# Differences in lung function between children with sickle cell anemia from West Africa and Europe

## Online data supplement

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## INTRODUCTION

Nigeria has the highest burden of SCA worldwide, with an estimated incidence of 85.000 neonates with SCA born per year.[1]

## METHODS

### Study design

Pediatric patients with SCA were enrolled at two tertiary care hospitals, respectively, in Nigeria and the United Kingdom (UK). We acknowledge there may be differences between these two centers. At the Evelina London Children's Hospital, UK, children are generally referred to the service at very young age, following diagnosis through newborn screening, from hospitals in South East London area. They receive multidisciplinary team care and advanced medical care with nationally agreed standards of care.[2] The costs of medical care are fully covered by the National Health Service. At the Barau Dikko Teaching Hospital, Kaduna, Nigeria, however, patients are generally diagnosed through



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haemoglobin electrophoresis, following hospital admission at the time of the first clinical manifestations (generally between 7 months and 2 years of age). Some of the patients may be referred at older age from rural clinics or other hospitals in the urban area of Kaduna city. Nevertheless, a minority with a known family history of SCA are diagnosed early during the first months of life. Most of the patients followed at this hospital are from the urban area of Kaduna city and with only a minority coming from rural areas of Kaduna state. While the Nigerian National Health Insurance Scheme covers the costs of medical care for some patients (although the insurance programme is currently under expansion), the majority are out of pocket expenses. Patients receive the same prophylaxis and similar frequency of follow-up consultations and blood tests assessments as those living in the UK,[2] though access to advanced medical care is more limited due to differences in healthcare resources. Availability of hydroxyurea at this centre, which was very limited at the time of data collection, has been implemented over the last two years.

While the standards of care for SCA patients in the UK are homogeneous across the country, this is not the case for Nigeria, where only a minority of patients have access to tertiary care[3], independent of disease severity. Patients living in remote rural areas of Nigeria, as well as those of low socio-economic status, may not access the required specialist care for SCA. As a consequence, they could have higher rates of SCA-related comorbidities compared to Nigerian patients followed at a tertiary care center, enrolled in this study.

Local controls were recruited in 4 schools in Kaduna state, Nigeria (one private and one public urban school in Kaduna city, two rural schools in Kaduna state within 30 km



Arigliani M, *et al. Thorax* 2019; 74:1154–1160. doi: 10.1136/thoraxjnl-2019-213717

from Kaduna city), that were chosen as they had previously collaborated with the local hospital for health campaigns. In each school the principal investigator presented the study to the school director. A formal authorization was requested for participation. No remuneration was offered for being enrolled in the study.

## Power of study

Comparison of data from 64 pediatric patients with SCA living in Nigeria and 64 patients living in the UK would provide 80% power at the 5% significance level (two tails) to detect a mean difference of 0.5 $FEV_1$ z-scores between the two groups, with a SD = 1 in each group.[4,5] There was over recruitment as all individuals with SCA who were seen at the specialist clinic in the days planned for the data collection were proposed to take part to the study. For controls we needed to include at least 150 boys and 150 girls to validate the GLI-reference values for Nigeria.[5] We enrolled all the individuals whose parents had given their consent to spirometry evaluation.

## Assessments

Socio-economic status was investigated using a modified version of the Family Affluence Scale (FAS)[6], based on collated score for number of computers (1 point for each computer up to 3 points), motorcycle (1 point) or car (2 points) ownership, and whether the child had his own bedroom (1 point).

Age was recorded with one decimal accuracy. Standing height was measured to the nearest mm using a stadiometer with a movable right angle headpiece (*Leicester stadiometer, Seca, Hamburg, Germany*). Weight was measured in light clothing and no shoes (*Seca digital scales, Germany*).



Arigliani M, *et al. Thorax* 2019; 74:1154–1160. doi: 10.1136/thoraxjnl-2019-213717

The principal investigator performed 95% of spirometry tests; coinvestigators experienced in spirometry performed the remainder. Children performed two up to seven forced expiratory maneuvers standing upright with nares occluded.

## RESULTS

Distribution by age group of patients with SCA and controls included in the final analysis is shown in table E1.

**Table E1.** Distribution of patients with sickle cell anemia (SCA) from Nigeria (n. 154) and the UK (n. 101) and of apparently healthy controls in Nigeria (n. 364) by age group

| Age (yr) group | 6-10 | 11-14 | 15-18 |
|---|---|---|---|
| % of SCA patients Nigeria | 48.8 | 33.7 | 17.5 |
| % of SCA patients UK | 36.6 | 49.5 | 13.9 |
| % of controls Nigeria | 58.1 | 36.2 | 5.7 |

Information regarding socio-economic status of participants and some environmental exposure relevant to respiratory health are presented in table E2.

**Table E2.** Socio-economic status, as indicated by modified Family Affluence Scale (FAS) score,[6] and environmental exposures in 101 pediatric patients with sickle cell anemia (SCA) from the UK, 154 from Nigeria, and 318 healthy controls from Nigeria.

| | SCA UK | SCA NIG | Controls NIG |
|---|---|---|---|
| FAS* | | | |
| High FAS (5-6) | 20% | 2% | 7% |
| Medium FAS (2-4) | 63% | 46% | 41% |



Arigliani M, *et al. Thorax* 2019; 74:1154–1160. doi: 10.1136/thoraxjnl-2019-213717

| | | | |
|---|---|---|---|
| Low FAS (0-1) | 17% | 52% | 52% |
| Tobacco smoke exposure | 12% | 9% | 11% |
| Exposure to indoor biomass smoke | 0% | 49% | 67% |

*Definition of abbreviations*: FAS: Family Affluence Scale

* FAS score is based collated score for number of computers (0-3 points), motorcycle (1 point) or car (2 points) ownership, and whether the child had his own bedroom (1 point). FAS score was available only for 35 SCA patients in the UK.

Our findings showed a difference of mean $FEV_1$ between the UK and Nigerian SCA group (0.41 z-scores, 95% CI 0.15 to 0.66) slightly lower than hypothesized according to literature data (0.5).[4,5]. A post-hoc power analysis showed that assuming a difference of 0.4 z-scores, a significance level of 5% and a two-sided test, with the enrolled sample size (101 SCA patients in the UK and 154 in Nigeria) the statistical power is equal to 87.6%.

The saturated models of the logistic regression for restrictive spirometry pattern and linear regression for $zFEV_1$ and zFVC are presented in table E3 and E4.

**Table E3.** Saturated model of multivariable logistic regression for restrictive spirometry pattern (vs normal) in 223 pediatric patients with sickle cell anemia (SCA) from Nigeria and the UK.

| | Restrictive spirometry pattern¶ | |
|---|---|---|
| **Predictor** | **Crude OR (95% CI)** | **Adjusted OR (95% CI)** |
| Residency in Nigeria (vs UK) | 2.4 (1.2 to 4.7)* | 2.6 (1.2 to 5.8)* |
| Age, yr | 1.2 (1.1 to 1.3)** | 1.2 (1.1 to 1.4)** |
| zBMI < -2 | 2.9 (1.4 to 5.8)* | 2.4 (1.1 to 5.2)* |
| Previous acute chest syndrome† | 1.6 (0.9 to 3.0) | 1.7 (0.8 to 3.4) |
| Male sex | 1.1 (0.6 to 2.0) | 1.2 (0.6 to 2.4) |
| No hydroxyurea | 2.0 (0.8 to 5.1) | 1.9 (0.7 to 5.2) |

| | | |
|---|---|---|
| A least 3 pain crises in the last year | 1.1. (0.6 to 2.0) | 0.8 (0.4 to 1.5 |

*Definition of abbreviations*: zBMI = z-score for body mass index; zBMI values based on World Health Organization growth charts.[7]

Spirometry z-scores based on Global Lung Function Initiative 2012 equations for African Americans.[8]

¶Restrictive spirometry pattern = FVC < LLN and $FEV_1$/FVC ≥ LLN; Adjusted $R^2$ = 0.12

†Fever and/or respiratory symptoms, plus a new pulmonary infiltrate on a chest x-ray.[9]

*$P$ < 0.05; **$P$ < 0.001

**Table E4.** Saturated model of multivariable linear regression models for $FEV_1$ and FVC z-scores in 255 patients with sickle cell anemia (SCA) aged 6-18 years from Nigeria (n. 154) and the UK (n. 101).

| Predictor | $FEV_1$ z-score¶ B (95% CI) | FVC z-score¶ B (95% CI) |
|---|---|---|
| Residency in Nigeria | -0.41 (-0.66 to -0.15)* | -0.53 (-0.78 to -0.28)** |
| Male sex | 0.26 (0.37 to 0.49)* | 0.18 (-0.04 to 0.40) |
| Age, yr | -0.09 (-0.12 to -0.05)** | -0.08 (-0.12 to -0.04)** |
| zBMI | 0.26 (0.16 to 0.36)** | 0.29 (0.19 to 0.36)** |
| No hydroxyurea | -0.27 (-0.59 to 0.04) | -0.33 (-0.70 to 0.02) |
| Previous acute chest syndrome † | -0.41 (-0.67 to -0.17)* | -0.33 (-0.60 to -0.11)* |
| At least 3 pain crises in the last year | 0.16 (-0.07 to 0.40) | 0.07 (-0.016 to 0.31) |

*Definition of abbreviations*: zBMI = z-score body mass index; zBMI values based on World Health Organization growth charts[7].

Spirometry z-scores based on Global Lung Function Initiative 2012 equations for African Americans.[8]

¶Adjusted $R^2$ 0.25 for $zFEV_1$ and 0.27 for zFVC

*$P$ < 0.05; **$P$ < 0.001

†Fever and/or respiratory symptoms, plus a new pulmonary infiltrate on a chest x-ray.[9]

Regarding the association between wasting (zBMI < -2) and lower lung function

outcomes in SCA patients, in a simple logistic regression model limited to the 154 SCA patients from Nigeria, wasting (zBMI < -2) had a borderline association with a restrictive spirometry pattern (OR 2.0, 95% CI 0.9 to 4.5, *P* = 0.05). Also among healthy Nigerian controls, though the frequency of a restrictive spirometry pattern was relatively low compared to SCA patients (8%, 29/364), wasting was associated with a 3.6-fold increased risk of restrictive spirometry (95% CI 1.4 to 9.0, *P* = 0.007).

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