Examining the Effect of Hydroxyurea Treatment on Acute Care Spending and Utilization among Patients with Sickle Cell Disease

Azalea Thomson

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Nicholas Kassebaum

Joseph Dieleman

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Abstract

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Azalea Thomson

Chair of the Supervisory Committee:

Nicholas Kassebaum

Department of Global Health

Background: Sickle cell disease (SCD) is one of the most common inherited diseases in the U.S. and disproportionately affects African Americans and Hispanic Americans. People with SCD suffer acute pain crises and chronic pain throughout the lifespan and since disease cure is often unattainable, most turn to intensive and costly disease management, often with particularly high emergency care use. Hydroxyurea (HU), an inexpensive therapeutic drug, has proven to be effective at reducing pain crises. However, HU is underutilized for a variety of reasons including lack of insurance coverage, misperceptions and negative beliefs, and lack of provider awareness of guidelines. This paper aims to quantify how healthcare utilization, spending, and pain crises in SCD patients change before and after prescription of hydroxyurea, as well as estimate the potential averted burden if those not prescribed hydroxyurea were to be placed on the treatment regimen.

Methods: MarketScan Commercial Claims and Encounters databases person-specific information on healthcare utilization, healthcare spending, prescriptions, and diagnoses from 2016 to 2019 was aggregated into 90-day periods. 2-tailed t-tests were used to compare their mean outcomes in care utilization, spending, and pain crises per 90 days, pre and post receipt of that prescription and negative

binomial regressions were run to estimate mean outcomes over 5, 90-day time periods. Control SCD patients who had never received a prescription for hydroxyurea were matched 1:1 using propensity score matching to the previously established treated group on age, sex and genotype. T-tests and regressions were repeated to compare mean outcomes between control and treated groups. The ratio of change in outcome pre and post HU prescription among treated patients was then applied to the control group to estimate the potential averted care utilization, pain, and spending if the control received the treatment.

Results: 7,793 patients between the ages of 0 and 65 with a diagnosis of SCD from ICD-10 with a minimum of 1 year data coverage were selected, of whom 25.7% (n =2008) received a prescription for hydroxyurea at any point. 631 patients met the inclusion criteria for at least 90 days prior to initial prescription of hydroxyurea and 360 days post prescription. Prior to initiating treatment, hydroxyurea-treated patients had worse outcomes per 90 days with an estimated total of 5.4 (95% confidence interval 5.0-5.9) visits, $15,691 (13,088 – 18,812) net pay, and 1.2 (1.1-1.4) pain crises, compared to matched controls who in cross section had 1.7 (1.6-1.8) total visits, $4,319 (3,750 – 4,975) total net pay, and 0.3 (0.3-0.3) pain crises. Though outcomes among those initiating hydroxyurea remained significantly higher than controls, across care utilization, spending, and pain crises, patient 90-day outcomes were significantly lower post hydroxyurea initiation, in all types of care except outpatient visits and outpatient net pay, and the greatest declines were in inpatient settings.

Interpretation: SCD patients have high care utilization, spending, and pain outcomes. Those treated with hydroxyurea may experience greater disease severity, but this study indicates that if hydroxyurea were more widely utilized, their outcomes may be improved, and a large health and financial burden could be averted.

Introduction

Sickle cell disease (SCD) is one of the most common genetic diseases in the U.S. and significantly undermines quality of life and life expectancy.[1] People born with SCD have propensity to develop misshapen hemoglobin cells that cannot flow freely through blood vessels, leading to deoxygenation of tissues and organs that results in cell and tissue death, acute pain crises, and eventually chronic pain.[2] In addition, SCD can cause severe anemia, kidney dysfunction, acute chest syndrome, and stroke, and increase risk of infection, pregnancy complications, and maternal mortality. While cures for SCD, such as hematopoietic stem cell transplantation and gene therapy, do exist, these treatments are not yet accessible to most patients due to cost, risks associated with transplant toxicity, and limited implementation in health care settings. As a result, most patients born with SCD continue to live with the disease and manage their pain through a variety of means.[3]

Sickle cell disease has genetic origins in historically malaria-endemic regions, a trend hypothesized to be associated with the protective genetic characteristics of SCD against malaria. SCD is most commonly found in people of African, Middle Eastern, and South Asian descent, however as a result of global migration is found in a majority of populations throughout the world.[4] Despite a number of states with neonatal screening programs for SCD, the United States still does not have reliable national SCD surveillance. In the absence of such a system, accounting for early mortality it is estimated that around 72,000 to 98,000 people in the U.S. are living with SCD. With large between-state variance, the estimated all-population birth rate in the U.S. ranges from 1 in 400 to 1 in 30,000, however some groups are disproportionately affected—approximately 1 in 365 African Americans and 1 in 16,300 Hispanic Americans are born with SCD.[5] Disease miscoding inaccuracies and common comorbidities have confused mortality estimates, however SCD is known to shorten life significantly, with estimates of life expectancy in the U.S. around 40 years.[5]

Hydroxyurea is one of the most effective drugs currently available for treating SCD patients. The therapy, an oral chemotherapeutic drug, ameliorates some of the clinical problems of SCD, pain in particular, by inhibiting production of adult beta haemoglobin (which leads to sickled red blood cells), and raising fetal haemoglobin (which can produce normal red blood cells).[3] However, hydroxyurea is underutilized—there is evidence in one clinical setting reporting underutilization up to 70%.[6] Several barriers preventing widespread use have been suggested, including healthcare provider lack of knowledge about hydroxyurea, patient/family misperceptions of risks, limited support from lay organizations, and inconsistent medical delivery systems.[7,8]

One potential lever to motivate policy action that reduces some of these barriers is to show the potential for hydroxyurea treatment to drive down acute care utilization and health spending. However, SCD is already less well funded than diseases such as hemophilia and cystic fibrosis, which affect far fewer individuals, and in regions without specialized health care providers, there are even fewer resources.[9] There is a clear need to demonstrate the value of investing in existing treatments to improve outcomes in a population that faces disproportionate health risks. The objective of this study is to examine, in a population with access to health care, the extent to which hydroxyurea is utilized as an intervention among SCD patients, to quantify outcomes in health utilization and spending prior to and after initiation of hydroxyurea therapy, and to examine the opportunity for gains in health if hydroxyurea were more widely utilized.

Methods

Data collection

Data was obtained from IBM's MarketScan Commercial Claims and Encounters from 2016 to 2019 and enrollees were included if they had a diagnosis code ranging from International Classification of Diseases codes (ICD-10) D57.0 to D57.8, excluding sickle cell trait. To ensure complete records, only individuals present in the dataset for at least 365 days and not enrolled in a clinical trial were included. Over the four-year period, this resulted in 18,045 total patients diagnosed with SCD among males and females aged 0 to 65 years. Patients were then linked to pharmaceutical claims data by enrollee ID such that cohorts could be stratified by hydroxyurea treatment using the national drug code (NDC) variable. NDC codes for hydroxyurea were verified using RxNorm. By this logic, 5,786 patients (74.2%) never received a prescription for hydroxyurea, and 2,007 (25.8%) patients received a prescription for hydroxyurea at any point in the study period. Patient demographics (unique on year, age, and location) are available in Table 1.

{{Table 1}}

Genotyping

Genotypes were assigned (Homozygous SCD, Hemoglobin SC disease, Mild SCD, and other SCD) to each patient using diagnosis codes for outpatient and inpatient visits. If a patient had more than one unique genotype from their entire collection of SCD diagnoses, a series of steps was taken to determine the patient's "true genotype." First, if a diagnosis was made by Pediatric Hematology, Oncology, or Hematology specialists, this were assigned as the "true genotype" (or genotypes). Following this prioritization, among the unique genotypes for a given patient, the genotype which had the greatest number of outpatient diagnoses was assigned the "true genotype." If there were no outpatient diagnoses or each genotype had an equal number of diagnoses, then the genotype with the greatest number of inpatient diagnoses was selected. Finally, if there were no outpatient or inpatient diagnoses, or each genotype had an equal number of diagnoses, then the genotype with the greatest number of total diagnoses was selected. This resulted in 14 patients who were dropped because their genotype could not be distinguished.

Matching

The treated cohort for analysis was established by including only patients who were present in the dataset at least 90 days prior to receiving an initial prescription for hydroxyurea, and at least 360 days following the initial prescription. 90 days was determined to be an adequate baseline period based on frequent utilization of care with SCD and 360 days was chosen for a sufficient follow-up period since hydroxyurea is quickly absorbed and studies show a clinical response will be observed within 3-6 months.[6,10] Controls were limited to the same study duration by selecting patients covered in the dataset for at least 450 days, and limiting analysis of encounters to a 450 day time window. Treated patients were matched 1:1 to a control not prescribed hydroxyurea, by age, sex, and genotype using propensity score matching via the "MatchIt" package in R statistical software. The control and treated group had nearly identical composition across age group, genotype, region, and sex (Table 2). The patients aged 10 to 29 years comprised nearly 50% of each cohort, with over an 80% majority of the

homozygous SCD genotype, over 50% of patients in the South, and at 53.4%, slightly more females than males in the sample.

{{Table 2}}

Outcomes of Interest

MarketScan Commercial Claims and Encounters capture person-specific information on healthcare utilization, healthcare spending, prescriptions, and specific diagnoses. Diagnoses with ICD-10 codes D57.0 to D57.8, excluding sickle cell trait, determined inclusion in the study and prescriptions from NDC codes determined hydroxyurea treatment. Encounters were designated a pain crisis based on ICD codes. If for a given patient, the crisis date was within 14 days of the previous crisis date, the encounter was not counted since it was assumed to be the same pain crisis event. Spending was analyzed as the amount received by the provider, excluding patient out-of-pocket and coordination of benefits, termed "net pay." Outcomes were further analyzed by type of care, using MarketScan tables marked as inpatient or outpatient, and further designating inpatient or outpatient visits as emergency visits by the service category variable. The number of distinct healthcare visits (unique by date), the net pay, and number of pain crises were aggregated by 90-day period and by type of care.

Statistical Analysis

Two-tailed t-tests at the 0.05 significance level were conducted to determine whether the mean outcome in care utilization, spending, and pain crises per 90 days differed pre- and post-hydroxyurea treatment. Estimates for patient outcomes per 90-day period pre-and post-hydroxyurea were obtained by running negative binomial regressions for over-dispersed count data using R version 4.0.5. Two degree-of-freedom chi-square tests were conducted for indication of significance of hydroxyurea initiation as a predictor of the outcome. The ratio of change in outcome before and after hydroxyurea prescription among treated patients was applied to the control group to estimate the potential averted care utilization, pain, and spending if the control received the treatment.

Results

Overview

Compared to controls, the 631 patients treated with hydroxyurea analyzed for the 450-day study period had significantly higher visits, pay, pain crises, and length of stay for inpatient visits. Prior to hydroxyurea initiation, and across the four SCD genotypes, per 90 days treated patients had a total of 5.4 (5.0-5.9) visits, compared to control patients who had 1.7 (1.6-1.8) visits, a total of $15,691 (13,088-18,812) in spending, compared to control patient spending of $4,319 (3,750-4,975), and a total of 1.2 (1.1-1.4) pain crises, compared to 0.3 (0.3-0.3) crises among control patients (Figure 1). However, in treated patients alone, outcomes across visits, pay, and pain crises decreased significantly post initiation of hydroxyurea in inpatient and emergency contexts. After initiation of hydroxyurea treatment, outcomes had the largest decrease in the first 90 days, following which outcomes decreased monotonically in outpatient and total visits, or mostly leveled off. Care utilization, spending, and pain crises were highest among SCD patients categorized as other sickle cell genotype (ICD-10 D57-D57.819), however sample size was low and findings were not significant. Similarly, since hemoglobin SC disease and mild SCD each made up less than 10% of the sample, the main genotype of interest was homozygous SCD, which, like all genotypes combined, had significantly lower outcomes post hydroxyurea except in outpatient visits and outpatient net pay (Figure 2).

{{Figure 1}}

{{Figure 2}}

Change in outcomes post hydroxyurea

Health care utilization among SCD patients was highest for outpatient visits, followed by emergency visits, with the fewest inpatient visits (Table 3). Patients treated with hydroxyurea had 5.4 (5.0-5.9) visits in the 90 days prior to initiation of treatment and decreased by 21.0% to an average of 4.3 (4.1-4.5) visits per 90 days post initiation. Inpatient visits decreased by 41%, emergency visits decreased 36%, and outpatient visits decreased 12%, with outpatient care still comprising the greater share of total visits, though to a greater extent, post treatment. Additionally, the average number of days spent in an inpatient visit per 90 days decreased from 1.8 (1.4-2.3) days prior to treatment, to 1.1 (0.9-1.2) days post treatment.

Spending was highest for patients prior to treatment at $15,691 (13,088-18,812) per 90 days, which decreased by 40% to $9,417 (8,601-10,311) post treatment. The type of care with the greatest proportion of total spending was inpatient, at $11,465 (7,023-18,717) prior to treatment, and $6,240 (4,883-7,972) post treatment. Similar to changes in care utilization post hydroxyurea, the type of care with the greatest decrease was in inpatient spending, which dropped by 46%, followed by emergency spending which decreased 37%, and outpatient spending, which fell to 14%.

Treated patients had 1.2 (1.1-1.4) crises per 90 days prior to treatment, averaging 4.8 total crises per year, which fell to 0.9 (0.8-0.9) crises per 90 days post treatment, for an annual average of 3.6 total crises. The type of care setting in which patients sought care for their pain crisis was highest in outpatient both before and after hydroxyurea, but outpatient crises comprised a greater proportion of total crises post treatment. After hydroxyurea initiation outpatient crises dropped by 22% and inpatient crises dropped 43%.

{{Table 3}}

Counterfactual outcomes among controls

When the ratio of change in outcome before and after hydroxyurea prescription among treated patients was applied to the control group patients with SCD would have reduced care utilization, spending, pain crises, and inpatient length of stay (Table 4). Per 90 days, the total number of visits would decrease from 1.7 visits to 1.4 visits, a total of $1727 would be saved, pain crises would drop from 0.3 to 0.2, or by 1.2 per year to less than 1 per year. Additionally, the length of inpatient visit stay would be lowered by 20% to less than half a day per 90 days.

{{Table 4}}

Discussion

Among patients with SCD, hydroxyurea is effective at reducing pain crises and can additionally ameliorate other negative health outcomes such as acute chest syndrome and contribute to increased survival. Despite its proven benefits, hydroxyurea is not currently utilized to its full potential due to factors such as physician lack of knowledge, pre-conceived fears about side effects[11], a lack of support from organizations with the power to more widely advocate for its use, and medical systems that lack consistent protocols for caring for patients with SCD. In this sample of 7,805 total patients with at least

one full year of coverage, diagnosed with SCD over four years, the vast majority (74.3%) never received a prescription for hydroxyurea. However, among those patients who did get treatment, after their initial prescription, care utilization was reduced up to 41%, spending up to 46%, and pain crises up to 43%. The ability of hydroxyurea to improve health outcomes and simultaneously reduce burden on the health care system represents an overlooked opportunity for health system strengthening.

By nature of the sudden onset of vaso-occlusive crises, care for patients with SCD often occurs within emergency departments, and hospital admission and prolonged inpatient stays are common.[12,13] Improved pain management through the use of hydroxyurea self-administered daily, and outpatient care monitoring can help prevent costly and life-threatening hospitalizations and emergency visits. This analysis showed a reduction in care utilization, spending and pain crises more than three times higher in the inpatient setting than in the outpatient setting after hydroxyurea initiation. Some researchers have suggested co-management of disease (coordinated care from a primary care non-hematologist and one hematologist), while currently uncommon in practice, is associated with improved hydroxyurea adherence and may influence emergency and inpatient care utilization.[14] Ultimately, reduction of care and spending among SCD patients will likely not reach zero without curative therapy and hydroxyurea thus plays a key role in transitioning patient health care out of inpatient and emergency settings and into outpatient clinics where their disease can be better managed.

Though the patients treated with hydroxyurea had lower outcomes after their initial prescription, care utilization, spending, and pain crises were lower in the control patients overall. This trend is similar to that observed by Stallworth and colleague's analysis of children on Medicaid in South Carolina which showed higher pain crises in treated patients, but a reduction in pain crises among the treated group after hydroxyurea was started.[15] Several hypotheses have been proposed for this pattern, the most likely hypothesis for this observation is that more severe symptoms require more interaction with the healthcare system, escalating the likelihood of seeing a specialist, and increasing the likelihood of hydroxyurea initiation.[16] This analysis attempted to control for confounding in disease severity by assigning patients genotypes, a marker for disease severity, however this method likely did not entirely capture the severity component. Additionally, when patients were matched by total number of pain crises in addition to genotype, age, and sex, indicated outcomes were still significantly lower in control patients than treated patients. Other studies have used blood counts and previous health complications as well as the annual number of crises before receiving treatment[17] in order to isolate the effect of hydroxyurea, however the inclusion of these variables would require a linkage analysis with more detailed hospital records and is beyond the scope of this analysis.

While clinical trials have examined efficacy in individuals with SCD with substantial disease severity, captured as at least three pain crises per year,[7] the use of hydroxyurea holds potential benefits for those who do not meet this limiting clinical cutoff. While this analysis estimated 0.3 pain crises per 90 days, or 1.2 pain crises annually, among control patients, and therefore may not have been suggested hydroxyurea treatment by their provider based on the three-crisis cutoff, any amount of pain interfering with daily life would make these patients eligible for treatment. The 2014 National Heart Lung and Blood Institute report on Evidence-Based Management of SCD suggests offering use of hydroxyurea in non-pregnant adults with SCD-associated pain that interferes with daily life, and in children at least 9 months of age, regardless of severity of disease, to reduce complications.[10] However, once individuals are prescribed hydroxyurea, consistent office visits and laboratory monitoring is necessary, which may cause an initial increase in care utilization and spending if patients were previously self-managing pain.

Additionally, a lack of insurance coverage can negatively impact ability to have consistent access to health care and prescriptions which points to the importance of equity considerations in hydroxyurea treatment.[18] The majority of individuals who have SCD are Black or Hispanic, and as a result of systemic racism, these individuals often experience higher rates of poverty and lower insurance coverage, leading to challenges in access to hydroxyurea.[9] A limitation of this analysis is that the MarketScan does not contain race and ethnicity information and only includes patients under the age of 65 with employer-based health insurance, making it not nationally representative. Alternative data sources however are lacking; for example, due to small sample size, the AHRQ's Medical Expenditure Panel Survey (MEPS) dataset, while nationally representative, lacks sufficient data on patients with SCD. However, despite the limitations of MarketScan data, it is useful to know under an ideal scenario where everyone has insurance, how outcomes of spending and care utilization vary by hydroxyurea treatment.

Evidence for increasing HU treatment shows the effectiveness of revised consent procedures[11] , implementation of a multidisciplinary treatment team comprised of a physician, nurse practitioner, and licensed clinical social worker[19], and targeted educational sessions about hydroxyurea for SCD patients followed by offer to begin treatment.[20] Beyond strengthening assessment of the effect of hydroxyurea by using additional variables to control for confounding in disease severity, future applications of this work could include efforts to increase duration of time analyzed to better understand patterns for initiation of hydroxyurea treatment. Additionally, mixed methods research would be helpful to gather more information on barriers to treatment with hydroxyurea and associated outcomes. Overall, until greater investment in SCD cures such as gene therapy and bone marrow transplantation lead to improved affordability and accessibility, hydroxyurea provides an ideal alternative for providing pain relief to patients, improving health outcomes, and reducing health care system utilization and cost.

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Tables and Figures

Table 1. Descriptive Summary of SCD Control and Hydroxyurea-treated Patients

Independent variable	Total (n=18045)	Control (n=12403, 68.7%)	HU Treated (n=5642, 31.3%)
Age group			
0-4	1373	1078 (8.7%)	295 (5.2%)
5-9	1551	1003 (8.1%)	548 (9.7%)
10-19	3599	2101 (16.9%)	1498 (26.6%)
20-29	3250	1954 (15.8%)	1296 (23.0%)
30-39	2794	2007 (16.2%)	787 (13.9%)
40-49	2685	1994 (16.1%)	691 (12.2%)
50-59	2076	1658 (13.4%)	418 (7.4%)
60-65	717	608 (4.9%)	109 (1.9%)
Sex			
Males	7684	5031 (40.6%)	2653 (47.0%)
Females	10361	7372 (59.4%)	2989 (53.0%)
Region			
Midwest	2660	1871 (15.1%)	789 (14.0%)
Nation	1656	1104 (8.9%)	552 (9.8%)
Northeast	3127	2142 (17.3%)	985 (17.5%)
South	9668	6645 (53.6%)	3023 (53.6%)
West	934	641 (5.2%)	293 (5.2%)
Genotype			
Homozygous SCD	12455	7728 (62.3%)	4727 (83.8%)
Hemoglobin SC disease	3486	3026 (24.4%)	460 (8.2%)
Mild SCD	1734	1330 (10.7%)	404 (7.2%)
Other SCD	370	319 (2.6%)	51 (0.9%)
Year			
2016	5539	4184 (33.7%)	1355 (24.0%)
2017	4379	2892 (23.3%)	1487 (26.4%)
2018	4463	2936 (23.7%)	1527 (27.1%)
2019	3664	2391 (19.3%)	1273 (22.6%)

Table 2. Descriptive summary of matched cohorts.

Independent variable	Control (n=631)	HU Treated (n=631)
Age group		
0-4	52 (8.2%)	46 (7.3%)
5-9	45 (7.1%)	46 (7.3%)
10-14	155 (24.6%)	167 (26.5%)
20-29	140 (22.2%)	151 (23.9%)
30-39	104 (16.5%)	90 (14.3%)
40-49	90 (14.3%)	83 (13.2%)
50-59	37 (5.9%)	39 (6.2%)
60-65	8 (1.3%)	9 (1.4%)
Sex		
Males	291 (46.1%)	294 (46.6%)
Females	340 (53.9%)	337 (53.4%)
Genotype		
Homozygous SCD	538 (85.3%)	528 (83.7%)
Hemoglobin SC disease	50 (7.9%)	52 (8.2%)
Mild SCD	36 (5.7%)	43 (6.8%)
Other SCD	7 (1.1%)	8 (1.3%)
Region		
Midwest	91 (14.4%)	87 (13.8%)
Nation	67 (10.6%)	78 (12.4%)
Northeast	89 (14.1%)	89 (14.1%)
South	355 (56.3%)	346 (54.8%)
West	29 (4.6%)	31 (4.9%)

Table 3. Predicted mean outcomes in initial 90 days prior to hydroxyurea initiation and across 360 days after initial hydroxyurea prescription among SCD patients.

Outcome	Pre HU initiation (95% CI)	Post HU initiation (95% CI)
Inpatient visits*	0.6 (0.5-0.6)	0.3 (0.3-0.4)
Outpatient visits*	3.6 (3.3-3.9)	3.2 (3-3.3)
Emergency visits*	1.2 (1.1-1.4)	0.8 (0.7-0.9)
Total visits*	5.4 (5-5.9)	4.3 (4.1-4.5)
Inpatient net pay*	11465 (7023-18717)	6240 (4883-7972)
Outpatient net pay	2267 (1895-2713)	1948 (1781-2131)
Emergency net pay*	1959 (1387-2767)	1230 (1035-1461)
Total net pay*	15691 (13088-18812)	9417 (8601-10311)
Total inpatient crises*	0.4 (0.4-0.5)	0.2 (0.2-0.3)
Total outpatient crises*	0.8 (0.7-0.9)	0.6 (0.6-0.7)
Total crises*	1.2 (1.1-1.4)	0.9 (0.8-0.9)
Average inpatient length of stay*	1.8 (1.4-2.3)	1.1 (0.9-1.2)

*HU initiation is a statistically significant predictor of the outcome at the .05 level

Table 4. Predicted mean outcomes among control cohort across 450 day study period and counterfactual outcomes

Outcome	Control cohort (95% CI)	Reduction	Counterfactual
Inpatient visits	0.1 (0.1-0.1)	0.05	0.1
Outpatient visits	1.3 (1.3-1.4)	0.16	1.2
Emergency visits	0.3 (0.2-0.3)	0.1	0.2
Total visits	1.7 (1.6-1.8)	0.36	1.4
Inpatient net pay	2623 (1782-3861)	1195	1428
Outpatient net pay	1362 (1174-1580)	192	1170
Emergency net pay	334 (333-335)	124	210
Total net pay	4319 (3750-4975)	1727	2592
Total inpatient crises	0.1 (0.1-0.1)	0.03	0
Total outpatient crises	0.2 (0.2-0.2)	0.05	0.2
Total crises	0.3 (0.3-0.3)	0.08	0.2
Average inpatient length of stay	0.4 (0.4-0.5)	0.19	0.3

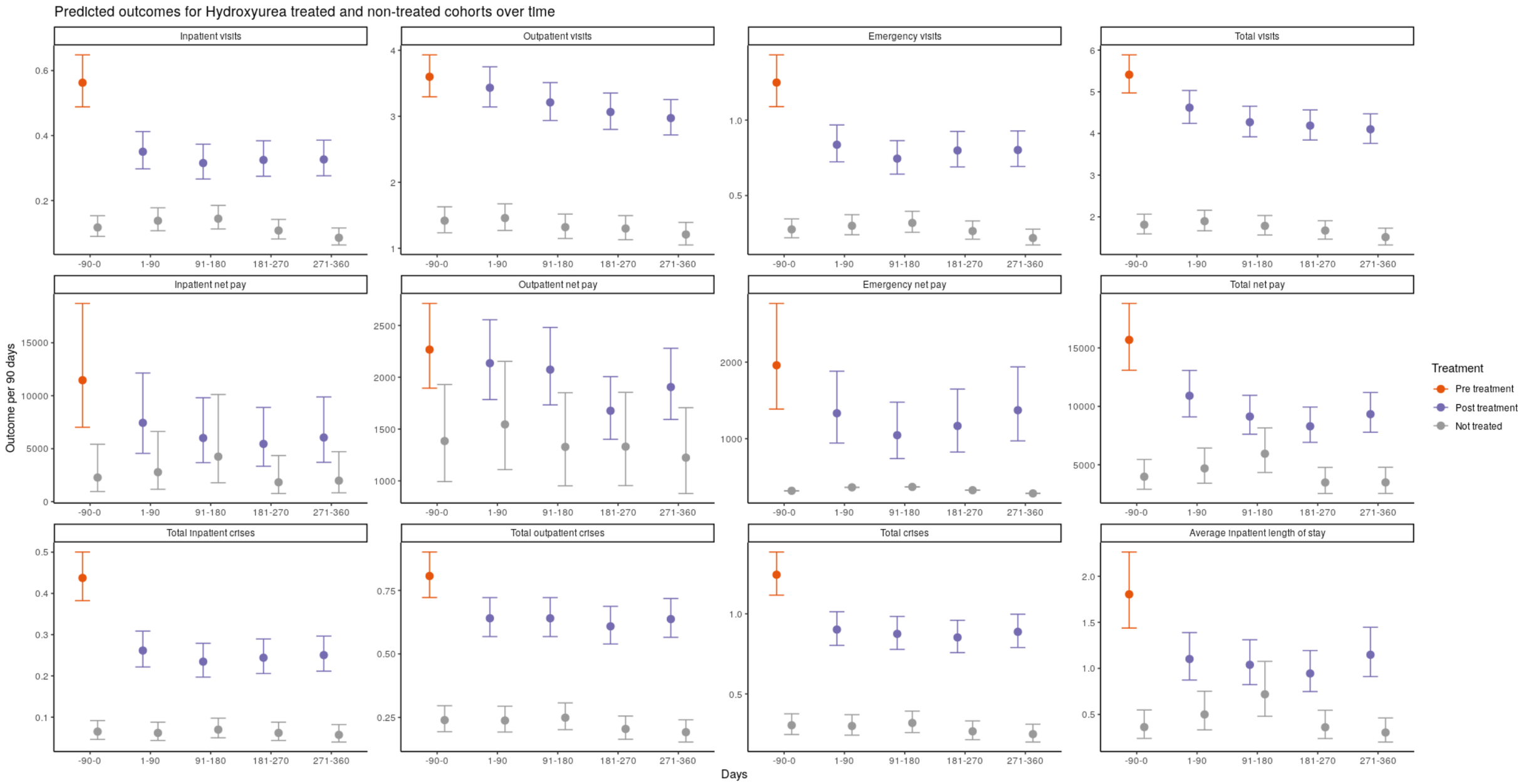

Figure 1. Predicted outcomes for hydroxyurea treated and non-treated cohorts over time, all genotypes combined, with 95% uncertainty intervals.

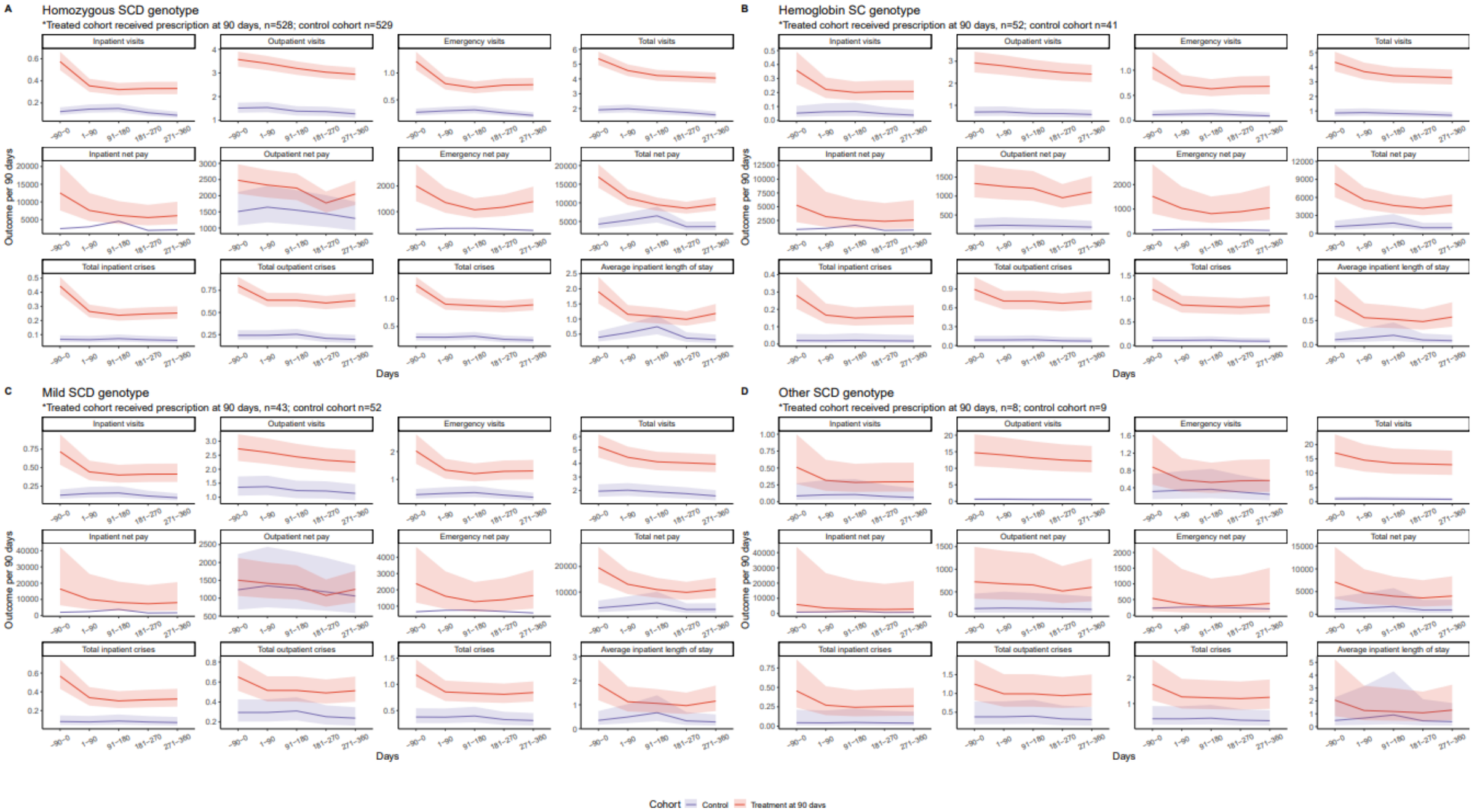

Figure 2. ***Predicted outcomes by genotype for SCD patients in hydroxyurea and control cohorts over time****. Mean number of health care visits, net pay, pain crises, and average inpatient length of stay by 90 days with 95% uncertainty interval. The treated cohort received their initial hydroxyurea prescription at 90 days*