BMI is an independent predictor of increase in lung function in children with sickle cell anemia

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A major cause of death in adults with SCD is cardiopulmonary disease. [1] Lung function assessment defined as low forced expiratory volume in 1 second (FEV1) % predicted is associated with earlier death in the general population, young adults with cystic fibrosis and young adults with SCA. [2] In a retrospective cohort study, a convenience sample (n=413) of children with sickle cell disease (8 to 18 years), demonstrated a longitudinal decline in FEV1% predicted (2.9 and 2.15% predicted in males and 2.95 and 2.43% predicted in females per year) with the most pronounced decline in the more severe form of anemia. [3] In one of the few studies evaluating BMI and its relationship to longitudinal lung function, Koumborulis et al. ~~but~~ did not reveal BMI as a significant risk factor for decline in FEV1% predicted (0.11; 95% CI -0.29 to 0.50, p=0.6.[4] Despite the extensive research demonstrating the relationship between BMI and lung function in children with cystic fibrosis and the relationship between lung disease and SCD related mortality, minimal research has been conducted to show the effects of BMI on lung function in children with SCD.

Our prior analysis in the Sleep and Asthma Cohort (SAC) study in an unselected cohort of children with sickle cell anemia (defined here as HbSS or HbSβ0 thalassemia) determined that age was the only risk factor for a decrease in FEV_1 % predicted.[5] Extending this analysis, we tested the hypothesis in the SAC cohort that BMI percentile was an independent predictor of FEV_1% predicted in children with sickle cell anemia. To calculate BMI percentiles, we used quantile regression to construct percentile growth curves using the Silent Cerebral Infarct Multi-Center Clinical Trial (SIT) as the reference population[6], as the BMI *z*-scores and percentiles from the World Health Organization (WHO) are based on mean anthropomorphic measurements for children without chronic illnesses, an inappropriate reference population. This version of BMI percentiles is specific to the sickle cell anemia population in the age range from 5 to 18 years old. We postulate that there will be a curvilinear effect of BMI percentile on FEV_1% predicted such that children with lower BMI percentile will have a greater change (increase) of FEV_1% predicted compared to children that are nutritionally replete and have a higher BMI percentile.

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A total of 182 participants in the SAC study had at least two spirometry evaluations in the age range of 5 to 18. The median age at first testing was 10.5 years (range 5.0-17.4 years), with an average follow up of 3.4 years (range 0.5-6.5 years) from baseline to endpoint. Previously in the SAC cohort, using a multivariable mixed model linear regression, age was the only predictor of FEV_1 % predicted, with a decline of 0.3% for every additional year of age (-0.30, 95% CI -0.56 to -0.05, p = .020).[5] Sex, asthma history, hemoglobin, reticulocyte count, white blood cell count,

incidence rate of severe acute pain, incidence rate of acute chest syndrome episodes, and hydroxyurea therapy were not associated with a decline in FEV_1 % predicted.

In the new multivariable mixed model, we used the same set of variables, adding only BMI percentile with both a linear and quadratic term to allow for the postulated curvilinear effect. In this modified model age and BMI percentile were significant. BMI percentile was found to be positively associated with FEV_1% predicted. The linear effect of BMI percentile is positive (0.21, 95% CI 0.06 to 0.35, p=0.006) while the quadratic term is negative (-0.001, 95% CI -0.003 to 0.000, p=0.046). Substantively, the positive linear term means that FEV_1% predicted increases with increasing BMI percentile; the negative quadratic term means that this effect declines as BMI percentile increases, Figure 1.
As in the previous study, age remained significant, with a 0.6% decrease in FEV_1% predicted for every additional year (-0.59; 95% CI -0.91 to -0.27, p<0.001). Similar to the prior analysis[5] without BMI percentile the following covariates were not associated with a decline in FEV1% predicted, asthma history (-2.97; 95% CI -6.62 to 0.69 , p= 0.11), hydroxyurea therapy (1.43; 95% CI -0.95 to 3.82, p=0.24), hemoglobin (0.56; 95% CI -0.84 to 1.97, p=0.43), reticulocyte count (0.10; 95% CI -0.21 to 0.42, p=0.51), white blood cell count (0.20; 95% CI -0.26 to 0.67, p=0.39), acute chest syndrome episode rate (-0.38; 95% CI -1.25 to 0.49, p=0.39), and incidence rate of severe acute pain (0.10; 95% CI -0.30 to 0.50, p=0.62) were not significant. Our results provide compelling support that increasing BMI in children with a low BMI may increase their FEV_1% predicted.

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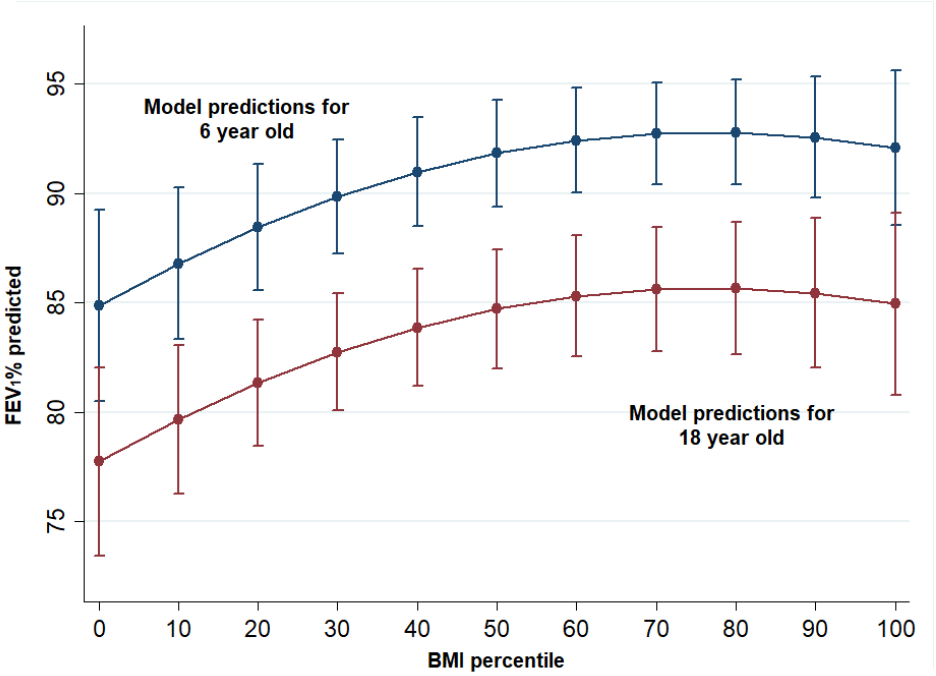

Figure 1. Predictions of FEV_1% predicted from a multivariable mixed model linear regression showing the effect of BMI percentile for ages 6 and 18, with 95% confidence limits. FEV_1% predicted increases as BMI percentile increases, peaks at 76.7%, after which it slowly declines as BMI percentile increases. As an example, at the 20th percentile of BMI, the predicted FEV_1% predicted for a 6-year-old is 88.5 compared to the predicted value of 81.3 for an18 year old. The difference of 7.2 in FEV_1% predicted is constant across BMI percentile.

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