CHANGES IN THE PULMONARY FUNCTIONS OF INDIVIDUALS WITH SICKLE CELL DISEASE: A SCOPING REVIEW.

ABSTRACT

Background: Individuals with sickle cell disease (ISCD) are often subject to various changes in crucial health profiles with a consequent need for reduced physical activities, which could be as a result of their declining pulmonary functions. Few studies have systematically attempted to examine the changes in the pulmonary function of ISCD comprehensively. **Objective:** The purpose of this review is to explore the changes in pulmonary functions of ISCD.

Methods: A scoping review comprising 36 studies was conducted to identify and examine the literature related to changes in the pulmonary functions of ISCD, and to compare how they correlate with their health profile.

Results: Most common changes cited were demographic factors (26 papers), followed by haematological indices (18 papers) followed by pulmonary complications (16 papers), and anthropometric values (13 papers), with the most common themes overall being age while FEV1, FVC, and FEV1/FVC where the most outcome measures examined.

Conclusion: With current advances in medicine, the life expectancy of ISCD is on the increase. We conclude that an evidence-based therapy for pulmonary functions maintenance will be a valid and valuable care for ISCD. Further research must be done, mainly to focus on each health profile holistically.

Key words: *ISCD, Sickle cell disease, pulmonary functions, health profile.*

Abbreviations: ISCD: Individuals with Sickle Cell Disease, **FEV1:** Forced Expiratory Volume in one second, **FVC:** Forced Vital Capacity, **TV:** Tidal Volume, **IRV:** Inspiratory Reserved Volume, **ERV:** Expiratory Reserved Volume, **RV:** Residual Volume, **TLC:** Total Lungs Capacity, **IC:** Inspiratory Capacity, **ACS:** Acute Chest Syndrome, **PHT:** Pulmonary Hypertension, **Rrs:** Respiratory Resistance, **kCO:** Diffusion coefficient, **DLCO:** Diffusion capacity, **VOC:** Vascular Occlusion Crisis, **6MWD:** Six minutes' walk Test, **HR:** Heart Rate, **RR:** Respiratory Rate, **PFT:** Pulmonary Function Test, **CPET:** Cardiopulmonary Exercise Test, **MMEFR:** Maximum Mid-expiratory Flow Rate, **PEFR:** Peak Expiratory Flow Rate, **MVV:** Maximal Voluntary Ventilation.

INTRODUCTION

Sickle cell disease (SCD) is a known autosomal recessive hemoglobinopathy leading to significant morbidity and mortality and related to chronic hemolytic anemia and vaso-occlusion, resulting to organ damage [1]. Many variants of the hemoglobinopathy are known and they include sickle cell hemoglobin C disease (HbC), sickle cell thalassemia and sickle cell anemia (HbSS) [2]. The variants that are known to cause illness in Nigeria include sickle cell hemoglobin C (HbC) and sickle cell anemia (HbSS) [3]. Sickle cell disease is a global endemic disease, and it is one of the most common autosomal recessive gene abnormalities [4, 5]. More than 50 million people are affected by SCD worldwide [6] with a global estimate of approximately 300,000 infants born with SCD annually [7], which could rise to 400,000 by the year 2050. The prevalence of SCD in Nigeria is about 4 million, with 150,000 children born with SCD annually [3]. Recently, advances in medicine have contributed to a substantial reported decrease in mortality rate among sickle cell anaemia patients in low-income countries and globally. This can be attributed to advances in the area of transfusion protocols, administration of hydroxyurea [8], early parental education and counselling, early administration of antibiotics for febrile episodes, penicillin prophylaxis, and adoption of newborn screening programs for sickle cell anaemia [9]. Despite the various advances in medicine, the current life expectancy of individuals with sickle cell disease is still suboptimal [10].

Pulmonary status in sickle cell disease (SCD) is a key source of health complications causing acute morbidity and, in the long term, a significant determinant of survival [11, 12]. However, most studies tracing the pathophysiology of health complications in individuals with sickle cell

disease (ISCD) had often focused on the cardiovascular manifestations of chronic hemolytic anemia [13]. It is essential to recognize that SCD can affect health profiles in variable ways. The literature discussing changes in the pulmonary functions of ISCD most often only relates to a specific location, mostly based on small sample sizes, and is usually limited to a particular age range making it difficult to generalize it to the population of ISCD [15-17]. Few studies have attempted to examine changes in the pulmonary functions of ISCD in a comprehensive fashion, either as an original study or review. An exception is a Nigerian study by Oko-Ose et al. [18] in Nigeria carried out Lung Function Tests in Sickle-Cell Patients in Benin City to determine the changes in lung functions and its association with gender, age, and body mass index (BMI) of stable state sickle-cell patients. The findings of the study with 60 participants made up of 30 patients and 30 control groups suggested that lung function differs significantly in individuals with SCD when compared with matched controls of a similar age and gender. Another study by Tambe et al. [12] reviewed pulmonary function in children with sickle cell disease (SCD) and its correlation with some selected clinical, laboratory, and hematological parameters were determined. They demonstrated poorer lung function, especially forced expiratory volume in 1s. Also, the static and dynamic pulmonary functions such as FVC, FEV1, MMEFR25-75%, PEFR and MVV were all significantly correlated compared to healthy controls, showing that pulmonary function disorders could develop early in ISCD.

There is a paucity of studies examining the correlates of pulmonary functions with the various health profiles of individuals with sickle cell disease in a comprehensive fashion. This leaves an unmet need for the care of ISCD [19]. Physiotherapist involved in the management of SCD patients is often faced with the challenge of engaging these patients in strenuous physical activities and also targeting the safe level of exercise to recommend and administer to these patients [20, 21]. This limited level of physical activity and exercise can be attributed to the chronic and worsening integrity of the pulmonary parameters of ISCD [22]. In view of severe anemia, decreased blood oxygen affinity, pulmonary arterial vaso-occlusion, microinfarction, and microfibrous complications being associated with sickle cell disease [5]; an analysis of pulmonary function in them will be of great interest [12]. Thus, this study proposes evidence-based guarded pulmonary functions parameters as a fundamental guideline in the management of ISCD to optimally make up to the improvements currently being experienced in the management of ISCD [22].

Study objective

The objectives of this review were: (i) to collate and appraise all available published literature which ascertained changes in pulmonary functions of individuals with sickle cell disease; (ii) to identify and examine the correlates of these changes; (iii) to identify clinical complications that could be associated with changes in lungs functions.

Review Methodology

This review followed the six-stage scoping review framework as outlined by Arksey and O'Malley [23].

Stage one: Identify the research question

As central to the study objective, this review will focus on the research question: will the maintenance of these pulmonary functions help in curbing the pulmonary changes and complications inherent in ISCD?

Stage two: Identify relevant studies

A comprehensive search of the literature, relevant peer-reviewed journals articles published between 2009 to 2019 were sought from the following eight electronic databases; AMED, Cochrane databases, PubMed, PubMed Central, MEDLINE, ProQuest, Embase, Web of Science Core Collection. The key search terms included: Lung OR pulmonary OR Respiratory AND function OR parameters OR measures AND changes OR complications OR disorder OR needs OR reactions OR impact OR manifestations OR conditions AND children OR adult OR individual OR patients OR persons AND & "sickle cell disease" OR "sickle cell disorder" OR "sickle cell anaemia" OR "sickle cell patients" AND "pulmonary function" OR "Lung function" OR "pulmonary parameters" OR "spirometry changes" AND relationship OR correlation AND "health profiles" OR "health complications" AND "sickle cell disease" OR "sickle cell anaemia" OR "sickle cell patients". Also, a thorough search of the reference lists from the selected articles were conducted and Google Scholar was used to access any other primary sources and full-

text versions of articles. All literature sources were exported from each of the database searches into references and bibliographic management software program.

Stage three: Study selection

The inclusion criteria are as follows; (1) journal articles written in English; (2) published original peer-reviewed journals; (3) those with an approved ethics statement; (4) studies which investigate changes in pulmonary functions of individuals with sickle cell disease, using pulmonary parameters as a critical outcome measure; and (5) in a population sample of ISCD only.

For this study, exclusion criteria included; (1) Articles that were poorly conducted; (2) extremely small sample sizes; (3) articles examining the various changes in the health profiles of ISCD but without direct correlative to pulmonary functions. A second author (AE) reviewed each paper included with the assistance of the lead author (LP) to make the critical decisions. Using the above key search terms, we identified 2460 articles across the eight databases. Of which, 36 were included in this scoping review (see Fig. 2).

Stage four: Charting the data

The fourth stage involved developing a framework for charting data. A summarizing process was utilized, as described by Arksey and O'Malley [23]. A data charting form was used for summarizing each primary reviewed article by; author, year, country of origin, study aim, correlative health profiles, study design and methods, sample size, an abridged summary of the findings, limitations for each study, and significant changes in pulmonary functions discovered. The second reviewer (AE) validated the data by reviewing selected articles based on the eligibility criteria; a consensus was made of the information presented in Table 1.

Stage five: Collating, summarizing and reporting results

This fifth stage of the review involved collating the various health profiles of ISCD that are correlated with changing pulmonary functions into themes (Table 2). This is based on the development of the themes on a low inference simple qualitative descriptive approach recommended by Sandelowski [24] and then used these themes to summarize changes in pulmonary function of ISCD. Reporting involved outlining an evidence-based physical therapy intervention for pulmonary function maintenance that could be additional key guidelines in the management of ISCD.

Stage six: Consultation Exercise

The sixth and final stage of this review involved a consultation meeting with the healthcare team members involved in the care of ISCD. The 10-man consultation panel was made up with Two (2) consultant haematologists, one (1) nurse, one (1) laboratory scientist, one (1) statistician, two (2) informed ISCD and the two authors (physiotherapists). Discussion on further studies were made, and agreement to exclude them from the scoping review was made.

Result

A total of 36 studies (Table 1) were reviewed. All studies were quantitative studies. Eighteen studies used cross-sectional methods, 8 used prospective longitudinal, 4 used retrospective, and 4 were literature reviews. In each of the studies, LFT was assessed as a primary outcome measures (n=36) and were examined for association with health profiles variables like; demography (n=26), pulmonary complications (n=16), cardiovascular complications (n=2), recovery indices (n=7), anthropometrics (n=13), hematological indices (n=18), Radiological changes (n=7), SCD phenotype (n=9). Of the 36 studies reviewed, FEV1 was the most cited outcome measure used as a determinant for declining lung functions (n=31, 86.6%). While aging (n=25, 70%) was most cited to be associated with impaired lung functions in ISCD. It was cited across the reviewed articles that as a group, individuals with SCD tend to have lower lung volumes compared with healthy controls [11, 25-57]. The findings are similar across varying age & ethnic lines regardless of the differences in body weight. Several mechanisms and risk factors have been proposed to explain these findings. The associated health profiles of ISCD are discussed in descending order of how often they were cited in the studies reviewed.

DEMOGRAPHY

Of the associated demographic factors cited, Age (n=25, 70%) was cited to be most frequently correlated to diminishing lung functions in ISCD [12, 25, & 26]. Lung function deteriorates with increasing age in children with SCD, and the rate is especially greater in younger children in whom ACS episodes are more common [15, 27, & 28]. The decline is slow and it is not associated with changes in somatic growth [15, 29]. The rate of this age-related decline is similar to that of children with cystic fibrosis and asthma [30, 31]. Also, Restrictive lung disease was associated with older patients, and obstructive lung disease was associated with younger patients [32], the initial decline in FEV1 is associated with worsening pulmonary dysfunction over time. The factors that influence the progression of FEV_1 mostly include the introduction of medications and promotion of adequate prepubertal growth [33]. It is strongly speculated that growth may be primarily responsible for the pulmonary function abnormalities in children with SCD [34].

The sex (n=15, 42%) of ISCD was the second most frequently cited theme in the demographic factors associated with pulmonary complications. Longitudinal FEV1 was found to be lower for 7 patients with HbSS compared to non-HBSS children. When compared to the HbCS cohort, girls with HbSS showed lower longitudinal FVC and FEV1/FVC; there was no difference in FVC or FEV1/FVC between boys in the HbSS & HbCS cohort [26]. Few other studies also cited the female gender to be associated with a heightened risk of a restrictive spirometry pattern [28].

Socioeconomic status (n=3, 8.4%) were also common factors cited to be associated with changes in pulmonary functions, especially regarding the nutritional needs of this population of ISCD [23, 24]. Malnutrition, increasing age, and female sex were all associated with increased risk of a restrictive spirometry pattern [23]. There was a difference in the level of impairment noticed in the different ethnic groups; Chronic pulmonary complications in adult Saudi ISCD were relatively mild but frequent as it also differs from that published for African-origin SCD patients. This difference may reflect a different natural history of SCD in the diverse geographic populations [33].

HAEMATOLOGICAL INDICES

Haematological changes (n=18 papers) were commonly cited across the reviewed articles to be associated with changes in pulmonary functions of ISCD. Changing Hemoglobin levels (n=14, 39.2%), was most frequently examined as a link to impaired lungs functions of ISCD [17, 37, 38].

However, most study results showed chronic anaemia of HbH disease in children does not affect PFT parameters [17]. No clear association of FEV1 or other PFTs with individual markers of hemolysis was shown [38]. Very commonly cited, Leucocytes or immunocytes levels were associated with increased lung function impairment (n=10, 28%). Lactate dehydrogenase (n=8, 22.4%), immunocytes (n=10, 28%), Vitamin D (n=1, 2.8%) and serum levels of inflammatory markers (n=3, 4.2%) were all commonly cited as predictors of impaired lungs functions in ISCD. Lung dysfunction, especially restrictive pattern, is common in SCA and is associated with variations in immunological markers, especially serum IL-8 and hs-CRP [25]. In children with SCA, AHR is prevalent. Younger age, serum IgE concentration and LDH level, a marker of hemolysis, is associated with AHR [26]. Children with SCD have low Vitamin D status, increased susceptibility to respiratory infections, asthma and a greatly heightened vulnerability to potentially fatal complications of respiratory disorders [33].

PULMONARY COMPLICATIONS

The complications of SCD are myriad; but, pulmonary complications are frequent. In addition to ACD and asthma, concomitant PHT significantly increases morbidity and mortality [39]. Pulmonary complications can interact with each other in numerous ways, like between asthma, airway hyperreactivity, nocturnal oxyhemoglobin desaturation, pulmonary hypertension, and sleep disordered breathing [37].

Acute chest syndrome was the most cited correlating pulmonary complications linked to impaired lungs functions parameters in ISCD (n=12, 36%). Active prevention and management of ACS and possibly the use of agents that inhibit chemokine gene activation and chronic inflammation may retard the development of lung dysfunction in children with SCA [25]. The rate of decline in lung functions was found to be higher in younger children in whom ACS episodes were more common [27]. The data demonstrate that obstructive lung dysfunction is relatively common in SCD and suggest that recurrent ACS may contribute specific obstructive defects. The increase in Rrs associated with ACS was accompanied by an increase in diffusion capacity, suggesting that it may have been related to the increase in lung blood volume [11]. However, SCD does have severe and long-term effects on lung-function, even in the absence of overt episodes of ACS [34].

Asthma and Increased airway reactivity were the second most cited themes of the pulmonary complications domain (n=12, 33.6%). Asthma and BHR are shown to be more common in children with SCD than in ethnic matched controls, and atopic asthma appears to be associated with

recurrent ACS [40, 41]. Wheezing and sleep-disordered breathing was also common factors cited across the reviewed articles (n=4, 11.4%). Studies demonstrated that adults with SCA have a higher prevalence of wheezing and lower FEV1% and FVC% than adults without SCA [26]. Pulmonary hypertension was also cited (n=2, 5.6%). Elevated pulmonary capillary blood volume was found to be associated with mixed obstructive/restrictive lung disease, hypoxia, and moderately severe anaemia [21]. Increased pulmonary capillary blood volume could contribute to the increased airways obstruction in children with SCD [42]. Vaso-occlusive crisis (n=2, 5.6%) and Chronic fibrosis (n=2, 5.6%) were as well common predictors. Lungs volume parameters showed a similar pattern of decline with that of children with cystic fibrosis and greater than that of children with asthma [30].

ANTHROPOMETRICS

Some studies cited pulmonary function to be directly related to body composition underscoring the need for early nutritional intervention for ISCD [43] while other studies reported that reduced lung function were not influenced by anthropometric variance [35, 44]. Out of the Anthropometrics themes, Height (n=13, 36.4%) and Weight (n=14, 39.2%), were well-cited to be associated with impaired lung functions in ISCD. BMI (n=9, 25.3) and Body circumference (n=3, 8.4%) were also commonly understudied. There were reported structural changes of the thorax (specifically the anteroposterior chest diameter and anteroposterior to lateral chest ratio) specific to SCD, which potentially interfere with healthy lung growth [35].

SICKLE CELL DISEASE GENOTYPE

HbSS (n=6, 17.2%) is the most commonly cited SCD Genotype and is associated with decreasing lung function. The decline in pulmonary functions in patients of HbSC follows the same pattern. The decline is slow, and it is not associated with changes in somatic growth [15]. It is associated with increasing age, patient- or family-reported history of asthma or wheezing, and higher LDH [36]. Longitudinal FEV1 was lower for patients with HbSS compared to children in the general population. When compared to the HbCS cohort, girls with HbSS showed lower longitudinal FVC and FEV1/FVC; there was no difference in FVC or FEV1/FVC between boys in the HbSS and HbCS cohort [26, 44].

RECOVERY INDICES

Themes on recovery indices domain were not much cited as a predictor of declining lung function in ISCD except for SPO2 (n=7, 19.2%). Causes of the reduced high volumes and decreased diffusion capacity, in SCD, implicate the normal SPO2 level [48].

CARDIOVASCULAR COMPLICATIONS

A significant interrelation between abnormalities of the structure and the function of both the pulmonary and cardiovascular system was reported, the severity of the cardiopulmonary parameters among SCA patients was cited to be higher than that among control patients [45]. A strong correlation between various parameters of lung volume and the cardiothoracic ratio was also cited. Cardiomegaly and relative small chest size were explained to be important causes of the reduced lung volumes and diffusion capacity in SCD [31]. An Echocardiography study cited the pattern of this cardiopulmonary interrelations. There was an association between small vessel pulmonary vascular dimensions on HRCT showing pulmonary vascular volume, lung function abnormalities and echocardiographic estimates of ventricular function and cardiac output in ISCD; in addition, the decline in lung function showed correlation with changes in vascular dimension [46].

LUNGS FUNCTIONS ABNORMALITIES

Studies most frequently examined FEV1 (n=31, 86.6%), FVC (n=26, 72.6%), FEV1/FVC (n=22, 61%) and TLC (n=21, 58.8%) as measures for lungs functions. Abnormal pulmonary function, most often obstructive, is common in children with HbSS and Sβ. Increase in age, patient- or family-reported history of asthma or wheezing and higher LDH concentration were independent predictors of obstruction as reflected in lower FEV1/FVC [36, 38, 47]. Adults with SCA have lower FEV1% and FVC% than adults without SCA [38, 48].

Forced expiratory flow (FEF) (n=15, 42%), Diffusion capacity (n=12, 32.6%), Respiratory system resistance (n=5, 14%) and Respiratory muscle strength (n=2, 5.6%) were also well cited across the reviewed articles. SCD-SS patients showed correlations between respiratory muscle force and lung volume, and reduced expiratory muscle force compared to inspiratory muscle force. Respiratory muscle strength may affect lung volumes in these patients, and expiratory muscles may be more susceptible [29]. A reported increase in respiratory resistance associated with ACS, accompanied by an increase in diffusion capacity, suggesting that it may have been related to an increase in lung blood volume [11].

Table 2 summarises the findings for reported health complications from the 36 papers reviewed in this scoping study. Demographics, haematological indices and pulmonary complications predictors dominated in the published literature, with the most common being aging in the demographic domain while FEV1, FVC, and FEV1/FVC where the most outcome measures examined.

Discussion

We have consistently found that the impairment of the pulmonary function is widespread and is the most frequent cause of morbidity and mortality among ISCD. Demographic factors, especially age was well correlated with declining lung functions in ISCD [15, 27, 28]. This finding is consistent with the study by Sharma and Goodwin [49], which reported that Respiratory muscle strength reduces with age and impair productive cough, which is very important for airway clearance. The lung matures by age 20–25 years, and thereafter aging is associated with a progressive decline in lung function. It is strongly speculated that growth may be primarily responsible for the pulmonary function abnormalities in children with SCD [34]. This applies, especially for restrictive lung diseases. Obstructive lung diseases are as a result of airways narrowing by spasms in the smooth muscles that are in the wall of the airways. Thus, Restrictive lung disease is more associated with older patients; and obstructive lung disease is associated with younger patients with other pulmonary complications like asthma [32].

The significant predictors and demographic factors of impaired pulmonary functions in ISCD is sex. The female sex is more associated with a restrictive pattern [28]. Thirty-two girls with HbSS showed lower longitudinal FVC and FEV1/FVC; in the study by Field et al., [26]. Several studies describing these differences in the sex have implicated the sex hormones (estrogen, progesterone, and testosterone) to have biological and pathophysiological actions in peripheral, non-reproductive organs, including the lung as their underlying cause. This is an essential finding as investigating and managing patients without taking their gender into account could be as imprecise as the omission of a patient's age from clinical decision making. The effect of the socioeconomic status of ISCD is also worthy of note, especially regarding the nutritional needs of this population of ISCD [23, 24].

Haematological changes were also well reported to be associated with declining lung functions, especially LDH, immunocytes, Vitamin D, inflammatory markers, and markers of haemolysis [17, 37, & 38]. In a study by Adegoke et al. [25], Lung dysfunction of the predominantly restrictive pattern was reported to be associated with alterations in immunological markers, especially serum IL-8 and hs-CRP. Serum IgE concentration, and LDH level, a marker of hemolysis, is associated with AHR. The pulmonary complications that were cited for having significant association with declining pulmonary functions include; acute chest syndrome (ACS), asthma, airway hyperreactivity, pulmonary hypertension, wheezing, and sleep-disordered breathing, and VOC. These pulmonary complications are all common morbidity in ISCD.

Linking ACS to changes in pulmonary functions, Dessap et al. [50] made similar discoveries. They explained that the development of ACS represents a vicious cycle of lung infarction, inflammation, and atelectasis leading to ventilation-perfusion mismatch, hypoxemia, and acute increases in the pulmonary artery and right ventricular pressures. Other complications follow similar restrictive pathophysiology.

Anthropometric variables were reported not to have a significant correlation with changes in pulmonary functions. However, there were reported structural changes of the thorax (specifically the anterior-posterior chest diameter and anterior-posterior to lateral chest ratio) specific to SCD, which potentially interfere with healthy lung growth [35]. Also, the haemoglobin genotype of ISCD was not reported to be significantly associated with changes in lung function.

The decline in pulmonary functions in patients of SCD follows the same pattern [15]. SPO2 level is associated with changes in pulmonary function. ISCD has low serum oxygen level. With any exertion, their body becomes quite stressed and have a hard time breathing. This, in the long run, could cause reduced lung volumes and decreased diffusion capacity [31].

Key issues of cardiovascular complications associated with changes in pulmonary functions include; cardiomyopathy, cardiomegaly, and cardiothoracic ratio in SCD [31]. Thomas et al. [51] explained that the lungs and heart both reside in a common enclosure (chest wall), and the cardiac muscle is less compliant than the lungs, progressive cardiac enlargement within the thoracic cavity is a potential cause. Such changes in

cardiac volume would be expected to result in primarily restrictive lung changes manifested as reductions in total lung volume and vital capacity [51 & 52].

Limitations of the review

This review utilized the seminal scoping study framework proposed by Arksey and O'Malley, [23]. It consisted of an iterative process whereby the authors were involved with each of the six stages of the scoping review process reflexively, and where necessary, repeating steps to ensure that the review of the literature has been comprehensively completed. Despite this, some limitations associated with the conduct of this scoping review needs to be acknowledged. The primary limitation was the search strategy that was limited to English-language studies only, and there may well be other literature equally relevant to the area of changes in pulmonary functions of ISCD that wasn't considered because it was published in another language. We also could not confirm a comprehensive list of health profiles, as such, it is possible there are essential health profiles that were not considered in this review.

Implications for further research and practice

The results of this review emphasize the lack of evidence-based therapy for pulmonary function maintenance and highlights a need for the treatment guideline of ISCD to be reviewed. A prospective longitudinal study is recommended to verify the possible role of spirometry exercises in the maintenance of lungs elasticity as well as healthy lung volume in ISCD.

Conclusion

We collated and appraised all available published literature, which investigates changes in pulmonary functions of ISCD to examine how these changes correlate with demography, SCD genotype, Anthropometrics, Haematological indices, pulmonary complications, cardiovascular complications, and recovery indices in ISCD. We noted the pathophysiology of the associated complications to the lung functions and the

evidence-based therapy for pulmonary function maintenance as a key addition in the treatment guidelines for ISCD. With current advances in medicine, the life expectancy of ISCD is on the increase. We conclude that an evidence-based therapy for pulmonary functions maintenance will be valid and valuable care for ISCD.

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INFLUENCING FACTORS

Environment
Age
Socioeconomic
Gender
Medical intervention
Physical therapy interventions
Education

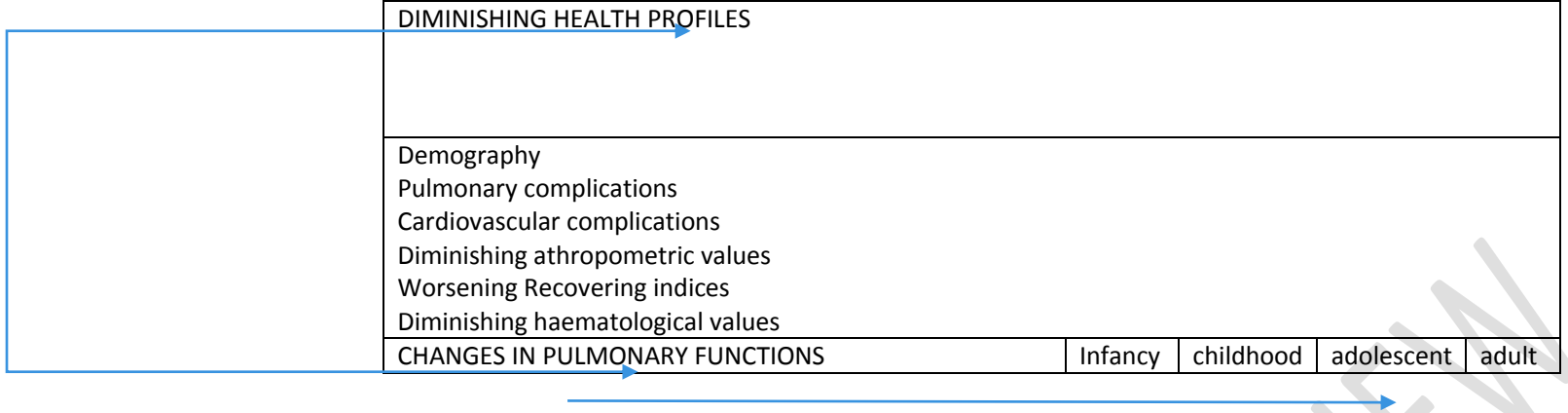

Fig.1: Framework of changes in pulmonary functions

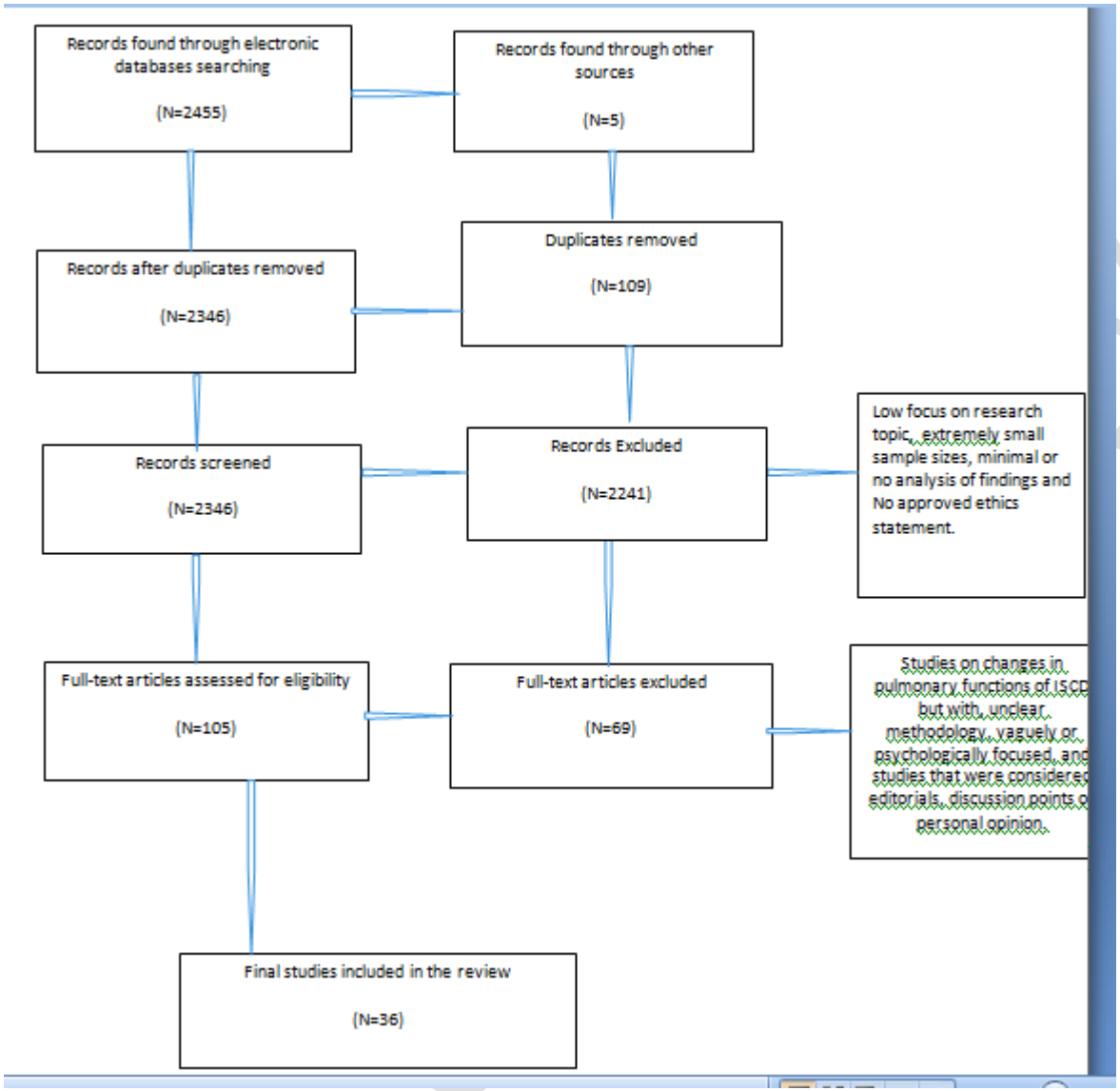
Records found through electronic databases searching
(N=2455)
Records found through other sources
(N=5)
Duplicates removed
(N=109)
Records after duplicates removed
(N=2346)
Records screened
(N=2346)
Records Excluded
(N=2241)
Low focus on research topic, extremely small sample sizes, minimal or no analysis of findings and No approved ethics statement.
Full-text articles assessed for eligibility
(N=105)
Full-text articles excluded
(N=69)
Studies on changes in pulmonary functions of ISCD but with, unclear methodology, vaguely or psychologically focused, and studies that were considered editorials, discussion points or personal opinion.
Final studies included in the review
(N=36)

Fig. 2. PRISMA flow diagram of scoping literature search and selection.

S/N	Author, Year, Country	Aim of the study	Pulmonary parameters assessed	Health Profiles	Method and Sample size	Summary of findings
1.	Adegoke et al., 2008, Nigeria.	To assess lung function of children with SCA and determine the possible role of acute chest syndrome (ACS), serum inflammatory cytokines, highly sensitive C-reactive protein (hs-CRP), leucocytes and 25-hydroxyvitamin D.	FEV1, L FEV1, % FVC, L FVC, % PEFR, L PEFR, % FEV1/FVC	Socio-demographic, clinical, haematological, biochemical and immunological data	A cross-sectional study/Lung function of children with SCA was determined by spirometer and classified into normal or impaired. n=76	Lung dysfunction, predominantly restrictive pattern, is common in SCA and is associated with previous ACS and alterations in immunological markers, especially serum IL-8 and hs-CRP. Active prevention and management of ACS and possibly the use of agents that inhibit chemokine gene activation and chronic inflammation may retard development of lung dysfunction in children with SCA.
2.	Caboot & Allen (2008), USA	To review the associations between asthma and airway hyperreactivity & SCD, as well as the link with (ACS) and vaso-occlusive pain crisis (VOC).	airway resistance, TLC, & RV,FEV1/FVC	airway hyperreactivity, ACS, chronic sickle lung disease, PHT, & sleep disordered breathing	Review of studies on pulmonary complications and management n=22	Pulmonary complications can interact with each other in numerous ways, like between asthma, airway hyperreactivity, nocturnal oxyhemoglobin desaturation, pulmonary hypertension, and sleep disordered breathing.
3.	Lunt et al., (2017), UK	To detect and characterise different phenotypes of respiratory disease in children and young adults SCD.	FEV1, VC, TLC, Rrs5, DLCO, PCBV,SpO2	(Hb), LDH, WCC, reticulocyte & age.	A retrospective study, for lung function & haematological biomarkers were analysed in a cohort of 114 subjects with SCD aged between 5 and 27yrs. n=144	Elevated pulmonary capillary blood volume was found to be associated with mixed obstructive/ restrictive lung disease, hypoxia and moderately severe anaemia; restrictive lung disease were associated with older patients; and obstructive lung disease were associated with younger patients, elevated serum,

						LDH & bronchodilator reversibility.
4.	Lunt et al., (2016), UK	To determine the underlying mechanism of Cold among ISCD to direct appropriate treatment.	FEV1, VC, FEF, FEV1/VC, TLC, RV, DLCO,KCO, DLNO	Airway NO flux & alveolar NO production, & pulmonary blood flow, Sex, Age.	Cross sectional study, Lung function, pulmonary blood flow were assessed in 18 SCD children and 18 controls.	Airway NO flux was not elevated in the SCD children nor correlated with airways obstruction, suggesting that airways obstruction, at least in some SCD children, is not due to asthma.
5.	Lunt et al., (2015), UK	To prospectively assess longitudinal lung function in children with SCD	RV, FEV1, VC, FEF25–75), TLC	Age, ACS	Prospective longitudinal studies. Patient-subject selection: Two cohorts of SCD children. Age and ethnic matched controls. n=144	Lung function deteriorated with increasing age in SCD children and the rate of decline was greater in younger children in whom ACS episodes were more common. Well conducted study, though static lung volume results were related to two reference ranges fixed correction factor which is quite imprecise.
6.	Lunt et al., (2014), UK	To verify if vascular abnormalities on HRCT would be associated with echocardiographic changes and lung function abnormalities in patients with SCD	FEV1, VC, FEF, TLC, RV, Rrs, kCO, DLCOVOC	Echocardiography, Vascular dimension (HRCT).	Prospective longitudinal study, HRCT, echocardiography & LFT were made in 35 adults.	This study shows an association between small vessel pulmonary vascular dimensions on HRCT reflecting pulmonary vascular volume, lung function abnormalities & echocardiographic estimates of ventricular function & cardiac output in adults with SCD; in addition, the decline in lung function correlated with changes in vascular dimension.
7.	Arigliani, et al., (2018), Congo	To examine if paediatric patients with SCA would have a high frequency of restrictive spirometry pattern, reflecting SCA-	FEV, FVC, FEV/FVC.	Age, Sex, Height, BMI, Hb, WBC, nutrition, platelets count.	Anthropometry and spirometry were evaluated in patients with SCA (HbSS) aged 6–18 years. A total of 112 patients	Spirometry findings suggestive of a restrictive pattern are common in paediatric patients with SCA. Malnutrition, increasing age and female sex were all associated with increased

		related cumulative lung injury.			& 377 controls were included.	risk of a restrictive spirometry pattern.
8.	Catanzaro, & Koumbourlis (2014), USA	To review the current knowledge regarding somatic growth and its relationship with lung function in SCD.	FVC, FEV1, PEFR	Height, weight, BMI, anterio-posterior chest diameter & anterio-posterior to lateral chest ratio	Pediatric respiratory Review n=7	Patients with SCD tend to have lower lung volumes. These findings are similar across the age & ethnic lines regardless of the differences in body weight. Factors like malnutrition, racial differences and socioeconomic status are thought to be involved.
9.	Wedderburn et al. (2013), UK.	To test the hypothesis that increased pulmonary capillary blood volume at least in part explained the increased airways obstruction.	FEV1, VC, MMEF25/75, RV, TLC, FRC.	Vc, VA, Rr5, Vc/VA	Cross sectional study Vc, alveolar volume (VA), & spirometry were assessed before & after bronchodilator. n=50	Increased pulmonary capillary blood volume contributes to the increased airways obstruction in children with SCD, hence, bronchodilators may be of limited benefit in reducing their airways obstruction.
10.	Koumbourlis (2014), USA	To examine the different patterns of lung function among ISCD.	FVC, FEV1, FEV1/FVC, FEF25-75	Age, Obstructive and Restrictive lung disease	Paediatric Respiratory Reviews. n=31	SCD does have serious and long-term effects on lung-function even in the absence of overt episodes of ACS.
11.	Koumbourlis et al., (2008), USA	To investigate the changes in lung function and somatic growth that occur over time in children with hemoglobin SC (Hb-SC) SCD.	FVC, FEV1, VC, FEF25–75	Age, Height, Weight, BMI.	A longitudinal study. Measurements of lung function & somatic growth were performed in Pts with Hb-SC comparisons were made with a group of patients with Hb-SS SCD, matched by age, race, and gender. n=26 (13, 13)	Lung function is generally normal among children with Hb-SC, but it declines over time in a fashion similar to that observed among patients with Hb-SS SCD. The decline is slow and it is not associated with changes in somatic growth. These findings suggest that patients with Hb-SC should probably have the same close follow-up as patients with Hb-SS.
12	Knight-Maddenet al.,	To test the hypotheses that asthma and bronchial	TLC, FEV1.	Weight, Height, ACS, BHR	Cross-sectional study, modified questionnaire was	Asthma & BHR are more common in children with SCD than in ethnic

	(2005), Jamaica.	hyperreactivity (BHR) are more common in children with SCD than in ethnic matched controls			administered & skin prick tests done in 80 children with SCD & 80 ethnic matched controls aged 5-10.	matched controls, & atopic asthma appears to be associated with recurrent ACS. Early & effective anti-asthma therapy might reduce the pulmonary morbidity associated with SCD.
13.	Pianosi et al., (1995), Canada	To determine whether abnormalities in expiratory flow rates and lung volumes were present in children with HbSS, the variant SC Hb, & the less severe hemoglobinopathies.	FVC,FEF2s-1s,FEV1/FVC,TLC RV/TLC,DLCO	Sex, Age, Height, Weight, Hb.	Cross sectional study. Comparison of PFT results in 37 children with SCA with those in 22 control matched for sex, race, & height.	Children with SCD have lower static & dynamic lung volumes & flow rates than control. Prior episodes of ACS do not appear to be associated with PFT abnormalities, a finding that militates against their role as a major etiologic factor.
14.	Santoli et al., (1998), France	To investigate if recurrent ACS is a risk factor for chronic lung dysfunction in SCD.	TLC, FVC, FRC, FEV1, FEV1/VC, FEF25–75, Rrs, KCO, TLCO, PaO2, PaCO2, SaO2.	HbSS disease, HbS β-thalassemia disease, HbSC disease, Age, Sex, BMI, Height, Weight, Hb.	Cross-sectional study. LFT were performed in 49 SCD outpatients, (23 pts with a history of 2-4 episodes of ACS & 26 with no history of ACS). 2 groups were compared. n=49	The data demonstrate that obstructive lung dysfunction is fairly common in SCD & suggest that recurrent ACS may contribute specific obstructive defects. The increase in Rr associated with ACS was accompanied by an increase in diffusion capacity.
15.	Maria et al., (2016), Brazil	To evaluate the association b/w clinical, pulmonary, & CVS findings in pts with SCD &, secondarily, to compare these findings between SCA patients & other SCDs.	TLC, FEV1/FVC	Sex, restrictive &, Obstructive abnormality, Reduced respiratory muscle strength, ACS, Asthma.	59 adults were included in this cross-sectional study; 47 had SCA, and 12 had other SCD. All pts underwent PFT, chest CT, and echocardiography. n=59	A significant interrelation b/w abnormalities of the structure and function of pulmonary & CVS was observed. Furthermore, the severity of the cardiopulmonary parameters among SCA pts was higher than that among other SCD pts.
16.	Vanderjagt et	To examine if Nigerian	FVC, FEV1, PEF	Age, MAC, Height,	A cross sectional study. Body	This study result confirmed that

	al., (2007), Nigeria	children & young adults with SCD, would show positive correlations b/w Fat-Free-Mass & FEV1, FVC & PEF.		Skin-fold, Sitting height, Weight, BMI, Phase angle (deg), Fat%, FFM	composition was determined using bioelectrical impedance & PFT by spirometry in age 7–35 yrs (n =102) as well as healthy age& gender-matched controls (n =104).	pulmonary function is reduced in ISCD compared to control & that for both groups, pulmonary function is directly related to body composition. These findings underscore the need for early nutritional intervention for ISCD.
17.	Arteta et al.,(2014), USA	To describe the patterns of pulmonary function abnormalities and determine their risk factors.	FVC, FEV1, FEV1/FVC, FEF 25-75, TLC, RV/TLC, DLCO	Age, sex, Height, Weight or wheezing, ACS, Hb, Reticulocytes, WBC, LDH, SpO2.	Prospective Study, spirometry, plethysmography & lung diffusing capacity in 146 children with Hb SS or Sβ.	Abnormal pulmonary function, (obstructive) is common in children with Hb SS & Sβ. Increasing age, patient- or family-reported history of asthma or wheezing, & higher LDH concentration were predictors of obstruction.
18.	Alameri et al., (2008), United Arab Emirates	To examine pulmonary function, dyspnea & exercise capacity in adult Saudi (SCD) patients.	FEV, FRC, FVC, FEV1/FVC, TLC & DLco	BMI, Hb, HTC, WBC, Platelets, HbSS, Urea, HbSC, LDH, ALT, Alkaline phosphatase, Albumin,Creatinine, Reticulocyte, Bilirubin.	Cross sectional study. Dyspnea, PFT, 6MWT & echocardiography. The 6MWT data were compared to BMI-matched healthy controls. n=39	Chronic pulmonary complications in adult Saudi SCD pts are relatively mild but common. Pulmonary function differs from that published for African-origin SCD pts. This difference may reflect a different natural history of SCD in the 2 populations.
19.	Field et al., (2008), USA	To examine how indices of lung function (FEV1, FVC, & FEV1/FVC) change longitudinally in children with HbSS compared to healthy controls.	FEV, FVC, FEV1/FVC	Gender, Age, Asthma	Retrospective cohort of HBSS children who had spirometry assessments. Lung function in these cases was compared to age, gender, and race-specific control.	Longitudinal FEV1 was lower for pts with HbSS compared to children in the general population. When compared to the HbCS cohort, girls with HbSS showed lower longitudinal FVC & FEV1/FVC; there was no difference in FVC or FEV1/FVC between boys in the HbSS & HbCS cohort.
20.	Field et al.,	To determine the	FEV1,FEV 1 /FVC	Age, LDH, Hb, IgE,	A multicenter,	In children with SCA, AHR is prevalent.

	(2011), USA	relationship between AHR, features of asthma, & clinical characteristics of SCA.		Eosinophil, WBC.	prospective cohort study of children with SCA, dose response slope (DRS) was used to describe methacholine responsiveness n=99.	Younger age, serum IgE concentration, & LDH level, a marker of hemolysis, are associated with AHR. The relationship b/w methacholine responsiveness and LDH suggests that factors related to SCA may contribute to AHR.
21	Andrew C. Miller & Mark T. Gladwin (2012), USA.	Reviews on the pathophysiology, diagnosis, & treatment of clinically significant pulmonary manifestations of SCD in adult and pediatric patients.	TLC, DLCO, FEV, FVC, FEV1/FVC	ACS, asthma, &PHT; Echocardiography	Concise Clinical Review. n=18	The complications of SCD are myriad; however, pulmonary complications are common. In addition to ACD & asthma, concomitant PHT significantly increases morbidity and/or mortality.
22.	Field et al., (2008), USA	To describe the changes in pulmonary function in ISCD and prevalence of abnormal patterns of pulmonary function.	FEV1,FVC, FEV1/FVC,RV, TLC	Gender, Age, ACS, Smoking, Pain, Asthma, Phenotype	A retrospective cohort study of adults with SCD who had repeated PFT performed over 20 yrs of age. n=92	The rate of decline in lung function is greater than would be expected from historical controls without SCD. Also, the prevalence of restrictive lung disease in adults may be less than previously thought.
23.	Hijazi et al., (2005), Kuwait.	To find out if there are demonstrable impairments of pulmonary function in clinically stable children with the Arab/Indian haplotype of SCD & elevated Hb F when compared with a group of normal controls as well as HbS children.	FEV1, FVC, FEV1/FVC, VC, PEF, TLC, TLCO	ACS, vaso-occlusive crisis, Hb phenotype	Cross sectional study PFT was carried out on 28 steady state children with SCD (21 HbSS, 7 HbSb) & two group of controls: 17 age- and sex matched healthy children and 10 children with HbH disease.	This study has shown that abnormal lung function of early restrictive and obstructive pattern may be present in patients with HbSS from childhood. No association was found between history of ACS and the severity of ventilatory defects. This study has also shown that chronic anaemia of HbH disease in children has had no effect on PFT parameters.
24.	MacLean et	To determine if the pattern	FEV1, FVC,	age, sex, Hb level,	Cross sectional study.	Lung volume, as a percentage of that

	al., (2008), Canada	of lung function in SCD differs from race-matched, predicted values across childhood, & to examine the effect of clinical covariates on lung function.	FEV1/FVC, FEF, TLC.	& b-globin	LFT for children with SCD, aged 8–18 yrs. The role of age, sex, Hb level, & b-globin genotype was examined. n=413	predicted, declines with age in children with SCD; this decline begins in childhood. The rate of decline is similar to that of children with cystic fibrosis and greater than that of children with asthma.
25.	Bellet et al., (1995), UK	To test the hypothesis that incentive spirometry can decrease the incidence of atelectasis & pulmonary infiltrates.	Inspiratory capacity	X-ray, spirometer, atelectasis, ACS	A prospective, RCT in 29 pts aged 8-21 years with SCD who were hospitalized, pts with normal chest radiographs on admission were randomly assigned to spirometry or to a control non-spirometry group. n=29	Incentive spirometry can prevent the pulmonary complications (atelectasis and infiltrates) associated with the ACS in patients with SCD who are hospitalized with chest or back pain above the diaphragm.
26.	Musa et al., (2017), Nigeria	To provide evidence that adults with SCA have a lung phenotype associated with occurrence of wheezing & abnormal respiratory function.	FEV, FVC, FEV/FVC.	Age, Gender, Asthma, Cough, Phlegm, Wheeze.	Cross-sectional study Patients were 150 adults with SCA aged between 18 & 65 yrs & 287 consecutive controls.	Adults with SCA have higher prevalence of wheezing & lower FEV1% & FVC% than adults without SCA.
27.	Dosunmu, et al, (2013), Nigeria	To determine the pattern of chronic lung lesions and possible risk factors in SC patients in Lagos, Nigeria.	FEV, FVC, FEV/FVC.	Age, x-ray Hematocrit, RBC, HbF level, SPO2, liver function tests, LHD, & tricuspid regurgitant jet	Prospective study. PFT & chest-x-ray done for 56 patients with SCD. RBC, LHD, Hematocrit, HbF level, SPO2, liver function tests were measured.	Chronic lung lesion is very common in adult SC patients and restrictive lesions predominate.

28.	Yvonne et al., (2019), Ghana	To determine the prevalence & pattern of lung function abnormalities among a cohort of adult Hb-SS pts compared to healthy non SCD controls and identify associated factors.	FEV, FVC, FEV/FVC.	Weight, Height, BMI, Demography, SPO2,TRV, echocardiogram, HTC, Hb level, serum urea, & creatinine	Cross-sectional study involving 76 clinically stable, hydroxyurea-naive adult Hb-SS & 76 non-SCD controls. PFT, SPO2, TRV, echocardiogram, HTC, Hb level, serum, Urea.	Lung volumes were significantly lower in Hb-SS pts when compared to non-SCD controls and this difference was not influenced by anthropometric variance. Lung function abnormalities, particularly restrictive defects, are prevalent in Hb-SS pts but showed no significant association with recognized markers of disease severity.
29.	Lee et al., (2018), USA	To determine whether oral Vit D3 (cholecalciferol) can reduce the risk for respiratory complications in children & adolescents, 3-20 yrs., with SCD (ViDAS trial).	FVC, FEV1, FEV1/FVC, FEF, RV, TLC, DLCO, MIP, MEP.	Age, Sex, asthma, SC phenotype, Hydroxyurea, SPO_2, 25Hydroxyvitamin D	A 2-year active-controlled double-blind RCT comparing monthly high-dose oral Vit D3 with standard-dose oral vitamin D3. n=40	Children with SCD typically have low Vit D status, heightened susceptibility to respiratory infections & asthma, & a greatly increased vulnerability to potentially fatal complications of respiratory illness.
30.	Williams et al., (2014), USA	To describe the longitudinal progression and identify specific markers that influence bronchial disease in SCD.	FEV1, FVC, FEV1/FVC, FEF, TLC, RV, RV/TLC, DLCO, VA, DL/VA, & FRC	Growth vocity, Demography Weight, Height, Stature percentile, BMI, ACS, VOC, asthma, Smoking, On medication.	Retrospective, 89 patients with SCD was reviewed. All patients had spirometry & body plethysmography as part of routine care.	Initial decline in FEV1% is associated with worsening pulmonary dysfunction over time. The factors most influential on the progression of FEV1% include the introduction of medications as well as the promotion of adequate prepubertal growth. Efforts to ensure normal prepubertal GV and treatment with bronchodilators, should be considered at an early age to delay progression of pulmonary dysfunction.
31.	Bendiak, et al., (2017), Canada	To investigate the relationships of longitudinal pulmonary	FVC, FEV1,FEV1/FVC	Age, sex, Hb genotype, ACS	Longitudinal study, using International Study of Asthma and Allergies in	This study show that in children with SCD, the clinical phenotype of wheezing is associated with more rapid PFT

		function decline with wheezing, asthma and atopy in a cohort of paediatric patients with SCD			Childhood (ISAAC) questionnaire, skin prick testing (SPT) and airway NO measurements n=145	decline over time. This association, while seen exclusively in measures of airway obstruction, & was independent of a diagnosis of asthma.
32.	Eduard J. van Beers et al., (2014), Netherland	To demonstrate that anemia is the most important determinant of reduced exercise tolerance observed in SCD patients without signs of PHT.	FVC , FEV1, FEV1/FVC, TLC, DLCO, DLCO/VA, VA	Cardiopulmonary exercise tests, Age, Gender, Hb level, Hb genotype, WBC, LDH.	Cross sectional study. 44 SCD patients had PFT, CPET, chest x-ray& echocardiography to further characterize exercise limitation in SCD. n=44	Strong correlation between various parameters of lung volume & cardiothoracic ratio & we hypothesize that cardiomegaly & relative small chest size may be important causes of the reduced long volumes & diffusion capacity, in SCD.
33.	Adekile et al., (2018), Kuwait	To compare PFTs in pediatric SCD patients to age-matched normal controls & to investigate the association of PFTs with selected clinical & laboratory parameters.	DLCO, FEV1, FVC, TLC.	Hb, Hct, WBC, LDH. Hb genotype.	Cross-sectional study involving 38 SCD & 36 controls (non-sickle cell siblings of the patients). FEV1, FVC, TLC, and other PFT were obtained, Hb, fetal Hb, body plethysmography, serum bilirubin, & LDH were assessed.	There was a significant reduction in PFT, especially FEV1, in the patients compared to controls, although they remained generally within the normal range. There was also no clear association of FEV1 or other PFTs with individual markers of hemolysis.
34	Vieira et al., (2016), Brazil	To evaluate pulmonary function and functional capacity in children & adolescents with SCD	PEF, FVC, FEV1, FEV1/FVC, FEF	6MWD, HR, RR, Age, sex, Hb, leukocytes, Reticulocytes, SaO_2, ACS, Asthma	A cross-sectional study involving 70 ISCDs (8-15 years) who had PFT & functional capacity testing. The PFT results were compared with SCD severity variables & history of asthma &	There was a significant prevalence of abnormal pulmonary function. The high prevalence of respiratory disorders suggests the need for a closer look at the lung function of this population, in childhood and thereafter.

					of ACS.	
35.	Ong et al.,(2013), USA	To identify respiratory muscle force & lung volume relationships in a paediatric SCD population.	FVC, FEV1, FEV1/FVC, FEF, TLC, RV, RV/TLC	Height, weight, age, Respiratory muscle force	Prospective study, 34 SCD-SS subjects underwent PFT. Height, weight, age, & gender predicted MIP & MEP values were compared to spirometry & lung volumes.	SCD-SS pts. showed correlations between respiratory muscle force and lung volume, and reduced expiratory muscle force compared to inspiratory muscle force. Respiratory muscle strength may affect lung volumes in these patients, and expiratory muscles may be more susceptible.
36	Tambe MK. (2017), India	In view of severe anemia, decreased blood oxygen affinity, pulmonary arterial vaso-occlusion, microinfarction & microfibrosis being associated with SCD; an analysis of pulmonary function in them will be of great interest	FVC, FEV1,MMEFR, PEFR & MVV	height, weight & body surface area, BMI, Age, Hb levels, chest circumference	Cross sectional study. 70 SCD (6-12 yrs) children with SCD (SS) were studied as cases along with age, sex and Socio-economic status matched 70 controls (AA) & comparisons drawn between the 2 groups.	All the static and dynamic pulmonary functions were found reduced in SCD, most of them significantly. Any restrictive, obstructive or combined pattern may be produced in SCD depending upon frequency & severity of the ACS and VOC in past.

Table 1: Details of primary studies identified and reviewed

Table 2: Summary of themes identified

Health Profiles	Identified Themes	n	%
Pulmonary complications(16 papers)	Acute chest syndrome (ACS)	12	33.6
	Obstructive lung dysfunction	2	5.6
	Restrictive lung disease	2	5.6
	Pulmonary oedema		
	Chronic fibrosis.	1	2.8
	Infections and infarctions		
	pulmonary hypertension	2	5.6
	Wheezing and sleep-disordered breathing	4	11.2
	Asthma, Increased airway reactivity	12	33.6
	Vaso-occlusive crisis	2	5.6
	Cough	2	5.6
Cardiovascular complications(5 papers)	valve regurgitation	2	5.6
	cardiac dysfunction		
	cardiac enlargement		
	Biventricular dysfunction		
	Decreased blood oxygen affinity		
	Thromboembolisms		
	Echocardiography	5	14
Recovery indices 7	Blood pressure		
	Oxygen saturation (SpO2)	7	19.6
	Heart rate	1	2.8
	Respiratory rate	1	2.8
	Pain	1	2.8
Anthropometrics(13 papers)	BMI	9	25.2

	Weight	13	36.4
	Height	14	39.2
	Body circumference	3	8.4
	% body fat	1	2.8
	Waist – Hip ratio	1	2.8
Demographics(26 papers)	Age	25	70
	Sex	15	42
	Social status	3	8.4
Haematological indices (18 papers)	Hemoglobin levels	14	39.2
	Lactate dehydrogenase	8	22.4
	25-OHD	1	2.8
	Haematocrit	4	11.2
	Inflammatory markers	3	8.4
	Leucocytes/immunocytes	10	28
Lungs functions abnormalities(36)	FVC	26	72.8
	VC	8	22.4
	RV	10	28
	FRC	3	8.4
	TLC	21	58.8
	FEV1	31	86.6
	FEV1/VC	6	17.2
	FEV1/FVC	22	61.6
	FEF	15	42
	PEFR	4	11.2
	Aerobic Capacity (VO2max).	4	11.2
	Lung blood volume	3	8.4
	Diffusion capacity	12	33.6
	Arterial blood gas values	3	8.4
	Respiratory muscle strength	2	5.6
	Respiratory system resistance	5	14
Sickle cell disease phenotype 9	HbSS	6	17.2
	HbSc	5	14
	HbS β+	5	14

	HbSBo		