Cost of Care Associated with BMI in Patients with Sickle Cell Disease

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Abbreviations:

BMI	Body mass index
SCD	Sickle cell disease
CoC	Cost of care
USD	United States dollar
EMR	Electronic medical record
CDC	Centers for Disease Control and Prevention
GLM	Generalized linear model
GEE	Generalized estimated equations
MCAR	Missing completely at random
SD	Standard deviation
SE	Standard error
LS	Least-squares

Abstract

BACKGROUND:

Children with sickle cell disease (SCD) incur greater medical expenditures than children without SCD. The prevalence of overweight has risen among children with SCD in recent years, but the impact of excess weight on both the disease burden and economic burden of SCD has not been determined.

PROCEDURE:

A convenience sample of patients with SCD under 18 years of age were asked to participate during a routine medical check-up. All participants were from one SCD clinic in North Carolina. Annual cost of care (CoC) in United States dollars (USD) was measured during four stages of adolescence (pre, early, middle, and late) for two groups of patients with SCD who were either above or below an age- and sex-specific 50th percentile for body mass index (BMI).

RESULTS:

A total of 33 African-American patients (mean age at enrollment 11.76 ± 3.13, 15 (45.5%) female) recorded 914 medical encounters spanning 306 patient-years. For patients over the 50th BMI percentile, CoC was estimated to increase by an additional $1,006 ($p < 0.001$) per year. The estimated difference in annual CoC became most pronounced in late adolescence, wherein patients in the higher percentile group incurred an additional annual CoC of $11,695 ($p = 0.019$).

CONCLUSIONS:

The differences we measured in cost of care for patients with SCD gives weight to the hypothesis that economic burden is exacerbated by excess bodyweight. Differences in the domain of healthcare costs also suggest potential benefits of weight-management interventions. Further studies implementing such interventions may provide insights for strategically managing SCD, reducing economic burden and improving patient outcomes.

1 INTRODUCTION

Sickle cell disease (SCD), a family of inherited autosomal recessive genetic disorders, affects approximately 1 in 500 African Americans and 100,000 individuals in the US.[1] Increasing life expectancy for patients with SCD[2] has facilitated the study of health-related quality of life[3] (HRQOL) and cost of care[4] (CoC). Children with SCD utilize healthcare more frequently[5,6] and incur greater CoC than peers without SCD.[7–9] Recent evidence suggests that overweight and obesity are becoming more prevalent among children and adults with SCD in both the developed and developing worlds,[10–13] but there is limited understanding regarding the economic impact of these health risk factors.

Obesity is associated with greater CoC amongst children in the US[14,15] and other developed nations.[16–19] Several factors influence the impact of obesity on CoC, including gender[20] and socioeconomic status.[19] With increasing rates of overweight and obesity among persons with SCD, there has been speculation regarding an association between excess weight and increased CoC,[11,13,21] and the current body of literature is in need of longitudinal studies to measure the impact of sustaining excess weight during adolescence for patients with SCD.

In this article, we summarize a retrospective cohort study that extracted medical encounter data from electronic medical records (EMR) for consecutive pediatric and adolescent patients with SCD. We statistically estimate and compare (1) the rate of change in annual CoC for patients with high and low standardized body mass index (BMI) values (Z scores) and (2) the expected annual CoC during four stages of adolescence, controlling for sex, insurance type, year, age at enrollment, and socioeconomic status. Our results make a case for further study of the association between overweight and increased medical and economic burden for patients with SCD in a more controlled setting involving one or more nutrition and exercise based interventions.

2 METHODS

2.1 Recruitment

As part of a larger study on the adolescent transition period for adolescents with chronic medical conditions, a convenience sample of patients with SCD under 18 years of age was recruited from one comprehensive sickle cell clinic. Details of the longitudinal sample and study design and inclusion and exclusion criteria have been previously published.[22] This current study's inclusion criteria included a confirmed diagnosis of SCD, ability to speak and understand English, and freedom of cognitive impairment (determined by health care provider) that would inhibit ability to complete study activities. After institutional review board approval, patients with SCD and their parents were invited to participate and informed consents were obtained from study participants and their parents.

2.2 Data Collection

Data were collected from the EMR at University of North Carolina Pediatric Sickle Cell Clinic. All participants' medical records were reviewed and anthropometric, financial, and demographic data were extracted from WebCIS, a Legacy record, (2004-2014) and EPIC (2014-2016) systems at each outpatient, inpatient, or emergency room visit.

2.3 Measures

The measurement of time is paramount in longitudinal studies, so we present results based on two perspectives of patient age. More specifically, age was considered as both a continuous and categorical variable. For the latter, we split numeric age values into a total of four stages of adolescence based on guidelines set by the American Academy of Pediatrics[23]: pre-adolescence (age 8 to 11), early adolescence (age 11 to 15), middle adolescence (age 15 to 18), and late adolescence (age 18 to 21). Regarding age as a continuous variable, we used the numeric values of 9.5, 13, 16.5, and 19.5 years in place of the group identifiers. Annual CoC in United States dollars (USD) for each stage was constructed by summing CoC at the encounter level for each patient within each stage and dividing by the spanning number of years. For example, if a patient’s total CoC from age 8 to 11 was 99 dollars, their annual CoC would be 99 / (11-8) = 33 dollars per year.

Some patients' data either began or ended near the borders of a stage (e.g., collection began at age 10.8 or ended at age 18.1). Allowing these borderline encounters to represent CoC for an entire stage leads to underestimation of the true CoC, yet overestimation results from pushing the borderline values into the closest stage (i.e. using the initial encounter at age 10.8 as an observation in the early adolescence stage). For these reasons we elected to exclude borderline encounters, which were defined as encounters that occurred during a patient’s final or initial stage but did not cover more than half of the stage's duration. Figure 1 illustrates our inclusion

and exclusion process for a fictional set of encounters from one patient as well as the formulation of three annual CoC values. The fictional patient's initial encounter is a borderline case and is excluded. Since the spanning time between the onset of the late adolescence stage and the final encounter is greater than 75% of the stage duration, the final encounter is included.

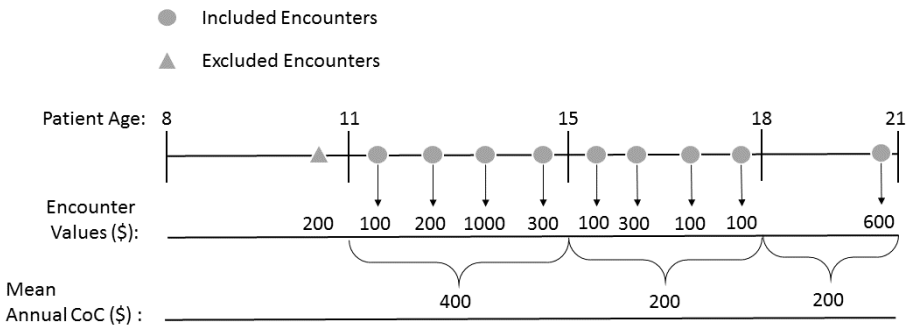

FIGURE 1 Data inclusion and exclusion process. NOTE: The cost values in the figure are fictional.

Standardized BMI values, often referred to as standard deviation or *Z* scores, were used to measure the weight status of patients throughout the study. The *Z* scores were formed by mapping BMI values into sex- and age-specific BMI percentiles that were based on reference data compiled by the Center for Disease Control and Prevention (CDC).[24] The documentation of the *y2z* function in the *AGD* package[25] describes how these values were mapped in full detail.

We split the sample into two exposure groups by setting observations with *Z* scores above or below zero as the upper or lower weight group, respectively. We did not compare overweight to

non-overweight patients, which would require splitting along the 85th percentile ($Z = 1.1$). Instead, we use the 50th percentile (1) to preserve statistical power and (2) because patients with SCD have historically maintained lower BMIs relative to their peers without SCD.[26] With regards to reason (2), a 'normal BMI' SCD patient according to standard growth charts may in fact be in the upper BMI percentiles of the SCD population.

Additional variables included patient's median neighborhood income (based on patient zip code), medical insurance type (private or public), sex (male or female), year at the onset of an age period (e.g., 2009 when patient was 15, 2012 when patient was 18), and age at enrollment.

2.4 Statistical Analyses

All statistical analyses were produced with R version 3.3.0.[27] Descriptive statistics (e.g. groupwise mean values and standard errors) were considered prior to application of the generalized linear model (GLM)[28] with generalized estimating equations (GEE)[29,30] and a log link function.[31] This technique is a generalization of analysis of variance with unequal sample sizes and clustered outcomes that do not maintain a bell shaped distribution.[32] Tests of difference between two means[33] using the GLM with GEE generalizes the paired t-test by using all observations from each participant (even if the participant had only one value) and also adjusting for the correlation between observations within subjects. For these comparisons, we fixed each of the continuous control variables (income and age at enrollment) upon their respective sample means.

2.5 Missing Data

Missing data at the encounter level included 121 (13%) height values and 67 (7%) weight values. We imputed these missing values using a weighted mean of previous and future values based

upon temporal proximity. Height values for patients over the age of 18 were carried forward for all subsequent observations.

Missing data at the subject level included 6 (6%) income values. We assumed these data were missing completely at random (MCAR) and conducted sensitivity analyses by separately constructing a model using the complete cases (excluding subjects with missing values) data and another using the full data (including imputed values). The complete cases model was in full agreement with inferences made by the full data model, indicating that the MCAR assumption was valid. After establishing the MCAR assumption, we applied multiple imputation using the conditional specification implemented by the MICE algorithm[34] to impute the missing income values.

3 RESULTS

3.1 Enrollment of Participants

A total of 33 patients recorded 914 medical encounters spanning 306 patient-years. After collapsing the encounter level data to form the annual outcomes within age periods, we had a total of 99 observations. Removing observations based on borderline encounters left a total of 96 observations.

3.2 Sample Characteristics

Mean age at entry and final encounter were 11.76 ± 3.13 and 18.74 ± 1.88 years, respectively. The sample had a total of 15 (45.5%) female participants and 18 (54.5%) males. Most participants (17 (51.5%)) were in the lower Z score group, and the mean Z score was -0.14 ±

1.09. All participants were identified by parents or guardians as African American and 32 (97%) were not of Hispanic ethnicity. The mean reported income plus or minus one standard deviation (SD) was $49,150.55 ± 13,787.84. Last, 22 (66.7%) patients were primarily insured with a type of public insurance (e.g. Medicaid) and 11 (33.3%) patients with a type of private insurance. Table 1 summarizes the sample characteristics for each Z score group.

TABLE 1 Sample Characteristics.

	Lower BMI n = 17 (51.5)	Higher BMI n = 16 (48.5)	All n = 33
Number of observations (p = 0.253)	3.1 ± 0.8	2.8 ± 0.7	2.9 ± 0.8
Age (years) at enrollment (p = 0.678)	12.0 ± 3.0	11.5 ± 3.4	11.8 ± 3.1
Age (years) at conclusion (p = 0.047)	19.4 ± 1.2	18.1 ± 2.3	18.7 ± 1.9
Income (USD) (p = 0.366)	47,008 ± 12,998	51,427 ± 14,650	49,151 ± 13,788
Z Value (p < 0.001)	-0.9 ± 1.0	0.7 ± 0.4	-0.1 ± 1.1
Sex (p = 0.024)			
Female	4 (23.5)	11 (68.8)	15 (45.5)
Male	13 (76.5)	5 (31.2)	18 (54.5)
Billing Party (p = 0.538)			
Public	10 (58.8)	12 (75.0)	22 (66.7)
Private	7 (41.2)	4 (25.0)	11 (33.3)

For continuous variables, values are mean ± standard deviation.
For categorical variables, values are frequency (%).
BMI: body mass index; USD: United States dollar

Figure 2 displays subject-specific annual CoC values (small grey points) for upper and lower BMI Z score groups across the four age periods. Mean annual CoC values are displayed as larger black points with error bars showing the width of one standard deviation above and below the mean. Observation counts and mean values plus or minus one standard deviation are also tabulated at the bottom of the figure.

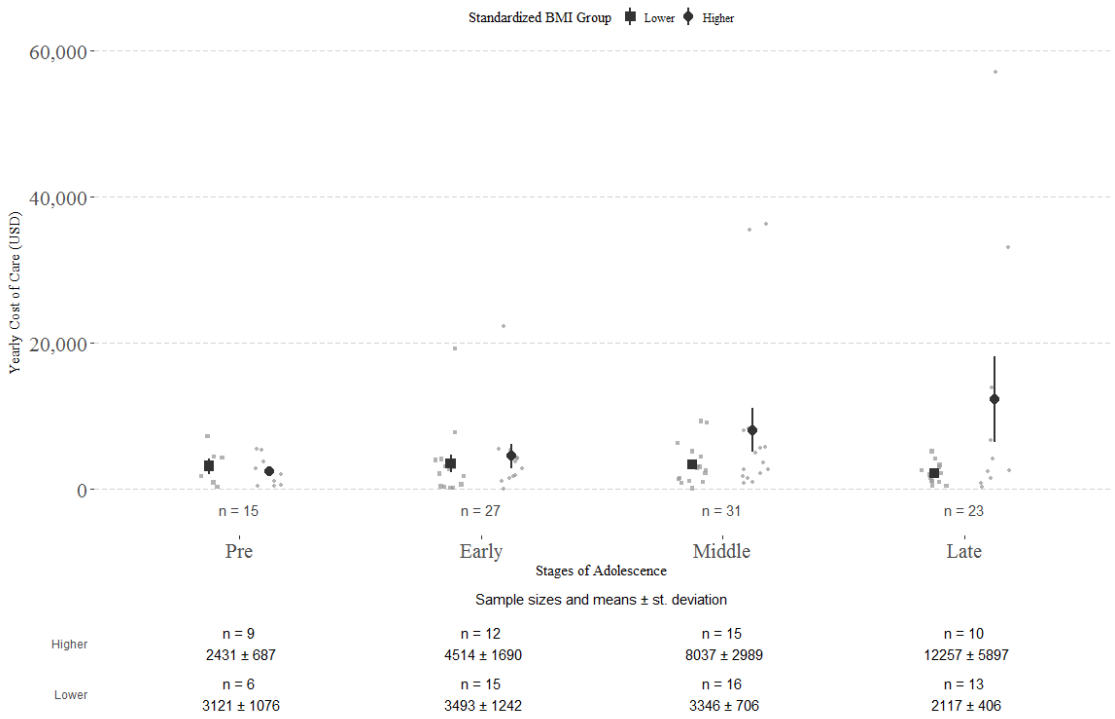

FIGURE 2 Unadjusted mean annual CoC (USD) ± SD

3.3 Difference in Slopes

The rate of change per year in annual CoC was estimated from the GLM with a continuous age predictor. For the low Z score group, the estimated change in annual CoC from age 8 to 21 was \$42 (95% CI: -71 to 155). For the high Z score group, the estimated slope was \$1,047 (95% CI: 488 to 1,607). To summarize, CoC was estimated to increase by an additional \$1,006 (95% CI: 445 to 1,566) per year for high Z score patients.

3.4 Difference in Means

Using the categorical formulation of age, Table 2 presents estimated least-squares (LS) means and standard errors (SE) of annual CoC as well as estimated differences between annual CoC

between Z score groups for each age period. Difference values are computed by subtracting the estimated mean of the lower Z score group from that of the higher Z score group. In the two earliest age periods (pre- and early adolescence), we estimated modest difference in CoC between groups. During middle adolescence we measured a nontrivial difference of $2,231 (95% CI: -1,768 to 6,230) that did not achieve statistical significance. A substantial and statistically significant (p = 0.019) difference of $11,695 (95% CI: 1,759 to 21,632) was measured during late adolescence.

TABLE 2 Comparison of estimated cost of care means

Age Group	Lower LS Mean (SE)	n	Higher LS Mean (SE)	n	Difference	p-value
Pre	1,308 (598)	6	959 (403)	9	-349	0.488
Early	2,260 (862)	15	2,361 (1146)	12	101	0.926
Middle	2,877 (895)	16	5,108 (2338)	15	2,231	0.264
Late	1,659 (510)	13	13,354 (4953)	10	1,1695	0.019

Means presented in United States dollars
LS: least-squares; SE: standard error

4 DISCUSSION

This retrospective cohort study aimed to estimate the rate of change in annual CoC for patients with high and low standardized BMI values and the expected annual CoC during four stages of adolescence. For higher Z score patients, CoC was estimated to increase by an additional $1,006 ($p < 0.001$) per year. The estimated difference in annual CoC became most pronounced in late adolescence, wherein patients with higher Z scores incurred an additional annual CoC of $11,695 ($p = 0.019$).

We experienced a number of challenges in the course of this study that may prove relevant for future studies. Data collection through EMR proved to be very accurate for cost data, but less so for data concerning age, weight, height, and other patient information relating to demographic and socioeconomic factors. Improving the accuracy and consistency of information kept in electronic medical records could potentially alleviate many of the limitations we experienced and allow more studies such as this to be conducted. One of the primary limitations of this research (in addition to a small number of patients) is that data were collected within a single hospital system and patients may have visited multiple hospitals over their adolescence. Pooling patient data from multiple institutions in future studies could alleviate this limitation.

These data suggest that at some point in adolescence, the CoC of patients with SCD becomes highest in overweight patients and this trend carries forward into adulthood. One of the main virtues of observational data is their capacity to generate relevant hypotheses for future research. Previous research has associated overweight status with increases in the burden of SCD,[11] and this has motivated exploration of how these patterns emerge over time. Based on these premises we have summarized several points in this article to present evidence of association between overweight and increased CoC for patients with SCD beginning in the late teen years. Our findings should not be interpreted as causal association but should motivate exploration of data-driven hypotheses.

A recent study[4] estimated that the annual CoC for patients with SCD in the United States exceeded one billion dollars. The authors also commented that a small proportion of patients with SCD accounted for a large proportion of healthcare expenditures, which we have also found to be the case in our sample. If excess weight plays a role in the development of severe symptoms that in turn account for a large proportion of the total CoC for SCD, then there may be

both clinical and economic benefits to healthcare providers informing patients about the likely consequences of the disease for different weight groups. Future research could address whether there is potential to reduce the medical cost of SCD in young adults with weight management interventions.

The relationship between excess weight and increased CoC may be supported by previous literature. Overweight status is associated with comorbidities that may be of particular significance for disease management and CoC in the SCD population. Recently, high BMI was found to be associated with hypertension and increased risk of stroke within an adult population with SS genotype.[35] Excess weight has also been associated with increased pain interference in daily activities among adults with SCD.[11] Children with SCD experience much higher rates of snoring and sleep apnea, associated in the general population with overweight status, than the general population[36] and it has been shown that lower nocturnal hemoglobin saturations appear to be associated with increased vaso-occlusive pain crises.[21] There is also strong evidence that snoring and sleep apnea are associated with increased cerebral, cognitive, and behavioral morbidity.[36] However, studies conflict on the presence of a direct relationship between weight status and sleep apnea or hypertension in children with SCD.[13,36] It could then be hypothesized that excess weight, through various mechanisms (e.g., metabolic syndrome, hypertension, and hypoxic sleep disturbances), has negative consequences for morbidity and CoC.

Current SCD care guidelines from the National Heart, Lung, and Blood Institute only superficially address weight management,[37] and we believe amendment of these guidelines to reflect the main points of this study and others[35] would be an important step towards higher quality healthcare and lower CoC for patients with SCD. Although we have mainly focused on the implications of excess weight in patients with SCD, the relationship between growth failure,

delayed puberty, and underweight status in many patients with SCD[26,38–41] should also be considered in potential amendments.

Another implication of these findings is for the financing of SCD care. Two thirds of this study's participants utilized public insurance, consistent with literature suggesting the majority of patients with SCD in the US rely on Medicaid.[42–44] If cost-effective weight management interventions can be validated for the SCD population, stakeholders such as the Centers for Medicare and Medicaid Services and other insurance and healthcare providers may be encouraged to invest further in health promotion efforts for patients with SCD.

5 CONCLUSION

Sickle cell disease affects around 100,000 individuals in the US and amounts to over a billion dollars of healthcare expenditures per year. Recent evidence suggests that the prevalence of overweight and obesity status for these individuals is growing. The relationship between obesity and rising healthcare costs has been studied thoroughly, but the nature of this relationship within the SCD population remains unexplored. In this study, we analyzed longitudinal EMR data to assess the association between standardized BMI values (Z scores) and CoC for patients with SCD. For higher Z score patients, CoC was estimated to increase by an additional \$1,006 ($p < 0.001$) per year. The estimated difference in annual CoC became most pronounced in late adolescence, wherein patients with higher Z scores incurred an additional annual CoC of \$11,695 ($p = 0.019$). These observational data have provided evidence that gives weight to the hypothesis that preventative therapy of SCD-related health complications via weight

management interventions may substantially reduce the economic burden of SCD for pediatric patients.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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