF statements were re-ordered to avoid PA overestimation as explained thoroughly elsewhere [53–56]. The IPAQ-SF psychometric properties in PA evaluation in adults have been established [57, 58]. The validity and reliability of the IPAQ-SF Yoruba-Nigerian version are appropriate [59]. In the present study, the Cronbach's α for IPAQ-SF was 0.800.

The risk of depression among the participants was evaluated by the Patient Health Questionnaire-9 (PHQ-9). The self-administered PHQ-9 has nine items requesting information on how individuals have felt in the past 2 weeks. Some of the PHQ-9 items are "feeling tired or having little energy", "feeling down, depressed, or hopeless", "thoughts that you would be better off dead, or of hurting yourself", etc., with responses ranging from 0 (not at all) to 3 (nearly every day) making a potential maximum score of 27 [16]. A higher score indicates a greater risk of depression [16]. In this study, participants with ≥ 10 scores were considered depressive [16]. It has been reported that a PHQ-9 score greater than 9 is 83% sensitive and 92% specific in depression diagnosis [60]. The questionnaire is well-validated in depression screening in line with the Diagnostic Manual of Mental Disorders Fourth Edition (DSM-IV) [61], and it is a common instrument in assessing depressive symptoms in SCD [62]. The Cronbach's α for PHQ-9 in this study was 0.812.

The DS of the participants was assessed by the modified disease severity scoring protocol [63–65]. This protocol employs clinical and laboratory parameters in determining disease severity in patients with SCD. The parameters are the number of crises per year with 0–1 time (0 scores), 2–3 times (1 score), and ≥ 4 times (2 scores); the presence (1 score) or absence (0 scores) of acute chest syndrome, osteomyelitis, renal failure, heart failure, avascular necrosis of head of the femur, pneumonia, Pigment gallstone /Jaundice or dehydration; and finally anemia with Hb ≥ 10 g/dL (0 scores), Hb ≥ 8 < 10 g/dL (1 score), Hb ≥ 6 < 8 g/dL (2 scores), Hb ≥ 4 < 6 g/dL (3 scores) and Hb < 4 g/dL (4 scores). The maximum severity score is 14 with a higher score suggesting higher DS. The DS was categorized as mild (≤ 3 scores), moderate (> 3 ≤ 7 scores), and severe (> 7 scores) [63–65]. The SF12, IPAQ-SF, and PHQ-9 were self-administered, while participants' DS was evaluated through laboratory assessment and medical records.

### Covariates

By using the findings of previous studies [5, 16, 18, 38, 62, 65], some covariates including age, gender, body mass index, types of SCD (Haemoglobin SS, Haemoglobin SC, Sickle Beta-Plus Thalassemia and Sickle Beta-Zero Thalassemia), marital, employment, education, and income status were assessed. The level of available perceived social support, pain severity, and number of painful site(s) were also examined. Education below tertiary level was classified as low education while monthly income below the Nigerian minimum wage was categorized as low income. Available social support was assessed with the multidimensional scale of perceived social support (MSPSS), having 12 items soliciting information on the level of social support received from family, friends, and significant others. The maximum score is 84 with higher scores indicating greater availability of perceived social support [66]. The pain severity and number of painful site(s) were assessed with the brief pain inventory (BPI). The pain severity was obtained by aggregating the four severity items of the instrument [67]. The Cronbach's α for MSPSS and BPI was 0.790 and 0.891. Data on covariates was obtained with a self-developed proforma.

### Data analysis

The Kolmogorov–Smirnov test was used to investigate the normality of the continuous data. Data was summarized with descriptive statistics of frequency, percentage, mean, and standard deviation. Pearson correlation coefficient was used to assess the correlations among DS, PA, depression, and HRQoL. Multiple hierarchical regression models were performed to investigate the relative impact of PA on DS, depression, and HRQoL. For each model, the independent variables were entered in two blocks: block 1—the socio-demographic, physical, and clinical variables; block 2—PA. To investigate the underlying mechanisms among DS, depression, HRQoL, and

PA, the SPSS PROCESS macro (version 4.0) with 10,000 bias-corrected bootstrap samples (model 4) was used to conduct the mediation analyses. In the first model, we tested the effect of PA (predictor) on depression and HRQoL (outcomes), separately, through DS (mediator). Secondly, the effect of DS (predictor) on depression (outcome) through the two-component summary (PCS-12 and MCS-12) of HRQoL (simple mediators) was determined. Lastly, the effect of PA (predictor) on depression (outcome) through the two-component summary (PCS-12 and MCS-12) of HRQoL (simple mediators) was also investigated. The alpha level was set at $p < 0.05$. The direct and indirect effects were considered significant if the 95% confidence interval (CI) bootstrap value did not include zero. Data was analyzed using SPSS IBM version 21.

## Results

The mean age of the participants was 35.45 ± 12.01 years. The majority (51.70%) were female, single (57.10%), with low income (56.90%), and had hemoglobin SS (77.92%). More than half (53.5%) did not engage in moderate to vigorous PA (MVPA), 25.20% had severe DS, and the prevalence of depression was 29.87% (Table 1). There were positive correlations between PA and MCS-12 ($r = 0.499$; $p < 0.001$) and PCS-12 ($r = 0.760$; $p < 0.001$), and negative correlations between PA and DS ($r = -0.727$; $p < 0.001$), and depression ($r = -0.584$; $p < 0.001$) (Table 2). This indicates that an increase in PA participation improves HRQoL and reduces DS (VOC) and symptoms of depression.

The results of the hierarchical regression models are presented in Table 3. The results showed that PA independently and negatively predicted DS (β = −0.627, $F = 65.235$, $p < 0.001$, $R^2 = 67.80\%$) and depression (β = −0.513, $F = 40.633$, $p < 0.001$, $R^2 = 56.70\%$), and independently and positively predicted PCS-12 (β = 0.744, $F = 52.010$, $p < 0.001$, $R^2 = 62.70\%$) and MCS-12 (β = 0.348, $F = 28.198$, $p < 0.001$, $R^2 = 47.60\%$). In addition, the change in $R^2$ indicated that PA can explain 27.50%, 18.40%, 38.80%, and 8.50% in the variation in the amount of DS, PHQ-9, PCS-12, and MCS-12, respectively.

The results of the mediation analyses showing the mechanisms among DS, depression, HRQoL, and PA are presented in Tables 4 and 5. The results show significant indirect effects of DS in the relationship between PA and depression (β = −0.0026; LLCI −0.0031; ULCI −0.0022), PCS-12 (β = 0.0019; LLCI 0.0013; ULCI 0.0024), and MCS-12 (β = 0.0009; LLCI: 0.0001; ULCI 0.0018). The result suggests a full mediation role of DS between PA and depression (Table 4). There was a significant direct effect of DS on depression (β = 0.8334; LLCI 0.7033; ULCI 0.9634) which was significantly mediated through PCS-12 (β = 0.2975; LLCI 0.1825; ULCI 0.4066). However, MCS-12 was not a significant mediator between DS and depression. Similarly, only PCS-12 significantly mediates the relationship between PA and depression (β = −0.0021; LLCI −0.0026; ULCI −0.0017) (Table 5).

**Table 1** Socio-demographic, physical, and clinical characteristics of the participants ($N = 385$)

| Variable | N/ % | Mean ± SD |
|---|---|---|
| Age (Years) | | 35.45 ± 12.01 |
| Gender | | |
| Female | 199/51.70 | |
| Male | 186/48.30 | |
| BMI (Kg/m$^2$) | | 24.41 ± 6.90 |
| Marital status | | |
| Single[a] | 220/57.10 | |
| Married | 165/42.90 | |
| Employment status | | |
| Yes | 197/51.20 | |
| No | 188/48.80 | |
| Education level | | |
| High | 303/78.70 | |
| Low | 82/21.30 | |
| Income level | | |
| High | 166/43.10 | |
| Low | 219/56.90 | |
| Social support | | 55.01 ± 13.44 |
| PCS-12 | | 39.76 ± 7.09 |
| MCS-12 | | 41.57 ± 8.48 |
| PA status | | |
| Active | 179/46.50 | |
| Inactive | 206/53.50 | |
| Risk of depression | | |
| Yes | 115/29.87 | |
| No | 270/70.13 | |
| Disease severity | | |
| Mild | 223/57.90 | |
| Moderate | 65/16.90 | |
| Severe | 97/25.20 | |

*BMI* body mass index, *PCS-12* physical component summary of SF-12, *MCS-12* mental component summary of SF-12, *PA* physical activity, *N* frequency, *%* percentage, *SD* standard deviation

[a] Included the unmarried, divorced, separated, and widowed

## Discussion

To our knowledge, this study is the first to assess the impact of PA on the level of DS, depression, and HRQoL, and investigate the mediation models of relationships among DS, depression, HRQoL, and PA in adults with SCD. This study was primarily aimed to investigate four hypotheses: (i) the level of DS, depression, and HRQoL

**Table 2** Correlation matrix among disease severity, depression, health-related quality of life, and physical activity in adults with sickle cell disease

| Variable | 1. Disease severity | 2. Depression | 3. PCS-12 | 4. MCS-12 | 5. Physical activity |
|---|---|---|---|---|---|
| 1 | 1 | 0.770* | −0.718* | −0.433* | −0.727* |
| 2 | _____ | 1 | −0.690* | −0.396* | −0.584* |
| 3 | _____ | _____ | 1 | 0.524* | 0.760* |
| 4 | _____ | _____ | _____ | 1 | 0.499* |
| 5 | _____ | _____ | _____ | _____ | 1 |

*PCS-12* physical component summary of SF-12, *MCS-12* mental component summary of SF-12

*Indicates significant correlation at $p < 0.001$

in adults with SCD would be associated with PA, (ii) the impact of PA on depression and HRQoL in adults with SCD would be mediated through DS, (iii) the impact of DS on depressive symptoms in adults with SCD would be mediated through HRQoL, and finally, (iv) the impact of PA on depressive symptoms would be mediated through HRQoL in adults with SCD. First, the results of this study showed that 53.5% of patients with SCD do not participate in health-enhancing PA. From this result, the prevalence of physical inactivity among patients with SCD was a bit higher than the prevalence of physical inactivity reported in a recent systematic review and meta-analysis for an average Nigerian adult (52.0%) [68]. Specifically, the rate of physical inactivity obtained in this study was greatly higher than what was reported for an adult living in the study setting, i.e., Southwest Nigeria (40.8%) [68].

Meanwhile, the hypothesis 1 was confirmed. PA was negatively associated with the level of DS and depressive symptoms, and positively associated with HRQoL. The findings of this study indicated that PA was responsible for 27.50%, 18.40%, 38.80%, and 8.50% of the variance observed in DS, depressive symptoms, and PCS-12 and MCS-12 of HRQoL, respectively. The relationship between PA and DS obtained in this study is consistent with earlier reports which have linked PA with lower inflammation and improvement in vascular function leading to fewer VOC in animal models, and individuals with sickle cell trait and disease [1, 33–38]. There is a dearth of data linking PA with depressive symptoms and HRQoL in SCD, however, evidence has shown consistent associations of PA with depression and HRQoL in chronic diseases [39, 40].

The second hypothesis was also established. The effect of PA on depression and HRQoL was mediated through DS. This finding suggests that increasing PA reduces DS which leads to a reduction in depressive symptoms and improvement in both physical and mental health HRQoL. Since DS is associated with both depression and HRQoL [18], and preliminary data showed that PA modulates the inflammatory response in SCD [1, 35–37], it is expected that the effect of PA on DS in patients with SCD indirectly affects their reported depressive symptoms and HRQoL. However, the third hypothesis was only partly confirmed. The results showed that while the physical health component of HRQoL mediated the effect of DS on depression, the mental health component of HRQoL did not mediate this relationship. This could indicate that the effect of DS on depression is more transmitted through the lowering of physical health components in patients with SCD. This is not unexpected as SCD directly limits the physical functions or functional capacity of these patients than any other variables which in turn may lead to more depressive symptoms [1]. It could be inferred that SCD patients with more physical function challenges are more prone to depression, and therefore require closer attention by clinicians.

Similarly, the fourth hypothesis was partially established. The effect of PA on depressive symptoms was only mediated through the physical health component of HRQoL in adults with SCD. This result is similar to the findings of McIntyre et al. who observed a significant mediating role of HRQoL between PA and depression in women with chronic illnesses including asthma, depression, diabetes, osteoarthritis, or osteoporosis [40]. However, they utilized a different measure of HRQoL and therefore did not attempt to delineate the mediating role of the components of HRQoL. Furthermore, our finding is in line with a previous study by Heesch et al. where they reported that physical inactivity worsens physical health more than mental health domains of HRQoL [69]. This scenario was also observed in this study as the results of correlation and regression analyses showed a higher impact of PA on PCS than MCS. Moreover, this finding indicates that PA improves depressive symptoms in patients with SCD more by increasing the physical health domains of HRQoL. This is particularly interesting as this finding showed that PA can counter the effect of DS on depression because the effects of both DS and PA are mediated through the physical health component of HRQoL.

**Table 3** Multiple hierarchical regression models showing the influence of physical activity on disease severity, depression, and health-related quality of life in adults with sickle cell disease

| Variable | Model 1[a] Disease severity | | | | Model 2[a] Depression | | | | Model 3[a] HRQoL (PCS-12) | | | | Model 4[a] HRQoL (MCS-12) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *B* | Beta | se | *t* | *B* | Beta | se | *t* | *B* | Beta | se | *t* | *B* | Beta | se | *t* |
| Constant | 10.304 | _____ | 0.988 | 10.433* | 11.468 | ___ | 1.685 | 6.806* | 33.933 | _____ | 2.319 | 14.660* | 40.090 | ___ | 3.281 | 12.218* |
| PA (METs) | −0.002 | −0.627 | 0.000 | −17.821* | −0.003 | −0.513 | 0.000 | −12.588* | 0.005 | 0.744 | 0.000 | 19.648* | 0.003 | 0.348 | 0.000 | 7.770* |
| *R*-square | 67.80% | | | | 56.70% | | | | 62.70% | | | | 47.60% | | | |
| Change in $R^2$ | 27.50% | | | | 18.40% | | | | 38.80% | | | | 8.50% | | | |
| *F* | 65.235 | | | | 40.633 | | | | 52.010 | | | | 28.198 | | | |

[a] Parameters are for the final block of the hierarchical regression model, and each model was adjusted for age, gender, body mass index, pain intensity, number of painful sites, type of sickle cell disease, income, education, employment status, marital status, and social support, *HRQoL* health-related quality of life, *PCS-12* physical component summary of SF-12, *MCS-12* mental component summary of SF-12, *PA* physical activity, *METs* metabolic equivalents; * indicates significant association at $p < 0.001$, *se* standard error

**Table 4** The mediating role of disease severity in the association of physical activity with depression and health-related quality of life in adults with sickle cell disease

| | | Beta | Se | *t* | LLCI | ULCI |
|---|---|---|---|---|---|---|
| Direct effects | | | | | | |
| | PA → depression | −0.0003 | 0.0002 | −1.1056 | −0.0007 | 0.0002 |
| | PA → PCS-12 | 0.0037 | 0.0003 | 11.2021 | 0.0030 | 0.0043* |
| | PA → MCS-12 | 0.0034 | 0.0006 | 6.0958 | 0.0023 | 0.0045* |
| Indirect effects | | Boot effect | Boot SE | | Boot LLCI | Boot ULCI |
| | PA → DS → depression | −0.0026 | 0.0002 | _____ | −0.0031 | −0.0022* |
| | PA → DS → PCS-12 | 0.0019 | 0.0003 | _____ | 0.0013 | 0.0024* |
| | PA → DS → MCS-12 | 0.0009 | 0.0005 | _____ | 0.0001 | 0.0018* |

*se* standard error, *LLCI* 95% lower limit confidence interval, *ULCI* 95% upper limit confidence interval, *PA* physical activity, *PCS-12* physical component summary of SF-12, *MCS-12* mental component summary of SF-12, *DS* disease severity, *Boot* output of bootstrap method; * indicates significant direct and indirect effects

**Table 5** The mediating role of health-related quality of life in the associations of disease severity and physical activity with depression in adults with sickle cell disease

| | | Beta | Se | *t* | LLCI | ULCI |
|---|---|---|---|---|---|---|
| Direct effects | | | | | | |
| | DS → depression | 0.8334 | 0.0661 | 12.6037 | 0.7033 | 0.9634* |
| | PA → depression | −0.0007 | 0.0003 | −2.3620 | −0.0012 | −0.0001* |
| Indirect effects | | Boot effect | Boot SE | | Boot LLCI | Boot ULCI |
| | DS → PCS-12 → depression | 0.2975 | 0.0564 | _____ | 0.1825 | 0.4066* |
| | DS → MCS-12 → depression | 0.0020 | 0.0200 | _____ | −0.0401 | 0.0391 |
| | PA → PCS-12 → Depression | −0.0021 | 0.0002 | _____ | −0.0026 | −0.0017* |
| | PA → MCS-12 → depression | −0.0001 | 0.0001 | _____ | −0.0003 | 0.0001 |

*se* standard error, *LLCI* 95% lower limit confidence interval, *ULCI* 95% upper limit confidence interval, *DS* disease severity, *PA* physical activity, *PCS-12* physical component summary of SF-12, *MCS-12* mental component summary of SF-12, *Boot* output of bootstrap method, * indicates significant direct and indirect effects

Thus, increasing engagement of patients with SCD in PA may reduce DS and depression, and improve their HRQoL. However, caution must be taken in prescribing PA for patients with SCD as evidence has shown that physical efforts sometimes initiate or contribute to the VOC experienced by these patients [27]. This phenomenon suggests that the PA recommendations for healthy adults may not apply to patients with SCD. Effective management of SCD and its attendant complications requires a combination of both pharmacological and non-pharmacological methods, and since emerging evidence is showing the positive influence of PA in mitigating SCD and its co-morbidities, physical activity guidelines specially designed for patients with SCD are desirable.

## Clinical implications

We demonstrated the potential direct contribution of PA to the level of DS, depression, and HRQoL observed in patients with SCD. Furthermore, the findings of this study indicated that patients with SCD are prone to depression due to the direct impact of the disease on their physical health. Thus, integrating PA guidelines in SCD management and protocols that improve general health, physical functioning, bodily pain, and the physical role of SCD patients is necessary.

## Limitations

This study is limited by the use of homogenous samples which may affect the generalizability of its findings to other non-similar settings. Adults with SCD from other settings may have different socio-economic and socio-demographic characteristics and thus present with different measures of psychosocial variables. In addition, the cross-sectional design of the study precludes us from making causal inferences and ruling out alternative directions of these complex associations. For instance, contrary to our findings wherein PA predicted depression, it is plausible that symptoms of depression

may also reduce PA self-efficacy and participation in patients with SCD. Finally, the use of self-report measures of PA and depression may have introduced recall bias and caused under- or over-representation of PA and depression rates. Therefore, further experimental and longitudinal studies with larger samples and objective measures of PA and depression in multiple centers are recommended.

## Conclusion

The rate of physical inactivity among Nigerian adults with SCD is high. PA is negatively associated with disease severity and depressive symptoms, and positively associated with HRQoL in adults with SCD, indicating that an increase in PA reduces disease severity and depression, and improves the HRQoL. Furthermore, improving the physical health component of HRQoL, including general health, physical functioning, bodily pain, and role physical may decrease depression in adults with SCD. Healthcare providers and policymakers should consider incorporating PA assessments and interventions into the care of patients with SCD. We further recommend the formulation of specific PA guidelines for patients with SCD.

**Abbreviations**

| | |
|---|---|
| SCD | Sickle cell disease |
| DS | Disease severity |
| VOC | Vaso-occlusive crisis |
| HRQoL | Health-related quality of life |
| PA | Physical activity |
| SF12 | 12-Item short-form health survey |
| MCS | Mental component summary |
| PCS | Physical component summary |
| IPAQ-SF | International Physical Activity Questionnaire Short Form |
| METs | Metabolic Equivalent of Tasks |
| PHQ-9 | Patient Health Questionnaire-9 |
| MSPSS | Multidimensional Scale of Perceived Social Support |
| BPI | Brief Pain Inventory |

**Acknowledgements**
Not applicable.

**Authors' contributions**
ABA was involved in the conceptualization and design of the study. ABA, MAA, BYA, AGI, OIA, TOA, and CEM were involved in the acquisition, analysis, and interpretation of data. All authors read and approved the final manuscript.

**Funding**
The study was self-funded by the authors.

**Data availability**
The datasets used and/ or analyzed during the current study are available from the corresponding author on reasonable request.

## Declarations

**Ethics approval and consent to participate**
Ethical clearance was obtained from the Ethical Review Committee of the Osun State University Teaching Hospital, Osogbo, Nigeria.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare that they have no competing interests.

**Author details**
[1]Department of Physiotherapy, Osun State University Teaching Hospital, Osogbo, Nigeria. [2]Department of Haematology, Royal United Hospitals, Bath, UK. [3]Department of Haematology and Blood Transfusion, Osun State University Teaching Hospital, Osogbo, Nigeria. [4]Department of Medical Rehabilitation, Obafemi Awolowo University, Ile-Ife, Nigeria. [5]Department of Health Professions, Manchester Metropolitan University, Manchester, UK.

Received: 30 May 2024 Accepted: 10 January 2025
Published online: 22 January 2025

**References**

1. Martin C, Pialoux V, Faes C, Charrin E, Skinner S, Connes P. Does physical activity increase or decrease the risk of sickle cell disease complications? Br J Sports Med. 2018;52(4):214–8.
2. Tebbi CK. Sickle Cell Disease, a Review. Hemato. 2022;3(2):341–66.
3. Adigwe OP, Onoja SO, Onavbavba G. A Critical Review of Sickle Cell Disease Burden and Challenges in Sub-Saharan Africa. J Blood Med. 2023;14:367–76.
4. Mukinayi MB, Tumba DG, Gulbis B. Sickle cell disease in the democratic republic of Congo: assessing physicians' knowledge and practices. Trop Med Infect Dis. 2020;5(3):127.
5. Colombatti R, Hegemann I, Medici M, Birkegård C. Systematic Literature Review Shows Gaps in Data on Global Prevalence and Birth Prevalence of Sickle Cell Disease and Sickle Cell Trait: Call for Action to Scale Up and Harmonize Data Collection. J Clin Med. 2023;12(17):5538.
6. Katamea T, Mukuku O, Mpoy CW, Mutombo AK, Luboya ON, Wembonyama SO. Newborn screening for sickle cell disease in Lubumbashi, Democratic Republic of the Congo: An update on the prevalence of the disease. Journal of Hematology and Allied Sciences. 2024;3(3):120–4.
7. Beli II, Ali LA, Onuoha CC, Jasseh M, Zentar M, Belakoul N, Layadi Y, Deblui JA, Fathi M, Sani AH, Adamu AG, Mbahi MA, Laachfoubi T, Umar M. Socio-economic burden of sickle cell disease on families attending sickle cell clinic in Kano state, northwestern Nigeria. Global Pediatrics. 2024;9:100193.
8. Oluwole EO, Adeyemo TA, Osanyin GE, Odukoya OO, Kanki PJ, Afolabi BB. Feasibility and acceptability of early infant screening for sickle cell disease in Lagos, Nigeria—A pilot study. PLoS ONE. 2020;15(12): e0242861.
9. Sahu T, Pande B, Verma HK, Bhaskar LVKS, Sinha M, Sinha R, Rao PV. Infection and Potential Challenge of Childhood Mortality in Sickle Cell Disease: A Comprehensive Review of the Literature from a Global Perspective. Thalassemia Reports. 2023;13(3):206–29.
10. Gonzales J, Chakraborty T, Romero M, Abu Mraheil M, Kutlar A, Pace B, Lucas R. Streptococcus pneumoniae and Its Virulence Factors $H_2O_2$ and Pneumolysin Are Potent Mediators of the Acute Chest Syndrome in Sickle Cell Disease. Toxins. 2021;13:157.
11. Swathi M, Manjusha S, Vadakkiniath IJ, Gururaj A. Prevalence and correlates of stress, anxiety, and depression in patients with chronic diseases: a cross-sectional study. Middle East Curr Psychiatry. 2023;30:66.
12. Oudin Doglioni D, Chabasseur V, Barbot F, Galactéros F, Gay MC. Depression in adults with sickle cell disease: a systematic review of the methodological issues in assessing prevalence of depression. BMC Psychol. 2021;9:54.
13. Rizio AA, Bhor M, Lin X, McCausland KL, White MK, Paulose J, et al. The relationship between frequency and severity of vaso-occlusive crises and health-related quality of life and work productivity in adults with sickle cell disease. Qual Life Res. 2020;29:1533–47.
14. Alharbi AA, Alqassim AY, Muaddi MA, Aldubayyan NH, Abuhadi RI, Akoor FA, et al. Exploring the Prevalence and Contributing Factors of Depression among Sickle Cell Anemia Patients in Saudi Arabia's Jazan Region. Int J Ment Health Promot. 2024;26(5):351–9.

15. Alsalman M, Alhabrati A, Alkuwaiti A, Alramadhan N, AlMurayhil N, Althafar A, Alsaad A. Depression Among Patient with Sickle Cell Disease: Prevalence and Prediction. Niger J Clin Pract. 2022;25(8):1274–8.
16. Chetcha Chemegni B, Kamga Olen JPO, Um Nyobe LJ, Ntone Enyime F, Mbanya D. Anxiety, Depression and Quality of Life in Adults with Sickle Cell Disease. Arch Med. 2018;10(1):10.
17. Ma Y, Xiang Q, Yan C, Liao H, Wang J. Relationship between chronic diseases and depression: the mediating effect of pain. BMC Psychiatry. 2021;2:436.
18. Adam SS, Flahiff CM, Kamble S, Telen MJ, Reed SD, De Castro LM. Depression, quality of life, and medical resource utilization in sickle cell disease. Blood Adv. 2017;1(23):1983–92.
19. Essien EA, Winter-Eteng BF, Onukogu CU, Nkangha DD, Daniel FM. Psychosocial challenges of persons with sickle cell anemia: A narrative review. Medicine. 2023;102(47):e36147.
20. Knisely MR, Pugh N, Kroner B. Patient-reported outcomes in sickle cell disease and association with clinical and psychosocial factors: report from the Sickle Cell Disease Implementation Consortium. Am J Hematol. 2020;95:1066–74.
21. Dairi M, Almatrfi SS, Alsharif MM, Fatani BA, Almatrafi OA, Mandourah AS, et al. Prevalence of Psychological Symptoms and Its Impact on the Quality of Life of Sickle Cell Disease Patients in Makkah, Saudi Arabia. Cureus. 2022;14(12): e32195.
22. Oudin Doglioni D, Chabasseur V, Barbot F, Galacteros F, Gay M. Depression in adults with sickle cell disease: a systematic review of the methodological issues in assessing prevalence of depression. BMC Psychol. 2021;9:54.
23. Pandarakutty S, Arulappan J. Health-related quality of life of children and adolescents with sickle cell disease: An evolutionary concept analysis. Appl Nurs Res. 2024;80: 151862.
24. Yaya I, Pourageaud A, Derbez B, Odièvre M-H, Oudin Doglioni D, Podevin M, et al. Predictors of health-related quality of life in a large cohort of adult patients living with sickle cell disease in France: the DREPAtient study. Front Public Health. 2024;12:1374805.
25. O'Brien JA, Hickman RL, Burant C, Dolansky M, Padrino S. Health literacy, perceived stigma, self-efficacy, and HRQOL in sickle cell disease. West J Nurs Res. 2023;45:335–43.
26. de Araujo JA, Rossi DA, Valadao TF, Milan-Mattos JC, Catai AM, Sato TO, Hueb JC, et al. Cardiovascular benefits of a home-based exercise program in patients with sickle cell disease. PLoS ONE. 2021;16(5): e0250128.
27. Ivo ML, de Carvalho EC. Nursing care for patients with sickle cell disease, in the light of Roy' model. Rev Lat Am Enfermagem. 2003;11(2):192–8.
28. Connes P, Simmonds MJ, Brun JF, et al. Exercise hemorheology: classical data, recent findings and unresolved issues. Clin Hemorheol Microcirc. 2013;53:187–99.
29. Olorunyomi OO, Liem RI, Hsu LL. Motivators and Barriers to Physical Activity among Youth with Sickle Cell Disease: Brief Review. Children. 2022;9:572.
30. Pinto DMS, Sacramento MS, Santos PHS, Silva WS, Oliveira EC, Gardenghi G, et al. Physical exercise in sickle cell anemia: a systematic review. Hematol Transf Cell Ther. 2021;43(3):324–31.
31. Ewuzie Z, Ezeano C, Zara S, Aaishah V, Aderinto N. The role of exercise in sickle cell anemia management: a narrative review of current evidence. Discov Med. 2024;1:29.
32. Antonelli Rossi DA, De Araujo Junior JA, Luvizutto GJ, Bazan R, Salmazo PS, Modolo GP, Hueb JC, Nunes HRC, Hokama NK, Minicucci MF, Roscani MG, Zanati Bazan SG. Effect of a physical exercise program on the inflammatory response, cardiac functions, functional capacity, and quality of life in patients with sickle cell disease. J Clin Med. 2023;12(12):3952.
33. Diaw M, Diop S, Soubaiga FY, Seck M, Faye BF, Niang MN, Samb A, Connes P. Blood viscosity is lower in trained than in sedentary sickle cell trait carriers. Clin Hemorheol Microcirc. 2015;61:23–9.
34. Faes C, Charrin E, Connes P, Pialoux V, Martin C. Chronic physical activity limits blood rheology alterations in transgenic SAD mice. Am J Hematol. 2015;90:E32–3.
35. Aufradet E, Monchanin G, Oyonno-Engelle S, Feasson L, Messonnier L, Francina A, Bezin L, et al. Habitual physical activity and endothelial activation in sickle cell trait carriers. Med Sci Sports Exerc. 2010;42:1987–94.
36. Aufradet E, Desouza G, Bourgeaux V, Bessaad A, Campion Y, Canet-Soulas E, Pialoux V, et al. Hypoxia/reoxygenation stress increases markers of vaso-occlusive crisis in sickle SAD mice. Clin Hemorheol Microcirc. 2013;54:297–312.
37. Aufradet E, Douillard A, Charrin E, Romdhani A, De Souza G, Bessaad A, Faes C, et al. Physical activity limits pulmonary endothelial activation in sickle cell SAD mice. Blood. 2014;123:2745–7.
38. Karlson CW, Baker AM, Bromberg MH, David Elkin T, Majumdar S, Palermo TM. Daily Pain, Physical Activity, and Home Fluid Intake in Pediatric Sickle Cell Disease. J Pediatr Psychol. 2017;42(3):335–44.
39. Imboden C, Claussen MC, Seifritz E, Gerber M. Physical activity for the treatment and prevention of depression: a rapid review of meta-analyses. Dtsch Z Sportmed. 2021;72:280–7.
40. McIntyre E, Lauche R, Frawley J, Sibbritt D, Reddy P, Adams J. Physical activity and depression symptoms in women with chronic illness and the mediating role of health-related quality of life. J Affect Disord. 2019;252:294–9.
41. Olowoselu FO, Uche E, Oyedeji OA, Enabuele O, Ogunnubi OP, Olowoselu OI, Ayanshina OA. Anxiety and depression in sickle cell anaemia: The impact of pain in a Nigerian population. Nigerian Hospital Practice. 2021;27:1–2.
42. Kasiulevicius V, Sapoka V, Filipaviciute R. Sample size calculation in epidemiological studies. Gerontologija. 2006;7(4):225–31.
43. Faul F, Erdfelder E, Buchner A, Lang AG. Statistical power analyzes using G*Power 3.1: Tests for correlation and regression analyses. Behav Res Methods. 2009;41:1149–60.
44. Ware JE, Kosinski M, Keller SD. How to Score the SF-12 Physical and Mental Health Summary Scales. 3rd ed. Lincoln: QualityMetric; 1998.
45. Ware J Jr, Kosinski M, Keller SD. A 12-item short-form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care. 1996;34:220–33.
46. Larson CO. Use of the SF-12 instrument for measuring the health of homeless persons. Health Serv Res. 2002;37:733–50.
47. Shah RM, Banahan BF, Holmes ER, Patel AS, Barnard M, Khanna R, Bentley JP. An evaluation of the psychometric properties of the sf-12v2 health survey among adults with hemophilia. Health Qual Life Outcomes. 2018;16:229.
48. Artz N, Zhang J, Meltzer D. Physical and Mental Health in Adults Hospitalized with Sickle Cell Disease: Impact on Resource Use. J Natl Med Assoc. 2009;101:139–44.
49. Mbada CE, Awokoya AS, Oyewole OO, Idowu AO, Akinsulore A, Fatoye C, Oke KI, Fatoye F. Translation, cross-cultural adaptation and psychometric evaluation of Yoruba version of the short-form 12 health survey. Ann Ig. 2021;33(3):254–67.
50. Chiang CC, Chiou ST, Liao YM, Liou YM. The perceived neighborhood environment is associated with health-enhancing physical activity among adults: a cross sectional survey of 13 townships in Taiwan. BMC Public Health. 2019;19:524.
51. World Health Organization (WHO). Physical activity. 2020. Available from: http://www.who.int/news-room/fact-sheets/detail/physical-activity.
52. Husejko JP, Strugała M, Modrzejewski M, Wąsicki M, Kędziora-Kornatowska K, Podhorecka M. Physical Activity of the Elderly in Light of the 2020 WHO Guidelines. Med Rehabil. 2021;25(1):30–6.
53. SPARC. The New Zealand Physical Activity Questionnaires. Report on the validation and use of the NZPAQ-LF and NZPAQ-SF self-report physical activity survey instruments. SPARC: Wellington. 2004. http://www.activenzsurvey.org.nz/Documents/validation-report-physical-activity-questionnaires.pdf.
54. Ainsworth BE, Macera CA, Jones DA, Reis JP, Addy CL, Bowles HR, Harold WK. Comparison of the 2001 BRFSS and the IPAQ Physical Activity Questionnaires. Med Sci Sports Exerc. 2006;38(9):1584–92.
55. Scholes S, Bridges S, Ng Fat L, Mindell JS. Comparison of the Physical Activity and Sedentary Behaviour Assessment Questionnaire and the Short-Form International Physical Activity Questionnaire: An Analysis of Health Survey for England Data. PLoS ONE. 2016;11(3): e0151647.
56. Ademoyegun AB, Mbada CE, Afolabi OE, Aghedo IA, Adelowokan OI, Awotidebe TO. Influence of neighborhood environment and social support on physical activity among patients with diabetes mellitus. J Contemp Stud Epidemiol Public Health. 2023;4(1):ep23001.
57. Balboa-Castillo T, Muñoz S, Serón P, Andrade-Mayorga O, Lavados-Romo P, Aguilar-Farias N. Validity and reliability of the international physical activity questionnaire short form in Chilean adults. PLoS ONE. 2023;18(10): e0291604.
58. Ács P, Veress R, Rocha P, Dóczi T, Raposa BL, Baumann P, et al. Criterion validity and reliability of the International Physical Activity

Questionnaire—Hungarian short form against the RM42 accelerometer. BMC Public Health. 2021;21:381.
59. Awotidebe TO, Bisiriyu LA, Oyeyemi AL, Oladejo OA, Akinola OT, Aliyu ES, Olawoye AA, Babalola NO, Adedoyin RA. Cultural adaptation, validation and reliability assessment of the Yoruba language version of the International Physical Activity Questionnaire in Nigeria. African Journal for Physical Activity and Health Sciences. 2021;27(4):408–23.
60. Kroenke K, Spitzer RL. The PHQ-9: A new depression diagnostic and severity measure. Psychiatr Ann. 2002;32:509–15.
61. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: Validity of abrief depression severity measure. J Gen Intern Med. 2001;16:606–13.
62. Ojelabi AO, Bamgboye AE, Ling J. Preference-based measure of health-related quality of life and its determinants in sickle cell disease in Nigeria. PLoS ONE. 2019;14(11): e0223043.
63. Hedo CC, Aken'ova YA, Okpala IE, Durojaiye AO, Salimonu LS. Acute phase reactants and severity of homozygous sickle cell disease. J InternMed. 1993;233:467–70.
64. Akinlade KS, Atere AD, Rahamon SK, Olaniyi JA. Serum levels of copeptin, C-reactive protein and cortisol in different severity groups of sickle cell anaemia. Niger J Physiol Sci. 2013;28:159–64.
65. Uche E, Adelekan O, Akinbami A, Osunkalu V, Ismail K, Ogbenna AA, Badiru M, Dosunmu A, Oluwole E, Kamson O. Serum homocysteine and disease severity in sickle cell anemia patients in Lagos. J Blood Med. 2019;10:127–34.
66. Zimet GD, Dahlem NW, Zimet SG, Farley GK. The multidimensional scale of perceived social support. J Pers Assess. 1988;52:30–41.
67. Jumbo SU, MacDermid JC, Kalu ME, Packham TL, Athwal GS, Faber KJ. Measurement Properties of the Brief Pain Inventory-Short Form (BPI-SF) and the Revised Short McGill Pain Questionnaire-Version-2 (SF-MPQ-2) in Pain-related Musculoskeletal Conditions: A Systematic Review Protocol. Arch Bone Jt Surg. 2020;8(2):131–41.
68. Adeloye D, Ige-Elegbede JO, Auta A, Ale BM, Ezeigwe N, Omoyele C, Dewan MT, et al. Epidemiology of physical inactivity in Nigeria: a systematic review and meta-analysis. J Pub Health. 2022;44(3):595–605.
69. Heesch KC, van Gellecum YR, Burton NW, van Uffelen JGZ, Brown WJ. Physical activity and quality of life in older women with a history of depressive symptoms. Prev Med. 2016;91:299–305.

## Publisher's Note