WHAT’S KNOWN ON THIS SUBJECT: Children with sickle cell disease (SCD) have a higher basal metabolic rate, and have historically been underweight. In the general pediatric population, the average BMI percentile has been rising over the past 2 decades.

WHAT THIS STUDY ADDS: BMI percentiles for children with SCD in New England are higher than historically reported, mimicking the weight status in the general pediatric population. In children with SCD, higher hemoglobin levels increased the odds of being overweight and obese.

abstract

OBJECTIVE: Historically, many children and adolescents with sickle cell disease (SCD) were underweight. Treatment advances like hydroxyurea have been associated with improved growth. We hypothesized that increased hemoglobin (Hb) levels would be associated with increased weight status of children with SCD.

METHODS: Investigators at 6 institutions conducted a retrospective chart review of all patients aged 2 to 19 years of age for the calendar years 2007–2009. Height, weight, baseline Hb levels, demographic information, and select comorbidities were recorded from the most recent clinic visit. Overweight and obesity were defined as ≥85th and ≥95th BMI percentiles for age and gender, respectively, and underweight was defined as <5th BMI percentile.

RESULTS: Data were collected on 675 children and adolescents in 3 New England states. In this sample, 22.4% were overweight or obese, whereas only 6.7% were underweight. Overweight or obese status was associated with sickle genotypes other than Hb SS or Hb Sβ0 disease, and were associated with higher baseline Hb levels. Underweight individuals were more likely to be male, older, and have had at least 1 SCD-related complication. After adjusting for demographic factors, any SCD-related complication, SCD-directed treatments, and obesity-related conditions, there was a 36% increased odds of overweight/obesity for each 1 g/dL increase in baseline Hb levels.

CONCLUSIONS: Nearly one-quarter of children and adolescents with SCD in New England are overweight or obese. Longitudinal studies are needed to determine the impact of elevated BMI on the morbidity and mortality of both children and adults with SCD.

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KEY WORDS
BMI, sickle cell disease, children, obesity, overweight

ABBREVIATIONS
Hb—hemoglobin
SCD—sickle cell disease

Dr Chawla conceptualized and designed the study, and was involved in designing the collection instrument and drafting the initial manuscript and its revision; Dr Heeney was involved in the conceptualization of the study, Dr Sprinz aided in the data analysis, Drs Sprinz, Heeney, Usmani, and Pashankar coordinated and supervised data collection at their sites and analysis, and critically reviewed the manuscript; Dr Welch aided in the conceptualization of the study, designed the collection instrument, coordinated the data collection effort from the centers, and reviewed the final manuscript; Dr Kavanagh was involved in the analysis and interpretation of data, and drafting the initial manuscript and its revision, and all authors approved the final manuscript as submitted.

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Sickle cell disease (SCD) is the most common genetic disorder in the United States, affecting up to 100,000 individuals. SCD is associated with high morbidity and mortality, stemming from complications arising from vaso-occlusion, impaired immune function, and chronic hemolytic anemia. Historically, many children and adolescents with SCD were underweight, in part because of the high resting metabolic demands associated with the underlying chronic anemia. As a consequence, some providers have advocated for the use of modified growth curves for children with SCD.

SCD-directed treatments, including chronic transfusion programs and hydroxyurea, are increasingly used for children with SCD and have been associated with improved growth. Recently, 2 small single-center reports found that 20% to 25% of children with SCD were overweight or obese, joining the estimated 12.5 million US children and adolescents who are overweight and obese. Nationally, overweight and obese children are disproportionately Hispanic and non-Hispanic black, as are most individuals with SCD in the United States. These findings require further investigation, especially because the obesity-related complication of systemic hypertension has been associated with increased mortality among individuals with SCD. In addition, elevated BMI percentile could exacerbate comorbid conditions, such as avascular necrosis and asthma, which is present in approximately 25% and 30% of children with SCD respectively.

The purpose of this study was to determine the prevalence of underweight, normal weight, overweight, and obesity in a large multicenter, urban population of children with SCD. We hypothesized that children with higher baseline hemoglobin (Hb) levels, including those receiving hydroxyurea and chronic transfusions, were more likely to be overweight or obese. We also expected that a greater proportion of children who are overweight or obese will have conditions often related to obesity, namely sleep apnea and hypertension. Finally, we determined factors associated with overweight and obesity among the study population to identify possible subpopulation(s) at risk to propose future interventions and prevention measures.

METHODS
Data Collection
Data were collected from 6 member institutions of the New England Pediatric Sickle Cell Consortium: Boston Medical Center, Children’s Hospital Boston, Floating Hospital for Children at Tufts Medical Center, Hasbro Children’s Hospital, University of Massachusetts Medical Center, and Yale-New Haven Children’s Hospital. Investigators at each institution conducted a retrospective chart review of all patients aged 2 to 19 years of age followed at their institution for the calendar years 2007–2009. Institutional review board approval was obtained at each site.

Weight Status
The primary outcome of this study was weight status among children with SCD. We collected the height and weight recorded in the most recent clinic visit within our period of interest. We used age- and gender-specific definitions of BMI percentile, based on the 2000 Centers for Disease Control and Prevention growth charts. Overweight and obesity were defined as ≥85th and ≥95th BMI percentiles for age and gender, respectively. Underweight status was defined as <5th BMI percentile for age and gender.

Independent Variables
The key independent variable in our multivariate models is baseline Hb level, which was collected via retrospective chart review. We defined baseline Hb level as the steady-state level determined by the child’s primary hematologist and provided in the clinic note at the time of anthropometric measurement. We also collected the data on potential covariates of weight status among children with SCD: (1) demographic information: age at the most recent clinic visit, gender, ethnicity, type of insurance; (2) sickle genotype; (3) history of SCD-related complications: acute chest syndrome, avascular necrosis, frequent pain episodes, priapism, splenic sequestration, and stroke; (4) SCD-directed treatments: chronic transfusions and hydroxyurea; and (5) obesity-related complications: hypertension and obstructive sleep apnea.

Data Analysis
Data were entered into Microsoft Excel 2003 (Redmond, WA) at each institution, deidentified, and compiled centrally. Statistical analyses were performed using SAS (version 9.1; SAS Institute Inc, Cary, NC). Descriptive statistics were performed to describe the demographic and clinical features of the study sample with respect to sickle genotype to reflect severity of disease: Hb SS and Hb Sβ⁰ versus Hb SC, Hb Sβ⁺, Hb SO and hereditary persistence of Hb F. In addition, we examined bivariate associations between weight status and the independent variables listed previously, using χ² for categorical variables and t tests for continuous variables. We used logistic regression models to determine the relationship between Hb and overweight/obesity, with normal-weight subjects with SCD serving as controls. The overweight and obesity groups were combined for these analyses because there were no significant differences between these groups with respect to major predictor (Hb) or key demographic variables.
RESULTS

Data were collected on 675 children and adolescents with SCD aged 2 to 19 years from 6 New England institutions, with contributions from each institution ranging from 26 to 192 subjects. We eliminated 4 subjects for implausible BMI percentiles and 5 subjects for missing data for height or weight. There were no significant differences in baseline Hb level, age, genotype, or BMI percentile by institution (data not shown). Approximately 60% and 26% of the population had Hb SS disease and Hb SC disease, respectively; the remainder had Hb Sβ0, Hb Sβ+, and other sickle Hb variants. The mean age was 10.8 years, most were black or African American, and nearly two-thirds were publicly insured (Table 1). At least 1 SCD-related complication occurred in more than 60% of subjects in this sample, and in 80% of those with Hb SS and Hb Sβ0 disease. At the time of chart review, nearly one-third of subjects were taking hydroxyurea and 9% were chronically transfused. Obstructive sleep apnea and hypertension affected less than 7% and 2% of the sample, respectively.

In this sample of children and adolescents with SCD, 22.4% were overweight or obese (Table 2). Most subjects who were overweight or obese had sickle genotypes other than Hb SS or Hb Sβ0 disease. In bivariate analyses, subjects with SCD who were overweight and obese were more likely to have higher baseline Hb levels and less likely to be on hydroxyurea compared with normal-weight and underweight subjects. In addition, 6.7% of subjects were underweight, of whom three-quarters had Hb SS or Hb Sβ0 disease. Underweight individuals were more likely to be male and older compared with children who had normal or elevated BMI percentiles. A history of any SCD-related complication was more prevalent among underweight children, but only priapism was statistically significant compared with normal and overweight/obese subjects (P = .046). Weight status did not differ by race or insurance status. We did also not find an association between weight status and obstructive sleep apnea or hypertension.

By using logistic regression analyses, we explored the relationship between Hb and overweight/obese status, using normal-weight individuals with SCD as the control group (Table 3). In the unadjusted model, there was a 38% increased odds of overweight/obesity for each 1 g/dL increase in baseline Hb levels. Adjusting for demographic factors, SCD-related factors (any SCD-related complication and SCD treatments) and obesity-related conditions (obstructive sleep apnea and hypertension) caused little change in the odds of overweight/obesity (odds ratio 1.36, 95% confidence interval 1.20–1.56).

DISCUSSION

To our knowledge, this is the first multicenter study to demonstrate elevated BMI percentiles among children with SCD in the United States in the past decade, with 22.4% being overweight or obese. In our sample, ∼3 times as many children with SCD were overweight or obese than were underweight. We also found higher baseline Hb levels significantly increased the odds of an elevated BMI percentile. A single-center cohort study among African American children with SCD found that at ages 6 to 11 years and 12 to 18 years, 18.9% and 24.7% of children were overweight or obese, respectively, which are comparable to our results. In that report, adolescent girls were more likely to be overweight or obese than their male counterparts; however, we did not find this association in our population. These findings argue against using modified growth curves for children with SCD.

Overweight and obesity may have a negative impact on health and quality of life of both children and adults with SCD. Elevated BMI percentile is associated with the development of obstructive sleep apnea,18,19 which in turn increases the risk of nighttime hypoxia and induction of acute pain episodes in children with SCD.20 Obesity is also implicated in the development of hypertension,21,22 which is independently associated with mortality among those with SCD.15 In this study, we did not find an association between elevated BMI percentile and obstructive sleep apnea or hypertension; however, the presence of these conditions were drawn from problem lists, and blood pressures and sleep studies were not explicitly captured. Also, these conditions are strongly related in adults with obesity, and may develop in these children over time.

Recent advances may be contributing to higher BMI percentiles in children with SCD. Hydroxyurea and chronic transfusion therapy began to be increasingly used in children with SCD in the past decade, especially among those with Hb SS or Hb Sβ0.23–28 However, these interventions are used to increase baseline Hb levels, which is a concern, given the findings of a positive association between higher Hb levels and weight status in this study. Although one-third of children who were overweight or obese in this study were receiving these treatments, we did not find a significant association between
them and weight status in our multivariate models; however, we did not collect data on the duration of either treatment as part of our chart review. Prospective studies need to be conducted on weight status among children receiving these treatments to further define this relationship.

SCD has historically been associated with growth delay or failure in the United States; therefore, children with SCD and their families are counseled about the need for increased energy intake (ie, nutrition) to prevent growth problems, including being underweight. Furthermore, current guidelines recommend that health care providers counsel patients and families about the risks of strenuous exertion, and caution patients from engaging in competitive athletics, given the possibility of dehydration and triggering acute sickle pain crises. As more children in the United States benefit from the increased use of SCD-directed therapies and mimic the lifestyle of their non-SCD peers, they may experience similar trends of increased weight because of the imbalance between energy intake and physical activity.

There were several limitations to this study. First, this study was a cross-sectional analysis of BMI percentile among children with SCD; therefore, we cannot comment on a causal relationship between Hb and weight status or trends in BMI percentile over time. Second, data were based on all children with SCD aged 2 to 19 years receiving care at academic institutions in New England. These findings may not be generalizable to the US population. Children in the New England states represented in this study (CT, MA, and RI) have lower BMI percentiles than the US average; therefore, our data may underestimate the prevalence of overweight and obesity among children with SCD in other areas of the United States. Third, we included only child-specific factors in our models of overweight and obesity, yet parental and environmental mediators are important contributors to weight status. Fourth, we conducted a retrospective chart review; therefore, the reporting of complications may not be reliable.

### TABLE 1 Demographics by Genotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>BMI percentile, mean (SD)***</th>
<th>Demographics</th>
<th>Hb SS + Hb Sβ⁰⁺ (n = 423)</th>
<th>Hb SC + Hb Sβ⁺⁺ Other (n = 242)</th>
<th>Total (n = 665)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)**</td>
<td>11.2 (5.2)</td>
<td>9.9 (5.1)</td>
<td>10.8 (5.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, %</td>
<td>51.5</td>
<td>48.8</td>
<td>50.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black/African American, %</td>
<td>85.3</td>
<td>88.3</td>
<td>86.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Public or no insurance, %</td>
<td>65.7</td>
<td>59.8</td>
<td>63.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Hb, g/dL, mean (SD)**</td>
<td>8.8 (1.3)</td>
<td>10.9 (1.3)</td>
<td>9.5 (1.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of any SCD-related complication, %***</td>
<td>78.3</td>
<td>37.6</td>
<td>63.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequent pain episodes***, *</td>
<td>40.9</td>
<td>19.8</td>
<td>33.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute chest syndrome***</td>
<td>57.7</td>
<td>22.9</td>
<td>45.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke***</td>
<td>9.2</td>
<td>1.3</td>
<td>6.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Splenic sequestration**</td>
<td>20.2</td>
<td>10.9</td>
<td>16.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Priapism*</td>
<td>5.8</td>
<td>1.7</td>
<td>4.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avascular necrosis</td>
<td>5.6</td>
<td>3.8</td>
<td>4.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCD-directed treatments, %**</td>
<td>51.8</td>
<td>7.9</td>
<td>35.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxyurea***</td>
<td>42.8</td>
<td>7.8</td>
<td>30.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic transfusions*</td>
<td>13.2</td>
<td>1.2</td>
<td>9.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity-associated conditions, %</td>
<td>8.6</td>
<td>3.3</td>
<td>9.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep apnea**</td>
<td>2.4</td>
<td>0.8</td>
<td>1.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

One subject was missing genotype.

* More than 3 pain episodes in the previous year.

** P < .05.

*** P < .001.

### TABLE 2 Demographics, SCD-Directed Treatments, and Obesity-Associated Conditions by Weight Status

<table>
<thead>
<tr>
<th>Weight Status</th>
<th>(n = 44)</th>
<th>(n = 475)</th>
<th>(n = 147)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD)**</td>
<td>11.9 (5.8)</td>
<td>10.7 (5.2)</td>
<td>10.5 (4.8)</td>
</tr>
<tr>
<td>Male, %</td>
<td>68.2</td>
<td>49.9</td>
<td>46.9</td>
</tr>
<tr>
<td>Black/African American, %</td>
<td>86.1</td>
<td>86.7</td>
<td>85.6</td>
</tr>
<tr>
<td>Public or no insurance, %</td>
<td>64.3</td>
<td>69.9</td>
<td>59.4</td>
</tr>
<tr>
<td>Baseline Hb, g/dL, mean (SD)**</td>
<td>8.8 (1.5)</td>
<td>9.4 (1.6)</td>
<td>10.2 (1.5)</td>
</tr>
<tr>
<td>Genotype, Hb SS and Hb Sβ⁰⁺, %***</td>
<td>79.6</td>
<td>67.9</td>
<td>44.9</td>
</tr>
<tr>
<td>History of any SCD-related complication, %*</td>
<td>79.6</td>
<td>64.4</td>
<td>55.8</td>
</tr>
<tr>
<td>Frequent pain episodes*</td>
<td>40.9</td>
<td>34.3</td>
<td>27.2</td>
</tr>
<tr>
<td>Acute chest syndrome</td>
<td>52.3</td>
<td>44.6</td>
<td>44.8</td>
</tr>
<tr>
<td>Stroke</td>
<td>13.6</td>
<td>5.4</td>
<td>6.9</td>
</tr>
<tr>
<td>Splenic sequestration</td>
<td>25.0</td>
<td>15.8</td>
<td>17.4</td>
</tr>
<tr>
<td>Priapism*</td>
<td>11.6</td>
<td>3.9</td>
<td>3.5</td>
</tr>
<tr>
<td>Avascular necrosis</td>
<td>4.7</td>
<td>4.9</td>
<td>4.8</td>
</tr>
<tr>
<td>SCD-directed treatment*</td>
<td>47.7</td>
<td>37.6</td>
<td>28.0</td>
</tr>
<tr>
<td>Hydroxyurea use**</td>
<td>34.1</td>
<td>33.0</td>
<td>19.2</td>
</tr>
<tr>
<td>Chronic transfusions*</td>
<td>15.9</td>
<td>8.2</td>
<td>8.9</td>
</tr>
<tr>
<td>Obesity-associated conditions, %</td>
<td>8.6</td>
<td>6.0</td>
<td>9.6</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>4.7</td>
<td>1.5</td>
<td>2.8</td>
</tr>
</tbody>
</table>

* More than 3 pain episodes in the previous year.

* Twenty subjects were on both treatments as they transitioned from chronic transfusions to hydroxyurea.

** P < .05.

*** P < .001.
Finally, we did not capture data on immigration status on the children included in this study, yet the participating institutions are located in urban areas with large immigrant populations from sub-Saharan Africa, the Caribbean, and Central and South America. Children with SCD from developing countries are often underweight for age and gender\(^4,39,40\); therefore, our results may underestimate the prevalence of elevated BMI percentiles among US-born children with SCD.

### CONCLUSIONS

A significant proportion of children and adolescents with SCD in New England are overweight or obese, which is associated with higher baseline Hb levels. Longitudinal studies are needed to determine if there is a causal relationship between increased Hb and weight status. Longitudinal studies are also needed to monitor the consequences of weight status over time, and to determine the impact of elevated BMI on the morbidity and mortality of both children and adults with SCD. Finally, research is needed to determine appropriate nutrition and exercise regimens for patients with SCD, both on and off SCD-directed therapy, to maintain a healthy weight throughout their lives. As therapeutic advances are provided to people with SCD, careful attention must be given to potential side effects to ensure these patients not only live longer, but live better.

### ACKNOWLEDGMENTS

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### REFERENCES


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**TABLE 3** Logistic Regression Models of Overweight/Obesity and Hemoglobin

<table>
<thead>
<tr>
<th>Model Description</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>R² (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted model</td>
<td>1.38 (1.23–1.56)</td>
<td>4.8</td>
</tr>
<tr>
<td>Adjusted for demographic factors</td>
<td>1.41 (1.25–1.59)</td>
<td>5.6</td>
</tr>
<tr>
<td>Adjusted for demographic factors + any SCD-related complications + SCD treatments</td>
<td>1.40 (1.24–1.59)</td>
<td>5.6</td>
</tr>
<tr>
<td>Adjusted for demographic factors + SCD-related complications + SCD treatments + obesity-associated conditions</td>
<td>1.36 (1.20–1.56)</td>
<td>6.6</td>
</tr>
</tbody>
</table>

Demographic factors: age, race (black versus other), gender, insurance status (Medicaid versus other).

SDC treatments: hydroxyurea, chronic transfusions, and interaction terms hydroxyurea*pain, transfusions*stroke.

Obesity-associated conditions: obstructive sleep apnea, hypertension.


24. Ware RE. How I use hydroxyurea to treat young patients with sickle cell anemia. *Blood*. 2010;115(26):5300–5311


Weight Status of Children With Sickle Cell Disease
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