



Review

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Variation in pulmonary function tests among children with sickle cell anemia: a systematic review and meta-analysis

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Abstract

Introduction: the spectrum of pulmonary complications in sickle cell anemia (SCA) comprises mainly of acute chest syndrome (ACS), pulmonary hypertension (PH) and airway hyper-responsiveness (AHR). This study was conducted to examine the abnormalities in pulmonary function tests (PFTs) seen in children with SCA. Methods: electronic databases (Cochrane library, PubMed, EMBASE, Scopus, Web of Science) were used as data sources. Two authors independently reviewed studies. All case-control studies with PFT performed in patients with SCA and normal controls were reviewed. Pulmonary functions were assessed with the help of spirometry, lung volume and gas diffusion findings. Results: nine studies with 788 SCA children and 1101 controls were analyzed. For all studies, the pooled mean difference for forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), FEV1/FVC ratio, peak expiratory flow rate (PEFR), total lung capacity (TLC) and carbon monooxide diffusing capacity (DLCO) were -12.67, (95% CI: -15.41,-9.94), -11.69, (95% CI: -14.24, -9.14), -1.90, (95% CI: -4.32, 0.52), -3.36 (95% CI: -6.69, -0.02), -7.35, (95% CI: -14.97, -0.27) and -4.68, (95% CI -20.64, -11.29) respectively. FEV1 and FVC and were the only parameters found to be significantly decreased. Conclusion: sickle cell anemia was associated with lower FEV1 and FVC, thus, supporting the role of routine monitoring for the progression of lung function decline in children with SCA with ACS. We recommend routine screening and lung function monitoring for early recognition of pulmonary function decline.

Introduction

Sickle-cell Anemia (SCA) is a monogenic, hematological, multi-system disease characterized by repeated episodes of acute disease exacerbations resulting in multi-organ damage. Globally, it has been projected that the number of individuals with SCA are set to increase dramatically from 305,800 in 2010 to 404,200 by 2050 [1]. The mortality rate among children is estimated to be 0.64 per 100 years of child observation with the maximal rate being among the children belonging to African ethnicity (7.3 per 100 years of observation) [2]. Pulmonary disease is a leading cause of mortality and morbidity among patients with SCA and is the second most common underlying pathology requiring hospital admission [3]. The disease spectrum of pulmonary complications in SCA comprises of acute chest syndrome (ACS), pulmonary hypertension (PH), lower airway obstruction and airway hyperresponsiveness (AHR). Frequent episodes of ACS are being increasingly recognized as a major risk factor for sickle-cell associated chronic lung disease [4]. Acute chest syndrome depicts a morbid chain of reaction of pulmonary infarction, inflammation and atelectasis resulting in ventilation-perfusion mismatch and acutely increased pressure in pulmonary artery [5]. In addition, these changes in lung parenchyma and its vasculature along with hemolysis contribute to the development of PH in SCA. The prevalence of pulmonary hypertension (PH) among children with SCA is approximately 1 in every 5 children with SCA [6] and is a major risk factor associated with mortality [6-8]. Airway hyper-responsiveness (AHR) was first evaluated by Leong et al among children with SCA [9]. Current literature and evidence have brought forth the fact that there may be significant overlap in the pathophysiology of pulmonary insults in asthma and SCA [10,11]. The prevalence of asthma in children with SCA has been reported be between 16.8% to 27% in studies to respectively [12,13]. As asthma is a modifiable risk factor, the morbidity associated with it may be decreased substantially by its early diagnosis and effective control. Pulmonary function tests (PFTs) helps to confirm the diagnosis and hence, significantly improve the clinical management of asthma [13]. Current evidence support the opinion that existence of pulmonary disease in children with SCA significantly increases the morbidity. However, the pattern of abnormal lung function in SCA has been disputed. Herein, we discuss the first systematic review and meta-analysis of studies evaluating the PFT in children with SCA in comparison to children without SCA. In addition,



we have tried to determine if there is an association of hydroxyurea therapy with PFT parameters among children with SCA.

Methods

PRISMA (Preferred Reporting Items for Systematic reviews and Meta-analyses) guideline was used to report this study [14]. The protocol for this systematic review and meta-analysis was registered at the International Prospective Register of Systematic Reviews (PROSPERO # CRD42020206113).

Search strategy for identifying relevant studies: the search strategy was implemented in two stages:

Bibliographic database search: electronic databases (Cochrane library, PubMed, EMBASE, Scopus, Web of Science) were used as data sources. Search was restricted to English language publications involving human subjects, but not restricted by date or publication type. The last electronic search was carried out on 20th August, 2020. The search strategy included the following terms: ("respiratory function tests"[MeSH Terms] OR ("respiratory"[All Fields] AND "function"[all fields] AND "tests"[all fields]) OR "respiratory function tests"[all fields] OR ("pulmonary"[all fields] AND "function"[all felds] AND "tests"[all fields]) OR "pulmonary function tests"[all fields]) AND ("anemia, sickle cell"[MeSH Terms] OR ("anemia"[all fields] AND "sickle"[all fields] AND "cell"[all fields]) OR "sickle cell anemia"[all fields] OR ("sickle"[all fields] AND "cell"[all fields] AND "disease"[all fields]) OR "sickle cell disease"[all fields]).

Searching other sources: we conducted manual searches which consisted of scanning the reference lists of eligible papers and other relevant review articles, specialist journals and conference proceedings. All studies were imported to the literature management software Endnote X7 to eliminate duplicated records.

Eligibility criteria for considering studies to include in the review: studies considered in this metaanalysis were case-control studies about any alteration in pulmonary functions in sickle cell anemia children.

Inclusion criteria: i) Studies meeting the defined PECO-S criteria were included [population-children (age range: 3-18 years) with SCA, exposure-sickle cell anemia (SCA), comparator-children without SCA, outcomes-pulmonary function parameters, study design-case-control or comparative study]. ii) Studies where main outcomes evaluated were forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), FEV1/FVC ratio and total lung capacity (TLC). FEV1, FVC and TLC were expressed as percent (%) predicted. FEV1/FVC ratio was expressed as an absolute value.

Exclusion criteria: i) Studies with no control group; ii) Studies not performed in human participants; iii) Case series, reviews, letters, commentaries and editorials, and iv) Studies with insufficient data, abstracts, adult studies, conference abstracts and duplicate publications.

Selection of studies for inclusion in the review: two authors (PZJ and DP) independently conducted a preliminary screening of studies by reading titles and abstracts. After screening titles and abstracts, the full texts of potentially relevant articles were downloaded. These investigators further independently assessed the full text of each study for eligibility and consensually retained studies were included. Disagreements when existing were resolved by a third author (AT). Studies were selected if they met the inclusion criteria. We used a screening guide to ensure that all review authors reliably applied the selection criteria. Agreement was measured using the kappa (κ) statistic [15]. Data in studies, using median and standard error as a measure of dispersion, was converted to mean and standard deviation [16].

Data extraction and management: data extraction and quality control was independently done by two reviewers (PZJ and DP). A third reviewer (AT) was



involved if conflict occurred. A standard data extraction form was used to retrieve relevant information and data from each study included in the analysis. Two review authors (PZJ and DP) participated in data extraction independently. PZJ and DP extracted data which included general information (authors, year, and country), design of the study, history of ACS and/or AHR and various parameters of pulmonary function test. Outcome measures included assessment of lung function by FEV1, FVC, FEV1/ FVC, PEFR, TLC and DLCO with their corresponding SD, SE or 95% CI. We focused on spirometry, lung volume and gas diffusion findings. Because FEV1, FVC, FEV1/FVC and TLC are the basic parameters needed to identify a functional deficit (i.e. restriction or obstruction), we primarily focused on these for our analysis. We looked at each endpoint separately and in combination to determine the variation in the various parameters of PFT in each study. We considered both the statistical and clinical significance of lung function results.

Statistical analysis: the mean differences of various parameters of pulmonary function test results were synthesized using a random-effects meta-analysis between the SCA children and control included FEV1 (unit in predictive percentage), FVC (unit in predictive percentage), FEV1/FVC (unit in the original ratio), PEFR (unit in predictive percentage), TLC (unit in predictive percentage) and DLCO (unit in predictive percentage). The software Review Manager 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark) was used to conduct metaanalyses for the outcome measures, reported as the mean difference with 95% confidence interval (CI). Heterogeneity was defined as low, moderate, or high according to I^2 values (25%, 50%, or 75%, respectively). A forest plot was used to display the results of the meta-analysis. Data analysis was performed using the fixed-effects model when the results showed low heterogeneity ($I^2 \le 25\%$) and the random-effects model when the results showed moderate or high heterogeneity $(l^2 > 25\%)$. Publication bias was assessed by viewing the symmetry of the funnel plot. We then investigated reasons for heterogeneity by fitting metaregression models. High-resolution forest plots, with random effects, were separately created.

Results

Literature search: initially, a total of 707 articles were identified. After elimination of duplicates, screening titles and abstracts, 303 papers were found completely irrelevant and excluded. Agreement between investigators on abstract selection was high (κ =0.90, p <0.001). Full texts of the remaining 80 studies were scrutinized for eligibility, among which 71 studies were excluded. There was no disagreement between investigators for full-text selection. Overall, case-control studies satisfied the eligibility criteria and hence, were included in the meta-analysis (Figure 1).

Basic characteristics of the included studies: after the application of the exclusion criteria, nine studies with a combined study population of 1889 were included in this meta-analysis. These included 788 children with SCA and 1101 normal controls. However, in the absence of controls for UK subgroup of SCA children in the study by Arigliani et al. [17], they are excluded from meta-analysis. The characteristics of the included studies are shown in Table 1. Studies were conducted in six countries, and they were published between 1993 and 2020 (Table 1). The sample size of individual studies ranged from 38 to 518 participants. Participant's age ranged from 3 to 18 years of age and included both male and female children. Although spirometry is an effort-dependent test, all study explicitly stated that they had performed lung function tests in accordance with international guidelines set forth jointly by the American Thoracic Society (ATS) and the European facilitating Respiratory Society (ERS), thus, spirometry maneuver standardization (Table 2).

Comparison of the sickle cell disease children and the normal children

Forced expiratory volume in 1 second (FEV1): the FEV1 % predictions of children with SCA were significantly lower than that of the controls [MD -



12.67, (95% CI -15.41,-9.94), P<0.00001, I^2 =74%] among the 9 included studies (Figure 2).

Forced vital capacity (FVC): the FVC % predictions of children with SCA were significantly lower than that of the controls [MD -11.69, (95% CI -14.24, -9.14), P <0.00001, I^2 =70%] among the 9 included studies (Figure 2).

Forced expiratory volume in 1 second (FEV1)/Forced vital capacity (FVC) ratio: the FEV1/FVC ratio of the children with SCA was not significantly lower than that of the controls [MD - 1.90, (95% CI -4.32, 0.52), P=0.12, I^2 =80%] among the 7 included studies (Figure 2).

Peak expiratory flow rate (PEFR): only four studies reporting PEFR of children with SCA in comparison to that of normal children as controls shows that the pooled estimates of PEFR for SCA children were lower than that for controls [MD -3.36, (95% CI - 6.69, -0.02), P=0.05, I^2 =0%] (Figure 3).

Total lung capacity (TLC): the TLC of children with SCA cases was observed to be lower than that of the controls [MD -7.35, (95% CI -14.97, 0.27), P= 0.06, I^2 =93%] among the 6 included studies (Figure 3).

Carbon mono-oxide diffusing capacity (DLCO): the DLCO of children with SCA was observed to be lower than that of control [MD -4.68, (95% CI - 20.64, 11.29), P=0.57, I^2 =97%] (Figure 3).

Pulmonary function tests changes in studies including children with ACS: four studies, which reported data on the basis of a history of ACS in SCA children were included. Pulmonary function test (PFT) parameters (FEV1, FVC, TLC, PEFR, and DLCO) of SCA children with ACS were observed to be lower than that of the control children. However, the ratio of FEV1/FVC was higher than the controls in three studies [18-21] while it was lower in one study [21]. The plots of pooled estimates for PFT parameters suggested no significant heterogeneity for FVC and DLCO (p \geq 0.05). However, moderate heterogeneity was observed for FEV1/FVC ratio and TLC (p <0.05) after the application of tests of homogeneity while the heterogeneity was extremely low for decline in FEV1 and PEFR (Figure 4).

Stratifying by AHR among subjects in the studies: the pooled estimated mean difference for comparing SCA cases versus control for FEV1 was -12.63 (95% CI: -16.47,-8.79) for inclusion of children with AHR and -12.76 (95% CI: -17.39,-8.14) for not inclusion of children with AHR. For FVC it was -11.28 (95% CI: -15.18,-7.39) for inclusion of children with AHR and -11.99 (95% CI: -15.94,-8.03) for not inclusion of children with AHR and for FEV1/FVC it was -2.37 (95% CI: -5.19,-0.44) inclusion of children with AHR and -1.35 (95% CI: -5.10, 2.40) for not inclusion of children with AHR (subgroup differences: FEV1 P =0.97, FVC P =0.80, FEV1/FVC P =0.61) (Figure 5). Sub-group analysis suggests FEV1, FVC and FEV1/FVC ratio suggests no significant correlation for AHR in children with SCA. This indicates that heterogeneity could not be explained by this variable.

Effect of hydroxyurea on PFT parameters in the studies: the pooled estimates for FEV1 were -12.92 (95% CI: -16.30,-9.55) for inclusion of SCA children on hydroxyurea and -12.51 (95% CI: -17.09,-7.93) for exclusion of SCA children on hydroxyurea. For FVC it was -11.29 (95% CI: -14.52,-8.06) for inclusion of SCA children on hydroxyurea and -12.53 (95% CI: -17.35,-7.72) for exclusion of SCA children on hydroxyurea and for FEV1/FVC it was -4.67 (95% CI: -6.50,-2.84) inclusion of SCA children on hydroxyurea and -1.10 (95% CI: -3.23, 1.02) for exclusion of SCA children on hydroxyurea (subgroup differences: FEV1 P=0.89, FVC P=0.67, FEV1/FVC P<0.00001) (Figure 6). Sub-group analysis suggests that there was no significant correlation of hydroxyurea intake in children with SCA on changes in PFT parameters (FEV1 and FVC) with no heterogeneity. However, FEV1/FVC ratio was significantly reduced but with a very high heretogeneity.

Effect of hydroxyurea on PFT parameters in children with ACS: four studies [18-21] had

included SCA children with history of ACS, with the cases being on hydroxyurea therapy in the study by Al-Biltagi *et al.* [20]. The pooled estimates for FEV1, FVC and FEV1/FVC ratio of SCA children with history of ACS on hydroxyurea therapy were -0.50 (95% CI: -0.79, -0.21; P=0.65), -0.54 (95% CI: -1.42, 0.33; P=0.29) and 2.81 (95% CI: 0.86, 4.75; P=0.003) (Figure 7). FEV1/FVC ratio was found to be significantly more in SCA children with history of ACS on hydroxyurea therapy while FEV1 and FVC were decreased, however, insignificantly (P \ge 0.05).

Publication bias: the funnel plots showed asymmetry indicative of the presence of potential publication biases (Annex 1).

Discussion

Existing pediatric literature on PFTs of children with SCA has shown conflicting results. While obstructive type of pathology has been reported to be the most common type [21-25], few studies have shown a restrictive pattern too [20,26,27]. Among the included studies, percentage of children with obstructive pattern ranged from 4.5% to 30.9% while for the restrictive pattern ranged from 2% to 30%. This variation has brought to light the importance of pulmonary function testing in children with sickle cell anemia. To the best of our knowledge, this is the first comprehensive systematic review aimed to explore the variations in the PFT parameters seen in children with SCA. All the studies included were exclusively case-control studies. Our study analyzed the variations in all the available parameters in lung volumes in children with SCA. Our meta-analysis illustrates, that even in the absence of a pulmonary pathology such as ACS or AHR, children with SCA showed a lower lung functions (FEV1 and FVC) when compared to the normal controls, thus, implicating SCA in the progressive decline in PFT. In addition, given the high prevalence of ACS and AHR among children with SCA, it is tempting to speculate that poorly managed SCA may accelerate the progressive lung function decline. However, by means of this systematic review, it is difficult to establish causality and conclusions on progression of pulmonary decline. Conditions with increased pulmonary demands such as ACS, AHR, pulmonary infection, PH could make the child manifest this pulmonary decline clinically.

Current literature supports evidence of a relationship between obstructive lung disease and acute chest syndrome (especially recurrent episodes), particularly in the pediatric agegroup [9,23,25-27]. Over a period of time, SCA is associated with chronic inflammation (ACS, AHR, recurrent chest infection, infarction, fat embolism, and smoking) that may affect the lower airways leading to the development of fibrosis and RLD; this may explain why restrictive lung disease (RLD) is more prevalent in adults than in children [28]. Children with SCA who have ACS episodes have worse pulmonary lung function than age-matched children with SCA who have not experienced ACS episodes [29]. In a retrospective analysis, Intzes et al. [30] found that a past history of ACS has a significant, positive correlation with obstructive lung disease but a negative, yet significant correlation with normal PFT values. Al-Biltagi et al. [20] also found a lower PFT parameters recording among patients who had a history of ACS in comparison to patients without ACS. Ozbek et al. [31] also reported a statistically significant (p <0.05) increase in % predicted values of FEV1 and FEV1/FVC ratio among children with no prior episode of ACS. The sub-group analysis of the 4 studies, which included children with previous or current episodes of ACS, showed that there was a decline in all the PFT parameters studied, except two (FVC and DLCO) where the decline was not statistically significant (P value >0.05). The significant decline in FEV1 and PEFR with extreme low heterogeneity, thus, support the role of routine FEV1 and/or PEFR in monitoring the progression of lung function decline in children with SCA with ACS.

In addition to the pathologies found in adults, children with SCA show a higher prevalence of AHR [12]. AHR among children with SCA was first evaluated by Leong *et al.* via lung volume measurements [9]. A large cohort study, based on Cooperative Study of Sickle Cell Disease (CSSCA),



which followed up 291 infants for a mean period of 11 years observed 16.8% of children to be suffering from asthma [12]. Shilo et al. [32] reported AHR in upto 72.5% of children with SCA via methacholine challenge test (MCT) while Field et al. [33] reported AHR in 55% via methacholine provocation among children. Younger age, recurrent episodes of ACS, serum IgE concentration, lactate dehydrogenase (LDH) levels have been found to be associated with AHR [33,34]. The possibility of an association between AHR and ACS has also been explored in various studies. Increasing frequency of ACS episodes was associated with increased prevalence of AHR [25,34]. AHR was found to be associated with more frequent episodes of ACS (0.39 vs 0.2 events per patient per year, p <0.001). Angel et al. [25] also observed a significantly higher occurrence of ACS (0.44±0.44 vs 0.25±0.23, p < 0.04) among asthmatic children with SCA. Although, the prevalence of AHR among children with SCA is higher than controls, this higher prevalence of AHR in SCA was found to be statistically insignificant in our meta-analysis as the decrease in PFT among SCA children with AHR for FEV1 (P=0.97), FVC (P=0.80) and FEV1/FVC ratio (P=0.48).

Hydroxyurea has evolved into a cornerstone of medical management of SCA. Hydroxyurea is a disease modifying therapy that is known to prevent and treat acute and chronic complications in SCA. As it reduces the frequency of vaso-occlusive episodes in SCA, treatment with hydroxyurea has been associated with a major 40% reduction in mortality [35]. Recent studies have shifted the focus to evaluate the additional benefits of hydroxyurea in SCA. Mclaren et al. [36] recorded the variations in PFT parameters in children with sickle cell disease before and after receiving hydroxyurea. A subgroup analysis of 56 HbSS patients before and after hydroxyurea initiation confirmed improved rates of decline in FEV1, FVC and forced expiratory flow between 25-75% of FVC (FEF_{25-75%}) over a median period of observation. Their data suggested that hydroxyurea therapy in children with SCA led to improvement in annual PFT decline. This was credited to the favourable hematological effects of hydroxyurea in SCD. However, our meta-analysis found no statistically difference among studies where children on hydroxyurea were evaluated by PFT in comparison to studies where children had received no hydroxyurea.

Limitations: age-group and gender based statistics could not be derived due to the absence of uniformity of data published among the included studies. Studies which evaluated PFT parameters in terms of z-score were not be analyzed. The predominant PFT abnormality could not be ascertained as different criteria's were used as definitions. Only a single study followed up children with abnormal lung function, therefore, the duration for worsening of PFT values could not be commented upon. The power for some subgroup analyses was limited, and relatively large heterogeneity was noted.

Strengths: this is the first comprehensive, quantitative analysis on the variations in PFTs in children with SCA. It includes a broad literature search, screening and data extraction performed in duplicate, a firm study quality assessment and a comprehensive data analysis, including numerous sensitivity analysis. A highly sensitive and comprehensive search of the literature was used in order to identify as many relevant studies as possible and to reduce potential publication bias. As there was no publication bias, this would extend the generalizability of the results greatly. Newcastle-Ottawa scale was used for guality assessment of the included studies. Our study reemphasized the need for regular and routine PFTs in children with SCA for early diagnosis and better management.

Recommendations: in the absence of a clear consensus on PFT monitoring in children with SCA, we recommend for further analytical studies to be carried out evaluating the role of PFT for earlier detection of lung abnormalities, their impact in reducing the disease burden and improving the healthcare delivered to children with SCA. Furthermore, trials need to be carried out to study the impact of hydroxyurea on PFT as the current



data available is insufficient in commenting on its efficiency.

Conclusion

Pulmonary disease is a major cause of mortality and morbidity among children with SCA. Among the various pulmonary function test (PFT) parameters evaluated, FEV1 and FVC and were the only parameters found to be significantly decreased (P<0.05) with moderate heterogeneity in children with SCA. In comparison, there was no significant difference (P≥0.05) with high heterogeneity in the decreased values of FEV1/FVC ratio, PEFR, TLC and DLCO of children with SCA and their controls. PFT abnormalities have been found to be more common among children with frequent episodes of ACS and asthma/AHR. Pulmonary function test (PFT) measurements could, thus, be an invaluable instrument in monitoring as well as screening the individuals high risk pulmonary at for complications.

What is known about this topic

- Pulmonary disease is a leading cause of morbidity and mortality in children with SCA;
- Both obstructive and restrictive pattern of lung functions can be seen in SCA.

What this study adds

- Forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC) showed a more significant decline in children with SCA than any other lung function parameters;
- No significant difference was seen in lung function parameters before and after the use of hydroxyurea in SCA.

Competing interests

The authors declare no competing interests.

Authors' contributions

AT and PZJ: contributed to study selection, data abstraction, data analysis, data interpretation, drafting of the manuscript, revising the article critically for important intellectual content. DP: contributed to designing the search strategy, data abstraction, data interpretation, revising the article critically for important intellectual content. BT: contributed to designing the search strategy, revising the article critically for important intellectual content. RM: contributed to screening titles, abstracts, and full texts, revising the article critically for important intellectual content. All the authors have read and approved the final version of this manuscript.

Tables and figures

Table 1: baseline characteristics of the includedstudies in the meta-analysis

 Table 2: screening methodology of the included studies

Figure 1: PRISMA flow chart diagram describing Process of identification and selection of studies for inclusion in the review

Figure 2: forest plot for FEV1 % predicted, FVC % predicted and FEV1/FVC ratio

Figure 3: forest plot of PEFR, TLC and DLCO

Figure 4: forest plot of forest plots of PFT parameters in children with SCA with history of ACS among the various studies

Figure 5: forest plot of FEV1, FVC and FEV1/FVC ratio stratified by AHR distribution

Figure 6: forest plots of FEV1, FVC and FEV1/FVC ratio stratified by SCA children on hydroxyurea **Figure 7**: forest plots of FEV1, FVC and FEV1/FVC ratio in SCA children with ACS on hydroxyurea

Annex

Annex 1: the funnel plot of: A) % predicted forced expiratory volume in 1 s (FEV1); B) % predicted forced vital capacity (FVC); C) forced expiratory volume in 1 s/forced vital capacity ratio (FEV1/FVC),



[SE: standard error; MD: mean difference] (PDF-151KB)

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Table	 baseline characteris 	tics of the includ	ed studies in t	he meta-an	alysis								
S.No.	Author	Year of	Country	Study	Popula	ation siz	e	Age (range r	nean±SD)	Sex (M	:F)		
		publication		design	Total	Cases	Controls	Cases	Controls	Cases	Controls		
1	Pianosi P <i>et al.</i>	1993	Canada	Case	33	11	22	14±4.1	12±3.5	3:8	9:13		
	(HbSS group)			control									
	Pianosi P <i>et al.</i> [18]	1993	Canada	Case	32	10	22	12±3.1	12±3.5	7:3	9:13		
	(ACS group)			control									
2	Hijazi Z <i>et al.</i> (HbSS)	2005	Kuwait	Case	38	21	17	12.1±4	10.8±12.6	NM	NM		
control													
3	Sylvester KP <i>et al.</i>	2007	UK	Case	48	24	24	11(8-16)	11(7-16)	14:10	14:10		
				control									
4	Wedderburn CJ <i>et</i>	2014	UK	Case	50	25	25	13.4(7.4-	13(7.4-18)	11:14	8:17		
	al.			control				18.2)					
5	Purohit R <i>et al.</i>	2016	India	Case	198	99	99	12.5±1.05	13.05±1.1	NM	NM		
				control									
6	Lunt A <i>et al.</i>	2016	UK	Case	73	47	26	8.8(3-13.1)	10.2(4-	21:26	7:19		
	(Cohort 1)			control					14.6)				
	Lunt A <i>et al.</i>	2016	UK	Case	69	45	24	10.2(4.3-	8.5(4-	19:26	8:16		
	(Cohort 2)			control				16)	17.8)				
7	Arigliani M <i>et al.</i>	2019	Nigeria	Case	489	112	377	11.3±3.3	9.5±1.6	66:46	207:170		
	(Central Africa)			control									
8	Arigliani M <i>et</i>	2019	Nigeria	Case	518	154	364	11.4±3.2	10.4±2.4	83:71	189:175		
	al.(Nigeria)			control									
	Arigliani M <i>et al.</i>	2019	United	Case	101	101	NA	11.7±2.7	NA	51:50	NA		
	(UK)		Kingdom	control									
9	Al-Biltagi M <i>et al.</i>	2020	Bahrain	Case	262	139	123	11.9±4.1	12.1±4	84:55	71:51		
				control									
NM=N	ot mentioned; NA=No	t applicable; SD=	Standard dev	riation									



Table 2	: screening method	dology of the included studies						
S.No.	Author	Spirometer/instrument used for PFT	Lung function	PFT measured (measured/residual/% predicted)	Criteria used	Inclusion of ACS in studies	Inclusion of children on hydroxyurea in studies	Inclusion of airway hyperresponsiveness (AHR) in studies
1	Pianosi P <i>et al.</i> (HbSS group)	Automated dry rolling seal spirometer (5000 IV: Gould inc., Oxnard, calif)	FEV1, FVC, FEV1/FVC, TLC, DLCO, FEF ₂₅₋₇₅ , RV/TLC	% predicted	NR	No	No	No
	Pianosi P <i>et al.</i> (ACS group)	Automated dry rolling seal spirometer (5000 IV: Gould inc., Oxnard, calif)	FEV1, FVC, FEV1/FVC, TLC, DLCO, FEF ₂₅₋₇₅ , RV/TLC	% predicted	NR	Yes (10/10)	No	No
2	Hijazi Z <i>et al.</i> (HbSS)	Constant volume- variable pressure body plethysmograph (Erich-jager master laboratory GmbH version 4.5, Hoechberg, Germany)	FEV1, FEV1/FVC, PEF, MEF 25/75, TLC	% predicted, measured	ATS	Yes (8/24)	No	No
3	Sylvester KP <i>et</i> al.	Dry rolling seal spirometer (Morgan TLC, Morgan medical, Rainham, UK)	FEV1, FVC, FEV1/FVC, PEFR, TLCpleth, VCpleth,	% predicted, residual	Values from study by Pellegrino <i>et</i> <i>al.</i>	Yes (4/24)	No	Yes (among controls - 7, 2 on medication)
4	Wedderburn CJ et al.	Whole body plethysmography with pnemutachograph based system (Jaeger masterscreen PFT, carefusion limited, Basingstoke, UK)	FEV1, VC, FEV1/VC, PEF, TLC, RV, DLCOc	% predicted	ATS/ETS	Yes (7/25)	Yes (7/25)	Yes (cases:8/25, controls: 4/25)
5	Purohit R <i>et al.</i>	Spirometer "spirolab 3" MIR010	FEV1, FVC, FEV1/FVC, PEFR	% predicted	ATS	Yes (11/99)	No	No
6	Lunt A <i>et al.</i> (Cohort 1)	Whole body plethysmography with pneumotachograph based system (Jaeger masterscreen PFT, carefusion limited, Basingstoke, UK))	FEV1, VC, FEV1/VC, TLC, RV, RV/TLC, FEF ₂₅₋₇₅	% predicted	ATS/ETS	Yes (10/47)	Yes (7/47)	Yes (cases: 9/47, controls: 2/26)
	Lunt A <i>et al.</i> (Cohort 2)	Whole body plethysmography with Pneumotachograph based system (Jaeger masterscreen PFT, carefusion limited, Basingstoke, UK))	FEV1, VC, FEV1/VC, TLC, RV, RV/TLC, FEF ₂₅₋₇₅	% predicted	ATS/ETS	Yes (12/45)	Yes (8/45)	Yes (cases: 3/45, controls: 4/24)
7	Arigliani M <i>et</i> <i>al.</i> (Central Africa)	Pony FX spirometer (COsmed, Rome, RM, Italy)	FEV1, FVC, zFEV1/FVC	% predicted	ERS	NR	NR	Yes (8/112)
8	Arigliani M <i>et al.</i> (Nigeria)	Easyon-PC ultrasonic flowmeter spirometer(ndd, Zurich Switzerland)	FEV1, FVC, FEV1/FVC	% predicted	ERS	Yes (33/154)	Yes (1/154)	Yes (10/154)
	Arigliani M et al. (UK)	Easyon-PC ultrasonic flowmeter spirometer(ndd, Zurich Switzerland)	FEV1, FVC, FEV1/FVC	% predicted	ERS	Yes (35/101)	Yes (48/101)	Yes (22/101)
9	Al-Biltagi M et al.	Jaeger masterscreen body/diffusion machine (vyaire medical inc, Chicago, II, USA)	FEV1, FVC, FEV1/FVC, TLC, DLCO, RV	% predicted	ATS	Yes (85/139)	Yes (95/139)	No
FEV1: f	orced expiratory vo t reported; ERS=Eu	plume in 1 second; FEF ₂₅₋₇₅ : forced expiratory to ropean respiratory society; ETS: European the	flow between 25-75% of pracic society; ATS=Ameri	FVC; FVC: forced vital capacity can Thoracic society	y; GLI: Global Lung	Initiative; PEF: p	beak expiratory flow; l	PFT: pulmonary function tests;







Figure 1: PRISMA flow chart diagram describing process of identification and selection of studies for inclusion in the review



FEV1

		SCD		C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
AJ-Biltagi M 2020	85.9	13.4	139	101.4	7.9	123	12.6%	-15.50 [-18.13, -12.87]	+
Arigliani M (Central Africa) 2019	80.2	13.1	112	97.9	10.2	377	12.6%	-17.70 [-20.34, -15.06]	-
Arigliani M (West Africa & UK) 2019	81.9	13.3	154	95.2	13	364	12.8%	-13.30 [-15.79, -10.81]	-
Hijazi 2004 (SS)	86.4	11.5	21	94.2	4.2	17	9.3%	-7.80 [-13.11, -2.49]	
Lunt A 2016 (Cohort 2)	90.7	13.3	45	100.55	13.75	24	7.7%	-9.85 [-16.59, -3.11]	
Lunt A 2016 (Cohort 1)	91.6	11.75	47	94.2	13.97	26	8.1%	-2.60 [-8.93, 3.73]	
Pianosi P 1993 (ACS)	84	18	10	105	12	22	3.7%	-21.00 [-33.23, -8.77]	•
Pianosi P 1993 (SS)	88	10	11	105	12	22	6.7%	-17.00 [-24.75, -9.25]	
Purohit 2016	86.79	11.6	99	94.83	16.1	99	11.1%	-8.04 [-11.95, -4.13]	
Sylvester KP 2007	79	10.5	24	94.5	8.5	24	9.2%	-15.50 [-20.90, -10.10]	
Wedderburn CJ 2014	90.58	14.78	25	104.37	14.62	25	6.3%	-13.79 [-21.94, -5.64]	
Total (95% CI)			687			1123	100.0%	-12.67 [-15.41, -9.94]	•
Heterogeneity: Tau ² = 13.59; Chi ² = 3	9.09, df=	= 10 (P	< 0.000	1); $ ^2 = 74$	1%				
Test for overall effect: Z = 9.09 (P < 0.	00001)			257.54 ² .000					-20 -10 0 10 20 SCD Control

FVC

		SCD		Ce	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Al-Biltagi M 2020	87	12.2	139	100.6	7.03	123	13.8%	-13.60 [-15.98, -11.22]	
Arigliani M (Central Africa) 2019	83	13	112	98.8	10.7	377	13.5%	-15.80 [-18.44, -13.16]	
Arigliani M (West Africa & UK) 2019	84.3	12.7	154	95.9	12.4	364	13.8%	-11.60 [-13.98, -9.22]	+
Hijazi 2004 (SS)	83.2	11.9	21	91.2	11.7	17	6.6%	-8.00 [-15.54, -0.46]	
Lunt A 2016 (Cohort 2)	97.6	13.53	45	102.175	14.97	24	7.0%	-4.58 [-11.75, 2.60]	
Lunt A 2016 (Cohort 1)	97.2	18.38	47	98.9	12.4	26	7.1%	-1.70 [-8.79, 5.39]	
Pianosi P 1993 (ACS)	89	15	10	106	13	22	4.1%	-17.00 [-27.77, -6.23]	
Pianosi P 1993 (SS)	89	7	11	106	13	22	7.4%	-17.00 [-23.83, -10.17]	
Purohit 2016	84.4	11.5	99	91.75	15.2	99	11.7%	-7.35 [-11.10, -3.60]	
Sylvester KP 2007	74.5	9.5	24	90.5	9.75	24	9.2%	-16.00 [-21.45, -10.55]	
Wedderburn CJ 2014	94.95	16.4	25	109.225	14.27	25	5.7%	-14.27 [-22.80, -5.75]	
Total (95% CI)			687			1123	100.0%	-11.69 [-14.24, -9.14]	•
Heterogeneity: Tau ² = 10.74; Chi ² = 3	3.65, df =	= 10 (P =	0.000	2); I* = 709	X 6				20 10 10 20
Test for overall effect: Z = 8.99 (P < 0.	00001)								Favours lexnerimentall Favours Icontroll

Favours [experimental] Favours [control]

FEV1/FVC

	1	SCD		C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Al-Biltagi M 2020	91.21	9.28	139	96.7	2.27	123	14.3%	-5.49 [-7.08, -3.90]	
Hijazi 2004 (SS)	102.6	7.3	21	103.5	9.8	17	8.4%	-0.90 [-6.51, 4.71]	
Lunt A 2016 (Cohort 2)	96.2	9.92	45	97.72	7.77	24	10.4%	-1.52 [-5.77, 2.73]	
Lunt A 2016 (Cohort 1)	94.7	9.5	47	98.5	6.62	26	11.2%	-3.80 [-7.52, -0.08]	
Pianosi P 1993 (ACS)	84	5	10	87	4	22	11.6%	-3.00 [-6.52, 0.52]	
Pianosi P 1993 (SS)	88	6	11	87	4	22	10.9%	1.00 [-2.92, 4.92]	
Purohit 2016	101.77	7.6	99	99.65	8.5	99	13.5%	2.12 [-0.13, 4.37]	
Sylvester KP 2007	103.75	5.25	24	103.5	5.5	24	12.3%	0.25 [-2.79, 3.29]	<u> </u>
Wedderburn CJ 2014	93.65	9.65	25	100.92	13.42	25	7.3%	-7.27 [-13.75, -0.79]	
Fotal (95% CI)			421			382	100.0%	-1.90 [-4.32, 0.52]	•
Heterogeneity: Tau ² = 10	.00; Chi# =	39.08	6, df = 8	(P < 0.0	0001); P	= 80%	,		
Test for overall effect: Z =	1.54 (P=	0.12)	891 S						-10 -5 0 5 10 Favours [experimental] Favours [control]

Figure 2: forest plot for FEV1 % predicted, FVC % predicted and FEV1/FVC ratio



PEFR

		SCD		0	Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Hijazi 2004 (SS)	77.6	16.5	21	76.5	15.5	17	10.7%	1.10 [-9.10, 11.30]	
Purohit 2016	78.24	15.6	99	81.41	14.6	99	62.8%	-3.17 [-7.38, 1.04]	
Sylvester KP 2007	92	16	24	100.5	12.5	24	16.9%	-8.50 [-16.62, -0.38]	
Wedderburn CJ 2014	90.85	23.2	25	91.35	14.75	25	9.6%	-0.50 [-11.28, 10.28]	
Total (95% CI)			169			165	100.0%	-3.36 [-6.69, -0.02]	•
Heterogeneity: Tau ² = 0	.00; Chi ²	= 2.5	5, df = 3	(P=0.	47); I ² =	0%			
Test for overall effect: Z	= 1.97 (P = 0.0	5)						Favours [experimental] Favours [control]

TLC

		SCD		C	ontrol			Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
Al-Biltagi M 2020	76.6	18.1	139	99.4	6.82	123	13.5%	-22.80 [-26.04, -19.56]		
Hijazi 2004 (SS)	92.6	10	21	98.6	9.5	17	12.7%	-6.00 [-12.22, 0.22]		
Lunt A 2016 (Cohort 2)	94.92	14.87	45	96.72	8.32	24	12.9%	-1.80 [-7.27, 3.67]		
Lunt A 2016 (Cohort 1)	97.2	13.75	47	94.8	8.67	26	13.0%	2.40 [-2.75, 7.55]		
Pianosi P 1993 (ACS)	85	17	10	100	13	22	10.4%	-15.00 [-26.85, -3.15]		
Pianosi P 1993 (SS)	90	12	11	100	13	22	11.6%	-10.00 [-18.93, -1.07]		
Sylvester KP 2007	86.25	10.75	24	87	9	24	12.9%	-0.75 [-6.36, 4.86]		
Wedderburn CJ 2014	87.42	9.43	25	93.4	7.1	25	13.1%	-5.98 [-10.61, -1.35]		
Total (95% CI)			322			283	100.0%	-7.35 [-14.97, 0.27]		
Heterogeneity: Tau ² = 10	9.44; Ch	i ² = 106	.32, df	= 7 (P <	0.000	01); I ² =	93%			+
Test for overall effect Z =	1.89 (P	= 0.06)							-20 -10 0 10 Favours [experimental] Favours [contro	20

DLCO

		SCD		С	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Al-Biltagi M 2020	67.6	16.2	139	99	5.52	123	17.7%	-31.40 [-34.26, -28.54]	+
Hijazi 2004 (SS)	98.4	21.9	21	108.2	17.3	17	16.1%	-9.80 [-22.26, 2.66]	
Pianosi P 1993 (ACS)	119	23	10	101	16	22	15.2%	18.00 [2.25, 33.75]	
Pianosi P 1993 (SS)	106	17	11	101	16	22	16.2%	5.00 [-7.07, 17.07]	
Sylvester KP 2007	62.25	10.75	24	71.5	8	24	17.5%	-9.25 [-14.61, -3.89]	
Wedderburn CJ 2014	88.45	12.75	25	85.35	9.9	25	17.3%	3.10 [-3.23, 9.43]	
Total (95% CI)			230			233	100.0%	-4.68 [-20.64, 11.29]	
Heterogeneity: Tau ² = 3	72.29; C	hi ² = 16	8.88, d	f= 5 (P	< 0.00	001); l ²	= 97%		
Test for overall effect: Z	= 0.57 (F	P = 0.57)						-50 -25 0 25 50 Favours [experimental] Favours [control]

Figure 3: forest plot of PEFR, TLC and DLCO



FEV1



Figure 4: forest plot of forest plots of PFT parameters in children with SCA with history of ACS among the various studies



FEV1

		SCD		C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.1.1 No inclusion of Asthmatics									
Al-Biltagi M 2020	85.9	13.4	139	101.4	7.9	123	12.6%	-15.50 [-18.13, -12.87]	-
Hijazi 2004 (SS)	86.4	11.5	21	94.2	4.2	17	9.3%	-7.80 [-13.11, -2.49]	
Pianosi P 1993 (ACS)	84	18	10	105	12	22	3.7%	-21.00 [-33.23, -8.77] +	
Pianosi P 1993 (SS)	88	10	11	105	12	22	6.7%	-17.00 [-24.75, -9.25]	
Purchit 2016	86.79	11.6	99	94.83	16.1	99	11.1%	-8.04 [-11.95, -4.13]	
Subtotal (95% CI)			280			283	43.4%	-12.76 [-17.39, -8.14]	•
Heterogeneity: Tau ² = 18.45; Chi ² = 16	6.00. df =	4 (P =	0.003);	12 = 75%					
Test for overall effect: Z = 5.41 (P < 0.	00001)								
1.1.2 Asthma Inclusion									
Aridiani M (Central Africa) 2019	80.2	13.1	112	97.9	10.2	377	12.6%	-17.70 (-20.34 -15.06)	
Aridiani M (West Africa & UK) 2019	81.9	13.3	154	95.2	13	364	12.8%	-13.30 [-15.7910.81]	
Lunt A 2016 (Cohort 2)	90.7	13.3	45	100.55	13.75	24	7.7%	-9.85 [-16.59, -3.11]	
Lunt A 2016 (Cohort 1)	91.6	11.75	47	94.2	13.97	26	8.1%	2.60[-8.93, 3.73]	
Sylvester KP 2007	79	10.5	24	94.5	8.5	24	9.2%	-15.50 (-20.90, -10.10)	
Wedderburn CJ 2014	90.58	14.78	25	104.37	14.62	25	6.3%	-13.791-21.94 -5.641	
Subtotal (95% CI)			407			840	56.6%	-12.63 [-16.47, -8.79]	◆
Heterogeneity: Tau? = 15.86; Chi2 = 2	1.99. df =	5 (P =	0.0005	: P = 77	%				-
Test for overall effect: Z = 6.45 (P < 0.	00001)								
Total (95% CI)			687			1123	100.0%	-12.67 [-15.41, -9.94]	•
Heterogeneity: Tau ² = 13.59; Chi ² = 3	9.09. df =	10 (P	< 0.000	1); ² = 74	4%			-	
Test for overall effect: Z = 9.09 (P < 0.	00001)								-20 -10 0 10 20
Test for subgroup differences: Chi2 = (0.00. df =	1 (P =	0.97), I	2 = 0%					SCD Control

FVC

		SCD		Co	ntrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
2.1.1 Asthamatic Inclusion									
Arigliani M (Central Africa) 2019	83	13	112	98.8	10.7	377	13.5%	-15.80 [-18.44, -13.16]	-
Arigliani M (West Africa & UK) 2019	84.3	12.7	154	95.9	12.4	364	13.8%	-11.60 [-13.98, -9.22]	-
Lunt A 2016 (Cohort 2)	97.6	13.53	45	102.175	14.97	24	7.0%	-4.58 [-11.75, 2.60]	
Lunt A 2016 (Cohort 1)	97.2	18.38	47	98.9	12.4	26	7.1%	-1.70 [-8.79, 5.39]	
Sylvester KP 2007	74.5	9.5	24	90.5	9.75	24	9.2%	-16.00 [-21.45, -10.55]	
Wedderburn CJ 2014	94.95	16.4	25	109.225	14.27	25	5.7%	-14.27 [-22.80, -5.75]	
Subtotal (95% CI)			407			840	56.3%	-11.28 [-15.18, -7.39]	•
Heterogeneity: Tau? = 15.94; Chi2 = 21	.83, df =	5 (P =	0.0006	(I ² = 77%)					
Test for overall effect: Z = 5.68 (P < 0.6	00001)								
2.1.2 No inclusion of Asthamatics									
Al-Biltagi M 2020	87	12.2	139	100.6	7.03	123	13.8%	-13.60 [-15.98, -11.22]	-
Hijazi 2004 (SS)	83.2	11.9	21	91.2	11.7	17	6.6%	-8.00 [-15.54, -0.46]	
Pianosi P 1993 (ACS)	89	15	10	106	13	22	4.1%	-17.00 [-27.77, -6.23]	
Pianosi P 1993 (SS)	89	7	11	106	13	22	7.4%	-17.00 [-23.83, -10.17]	
Purohit 2016	84.4	11.5	99	91.75	15.2	99	11.7%	-7.35 [-11.10, -3.60]	
Subtotal (95% CI)			280			283	43.7%	-11.99 [-15.94, -8.03]	•
Heterogeneity: Tau ² = 11.64; Chi ² = 11	.59, df =	4 (P =	0.02); P	2 = 65%					
Test for overall effect: Z = 5.94 (P < 0.0	00001)								
Total (95% CI)			687			1123	100.0%	-11.69 [-14.24, -9.14]	•
Heterogeneity: Tau ² = 10.74; Chi ² = 33	.65, df =	10 (P =	= 0.000	2); 2 = 704	6				-20 -10 0 10 20
Test for overall effect: Z = 8.99 (P < 0.0	00001)								Favours [experimental] Favours [control]
Test for subgroup differences: Chi ² = 0	.06. df =	1 (P =	0.80), P	= 0%					(- + ()

FEV1/FVC

	5	SCD		С	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
3.1.1 Hyperresponsive									
Lunt A 2016 (Cohort 1)	94.7	9.5	47	98.5	6.62	26	7.0%	-3.80 [-7.52, -0.08]	
Lunt A 2016 (Cohort 2)	96.2	9.92	45	97.72	7.77	24	5.4%	-1.52 [-5.77, 2.73]	
Sylvester KP 2007	103.75	5.25	24	103.5	5.5	24	10.5%	0.25 [-2.79, 3.29]	<u> </u>
Wedderburn CJ 2014	93.65	9.65	25	100.92	13.42	25	2.3%	-7.27 [-13.75, -0.79]	
Subtotal (95% CI)			141			99	25.2%	-1.95 [-3.91, 0.02]	◆
Heterogeneity: Chi ² = 5.5	9, df = 3 (P = 0.	13); l²=	46%					
Test for overall effect: Z =	1.94 (P =	0.05)						
3.1.2 Non-hyperrespons	ive								
AL Piltori LI 2020	04.04	0.00	120	02.7	0.07	102	20.26	E 40 E 7 00 2 001	
Hist 2004 (SS)	102.6	7.2	24	102 5	0.0	17	2.4%	-0.00[.0.51_4.74]	
Dianosi D 1993 (409)	9.4	1.5	10	97	9.0	22	7.9%	-3.00[-6.51, 4.11]	
Pianosi P 1993 (ACG)	04	6	11	97	4		6.3%	1.00[-0.02, 0.02]	
Purobit 2018	101 77	7.6	00	99.65	2.5	00	10.3%	2 12 [-0 13 4 37]	
Subtotal (95% CI)	101.77	1.0	280	55.00	0.0	283	74.8%	-2.53 [-3.67, -1.39]	•
Heterogeneity: Chi ² = 33.	22. df = 4	(P < 0	0.00001	k ² = 88'	%	200			•
Test for overall effect: Z =	4.35 (P	0.00	01)						
Total (95% CI)			421			382	100.0%	-2.38 [-3.37, -1.40]	•
Heterogeneity: Chi ² = 39.0	06. df = 8	(P < 0	0.00001	k ² = 80'	%			-	i
Test for overall effect 7 =	4 74 (P	0.00	001)						-10 -5 0 5 10
Test for subgroup differen	ices: Chi2	= 0.2	5. df = 1	(P=0.6	1), ² =	0%			Favours [experimental] Favours [control]

Figure 5: forest plot of FEV1, FVC and FEV1/FVC ratio stratified by AHR distribution



FEV1

Shifty of Subgroup Mean SD Total Mean SD SD <th></th> <th></th> <th>SCD</th> <th></th> <th>0</th> <th>Control</th> <th></th> <th></th> <th>Mean Difference</th> <th>Mean Difference</th>			SCD		0	Control			Mean Difference	Mean Difference	
11.11br on Hydrorywea Hipd 2004(SS) 86.4 11.5 21 94.2 2.2 7.7 2.780 [-13.11, -2.49] Hipd 2004(SS) 84 16 10 105 12 22 3.7% -1700 [-24.75, -8.21] Pinnet P1893(SS) 84 10 105 12 22 3.7% -1700 [-24.75, -8.21] Sylvester KP 2007 79 105 24 94.5 8.5 34 82.1% 11.1% -30.4 [1.16, -4.13] Sylvester KP 2007 79 10.5 24 9.15 11.4 39.9% -4.251 [47.09, -7.93] Hetrogrenity, Tar ² = 16.20, ChiP + 11.13, df = 4.17 9.13 11.2 171.9 10.2 177.16 -385 [+5.80, -16.50] 1.108 11.2 11.12 11.2 11.12 11.12 11.12 11.12 11.12 11.12 11.12 12.26 11.33 11.12 <t< td=""><td>Study or Subaroup</td><td>Mean</td><td>SD</td><td>Total</td><td>Mean</td><td>SD</td><td>Total</td><td>Weight</td><td>IV. Random. 95%</td><td>CI IV. Random, 95% CI</td></t<>	Study or Subaroup	Mean	SD	Total	Mean	SD	Total	Weight	IV. Random. 95%	CI IV. Random, 95% CI	
$\begin{aligned} H_{12}(2) S(1) & S(1) & S(2) & S(2) & S(2) & S(3) & S($	1.1.1 Not on Hydroxyurea										
Pinnel P1933 (CS) 84 18 19 105 102 22 3.7% -1201 323 3.8.77 Pinnel P1933 (SS) 88 10 11 105 12 22 3.7% -1201 323 3.8.77 Pinnel P1933 (SS) 88 10 11 105 12 22 3.7% -1201 323 3.8.77 Pinnel P1933 (SS) 88 10 11 105 12 22 3.7% -1201 323 3.8.77 Pinnel P1933 (SS) 88 10 11 105 12 22 3.7% -1201 323 3.8.77 Heterogenelly, Tar's 16 2; CDr's 113, df = 4 (P = 0.03); (F = 64% Tast to eval disc 2 5.5 (P < 0.0001) 11.2 Indicator 65 Ca on Hydroxymea ARBing in 200 85 13 13 151 951 20 377 126% -1770 (5.034 -1550) Anglami M (Aret Africa 2 UK) 2019 813 133 154 952 11 364 12.6% -1330 (-15.79, -10.81) Link 2.016 (Cohor1) 813 13 154 952 11 364 12.6% -1330 (-15.79, -10.81) Link 2.016 (Cohor1) 813 13 154 952 11 364 12.6% -1330 (-15.79, -10.81) Link 2.016 (Cohor1) 813 13 154 952 11 364 12.6% -1330 (-15.79, -10.81) Link 2.016 (Cohor1) 813 13 154 952 11 364 12.6% -1330 (-15.79, -10.81) Link 2.016 (Cohor1) 813 13 154 952 11 364 12.6% -1330 (-15.9, -13.39) (-15.9, -13.9) (-15	Hijati 2004 (SS)	86.4	11.5	21	94.2	4.2	17	9.3%	-7 80 [-13, 11, -2.4]	91	
Pinnapi Pianajel Pian	Pianosi P 1993 (ACS)	84	18	10	105	12	22	3.7%	-21.00 [-33.238.7]	71 +	
Purch 2016 Purch 2017 Purch	Pianosi P 1993 (SS)	88	10	11	105	12	22	6 7%	-17 00 [-24 75 -9 2		
Spreater LP 2007 Subtract (95°, C) Hetersgenet): Tai' = (122): Chi' = (11.13, df = 4 (P = 0.03); P = 44% Testfor overall effect Z = 5.55; P < 0.00001) 11.2 Inclusion of SCA on Hydroxynes Addinal (Central Africa) 2018 Solution (Central Africa) 2018 Solution (Central Africa) 2018 Solution (Central Africa) 2019 Solution (Central Africa) 2014 Solution (Central Africa) 2014	Purabit 2016	86 79	11.6	99	94 83	16.1	99	11 1%	-8 04 [-11 95 -4 13	31	
Subtral (55, C) 100000000000000000000000000000000000	Svivester KP 2007	79	10.5	24	94.5	8.5	24	9 2%	-15 50 1-20 90 -10 10	n	
Heterogenety: Tur' = 16.20; Chi ² = 11.13, df = 4 (P = 0.03); P = 64/5 Test for verail effect Z = 5.35; (P = 0.0001) 11.2 Inclusion of SCA on Hydroxyurea Anglani M (Central Africa) 2018 60.2 11.31 112 97.9 110.2 377 12.66 + 17.70 [20.34, -15.60] Anglani M (Central Africa) 2018 60.2 11.31 112 97.9 110.2 377 12.66 + 17.70 [20.34, -15.60] Anglani M (Central Africa) 2019 60.2 11.31 112 97.9 110.2 377 12.66 + 1.30 [15.70, -10.81] Lun A 2016 (Cohort 1) 91.6 11.75 47 94.2 13.97 26 8.11% - 2.20 [2.84, 5.83] Lun A 2016 (Cohort 1) 91.6 11.75 47 94.2 13.97 26 8.11% - 2.20 [2.84, 5.84] Wedetekun C.2014 90.36 df = 10 (P = 0.0004); P = 78% Test for verail effect Z = 7.50 (P < 0.00001) Total (65% C) 667 1123 10.07 42 22 [1.65.01, -12.94] Heterogenetic, Tur' = 13.50; Chi ² = 30.99, df = 10 (P = 0.0001); P = 74% Test for verail effect Z = 7.50 (P < 0.00001) Total (65% C) 687 11.79 12 00.0001) Test for subgroup 80.2 01 10 P = 0.0001; P = 74% Test for verail effect Z = 7.50 (P < 0.00001) Test for subgroup 80.2 01 10 90 10 10 10 12 22 4.74 + 17.01 52.77, -6.57 Heterogenetic, Tur' = 13.82; Chi ² = 30.99, d = 10 (P = 0.0001); P = 74% Test for verail effect Z = 5.00 (P < 0.0001) Test for subgroup 80.2 01 17 17 17 8.6% -0.000 [15.44, -0.46] Planox P (P = 0.02, d = 11.P = 0.89); P = 9% WCC Test for subgroup 80.2 01 91 11.5 01 17.7 17 8.6% -0.000 [15.44, -0.46] Planox P (P = 0.02, d = 11.P = 0.89); P = 9% WCC Test for subgroup 77 74.5 9.5 124 90.5 91.7 122 13.8% -13.00 [15.98, -11.22] Adjust M (Central Africa 2019 80 0000; P = 70% Test for evaluations a low 2011 80.8 11.7 11 12 80.7 17.7 12.24 - 148.4, -13.10 4 Adjust M (Central Africa 2010 81, 93 13 12 12 88 17 16 21 13.97 13.84 + 15.80 + 18.44, -13.10 4 Adjust M (Central Africa 2019 83 13 12 12 88 17 16 2 13.77 13.28 + 15.80 + 15.84, -13.24 4 Adjust M (Central Africa 2019 83 11 22 12 13 8 12 12 13 12.85 + 15.80 + 15.84, -13.24 4 Adjust M (Central Africa 2019 83 11 21 24 88 10.7 377 13.28 + 15.80 + 15.84, -13.24 4 Adjust M (Central Africa 2019 83 16	Subtotal (95% CI)	22		165			184	39.9%	-12.51 [-17.09, -7.93	n 🔶	
Test for overall effect Z = 5.35 (P < 0.00001)	Heterogeneity: Tau ² = 16.26; Chi ²	= 11.13, df	= 4 (P =	0.03); [² = 64%				•		
11.2 Inclusion of SCA on Hydroxyures AkBitraji M 2020 85.9 13.4 13.9 101.4 7.8 12.3 12.6% -15.50 [18.13, -12.87] Angliani M (Vent Alfria 2019 80.2 13.1 11.2 97.8 10.2 37.7 12.6% -17.70 20.33, -15.50 Angliani M (Vent Alfria 2019 90.2 13.3 15.4 95.2 13.3 95.1 12.5% -13.30 [15.7, -10.81] Lunt A 2016 (Cohort 1) 91.5 11.75 47 94.2 13.8 95.9 8.1% -2.50 [6.83, 3.73] Wedderhun CJ 2014 90.56 11.25 10.00 % 42.67 [45.41, -9.94]	Test for overall effect: Z = 5.35 (P	< 0.00001)									
Al-Bittag M 2020 859 134 139 1014 79 123 12.6% -15.50 [-18.13, -12.27] Anglan M (Vex Ha Africa) 2019 802 13.1 112 97.9 10.2 377 12.6% -17.01 [-2.0.4, -15.06] Anglan M (Vex Ha Africa) 2019 802 13.1 112 97.9 10.2 377 12.6% -17.01 [-2.0.8, -17.01 [-2.0.8, -15.00] Lun A 2016 (Cohot 1) 90.7 13.3 45 100.55 13.7 34 17.7% -3.85 [-1.6.9, -3.10] Lun A 2016 (Cohot 1) 91.6 11.75 47 94 21.387 26 8.1% -2.50 [-6.30, -3.55] Subtotal (95% C) 91.6 17.5 24 7.7% -2.85 [-1.6.9, -3.55] Total (95% C) 667 1123 100.0% -12.67 [-1.6.9, -0.55] Total (95% C) 667 1123 100.0% -12.67 [-1.6.9, -0.55] Total (95% C) 667 1123 100.0% -12.67 [-1.6.9, -0.55] Total (95% C) 600001) Test for subaroup differences Chi ² = 0.00, df = 1 (P = 0.89), P = 0% VC Subtotal (95% C) 89 12 119 21 91.2 11.7 17 6.5% -0.00 [-1.554, -0.44] Pino.91 1933 QCB 89 22 11.9 21 91.2 11.7 17 6.5% -0.00 [-1.554, -0.44] Pino.91 1933 QCB 89 23 21 19 21 91.2 11.7 17 6.5% -0.00 [-1.554, -0.44] Pino.91 1933 QCB 89 7 11 106 13 22 4.1% -17.00 [-2.77, -0.23] Test for subaroup differences Chi ² = 0.00, df = 0.00, P = 0.00, P = 0.5% test Subtotal effect 2 = 51.0 P - 0.00001) Test for overall effect 2 = 51.0 P - 0.00001) Test for overall effect 2 = 51.0 P - 0.00001) 21.2 Inclusion of SCA on Hydroxymee Al-Bittag 204 (16.2, -0.0001) 21.2 Inclusion of SCA on Hydroxyme Al-Bittag 204 (16.2, -0.00001) 21.2 Inclusion of SCA on Hydroxyme Al-Bittag 204 (16.2, -0.00001) 21.2 Inclusion of SCA on Hydroxyme Al-Bittag 204 (16.2, -0.00001) 21.2 Inclusion (12.0, -1.16, 0.16, df = 0.0000), P = 76% Test for overall effect 2 = 51.0 P - 0.00000) Test for overall effect 2 = 51.0 P - 0.000001 21.2 Inclusion (12.0, -1.16, 0.16, df = 0.0000), P = 76% Test for overall effect 2 = 51.0 P - 0.000001 21.2 Inclusion (12.0, -1.16, 0.16, df = 0.00000), P = 76% Test for overall effect 2 =	1.1.2 Inclusion of SCA on Hydro	xyurea									
Anglani M (Central Africa) 2019 802 13.1 112 97.3 10.2 377 12.5% -17.70 [203.4.15.05] Anglani M (Central Africa) 2019 80.2 13.1 112 97.3 10.2 377 12.5% -17.70 [203.4.15.05] Anglani M (Central Africa) 2019 80.2 13.3 154 95.2 13 384 12.8% -13.30 [15.78, -10.81] Lunk 2.016 (Cohort 1) 90.7 13.3 454 95.2 13 24 7.5% +385 [16.83, 3.13] Lunk 2.016 (Cohort 1) 90.8 14.78 25 10.35 114.52 25 53% -1.375 [21.84, -5.85] Subbal (65% C) 522 939 60.1% -12.02 [16.30, -8.55] Heterogenetic, Tax' = 12.10 Ch ² = 22.53, df = 10 (P < 0.0001); Te 78% Testfor verall effect 2 = 8.09 (P < 0.00001) Total (95% C) 657 1123 100.0% -42.67 [45.41, -9.40] Heterogenetic, Tax' = 13.59, Ch ² = 30.90, df = 10 (P < 0.0001); Te 74% Testfor verall effect 2 = 5.00 (P < 0.00001) Total (95% C) 657 1123 100.0% -42.67 [45.41, -9.40] Heterogenetic, Tax' = 13.59, Ch ² = 30.90, df = 10 (P < 0.0001); Te 74% Testfor verall effect 2 = 6.000, df = 10 (P < 0.0001); Te 74% Testfor verall effect 2 = 5.00 (P < 0.00001) Total (95% C) 632 119 21 119 21 012 117 10 635 .4 0.00 (F 554, -0.46) W.Random, 95% C) 74 55 24 90 17.5 152 90 11.7% -7.328 [1-10, -0.60] Subtor of hyperogenetic 1 106 13 22 27 44 -17.00 (P = 2.74, -7.23) Heterogenetic True* 18.82; Ch ² = 11.80, df = 4.0° - 0.022; P = 6.6% Testfor verall effect 2 = 5.00 (P < 0.00001) Total (95% C) 74 5 55 24 90 11.7% -7.328 [1-10.3, -0.60] Subtor 100 (S0% C) 74 5 55 24 90 11.7% -7.328 [1-10.3, -0.60] Subtor 100 (S0% C) 74 5 152 90 11.7% -7.328 [1-10.3, -0.60] Subtor 100 (S0% C) 74 5 152 90 11.7% -7.328 [1-10.3, -0.60] Subtor 100 (S0% C) 74 5 152 90 11.7% -7.328 [1-10.3, -0.60] Subtor 100 (S0% C) 74 5 152 90 11.7% -7.328 [1-10.3, -0.60] Subtor 100 (S0% C) 74 5 152 90 11.7% -7.328 [1-10.3, -0.60] Subtor 100 (S0% C) 74 5 152 90 11.7% -7.328 [1-10.3, -0.60] Subtor 100 (S0% C) 74 5 152 90 11.7% -7.328 [1-10.3, -0.60] Subtor 100 (S0% C) 74 5 152 90 11.7% -7.328 [1-10.3, -0.60] Subtor 100 (S0% C) 74 5 153 84 40 10.9% -12.48 [1-2.4, -0.44] Heterogenetic True* 10.46 (Ch ² = 20.65, df = 0.000, P	Al-Biltagi M 2020	85.9	13.4	139	101.4	7.9	123	12.6%	-15.50 [-18.13, -12.8]	71 [7	
Anglani M (Vest Africa S UK) 2019 81.9 13.3 15.4 95.2 13 36.4 12.8% -13.00 [+15.79, -10.81] Lunt A 2016 (Cohot 2) 90.7 13.3 45 100.55 13.7 24 7.7% -43.85 [16.59, -3.11] Lunt A 2016 (Cohot 2) 90.8 14.7 92.1 13.7 26 8.1% -2.2015 (20.014) 90.8 13.7 24 17.7% -43.85 [16.59, -3.11] Lunt A 2016 (Cohot 2) 90.8 14.7 92.1 93.9 60.4% -12.87 [24.33, 37] -41.23 Wedgethum CJ 2014 90.8 60.7% 12.3 100.0% -12.67 [45.41, -9.94] -9.94 Test for verail effect Z = 9.09 (P < 0.0001)	Arigliani M (Central Africa) 2019	80.3	13.1	112	97.9	10.2	377	12.6%	-17.70 -20.3415.06	ai —	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Arigliani M (West Africa & UK) 20	19 81.9	13.3	154	95.2	13	384	12.8%	-13.30[-15.79, -10.8]		
$ \begin{array}{c} \text{Link } 2.016 (1000 \text{LT}) & \text{OI} & $	Lunt A 2016 (Cohort 2)	90.7	133	45	100 55	13.75	24	7 7%	-9.85 [-16 59 -3 1	1	
$\begin{aligned} \begin{array}{c} \text{Link transform} (2011) & 0.0.8 & 14.7 & 2.5 & 10.4 & 11.42 & 2.5 & 0.3.8 & -17.9 & -2.0.9 & -0.0.0.51 \\ \text{Subtrail (S%, C)} & 5.22 & 9.39 & 60.1\% & -12.92 & -10.6 & -2.0.851 \\ \text{Subtrail (S%, C)} & 5.22 & 3.93 & 60.1\% & -12.92 & -16.0 & -0.0.001 \\ \text{Heterogeneity: Tau' = 12.10; Chi2 = 2.253, df = 5 (P = 0.0004); P = 78\% \\ \text{Testfor overall effect Z = 7.50 (P < 0.00001) \\ \text{Total (S%, C)} & 667 & 1123 & 100.0\% & -12.67 & -14.9.40 \\ Heterogeneity: Tau' = 13.59; Chi2 = 3.0.9, df = 10 (P < 0.0001); P = 74\% \\ \text{Testfor overall effect Z = 9.00 (P < 0.00001) \\ \text{Testfor overall effect Z = 9.00 (P < 0.00001) \\ \text{Testfor overall effect Z = 9.00 (P < 0.00001) \\ \text{Testfor overall effect Z = 9.00 (P < 0.00001) \\ \text{Testfor overall effect Z = 9.00 (P < 0.00001) \\ \text{Testfor overall effect Z = 9.00 (P < 0.00001) \\ \text{Testfor overall effect Z = 9.00 (P < 0.00001) \\ \text{Testfor overall effect Z = 9.00 (P < 0.00001) \\ \text{Testfor overall effect Z = 9.00 (P < 0.00001) \\ \text{Testfor overall effect Z = 9.00 (P < 0.00001) \\ \text{Testfor overall effect Z = 9.00 (P < 0.00001) \\ \text{Testfor overall effect Z = 9.00 (P < 0.00001) \\ \text{Testfor overall effect Z = 9.00 (P < 0.00001) \\ \text{Testfor overall effect Z = 9.00 (P < 0.00001) \\ \text{Testfor overall effect Z = 5.10 (P < 0.00001) \\ \text{Testfor overall effect Z = 5.10 (P < 0.00001) \\ \text{Testfor overall effect Z = 5.10 (P < 0.00001) \\ \text{Testfor overall effect Z = 4.10 (P < 0.00001) \\ \text{Testfor overall effect Z = 4.10 (P < 0.00001) \\ \text{Testfor overall effect Z = 4.10 (P < 0.00001) \\ \text{Testfor overall effect Z = 4.10 (P < 0.00001) \\ \text{Testfor overall effect Z = 4.10 (P < 0.00001) \\ \text{Testfor overall effect Z = 4.10 (P < 0.00001) \\ \text{Testfor overall effect Z = 4.10 (P < 0.00001) \\ \text{Testfor overall effect Z = 4.10 (P < 0.00001) \\ \text{Testfor overall effect Z = 4.10 (P < 0.00001) \\ \text{Testfor overall effect Z = 4.10 (P < 0.00001) \\ \text{Testfor overall effect Z = 4.10 (P < 0.00001) \\ \text{Testfor overall effect Z = 4.10 (P < 0.00001) \\ \text{Testfor overall effect Z = 4.10 (P < 0.00001) \\ \text{Testfor overall e$	Lunt A 2016 (Cohort 1)	91.6	11 75	47	94.2	13.97	26	8 1%	-2 60 68 93 37	31	
$ \begin{array}{c} \text{Heterogeneity, } Tau^2 = 12.10; \ Chi^2 = 22.53, \ df = 5 (P = 0.0004); \ P = 78\% \\ \text{Test for overall effect } 2 = 7.50, \ (P < 0.00001) \\ \text{Test for overall effect } 2 = 7.50, \ (P < 0.00001) \\ \text{Test for overall effect } 2 = 7.50, \ (P < 0.00001) \\ \text{Test for overall effect } 2 = 9.00, \ P < 0.00001) \\ \text{Test for overall effect } 2 = 9.00, \ P < 0.00001) \\ \text{Test for overall effect } 2 = 9.00, \ P < 0.00001) \\ \text{Test for overall effect } 2 = 9.00, \ P < 0.00001) \\ \text{Test for overall effect } 2 = 9.00, \ P < 0.00001) \\ \text{Test for overall effect } 2 = 9.00, \ P < 0.00001) \\ \text{Test for overall effect } 2 = 9.00, \ P < 0.00001) \\ \text{Test for overall effect } 2 = 9.00, \ P < 0.00001) \\ \text{Test for overall effect } 2 = 9.00, \ P < 0.00001) \\ \text{Test for overall effect } 2 = 9.00, \ P < 0.00001) \\ \text{Test for overall effect } 2 = 9.00, \ P < 0.00001) \\ \text{Test for overall effect } 2 = 9.00, \ P < 0.00001) \\ \text{Test for overall effect } 2 = 9.00, \ P < 0.00001) \\ \text{Test for overall effect } 2 = 9.00, \ P < 0.00001) \\ \text{Test for overall effect } 2 = 9.00, \ P < 0.00001) \\ \text{Test for overall effect } 2 = 9.00, \ P < 0.00001) \\ \text{Test for overall effect } 2 = 9.00, \ P = 0.000001 \\ \text{Test for overall effect } 2 = 9.00, \ P = 0.000001 \\ \text{Test for overall effect } 2 = 9.00, \ P = 0.000001 \\ \text{Test for overall effect } 2 = 9.00, \ P = 0.000001 \\ \text{Test for overall effect } 2 = 9.00, \ P = 0.000001 \\ \text{Test for overall effect } 2 = 9.00, \ P = 0.000001 \\ \text{Test for overall effect } 2 = 9.00, \ P = 0.000001 \\ \text{Test for overall effect } 2 = 9.0000001 \\ \text{Test for overall effect } 2 = 9.0000001 \\ \text{Test for overall effect } 2 = 9.0000001 \\ \text{Test for overall effect } 2 = 9.0000001 \\ \text{Test for overall effect } 2 = 9.000001 \\ \text{Test for overall effect } 2 = 9.000001 \\ \text{Test for overall effect } 2 = 9.000001 \\ \text{Test for overall effect } 2 = 9.000001 \\ \text{Test for overall effect } 2 = 9.000001 \\ \text{Test for overall effect } 2 = 9.0000001 \\ \text{Test for overall effect } 2 = 9.0000001 \\ \text{Test for overall effect } 2 = 9.000000$	Madarburn CL2014	00.59	11.70	25	104.27	14.62	25	6 3%	-13 70 [21 04 .5 6		
Heterogeneity: Tau" = 12.10; ChP = 22.53, df = 5 (P = 0.0004); P = 78% Test for viral effect: $Z = 7.50$ (P < 0.00001) Total (95%; C) 687 1123 100.0%, -12.67 [-15.41, -9.94] Heterogeneity: Tau" = 13.59; ChP = 33.09, df = 10 (P < 0.0001); P = 74% Test for viral effect: $Z = 9.09$ (Control Test for viral effect: $Z = 5.00$	Subtotal (95% CI)	30.00	14.70	522	104.01	14.02	939	60.1%	-12.92 [-16.30, -9.55	5 🔶	
Testfor overall effect Z = 7.50 ($P < 0.0001$) Total (95%, CI) 667 1123 100.0%, -12.67 [-15.41, -9.94] Heterogeneity, Tau" = 13.59; ChP = 33.09, df = 10 ($P < 0.0001$); P = 74% Testfor overall effect Z = 9.09 ($P < 0.0001$) Testfor subgroup Mean SD Total Mean SD Total Veight N. Random, 99% CI N	Heterogeneity: Tau ² = 12 10: Chi ²	= 22.53, df	= 5 (P =	0.0004	$ ^2 = 78$	%					
Total (95%, CI) 667 1123 100.0% -12.67 [-15.41, -9.94] Heterogeneity: Tau" = 13.59; ChP = 30.90; P = 00:0001) Test for vuerall effect Z = 9.90; P < 0.00001)	Test for overall effect: Z = 7.50 (P	< 0.00001)				10					
Heterogeneity: Tau" = 13.58; Chi ^p = 39.09, df = 10 (P < 0.0001); P = 74% Test for varial effect Z = 9.09 (P < 0.0001) Test for subaroup differences; Chi ^p = 0.02, df = 1 (P = 0.89); P = 0% VC Study or Subgroup Mean SD Total Mean SD Total Weight M, Random, 95% CI Planosi P 1993 (ACS) 89 15 10 106 13 22 74% -17.00; 23.77, 76.38 Planosi P 1993 (SS) 89 7 11 106 13 22 74% -17.00; 23.77, 76.38 Subtol (5% C) 74.5 95 22 99 1.75 152 99 11.7% -7.35; F1.10, 3.80 Heterogeneity: Tau" = 18.82; Chi ^p = 11.60, df = 4 0 ^p = 0.02; P = 6% Test for varial effect Z = 5.10 (P < 0.0001) Z1.2 Inclusion of SCA on Hydroxyurea Aleiling M 2020 01 97 21 22 139 100.6 7.03 123 13.8% -13.60 [+15.98, -11.22] Anglian M (Yesh Kina & K/C, 2010) Test for varial effect Z = 5.10 (P < 0.00001) Z1.2 Inclusion of SCA on Hydroxyurea Aleiling M 2020 01 97 21 52 05 71 14.97 22 73 77 13.5% -15.80 [+15.98, -11.22] Anglian M (Yesh Kina & K/C, 2010) 83 13 112 98.8 10.7 377 15.369 +13.84, -13.60 [+15.98, -11.22] Anglian M (Yesh Kina & K/C, 2014) 84.3 12.7 154 95.9 12.4 24 71.73, 54.72] Heterogeneity: Tau" = 10.74; Chi ^p = 33.85, df = 10.0 ^p = 0.0002; P = 76% Test for varial effect Z = 6.90 (0.0001) Total (95% CI) Test for varial effect Z = 6.90 (- 0.00001) Total (95% CI) Test for varial effect Z = 6.90 (- 0.00001) Total (95% CI) Total (95% CI) Mean <u>SD Total Mean SD Total Mean SD Total Mean SD Total Weight N, Kreed, 95% CI</u> N, Fixed, 95% CI Total (95% CI) Total (95% CI) Total (95% CI) Mean SD Total Mean <u>SD Total Mean SD Total Mean SD Total Weight N, Kreed, 95% CI</u> N, Fixed, 95% CI Total (95% CI) Total (95% CI) Mean <u>SD Total Mean SD Total Mean SD Total Mean SD Total Weight N, Kreed, 95% CI</u> N, Fixed, 95% CI Total (95% CI) Total (95% CI) Total (95% CI) Mean SD Total Mean <u>SD Total Mean SD Total Mean SD Total Mean SD Total Weight N, Kreed, 95% CI</u> N, Fixed, 95% CI Total (95% CI) Total (95% CI) SUD Total Mean SD Total Mean <u>SD Total Mean SD </u>	Total (95% CI)			687			1123	100.0%	-12.67 [-15.41, -9.94	1] 🔶	
Test for visual leffect Z = 9.09 (P < 0.00001)	Heterogeneity: Tau ² = 13.59: ChP	= 39.09 df	= 10 /P	< 0.000	$1): ^2 = 7$	4%					
SCD Control SCD Control SCD Control Mean SD Total Mean SD Total Weight IV, Random, 95% CI IV Readom, 95% CI SCD Control Mean SD Total Mean SD Total Weight IV, Random, 95% CI IV Random, 95% CI VCC Study or Subgroup SCD Control Mean SD Total Weight IV, Random, 95% CI IV, Random, 95% CI VIC SCD Control Mean SD Total Weight IV, Random, 95% CI IV, Random, 95% CI VIC SCD Control Mean SD Total Weight IV, Random, 95% CI IV, Random, 95% CI VIC SCD Control Mean SD Total Weight IV, Random, 95% CI IV, Random, 95% CI VIC Mean SD Total Mean DIfference Mean DIfference VIC SCD Control Mean SD Total Weight IV, Random, 95% CI VIC SCD Control Mean SD Total Weight IV, Random, 95% CI VIC SCD Control Mean SD Total Weight IV, Random, 95% CI VIC	Test for overall effect 7 = 9.09 (P	< 0.000011	- 10 (i	0.000	19,1 = 1	470				-20 -10 0 10 20	
VC Subject of Subgroup Mean SD Control Mean Difference Mean Difference Nuthor on hydroxyurea Hilds 2004 (65) 83 11 9 21 11 70 6.5% Control Mean Difference Mean SD Vice Mean Difference Planois P1993 (ACS) 83 11 9 21 11 70 6.5% -20 11 7.7% -7.76 12.7 7.76 -2.3 Planois P1993 (ACS) 84 11 5.9 0 9 17.5 15.2 9 11 7.7 74 -7.77 13.5% -7.72 1.74% -7.70 1.75 1.5 2.1 7.72 1.75 1.7 7.2 1.74% -7.72 1.7 1.7 1.7 1.7 1.7 1.7 1.7 1.7 1.7 1.7	Test for subgroup differences: Chi	² = 0.02 df	= 1 /D =	0.801	2 = 0%					SCD Control	
Study or Subgroup Mean SD Total Mean SD	FVC										
SCD Control Mean Difference Mean Difference Mean Difference 21.11 Not on Hydroxyurea Hean SD Total Weight Nr, Random, 95% CI IV, Random, 95% CI Planos P1933 (ACS) 89 15 10 106 13 22 4.1% -17.00 (+27.77, e.2.3) Planos P1933 (ACS) 89 15 10 106 13 22 7.4% -17.00 (+27.77, e.2.3) Planos P1933 (SS) 89 7.11 106 13 22 7.4% -17.00 (+27.77, e.2.3) Subtoal (S% CD) 74.4 15 99 91.75 152 99 11.7% -7.35 (+11.0.3.60) Symbola (S% CD) 74.4 9.5 9.5 49 92.0% +16.50 (+14.4, +13.16) Symbola (S% CD) 87 12.2 139 100.6 7.03 123 13.8% (+13.60 (+15.96, -11.22) Arbilitagi M 2020 87.53 45 102.75 14.97 2.60 +3.60 +3.61 +3.62 +4.61 +4.638 +1.76 +3.63 <td></td>											
21.1 Not on hydroxyurea Hijazi 2004 (65) 83.2 11.9 21 91.2 11.7 17 6.6% -8.00 [-15.54, -0.46] Planos IP 1993 (ACS) 89 15 10 106 13 22 4.1% -17.00 [-27.77, -6.23] Planos IP 1993 (ACS) 89 7 11 106 13 22 7.4% -17.00 [-27.77, -6.23] Planos IP 1993 (ACS) 89 7 11 106 13 22 7.4% -17.00 [-27.77, -6.23] Planos IP 1993 (ACS) 89 7 11 106 13 22 7.4% -17.00 [-27.77, -6.23] Sybester KP 2007 74.5 9.5 24 9.2% -16.00 [-21.45, -10.55] -16.55] Sybolat (95% CI) 106 7.03 123 13.8% -13.60 [-15.98, -11.22] Ariglian M (Verital Africa 2016) 83 13 112 98.9 12.4 7.7% -17.08, -17.52, 260] Lunt A 2016 (Cohort 1) 97.6 13.53 45 102.175 14.97 12.28, 67 -10.6, -10.20 -20 Viedderbourn CJ 2014 9	Study or Subgroup	Mean	SCD SD T	otal	Con	SD 1	otal W	/eight	Mean Difference IV, Random, 95% Cl	Mean Difference IV, Random, 95% CI	
High 2004 (65) B32 11.9 21 91.2 11.7 17 6.5% -80.01/1540.46 Finanse P 1993 (65) 89 7 11 106 13 22 7.4% -17.00 [+2540.46] Finanse P 1993 (65) 89 7 11 106 13 22 7.4% -17.00 [+2540.46] Finanse P 1993 (65) 89 7 11 106 13 22 7.4% -17.00 [+2540.46] Finanse P 1993 (65) 89 7 11 106 13 22 7.4% -17.00 [+2540.46] Finanse P 1993 (65) 89 7 11 106 13 22 7.4% -17.00 [+2540.46] Finanse P 1993 (65) 89 7 11 106 13 22 7.4% -17.00 [+2540.46] Finanse P 1993 (65) 89 7 12 2 139 10.6 7.03 123 13.6% -13.60 [+15.96, -11.22] Heterogeneity. Tau* = 18.62; Chi* = 11.60, df = 4 (P = 0.02); P = 66% Test for overall effect Z = 5.10 (P < 0.00001) 21.2 Inclusion of SCA on Hydroxyurea Arbitisgi M 2020 87 12.2 139 100.6 7.03 123 13.6% -13.60 [+15.96, -11.22] Arbitisgi M 2020 87 12.2 139 100.6 7.03 123 13.6% -13.60 [+15.96, -11.22] Arbitisgi M 2020 87 12.2 139 100.6 7.03 123 13.6% -13.60 [+15.96, -11.22] Arbitisgi M 2020 87 12.2 139 100.6 7.03 123 13.6% -13.60 [+15.96, -11.22] Arbitisgi M 2020 87 12.2 139 100.6 7.03 123 13.6% -13.60 [+15.96, -11.22] Lunk A 2016 (Cohort 1) 97.2 18.38 47 99.9 12.4 26 7.1% -1.70 [+1.75, 2.60] Lunk A 2016 (Cohort 1) 97.2 18.38 47 99.9 12.4 26 7.1% -1.70 [+1.76, 7.8, 9.22] Heterogeneity. Tau* = 10.44; Chi* = 20.95; df = 5 (P = 0.00005); P = 76% Test for overall effect Z = 6.85 (P < 0.00001) Test for overall effect Z = 6.85 (P < 0.00001) Test for overall effect Z = 6.95 (P < 0.00001) Test for overall effect Z = 6.99 (P < 0.00001) Test for overall effect Z = 6.99 (P < 0.00001) Test for overall effect Z = 6.99 (P < 0.00001) Test for subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI IV, Fixed, 95% CI Lunk A 2016 (Cohort 1) 94.7 9.5 47 99.5 6.62 26 7.0% -3.80 [-7.52, -0.08] Lunk A 2016 (Cohort 1) 94.7 9.5 47 99.5 6.62 26 7.0% -3.80 [-7.52, -0.08] Lunk A 2016 (Cohort 1) 94.7 9.5 47 99.5 6.62 26 7.0% -3.80 [-7.52, -0.08] Lunk A 2016 (Cohort 1) 94.7 9.5 47 99.5 6.62 26 7.0% -3.80 [-7.52, -0.08] Lunk A 2016 (Cohort 1) 94.7 9.5 47 99.5 6.62 26 7.0% -3.80 [-7.52, -0.08] Lunk	2.1.1 Not on Hydroxyurea										
Plance P 1993 (65) Plance P 1993 (65) (61) Plance P 1993 (61) (61) (61) (61) (61) (61) (61) (61)	Hijazi 2004 (SS) Pianosi P 1993 (ACS)	83.2	11.9	21	91.2	11.7	17	6.6%	-8.00 [-15.54, -0.46] 17.00 [-27.77, -6.23]		
Purchil 2016 84.4 11.5 99 91.75 15.2 93 11.7% -7.35 (1-11.0,-3.60) Symbolic KS CD 165 9.5 2.4 9.5 (24 9.2, 24 9.2, 24 9.2, 24 9.2, 24 9.2, 24 9.2, 24 9.2, 24 9.2, 24 9.2, 24 9.2, 24 9.2, 24 9.2, 24 9.2, 24 9.2, 24 9.2, 24 9.2, 24 9.2, 24 9.6, 26 16.0 (1-10.5) 9.1 16.5 16.5 16.6 16.5 16.6 16.5 16.6 17.5 7.7 (2 24 9.2, 44 16.5 11.28 16.6 17.5 7.7 (2 17.3, 5% 16.60 (-10.55) 11.22 11.22 11.28 11.28 12.2 13.8 12.2 13.8 11.28 13.8% 11.28 13.8% 13.8% 13.8% 13.8% 13.8% 13.8% 13.8% 13.8% 13.8% 13.8% 13.8% 13.8% 13.8% 13.8% 13.8% 13.8% 13.8% 13.8% 13.8% 15.80 (-13.56, -13.6) 10.21 (5.10, -15.5, -7.72) 10.21 (5.10, -15.5, -7.75) 10.21 (5.10, -15.5, -7.75) 10.21 (5.10, -15.5, -7.75) 12.21 (5.10	Planosi P 1993 (SS)	89	7	11	106	13	22	7.4% -1	7.00 [-23.83, -10.17]		
Sylvester KP 2007 74.5 9.5 24 90.5 9.7 24 9.2% +16.00.5[14.3, -10.5] Heterogeneity: Tau" = 16.52; Chi" = 11.60, df = 4 (P = 0.02); P = 66% Test for overall effect Z = 61.0 (P < 0.00001) 2.12 Inclusion of SCA on Hydroxyurea A+Biltagi M 2020 87 12.2 139 100.6 7.03 123 13.6% -13.60 [-15.98, -11.22] Ariginal M (Ventral Africa) 2019 83 13 112 98.8 10.7 377 13.5% -15.80 [-15.98, -11.22] Ariginal M (Ventral Africa) 2019 83 13 112 98.8 10.7 377 13.5% -15.80 [-11.75, 2.60] Lunt A 2016 (Cohort 1) 97.2 13.83 47 98.9 12.4 26 7.1% -1.70 [-8.76, 5.39] Wedgetourn CJ 2014 94.95 16.4 25 109.225 14.27 25 5.7% -14.27 [-22.80, -5.76] Heterogeneity; Tau" = 10.74; Chi" = 33.65; df = 10 (P = 0.0002); P = 70%. Test for overall effect Z = 0.89 (P < 0.00001) Total (95% Cl) 667 1123 100.0% -11.69 [-14.24, -9.14] Heterogeneity; Tau" = 10.74; Chi" = 33.65; df = 10 (P = 0.670; P = 0%) Test for overall effect Z = 0.89 (P < 0.00001) Total (95% Cl) 667 1123 100.0% -11.69 [-14.24, -9.14] Heterogeneity; Tau" = 10.74; Chi" = 33.65; df = 10 (P = 0.670; P = 0%) Test for overall effect Z = 0.89 (P < 0.00001) Test for subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% Cl IV, Fix	Purohit 2016	84.4	11.5	99	91.75	15.2	99 1	1.7%	-7.35 [-11.10, -3.60]		
Heterogeneity: Tau ² = 18.62; Chi ² = 11.60, df = 4 ($P = 0.02$); P = 66% Test for overall effect Z = 5.10 ($P = 0.00001$) 2.1.2 Inclusion of SCA on Hydroxyurea Aribitagi M 2020 87 12.2 139 100.6 7.03 123 13.8% -13.60 [-15.98, -11.22] Ariginani M (Vectral Africa 2) 2019 83 13 112 98.8 10.7 377 13.5% -13.60 [-15.98, -11.22] Ariginani M (Vectral Africa 2) 2019 84.3 12.7 154 95.9 12.4 364 13.8% -11.60 [-13.98, -9.22] Lunf A 2016 (Cohord 2) 97.6 13.53 45 102.175 14.97 24 7.0% -4.56 [-11.75, 2.60] Lunf A 2016 (Cohord 1) 97.2 18.38 47 98.9 12.4 26 7.1% -17.0P (8.70, 5.39] Vedderburn CJ 2014 94.95 16.4 25 109.25 11.27 5 .5.7%, -14.27 [-2.28, 0.5.75] Subtolat (95% CI) 667 1123 100.0% -11.69 [-14.24, -9.14] Heterogeneity: Tau ² = 10.74; Chi ² = 33.65, df = 10 ($P = 0.0002$); P = 70% Test for overall effect Z = 6.85 ($P < 0.00001$) Total (95% CI) 667 1123 100.0% -11.69 [-14.24, -9.14] Heterogeneity: Tau ² = 10.74; Chi ² = 33.65, df = 10 ($P = 0.0002$); P = 70% Test for overall effect Z = 6.93 ($P < 0.00001$) Total (95% CI) 67 0.00001) Total (95% CI) 80.7 0.18, df = 1 ($P = 0.67$); I ³ = 0% EVU/FVC SCD Control Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI	Sylvester KP 2007 Subtotal (95% CI)	74.5	9.5	24 165	90.5	9.75	184 :	9.2% -1 39.0% -1	6.00 [-21.45, -10.55] 12.53 [-17.35, -7.72]	•	
2.1.2 Inclusion of SCA on Hydroxyurea A+Billagi M (2020 87 12.2 139 100.6 7.03 123 13.8% -13.60 [+5.96, -11.22] Arigliani M (WestAfrica & UK) 2019 84.3 12.7 154 95.9 12.4 364 13.5% -15.80 [+18.44, -13.16] Arigliani M (WestAfrica & UK) 2019 84.3 12.7 154 95.9 12.4 364 13.5% -15.80 [+18.44, -13.16] Arigliani M (WestAfrica & UK) 2019 84.3 12.7 154 95.9 12.4 364 13.5% -11.60 [+13.98, -9.22] Lunt A 2016 (Cohort 1) 97.2 18.38 47 96.9 12.4 364 13.5% -11.60 [+13.98, -9.23] Wedgetourn CJ 2014 94.95 16.4 25 109.225 14.27 25 5.7% -14.27 [+2.280, -5.78] Subtotal (95% CI) 522 939 61.0% -11.59 [-14.24, -9.14] Heterogeneity, Tau ² = 10.4%, Chi ² = 33.65, df = 10 (P = 0.0002); P = 70% Test for overall effect Z = 6.85 (P < 0.00001) Total (95% CI) 687 1123 100.0% -11.69 [-14.24, -9.14] Heterogeneity, Tau ² = 10.74; Chi ² = 33.65, df = 10 (P = 0.0002); P = 70% Test for overall effect Z = 6.89 (P < 0.00001) Test for subaroup differences: Chi ² = 0.18, df = 1 (P = 0.67); P = 0% EVUI/FVC SCD Control Mean Difference Mean Difference Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI Lunt A 2016 (Cohort 1) 94.7 9.5 47 98.5 6.62 26 7.0% -3.80 [-7.52, -0.08] Lunt A 2016 (Cohort 2) 96.2 9.92 45 9.72 7.77 24 5.4% -1.52 [-5.7, 2.73] Huterogeneity Chi ² = 28.00 (ff = 20.92 F = 71%, Subtotal (95% CI) 93.59 .65 25 100.32 13.42 25 2.3% -7.27 [+3.75, -0.78] Subtotal (95% CI) 93.59 .65 25 100.92 II.342 Subtotal (95% CI) 94.59 .91.79 .777 24 5.4% -4.52 [-5.77, 27.3] Huterogeneity Chi ² = 28.00 (ff = 20.92 P = 71%, Subtotal (95% CI) 93.59 .95 .91 .92 .92 P = 71%, Subtotal (95% CI) 93.59 .95 .91 .92 .92 P = 71%, Subtotal (95% CI) 93.59 .95 .91 .92 .92 P = 71%, Subtotal (95% CI) 93.59 .96 .90 .92 .92 P = 71%, Subtotal (95% CI) 94.59 .91 .92 .92 .92 .92 .92 .92 .92 .92 .92 .92	Heterogeneity: Tau ² = 18.62; Chi ² = Test for overall effect $Z = 5.10$ (P <	11.60, df = 4 0.00001)	4 (P = 0.0)2); l²=	66%						
A+Bitagi M 2020 87 12.2 139 100.6 7.03 123 13.6% -13.60 [+13.9, -13.2] Arigliani M (West Africa & UK) 2019 84.3 12.7 154 95.9 12.4 364 13.8% -15.80 [+13.4, -13.6] Arigliani M (West Africa & UK) 2019 84.3 12.7 154 95.9 12.4 364 13.8% -16.80 [+13.6], -13.6] Arigliani M (West Africa & UK) 2019 84.3 12.7 154 95.9 12.4 364 13.8% -16.80 [+13.6], -13.6] Arigliani M (West Africa & UK) 2019 84.3 12.7 154 95.9 12.4 364 13.8% -16.80 [+13.6], -13.6] Arigliani M (West Africa & UK) 2019 84.3 12.7 154 95.9 12.4 364 13.8% -16.80 [+13.6], -13.6] Unt A 2016 (Cohort 1) 97.2 18.38 47 96.9 12.4 26 7.1% -1.70 [+7.76, -5.3] Wedderburm CJ 2014 94.95 16.4 25 109.225 14.27 25 5.7% -14.27 [+2.2.80, -5.76] Heterogeneity, Tau" = 10.4% Chi" = 20.95, df = 5 (P = 0.0006); P = 76% Test for overall effect Z = 6.85 (P < 0.00001) Total (95% Cl) 687 1123 100.0% -11.69 [-14.24, -9.14] Heterogeneity, Tau" = 10.74; Chi" = 33.65, df = 10 (P = 0.0002); P = 70% Test for overall effect Z = 8.99 (P < 0.00001) Test for subaroup differences: Chi" = 0.18, df = 1 (P = 0.67); P = 0% FEV1/FVC FEV1/FVC Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% Cl III (-12.16) [-1.29 (-1.20 (-1	2.1.2 Inclusion of SCA on Hydroxy	irea									
Angliant M (Ventral Aurca 2019 83 13 112 988 10.7 377 13.5% -15.00 [H3.4,-13.16] Angliant M (Ventral Aurca 2019 843 12.7 154 95.9 12.4 284 13.8% -11.60 [-13.89, 9.27] Lunk 2016 (Cohort 2) 97.6 13.53 45 102.175 14.97 24 7.0% -45.61 [1.75, 2.60] Lunk 2016 (Cohort 2) 97.6 13.53 45 102.175 14.97 24 7.0% -45.61 [1.75, 2.60] Lunk 2016 (Cohort 2) 97.6 13.53 45 102.175 14.97 24 7.0% -45.61 [1.75, 2.60] Heterogeneity: Tau" = 10.44; Chi" = 20.95; df = 5 (P = 0.0006); P = 76% Test for overall effect Z = 8.95 (P < 0.00001) Total (95% CI) 687 1123 100.0% -11.69 [-14.24, -9.14] Heterogeneity: Tau" = 10.44; Chi" = 33.65; df = 10 (P = 0.0002); P = 70% Test for overall effect Z = 8.95 (P < 0.00001) Test for overall effect Z = 8.95 (P < 0.00001) Test for subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI IV, Fixed, 95% CI 3.2.1 Hydroxyurea A-Biltagi M 2020 91.21 9.28 139 96.7 2.27 123 38.3% -5.49 [-7.08, -3.90] Lunk 2016 (Cohort 2) 96.2 9.92 45 97.72 7.77 24 5.4% -1.52 [-5.7, 2.73] Huetarogeneity: Chi" = 38.65 25 100.92 13.42 25 2.3% -7.27 [-13.75, -0.79] Subtotal (95% CI) 96.5 9.90 47 - 20.92 F 21%.	Al-Biltagi M 2020	87	12.2	139	100.6	7.03	123 1	3.8% -1	3.60 [-15.98, -11.22]		
Start for the set of th	Arigliani M (Central Africa) 2019 Arigliani M (West Africa & LK) 2019	83	13	112	98.8 95.9	10.7	377 1	3.5% -1	5.80 [-18.44, -13.16] 11.60 [-13.98 -9.22]		
Lunk 2016 (Cohort 1) 97.2 18.38 47 98.8 12.4 26 7.1% -1.70 (P.79, 5.39) Weiderburn CJ 2014 94.95 16.4 25 109.225 14.27 25 5.7% -14.27 (P.29, 5.76) 939 61.0% -11.29 [-14.52, -8.06] Heterogeneily: Tau"=10.4%; Chi"= 30.95, df = 5 (P = 0.00026); P = 76% Test for overall effect Z = 6.95 (P < 0.00001) Total (95% Cl) 687 1123 100.0% -11.69 [-14.24, -9.14] Heterogeneily: Tau"= 10.74; Chi"= 33.65, df = 10 (P = 0.0002); P = 70% Test for overall effect Z = 0.99 (P < 0.00001) Test for overall effect Z = 0.99 (P < 0.00001) Test for overall effect Z = 0.99 (P < 0.00001) Test for overall effect Z = 0.99 (P < 0.00001) Test for overall effect Z = 0.99 (P < 0.00001) Test for overall effect Z = 0.99 (P < 0.00001) Test for overall effect Z = 0.99 (P < 0.00001) Test for subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% Cl IV,	Lunt A 2016 (Cohort 2)	97.6	13.53	45 10	2.175	14.97	24	7.0%	-4.58 [-11.75, 2.60]		
Treduction (C 2011) 9:3/5 10:4.20 14:27 20 5.7% -14:27 [-22:80, -57/3] Heterogeneity: Tau" = 10:41; Chi" = 20:95; df = 5 (P = 0.0008); P = 76% 522 939 61:0% -11:29 [-14:52, -8:06] Test for overall effect Z = 6.85 (P < 0.00001)	Lunt A 2016 (Cohort 1)	97.2	18.38	47	98.9	12.4	26	7.1%	-1.70 [-8.79, 5.39]		
Heterogeneity: Tau ² = 10.44; Chi ² = 20.95, df = 6 (P = 0.0008); P = 76% Test for overall effect Z = 0.85 (P < 0.00001) Total (95% Cl) Test for overall effect Z = 0.89 (P < 0.00001) Test for subaroup differences: Chi ² = 0.18, df = 1 (P = 0.67); P = 0% Test for subaroup differences: Chi ² = 0.18, df = 1 (P = 0.67); P = 0% Test for subaroup differences: Chi ² = 0.18, df = 1 (P = 0.67); P = 0% Test for subaroup differences: Chi ² = 0.18, df = 1 (P = 0.67); P = 0% Test for subaroup differences: Chi ² = 0.18, df = 1 (P = 0.67); P = 0% Test for subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% Cl IV, Fixed, 95\% Cl	Subtotal (95% CI)	94.95	16.4	20 10 522	9.225	14.27	939	5.7% - 61.0% -	14.27 [-22.80, -5.75]	•	
SCD Control Mean Difference Mean Difference Mean Difference Study or Subgroup SCD Control Mean Difference IV, Fixed, 95% CI IV, Fixed, 95% CI Study or Subgroup Mean SD Total Meing SD Total Meing SD IV, Fixed, 95% CI IV, Fixed, 95% CI LuntA 2016 (Cohort 1) 94.7 95.5 66.2 26 7.0% -3.80 (F - 5.7, 2.7) IV Veidedrunc U 2014 93.65 25 10.09.13.42 2.5 2.5% CI IV, Fixed, 95% CI LuntA 2016 (Cohort 2) 96.2 9.02.2 10.32 2.3% - 7.27 (F 3.75, -0.78) IV IV Subtotal (95% CI) 256 198 53.0% - 4.94 (-6.30, -3.59) IV IV	Heterogeneity: Tau ² = 10.44; Chi ² = Test for overall effect: Z = 6.85 (P <	20.95, df = 6 0.00001)	5 (P = 0.0	0008); I ²	= 76%						
Heterogeneity: Tau"= 10.74; Chi" = 33.65; df = 10 (P = 0.0002); P = 70% Test for overall effect Z = 0.99 (P < 0.00001)	<td>Total (95% CI)</td> <td></td> <td></td> <td>687</td> <td></td> <td>1</td> <td>123 1</td> <td>. %0.00</td> <td>11.69 [-14.24, -9.14]</td> <td>•</td>	Total (95% CI)			687		1	123 1	. %0.00	11.69 [-14.24, -9.14]	•
Test for overall effect 2 = 0.99 (P < 0.00001) Total for subaroup differences: Chi ² = 0.18, of = 1 (P = 0.67), P = 0% FEV1/FVC SCD Control Mean Difference Mean Difference SUdy or Subgroup Mean SD Total Mean SD Total Mean Difference Al-Biltagi N2020 91.21 9.28 139 96.7 2.27 123 38.3% -5.49 [-7.08, -3.90] Image: Colspan="2">Image: Colspan="2">Image: Colspan="2">Total Mean Difference Mean Difference JunitA 2016 (Cohort 1) 94.7 9.5 6.62 26 7.0% -3.80 [-7.52, -0.08] Image: Colspan="2">Image: Colspan="2">Image: Colspan="2">Image: Colspan="2">Total Weight colspan="2">Colspan="2">Colspan="2" LunitA 2016 (Cohort 2) 96.2 97.72 7.77 24 5.4% -1.52 [-5.77, 2.73] Image: Colspan="2"	Heterogeneity: Tau ² = 10.74; Chi ² =	33.65, df = 1	10 (P = 0	.0002);	F= 70%					-20 -10 0 10 20	
SEV1/FVC SCD Control Mean Difference Mean Difference Mean Difference Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI IV, Fixed, 95% CI J.2.1 Hydroxyurea Ax-Biltagi M 2020 91.21 9.28 139 96.7 2.27 123 38.3% -5.49 [-7.08, -3.90] Image: Control M 2016 (Cohort 1) 94.7 95.5 6.62 26 7.0% -3.80 [-7.52, -0.08] Image: Control M 2016 (Cohort 2) 96.2 9.92 45 97.72 7.77 24 5.4% -1.52 [-5.77, 2.73] Image: Control M 2016 (Cohort 2) Image: Control M 2016 (Cohort 2) 96.5 256 100.82 13.42 25 2.3% -7.27 [-1.375, -0.78] Image: Control M 2016 (Cohort 2) Image: Controt 2) Ima	Test for overall effect Z = 8.99 (P < Test for subgroup differences: Chi ²	0.00001) = 0.18, df=	1 (P = 0.	67), l² =	0%					Favours (experimental) Favours (control)	
SCD Control Mean Difference Mean Difference Mean Difference 3.2.1 Hydroxyurea Al-Biltagi M 2020 91.21 9.26 139 96.7 2.27 123 38.3% -5.49 [-7.08, -3.90] Image: Control Mean Difference Image: Contro	FEV1/FVC										
SCD Control Mean Difference Mean Difference 3.2.1 Hydroxyurea Al-Biltagi M 2020 91.21 9.28 139 96.7 2.27 123 38.3% -5.49 [-7.08, -3.90] Image: Control Mean Difference Image: Control Mean Difference Mean Difference<	99999999999999999999999999999999999999	1111		1 spec	marcas					Contract and Contract of Contract	
Statuy of subgroup Mean Statuy of subgroup Mean Statuy of version IV, Fixed, 95% CI IV, Fixed, 95% CI Al-Biltagi M 2020 91.21 9.28 139 96.7 2.27 123 38.3% -5.49 [7.08, -3.90] Image: Comparison of the co	Study or Subarrow	SCD	Tota!	C	ontrol	Total	Maint	Mean	Difference	Mean Difference	
Al-Billagi M 2020 91.21 9.28 139 96.7 2.27 123 38.3% -5.49 [-7.08, -3.90] LuntA 2016 (Cohort 1) 94.7 9.5 47 98.5 6.62 26 7.0% -3.80 [-7.52, -0.08] LuntA 2016 (Cohort 2) 96.2 9.92 45 97.72 7.77 24 5.4% -1.52 [-5.77, 2.73] Wedderburn CJ 2014 93.65 9.65 25 100.92 13.42 25 2.3% -7.27 [-1.375, -0.79] Subtotal (95% CI) 256 9.67 25 100.92 13.42 15 2.3% -7.27 [-1.375, -0.79] Hoterwareneity Chiller 2 9.0 df = 2 (-0.9 - 1	Study of Subgroup Mea	an SD	otal	mean	SD	rotal	weigh	t IV,	Fixed, 95% CI	IV, Fixed, 95% CI	
Lunt A 2016 (Cohort 1) 94.7 9.5 47 98.5 6.62 26 7.0% -3.80 (7.52, -0.08) Lunt A 2016 (Cohort 2) 96.2 9.92 45 97.72 7.77 24 5.4% -1.52 (-5.77, 2.73) Wedgerburn CJ 2014 93.65 9.65 25 100.92 13.42 25 2.3% -7.27 [-13.75, -0.78] Subtotal (95% CI) 256 198 53.0% -4.94 [-6.30, -3.59] Heterogeneity Chill - 3.80 df = 3.0P - 12%	Al-Biltadi M 2020 91 1	1 9.28	139	96.7	2 27	123	38.3%	-5.49	1-7 08 -3 901	-	
Lunt A 2016 (Cohort 2) 96.2 9.92 45 97.72 7.77 24 5.4% -1.52 [-5.77, 2.73]	Lunt A 2016 (Cohort 1) 94	.7 9.5	47	98.5	6.62	26	7.0%	-3.80	[-7.52, -0.08]	-	
Wedderburn CJ 2014 93.65 9.65 25 100.92 13.42 25 2.3% -7.27 [-13.75, -0.79] Subtotal (95% CI) 256 198 53.0% -4.94 [-6.30, -3.59] ↓ Heterongeneity Chil= 2.90 of = 3 (2 ⊂ 0.29) (2 ⊂ 11%	Lunt A 2016 (Cohort 2) 96	2 9.92	45	97.72	7.77	24	5.4%	-1.5	2 [-5.77, 2.73]	+	
Subtrance (co.c.) 200 100 0.00 4.00 [0.00] (0.00]	Wedderburn CJ 2014 93.6 Subtotal (95% CI)	9.65	25 1	00.92	13.42	25	2.3%	-7.27	-13.75, -0.79]	-	
1 = 0 = 0 = 0 = 0, $M = 0 = 0 = 0 = 0 = 0 = 0 = 0 = 0 = 0 =$	Heterogeneity Chi ² = 3.80 df = 1	3 (P = 0.29	250	96		130	55.09	-4.94	[.0.00, -0.00]	· · · · · ·	

Wedderburn CJ 2014 Subtotal (95% CI)	93.65	9.65	25 256	100.92	13.42	25 198	2.3% 53.0%	-7.27 [-13.75, -0.79] -4.94 [-6.30, -3.59]	_	
Heterogeneity: Chi ² = 3.8	30, df = 3 (P = 0.2	8); I ² =	21%						
Test for overall effect Z =	= 7.15 (P <	0.000	01)							
3.2.2 Non Hydroxyurea										
Hijazi 2004 (SS)	102.6	7.3	21	103.5	9.8	17	3.1%	-0.90 [-6.51, 4.71]		-
Pianosi P 1993 (ACS)	84	5	10	87	4	22	7.8%	-3.00 [-6.52, 0.52]		-
Pianosi P 1993 (SS)	88	6	11	87	4	22	6.3%	1.00 [-2.92, 4.92]		+
Purohit 2016	101.77	7.6	99	99.65	8.5	99	19.3%	2.12 [-0.13, 4.37]		+
Sylvester KP 2007 Subtotal (95% CI)	103.75	5.25	24 165	103.5	5.5	24 184	10.5% 47.0%	0.25 [-2.79, 3.29] 0.50 [-0.94, 1.94]		1
Heterogeneity: Chi ² = 6.1	2, df = 4 (P = 0.1	9); ² =	35%						
Test for overall effect Z =	= 0.68 (P =	0.50)								
Total (95% CI)			421			382	100.0%	-2.38 [-3.37, -1.40]		
Heterogeneity: Chi ² = 39	.06, df = 8	(P < 0.	00001); I ² = 809	16				100 10	1 10 100
Test for overall effect Z =	= 4.74 (P <	0.000	-100 -50 Favours (experimental	I Favours [control]						

Test for subgroup differences: Chi² = 29.14, df = 1 (P < 0.00001), l² = 96.6%

Figure 6: forest plots of FEV1, FVC and FEV1/FVC ratio stratified by SCA children on hydroxyurea



FEV1

		SCD		C	ontrol			Std. Mean Difference	e Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95%	CI IV, Random, 95% CI
1.2.1 HU-									
Hijazi 2004 (SS)	86.7	9.2	8	88.8	13.5	13	10.7%	-0.17 [-1.05, 0.7	2]
Pianosi P 1993 (ACS)	84.71	10.2	11	87.12	12.4	88	20.5%	-0.20 [-0.82, 0.4	3]
Purohit 2016	82.2	9,4	85	89.1	9.8	54	57.7%	-0.72 [-1.07, -0.3]	7] 🛨
Subtotal (95% CI)			104			155	88.8%	-0.48 [-0.87, -0.10	0] •
Heterogeneity: Tau ² = (0.04; Chi ²	= 2.8	2, df = 1	2 (P = 0.	24); P	= 29%			
Test for overall effect: 2	2 = 2.45 (P = 0.	01)						
1.2.2 HU+									
Al-Biltagi M 2020	84	18	10	88	10	11	11.2%	-0.27 [-1.13, 0.5	91
Subtotal (95% CI)			10			11	11.2%	-0.27 [-1.13, 0.59	9j 🔶 🔶
Heterogeneity: Not app Test for overall effect: 2	licable Z = 0.61 (P = 0.	54)						e - 200
Total (95% CI)			114			166	100.0%	-0.50 [-0.79, -0.21	1] 🔶
Heterogeneity: Tau ² = (0.01: Chi ²	= 3.1	9. df = 3	3(P = 0)	36): P	= 6%		•	· · · · · · · · · · · · · · · · · · ·
Test for overall effect: 7	7 = 3 36 (P = 0	(8000						-4 -2 0 2 4
Test for subgroup differ	ences: C	hi² = (0.20, df	= 1 (P =	0.65).	, l² = 04	6		Favours [experimental] Favours [control]
VC									
ve									
Study or Subgroup	Mean	SCD	Total	Mean	ontrol	Total	Weight	IV, Random, 95%	ce Std. Mean Difference CI IV, Random, 95% CI
2.2.1 HU-									
Hijazi 2004 (SS)	83.5	9.7	8	85.5	12.4	13	22.9%	-0.17 [-1.05, 0.	72]
Pianosi P 1993 (ACS) Purobit 2016	82.83	11.3	11	86.35	13.5	88	25.8%	-0.26 [-0.89, 0.	37]
Subtotal (95% CI)	61.9	0.0	104	93	7.0	155	76.8%	-0.71 [-1.71, 0.	30]
Heterogeneity: Tau ² = 0 Test for overall effect: Z	.68; Chi² = 1.38 (P	= 16.3 = 0.1	26, df= 7)	2 (P = 0	0.0003); l² = 8	8%		
2.2.2 HU+									
Al-Biltagi M 2020	89	15	10	89	7	11	23.2%	0.00 [-0.86, 0.	86]
Subtotal (95% CI)			10			11	23.2%	0.00 [-0.86, 0.	86]
Test for overall effect: Z	= 0.00 (P	= 1.0	10)						
		0.01000							
Total (95% CI)			114			166	100.0%	-0.54 [-1.42, 0.	33]
Heterogeneity: Tau ² = 0	.67; Chi [#]	= 21.5	55, df =	3 (P < 0	0.0001); l ² = 8	6%		-4 -2 0 2 4
Test for subgroup differ	= 1.22 (F ences: C	= 0.2 hi ² = 1	1.10, df	= 1 (P =	0.29)	, I ² = 8.	9%		Favours [experimental] Favours [control]
EV1/FVC									
		SCD.		0	ontrol			Moon Difforence	Magn Difference
Study or Subgroup	Maan	SD	Total	Mean	SD	Total	Weight	IV Fixed 95% CI	IV Fixed 95% CI
3.2.1 HU-	ntedii	50	rotal	mean	50	IVId	mergint	14, 1 IACU, 20 /0 CI	14, 11ACG, 00 /0 CI
Hijazi 2004 (SS)	104 3	6.9	8	102.3	84	13	8 6%	2 00 [-4 61 8 61]	+-
Dianoci D 1002 (ACC)	04.0	0.0 E	10	002.0	6	14	17.0%	4 00 [9 71 0 71]	
Pidilusi P 1993 (ACS)	100.04		10	100 00	0	0.0	11.070	-4.00 [-0.11, 0.11]	
Subtotal (95% CI)	102.24	1.1	29	100.96	9.2	112	41.2%	-0.75 [-3.78, 2.28]	•
Heterogeneity: Chi ² = 3	.14. df = 1	2 (P =	0.21):	² = 36%					
Test for overall effect: Z	. = 0.49 (1	P = 0.	63)		60				
3.2.2 HU+									
Al-Biltagi M 2020	93.7	8.2	85	88.4	6.9	54	58.8%	5.30 [2.77, 7.83]	
Subtotal (95% CI)	Each!		85			54	58.8%	5.30 [2.77, 7.83]	•
Heterogeneity: Not app Test for overall effect: Z	licable : = 4.10 (l	P < 0.	0001)						
Total (95% CI)			114			166	100.0%	2.81 [0.86, 4.75]	•
Heterogeneity: ChP = 1	2 17 df =	3/P	= 0.007) 2 = 7	5%				
Test for overall effect: 7	= 2 83 /	0 = 0	0051	,I	v /v:				-100 -50 0 50 100
Test for subgroup differ	ences: C	hi ² = 9).02. df	= 1 (P =	0.003	3), ² =	88.9%		Favours [experimental] Favours [control]

Figure 7: forest plots of FEV1, FVC and FEV1/FVC ratio in SCA children with ACS on hydroxyurea