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Estimated Life Expectancy and Income of Patients With Sickle Cell Disease Compared With Those Without Sickle Cell Disease

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Abstract

IMPORTANCE Individuals with sickle cell disease (SCD) have reduced life expectancy; however, there are limited data available on lifetime income in patients with SCD.

OBJECTIVE To estimate life expectancy, quality-adjusted life expectancy, and income differences between a US cohort of patients with SCD and an age-, sex-, and race/ethnicity-matched cohort without SCD.

DESIGN, SETTING, AND PARTICIPANTS Cohort simulation modeling was used to (1) build a prevalent SCD cohort and a matched non-SCD cohort, (2) identify utility weights for quality-adjusted life expectancy, (3) calculate average expected annual personal income, and (4) model life expectancy, quality-adjusted life expectancy, and lifetime incomes for SCD and matched non-SCD cohorts. Data sources included the Centers for Disease Control and Prevention, National Newborn Screening Information System, and published literature. The target population was individuals with SCD, the time horizon was lifetime, and the perspective was societal. Model data were collected from November 29, 2017, to March 21, 2018, and the analysis was performed from April 28 to December 3, 2018.

MAIN OUTCOMES AND MEASURES Life expectancy, quality-adjusted life expectancy, and projected lifetime income.

RESULTS The estimated prevalent population for the SCD cohort was 87 328 (95% uncertainty interval, 79 344-101 398); 998 were male and 952 were female. Projected life expectancy for the SCD cohort was 54 years vs 76 years for the matched non-SCD cohort; quality-adjusted life expectancy was 33 years vs 67 years, respectively. Projected lifetime income was $1 227 000 for an individual with SCD and $1 922 000 for a matched individual without SCD, reflecting a lost income of $695 000 owing to the 22-year difference in life expectancy. One study limitation is that the higher estimates of life expectancy yielded conservative estimates of lost life-years and income. The analysis only considered the value of lost personal income owing to premature mortality and did not consider direct medical costs or other societal costs associated with excess morbidity (eg, lost workdays for disability, time spent in the hospital). The model was most sensitive to changes in income levels and mortality rates.

CONCLUSIONS AND RELEVANCE In this simulated cohort modeling study, SCD had societal consequences beyond medical costs in terms of reduced life expectancy, quality-adjusted life expectancy, and lifetime earnings. These results underscore the need for disease-modifying therapies to improve the underlying morbidity and mortality associated with SCD.

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Key Points

Question What is the association between sickle cell disease and life expectancy and lifetime income?

Findings This cohort simulation modeling study showed that projected life expectancy (54 vs 76 years) and quality-adjusted life expectancy (33 vs 67 years) were lower in the sickle cell disease cohort relative to the non–sickle cell disease cohort. Projected lifetime income was also lower in individuals with sickle cell disease ($1 227 000 vs $1 922 000), reflecting lost income ($695 000) owing to reduced life expectancy.

Meaning Sickle cell disease appears to have important societal consequences in terms of reductions in life expectancy and lifetime income, underscoring the need for disease-modifying therapies to improve sickle cell disease–related morbidity and mortality.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Introduction

There are an estimated 100 000 individuals in the United States living with sickle cell disease (SCD), most of whom are African American or Hispanic American.[1-3] An inherited disorder that causes red blood cells to deform into a sickle shape and damage cell membranes,[4] SCD is associated with significant and costly long-term complications and reduced life expectancy.[4-6] Children and adolescents make up 40% of the individuals in the United States with SCD.[2]

Owing to the pathophysiologic characteristics of SCD, most patients experience significant lifelong morbidities as a result of the underlying hemolysis and vascular damage that results in acute (eg, vaso-occlusive crises and acute chest syndrome) and chronic injury to multiple end organs, including brain (eg, stroke and silent infarcts), kidney (eg, renal failure), and the cardiopulmonary system (eg, pulmonary hypertension).[5,6] These acute and chronic injuries lead to increased use of outpatient and inpatient health care resources[7-10] and functional physical and cognitive impairments reflected in patient-reported reductions in quality of life and reduction in school and work productivity.

The life expectancy of individuals with SCD is decades shorter compared with those without SCD, primarily owing to early mortality during adulthood.[5,11-13] The mortality rate of infants and children with SCD in the United States has decreased with the implementation of multiple interventions, including newborn screening, immunizations, use of prophylactic antibiotics to prevent infections, and use of hydroxyurea.[11,14] Because of the widespread adoption of comprehensive guidelines that govern the management of childhood SCD in high-income countries, more than 95% of children will survive to adulthood.[15,16] Despite these advances, mortality and quality-of-life improvements in adults with SCD have been harder to achieve owing to the limited access to comprehensive care and the paucity of currently available treatment options that address the long-term clinical outcomes of this chronic disease.[11,12,17]

The total burden of SCD includes not only direct medical costs, but also income and productivity loss[18-20]; however, there are limited data available on the association between SCD mortality and morbidity and lifetime income. In this study, we estimated the average life expectancy of patients with SCD, compared this with a matched, non-SCD cohort, and calculated loss of lifetime income. In a second, separate analysis, we estimated the decrements in quality-adjusted life-years (QALYs) due to SCD. Together, these 2 outcomes provide a clearer picture of both the disease burden, from the perspective of individuals with SCD and the health economic burden from the perspective of society.

Methods

The approach used to estimate the future lifetime outcome of SCD from a societal perspective was to (1) establish a simulated SCD-prevalent cohort by combining an estimate of current newborns with SCD in the United States with an estimate of available death rates for the US SCD population, (2) establish 2 hypothetical cohorts for comparison: a non-SCD population cohort with the same age, sex, and race/ethnicity (African American race and Hispanic ethnicity) composition as that of the individuals with SCD (3) determine the life expectancy for each cohort, (4) estimate the additional burden of SCD by identifying utility weights for individuals with SCD compared with individuals without SCD and by translating these utility weights to QALYs, (5) estimate expected annual personal income for each cohort, and (6) estimate the loss of lifetime income for individuals with SCD compared with the matched cohorts without SCD owing to premature mortality. Each population was followed up over a complete lifetime horizon and all results were calculated separately for each cohort and by sex. Results were pooled across race/ethnicity categories because of the small numbers of non–African Americans with SCD. Each step is described in detail below. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) reporting guideline was implemented where applicable.

This modeling study did not require institutional review board approval or informed consent per the University of Alabama at Birmingham because it relied solely on publications and deidentified publicly available data.

Model Development

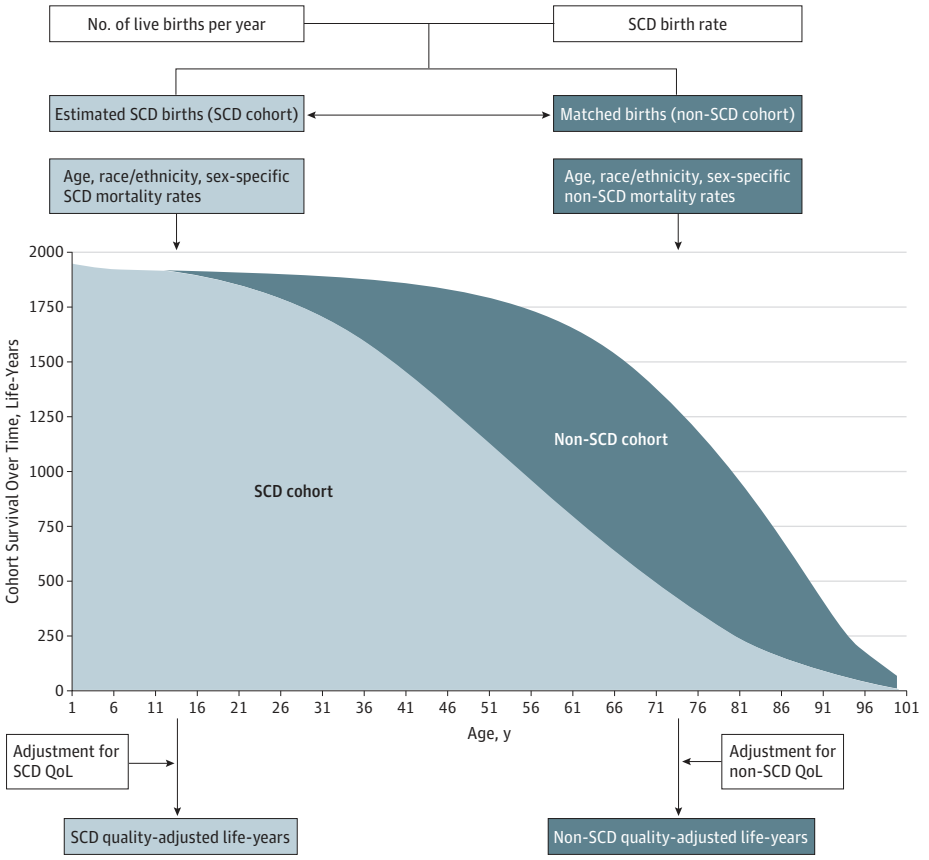
To evaluate the association between SCD and life expectancy and lifetime income, we developed a cohort simulation model. The model calculated the life-years, QALYs, and income for the cohort with SCD and for a matched cohort without SCD. **Figure 1** outlines the conceptual model and **Table 1** and **Figure 2** summarize model inputs and data sources, which are detailed below.

Different mortality risk profiles were used for the age- and race/ethnicity-matched SCD and non-SCD cohorts. The profiles included mortality rates (2007-2016) from the Centers for Disease Control and Prevention (CDC)[30] for the overall population to estimate life expectancy by sex accounting for the SCD race/ethnicity distribution and CDC multiple cause of death (MCOD) mortality rates for the non-SCD cohort. These differences resulted in a decreased life expectancy as well as lost income for the individual with SCD. The model then calculated the difference in life-years and income for these 2 populations. For comparison, we also calculated life expectancy and income for the US general population. Data for the model were collected from November 29, 2017, to March 21, 2018, and the analysis was performed from April 28 to December 3, 2018.

SCD and Non-SCD Populations

Data from the CDC provided the estimate for the number of newborns in the United States; the number of live births in 2015 was 3 978 497 with a male to female ratio of 1048:1000.[21] The SCD birth rates were derived from the National Newborn Screening Information System and summarized for

Figure 1. Model Concept



Abbreviations: QoL indicates quality of life; SCD, sickle cell disease.

the 10 years from 2001 to 2010.[22] Rates are reported separately for homozygous sickle mutation, hemoglobin sickle cell, and deoxy sickle hemoglobin β-thalassemia. All subtypes were combined to yield an overall SCD birth rate of 0.00049.[22] The estimated number of newborns with SCD using this overall SCD birthrate was 1950 per year. Therefore, both the SCD and non-SCD populations had 1950 individuals at entry into the model.

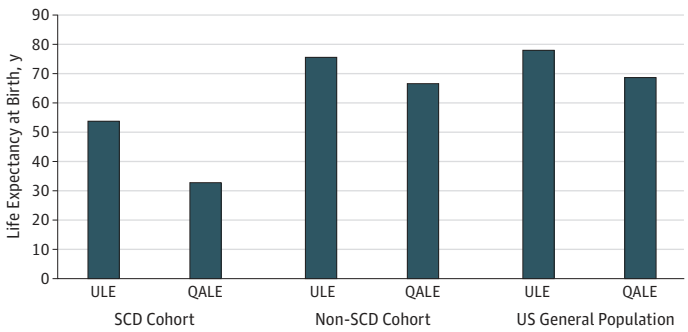
We applied the national SCD birth rates as reported by Therrell and colleagues[22] to the number of live births in 2015, and then categorized the number of SCD births by race/ethnicity as observed in the CDC MCOD data (described below). This action allowed capture of births assigned to multiple race/ethnicity categories (eg, white or Asian/Pacific Islander) that otherwise would not have been

Table 1. Model Inputs and Sources

Description of Data Input	Population Value (Data Source)		
	SCD	Non-SCD	General
Estimate of SCD newborns derived from:			
No. of newborns in US, 2015	1950 = estimate of newborns based on CDC live births × Therrell rate	Same as SCD population	NA
SCD rates per 1000 births	3 978 497 (CDC, 2015[21])		
	0.00049 (Therrell et al, 2015[22])		
Create life table derived from			
Published death rates by age group	Death rates for SCD derived from Paulukonis, Figure 2 (Paulukonis et al, 2016[12])	Death rates for non-SCD population (African American and Hispanic) (eFigure 1 in the Supplement); from CDC/NCHS, National Vital Statistics System, mortality for race and sex distribution for SCD population[23]	Death rates for general population eFigure 1 in the Supplement); from CDC/NCHS, National Vital Statistics System, mortality data for entire US population[23]
Observed SCD deaths from CDC MCOD file	See eTable 1 in the Supplement) for observed deaths from CDC (CDC MCOD data[24])		
CDC National Vital Statistics data			
Estimate of QALYs			
Link visual analog scale pain for SCD children/adolescents to EQ-5D	Anie et al, 2012[25] provides algorithm linking pain to EQ-5D	See eTable 2b in the Supplement) for EQ-5D normative values by age for US population (Fryback et al, 2007)[26]	See eTable 2b in the Supplement) for EQ-5D normative values by age for US population (Fryback et al, 2007)[26]
Link visual analog scale pain for SCD adults to EQ-5D	See eTable 2a in the Supplement) for pain scores and linked EQ-5D by age (Graves and Jacob, 2014[27]; Smith et al, 2008[28])		
EQ-5D US normative values			
Calculate income losses			
Observed annual personal income by sex and race/ethnicity for 2014	See eTable 3 in the Supplement) (US Bureau of Census[29]): data for African American men, African American women, Hispanic men, Hispanic women	See eTable 3 in the Supplement) (US Bureau of Census[29]): data for African American men, African American women, Hispanic men, Hispanic women	See eTable 3 in the Supplement) (US Bureau of Census[29]): data for all US men, all US women

Abbreviations: CDC, Centers for Disease Control and Prevention; EQ-5D, Euroqual-5 Dimensions; MCOD, multiple causes of death; NA, not applicable; NCHS, National Center for Health Statistics; QALYs, quality-adjusted life-years; SCD, sickle cell disease.

Figure 2. Expected Life-Years and Quality-Adjusted Life-Year Decrements by Age



Data shown for the sickle cell disease (SCD), non-SCD, and US general population. QALE indicates quality-adjusted life expectancy; ULE, unadjusted life expectancy.

counted. All non–African American race groups with SCD (eTable 1 in the Supplement) were included in the Hispanic group owing to small numbers.

Mortality rates for the SCD and the comparable non-SCD populations were estimated based on published and publicly available information, and this information was used to estimate life expectancy for the populations by sex and race/ethnicity. Mortality rates were also available from national vital statistics for the same age, sex, and race/ethnicity populations without SCD.[24] These rates were combined proportional to their race/ethnic representation in the SCD population (ie, proportional African American and Hispanic) to estimate outcomes for the non-SCD population. The SCD and non-SCD populations were then compared to quantify the early mortality.

The estimates of SCD births and available mortality rates were used to develop a prevalent SCD population. United States mortality and cause of death statistics for 2007 to 2016 were downloaded from the CDC Wide-ranging Online Data for Epidemiologic Research (WONDER) website using the MCOD files,[24] which include information on age at death, race, ethnicity, sex, and cause of death (up to 20 causes listed). An SCD cause of death was defined as any *International Statistical Classification of Disease, Tenth Revision* code D57.0 to D57.8 (excluding D57.3, sickle cell trait) reported anywhere in the death certificate. These codes have been used and validated in other studies,[11,17] including the source of the death rates for the model.[12] Because the probability of death is the ratio of observed deaths to the number of individuals at risk for death, we calculated the number at risk (prevalence) when deaths and probabilities were known. Therefore, the number of deaths from US mortality statistics, corrected for underreporting,[12] was combined with age-specific death probabilities to calculate the expected SCD prevalence.

Utility-Adjusted Life-Years

To quantify the morbidity outcome of SCD, patient-reported assessment of the effect of pain was linked to health utility values derived from the Euroqual-5 Dimensions (EQ-5D) (EuroQol Research Foundation) from 3 SCD studies that reported on pain using visual analog scales.[25,27,28] We used the published polynomial fit equation to connect the pain visual analog scale with the EQ-5D[25] to estimate the EQ-5D utility scores to be used in the model for the SCD population. The model compares SCD results with US normative data for the EQ-5D as reported by Fryback et al[26] applied to the non-SCD population. eTable 2a in the Supplement reports the data inputs for the EQ-5D for adults and children/adolescents used in our model (mean values) and the corresponding visual analog scale pain values that were derived from the Anie et al[25] study. eTable 2b in the Supplement summarizes the normative data inputs for the US population.[26]

Calculation of Lost Income for SCD

We calculated the lost income associated with premature mortality. The model assigned expected mean annual personal income based on age (starting at age 15 years), sex, and race/ethnicity as reported by the US Bureau of the Census.[29] Personal income included income received from wages or salary, self-employment income, unemployment or disability compensation, and other periodic income (eg, interest or rental income). This approach does not account for decreased earnings by patients with SCD to the extent that they are replaced through government disability payments (see Discussion). The values incorporated in the model are reported in eTable 3 in the Supplement (2014 $US). Undiscounted income was used with income inflation being cancelled out by the need to discount future income. The average annual value was assigned to each year of age for the SCD and non-SCD populations by sex and race/ethnicity. The expected lifetime income was estimated by cumulating the results for each year of age through age 100 using methods similar to those used in estimating life expectancy.

To quantify the potential effect of SCD on productivity losses associated with hospital stays, we conducted analyses of data from the National Inpatient Sample (NIS) and the Nationwide Readmissions Database (NRD) for 2014 from the Agency for Healthcare Research and Quality, Healthcare Cost and Utilization Project. The NIS is an annual 20% stratified sample of all

hospitalizations in nonfederal US hospitals and contains information on primary and secondary diagnoses, discharge status, and demographics. Details on the NIS are available from the Agency for Healthcare Research and Quality.[31] The NRD is a database designed to support analyses of national readmission rates.

Statistical Analysis

The model was constructed based on published data and publicly available, deidentified vital statistics data. Because the cohorts were simulated, no demographic or clinical characteristics could be reported or summarized. Mortality rates by age group for SCD, as reported for California and Georgia for 2004-2008,[12] were smoothed by fitting a Poisson regression model to estimate mortality rates by single year of age (eFigure 1 in the Supplement compares model-predicted mortality rates with the rates from Paulukonis et al[12]). Paulukonis et al identified underreporting in the MCOD data after reviewing death statistics and accounted for this underreporting. Analyses of mortality rates and prevalence incorporated Monte Carlo sampling of the Poisson model to characterize uncertainty. Results were reported for the 95% uncertainty interval based on the 2.5% and 97.5% of the distribution of results over 200 iterations of the Poisson model (eFigure 2 in the Supplement). Small differences in mortality rates at the youngest ages lead to large differences in prevalence estimates by year of age because of the inherent uncertainty in the published data; therefore, prevalence was further smoothed by using a Loess curve.

To understand the key factors associated with of income losses in the model, we conducted 1-way sensitivity analyses. Baseline parameters, including annual mean income, disutility associated with SCD, EQ-5D by age, male death rate relative to female rate in the SCD population, predicted SCD mortality for single age 0 to 99 years, and the proportion of SCD population that is African American vs Hispanic were each varied by ±20%. Analyses of hospital data (NIS and NRD) were weighted according to Agency for Healthcare Research and Quality guidelines to provide nationally representative counts for the United States. All analyses, including the model, were performed using the R statistical programming language, version 3.4.4 (R Project for Statistical Computing).[32]

Results

The estimated prevalent population for the SCD cohort was 87 328 (95% uncertainty interval, 79 344-101 398) (eFigure 3 in the Supplement), with a birth cohort of 998 male individuals and 952 female individuals. The estimated mortality rates for the SCD and matched non-SCD cohorts are provided in eFigure 4 in the Supplement. Mortality rates in the SCD and the matched non-SCD cohorts were similar up to age 25 years and then were notably higher for the SCD cohort between the ages of approximately 25 and 80 years.

Model estimates for life expectancy at birth and QALYs for the SCD, matched non-SCD, and general populations showed that both measures were markedly lower in the SCD cohort (Figure 2). Life expectancy for the SCD cohort was estimated at 54 years, which was 22 years lower than the life expectancy for the matched non-SCD cohort, and 25 years lower than the US general population (life expectancies of 76 and 79 years, respectively). When the quality-of-life decrement was considered, the SCD cohort had a quality-adjusted life expectancy of 33 years, compared with 67 years for the matched non-SCD cohort and 69 years for the US general population (Figure 2).

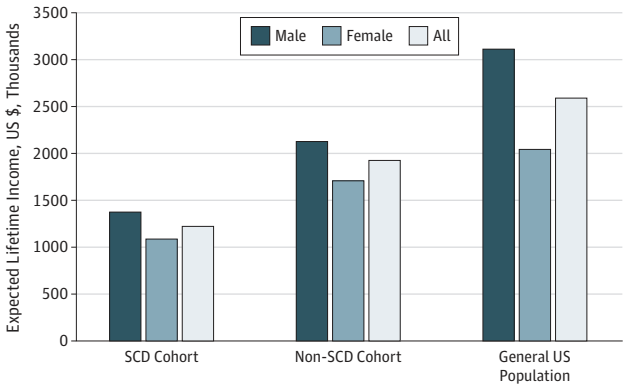
The model projected a lower lifetime income for the SCD population vs the non-SCD population (**Figure 3**). The estimated lifetime income was $1 227 000 for the SCD cohort and $1 922 000 for the matched non-SCD cohort, and just over $2 500 000 for the general population, reflecting a lost income of approximately $695 000 for an individual with SCD compared with a similar individual without SCD.

Comparable results for life expectancy, QALYs, and income losses are presented by sex as well as for the SCD and matched non-SCD cohorts. The life expectancies for women were 54 years for the SCD, 79 years for the non-SCD, and 81 years for the US general populations; life expectancies for men

were 54 years for the SCD, 73 years for the non-SCD, and 76 years for the US general populations (eFigure 5 in the Supplement). The quality-adjusted life expectancy was the same (33 years) for men and women in the SCD group (eFigure 6 in the Supplement). The expected lifetime incomes by age and sex for the SCD cohort, the matched non-SCD cohort, and the general population (eFigure 7 in the Supplement) were in line with the data for the overall population (Figure 3). The values for expected lifetime income for the SCD and matched non-SCD cohorts, respectively, were $1 072 000 and $1 710 000 for females and $1 376 000 and $2 124 000 for males. Mean annual personal income and the predicted SCD mortality rate by single year of age were the 2 most important drivers of lost lifetime income in a univariate sensitivity analysis (eFigure 8 in the Supplement). Sensitivity analysis of utility values had no association with income or mortality as indicated in Figure 2. In a separate sensitivity analysis of quality-adjusted life expectancy, the range was from 27 to 37 QALYs compared with the base case of 33 QALYs.

Results for frequency of admissions and length of stay and for SCD hospitalizations are presented in **Table 2**. These data were derived from the NIS for length of stay and the NRD accounting for repeat hospitalizations to allow for reporting of number of admissions. In 2014, there were 18 520 inpatient visits for individuals with SCD aged 0 to 14 years, 30 540 for those 15 to 24 years, and 22 695 for those 25 to 29 years. When averaging data reported in Table 2 over all ages,

Figure 3. Expected Lifetime Income by Sex



Data shown for the sickle cell disease (SCD) and matched non-SCD cohorts.

Table 2. Mean Annual LOS for Sickle Cell Disease Inpatient Visits and Mean Number of Inpatient Admissions, by Age Group, 2014[a]

	Total Inpatient Visits		Total Individuals With an Inpatient Visit	
Age Group, y	No. of Visits (SE)	LOS per Visit, Mean (SE), d	No. of Individuals (SE)	Admissions per Patient, Mean (SE), No.
0-14	18 520 (1648)	3.58 (0.09)	12 996 (1668)	1.8 (0.03)
15-24	30 540 (1369)	5.04 (0.10)	11 934 (814)	2.93 (0.08)
25-29	22 695 (927)	5.54 (0.11)	7284 (439)	3.42 (0.09)
30-34	11 825 (559)	6.04 (0.16)	3585 (214)	3.34 (0.10)
35-39	9345 (445)	5.73 (0.15)	3492 (189)	3.01 (0.09)
40-44	6390 (319)	6.00 (0.19)	2673 (166)	2.78 (0.09)
45-49	4770 (248)	6.18 (0.28)	1900 (116)	2.52 (0.10)
50-54	3755 (210)	5.99 (0.27)	1662 (104)	2.46 (0.12)
55-59	1935 (129)	6.21 (0.34)	1149 (74)	2.14 (0.10)
60-64	1255 (107)	6.59 (0.68)	728 (61)	1.95 (0.10)
65-69	545 (57)	5.94 (0.53)	474 (44)	1.54 (0.10)
70-74	390 (51)	6.45 (0.69)	211 (26)	1.62 (0.19)
≥75	480 (58)	5.98 (0.55)	336 (37)	1.14 (0.05)

Abbreviation: LOS, length of stay.

[a] Number of visits and LOS are calculated from the National Inpatient Sample.[33] Number of individuals with at least 1 admission and the mean number of admissions per patient are calculated from the Nationwide Readmissions Database.

hospitalized individuals with SCD spend an average of 5 to 6 days per admission with an average of 2 to 3 admissions each year.

Discussion

The results from this analysis suggest that individuals with SCD experience reduced life expectancy, diminished quality-adjusted life expectancy, and lower lifetime income than individuals without SCD. We estimated that individuals with SCD live 22 fewer years (54 vs 76 years) and have a quality-adjusted life expectancy of about one-half that of individuals without SCD (33 vs 67 years). The reduced life expectancy translates into lower lifetime income for individuals with SCD, which is almost $700 000 less than that of individuals without SCD. To our knowledge, our study is the first to provide information on lost income owing to SCD, providing information on the association between SCD and productivity from a lifetime societal perspective.

Our analysis showed substantial reductions in lifetime income as a result of premature mortality. Given that the 22-year difference in life expectancy results in approximately $700 000 in lost lifetime income for individuals born with SCD, a contemporary SCD birth population of 1950 individuals per year in the United States would lose over $1.4 billion in lifetime income owing to premature mortality. These losses do not include other societal costs, such as lost workdays for disability, lost educational potential, lost workdays for caregivers caring for their affected children, and patient time spent in the hospital or the emergency department.[9,34-38] Moreover, unemployment and underemployment is higher for patients with SCD and, therefore, even when they are alive, patients with SCD have income losses that are not captured by this analysis. In one study, patients with SCD were less likely to be employed compared with their siblings without SCD (20% vs 75%), with 70% of patients with SCD reported as disabled.[39] Similarly low employment rates for patients with SCD have also been reported in other studies.[34,40] Therefore, while patients with SCD may receive income, their earnings are likely to be lower. Our analysis did not capture the economic burden to society from the replacement of earnings with government-funded disability support. Similarly, there are scant contemporary data available to quantify underemployment in this population. Moreover, caregiver loss of productivity and productivity losses associated with lost school, work, and other activities associated with SCD were not captured in our analysis, further underestimating income losses related to SCD; however, estimating these losses requires a prospective study that was out of the scope of this analysis. The overall societal perspective is that investing in interventions that prevent the morbidity and mortality associated with SCD can lead to large gains in income that are underestimated by this study; nonetheless, this study describes the potential magnitude of these income losses.

The model estimated a prevalent population of 87 328 (95% uncertainty interval, 79 344-101 398) individuals with SCD in the United States, which is similar to that reported in other US studies when corrected for early mortality.[1,2,36] However, this number may be an underestimate, especially because the derivation of the estimate from newborn screening cannot account for the contribution of immigration to the overall current prevalence of SCD in the United States. Because we had MCOD data sets, we calculated observed age at death over several time periods and noticed a trend toward increasing survival (eTable 4 in the Supplement), consistent with the literature.[11,17] An early study that prospectively followed up a cohort of individuals with SCD between 1978 and 1988 noted that the median age at death in individuals with sickle cell anemia (homozygous for sickle hemoglobin) was 42 years in men and 48 years in women, but the corresponding median age at death was higher (60 and 68 years) in individuals with sickle cell hemoglobin C disease (included in our estimates).[13] We did not have genotype information and did not categorize life expectancy for sickle cell anemia or other hemoglobinopathies. The projected life expectancy for SCD based on current mortality rates (54 years) is higher in our study than values reported from studies based on mortality databases (median range, 38-44 years)[11,12]; nonetheless, our results reflect a more updated

use of data resources and still represent a significant reduction in life expectancy of 22 years compared with a race/ethnicity- and age-matched population.

In addition to reduced mortality, SCD is associated with significant morbidity resulting in a 34-year quality-adjusted life expectancy difference between the SCD and non-SCD cohorts. It is well established that health-related quality of life is diminished in individuals with SCD.[41-43] Affected individuals experience a variety of SCD symptoms and long-term chronic morbidities, including pain,[25,44] vaso-occlusive crises,[45,46] fatigue,[47,48] depression,[41,49] and reduced social and school functioning,[47,50] that diminish patient well-being. Individuals with SCD report health-related quality of life similar to that of individuals undergoing hemodialysis.[51] Furthermore, this study only considered the association between pain and overall health-related quality of life, ignoring other symptoms, and therefore is likely an underestimation of the QALY loss. Nevertheless, our results suggest a substantial reduction in QALYs of patients with SCD who already have diminished life expectancy relative to individuals without SCD.

This analysis also did not include any direct medical costs associated with SCD, which are substantial. We observed that hospitalized patients with SCD aged 15 to 64 years spend an average of 5 to 7 days in the hospital and younger individuals in our analysis had an average length of stay of about 4 days, consistent with other studies.[52,53] Hospitalization and emergency department visits account for a substantial portion of the direct cost burden of SCD[54-61] and are potentially linked to additional lost productivity and income, which increase the burden of the condition, but which we did not quantify in our future income losses. To our knowledge, recent data for direct health care costs of SCD in the United States are not available. One study estimated the total lifetime health care costs (Medicare claims) to be nearly $1 million.[62] This figure may be a conservative estimate, as another study reported total lifetime health care costs (based on fees, 2008 $US) of $8.7 million in an individual with SCD living to age 50 years ($174 000 per year or $13.9 billion-17.4 billion per year overall).[20] Our analysis also did not consider lost income owing to unemployment and/or individuals receiving disability payments as their only sources of income, which may be considerable. A retrospective medical records review of 50 patients with SCD attending an outpatient hematology clinic reported an unemployment rate of 44%.[19] A survey study of 115 patients with SCD as part of the Cooperative Study of Sickle Cell Disease reported an unemployment rate of 39%, with women being nearly 3 times more likely to be employed than men.[18] When direct medical costs and lost income owing to unemployment or disability associated with SCD are considered in conjunction with our estimates of lost income owing to reduced life expectancy, it is apparent that the overall societal cost of SCD in the United States is considerable.

Limitations

There are a number of study limitations to consider. Our SCD prevalence estimates depended on correcting the CDC MCOD counts for underreporting; in age groups where the death rate was 0 (because of the small sample size in the study of Paulukonis et al[12]), we used the adjacent (lower) age group as a proxy. Our utility estimates did not account for fatigue and other important SCD symptoms, and therefore may not be reflective of the full range of quality-of-life outcomes. We also estimated future deaths for a contemporary birth population of SCD based on current death rates. Potential clinical advances or other factors may alter those death rates. Our higher estimates of life expectancy yielded more conservative estimates of lost life-years (approximately 20 years) than for life expectancy in the mid-40s. The analysis only considered the value of lost personal income owing to premature mortality. These losses do not include any direct medical costs or other societal costs, such as lost educational potential, lost workdays owing to caregivers caring for their affected children, or patient time spent in the hospital or the emergency department, nor do they account for additional challenges in finding and maintaining active employment because of SCD.

In a 1-way sensitivity analysis, personal income and mortality rates stood out as an important factor associated with the total lost lifetime income in this model. However, we were limited to a data set that only includes mortality data from 2 states (California and Georgia) in this study. The lack of

contemporaneous countrywide mortality data underscores the need for national registries that track the natural history of SCD and provide robust data on mortality, resource use, quality of life, employment, underemployment, and other metrics that can help quantify the true societal costs of SCD. This information would facilitate the appropriate deployment of resources and encourage innovation in a disease that disproportionately affects an underserved population.

Conclusions

A contemporary simulated population of individuals born with SCD was projected to live approximately 22 years less than a matched population of individuals without SCD. Moreover, when adjusted for the overall decrease in quality of life, our model suggests that individuals living with SCD lose over 3 decades in quality-adjusted life expectancy and approximately $700 000 in lifetime income compared with a matched non-SCD population. These losses do not include any direct medical costs or other societal costs. Nonetheless, our results suggest that, even measured solely as lost productivity and income, SCD has serious societal consequences beyond the resources required to provide medical care for individuals with SCD, information that can be used to anticipate public health care service needs and develop policy for this condition. Therefore, there is a need to develop disease-modifying therapies that can improve the underlying morbidity and mortality of individuals with SCD.

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SUPPLEMENT.

eTable 1. Centers for Disease Control: Estimates of Sickle Cell Disease Mortality by Age Group and Race/Ethnicity, Multiple Cause of Death 2007-16

eTable 2a. Mean Visual Analog Pain Scores for Sickle Cell Patients and Mapped EQ-5D Values

eTable 2b. Normative Mean EQ-5D Scores for US Adults