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Paul E. George Date

The Impact of Air Pollution and Long-term Hydroxyurea Use on Health Outcomes in Children with Sickle Cell Disease

By

Paul E. George
Doctor of Philosophy

Health Services Research and Health Policy

_____
David Howard, PhD
Advisor

_____
Stefanie Ebelt, ScD
Committee Member

_____
Wilbur Lam, MD PhD
Committee Member

_____
Joseph Lipscomb, PhD
Committee Member

Accepted:

_____
Kimberly Jacob Arriola, PhD, MPH
Dean of the James T Laney School of Graduate Studies

_____
Date

The Impact of Air Pollution and Long-term Hydroxyurea Use on Health Outcomes in Children with Sickle Cell Disease

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Paul E. George, MD

Advisor: David Howard, PhD

An abstract of
A dissertation submitted to the Faculty of the
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Abstract

The Impact of Air Pollution and Long-term Hydroxyurea Use on Health Outcomes in Children with Sickle Cell Disease

By Paul E. George, MD

Sickle cell disease (SCD) is a chronic condition characterized by acute, severe pain events, lung disease, and other end-organ damage. Despite being a monogenetic defect, the clinical course of SCD is quite variable and difficult to predict, with some children remaining relatively unaffected in childhood, and others with severe, debilitating disease. Understanding factors that contribute to this phenotypic variability is crucial, as it may unveil modifiable risk factors at the patient level and areas for policy intervention at the population level. For this dissertation, I examine the impact of air pollution exposure on outcomes in children with SCD. I find that air pollution exposure, both short-term and long-term, and at the cohort level and individual level, is associated with significantly worse outcomes in children with SCD. Separately, I examine the long-term, time-varying impact of hydroxyurea, the main disease modifying medication in SCD. Using contemporary difference-in-differences and event study analyses, I find that hydroxyurea has sustained, positive impact on clinical outcomes, whereas its impact on hematologic parameters diminishes over time. In summary, this work contributes to a deeper understanding of the multifaceted influences on SCD outcomes, emphasizing the need for comprehensive and sustained interventions. Lastly, I study the diffusion of a specific cost-saving innovation – outpatient treatment for appendicitis – to better understand why it was widely-adopted.

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A heartfelt thanks goes to the Aflac Sickle Cell Database Team for their invaluable assistance with data extraction, which was crucial to the success of my project. I would also like to acknowledge the many clinical mentors who have generously shared their time and expertise throughout. While they are too numerous to name individually, I am sincerely grateful for their guidance and insights.

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Chapter 1

Are children with sickle cell disease at particular risk from the harmful effects of air pollution? Evidence from a large, urban/peri-urban cohort.

Abstract

Introduction: Pathophysiologic pathways of sickle cell disease (SCD) and air pollution involve inflammation, oxidative stress, and endothelial damage. It is therefore plausible that children with SCD are especially prone to air pollution's harmful effects.

Methods: Patient data were collected from a single center, urban/peri-urban cohort of children with confirmed SCD. Daily ambient concentrations of particulate matter ($PM_{2.5}$) were collected via satellite-derived remote-sensing technology, and carbon monoxide (CO), nitrogen dioxide (NO_2), and ozone from local monitoring stations. We used multivariable regression to quantify associations of pollutant levels and daily counts of emergency department (ED) visits, accounting for weather and time trends. For comparison, we quantified the associations of pollutant levels with daily all-patient (non-SCD) ED visits to our center.

Results: From 2010-2018, there were 17 731 ED visits by 1740 children with SCD (64.8% HbSS/HbSβ_0). Vaso-occlusive events (57.8%), respiratory illness (17.1%), and fever (16.1%) were the most common visit diagnoses. Higher three-day (lags 0-2) rolling mean $PM_{2.5}$ and CO levels were associated with daily ED visits among those with SCD ($PM_{2.5}$ incident rate ratio (IRR) 1.051 (95% CI 1.010-1.094) per 9.4 $\mu g/m^3$ increase; CO 1.088 (1.045-1.132) per 0.5 ppm). NO_2 showed positive associations in secondary analyses; ozone levels were not associated with ED visits. The comparison, all-patient ED visit analyses showed lower IRR for all pollutants.

Conclusions: Our results suggest short-term air pollution levels as triggers for SCD events and that children with SCD may be more vulnerable to air pollution than those without SCD. Targeted pollution-avoidance strategies could have significant clinical benefits in this population.

Introduction

Air pollution is a major cause of death and disability and is particularly harmful for those with underlying chronic disease, including cardiovascular, cerebrovascular, and lung disease.[1, 2] Pollution exposure is highest among minorities and otherwise marginalized populations.[3] Young children are also especially sensitive to its effects: they breathe more air per bodyweight than adults and their metabolic pathways are unable to rapidly detoxify pollutants.[4, 5] The most well-studied air pollutant with regards to human health is particulate matter with a diameter of 2.5 microns or less ($PM_{2.5}$) and no safe threshold of $PM_{2.5}$ has been identified.[6] Carbon monoxide (CO), nitrogen oxides (NOx), and ozone are other key pollutants.[7]

Sickle cell disease (SCD) is one of the most common monogenetic disorders in the United States, with an estimated prevalence of 100 000.[8] Hallmarks of the disease are recurrent, painful, inflammatory vaso-occlusive events (VOE), severe pneumonias/acute chest syndrome, and multi-organ damage.[9, 10] VOE are the main source of morbidity and mortality in SCD, with population-wide studies showing that VOE and fever account for the majority (60-80%) of pediatric emergency department (ED) visits.[11, 12] Hydroxyurea and other disease-modifying therapies such as L-glutamine and crizanlizumab have been proven efficacious in reducing the number of VOE; however, they do not completely eliminate VOE and clinical management during an acute event consists mainly of supportive care.[13] Though there are several well-known causes of VOE (*e.g.,* infection, dehydration), many patients present without a clear trigger.[14] As such, identifying underlying triggers and associated biologic pathways is key in improving patient care.

There are well-known biologic pathways that indicate exposure to air pollution could be an unrecognized yet important trigger for VOE. First, it is well-established that air pollution exposure induces a systemic inflammatory response.[15–17] Additionally, air pollution directly damages the lungs; acute chest syndrome is characterized by acute lung injury, often of unknown etiology.[18, 19] Other pathways that connect air pollution exposure to poor health outcomes in other settings include altered

metabolic pathways and direct endothelial injury;[20] SCD is a chronic inflammatory disease with baseline oxidative stress and the ongoing endothelial damage is recognized as contributing to the disease's substantial morbidity and mortality.[21, 22]

Several studies have examined the associations of daily increases in air pollution with acute SCD complications, with city-wide, retrospective studies demonstrating a positive association between SCD complications and higher levels of daily ambient pollution.[23–25] While representing important first steps, these studies have all had limitations which hamper interpretation. From a pollution standpoint, data was obtained from a single or only a few monitoring stations, which may not account for city-wide pollution variability. From an SCD standpoint, they have relied on ICD-9/10 codes to identify SCD patients, which are subject to error and often do not reliably distinguish between different types of SCD (*e.g.* HbSS vs HbSβ+ vs HbSC). For example, an analysis of such hospital discharge coding found that 17% of patients with HbSS/HbSβ0 and nearly 77% of patients with HbSC were misclassified by genotype; this is a serious limitation given the clinical, laboratory, and treatment differences across genotypes.[26] Studies to date have also not included a comparison group to investigate the relative impact of air pollution. Finally, prior studies have relied on cross-sectional snapshots of ED visits rather than following a single cohort of patients over time [23–25].

In this study, we aim to measure the effects of ambient (outdoor) air pollution on pediatric SCD. We hypothesized that short-term changes in air pollutant levels are significantly associated with daily burden of ED visits in this population, with the majority of visits due to inflammatory events (*e.g.,* VOE, fever). Furthermore, we hypothesize that children with SCD are especially sensitive to air pollution's harmful effects as compared to the general pediatric population. This study augments existing literature by a) utilizing data from a large, longitudinal cohort of children with confirmed SCD in the United States, thereby eliminating errors inherent with ICD-9/10 codes, allowing us to analyze patients by specific SCD genotype, and including only patients who live within the area of interest, b) focusing on the pediatric population, a group uniquely vulnerable to air pollution's effects, c) incorporating satellite-derived $PM_{2.5}$

data and data from multiple monitoring stations, which incorporates city-wide variability in air pollution levels, and d) including an all-patient (non-SCD) analysis for comparison.

Methods

SCD Patient Database

Patient data were abstracted from electronic medical records of patients in an ongoing cohort of children with SCD at Children's Healthcare of Atlanta (CHOA), a comprehensive, clinical database and linked to CHOA's electronic health record database. Specifically, every child with SCD (verified by hemoglobin analysis) with ≥ 1 clinical encounter at CHOA, including the affiliated hospitals and outpatient clinics, is included in this database. Of note, CHOA is the primary pediatric healthcare system in the Atlanta metropolitan area, including three academic hospitals that provide inpatient, outpatient, and ED care; our analysis included data from all three hospitals. Importantly, CHOA accounts for ~95% of pediatric SCD hospitalizations within the Atlanta metropolitan area [27], representing a nearly complete population-based sample. Patient information included sociodemographic (including home address at time of encounter) and clinical information.

Given variable levels of fetal hemoglobin and disease severity under 1 year of age, we limited our analysis to patients 1.0-17.9 years of age at time of visit. To only include patients who would plausibly seek ED care at a CHOA facility, our geographic area of interest (buffer zone) was defined to include those with a home address (and associated pollution levels) within 20 miles of the nearest CHOA ED. Of note, we also performed secondary analyses that further narrowed the buffer 10 and 5-mile radiuses. Finally, patients were excluded if they were coded as lost to follow up, which we defined as patients who went more than 365 days without being seen by a CHOA provider, with the goal of excluding the minority of patients who receive their SCD care elsewhere. Note that our analysis is ED-focused, and thus only includes children who have visited an ED during the study timeframe. We abstracted ICD-9/10 codes to determine cause of ED visit. This study was approved by the CHOA Institutional Review Board.

To test our hypothesis that children with SCD are especially impacted by air pollution, we quantified the associations of pollutant levels with daily all-patient ED visits to our center. Specifically, this comparison analysis included daily counts of ED visits from all children aged 1.0-17.9 years, minus children with SCD, at a CHOA ED (data available June 2013 – December 2018).

Air Pollution Data

Daily air pollution data were acquired from two main sources. For $PM_{2.5}$, we accessed publically avaliable, remote-sensing data developed by the NASA Socioeconomic Data and Applications Center (SEDAC) [28] to create a database of daily $PM_{2.5}$ levels in 1km*1km grids covering the Atlanta metropolitan area. We then averaged the grid values over our buffer zones of interest to obtain daily $PM_{2.5}$ values for buffers around each facility. As the three CHOA EDs are all within 10 miles of each other, we then averaged the values to obtain one daily $PM_{2.5}$ value for each buffer to apply in our analyses. Remote-sensing data allow for measurement and inclusion of neighborhood-level variations in pollutant levels and have been well-validated and published in other health settings.[29–31] SEDAC data were available for the period January 1, 2001 – December 31, 2016.

For other air pollutants of interest, we did not have such granular data and instead relied on four Environmental Protection Agency (EPA) pollution monitoring stations in the Atlanta area (Supplemental Figure 1). Data from EPA monitoring stations included $PM_{2.5}$ (for validation of SEDAC remote-sensing data), CO, NO_2, and ozone, with data available from January 1, 2010 – December 31, 2018. We used daily averages across all monitoring stations for each pollutant of interest. Weather data came from Atlanta Hartsfield-Jackson International Airport.

Measures and Statistical Analysis

Our primary exposures of interest were individual air pollutant levels for $PM_{2.5}$, CO, NO_2, and ozone. Specifically, we assessed 3-day rolling means (*i.e.,* average of day of ED visit, 1 day prior, 2 days prior) of pollutants. This strategy is consistent with air pollution literature and the clinical course of SCD,

which suggests children most often present to the ED 2-4 days after symptom onset.[14, 19] We also analyzed how specific day (relative to ED presentation) pollutant levels impacted ED visits, both for clinical information and as sensitivity analyses/validation of our models. Our outcome of interest was a count variable of the total number of ED visits per day (summed across the three CHOA EDs) by the 1740 patients in our SCD cohort and total daily ED visits summed across the three EDs for the comparison group.

To estimate the effect of air pollution levels on daily ED visits, we created generalized linear models (negative binomial distribution [32, 33]), with the general form

$$log(y) = \alpha + \beta_1 pollutant + I_{day} + I_{rain} + g(temp) + g(time_{trend}) \quad (1)$$

where y is total ED visits/day by our population of interest and β_1 is our coefficient of interest on pollutant values (continuous, mean-centered and scaled by 2 times their standard deviation (s.d.) to allow for comparison of effects amongst different pollutants).[34] The model accounts for other factors potentially associated with both air pollution levels and ED visits, including day of week, rain (indicator variable, 1 = rainfall > 0.5 inches/day, on day of visit), temperature (cubic spline of minimum daily temperature with knots at 25th, 75th percentiles, on day of visit), and long-term time trends (cubic spline with knots at changes in season). Days with missing pollutant values were represented as missing. Incident rate ratios (IRR) were obtained by exponentiating the β_1 coefficients ($e^{\beta} = IRR$), where IRR is the relative change in ED visits per 2 s.d. change in air pollutant levels. For example, an IRR of 1.04 can be interpreted as, for every 2 s.d. increase in air pollutant level, ED visits increase by 4%.

We performed sensitivity analyses and robustness checks on our model, including quasi-Poisson distribution (which allows for overdispersion), different temperature and time-trend splines and lags, different lag-day models, lead day analyses for identifying model misspecification such as lack of adequate time trend control, and multi-pollutant models (see Supplement Tables S2, S3, S4). Analyses were performed in R, v4.1.1. We followed STROBE reporting guidelines.[35]

Results

Our final sample consisted of 17 731 ED visits by 1740 unique children with SCD (age range 1.0-17.9, Table 1 and Supplemental Figure 1). The patient population self-identified as mainly Black/African American (91.4%) and most patients were hemoglobin type SS/Sβ_0 (64.8% patients, 70.9% ED visits). The study population of interest spanned 11 counties in the Atlanta metropolitan area; 28.5% of the cohort lived in 2 counties with the highest annual pollution levels, and only 2.7% lived in the 2 counties with the lowest annual pollution levels. Table 2 shows the primary and secondary diagnoses associated with ED visits among the SCD cohort, with VOE (defined as SCD crisis or pain, 58.7%), respiratory diagnoses (17.1%), and fever (16.1%) as the most common diagnoses. Figure 1 shows the daily pollutant values during the study period, demonstrating significant day-to-day variability and seasonal trends.

Figure 2 shows the results of our primary analyses, focusing on the single pollutant models from Equation (1). Within our *a priori* primary area of interest (20 miles from nearest CHOA ED), both $PM_{2.5}$ (IRR 1.051 (95%CI 1.010-1.094) per 2 s.d. (9.4 $\mu g/m^3$) increase) and CO (IRR 1.087 (1.039-1.138) per 2 s.d. (0.5 ppm) increase) were significantly associated with ED visits (see Supplemental Table S1 for all values). The IRR estimates for our comparison analyses of total daily ED visits (minus patients with SCD) were lower for all pollutants as compared to the estimates for the SCD cohort for all buffer areas. CO and NO_2 were both positively and significantly associated with ED visits amongst the comparison group, which is consistent with the broader air pollution literature.

As secondary analyses (Figure 2), we reduced the buffer area, including only those patients with SCD who live within 10 and 5 miles of the nearest CHOA facility. For all monitoring station-derived pollutants (CO, NO_2, ozone), the IRRs were larger for the smaller areas (more urban environments, as all CHOA EDs are within the city of Atlanta) compared to the 20-mile primary area of interest. In contrast, the IRR for $PM_{2.5}$ was similar across the different areas of interest, except for confidence interval widths reflecting differences in power. For remote-sensing $PM_{2.5}$ exposure assignment, we were able to account for area of interest size by including only those 1 km x 1 km grids within each area of interest. However,

for the other pollutants, we were limited by the few monitoring stations available – 3 of 4 monitoring stations were within 5 miles of the nearest CHOA facility – and as such, our exposure variable did not change with area for CO, NO_2, and ozone. Note that the 5 miles estimates for $PM_{2.5}$, CO, NO_2, and ozone are all positive, though only CO and NO_2 were statistically significant.

Though our *a priori* exposure of interest was 3-day rolling mean pollutant levels, we also tested specific day (relative to ED visit) pollutant levels for the SCD analyses (Figure 3). Here, we present results for those pollutants, $PM_{2.5}$ and CO, that were significantly associated with ED visits in our primary analysis. We find that individual lags 0-2 had the strongest associations, which supports the decision to make lags 0-2 our primary days of interest. Furthermore, that lead days (*i.e.,* days after hospital admission) showed no association with ED visits suggests our models were adequately specified for temporal confounders, adding robustness to the models.

Lastly, we stratified the cohort by severe SCD (*i.e.* HbSS, $HbS\beta_0$) vs. all other genotypes (Figure 4), to determine if there was a differential effect based on hemoglobin type. Although our model showed higher estimates for children with severe SCD, especially in the 5-mile capture area, the confidence intervals significantly overlapped. Our models were robust to the other sensitivity analyses described in the methods section (Supplement).

Discussion

The results of this retrospective study on a cohort of children with SCD in Atlanta, GA show that increases in daily $PM_{2.5}$, CO (primary analyses) and NO_2 levels (secondary analysis) were significantly and positively associated with number of ED visits; ozone levels did not show significant associations. For all pollutants, IRR estimates relating pollution levels to ED visits were higher for the SCD group than the comparison analysis of all non-SCD patient visits. Importantly, our results were robust to a variety of sensitivity analyses, including modifications in distributional assumptions, weather covariates, and inclusion/exclusion criteria.

This study augments the growing literature in air pollution effects on health. First, there are strong pathophysiologic and sociodemographic reasons to suspect that children with SCD are especially prone to harms from air pollution. As previously mentioned, the key pathophysiologic pathways of air pollution and SCD significantly overlap.[8] From an epidemiologic standpoint, much of the pediatric air pollution literature has focused on children with underlying lung disease, such as children with asthma and cystic fibrosis, while adult data has shown pollution worsens disease outcomes in many other health settings, including cardiovascular and cerebrovascular conditions.[36, 37] The pathophysiology of SCD encompasses lung, cardiovascular, and cerebrovascular damage, potentially placing these patients at increased risk. Indeed, for all pollutants modeled, the IRR estimates were higher for the SCD group than the comparison group, which supports our hypothesis that children with SCD are especially prone to harms from air pollution, as compared to the general pediatric population. Furthermore, our results suggest that children with SCD may be even more susceptible to air pollution as compared to other high-risk populations. A meta-analysis of 87 publications that assessed the effect of pollutants on ED visits among children with asthma found increases in ED visits of 2.3% per 10 $\mu g/m^3$ of $PM_{2.5}$ (vs. our estimate of IRR 1.051 = 5.1% per 2 s.d. increase, which corresponds to 9.4 $\mu g/m^3$ in our data), 4.5% for 1 mg/m^3 CO (vs. 8.8%), 1.8% for NO_2 (vs. 3%, not significant), and 0.9% for ozone (vs. 0.5%, not significant).[38]

Another comparison of effect size can be made within the SCD field. A 2017 analysis, using a subset of our current study's population, found the IRR for ED visits among patients who started hydroxyurea treatment compared to those not starting this treatment was 0.57 (95%CI 0.49-0.67).[27] To place our study into context, a reduction in daily pollution from the 97.5^{th} to 2^{nd} percentile (*i.e.*, a 4 standard deviation change, similar to comparing the highest and lowest pollution days) results in IRRs of 0.91 (0.84-0.98) for $PM_{2.5}$ and 0.78 (0.71-0.86) for CO. While these estimates are not as large in magnitude as the change associated with hydroxyurea initiation, they are nonetheless within the same order of magnitude.

Beyond the biologic basis for harm, children with SCD are at potentially higher risk due to their underlying sociodemographic characteristics.[39] Due to a legacy of systemic racism, racial and ethnic minorities are exposed to higher-than-expected levels of air pollution, even when accounting for neighborhood income.[40, 41] Given that SCD overwhelmingly affects the Black population and our findings that 28.5% of the patients in the SCD cohort lived in the two most polluted counties and only 2.7% lived in the two least polluted counties, it is likely that the patients in our cohort are actually exposed to higher than the city-wide averages included here, which could cause our results to under-estimate the true pollution effects. As such, our results suggest that improvements in air quality would disproportionately benefit the SCD population and lessen ongoing health disparities.

From a clinical perspective, our results have important implications. First, they suggest that pollution avoidance strategies could be considered as routine patient counseling for VOE avoidance and prevention. Such strategies, such as those recommended for patients with respiratory conditions, include: limiting outdoor exertion on high pollution days (many smart phones offer pollution warning messages and apps), avoiding physical exertion near major roadways and other sources of pollution, ventilating and isolating cooking areas (especially those with gas stoves), avoidance of indoor fires, and wearing high quality facemasks when near sources of pollution for prolonged or high-intensity periods.[42] High-efficiency particulate air/arresting (HEPA) filters can substantially improve air quality and have been shown to have significant, cost-effective benefits to human health [43, 44]; encouraging routine (every 4-6 months) replacement of school and household air conditioning filters significantly reduces pollution exposure.

There are specific limitations to the study. We have performed an observational study, so causality cannot be verified. Patients may seek care at facilities not included in the database, notably urgent care centers or adult EDs. However, we performed a sub-analysis on patients who lived especially close (within 5 miles) to a CHOA facility and were therefore more likely to seek care at CHOA – that analysis showed similar (and, in fact, slightly larger) IRR estimates as compared to the 20-mile models, adding

evidence to support our main model and its assumptions. Specifically, with the underlying assumption that patients' choice of care location (*i.e.,* CHOA vs outside facility) does not systematically differ with air pollution levels, our results remain unbiased. Another limitation is that we did not distinguish cause of ED visit and our analyses therefore include some visits whose cause are unlikely to be pollution-related, even tangentially (*e.g.* broken bone). We also did not have reason-for-visit data available for the comparison group; it is likely these children have a different mix of reasons for visit. However, as above, if these other visits are not systematically correlated with air pollution levels, our results remain unbiased. It also warrants mention that respiratory symptoms, headache, viral and other pediatric infections, significant sources of ED visits, are also known to be associated with air pollution, adding validity to our model.[45, 46]

Our patient population comes from an urban/peri-urban environment and caution must be used when extrapolating to a rural environment. Similarly, nearly 10% of our SCD cohort had an address that was unlisted or listed as a PO box. While our database updates a patient's address at each visit which helps account for housing instability, families experiencing homelessness are an especially vulnerable population and those patients with unlisted or PO box addresses were not included in our analyses. Furthermore, our comparison analysis of daily visits by all children minus children with SCD likely includes different sociodemographic characteristics than the SCD group. Given the association of poverty, race and other sociodemographic variables with air pollution exposure, a combination of these factors, as opposed to air pollution alone, could contribute to the difference between the SCD and non-SCD analyses; due to data limitations in the non-SCD analysis, we were unable to explore individual contributions. However, this study's focus was to describe associations between ambient air pollution levels and population-wide ED visits and we made no predictions on how patient-level characteristics, such as neighborhood poverty level, medication usage, or tobacco smoke, interact with pollution exposure; additional research is needed in this area.

In conclusion, we find that increases in daily $PM_{2.5}$, CO, and NO_2 levels are associated with significantly higher ED utilization amongst our cohort of 1740 children with SCD. Furthermore, the IRRs obtained in the comparison analyses were lower than those of the SCD cohort, which supports the hypothesis that children with SCD are at especially high-risk for air pollution's harms. These results provide a potential trigger and underlying pathophysiologic pathway for VOE in patients with SCD. Further research is needed to identify children with SCD most at-risk from air pollution's harms, as this risk factor is modifiable via targeted clinical counseling, personal and family-level pollution avoidance strategies, and pollution reduction via home and school air filtration systems.

Figure Legend List

Figure 1: Daily Pollutant Levels, Atlanta, GA (2010-2018).

This time series graph shows daily pollutant values during the study period. $PM_{2.5}$ (SEDAC-derived data, average value of 20-mile buffers around 3 CHOA emergency departments) mean 10.6 (standard deviation (s.d.) 4.7) ug/m3; CO (EPA monitoring station data) mean 0.57 (s.d. 0.25) ppm; NO_2 (EPA) mean 26.7 (s.d. 11.4) ppb; ozone (EPA) mean 0.04 (s.d. 0.01) ppb.

Figure 2: Estimated associations of 3-day rolling mean ambient pollutant levels and ED visits by buffer zone and SCD status

Plot above shows results of 16 separate models (4 pollutants x 4 areas). Pollutant values are standardized (mean centered and divided by 2 times their standard deviation). Thus, $PM_{2.5}$ 20-mile radius incidence rate ratio of 1.051 can be interpreted as for every 2 standard deviation change in 3 day rolling mean $PM_{2.5}$ levels, the daily number of emergency visits in this cohort increases by 5.1%. All ED visits (all patients) refers to all children 1.0-17.9 years who visited a CHOA emergency department (excluding only patients

with SCD), included as comparison analysis. $PM_{2.5}$ models include data from Jan 1, 2010 - Dec 31, 2016, all patient models from June 1, 2013 - Dec 31, 2018 (due to $PM_{2.5}$ and all patient data restrictions), all other models from Jan 1, 2010 - Dec 31, 2018.

Figure 3: Estimated associations of ambient pollutant levels and ED visits within a 20-mile buffer zone: comparison of pollutant lags relative to day of visit.

Plot above shows the effect of $PM_{2.5}$ and CO on daily emergency department visits for the SCD cohort. Lag day means day prior to encounter. For example, 2-day lag refers to the pollution levels 2 days prior to encounter. Solid vertical lines represent day of encounter.

Figure 4: Estimated associations of 3-day rolling mean ambient pollutant levels and ED visits by SCD genotype (among 5-mile buffer zone cohort).

Plot above shows results of 8 separate models (4 pollutants x 2 SCD types). Severe includes patients with HbSS, HbSβ0; moderate includes all other sickle cell disease variants, does not include sickle cell trait. Of note, analysis of 10- and 20-mile buffer zones showed similar, non-significant differences when grouping by genotype.

References

1. Landrigan PJ, Fuller R, Acosta NJR, Adeyi O, Arnold R, Basu N (Nil), Baldé AB, Bertollini R, Bose-O'Reilly S, Boufford JI, Breysse PN, Chiles T, Mahidol C, Coll-Seck AM, Cropper ML, Fobil J, Fuster V, Greenstone M, Haines A, Hanrahan D, Hunter D, Khare M, Krupnick A, Lanphear B, Lohani B, Martin K, Mathiasen KV, McTeer MA, Murray CJL, Ndahimananjara JD, Perera F, Potočnik J, Preker AS, Ramesh J, Rockström J, Salinas C, Samson LD, Sandilya K, Sly PD, Smith KR, Steiner A, Stewart

RB, Suk WA, van Schayck OCP, Yadama GN, Yumkella K, Zhong M. The Lancet Commission on pollution and health. The Lancet , 2018 391: 462–512.

2. Wang H, Naghavi M, Allen C, Barber RM, Bhutta ZA, Carter A, Casey DC, Charlson FJ, Chen AZ, Coates MM, Coggeshall M, Dandona L, Dicker DJ, Erskine HE, Ferrari AJ, Fitzmaurice C, Foreman K, Forouzanfar MH, Fraser MS, Fullman N, Gething PW, Goldberg EM, Graetz N, Haagsma JA, Hay SI, Huynh C, Johnson CO, Kassebaum NJ, Kinfu Y, Kulikoff XR, Kutz M, Kyu HH, Larson HJ, Leung J, Liang X, Lim SS, Lind M, Lozano R, Marquez N, Mensah GA, Mikesell J, Mokdad AH, Mooney MD, Nguyen G, Nsoesie E, Pigott DM, Pinho C, Roth GA, Salomon JA, Sandar L, Silpakit N, Sligar A, Sorensen RJD, Stanaway J, Steiner C, Teeple S, Thomas BA, Troeger C, VanderZanden A, Vollset SE, Wanga V, Whiteford HA, Wolock T, Zoeckler L, Abate KH, Abbafati C, Abbas KM, Abd-Allah F, Abera SF, Abreu DMX, Abu-Raddad LJ, Abyu GY, Achoki T, Adelekan AL, Ademi Z, Adou AK, Adsuar JC, Afanvi KA, Afshin A, Agardh EE, Agarwal A, Agrawal A, Kiadaliri AA, Ajala ON, Akanda AS, Akinyemi RO, Akinyemiju TF, Akseer N, Lami FHA, Alabed S, Al-Aly Z, Alam K, Alam NKM, Alasfoor D, Aldhahri SF, Aldridge RW, Alegretti MA, Aleman AV, Alemu ZA, et al. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. The Lancet , 2016 388: 1459–1544.

3. Pratt GC, Vadali ML, Kvale DL, Ellickson KM. Traffic, Air Pollution, Minority and Socio-Economic Status: Addressing Inequities in Exposure and Risk. International Journal of Environmental Research and Public Health , 2015 12: 5355–5372.

4. Landrigan PJ, Fuller R, Fisher S, Suk WA, Sly P, Chiles TC, Bose-O'Reilly S. Pollution and children's health. Science of The Total Environment , 2019 650: 2389–2394.

5. Brumberg HL, Karr CJ, Bole A, Ahdoot S, Balk SJ, Bernstein AS, Byron LG, Landrigan PJ, Marcus SM, Nerlinger AL, Pacheco SE, Woolf AD, Zajac L, Baum CR, Campbell CC, Sample JA, Spanier AJ,

Trasande L, COUNCIL ON ENVIRONMENTAL HEALTH. Ambient Air Pollution: Health Hazards to Children. Pediatrics , 2021 147: e2021051484.

6. Ambient (outdoor) air pollution [Internet][cited 2021 Dec 23] Available from: https://www.who.int/news-room/fact-sheets/detail/ambient-(outdoor)-air-quality-and-health

7. World Health Organization. WHO global air quality guidelines: particulate matter (PM2. 5 and PM10), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide. World Health Organization, 2021

8. Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. The Lancet , 2010 376: 2018–2031.

9. Dampier C, Barry V, Gross HE, Lui Y, Thornburg CD, DeWalt DA, Reeve BB. Initial Evaluation of the Pediatric PROMIS® Health Domains in Children and Adolescents With Sickle Cell Disease. Pediatric Blood & Cancer , 2016 63: 1031–1037.

10. Panepinto JA, Bonner M. Health-related quality of life in sickle cell disease: Past, present, and future. Pediatric Blood & Cancer , 2012 59: 377–385.

11. Shah N, Bhor M, Xie L, Paulose J, Yuce H. Sickle cell disease complications: Prevalence and resource utilization. PLOS ONE , 2019 14: e0214355.

12. Yusuf HR, Atrash HK, Grosse SD, Parker CS, Grant AM. Emergency Department Visits Made by Patients with Sickle Cell Disease: A Descriptive Study, 1999–2007. American Journal of Preventive Medicine , 2010 38: S536–S541.

13. Kavanagh PL, Fasipe TA, Wun T. Sickle Cell Disease: A Review. JAMA , 2022 328: 57–68.

14. Jang T, Poplawska M, Cimpeanu E, Mo G, Dutta D, Lim SH. Vaso-occlusive crisis in sickle cell disease: a vicious cycle of secondary events. J Transl Med , 2021 19: 397.

15. Chuang K-J, Chan C-C, Su T-C, Lee C-T, Tang C-S. The Effect of Urban Air Pollution on Inflammation, Oxidative Stress, Coagulation, and Autonomic Dysfunction in Young Adults. Am J Respir Crit Care Med , 2007 176: 370–376.

16. Feng S, Gao D, Liao F, Zhou F, Wang X. The health effects of ambient PM2.5 and potential mechanisms. Ecotoxicology and Environmental Safety , 2016 128: 67–74.

17. Anderson JO, Thundiyil JG, Stolbach A. Clearing the Air: A Review of the Effects of Particulate Matter Air Pollution on Human Health. J Med Toxicol , 2012 8: 166–175.

18. Korten I, Ramsey K, Latzin P. Air pollution during pregnancy and lung development in the child. Paediatric Respiratory Reviews , 2017 21: 38–46.

19. Khalili R, Bartell SM, Hu X, Liu Y, Chang HH, Belanoff C, Strickland MJ, Vieira VM. Early-life exposure to PM2.5 and risk of acute asthma clinical encounters among children in Massachusetts: a case-crossover analysis. Environ Health , 2018 17: 20.

20. Hamanaka RB, Mutlu GM. Particulate Matter Air Pollution: Effects on the Cardiovascular System [Internet]. Frontiers in Endocrinology , 2018 9. [cited 2022 Oct 11] Available from: https://www.frontiersin.org/articles/10.3389/fendo.2018.00680

21. Zhang D, Xu C, Manwani D, Frenette PS. Neutrophils, platelets, and inflammatory pathways at the nexus of sickle cell disease pathophysiology. Blood , 2016 127: 801–809.

22. Teixeira RS, Terse-Ramos R, Ferreira TA, Machado VR, Perdiz MI, Lyra IM, Nascimento VL, Boa-Sorte N, Andrade BB, Ladeia AM. Associations between endothelial dysfunction and clinical and laboratory parameters in children and adolescents with sickle cell anemia. PLOS ONE , 2017 12: e0184076.

23. Blumberg AH, Ebelt ST, Liang D, Morris CR, Sarnat JA. Ambient air pollution and sickle cell disease-related emergency department visits in Atlanta, GA. Environmental Research , 2020 184: 109292.

24. Yallop D, Duncan ER, Norris E, Fuller GW, Thomas N, Walters J, Dick MC, Height SE, Thein SL, Rees DC. The associations between air quality and the number of hospital admissions for acute pain and sickle-cell disease in an urban environment. British Journal of Haematology , 2007 136: 844–848.

25. Barbosa SM de M, Farhat SCL, Martins LC, Pereira LAA, Saldiva PHN, Zanobetti A, Braga ALF. Air pollution and children's health: sickle cell disease. Cadernos de Saúde Pública , 2015 31: 265–275.

26. Snyder AB, Lane PA, Zhou M, Paulukonis ST, Hulihan MM. The accuracy of hospital ICD-9-CM codes for determining Sickle Cell Disease genotype. J Rare Dis Res Treat , 2017 2: 39–45.

27. Quarmyne M-O, Dong W, Theodore R, Anand S, Barry V, Adisa O, Buchanan ID, Bost J, Brown RC, Joiner CH, Lane PA. Hydroxyurea effectiveness in children and adolescents with sickle cell anemia: A large retrospective, population-based cohort. American Journal of Hematology , 2017 92: 77–81.

28. Di Q, Wei Y, Shtein A, Hultquist C, Xing X, Amini H, Shi L, Kloog I, Silvern R, Kelly J, Sabath MB, Choirat C, Koutrakis P, Lyapustin A, Wang Y, Mickley LJ, Schwartz J. Daily and Annual PM2.5 Concentrations for the Contiguous United States, 1-km Grids, v1 (2000 - 2016) [Internet], 2021. [cited 2022 Jul 20] Available from: https://sedac.ciesin.columbia.edu/data/set/aqdh-pm2-5-concentrations-contiguous-us-1-km-2000-2016

29. Li J, Lu X, Liu F, Liang F, Huang K, Yang X, Xiao Q, Chen J, Liu X, Cao J, Chen S, Shen C, Yu L, Lu F, Wu X, Zhao L, Wu X, Li Y, Hu D, Huang J, Zhu M, Liu Y, Shen H, Gu D. Chronic Effects of High Fine Particulate Matter Exposure on Lung Cancer in China [Internet]. Am J Respir Crit Care Med , 2020. [cited 2020 Nov 22] Available from: https://www.atsjournals.org/doi/abs/10.1164/rccm.202001-0002OC

30. Carrasco-Escobar G, Schwalb A, Tello-Lizarraga K, Vega-Guerovich P, Ugarte-Gil C. Spatio-temporal co-occurrence of hotspots of tuberculosis, poverty and air pollution in Lima, Peru. Infectious Diseases of Poverty , 2020 9: 32.

31. Feng Y, Jones MR, Ahn JB, Garonzik-Wang JM, Segev DL, McAdams-DeMarco M. Ambient air pollution and posttransplant outcomes among kidney transplant recipients. American Journal of Transplantation , 2021 21: 3333–3345.

32. Ver Hoef JM, Boveng PL. Quasi-Poisson Vs. Negative Binomial Regression: How Should We Model Overdispersed Count Data? Ecology , 2007 88: 2766–2772.

33. Pan A, Sarnat SE, Chang HH. Time-Series Analysis of Air Pollution and Health Accounting for Covariate-Dependent Overdispersion. Am J Epidemiol , 2018 187: 2698–2704.

34. Gelman A. Scaling regression inputs by dividing by two standard deviations. Statistics in medicine , 2008 27: 2865–2873.

35. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for reporting observational studies. International Journal of Surgery , 2014 12: 1495–1499.

36. Shah ASV, Lee KK, McAllister DA, Hunter A, Nair H, Whiteley W, Langrish JP, Newby DE, Mills NL. Short term exposure to air pollution and stroke: systematic review and meta-analysis. BMJ , 2015 350: h1295.

37. Hadley MB, Vedanthan R, Fuster V. Air pollution and cardiovascular disease: a window of opportunity. Nature Reviews Cardiology , 2018 15: 193–194.

38. Zheng X, Ding H, Jiang L, Chen S, Zheng J, Qiu M, Zhou Y, Chen Q, Guan W. Association between Air Pollutants and Asthma Emergency Room Visits and Hospital Admissions in Time Series Studies: A Systematic Review and Meta-Analysis. PLOS ONE , 2015 10: e0138146.

39. Khan H, Krull M, Hankins JS, Wang WC, Porter JS. Sickle cell disease and social determinants of health: A scoping review. Pediatric Blood & Cancer , 2022 e30089.

40. Woo B, Kravitz-Wirtz N, Sass V, Crowder K, Teixeira S, Takeuchi DT. Residential Segregation and Racial/Ethnic Disparities in Ambient Air Pollution. Race Soc Probl , 2019 11: 60–67.

41. Jones MR, Diez-Roux AV, Hajat A, Kershaw KN, O'Neill MS, Guallar E, Post WS, Kaufman JD, Navas-Acien A. Race/Ethnicity, Residential Segregation, and Exposure to Ambient Air Pollution: The Multi-Ethnic Study of Atherosclerosis (MESA). Am J Public Health , 2014 104: 2130–2137.

42. Carlsten C, Salvi S, Wong GWK, Chung KF. Personal strategies to minimise effects of air pollution on respiratory health: advice for providers, patients and the public [Internet]. European Respiratory Journal , 2020 55. [cited 2022 Oct 11] Available from: https://erj.ersjournals.com/content/55/6/1902056

43. Allen RW, Barn P. Individual- and Household-Level Interventions to Reduce Air Pollution Exposures and Health Risks: a Review of the Recent Literature. Curr Envir Health Rpt , 2020 7: 424–440.

44. Gilraine M. Air Filters, Pollution and Student Achievement [Internet]. Annenberg Institute at Brown University, 2020[cited 2020 Oct 11] Available from: https://www.edworkingpapers.com/ai20-188

45. Brugha R, Grigg J. Urban Air Pollution and Respiratory Infections. Paediatric Respiratory Reviews , 2014 15: 194–199.

46. Bowatte G, Tham R, Perret JL, Bloom MS, Dong G, Waidyatillake N, Bui D, Morgan GG, Jalaludin B, Lodge CJ, Dharmage SC. Air Pollution and Otitis Media in Children: A Systematic Review of Literature. International Journal of Environmental Research and Public Health , 2018 15: 257.

Tables and Figures

TABLE 1. Sociodemographic Characteristics of Children with Sickle Cell Disease (January 2010 - December 2018).

	By patients (n = 1 740)	By visits (n = 17 731)
Age at visit	na	1.0-17.9
Gender (Female)	49.2%	49.8%
Ethnicity		
Non-Hispanic	92.8%	94.9%
Hispanic	2.6%	3.6%
Not answered	4.6%	1.5%
Race		
Black/African American	91.4%	90.1%
White	1.1%	1.4%
Native American	0.1%	0.2%
Not answered	7.4%	7.9%
Genotype		
HbSS/HbSβ0	64.8%	70.9%
HbSC	26.3%	21.9%
HbSβ+	7.4%	6.4%
Other	1.5%	0.8%
Insurance at visit		
Medicaid	na	64.6%
Private	na	23.3%
Self-pay	na	1.7%
Not listed	na	10.3%

Includes patients who live within 20 miles of nearest CHOA hospital and who had at least 1 emergency department visit from 2010-2018.
Ethnicity, race, and gender are self/parent identified.

TABLE 2: Most Common Emergency Department Diagnoses Among Cohort

Reason for Visit	Percentage*
Sickle cell disease crisis / pain	58.7%
Respiratory illness**	17.1%
Fever	16.1%
Acute chest syndrome	6.0%
Nausea/Vomiting/Diarrhea	1.7%
Constipation	1.4%
Headache	1.4%
Priapism	0.8%
Gallstone	0.7%
Splenic sequestration	0.6%
Avascular necrosis	0.5%

*Percentages of primary and secondary diagnoses for ED visit amongst the cohort, by ICD9/10 code (n = 17,731). The above percentages exclude 2325 (13.1%) ED visits for which there was no associated diagnosis code documenting reason of visit. Percentages do not add to 100 due to multiple reasons per visit (e.g., patient may present with both fever and pain).

**Most common respiratory diagnoses included: cough, asthma, pneumonia, hypoxemia. Of note, acute chest syndrome is coded separately, and patients can be coded as both respiratory illness and acute chest syndrome.

Figure Legend List

Figure 1: Daily Pollutant Levels, Atlanta, GA (2010-2018).

This time series graph shows daily pollutant values during the study period. $PM_{2.5}$ (SEDAC-derived data, average value of 20-mile buffers around 3 CHOA emergency departments) mean 10.6 (standard deviation (s.d.) 4.7) ug/m3; CO (EPA monitoring station data) mean 0.57 (s.d. 0.25) ppm; NO_2 (EPA) mean 26.7 (s.d. 11.4) ppb; ozone (EPA) mean 0.04 (s.d. 0.01) ppb.

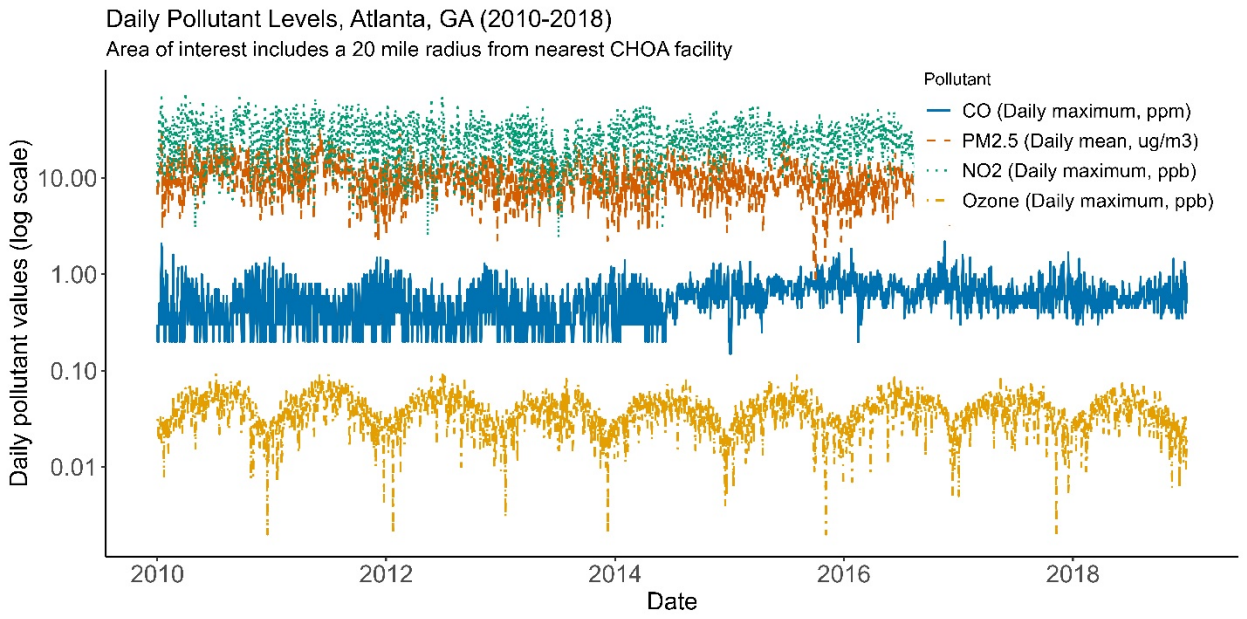


Figure 2: Estimated associations of 3-day rolling mean ambient pollutant levels and ED visits by buffer zone and SCD status

Plot above shows results of 16 separate models (4 pollutants x 4 areas). Pollutant values are standardized (mean centered and divided by 2 times their standard deviation). Thus, $PM_{2.5}$ 20-mile radius incidence rate ratio of 1.051 can be interpreted as for every 2 standard deviation change in 3 day rolling mean $PM_{2.5}$ levels, the daily number of emergency visits in this cohort increases by 5.1%. All ED visits (all patients) refers to all children 1-17.99 years who visited a CHOA emergency department (excluding only patients with SCD), included as comparison analysis. $PM_{2.5}$ models include data from Jan 1, 2010 - Dec 31, 2016, all patient models from June 1, 2013 - Dec 31, 2018 (due to $PM_{2.5}$ and all patient data restrictions), all other models from Jan 1, 2010 - Dec 31, 2018.

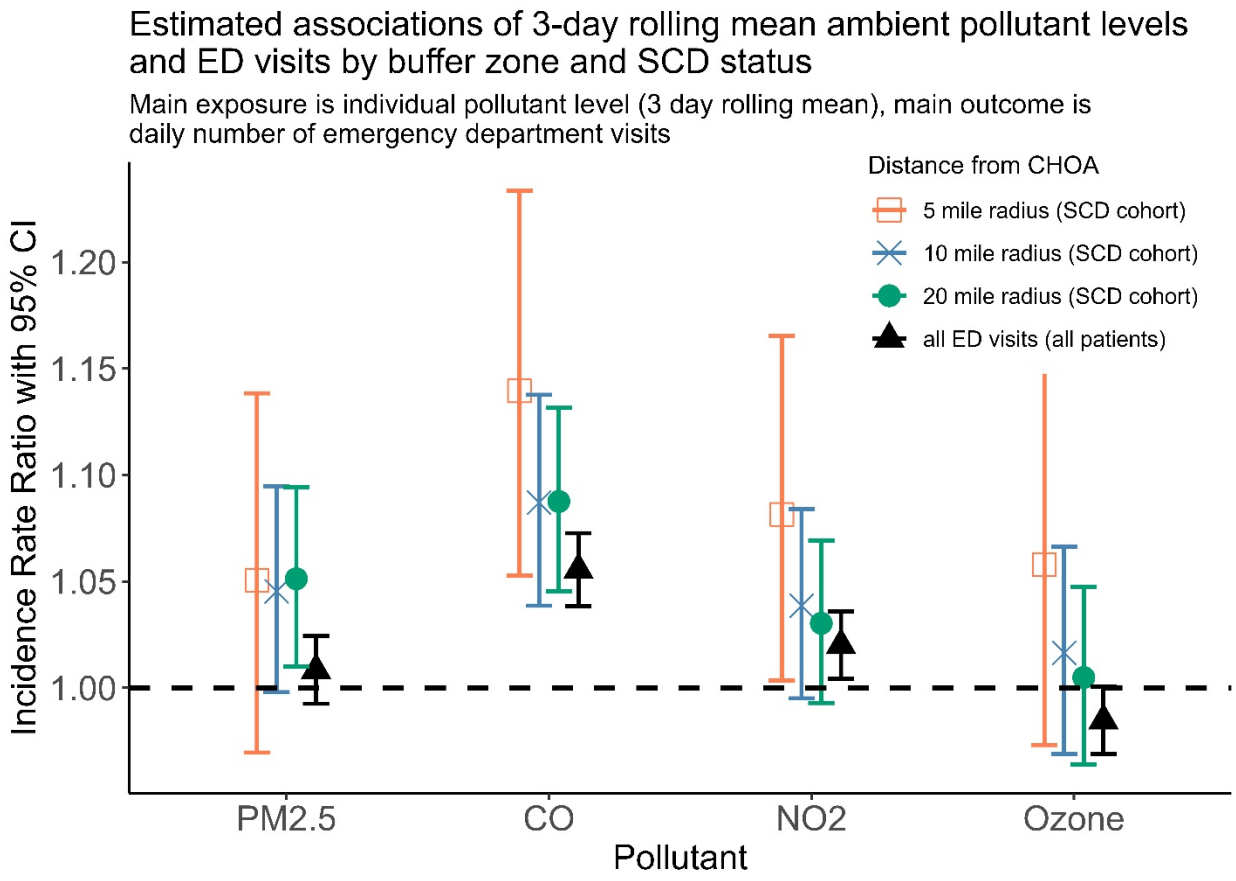


Figure 3: Estimated associations of ambient pollutant levels and ED visits within a 20-mile buffer zone: comparison of pollutant lags relative to day of visit.

Plot above shows the effect of $PM_{2.5}$ and CO on daily emergency department visits for the SCD cohort. Lag day means day prior to encounter. For example, 2-day lag refers to the pollution levels 2 days prior to encounter. Solid vertical lines represent day of encounter.

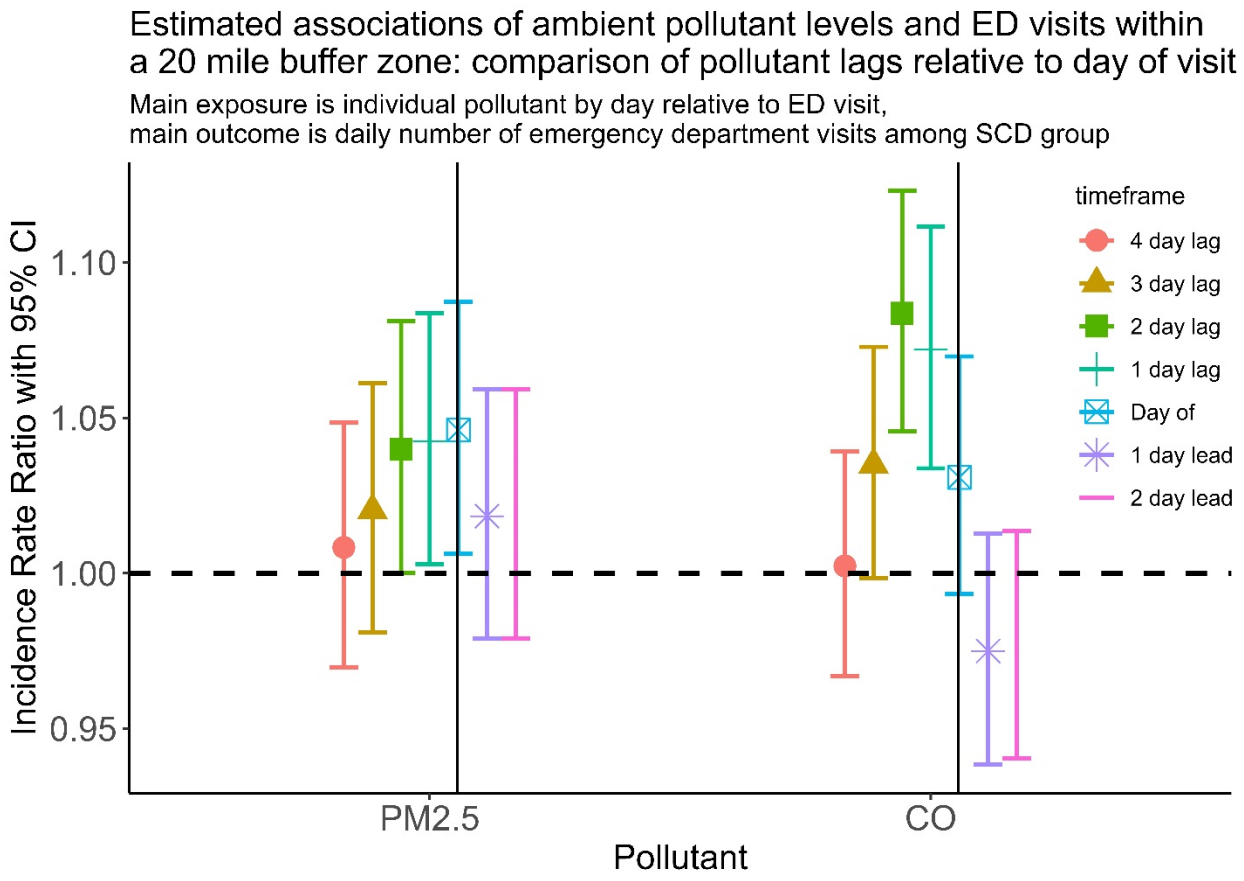
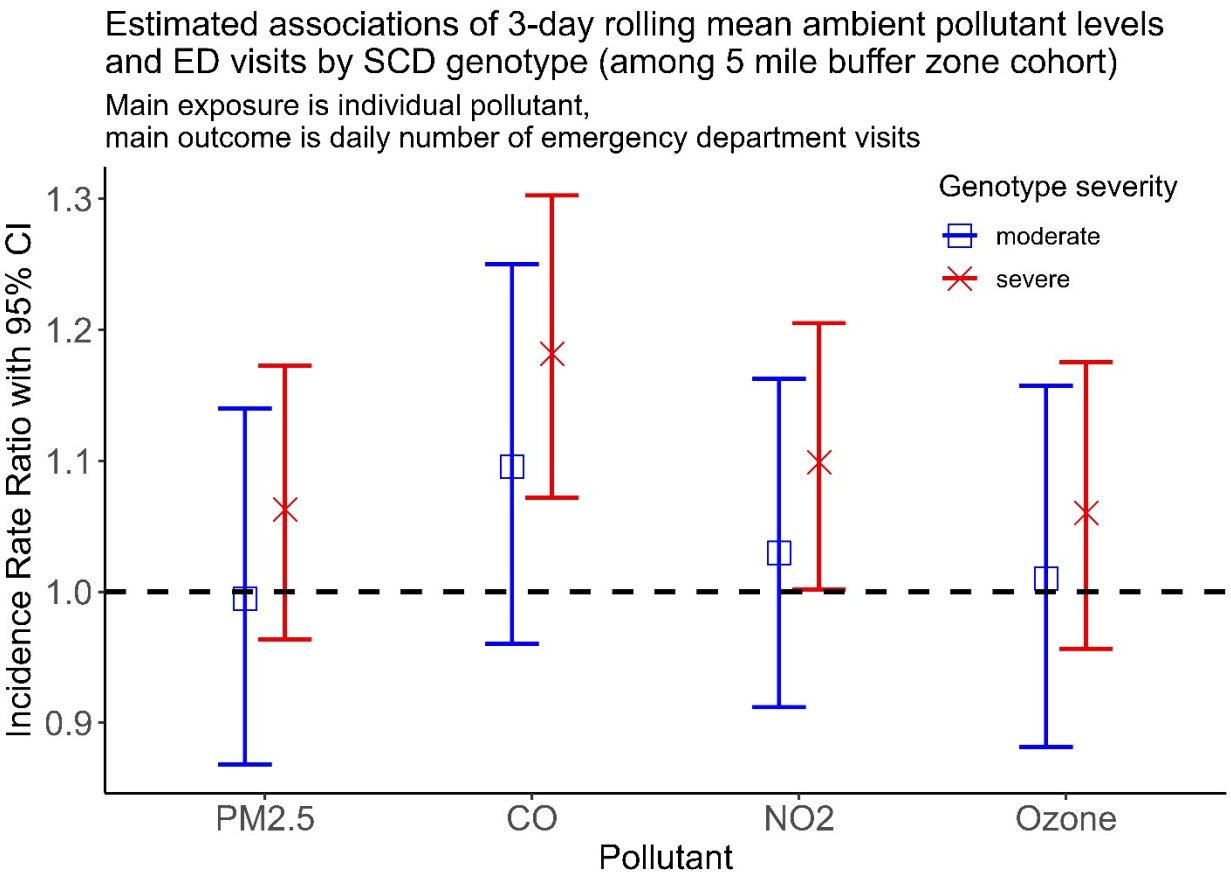


Figure 4: Estimated associations of 3-day rolling mean ambient pollutant levels and ED visits by SCD genotype (among 5-mile buffer zone cohort).

Plot above shows results of 8 separate models (4 pollutants x 2 SCD types). Severe includes patients with HbSS, HbSβ0; moderate includes all other sickle cell disease variants, does not include sickle cell trait. Of note, analysis of 10- and 20-mile buffer zones showed similar, non-significant differences when grouping by genotype.



Supplemental text

Below is a summary of the different robustness checks performed on the model, beyond those outlined in the main text.

Model type

As discussed in the main text, we chose a negative binomial model given the dispersion parameters. We also modeled using a Poisson model, accounting for overdispersion. As shown in **Supplemental Table S2: Poisson Model Results,** the estimates and standard errors assuming a Poisson distribution are very similar to the results assuming a negative binomial distribution.

Pollutant Levels (Main exposure variables)

We also performed two pollutant models, in which PM2.5 (our main exposure of interest) was combined with all other pollutants in separate models, as was CO (the pollutant with the highest associated incidence rate ratio). See **Supplemental Table S3, Two Pollutant Models** for results. Finally, we performed a 4-pollutant model, in which only CO remained significantly associated with ED visits. However, there is significant correlation in air pollutant levels, which results in large standard errors and difficult to interpret results in the multi-pollutant models, which is why our primary analysis plan *a priori* included only single pollutant models.

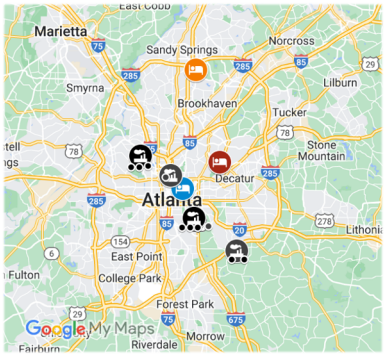
Temperature

In our main model, we include a cubic spline with minimum temperature (lag 3 day rolling mean), with knots at 25th and 75th percentiles for daily minimum temperature (temperature = 42F and 69F, respectively). As a robustness check, we substituted maximum temperature (daily) cubic splines at 25th and 75th percentiles, which provided similar results. Additionally, we modeled day of minimum and maximum temperatures as linear, continuous variables, again providing similar results. Finally, we modeled temperature values as 3-day lagged values (similar to our pollutant exposures of interest), without significant changes in results.

Time

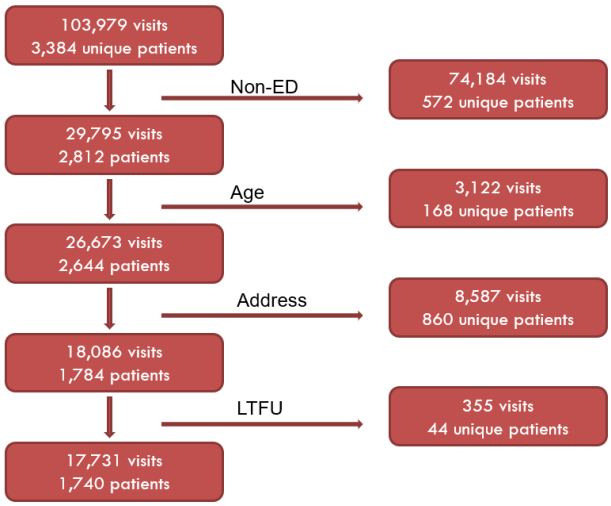
In our main model, we include a cubic spline for time with knots at seasonal locations. As a robustness check, we substituted for a cubic spline for time with yearly knots *(i.e.*, day 365, 730, 1095, etc), which provided similar results.

Supplemental Figure 1



Supplemental Figure 1 shows the location of the three main Children's Healthcare of Atlanta (CHOA) Hospitals (beds) and Environmental Protection Agency (EPA) monitoring stations (smoke towers, EPA site 1312100056 1 dot, site 130890002 2 dots, site 1312100039 3 dots, site 131210055 4 dots). Carbon monoxide was collected from 130890002, 1312100056; nitrogen dioxide from 130890002, 1312100056; Ozone from 130890002, 131210055, and PM2.5 (for validation of satellite data) from 130890002, 1312100039).

Supplemental Figure 2



Supplemental Figure 2 explains how we arrived at our final sample of 17,731 visits by 1,740 unique patients. Non-ED refers to visits that were not in the emergency department; age refers to patients younger than 365 days of age or older than 18 years of age; address refers to those who lived outside our area of interest (greater than 20 miles from the nearest CHOA hospital for the main analysis, 5, 10 miles for secondary analyses) or had missing address (n = 221)/PO box addresses listed (n = 52); LTFU (lost to follow up) refers to patients who went 365 days or more without being seen in a CHOA facility, to exclude patients who receive their healthcare elsewhere.

Supplemental Table S1: Numerical Results of Primary Analysis, as Visualized in Figure 2.

Pollutant	distance	estimate	std.error	p.value	IRR	95% CI	
PM2.5	5 mile radius	0.049	0.041	0.228	1.051	0.97	1.138
CO	5 mile radius	0.131	0.04	0.001	1.14	1.053	1.234
NO2	5 mile radius	0.078	0.038	0.04	1.081	1.003	1.165
Ozone	5 mile radius	0.056	0.043	0.186	1.058	0.973	1.15
PM2.5	10 mile radius	0.044	0.024	0.061	1.045	0.998	1.095
CO	10 mile radius	0.083	0.023	<0.001	1.087	1.039	1.138
NO2	10 mile radius	0.038	0.022	0.083	1.039	0.995	1.084
Ozone	10 mile radius	0.016	0.024	0.505	1.016	0.969	1.066
PM2.5	20 mile radius	0.05	0.02	0.015	1.051	1.01	1.094
CO	20 mile radius	0.084	0.02	<0.001	1.088	1.045	1.132
NO2	20 mile radius	0.03	0.019	0.114	1.03	0.993	1.069
Ozone	20 mile radius	0.005	0.021	0.82	1.005	0.964	1.048
PM2.5	all ED visits (all patients)	0.009	0.008	0.280	1.009	0.993	1.025
CO	all ED visits (all patients)	0.054	0.008	<0.001	1.056	1.039	1.073
NO2	all ED visits (all patients)	0.020	0.008	0.012	1.020	1.004	1.036
Ozone	all ED visits (all patients)	-0.015	0.008	0.066	0.985	0.969	1.001

Pollutant values into the model are 3 day rolling means, standardized (mean centered and divided by 2*standard deviation).
Distance refers to capture area (i.e. for our primary analysis of 20-mile capture area, the cohort included all patients who lived within 20 miles of our facility on day of interest).
IRR is incident rate ratio.

Supplemental Table 1 shows the results of the primary analysis, as visualized in Figure 2 (main text)

.

Supplemental Table S2: Poisson Model Results

Pollutant	estimate	std.error	p.value	distance	IRR	95% CI	
PM2.5	0.049	0.041	0.231	5 mile radius	1.051	0.969	1.139
CO	0.131	0.041	0.001	5 mile radius	1.14	1.052	1.234
NO2	0.079	0.038	0.041	5 mile radius	1.082	1.003	1.166
Ozone	0.057	0.043	0.186	5 mile radius	1.058	0.973	1.151
PM2.5	0.044	0.024	0.063	10 mile radius	1.045	0.998	1.095
CO	0.083	0.023	0	10 mile radius	1.087	1.038	1.137
NO2	0.038	0.022	0.082	10 mile radius	1.039	0.995	1.084
Ozone	0.017	0.025	0.5	10 mile radius	1.017	0.969	1.067
PM2.5	0.049	0.02	0.016	20 mile radius	1.051	1.009	1.094
CO	0.083	0.02	0	20 mile radius	1.087	1.044	1.13
NO2	0.03	0.019	0.111	20 mile radius	1.031	0.993	1.07
Ozone	0.005	0.021	0.827	20 mile radius	1.005	0.964	1.047

Pollutant values are 3 day rolling means, standardized (mean centered and divided by 2*standard deviation), and distance refers to radius of buffer zone/capture area, with nearest CHOA ED as center).

Supplemental Table 2 shows the results of the primary analysis, with distribution changed from negative binomial to quasi-Poisson (to account for overdispersion of our outcome variable, ED visits/day).

Supplemental Table S3: Two Pollutant Models

Model	Pollutant	estimate	std.error	p.value
PM2.5 + CO	PM2.5	0.011	0.025	0.674
	CO	0.079	0.027	0.004
PM + NO2	PM2.5	0.041	0.025	0.094
	NO2	0.014	0.024	0.550
PM + Ozone	PM2.5	0.054	0.022	0.015
	Ozone	-0.009	0.026	0.727
CO + NO2	CO	0.098	0.024	0.000
	NO2	-0.022	0.023	0.341
CO + Ozone	CO	0.078	0.021	0.000
	Ozone	-0.012	0.021	0.573

Above are the results of the models in which we include 2 pollutants per model as exposures of interest. Capture area is 20 miles from nearest CHOA facility. Exposure values are 3-day lag rolling means.

Supplemental Table 3 shows the results of our two pollutant models, in which we include 2 pollutants as the exposures of interest.

Supplemental Table S4: Associations of pollutants with ED visits, by day relative to ED visit.

Pollutant	timeframe	estimate	std.error	p.value	IRR	95% CI	
PM2.5	2 day lead	0.002	0.02	0.913	1.002	0.964	1.042
CO	2 day lead	-0.024	0.019	0.211	0.976	0.94	1.014
PM2.5	1 day lead	0.018	0.02	0.365	1.018	0.979	1.059
CO	1 day lead	-0.025	0.019	0.192	0.975	0.938	1.013
PM2.5	Day of	0.045	0.02	0.023	1.046	1.006	1.087
CO	Day of	0.03	0.019	0.109	1.031	0.993	1.07
PM2.5	1 day lag	0.042	0.02	0.035	1.043	1.003	1.084
CO	1 day lag	0.07	0.019	0	1.072	1.034	1.112
PM2.5	2 day lag	0.039	0.02	0.049	1.04	1	1.081
CO	2 day lag	0.08	0.018	0	1.084	1.046	1.123
PM2.5	3 day lag	0.02	0.02	0.316	1.02	0.981	1.061
CO	3 day lag	0.034	0.018	0.06	1.035	0.998	1.073
PM2.5	4 day lag	0.008	0.02	0.678	1.008	0.97	1.048
CO	4 day lag	0.002	0.018	0.899	1.002	0.967	1.039

Timeframe refers to day of pollutant measurement, relative to ED visit. Lead refers to day after visit, lag refers to day prior to visit. For example, if day of ED visit is March 10, then 2 day lead is March 12, and 3 day lag is March 7. Capture area is 20 miles from nearest CHOA facility. IRR is incident rate ratio.

Chapter 2

Impact of Annual $PM_{2.5}$ Exposure on Clinical and Laboratory Outcomes in Children with Sickle Cell Disease: A Retrospective Cohort Study

Abstract

Background: Sickle cell disease (SCD), a genetic disorder affecting approximately 7 million people worldwide, leads to severe morbidity and early mortality but varies phenotypically. Both air pollution and SCD impact the cardiorespiratory and inflammatory systems; despite this overlap, the role of air pollution in driving phenotypic variability in SCD has not been evaluated. We hypothesized that annual ambient $PM_{2.5}$ concentrations at a child's home address would be significantly associated with higher numbers of annual emergency department (ED) visits, hospital days, and markers of inflammation.

Methods: Patient data for this retrospective study was obtained from a longitudinal, single-center cohort of children with SCD (2010-2019). Annual $PM_{2.5}$ exposure was estimated using publicly available remote-sensing ambient air pollution datasets, with annual $PM_{2.5}$ concentrations matched to each child's home address. Statistical analyses employed fixed effects multivariable models to control for individual-specific, time-invariant confounders, with additional models examining the effect modification of hydroxyurea use and socioeconomic status.

Results: The cohort comprised 1,089 children with severe SCD, with a mean follow-up of 5.1 years. Higher annual $PM_{2.5}$ concentrations were significantly associated with more annual hospital days (incident rate ratio (IRR)=1.16, p=0.047), higher likelihood of hospitalization (odds ratio (OR)=1.02, p=0.024), abnormal stroke risk screenings (OR=1.05, $p<0.001$), and elevated white blood cell ($\beta=0.19$, p=0.017) and absolute neutrophil count ($\beta=0.14$, p=0.01). No significant association was found between $PM_{2.5}$ and ED visits. Hydroxyurea use mitigated the inflammatory response to $PM_{2.5}$ but did not mitigate the effect of $PM_{2.5}$ on clinical outcomes.

Conclusions: By employing a novel fixed effects methodology on a large longitudinal cohort of children with SCD, this study isolated the impact of annual air pollution exposure on clinical and inflammatory outcomes. $PM_{2.5}$ exposure correlated with worse clinical outcomes and increased inflammation in children

with SCD, highlighting the need for stringent air quality regulations. Further research should explore the potentially protective role of hydroxyurea in mitigating the effects of air pollution exposure.

Background

Sickle cell disease (SCD) is one of the commonest genetic disorders, with ~100,000 Americans and an estimated ~7 million people worldwide living with the disease.(1) As a monogenic disorder, SCD arises from a mutation in the *HBB* gene that encodes hemoglobin. Despite being a monogenic defect, SCD is phenotypically variable.(2) While nearly everyone with SCD experiences ongoing morbidity and reduced life expectancy, the severity of the disease, especially in childhood and adolescence, is quite variable. Some children and young adults experience frequent pain crises, severe lung injury (acute chest syndrome), and frequent hospitalizations, whereas others are rarely hospitalized and are less affected by SCD in childhood.(3) Previous work has examined co-inheritance of other genetic factors (e.g., alpha thalassemia), laboratory findings (e.g., baseline fetal hemoglobin) and social-environmental factors (e.g., temperature, physical activity, access to healthcare) as drivers of disparate clinical outcomes, though characterization of the phenotypic diversity within SCD remains incomplete.(4–6)

Exposure to air pollutants is well-characterized as a driver of disparate health outcomes in other health settings, with clinical effects ranging from worse cardiovascular disease, higher rates of asthma and other lung disease, and poor birth outcomes.(7–10) While there are many distinct pollutants, the most well-known to cause adverse health effects in humans is fine particulate matter ($PM_{2.5}$), particles with a diameter of 2.5 microns or less. From a pathophysiologic perspective, $PM_{2.5}$ causes both local damage via direct lung injury and systemic harm via induction of an inflammatory response, oxidative stress, and endothelial damage.(11–15) Notably, these same pathophysiologic pathways (i.e., inflammation, endothelial damage, oxidative stress, lung injury) are drivers of the severe morbidity and early mortality observed in people with SCD.(3,16,17) Furthermore, in the American context, SCD is concentrated in the

Black community, and predominately Black neighborhoods are exposed to disproportionately high levels of $PM_{2.5}$.(18)

Despite the overlapping pathophysiologic pathways and sociodemographic factors that suggest $PM_{2.5}$ may be especially harmful to people with SCD, research directly examining the link between $PM_{2.5}$ and SCD morbidity is relatively scant.(19) Published studies have examined the impact of daily ambient (outdoor) air pollution on numbers of emergency department (ED) visits among groups of patients with SCD, with most finding positive associations between ED visits and higher daily ambient air pollution concentrations.(20–24) These studies represent important first steps, though they have key limitations. While the data used in these studies were population-wide, it did not include individual-level variables such as SCD genotype, medications, and sociodemographic details. From a pollution viewpoint, these studies did not examine the effects of long-term air pollution exposures on SCD-associated clinical or laboratory outcomes. Because SCD is a chronic disease, it is plausible that long-term $PM_{2.5}$ exposure, as opposed to daily fluctuations, has more significant clinical impact. This study aimed to address these critical gaps by providing a comprehensive, individual-level examination of the association between long-term air pollution exposure and health outcomes in children with SCD. We hypothesized that annual $PM_{2.5}$ concentrations at a child's home address would be significantly associated with higher number of ED visits, hospital days, and markers of inflammation.

Methods

Data sources

Patient data were abstracted from the electronic medical records of patients in an ongoing, longitudinal cohort of children with SCD at Children's Healthcare of Atlanta (CHOA), a network of hospitals, urgent care, and outpatient clinics representing the largest pediatric hospital system and subspecialty care provider in Georgia. Briefly, this cohort includes all children with SCD (as verified by hemoglobin analysis), who have at least 1 clinical encounter at CHOA. Importantly, CHOA accounts for

~95% of pediatric SCD hospitalizations in the Atlanta metropolitan area; as such, the data included represents a nearly complete population-based sample of children with SCD in Atlanta.(25) Patient information abstracted included clinical, laboratory, and sociodemographic (including home address at each encounter) data. Our analysis included pediatric patients (age <18 years at time of encounter), from January 1, 2010 through December 31, 2019, with the first and last time points being the first and last clinical encounters that occur within this period, up to the child's 18th birthday. We included only patients with HbSS/HbSβ0, the most common and severe forms of SCD. We censored children once their home address was listed as either unknown or >30 miles from the nearest CHOA facility. Lastly, children were excluded if they had insufficient clinical data in our system, including <3 clinical visits (inpatient + ED + outpatient) in total, to limit the study population to children who would likely use CHOA as their primary source of inpatient and outpatient care (**Supplemental Figure 1**).

For socioeconomic status, we integrated the Centers for Disease Control and Prevention's Social Vulnerability Index (SVI), matching each child with the census-tract level SVI.(26) The SVI is an index that incorporates various census-tract level indicators, including socioeconomic status, household composition, minority status, and housing type, allowing for a nuanced assessment of social vulnerability.

Air pollution data were acquired from the NASA Socioeconomic Data and Applications Center (SEDAC), which provides publicly available data on key pollutants. We specifically utilized the annual mean $PM_{2.5}$ and $PM_{2.5}$ components datasets, which combine remote sensing (satellite) and ground-level monitoring data into a machine learning algorithm to provide annual, high resolution (1km*1km for $PM_{2.5}$, 50m*50m for $PM_{2.5}$ components) pollutant concentrations - see reference (27) for further details. Annual $PM_{2.5}$ values (and $PM_{2.5}$ components) were matched to each child using the child's geocoded home address for the given year. Annual weather data came from National Climatic Data Center.(28)

Measures

The primary exposures of interest were annual $PM_{2.5}$ concentrations, assigned for each child based on values for the 1km*1km grid cell in which their home address was located each year. If a child changed addresses during the year, we calculated the annual $PM_{2.5}$ concentration as the average across the grid cells in which they resided, weighted by days at each address. As a secondary analysis, we estimated the effect of long-term, lagged $PM_{2.5}$ exposures on the outcomes of interest, by averaging $PM_{2.5}$ values at the home address across 3 years prior, 2 years prior, and 1 year prior. For example, the 3-year average value for a 5-year-old child was calculated as the average of annual $PM_{2.5}$ values at the child's home address for age-years 2, 3, and 4, with the outcomes of interest (e.g., annual hospital days, average white blood cell (WBC) value) occurring at 5 years of age.

As secondary exposure analyses, we estimated the impact of $PM_{2.5}$ components on the outcomes of interest. We focused on five major components: elemental carbon (EC), often referred to as black carbon and a marker for diesel exhaust; organic carbon (OC), which includes a vast array of organic compounds arising from combustion processes; ammonium ($NH4^{+}$), which typically originates from agricultural sources and traffic; sulfate (SO_4), which is mainly derived from the burning of fossil fuels; and nitrate (NO_3), also a common byproduct of fossil fuel combustion and agricultural activities.(10) Exposure assignment methodology was consistent for $PM_{2.5}$ and its components, utilizing annual concentrations based on the child's home address.

The primary outcomes of interests were measures of SCD clinical severity, including number of inpatient hospital days and ED visits per year of age (e.g., from 2.00-2.99 years of age). To mitigate the influence of extreme outliers due to prolonged hospitalizations in few children, statistical outliers for hospital days were Winsorized, meaning that values above the 95^{th} percentile were replaced with the value at the 95th percentile. Given the known impact of $PM_{2.5}$ on the endothelium and inflammation, secondary outcome variables of interest included abnormal stroke screening by transcranial doppler (abnormal versus conditional or normal per year), and markers of inflammation including WBC and absolute

neutrophil count (ANC). Laboratory values were annual, averaged across values in a given year taken at baseline (i.e., during an outpatient well visit).

Statistical analyses

Univariate and bivariate analyses were conducted to assess the distributions and associations of our primary exposures and outcomes. Next, a fixed effects model was implemented to investigate the relationship between air pollution exposure and SCD clinical severity within our panel dataset. The estimating equation is shown below,

$$Y_{it} = \alpha_i + \beta_1 pollution_{it} + \beta_2 hydroxyurea_{it} + \beta_3 age + \beta_4 insurance_{it} + \beta_5 distance_{it} + \beta_6 SVI_{it} + \beta_7 temperature_t + \epsilon_{it} \quad (1)$$

where Y is the outcome of interest for individual i at age-year t (e.g., 2 years of age, 3 years of age, etc.), α_i is the individual fixed effect, and β_1 is the primary coefficient of interest. Covariates of interest were chosen a priori based on potential associations with air pollution exposure and/or SCD severity, and included: age (continuous variable, chosen as continuous due to worsening SCD severity with age and because modeling age as continuous and linear would account for trends across time in the fixed effects model), insurance (private versus Medicaid versus uninsured), distance to nearest hospital (continuous), SVI (continuous, higher number represents higher vulnerability), and annual average daily minimum temperature. Hydroxyurea use, defined as reporting hydroxyurea use for more than half of all clinical visits for a given age year, was included as a covariate in the primary models (without effect modification).

In separate models, hydroxyurea use was included as an interaction term with annual pollution exposure, hypothesizing that the anti-inflammatory properties of hydroxyurea would mitigate the harms from $PM_{2.5}$ exposure. Proxies of socioeconomic status, including insurance use and census-tract SVI, were also measured as effect modifiers, hypothesizing that families with higher socioeconomic status may be able to better mitigate the harmful effects of air pollution (e.g., through better home air filtration systems).

The fixed effects models assign a unique fixed effect to each person, effectively controlling for unobservable and time-invariant individual characteristics that could confound the relationship between air pollution exposure and clinical and laboratory outcomes in SCD.(29) Via this model, we were able to focus on the variations in air pollution exposure levels and their impact on SCD clinical severity across different time points for the same individuals. This approach minimizes the bias in our estimates that could arise from omitted variables specific to each person, such as genetic factors or long-term health conditions, by comparing the same individual under different conditions of exposure. Consequently, this model enhances the reliability of our findings by using the within-individual changes over time to infer the causal relationship between air pollution and SCD severity, while holding constant all unobserved, individual-specific factors that do not vary over time. Given the precise nature of our exposure data – time-varying, annual pollutant concentrations matched to each individual's home address and adjusted for any address changes during the study period – this model is particularly appropriate for examining the specific impact of air pollution on health outcomes among this cohort of children with SCD.

Count outcome variables were analyzed using a quasi-Poisson regression, continuous variables were assessed through linear regression, and dichotomous outcome variables were examined with logistic regression models.(30) Given repeat measurements, standard errors were clustered at the individual level to account for within-individual correlation. Children with missing outcome or primary exposure data were excluded from the relevant analysis. As a check on the validity of the fixed effects model, we reviewed the estimated effect of hydroxyurea use on WBC, ANC, and hemoglobin, whose effects are well-documented in the literature.(31,32) All analyses were performed in R v4.3.3.

Results

There were 1,089 children with severe SCD who were seen for a clinical encounter at CHOA from January 1, 2010 through December 31, 2019 who fit inclusion/exclusion criteria (see **Supplemental Figure 1**). The cohort had average length of follow-up of 5.1 years (range 1-12 years), for a total of 5,531 individual-years. **Table 1** shows the descriptive statistics for the sample of interest.

The primary exposure of interest was annual $PM_{2.5}$ values at the child's home address. The variability of this exposure across time and location, which is exploited in our statistical model, is demonstrated in **Figure 1**, and shows that children experienced a range of exposure contrasts (0 to >4 $\mu g/m^3$) over their course of follow up. The main driver of this $PM_{2.5}$ variability was the overall decrease in $PM_{2.5}$ levels over the study timeframe (**Supplemental Figure 2**), following national trends of air quality improving during the 2010-2019 period. In addition, 216 individuals (19.8% of the cohort of interest) changed addresses during the follow up period, which was an additional driver of observed $PM_{2.5}$ variability. Regarding the primary outcomes of interest, annual hospital days and number of ED visits (**Supplemental Figure 3**) were significantly right skewed.

Associations of annual $PM_{2.5}$ and the clinical, inflammation-related, and binary outcome variables are presented in **Figure 2**. After accounting for individual fixed-effects and the covariates/confounders of interest, the following were significantly associated with higher annual $PM_{2.5}$ levels at the individual's home address: number of hospital days per year (incident rate ratio (IRR)=1.16, p=0.047), likelihood of having a hospitalization in a given year (odds ratio (OR)=1.02, p=0.024), likelihood of an abnormal stroke risk screen (transcranial doppler) (OR=1.05, p<0.001), higher WBC (β=0.19, p=0.017), and higher ANC (β=0.14, p=0.01). Number of ED visits per year were not significantly associated with annual $PM_{2.5}$ values (incident rate ratio (IRR)=1.02, p=0.592).

Importantly, as a check of our model, we found that hydroxyurea use decreased WBC and ANC, and increased hemoglobin, similar to previously published outcomes (**Supplemental Figure 4**).(31)

Additionally, we performed several sensitivity analyses, including substituting maximum or average for minimum temperature, and substituting capita income for the SVI, and including age as a categorical rather than continuous variable; our results were robust to these sensitivity analyses (**Supplemental Table 1**).

In separate models, we included interaction terms to determine if hydroxyurea use (due to its anti-inflammatory properties), or SVI or insurance status (as proxies for socioeconomic status) mitigated the effect of $PM_{2.5}$ on clinical and laboratory outcomes. As demonstrated in **Figure 3**, hydroxyurea use significantly mitigated the effect of $PM_{2.5}$ on inflammatory markers (WBC, ANC), consistent with our hypothesis. However, hydroxyurea use did not significantly affect the impact of $PM_{2.5}$ on clinical outcomes. The interaction term estimates for SVI and insurance with $PM_{2.5}$ were statistically insignificant, suggesting no considerable modification of $PM_{2.5}$ effects by these factors.

As opposed to current year annual $PM_{2.5}$ concentrations, prior $PM_{2.5}$ exposures did not have significant impact on hospital days, WBC, or ANC. However, prior $PM_{2.5}$ exposures were significantly associated with likelihood of abnormal stroke risk screening, with longer exposure time frames demonstrating slightly increasing association (**Supplemental Figures 5 and 6**).

Figure 4 illustrates that, although the effects vary among the components, SO_4 and NH_4 were the most strongly associated with inflammatory markers (WBC, ANC). In contrast, OC demonstrates no statistically significant impact across all examined health outcomes. The concentrations of $PM_{2.5,}$ SO_4, NH_4, and NO_3 were spatially correlated; EC and OC showed less correlation (**Supplemental Figure 7**).

Discussion

In this retrospective, longitudinal analysis of 1,089 children with severe SCD encompassing 5,531 individual-years, high overall levels of ambient $PM_{2.5}$ exposure were observed, with the mean annual $PM_{2.5}$ exposure (9.8 $\mu g/m^3$) at the child's home address above the current national ambient air quality standard of 9.0 $\mu g/m^3$.(33) In the fixed effects analyses, annual $PM_{2.5}$ concentrations were

significantly associated with worse clinical outcomes (e.g., hospital days per year, likelihood of abnormal stroke risk screening) and higher annual values for inflammatory markers (e.g., WBC, ANC). Observed associations were largely similar for major $PM_{2.5}$ components, including secondary $PM_{2.5}$, SO_4 and NH_4, suggesting these to be important drivers of the overall $PM_{2.5}$ effect and potential areas for targeted environmental health policy. Hydroxyurea use acted as an effect modifier for inflammatory markers, though this effect modification was not observed for clinical outcomes.

Consistent with our primary hypotheses, higher annual $PM_{2.5}$ concentrations were associated with worse outcomes. In other words, our results demonstrate that for an individual, residing in an area with higher annual $PM_{2.5}$ values are associated with worse outcomes for that individual. These findings are both statistically and clinically significant, with a one unit increase of $PM_{2.5}$ associated with an incidence rate ratio of 1.163, or 16.3% increase in expected hospital days, holding other factors constant. To put this in perspective, in February 2024, the EPA reduced the annual $PM_{2.5}$ National Ambient Air Quality Standard from 12 to 9 $\mu g/m^3$;(33) in the context of our fixed effects Poisson regression model, a reduction of $PM_{2.5}$ of this magnitude would be associated with an expected decrease in the incidence rate of hospital days by 36.5% for a child whose baseline $PM_{2.5}$ exposure is 12 $\mu g/m^3$. Notably, the World Health Organization has more stringent standards, recommending annual $PM_{2.5}$ exposure of 5 $\mu g/m^3$; given our results, we would expect to see even further improvements in health outcomes in children with SCD if the United States adopted these recommendations.

Beyond solely confirming previous work that documents harms of $PM_{2.5}$ on clinical outcomes, our findings extend the literature in several key areas. Prior literature, especially with regards to SCD, has focused on the impact of short-term (e.g., daily) fluctuations in air pollutant levels.(21–23) In contrast, the exposures of interest in this study were annual $PM_{2.5}$ levels. Annual $PM_{2.5}$ levels are a critical exposure metric because they reflect the sustained environmental conditions individuals face, which is particularly relevant for chronic diseases like SCD where long-term environmental factors may significantly influence disease progression and management. This long-term perspective can reveal cumulative health effects that

short-term exposure assessments might miss, providing a more comprehensive understanding of how persistent air pollution exposure impacts health outcomes over time. Furthermore, it is annual $PM_{2.5}$ levels that have been the subject of recent policy changes in the United States.(33) Understanding the distinct health impacts of $PM_{2.5}$ components can lead to more precise public health interventions and policies, enhancing protection for sensitive groups like children with SCD. As the Environmental Protection Agency is mandated to provide standards that protect the health of all populations, including vulnerable populations (e.g., children with SCD), it is imperative that rigorous data on the impacts of long-term pollutant exposure are well-documented.

Notably, ED visits were not correlated with annual $PM_{2.5}$ concentrations. One potential explanation for the differential outcomes observed between ED visits and hospital days lies in the nature of these metrics. ED visits typically signify acute exacerbations, while hospital days may be indicative of more severe underlying disease. Previous research has demonstrated a correlation between ED visits and acute increases in daily air pollution levels for children with SCD,(22,23) suggesting that acute rises in pollution levels are likely to trigger immediate health issues, leading to an increase in ED visits. Conversely, chronic exposure to elevated $PM_{2.5}$ levels appears to exacerbate the severity of the underlying disease, resulting in more frequent and/or longer hospital stays. This hypothesis aligns with our data and highlights the distinct impact of acute versus chronic exposure to air pollution on health outcomes in children with SCD.

Another unique strength of this study lies in its longitudinal analysis of a cohort of children with SCD. These data and modeling strategy allowed for individual tracking over time. The fixed effects multivariable model takes advantage of this panel data and controls for time-invariant confounders, such as baseline SCD severity and underlying genetics. This methodology strengthens our ability to make causal inferences on the impact of long-term $PM_{2.5}$ exposure on health outcomes in children with SCD. Additionally, by including hydroxyurea use as an interaction term, our study investigated whether this medication as an effect modifier. We found that hydroxyurea significantly reduced $PM_{2.5}$'s impact on two

markers of inflammation, WBC and ANC, although it did not alter $PM_{2.5}$'s effects on clinical outcomes. This finding introduces a potential new avenue for mitigating air pollution-related harms, beyond traditional avoidance strategies.

There exist several limitations that warrant mention. First, our focus on CHOA's patient data, though comprehensive, may not fully capture the experiences of children with SCD outside the Atlanta metropolitan area. Regarding our outcomes, hospital days and ED visits do not fully capture the experience or severity of SCD, and WBC and ANC are imperfect markers of inflammation. Future studies that more precisely document the impact of air pollution on SCD severity and inflammation are needed. Regarding confounding, while our fixed effects model controlled for unobserved individual time-invariant factors, it did not account for any unobserved time-varying factors, such as indoor pollution or unrecorded fluctuations in individual health behaviors; thus, there is a possibility for residual confounding if such factors are correlated with ambient $PM_{2.5}$ levels. Air pollution exposures were assessed based on home address only; we were not able to characterize children's overall exposures to ambient $PM_{2.5}$ that account for time-activity patterns such as time spent at school and other locations.

In conclusion, in this longitudinal study of 1,089 children with SCD, we identified significant associations between annual $PM_{2.5}$ exposure and adverse clinical and laboratory outcomes, underscoring the importance of addressing air quality in vulnerable populations. The study's innovative approach, particularly the fixed effects methodology and examination of hydroxyurea as an effect modifier, opens new avenues for research and intervention beyond traditional pollution avoidance strategies. Future studies that examine the impact of long-term air pollution exposure and hydroxyurea use on more precise inflammatory markers and respiratory specific outcomes are needed.

References

1. Thomson AM, McHugh TA, Oron AP, Teply C, Lonberg N, Tella VV, et al. Global, regional, and national prevalence and mortality burden of sickle cell disease, 2000–2021: a systematic analysis from the Global Burden of Disease Study 2021. The Lancet Haematology. 2023 Aug 1;10(8):e585–99.

2. Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. The Lancet. 2010 Dec 11;376(9757):2018–31.

3. Kavanagh PL, Fasipe TA, Wun T. Sickle Cell Disease: A Review. JAMA. 2022 Jul 5;328(1):57–68.

4. Fertrin KY, Costa FF. Genomic polymorphisms in sickle cell disease: implications for clinical diversity and treatment. Expert Review of Hematology. 2010 Aug 1;3(4):443–58.

5. Quinn CT. Minireview: Clinical severity in sickle cell disease: the challenges of definition and prognostication. Exp Biol Med (Maywood). 2016 Apr 1;241(7):679–88.

6. Rees DC, Brousse VAM, Brewin JN. Determinants of severity in sickle cell disease. Blood Reviews. 2022 Nov 1;56:100983.

7. Brumberg HL, Karr CJ, Bole A, Ahdoot S, Balk SJ, Bernstein AS, et al. Ambient Air Pollution: Health Hazards to Children. Pediatrics. 2021 Jun 1;147(6):e2021051484.

8. George PE, Thakkar N, Yasobant S, Saxena D, Shah J. Impact of ambient air pollution and socio-environmental factors on the health of children younger than 5 years in India: a population-based analysis. The Lancet Regional Health - Southeast Asia [Internet]. 2024 Jan 1 [cited 2023 Dec 5];20. Available from: https://www.thelancet.com/journals/lansea/article/PIIS2772-3682(23)00188-9/fulltext

9. Patel L, Friedman E, Johannes SA, Lee SS, O'Brien HG, Schear SE. Air pollution as a social and structural determinant of health. The Journal of Climate Change and Health. 2021 Aug 1;3:100035.

10. Masselot P, Sera F, Schneider R, Kan H, Lavigne É, Stafoggia M, et al. Differential Mortality Risks Associated With PM2.5 Components: A Multi-Country, Multi-City Study. Epidemiology. 2022 Mar;33(2):167.

11. Feng S, Gao D, Liao F, Zhou F, Wang X. The health effects of ambient PM2.5 and potential mechanisms. Ecotoxicology and Environmental Safety. 2016 Jun 1;128:67–74.

12. Anderson JO, Thundiyil JG, Stolbach A. Clearing the Air: A Review of the Effects of Particulate Matter Air Pollution on Human Health. J Med Toxicol. 2012 Jun 1;8(2):166–75.

13. Chuang KJ, Chan CC, Su TC, Lee CT, Tang CS. The Effect of Urban Air Pollution on Inflammation, Oxidative Stress, Coagulation, and Autonomic Dysfunction in Young Adults. Am J Respir Crit Care Med. 2007 Aug 15;176(4):370–6.

14. Korten I, Ramsey K, Latzin P. Air pollution during pregnancy and lung development in the child. Paediatric Respiratory Reviews. 2017 Jan 1;21:38–46.

15. Hamanaka RB, Mutlu GM. Particulate Matter Air Pollution: Effects on the Cardiovascular System. Frontiers in Endocrinology [Internet]. 2018 [cited 2022 Oct 11];9. Available from: https://www.frontiersin.org/articles/10.3389/fendo.2018.00680

16. Zhang D, Xu C, Manwani D, Frenette PS. Neutrophils, platelets, and inflammatory pathways at the nexus of sickle cell disease pathophysiology. Blood. 2016 Feb 18;127(7):801–9.

17. Teixeira RS, Terse-Ramos R, Ferreira TA, Machado VR, Perdiz MI, Lyra IM, et al. Associations between endothelial dysfunction and clinical and laboratory parameters in children and adolescents with sickle cell anemia. PLOS ONE. 2017 Sep 1;12(9):e0184076.

18. Collins TW, Grineski SE, Shaker Y, Mullen CJ. Communities of color are disproportionately exposed to long-term and short-term PM2.5 in metropolitan America. Environmental Research. 2022 Nov 1;214:114038.

19. Khan H, Krull M, Hankins JS, Wang WC, Porter JS. Sickle cell disease and social determinants of health: A scoping review. Pediatric Blood & Cancer. 2022;e30089.

20. Yallop D, Duncan ER, Norris E, Fuller GW, Thomas N, Walters J, et al. The associations between air quality and the number of hospital admissions for acute pain and sickle-cell disease in an urban environment. British Journal of Haematology. 2007;136(6):844–8.

21. Barbosa SM de M, Farhat SCL, Martins LC, Pereira LAA, Saldiva PHN, Zanobetti A, et al. Air pollution and children's health: sickle cell disease. Cadernos de Saúde Pública. 2015;31:265–75.

22. Blumberg AH, Ebelt ST, Liang D, Morris CR, Sarnat JA. Ambient air pollution and sickle cell disease-related emergency department visits in Atlanta, GA. Environmental Research. 2020 May 1;184:109292.

23. George PE, Maillis A, Zhu Y, Liu Y, Lane PA, Lam W, et al. Are children with sickle cell disease at particular risk from the harmful effects of air pollution? Evidence from a large, urban/peri-urban cohort. Pediatric Blood & Cancer. 2023 May 29;e30453.

24. Piel FB, Tewari S, Brousse V, Analitis A, Font A, Menzel S, et al. Associations between environmental factors and hospital admissions for sickle cell disease. Haematologica. 2017 Apr;102(4):666–75.

25. Quarmyne MO, Dong W, Theodore R, Anand S, Barry V, Adisa O, et al. Hydroxyurea effectiveness in children and adolescents with sickle cell anemia: A large retrospective, population-based cohort. American Journal of Hematology. 2017;92(1):77–81.

26. CDC/ATSDR Social Vulnerability Index (SVI) [Internet]. 2022 [cited 2023 Mar 22]. Available from: https://www.atsdr.cdc.gov/placeandhealth/svi/index.html

27. Amini H, Danesh-Yazdi M, Di Q, Requia W, Wei Y, AbuAwad Y, et al. Annual Mean PM2.5 Components (EC, NH4, NO3, OC, SO4) 50m Urban and 1km Non-Urban Area Grids for Contiguous U.S., 2000-2019 v1 [Internet]. Palisades, New York: NASA Socioeconomic Data and Applications Center (SEDAC); 2023. Available from: https://doi.org/10.7927/7wj3-en73

28. National Climatic Data Center [Internet]. National Oceanic and Atmospheric Administration (NOAA); [cited 2023 Dec 12]. Available from: https://www.sciencebase.gov/catalog/item/5526e945e4b026915857c713

29. McNeish D, Kelley K. Fixed effects models versus mixed effects models for clustered data: Reviewing the approaches, disentangling the differences, and making recommendations. Psychological Methods. 2019;24(1):20.

30. Croissant Y, Millo G, Tappe K, Toomet O, Kleiber C, Zeileis A, et al. plm: Linear Models for Panel Data [Internet]. 2023 [cited 2024 Mar 7]. Available from: https://cran.r-project.org/web/packages/plm/index.html

31. Zimmerman SA, Schultz WH, Davis JS, Pickens CV, Mortier NA, Howard TA, et al. Sustained long-term hematologic efficacy of hydroxyurea at maximum tolerated dose in children with sickle cell disease. Blood. 2004 Mar 15;103(6):2039–45.

32. Agrawal RK, Patel RK, shah V, Nainiwal L, Trivedi B. Hydroxyurea in Sickle Cell Disease: Drug Review. Indian J Hematol Blood Transfus. 2014 Jun;30(2):91–6.

33. Final Rule to Strengthen the National Air Quality Health Standard for Particulate Matter [Internet]. Environmental Protection Agency; 2024 [cited 2024 Apr 1]. Available from: https://www.epa.gov/system/files/documents/2024-02/pm-naaqs-overview.pdf

Table 1: Dependent and Independent Variable Values for 1,089 Children with HbSS/HbSβ0 treated at CHOA from Jan 1, 2010 - Dec 31, 2019.

Dependent Variables	**n**	**Min**	**Mean**	**Max**	**Standard Deviation**
Clinical					
Annual inpatient hospital days	5531	0	3.1	82	6.1
Annual ED visits	5531	0	1	18	1.6
Average annual Hgb	4569	5.6	9.1	15.1	1.2
Inflammatory					
Average annual WBC	4569	2.4	9.8	25.4	3.2
Average annual ANC	4508	0.5	4.7	21.4	2.1
Binary					
Hospitalization this year (% yes with hospitalization for given patient-year)	5531	39.40%			
Abnormal stroke risk screening (% yes for annual stroke-risk screen, among those who obtained TCD)	2284	10.40%			
Independent Variables	**n**	**Min**	**Mean**	**Max**	**Standard Deviation**
Individual Level					
Annual $PM_{2.5}$ exposure ($\mu g/m^3$)	5531	7.9	9.8	12.7	1.0
Age (years)	5531	0	8.5	17	5.1
Sex (% female)	1089	51%			
Distance to hospital (km)	5531	1	23.2	48.2	11.3
Insurance	5531				
Private (% of encounters)		29.40%			
Medicaid (% of encounters)		62.10%			
Other (% of encounters)		8.50%			
Census Tract Level					
Social Vulnerability Index (SVI)	5531	0	0.5	1	0.3
SVI Socioeconomic Status Category	5531	0	0.5	1	0.3
Area Deprivation Index (ADI)	4840	4	60.8	100	20.2
ACS per capita income ($/year)	5531	8426	25094.4	94459	9240.6

ACS: American Community Survey; ANC: Absolute Neutrophil Count; ED: Emergency Department; Hgb: Hemoglobin.

Table 1 compiles the yearly averaged variables for 1,089 children with HbSS/HbSβ0 treated at CHOA from January 1, 2010 through Dec 31, 2019.

Note that the unit of analysis is 'patient-year,' meaning that individual patients contribute multiple entries.

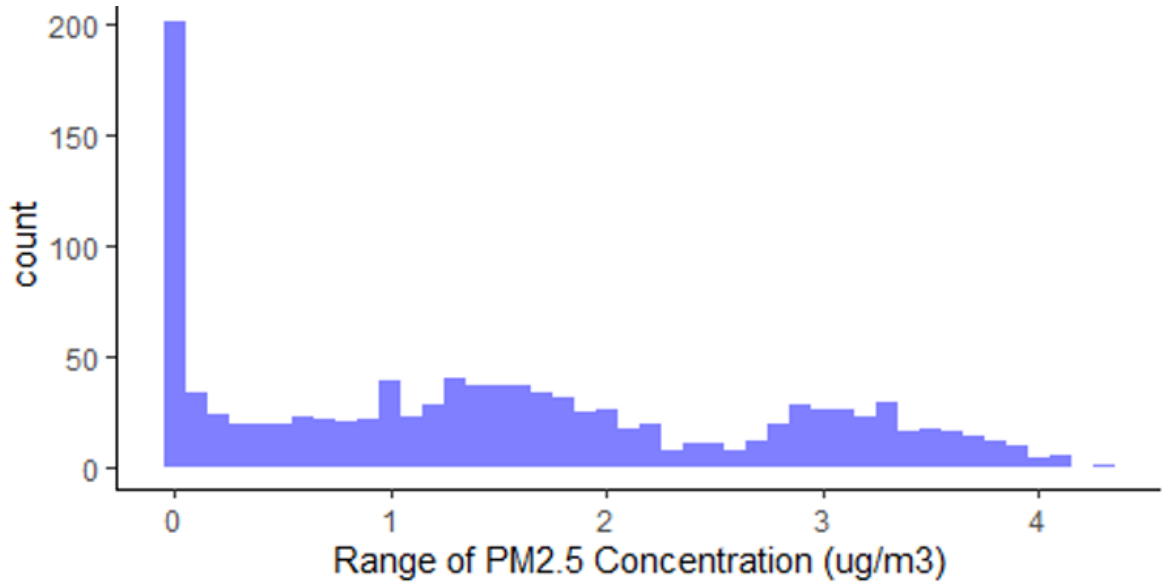


Figure 1: Individual $PM_{2.5}$ variation in cohort. This figure shows the $PM_{2.5}$ range for each individual in the cohort over their course of follow up in the study, where range is defined as the maximum minus the minimum annual $PM_{2.5}$ concentration ($\mu g/m^3$) at the individual's home address.

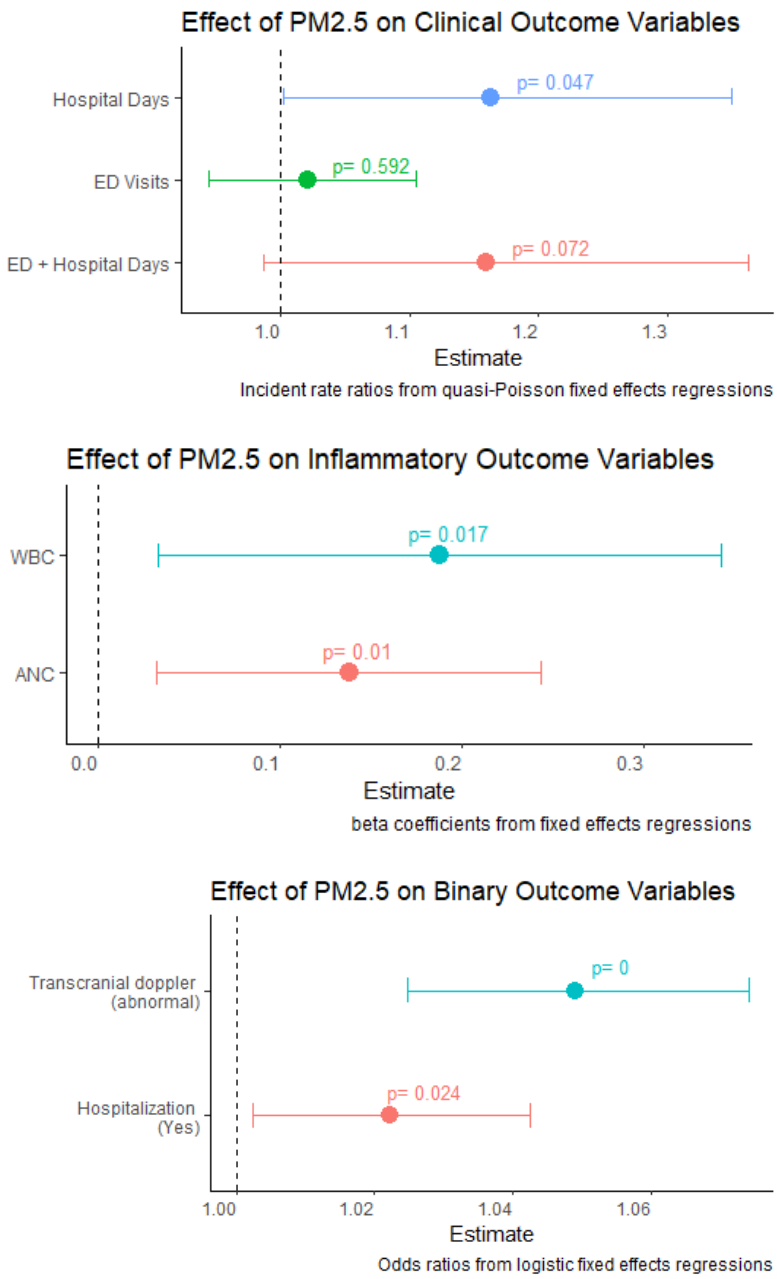


Figure 2: Results of primary models. This figure shows the main results from the primary models. Each estimate and 95% confidence interval (CI) shown comes from a separate model, whose dependent (outcome) variable is labeled on the y-axis. All models include individual fixed effects and adjust for hydroxyurea use, insurance, census tract social vulnerability index (SVI), distance from hospital, age, and yearly average minimum daily temperature.

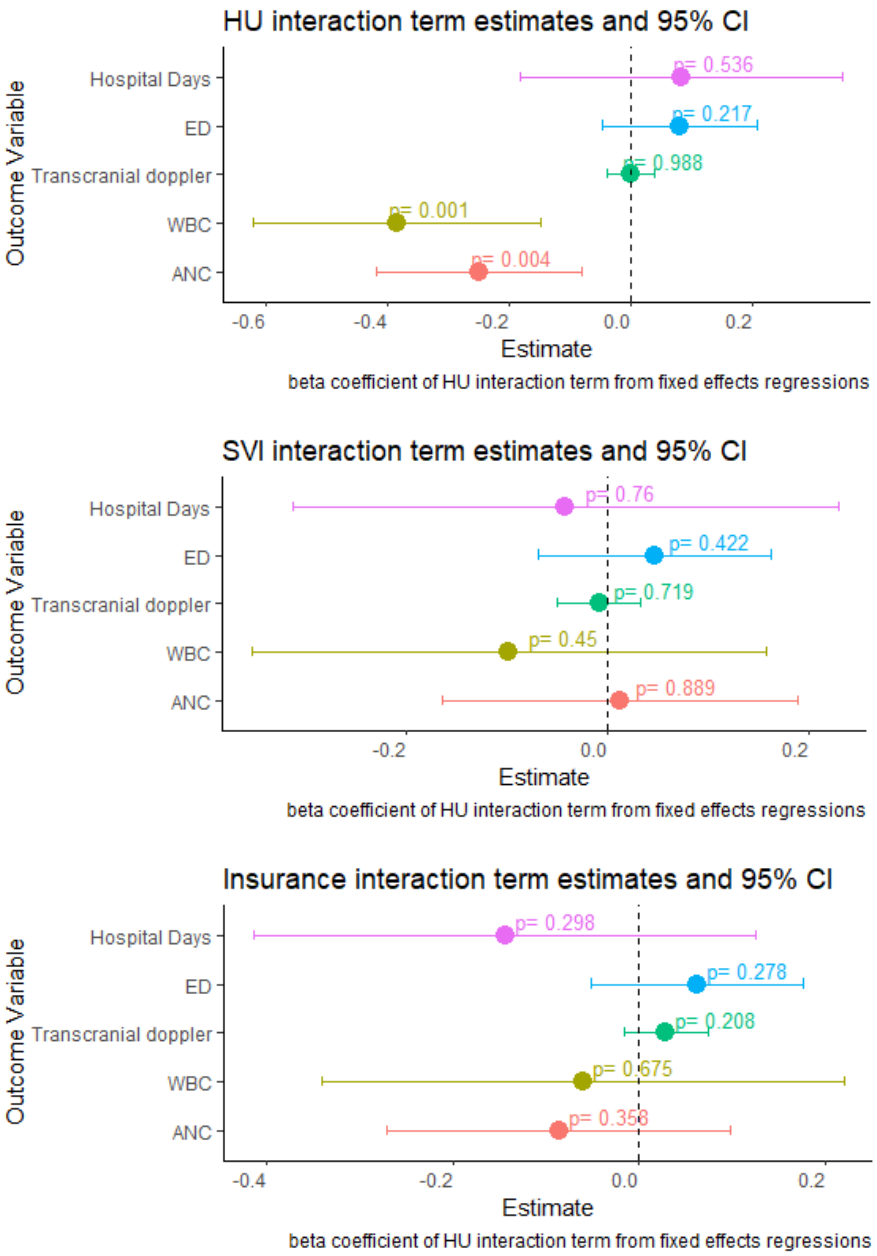


Figure 3: Results of interaction term models. This figure shows the main results of the models with interaction terms. Each estimate and 95% confidence interval (CI) shown comes from a separate model, whose dependent (outcome) variable is labeled on the y-axis. All models include individual fixed effects and adjust for hydroxyurea use, insurance, census tract social vulnerability index (SVI), distance from hospital, age, yearly minimum temperature, and contain the interaction terms as shown above. For interaction terms, SVI was dichotomized to above versus below 50th percentile, and insurance was dichotomized to private/commercial versus other.

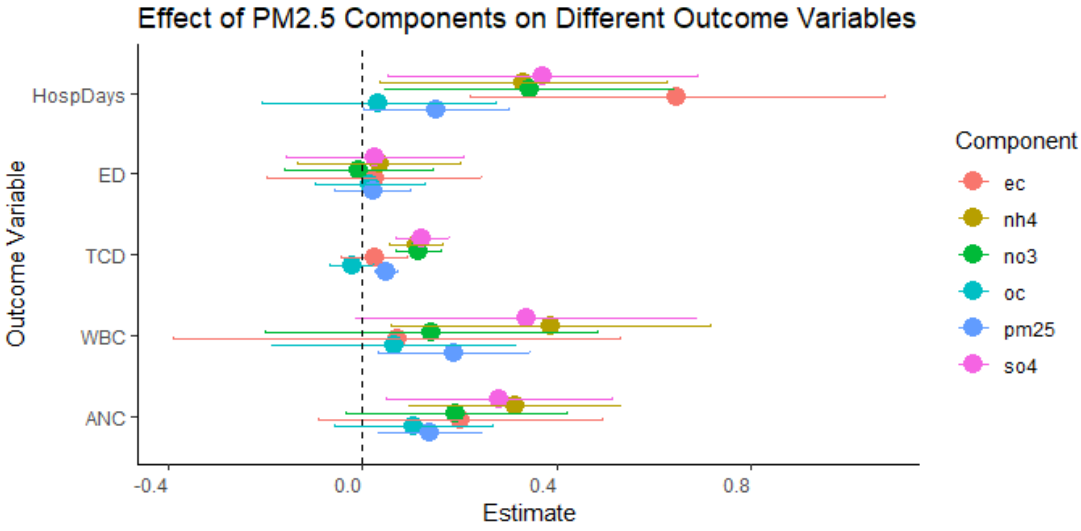
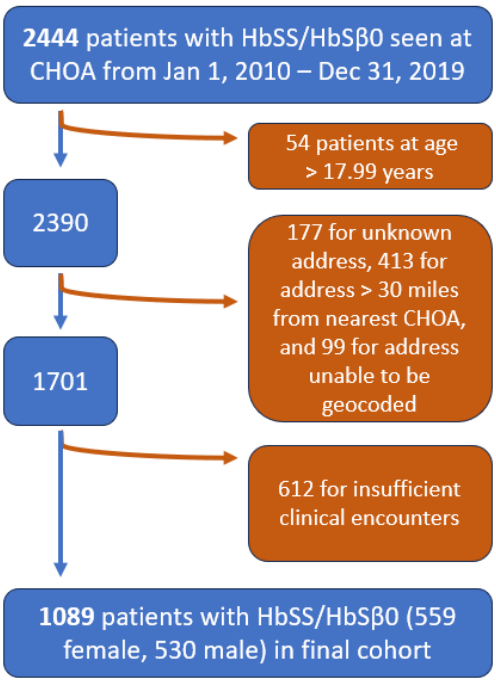
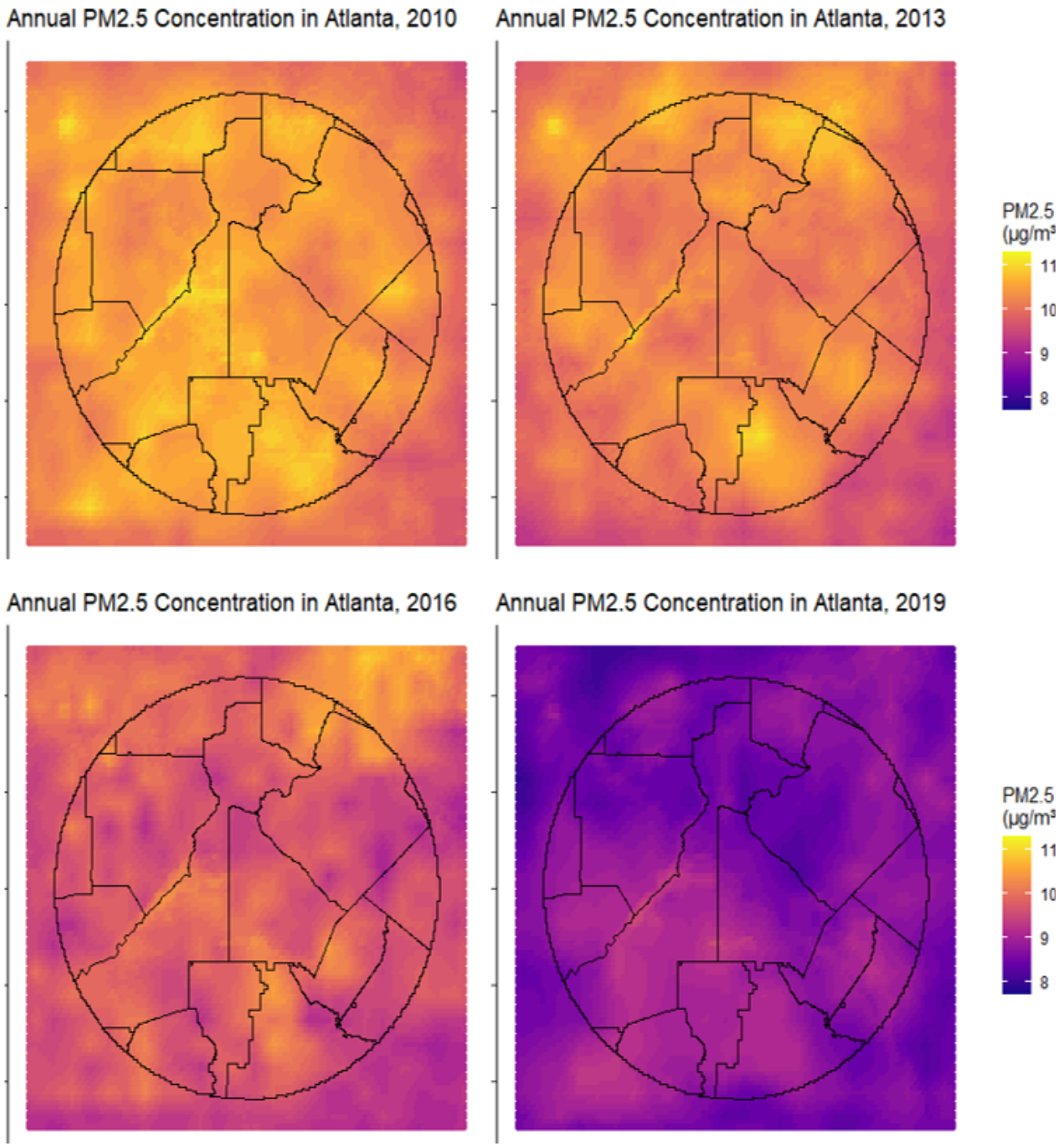


Figure 4: Effect of $PM_{2.5}$ components on different outcomes. Each beta coefficient estimate and 95% confidence interval (CI) shown on the x-axis represents a unique fixed effects model, where the outcome of interest is shown on the y-axis, and the exposure of interest is a different $PM_{2.5}$ component, including elemental (black) carbon (EC), organic carbon (OC), ammonium (NH_4^+), sulfate (SO_4), and nitrate (NO_3). For comparison, $PM_{2.5}$ components have been standardized (mean centered and divided by their standard deviation).

Supplemental material

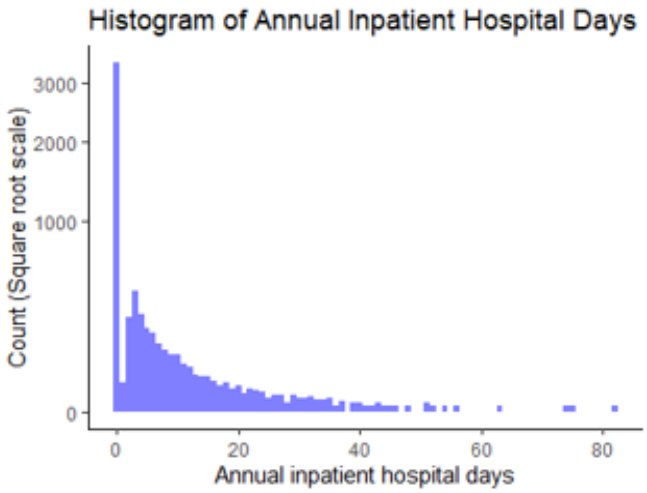


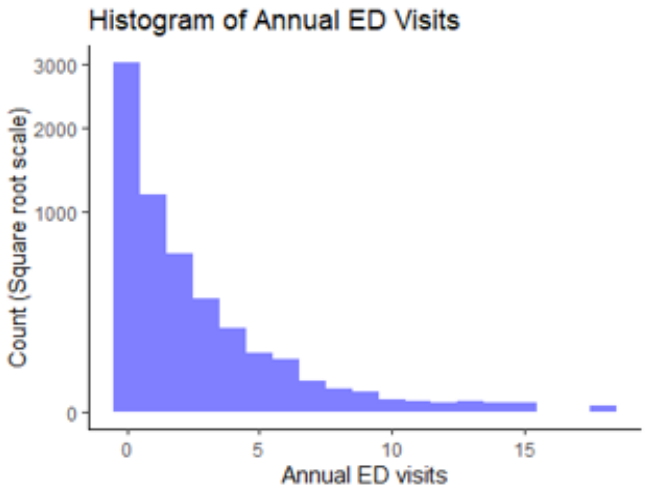
Supplemental Figure 1: Patient Inclusion/Exclusion Flow Chart. CHOA: Children's Healthcare of Atlanta. Insufficient clinical encounters: <2 years of follow up, of <3 clinical visits in total (excluding encounters for bone marrow transplant).

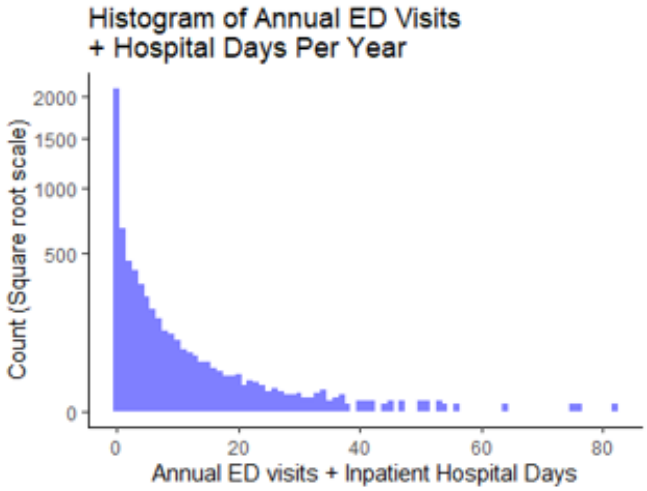


Supplemental Figure 2, Change in $PM_{2.5}$ across Atlanta, GA, from 2010 to 2019. This figure shows the change in annual $PM_{2.5}$ concentration across Atlanta, GA. The color scale is the same for each panel. The black lines show the county outlines within Atlanta. The outer black circle represents 30 miles from the midpoint of the 3 Children's Healthcare of Atlanta (CHOA) hospitals. Annual $PM_{2.5}$ data was abstracted from the NASA Socioeconomic Data and Applications Center (SEDAC) Annual $PM_{2.5}$ Concentrations Database.

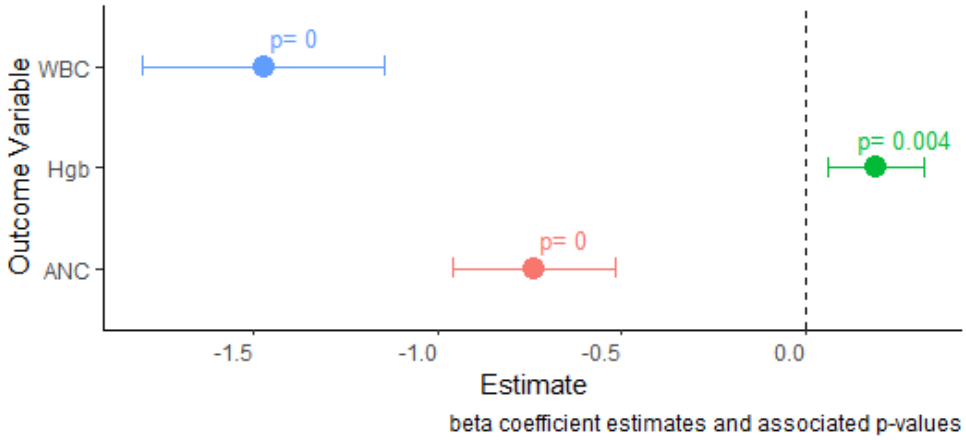
Supplemental Figure 3.



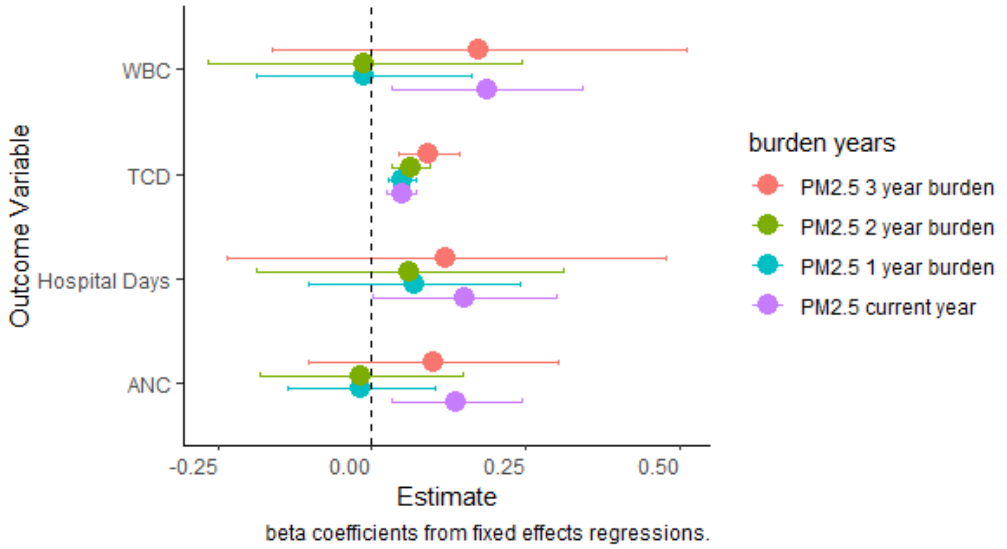




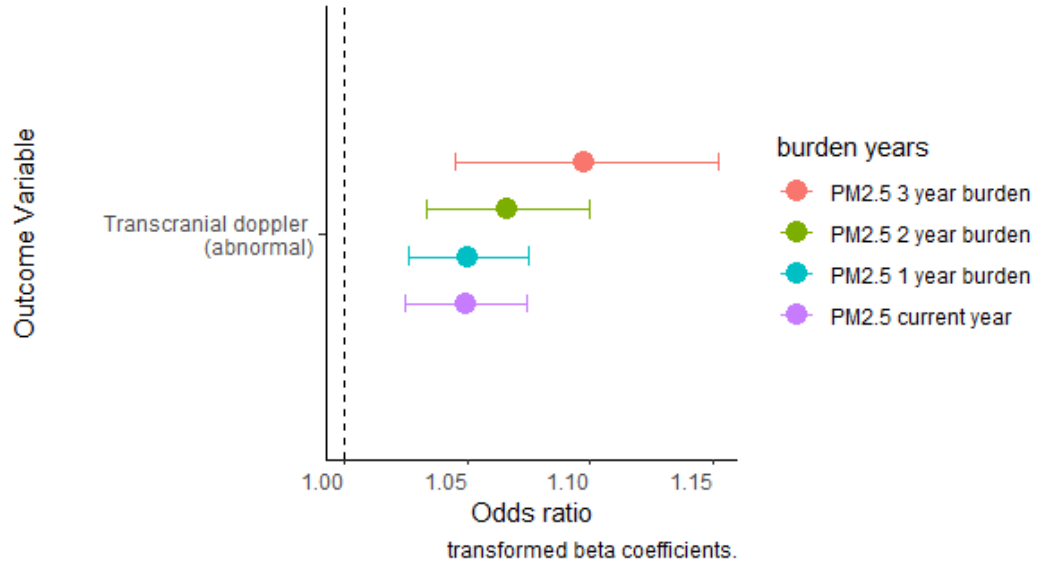
This figure displays the primary clinical outcomes of interest, annual inpatient days and annual number of emergency department (ED) visits. Note that for inpatient days, there appear to be two distributions – one for patients who never have a hospitalization, and another for patients who do have hospitalizations. This bimodal distribution is not observed for annual ED visits.



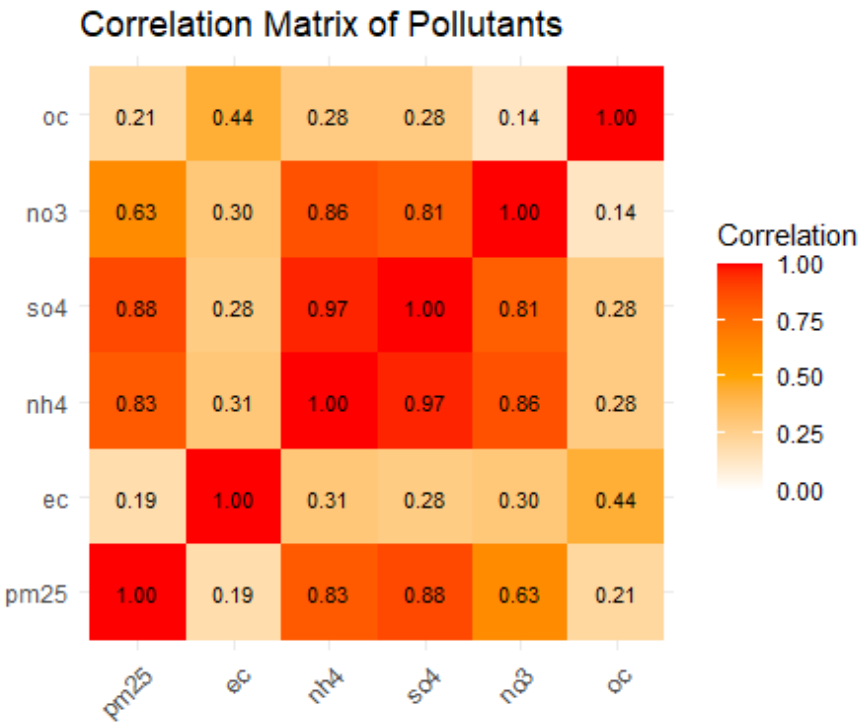
Supplemental Figure 4, Effect of hydroxyurea on laboratory outcomes. These results serve as a test on the fixed effects model, as it is well-described that hydroxyurea use reduces white blood cell count (WBC) and absolute neutrophil count (ANC), and increases hemoglobin (Hgb). The magnitude and direction of the values observed in this figure are consistent with published results.



Supplemental Figure 5, Effect of prior $PM_{2.5}$ burden on different outcomes. This figure shows the impact of $PM_{2.5}$ burden, which is defined as the average $PM_{2.5}$ values at the home address across 3 years prior, 2 years prior, and 1 year prior to the year of interest. For example, the 3-year burden value for a 5-year-old patient would be the average of annual $PM_{2.5}$ values at the patient's home address for 2, 3, and 4 years of age, with the outcomes of interest (e.g., annual hospital days, average WBC value) occurring at 5 years of age.



Supplemental Figure 6, Effect of prior $PM_{2.5}$ burden on likelihood of abnormal transcranial doppler. This figure shows the impact of $PM_{2.5}$ burden, which is defined as the average $PM_{2.5}$ values at the home address across 3 years prior, 2 years prior, and 1 year prior to the year of interest, on the likelihood of an abnormal transcranial doppler ultrasound. Note that transcranial doppler ultrasound is the standard means of screening for stroke risk in children with SCD, and is recommended for every child between 2 and 16 years of age with HbSS/HbSβ0. Abnormal screening, defined as a velocity of 200 cm/s or higher, is associated with significantly increased risk of stroke and has important treatment implications.



Supplemental Figure 7: Correlation matrix of PM2.5 and components. As expected, all pollutants are positively correlated.

Chapter 3

Evaluating the Long-Term, Time-Dependent Efficacy of Hydroxyurea in Pediatric Sickle Cell Disease: A Difference-in-Differences and Event Study Analysis

Abstract

Background: Hydroxyurea is the primary disease-modifying medication for sickle cell disease (SCD), but its long-term, time-varying effects are not well understood. This study aimed to quantify the time-varying effects of hydroxyurea on clinical and laboratory outcomes in children with SCD over a prolonged period of use.

Methods: We conducted a quasi-experimental study using difference-in-differences and dynamic event study analyses on a longitudinal cohort of 2,265 children with severe SCD (HbSS/HbSβ0) followed at Children's Healthcare of Atlanta from 2010-2021. Primary outcomes included emergency department (ED) visits per year, hospital days per year, and annual hemoglobin concentration.

Results: Hydroxyurea use was associated with fewer ED visits per year (average treatment effect on the treated [ATT] -0.33, 95% CI -0.53, -0.12) and fewer hospital days per year (ATT -0.67, 95% CI -1.47, 0.14), with sustained effects over time. Hemoglobin concentration initially increased with hydroxyurea use (ATT 0.28, 95% CI 0.13, 0.43) but this effect diminished over time. Results remained consistent in sensitivity analyses.

Conclusions: This study demonstrates that hydroxyurea has sustained clinical benefits in reducing ED visits and hospitalizations over years of use in children with SCD. However, the initial improvement in hemoglobin concentration was not sustained long-term. These findings provide valuable insights for clinicians and families regarding the long-term efficacy of hydroxyurea in pediatric SCD management.

Background

Hydroxyurea is the first-line and most prescribed disease-modifying medication in sickle cell disease (SCD).(1) Hydroxyurea induces the production of fetal hemoglobin and has anti-inflammatory properties, both of which lessen SCD severity, though the exact mechanism of action is not fully understood.(2) Hydroxyurea therapy confers significant clinical benefits as compared with no hydroxyurea therapy and has become the primary disease-modifying treatment modality in SCD.(2–5) The National Heart, Lung, and Blood Institute expert panel report for the management of SCD recommend hydroxyurea be offered for all children aged 9-12 months and older with HbSS/HbSβ0 (the most common and severe forms of SCD), regardless of clinical severity.(6) Currently, hydroxyurea is recommended as a lifelong medication for patients who meet treatment criteria, and there is not a similarly efficacious second-line medication.(2)

Observational studies document the long-term efficacy of hydroxyurea, relative to never using hydroxyurea. Among a cohort of patients followed for 17.5 years, long-term use of hydroxyurea was associated with reductions in pulmonary complications and overall mortality.(7) A separate study documented that, as compared to historical controls who never took hydroxyurea, infants and young children with SCD had fewer episodes of acute chest syndrome and better growth after 4 years on hydroxyurea.(8) Other observational studies have confirmed long-term safety.(8–10)

Notably, there are no available data on the time-varying effect of hydroxyurea. While it has been shown that long-term use of hydroxyurea is beneficial relative to no hydroxyurea use, the available studies do not examine whether the effect of hydroxyurea changes over time. It is possible that the body might adapt to hydroxyurea, causing decreased efficacy over time, similar to tolerance observed in long-term use of other anti-inflammatory medications and opioids.(9) From a SCD-pathophysiological standpoint, the effects of a vaso-occlusive event or acute chest syndrome episode are not limited to the acute event; instead, the damage caused from the event can have ongoing consequences in the form of chronic pain and persistent lung damage, respectively. As such, it is possible that the benefits of long-term hydroxyurea use would compound, resulting in increasing effect over time.

Thus, the primary objective of this study was to quantify the time-varying effects of hydroxyurea on outcomes in children with SCD. Specifically, using real-world (i.e., outside clinical trial) data on a longitudinal cohort of children with SCD, we implemented a quasi-experimental study design (difference-in-differences (DiD) and dynamic event study) that analyzed how the effects of hydroxyurea change over time. We hypothesized that hydroxyurea would demonstrate increasing efficacy across time.

Methods

The patient data came from a longitudinal cohort of children with SCD, followed at Children's Healthcare in Atlanta (CHOA), and has been described in detail elsewhere.(11,12) Briefly, children with laboratory-confirmed SCD who received care at CHOA from January 1, 2010 – December 31, 2021 were automatically enrolled in the cohort. Clinical, laboratory, and sociodemographic details were abstracted from the CHOA electronic record, with results verified by research epidemiologists. CHOA comprises the only pediatric SCD clinic and pediatric hospitals in the Atlanta metropolitan area; therefore, ~95% of all hospitalizations and all pediatric SCD-specialty outpatient appointments were captured in the database, representing a nearly complete population sample of children with SCD in Atlanta.(4) Inclusion criteria for the study were: children with HbSS/HbSβ0 (as this is the only group of patients with SCD in whom HU is regularly utilized), under age 18.0 years. Children were excluded from analysis if they had <3 total clinical visits and were censored if they went >2 years without a clinical visit, underwent bone marrow transplant, or started chronic transfusion therapy.

For the analysis, patient data were grouped by age-years (e.g., from 0 to 1 year of age, 1 to 2 years, etc.). The primary outcomes of interest were clinical (ED visits per year and hospital days per year) and laboratory (average annual hemoglobin value, mean corpuscular volume (MCV, which corresponds to the size of a red blood cell), and absolute neutrophil count (ANC)). ED visits and hospital days were summed over a given age-year. Laboratory variables were averaged within each age-year, excluding lab results from ED visits and hospitalizations. Baseline (i.e., pre- hydroxyurea) values were established by retrieving data from the initiation date of hydroxyurea treatment. If lab results from this date were not

available, the most recent lab values from a non-sick clinic visit within one year prior to starting hydroxyurea were used.

The exposure of interest was hydroxyurea use during a specific age-year. Research epidemiologists reviewed the clinical note and prescription details from each office visit and marked a patient as taking or not taking hydroxyurea accordingly. Patients were classified as hydroxyurea users for a given age-year if they were recorded as taking hydroxyurea at more than 50% of their clinical visits within that year. Sensitivity analyses were conducted with the threshold increased to 80%, which did not significantly change the results.

To test the time-varying impact of hydroxyurea on clinical and laboratory outcomes, we performed a dynamic DiD analysis (also known as a dynamic two-way fixed effects study, or event study with control group). In our analysis, the unit of observation was the individual patient per given age-year. Importantly, this methodology estimates an independent effect of hydroxyurea treatment for each year before and after treatment initiation. Mathematically, this can be written:

$$Y_{i,t} = \alpha_t + \alpha_g + \Sigma_{e=-k}^{-1}\beta_e^{anticip} * D_{i,t}^{e} + \Sigma_{e=0}^{l}\beta_e * D_{i,t}^{e} + \epsilon_{i,t} \qquad (1)$$

where *Y* is the outcome variable for individual *i* at age-year t (e.g., hospital days per year), α are time (age-year) and group (age at hydroxyurea initiation) fixed effects, *D* is an indicator variable that equals 1 if individual *i* is treated with hydroxyurea in year *e*, and *k* and *l* are positive constants indicating number of years *e* before and after treatment.[1]

By providing unique β across different time periods *e*, this framework allows for time-varying treatment estimation. More specifically, the β coefficients show the effect of hydroxyurea on the clinical outcomes for each specific year before and after treatment initiation. The coefficients with positive

[1] Note regarding Equation (1): (a) subscript *t* represents the age-year of the observation (e.g., patient i at age-year 2 years old, or 3 years old), not to be confused with subscript *e*, which represents the number of years before or after treatment initiation.

subscripts (e.g., β_2) indicate the impact of hydroxyurea in the years after starting treatment. For instance, a significantly positive β_2 suggests that hydroxyurea had a beneficial impact in the second year after starting the medication. Conversely, the coefficients with negative subscripts (e.g., β_{-3}) represent the years before treatment initiation. We would expect these β values to be insignificant because hydroxyurea should not impact outcomes before its initiation. If these pre-treatment β values are indeed insignificant, it supports the parallel trends assumption, which is crucial for the validity of the DiD analysis. By examining the β coefficients year-by-year, this methodology allows us to capture the dynamic, time-varying impact of hydroxyurea, rather than just an average or overall effect, providing a detailed picture of how the treatment's impacts evolve over time.

To address recent econometrics literature demonstrating that classical DiD estimators give biased results when the treatment of interest has staggered initiation timing and/or a time-varying response, we adapted the framework as described by Callaway and Sant'Anna.(13) This framework uses both never-treated and not-yet-treated patients as the control. For example, the controls for two-year-old group include two-year-olds not yet taking hydroxyurea (e.g., those who start hydroxyurea at age three), and children who are two years old who never started hydroxyurea. The purpose of the control group is to account for time-varying effects that might impact both the treated and untreated groups similarly, thereby controlling for time-varying confounding effects to obtain a more accurate estimate of the true treatment effect. Note that this framework has not been validated for non-continuous (i.e., on-off-on) treatment; thus, patients were censored at first stoppage of hydroxyurea. For robustness checks, we have included results from alternative estimators.(14–16)

We performed several sensitivity analyses. First, to address the potential bias that patients may start hydroxyurea in response to complications of SCD (such as ED visits or hospital days), we conducted analyses where the treatment group was limited to those who began hydroxyurea treatment at 1 year of age. This approach accounts for the fact that SCD manifestations are relatively rare in infants due to the protective effects of fetal hemoglobin. By focusing on a uniform starting age of hydroxyurea – and, specifically, an age prior to which the severe manifestations of SCD commonly occur – we aimed to

eliminate the confounding effects of those who start hydroxyurea in response to severe manifestations of the disease. Another sensitivity analysis focused on medication adherence. Since hydroxyurea reliably increases MCV, we restricted the treatment group to those with laboratory evidence of good adherence, defined as an MCV while on hydroxyurea that is at least 5% above the baseline MCV.

We performed several tests to analyze the validity of the parallel trends assumption, which for this analysis can be stated as "absent treatment with hydroxyurea, the control group (i.e., those not treated or not-yet-treated with hydroxyurea) and treatment group would have similar outcomes across time." (17) First, pre-treatment trends were assessed visually, using the event study graphs. Next, differences in pre-treatment trends in the outcomes of interest pre-treatment were quantified statistically, by interacting treatment year with ever treated status, including only the pre-treatment years. For all analyses, given the large number of individual patients, we focused on clinically significant, rather than solely statistically significant, differences in outcomes.

Results

Of the 2,444 patients with severe SCD (HbSS/HbSβ0) seen for a clinical encounter at CHOA from 2010-2021, 2,265 (93%) met inclusion criteria (See **Supplemental Figure 1**). The average follow-up time was 6.3 years, providing a total of 14,312 patient-years of data. 1,381 (61%) patients had ever used hydroxyurea; of those, the average time on hydroxyurea was 5.3 years, with 340 children with ≥9 years of continuous hydroxyurea therapy. On average, there were 1.1 ED visits per year and 3.6 hospital days per year for the cohort. See **Table 1** and **Table 2** for more details.

To check the validity of the DiD and event study models, we first quantified the impact of hydroxyurea use on changes in mean corpuscular volume (MVC, the size of the red blood cell) and changes in absolute neutrophil count (ANC, a type of white blood cell) using our model. It is well-established that hydroxyurea use reliably increases MCV and decreases ANC. (1,2,18) Both the magnitude and direction of the results obtained via our models correspond well with clinical experience

and published literature on the effects of hydroxyurea in these hematologic parameters, supporting the validity of the models (**Supplemental Figure 2**).

Regarding the primary outcome of interest, hydroxyurea use was significantly associated with fewer ED visits per year (average treatment effect on the treated (ATT) -0.33, 95% confidence interval (CI) -0.53, -0.12). The results of the event study analysis can be found in **Figure 1**. We obtain similar results for the ATT and the time-varying effect of hydroxyurea when limiting the treatment group to patients who start treatment at 1 year of age, accounting for potential regression to the mean among those who begin treatment after a year with many ED visits. Additionally, the ATT and time-varying effect remain consistent when we restrict the treatment group to those with laboratory markers indicating good adherence, thus mitigating potential biases due to poor medication adherence (**Supplemental Figure 3**). Our results are not substantially different when using other contemporary event study estimators, further reinforcing the robustness of our findings (**Supplemental Figure 4**).

Hydroxyurea use was also associated with a reduction in hospital days per year, with an ATT of -0.67 (95%CI -1.47, 0.14), though not statistically significant. The event study analysis, depicted in **Figure 2** (top panel), indicates steady effect over time. Interestingly, the effect at year -1 (i.e., the year before treatment initiation), is positive. This statistically significant finding suggests that higher number of hospital days is associated with subsequent initiation of hydroxyurea, which violates the parallel trends assumption. To mitigate this potential bias, we performed an additional analysis which limits the treatment group to those beginning hydroxyurea at 1 year of age. When limiting the sample of hydroxyurea users to those who start treatment at 1 year of age, as expected we do not see this statistically significant difference in outcomes prior to hydroxyurea initiation. Furthermore, the results of this analysis, both the ATT (-0.75, 95%CI -2.0, 0.52) and event study analysis are similar to the original analysis **(Figure 2**, bottom panel).

Our laboratory outcome of interest was annual hemoglobin concentration. The DiD estimator resulted in an ATT of 0.28 (95%CI 0.13, 0.43). The event study analysis is depicted in **Figure 3;** in contrast to the clinical outcomes, we find the effect of hydroxyurea use on hemoglobin concentration

decrease with time. This trend in decreasing effect on hemoglobin concentration is also seen among the subgroup of treated patients with laboratory markers of good adherence. **Supplemental Figure 5** shows the unadjusted data of average hemoglobin values by hydroxyurea across time. Hemoglobin values are higher on average for males than females, and show an overall slight increase that begins in adolescence, consistent with previously reported values and trends.(20,21)

Parallel trends were analyzed both visually and statistically. As discussed above, with the exception of hospital days per year, visual inspection of all event study analyses supported the parallel trends assumption. **Supplemental Table 1** shows the results of the interaction term of the pre-treatment analyses, providing statistical quantification of differences in pre-treatment outcome trends.

Discussion

In this quasi-experimental analysis of hydroxyurea in 2,265 children and adolescents with severe SCD, we find that hydroxyurea use has sustained impact on ED visits and hospital days across prolonged use. These results remain evident when we account for potential sources of bias, both by limiting the treated sample to those who start hydroxyurea at a young age and to those with laboratory evidence of good medication adherence. Interestingly, the initial improvements seen in hemoglobin concentration with hydroxyurea use were not sustained over time in this cohort, even among those with laboratory evidence of good medication adherence. These data and results arise from outside the confines of clinical trials, expanding the generalizability to real-world settings and a broader population of children and adolescents with SCD.

Our study addresses a significant gap in the existing literature on the long-term, time-varying effects of hydroxyurea in children with SCD. Randomized controlled trials provide strong and consistent evidence of the short-term benefits of hydroxyurea. The landmark study by Charache et al. (1995) demonstrated a reduction in vaso-occlusive events and acute chest syndrome, though with a mean follow-up time of only 21 months, as the trial was stopped early due to the effectiveness of hydroxyurea.(3) Similarly, randomized trials on hydroxyurea use in children and adolescents have found fewer

hospitalizations and pain episodes, with a follow-up periods of 1-2 years.(22–24) Additionally, a quasi-experimental by Quarmyne et al. (2017), which compared patient outcomes two years before and after hydroxyurea initiation, found significant reductions in hospitalizations and emergency department visits, along with an increase in hemoglobin levels.(4) These studies provide strong evidence on the short-term impact of hydroxyurea, but given their follow-up time constraints, they do not provide a comprehensive understanding of the time-varying effects of hydroxyurea over more extended periods.

Observational studies have documented the prolonged impact of hydroxyurea over longer periods. When comparing those on hydroxyurea to those not taking hydroxyurea, reductions in mortality are consistently documented, even over follow up periods ranging 5-20 years.(7,10,25) Similarly, studies have reported sustained hematologic efficacy for years following hydroxyurea initiation.(8,18,26) However, observational studies are susceptible to potential biases that can obscure the true effect of hydroxyurea. For instance, children prescribed hydroxyurea may be those with more severe disease at baseline or might come from families with more proactive healthcare management, leading to different outcomes regardless of hydroxyurea use. Additionally, long-term follow-up must account for evolving SCD management practices that can influence outcomes; traditional observational studies often do not adequately control for such changes.

Difference-in-differences (DiD) is a method that allows for comparison between treatment and control groups, even if they are not identical at the beginning of the study. This technique helps to isolate the effect of hydroxyurea by comparing the changes in outcomes over time between those who receive hydroxyurea and those who do not. In this study's context, DiD controls for time-invariant unobserved confounders such as baseline health status, socioeconomic status, family health beliefs, and adherence to other medications, that might be different between the treatment and control groups. By focusing on changes within each group, DiD effectively accounts for these consistent, unobserved differences that might otherwise bias the results. Moreover, DiD controls for time-varying unobserved confounders that impact the entire cohort, such as changes in healthcare practices, SCD management protocols unrelated to hydroxyurea, environmental factors, and policy changes that could influence outcomes over the study

period. For instance, if there were improvements in general SCD care or new public health policies introduced during the study period, DiD helps to account for these factors by comparing the treatment and control groups over the same periods, ensuring that such external influences are considered in the analysis. By leveraging the DiD approach, our study provides a robust analysis of hydroxyurea's long-term effects, mitigating biases and offering a clearer picture of its impact on children with SCD in real-world settings.

Previous studies often report averaged differences across groups without analyzing whether the effect of hydroxyurea changes over time. This temporal aspect of treatment efficacy is crucial information for patients and providers, as it can influence treatment plans and expectations for health outcomes. Understanding how the benefits of hydroxyurea evolve over time helps clinicians make informed decisions about long-term management strategies for children with SCD. Additionally, this information is vital for families who are considering or currently using hydroxyurea. Knowing that the efficacy of hydroxyurea may vary over the years can help families set realistic expectations and make better-informed choices regarding their child's treatment. One commonly reported barrier to hydroxyurea use is concerns about its long-term efficacy and safety.(2,27,28) Families may worry whether the initial benefits observed with hydroxyurea will persist, diminish, or potentially lead to adverse effects over extended use. By providing a detailed analysis of how hydroxyurea impacts clinical and laboratory outcomes over time, this study addresses these concerns directly. It reassures families and healthcare providers that hydroxyurea not only has immediate benefits but also continues to offer significant clinical advantages throughout prolonged use. This evidence can help alleviate fears and encourage adherence to hydroxyurea therapy, ultimately leading to better health outcomes for children with SCD.

Interestingly, while previous observational studies have reported sustained elevations in hemoglobin associated with hydroxyurea use, our study did not find this same long-term effect. Instead, our results demonstrate decreasing efficacy across time, such that the relative increases in hemoglobin observed in those taking hydroxyurea are not observed once time on treatment reaches about 9-10 years. This discrepancy may be due to the advantages of our methodological approach. Specifically, our study

accounts for the rise in hemoglobin levels around the age of 13, observed in both hydroxyurea users and non-hydroxyurea users, and also reported in previous literature in changes in hemoglobin across adolescence.(20,21) If this increase is not considered, it might incorrectly appear as though hydroxyurea users experience unique benefits from the medication. Our study design, by accounting for this age-related rise, provides a more accurate assessment of hydroxyurea's impact on hemoglobin levels. It is important to note that we defined hemoglobin concentration based on annual averages during stable periods, excluding values from ED visits and hospitalizations. This distinction is crucial because, as we and others have demonstrated, hydroxyurea use reduces hospitalizations and ED visits. If hemoglobin values from all visits, including acute SCD events, were averaged together, hydroxyurea users might have higher hemoglobin levels due to fewer acute complications, as hemoglobin tends to be lower during such events. Additionally, we did not account for transfusions in this analysis (apart from chronic transfusion therapy), which could also influence hemoglobin levels and potentially bias the results. By focusing on stable, annual averages, our study design mitigates these confounding factors, offering a clearer picture of hydroxyurea 's true effect on baseline hemoglobin concentration over time.

Limitations

Similar to other DiD/event studies, a key limitation is that the parallel trends assumption cannot be verified. In this study, there may be reasons to suspect that hydroxyurea users and non-hydroxyurea users would follow different trajectories in outcomes, absent treatment. Similarly, if patients initiated hydroxyurea in response to poor outcomes in a given year, this would violate the parallel trends assumption and bias the results.(29) However, in observing the trajectories prior to starting hydroxyurea, we do not see different outcomes, indicating that the parallel trends assumption holds. In our event study graphs for ED visits and hemoglobin, the β coefficients are non-significant and without notable trends prior to hydroxyurea initiation, suggesting no significant differences between the groups. Furthermore, the year after hydroxyurea initiation, a clear change in outcomes is observed, indicating that hydroxyurea is the driving factor behind these changes rather than an unobserved factor. Interestingly, however, we do

observe a potential source of bias in the hospital days analysis, as patients have statistically significant increases in hospital days one year prior to hydroxyurea initiation. These results suggest that patients may initiate hydroxyurea in response to an increase in hospital days.

Our data were collected from a single healthcare center, CHOA, which, while providing a nearly complete population-wide picture of pediatric SCD in Metropolitan Atlanta, may limit the generalizability of our findings to other settings or populations. However, CHOA being the only SCD specialty care provider in Atlanta greatly minimizes selection bias, as patients of all severities are included and follow-up is comprehensive, not restricted to only the most severe cases. Another limitation is relying on ED visits and hospital days as outcome measures, which do not fully capture the complexity of SCD severity. Moreover, while it is less likely, there remains a possibility that some patients were treated in other EDs and hospitals, which could lead to underestimation of the true severity of their condition and bias the results if these values differed systematically based on hydroxyurea use status.

Conclusions

In conclusion, this quasi-experimental study demonstrates that hydroxyurea has a sustained clinical impact over years of use in children and adolescents with SCD, providing significant long-term benefits in reducing hospitalizations and ED visits. Interestingly, we observed an initial but not sustained improvement in hemoglobin. These findings reinforce the importance of hydroxyurea as a key treatment modality in SCD and provide valuable insights for clinicians and families regarding its long-term efficacy. Given the overall rarity of mortality in the pediatric population, our study was not powered to determine an impact on mortality; future studies should examine the impact of hydroxyurea on this and other key health related quality of life measures. Additionally, future research should continue to explore these effects in diverse settings and populations, notably adults with SCD, to further validate and expand upon our results.

References

1. Agrawal RK, Patel RK, shah V, Nainiwal L, Trivedi B. Hydroxyurea in Sickle Cell Disease: Drug Review. Indian J Hematol Blood Transfus. 2014 Jun;30(2):91–6.

2. McGann PT, Ware RE. Hydroxyurea therapy for sickle cell anemia. Expert Opin Drug Saf. 2015;14(11):1749–58.

3. Charache S, Terrin ML, Moore RD, Dover GJ, Barton FB, Eckert SV, et al. Effect of Hydroxyurea on the Frequency of Painful Crises in Sickle Cell Anemia. New England Journal of Medicine. 1995 May 18;332(20):1317–22.

4. Quarmyne MO, Dong W, Theodore R, Anand S, Barry V, Adisa O, et al. Hydroxyurea effectiveness in children and adolescents with sickle cell anemia: A large retrospective, population-based cohort. American Journal of Hematology. 2017;92(1):77–81.

5. Wang WC, Ware RE, Miller ST, Iyer RV, Casella JF, Minniti CP, et al. Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (BABY HUG). The Lancet. 2011 May 20;377(9778):1663–72.

6. Yawn BP, Buchanan GR, Afenyi-Annan AN, Ballas SK, Hassell KL, James AH, et al. Management of Sickle Cell Disease: Summary of the 2014 Evidence-Based Report by Expert Panel Members. JAMA. 2014 Sep 10;312(10):1033–48.

7. Steinberg M, McCarthy W, Castro O, Ballas S, Armstrong F, Smith W, et al. The Risks and Benefits of Long-term Use of Hydroxyurea in Sickle Cell Anemia: A 17.5 Year Follow-Up. Am J Hematol. 2010 Jun;85(6):403–8.

8. Hankins JS, Ware RE, Rogers ZR, Wynn LW, Lane PA, Scott JP, et al. Long-term hydroxyurea therapy for infants with sickle cell anemia: the HUSOFT extension study. Blood. 2005 Oct 1;106(7):2269–75.

9. de Montalembert M, Brousse V, Elie C, Bernaudin F, Shi J, Landais P, et al. Long-term hydroxyurea treatment in children with sickle cell disease: tolerance and clinical outcomes. haematologica. 2006;91(1):125–8.

10. Lê PQ, Gulbis B, Dedeken L, Dupont S, Vanderfaeillie A, Heijmans C, et al. Survival among children and adults with sickle cell disease in Belgium: Benefit from hydroxyurea treatment. Pediatric Blood & Cancer. 2015;62(11):1956–61.

11. George PE, Maillis A, Zhu Y, Liu Y, Lane PA, Lam W, et al. Are children with sickle cell disease at particular risk from the harmful effects of air pollution? Evidence from a large, urban/peri-urban cohort. Pediatric Blood & Cancer. 2023 May 29;e30453.

12. Yee ME, Lai KW, Bakshi N, Grossman JK, Jaggi P, Mallis A, et al. Bloodstream Infections in Children With Sickle Cell Disease: 2010–2019. Pediatrics. 2022 Jan;149(1):e2021051892.

13. Callaway B, Sant'Anna PHC. Difference-in-Differences with multiple time periods. Journal of Econometrics. 2021 Dec 1;225(2):200–30.

14. Sun L, Abraham S. Estimating dynamic treatment effects in event studies with heterogeneous treatment effects. Journal of Econometrics. 2021 Dec 1;225(2):175–99.

15. Gardner J. Two-stage differences in differences [Internet]. arXiv; 2022 [cited 2024 Apr 12]. Available from: http://arxiv.org/abs/2207.05943

16. Wooldridge JM. Two-Way Fixed Effects, the Two-Way Mundlak Regression, and Difference-in-Differences Estimators [Internet]. Rochester, NY; 2021 [cited 2024 Apr 12]. Available from: https://papers.ssrn.com/abstract=3906345

17. Angrist JD, Pischke JS. Mostly Harmless Econometrics: An Empiricist's Companion. Princeton University Press; 2009. 392 p.

18. Zimmerman SA, Schultz WH, Davis JS, Pickens CV, Mortier NA, Howard TA, et al. Sustained long-term hematologic efficacy of hydroxyurea at maximum tolerated dose in children with sickle cell disease. Blood. 2004 Mar 15;103(6):2039–45.

19. Akinsheye I, Alsultan A, Solovieff N, Ngo D, Baldwin CT, Sebastiani P, et al. Fetal hemoglobin in sickle cell anemia. Blood. 2011 Jul 7;118(1):19–27.

20. Jorgensen JM, Crespo-Bellido M, Dewey KG. Variation in hemoglobin across the life cycle and between males and females. Annals of the New York Academy of Sciences. 2019;1450(1):105–25.

21. Stewart West M, Wethers D, Smith J, Steinberg M, The Cooperative Study of Sickle Cell Disease. Laboratory profile of sickle cell disease: A cross-sectional analysis. Journal of Clinical Epidemiology. 1992 Aug 1;45(8):893–909.

22. Ferster A, Vermylen C, Cornu G, Buyse M, Corazza F, Devalck C, et al. Hydroxyurea for treatment of severe sickle cell anemia: a pediatric clinical trial. Blood. 1996 Sep 15;88(6):1960–4.

23. Thornburg CD, Files BA, Luo Z, Miller ST, Kalpatthi R, Iyer R, et al. Impact of hydroxyurea on clinical events in the BABY HUG trial. Blood. 2012 Nov 22;120(22):4304–10.

24. Wang WC, Ware RE, Miller ST, Iyer RV, Casella JF, Minniti CP, et al. A multicenter randomised controlled trial of hydroxyurea (hydroxycarbamide) in very young children with sickle cell anaemia. Lancet. 2011 May 14;377(9778):1663–72.

25. Rigano P, De Franceschi L, Sainati L, Piga A, Piel FB, Cappellini MD, et al. Real-life experience with hydroxyurea in sickle cell disease: A multicenter study in a cohort of patients with heterogeneous descent. Blood Cells, Molecules, and Diseases. 2018;69:82–9.

26. Hankins JS, Aygun B, Nottage K, Thornburg C, Smeltzer MP, Ware RE, et al. From Infancy to Adolescence: Fifteen Years of Continuous Treatment With Hydroxyurea in Sickle Cell Anemia. Medicine (Baltimore). 2014 Dec 2;93(28):e215.

27. Sinha CB, Bakshi N, Ross D, Krishnamurti L. From trust to skepticism: An in-depth analysis across age groups of adults with sickle cell disease on their perspectives regarding hydroxyurea. PLOS ONE. 2018 Jun 27;13(6):e0199375.

28. Strouse JJ, Heeney MM. Hydroxyurea for the treatment of sickle cell disease: Efficacy, barriers, toxicity, and management in children. Pediatric Blood & Cancer. 2012;59(2):365–71.

29. Ashenfelter O. Estimating the Effect of Training Programs on Earnings. The Review of Economics and Statistics. 1978;60(1):47–57.

Table 1: Summary statistics per patient by hydroxyurea use (ever)

Variable	n	Never used hydroxyurea (n=884)	Used hydroxyurea (n=1381)	p-value*
Sex	2,264			0.031
Female		472 (53%)	674 (49%)	
Male		411 (47%)	707 (51%)	
Years in dataframe (sd)	2,265	4.0 (3.6)	7.2 (3.8)	<0.001
Years on hydroxyurea (sd)	2,265	0.0 (0.0)	5.3 (3.2)	
Insurance	2,265			0.012
Commercial		216 (24%)	363 (26%)	
Medicaid		479 (54%)	791 (57%)	
Uninsured/None Listed		189 (21%)	227 (16%)	

Unit of analysis for this table is individual person.

Mean (standard deviation (sd)) for continuous variables; n (%) for categorical variables

*Pearson's Chi-squared test; Wilcoxon rank sum test.

Table 2: Summary statistics per patient age-year by hydroxyurea use (for given age-year)

Variable	n	Hydroxyurea use this year (n=7271)	No hydroxyurea use this year (n=7041)	p-value*
Age	14,312	9.9 (4.5)	7.3 (5.3)	<0.001
Sex	14,311			<0.001
Female		3,484 (48%)	3,768 (54%)	
Male		3,787 (52%)	3,272 (46%)	
Calendar year	14,312	2,017 (3)	2,015 (4)	<0.001
MCV	11,779	95.4 (12.1)	83.9 (8.3)	<0.001
Hgb	11,773	9.1 (1.2)	9.1 (1.3)	0.069
ANC	11,649	4.6 (1.9)	5.2 (2.5)	<0.001
ED visits per year	14,312	1.2 (2.0)	1.1 (1.9)	0.005
Hospital days per year	14,312	4.2 (6.2)	3.1 (5.0)	<0.001
Adherence to hydroxyurea	5,569	4,300 (77%)	NA	

Unit of analysis for this table is individual person-year, where year is by age.

Mean (standard deviation (sd)) for continuous variables; N (%) for categorical variables

*Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test.

ANC: absolute neutrophil count; ED: Emergency department; Hgb: hemoglobin; MCV: mean corpuscular volume; TCD: transcranial doppler.

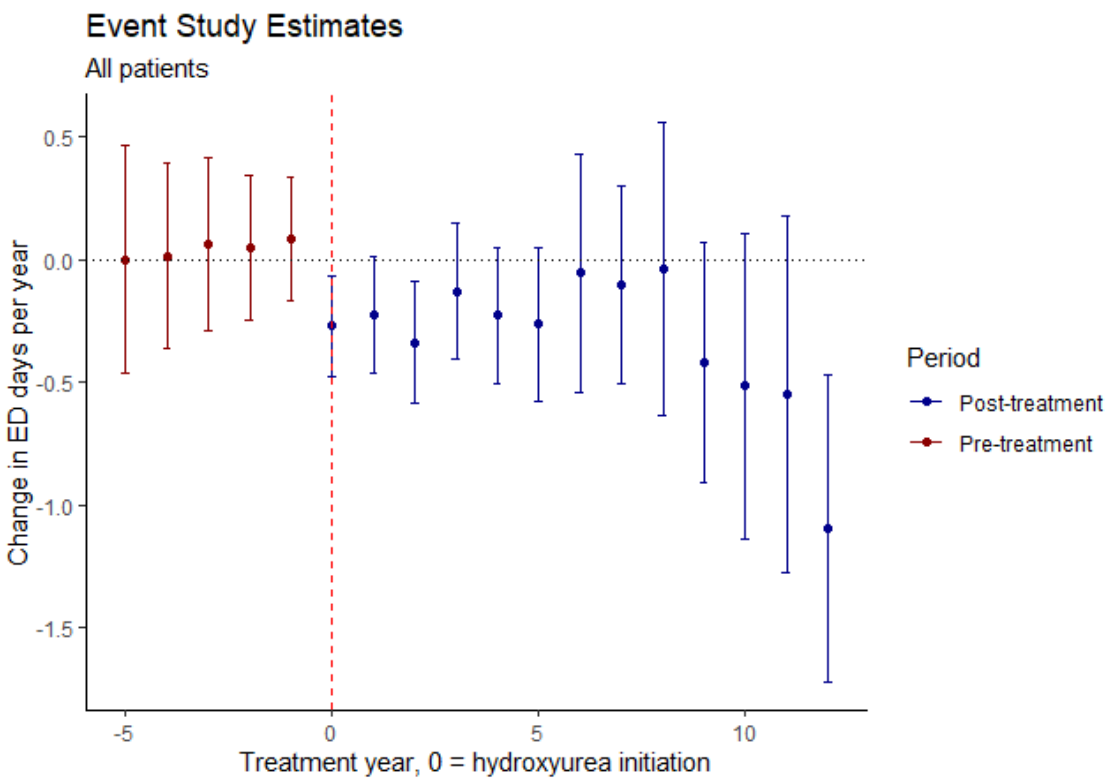
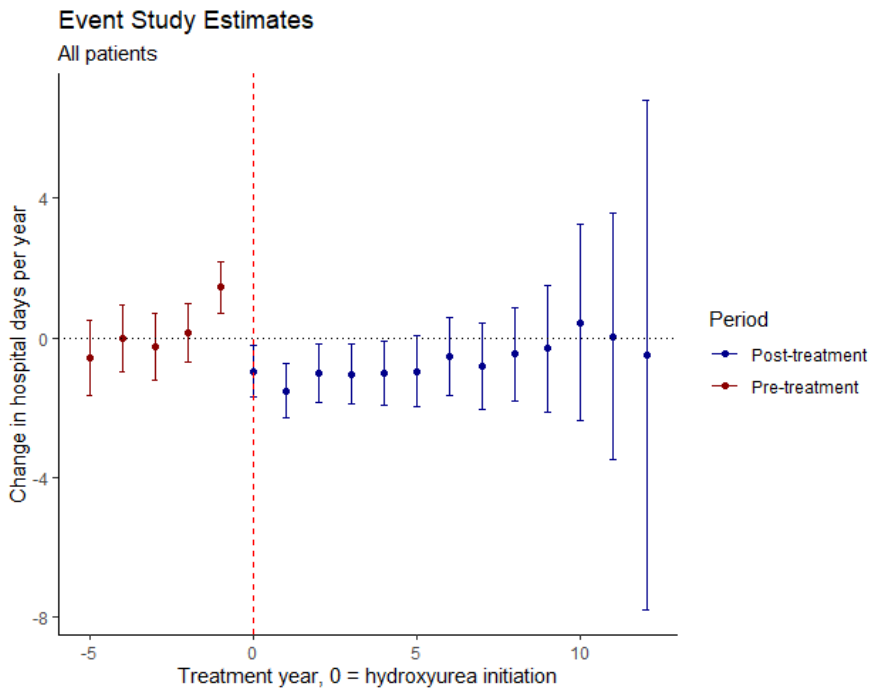


Figure 1 – Event study estimates of hydroxyurea use on annual emergency department (ED) visits. Points with 95% confidence intervals (y-axis) estimate the average treatment effect on those treated with hydroxyurea for the given year of therapy (x-axis), relative to not using hydroxyurea. Year 0 is the year of hydroxyurea initiation. Of note, the difference-in-differences estimate for this analysis was -0.33 (95% confidence interval -0.53, -0.12), meaning on average (across treatment year and age-group), hydroxyurea use was associated with 0.33 fewer ED visits per year.



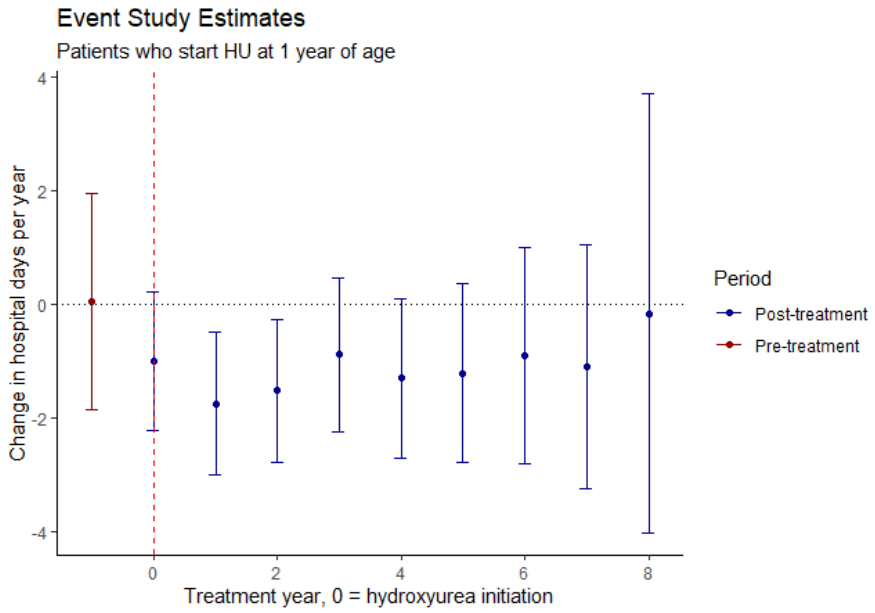


Figure 2 – Event study estimates of hydroxyurea use on annual hospital days, with entire sample (top panel) and limiting the treatment group to those beginning treatment at 1 year of age (bottom panel). Points with 95% confidence intervals (y-axis) estimate the average treatment effect on those treated with hydroxyurea for the given year of therapy (x-axis), relative to never using hydroxyurea. Year 0 is the year of hydroxyurea initiation.

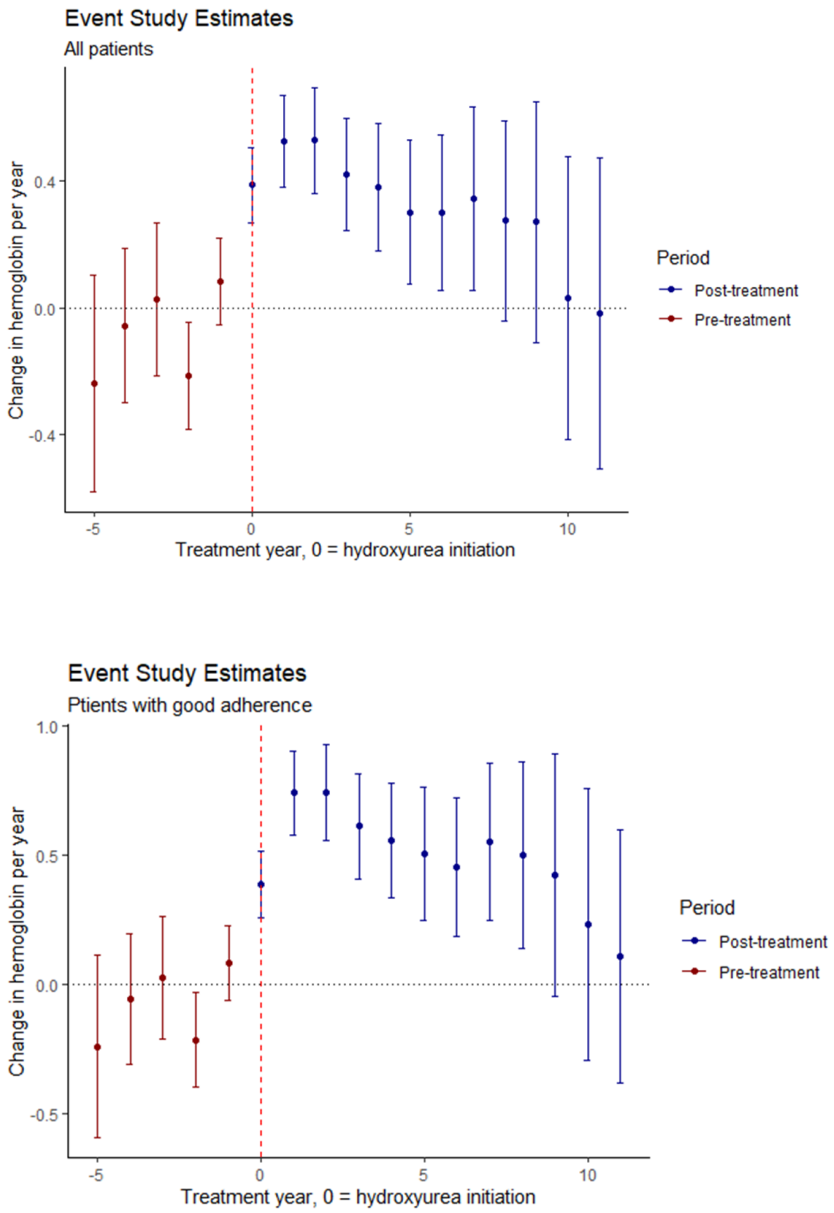
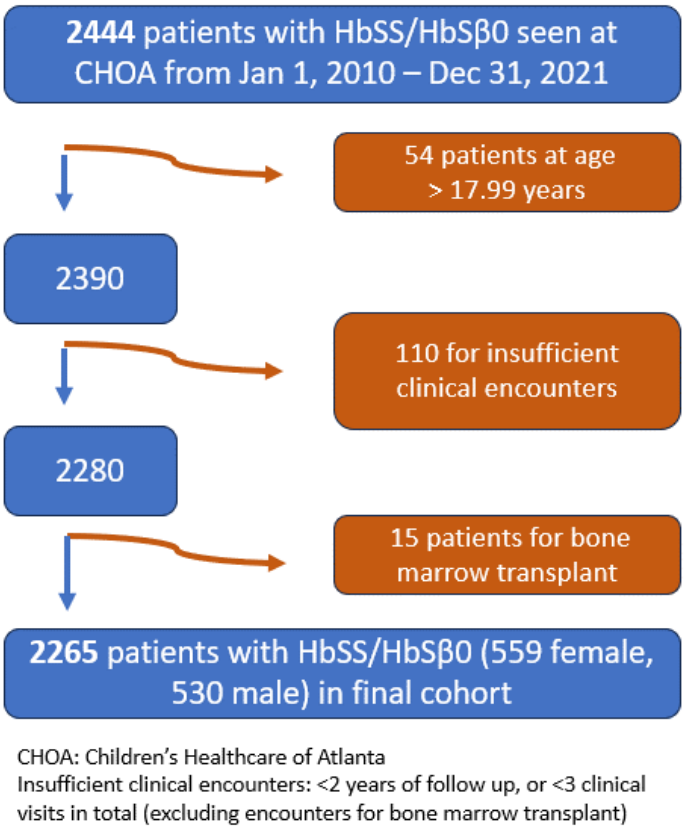
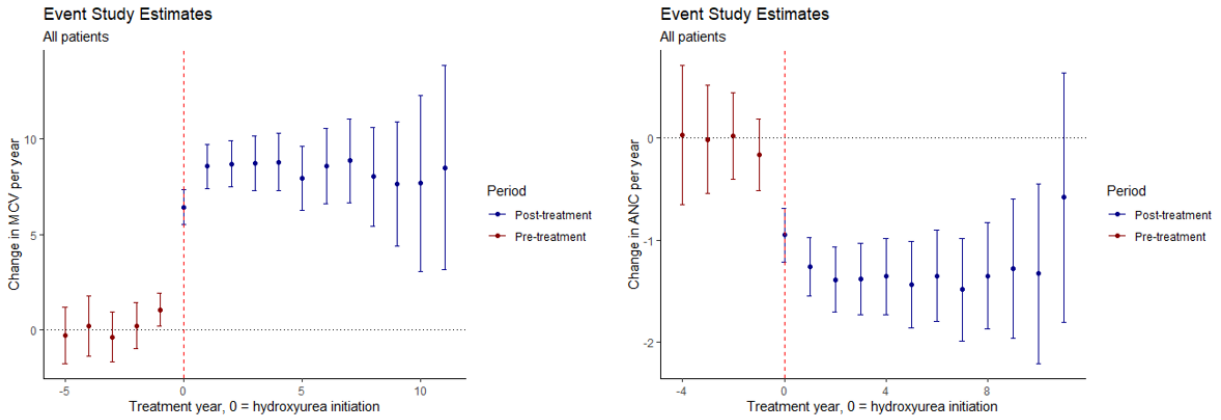


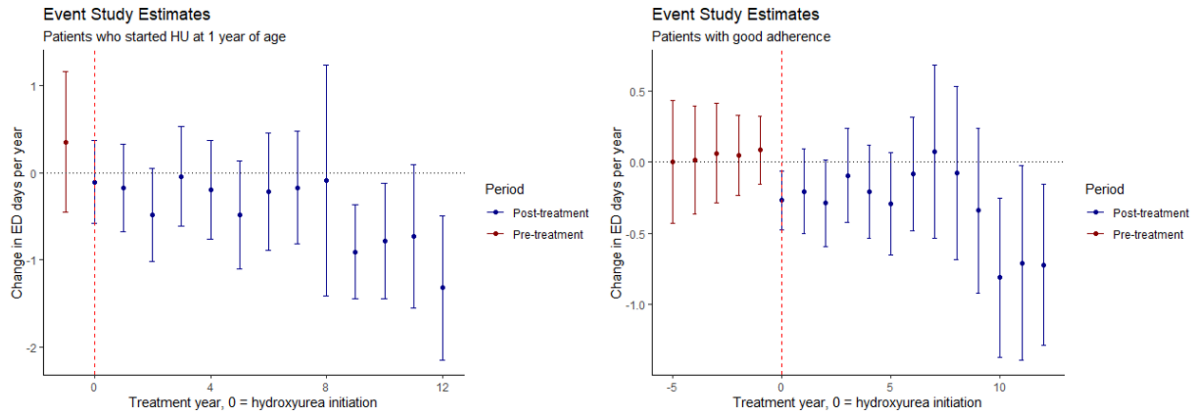
Figure 3 – Event study estimates of hydroxyurea use on annual hemoglobin values, with entire sample (top panel) and limiting the treatment group to with laboratory evidence (i.e., increase in mean corpuscular volume) of hydroxyurea adherence (bottom panel). Points with 95% confidence intervals (y-axis) estimate the average treatment effect on those treated with hydroxyurea for the given year of therapy (x-axis), relative to never using hydroxyurea. Year 0 is the year of hydroxyurea initiation. Patients are grouped by age, and additionally account for sex, baseline insurance status, and social vulnerability index at home address.



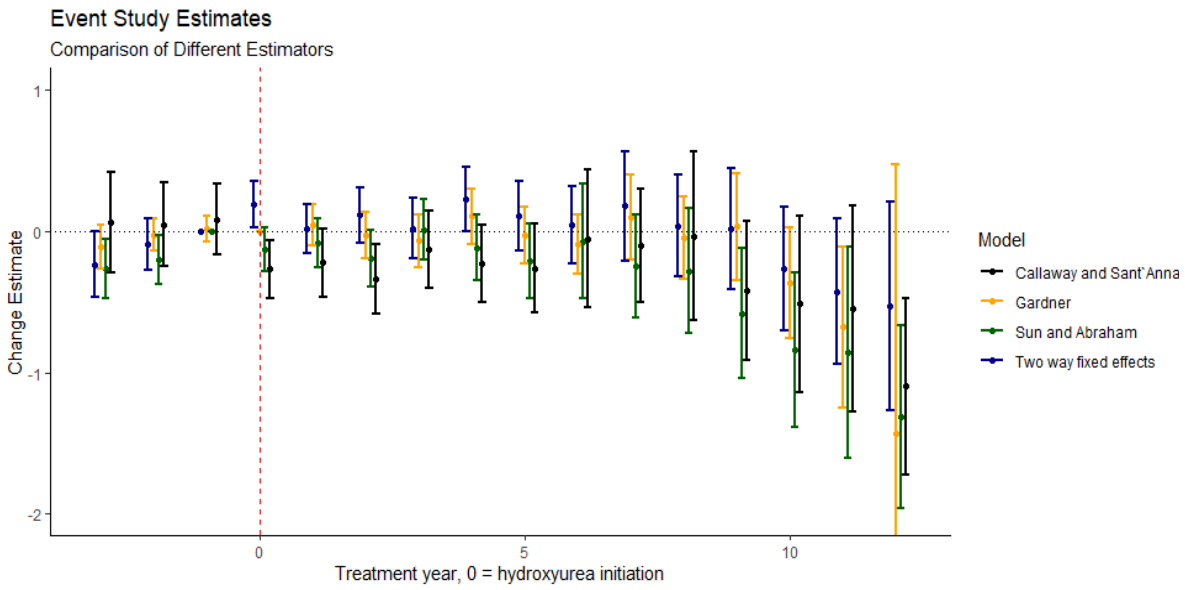
Supplemental Figure 1 – Patient Inclusion/Exclusion Flow Chart.



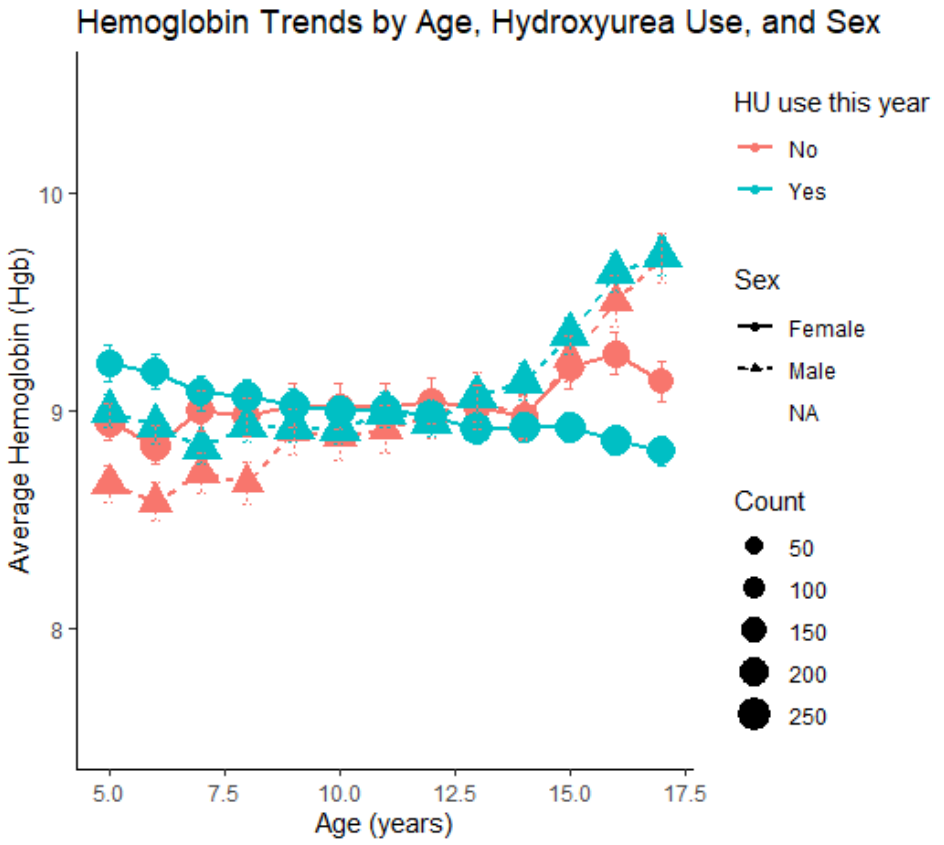
Supplemental Figure 2 – Event study estimates of hydroxyurea use on the yearly changes in mean corpuscular volume (MCV, left panel) and absolute neutrophil count (ANC, right panel). Points with 95% confidence intervals (y-axis) estimate the average treatment effect on those treated with hydroxyurea for the given year of therapy (x-axis), relative to never using hydroxyurea. Year 0 is the year of hydroxyurea initiation.



Supplemental Figure 3 – Event study estimates of hydroxyurea use on ED visits per year, with treatment group limited to those beginning treatment at 1 year of age (left panel), and limited to those with laboratory markers of good adherence (i.e., annual MCV ≥ 5% above baseline MCV). Points with 95% confidence intervals (y-axis) estimate the average treatment effect on those treated with hydroxyurea for the given year of therapy (x-axis), relative to never using hydroxyurea. Year 0 is the year of hydroxyurea initiation. Patients are grouped by age, and additionally account for sex, baseline insurance status, and social vulnerability index at home address.



Supplemental Figure 4 – Event study estimates of hydroxyurea use on the yearly changes in emergency department (ED) visits, using different estimators. Points with 95% confidence intervals (y-axis) estimate the average treatment effect on those treated with hydroxyurea for the given year of therapy (x-axis), relative to never using hydroxyurea. Year 0 is the year of hydroxyurea initiation.



Supplemental Figure 5 – Unadjusted average hemoglobin values by age, separated by hydroxyurea use and sex.

Supplemental Table 1: Results of pre-treatment trend analyses between hydroxyurea users and non-users

Model	Difference in trends	Pre-treatment mean	Percentage
ED visit per year	-0.028	1.092	-2.61
Hospital days per year	-0.102	2.938	-3.46
Hemoglobin	-0.026	9.123	-0.28
MCV	0.201	83.805	0.24
ANC	0.066	5.154	1.29

This table summarizes the pre-treatment differences in trends and mean values for the outcomes of interest, comparing individuals who ever used hydroxyurea versus those who did not. For example, for the ED visits per year model, prior to treatment, hydroxyurea users had a trend of 0.028 ED visits per year fewer than those who never used hydroxyurea.

Difference in trends was obtained using linear regression models that included an interaction term between age and HU usage, with robust standard errors clustered by individual.

Percentage = Difference in trends / pre-treatment mean * 100.

ANC: Absolute neutrophil count; ED: Emergency department; MCV: Mean corpuscular volume (measure of red blood cell size).

Chapter 4

Diffusion of a cost-saving innovation in health care:

The case of outpatient treatment for appendicitis

Abstract

Cost-saving innovations are common in many industries but rare in healthcare. We study the diffusion of a specific cost-saving innovation – outpatient treatment for appendicitis – to better understand why it was widely-adopted even though hospitals receive lower payments for outpatient care. Using private claims and state-wide emergency department records from five large states, we show that outpatient treatment reduces insurers' payments (-$4,500) and length-of-stay (-1.6 days) without increasing revisit rates. We evaluate the role of patient and physician preferences and private insurers in the uptake of outpatient treatment. Our results suggest that pressure from private insurers – as proxied by hospitals' baseline share of privately-insured patients – drove diffusion. Policies that limit insurers' ability to manage care via prior authorization or other means may retard the adoption of cost-saving innovations.

Introduction

Innovations have reduced the cost of producing nails (Sichel 2022), lighting (Nordhaus 1997), semiconductors (Byrne et al. 2018), and many other products. But there appears to be little cost-saving innovation in healthcare. An analysis of over 6,000 studies of the cost-effectiveness of new medical innovations found that 78% were cost-increasing. In their recent book on the topic, James and Robert S. Rebitzer (2023) offer the following explanations for the absence of cost-saving innovations in healthcare. First, insurers pay physicians and hospitals on a fee-for-service basis, so that providers who adopt cost-saving technologies may see their revenues and profits decline: "…the health sector generates the wrong kinds of innovation. It is

too easy to profit from low-value innovations and too difficult to profit from innovations that reduce care costs." Neither physicians nor patients, most of whom are well-insured at the margin, are able to recoup cost-savings. Second, barriers to entry protect incumbent providers, making it difficult for entrepreneurs to offer new, low-cost options for health care. Third, regulations and ethical norms limit the development and adoption of innovations that save money but are associated with even slightly worse patient outcomes.

Analyzing the adoption of the relatively few cost-saving innovations in health care can help identify the forces that impede or encourage their use. In this paper, we study the uptake of a specific cost-saving innovation: outpatient treatment for appendicitis. Historically, the vast majority of appendicitis patients were admitted to the hospital for surgery. Beginning around 2010, treatment shifted to the outpatient setting. Insurers pay less for outpatient treatment, which begs the question: Why did hospital adopt outpatient treatment? Although it is possible that outpatient treatment is more profitable, the hospital trade press has reported that the general shift to outpatient care has been a source of financial distress for the hospital industry (Assar 2022; Herman 2024; Pearl 2017). Also, hospitals have successfully lobbied against relaxing regulations that limit the types of procedures that can be performed in an outpatient setting.

Using emergency department and inpatient data from five large states, we describe the shift from inpatient to outpatient care among patients with appendicitis. We show that the use of outpatient treatment was a true innovation. It reduced insurers' spending and patients' length-of-stay without increasing patient revisit rates, a proxy for patient outcomes. Next, we evaluate explanations for why hospitals adopted outpatient treatment. Despite the reduction in revenues, outpatient treatment could still be more profitable if hospitals' costs are sufficiently lower. We find that patients treated in for-profit hospitals are less likely to be treated on an outpatient basis,

suggesting that this is not the case. We reject the hypothesis that patients are more likely to choose hospitals that offer outpatient treatment, and we find that several proxies of physician power are unrelated to the use of outpatient treatment, and so it is unlikely that adoption was driven by physician preferences.

We find that adoption is strongly related to the share of privately-insured patients at each hospital. Private insurers use prior authorization to discourage treatment in the more costly inpatient setting, and this result suggests that prior authorization policies are effective. The choice of treatment setting for appendicitis is amenable to external oversight from insurers. Appendicitis is an acute, high-volume condition that affects a relatively healthy patient population. Treatment is relatively standardized, and the main factor that necessities inpatient care, the presence of complicated appendicitis, is well-defined and does not depend on physicians' subjective judgements.

Our results have a number of policy implications. First, policies to restrict prior authorization, which are currently under consideration at the federal and state level, may retard the adoption of cost-saving innovation. Second, the government should continue to investigate hospitals for admitting patients unnecessarily. Previously, a number of hospitals have faced sanctions under the False Claims Act for billing for inpatient care when patients were or should have been treated in the outpatient setting. We find evidence that for-profit hospitals may be overadmitting appendicitis patients. Third, the federal government should relax the "inpatient only" regulation that requires hospitals to perform certain procedures in the inpatient setting only. The Trump administrated proposed to phase-out the inpatient only regulation, but scrapped the proposal under pressure from the hospital industry. We find that the shift to outpatient

treatment of appendicitis reduced costs while improving welfare, suggesting there may be more opportunities to perform low-risk procedures in the outpatient setting.

Below we provide the necessary institutional background, describe trends and hospital-level variation in the use of outpatient surgery, assess the impact of outpatient treatment on costs, length-of-stay, and readmissions, and evaluate the reasons for adoption.

Background

Appendicitis patients arrive in the emergency department with abdominal pain. Diagnosis is usually based on symptoms and imaging via computerized tomography. Recent trials have shown that non-operative management with antibiotics resolves around 70% of cases (Thomson et al. 2015; Yant et al. 2019), but this approach has not caught on. Over 80% of the patients in our sample undergo appendectomy, a surgical procedure to remove the appendix. The main technological development facilitating outpatient treatment was the use of laparoscopic versus open appendectomy. Laparoscopic appendectomy is minimally invasive, leading to shorter recovery times and fewer complications. The adoption of oral rather than intravenous antibiotics that patients self-administer at home and new devices and methods for closing the appendix stump have also contributed to shorter length of stays. The shift to outpatient treatment for appendicitis mirrors a general trend towards outpatient surgery. A number of procedures that used to be performed only on an inpatient basis are not routinely performed in the outpatient setting. In some cases, hospitals have shifted care to the outpatient setting in response to competitive pressures from ambulatory surgery centers, non-hospital facilities that are often physician-owned. Other procedures, like appendectomy, are only performed at hospitals, and the motivation for the shift to outpatient care is less clear.

The term “outpatient care” is somewhat misleading. Appendicitis patients treated on an outpatient basis are still assigned to a hospital bed and may have stays that last longer than 24 hours. They are typically managed in “observation” units that are a close substitute for and may be physically indistinguishable from inpatient wards. Patients do not necessarily know whether they are being treated on an outpatient basis, and their physicians may not realize it either. We reached out to several surgeons to gather background information for this study, and several were unfamiliar with the distinction and did not know whether the patients they treated were classified as inpatients or outpatients.

The distinction Is important for billing purposes. Inpatient and outpatient care are reimbursed by insurers under different fee schedules, and the payments for outpatient care are lower. The decision whether to bill for inpatient or outpatient care is made by hospital billing staff following the encounter, subject to the restrictions imposed by insurers. Private insurers may require hospitals to seek prior authorization before admitting a patient or, in emergency situations, they may retroactively refuse to pay for care at the higher inpatient rate (Kumar and Parthasarathy 2020; Herman 2024). Insurers rely on proprietary guidelines for determining when inpatient care is appropriate, though these are somewhat vague owing to the wide range of conditions treated in the emergency department. Government insurers do not prior authorize care, but government contractors may retroactively review inpatient admissions to ensure they were appropriate. Hospitals that inappropriately assign Medicare or Medicaid patients to inpatient status are also liable for substantial penalties under the False Claims Act. The Department of Justice has pursued successful cases against many hospital systems for overadmitting patients for procedures, notably the spinal procedure kyphloplasy, that should have been performed on an outpatient basis and for overadmitting patients generally.

Methods & Results

A simple model of hospitals' choice between inpatient and outpatient treatment in the presence of financial incentives is useful for framing the analsyis. Suppose patients' severity of illness is is described by $s\epsilon[0,1]$, where $s\sim f(s)$ and $F(\cdot)$ is the continuous density function. Let $b^k(s)$ with $k \in (I, O)$ be the benefits that patients derive from inpatient and outpatient treatment. Assume that the benefits of treatment are increasing in pateint severity, $b' > 0$, and that all patients benefit from treatment, $b^k(0) > 0$. The only decision facing physicians and hospitals is whether to treat patients on an inpatient or outpatient basis. Further assume that there is some s such that $b^I(s) > b^O(s)$ and that these benefit functions cross only once, so the optimal treatment rule assigns all patients with severity above some threshold to inpatient treatment and all patients with severity below that threshold to outpatient treatment.

Hospitals' revenues and costs for inpatient treatment are r^I and c^I and revenues and costs for outpatient treatment are defined analogously. From a societal standpoint, social welfare is maximized when patients with $s > s^S$ receive inpatient treatment, where

$$b^I(s^S) - b^O(s^S) = c^I - c^O.$$

Let α and $1 - \alpha$ be the weights that hospitals assign to profits and patient welfare. Hospitals' utility is $\alpha(r^I - c^I) + (1 - \alpha)b(s)$ for a patient of type s treated on an inpatient basis and

Hospitals choose s^*, the cutoff such that patients with $s > s^*$ are admitted and the remainder are treated on an outpatient basis so that

$$\alpha(r^I - c^I) + (1-\alpha)b^I(s^*) = \alpha(r^O - c^O) + (1-\alpha)b^O(s^*).$$

The benefits of inpatient and outpatient treatment are equal at the margin. Rearranging terms yields

$$b^I(s^*) - b^O(s^*) = \frac{\alpha}{1-\alpha}(c^I - c^O) - \frac{\alpha}{1-\alpha}(r^I - r^O).$$

If profits from inpatient care exceed profits from outpatient treatment, then the right-hand side is negative, and hospitals will admit patients whose benefit from inpatient care is negative, i.e, $b^I(s) < b^O(s)$, when $\alpha > 0$. The share of patients who are overadmitted is $F(s^s) - F(s^*)$.

The model predicts that improvements in technology that allow patients to be treated on an outpatient basis will lead to increases in the use of outpatient treatment. However, as we show below, the main technology that facilitated the shift to outpatient treatment, laproscopic surgery, had largely diffused by the beginning of our study period.

The Department of Justice sanctions hospitals and other health care providers for fraud and abuse. The conduct described by the model is best characterized as abuse, i.e., treating patients as inpatients who should be treated on an outpatient basis. A hospital that billed for inpatient care when it provided outpatient care (or treated a patient as if he were an outpatient) would be guilty of fraud. In that case, a hospital would incur costs c^O but receive payment r^I. We report suggestive evidence below that some hospitals are engaging in fraud.

The model takes insurers' payment rates as a given, but an insurer, cognizent of hospitals' ability to distort treatment setting, may wish to set payment rates to better align hospitals'

incentives with social welfare. For example, an insurer could set payment rates so that hospitals' profits for inpatient and outpatient treatment are equal. However, there are a number of reasons why there may be a misalignment between insurers' payment rates and social welfare. First, hospitals deal with many different insurers, and the payment rates established during multiple, independent negotiations may differ from those that would be set by an insurer with a monopoly. Second, it is unclear if insurers negotiate specifically over the payment rates for appendectomy or payment rates are determined using a broad formula (e.g., a multiple of the corresponding Medicare payment) that reduces bargaining costs. Third, insurers may set payment rates to minimize insurers' costs and rely on other tools, such as prior authorization, to influence treatment setting.

Results

In this section, we present descriptive statistics on the shift to outpatient surgery and variation in hospital-level use of outpatient surgery over time. Our data consist of statewide emergency department and inpatient records from Arizona, Florida, Kentucky, Maryland, and New Jersey. Hospitals are required to report these data to states, which make them available to researchers through the Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project. They include the types of information typically found in insurance claims: basic patient demographics, diagnosis and procedure codes, length-of-stay, and hospital identifiers. They report the quarter of the year but not exact dates. We merged these data to the RAND Hospital Data to obtain hospital characteristics.

We identify patients with appendicitis using International Classification of Diseases codes (see the Appendix for a code list). We restrict the sample to patients with a primary diagnosis of appendicitis. Our sample includes 637,227 patients with an average age of 33.7 years. Table 1 shows characteristics of the sample. We also display characteristics in 2008-2010 and 2017-2019 to give an idea how the composition of the sample has changed over time.

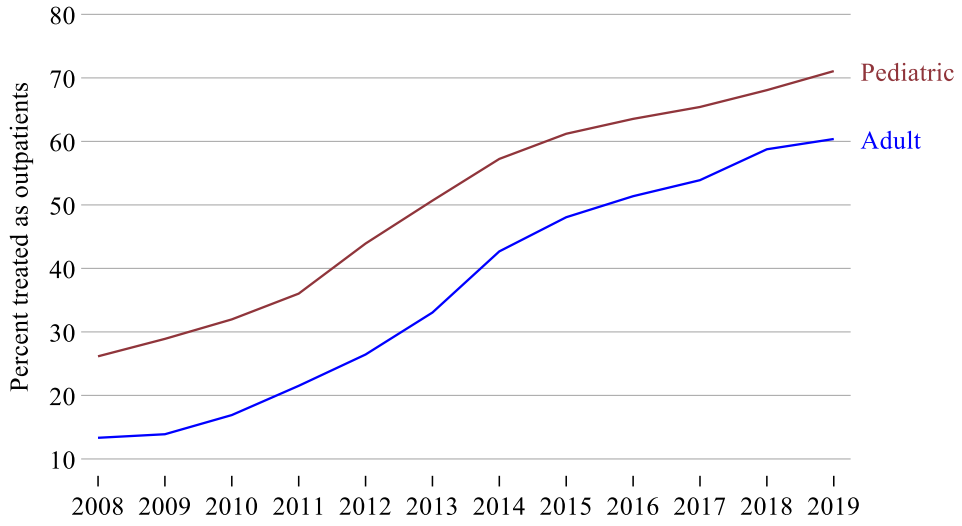
Table 1: Sample characteristics

		Period	
	All	2001-2010	2017-2019
Age	33.73	32.91	34.82
Female	0.43	0.34	0.47
Medicare	0.09	0.08	0.10
Medicaid	0.22	0.17	0.24
Private	0.52	0.55	0.50
Self	0.13	0.15	0.11
Other insurance	0.05	0.04	0.05
White	0.37	0.37	0.41
Black	0.05	0.04	0.06
Hispanic	0.23	0.15	0.26
Other race	0.35	0.44	0.27
Weekend	0.15	0.15	0.18
0 comorbidities	0.65	0.69	0.59
1 comorbidity	0.21	0.20	0.24
2 comorbidities	0.08	0.07	0.10
3+ comorbidities	0.05	0.04	0.07
N	632,011	152,679	161,067

Figure 1 shows that there was a large shift in the treatment setting of patients presenting to the emergency department for treatment of appendicitis. We stratify trends by age (<18, ≥18), but throughout the rest of the paper we pool age groups. The proportion of pediatric patients treated on an outpatient basis increased from 26.2% in 2008 to 71.1% in 2019, and the

proportion of adult patients treated on outpatient basis increased from 13.3% to 60.3%. Most appendectomies were performed laparoscopically in 2010, and so the adoption of outpatient treatment lagged the adoption of laparoscopic surgery.

Figure 1: Proportion of patients with appendicits treated on an outpatient basis



The figure displays the proportion of patients presenting to the mergency department with a primary diagnosis of appendicitis who were treated as outpatients in Arizona, Florida, Kentucky, Maryland, and New Jersey.

To quantify hospital-level variation in the use of outpatient treatment, net of differences in observable patient characteristics, we estimated linear probability models of treatment setting that adjust for patient characteristics and include hospital fixed effects:

$$y_{ih} = \beta x_i + \mu_h + \epsilon_{ih},$$

where $y_{ih} = 1$ if patient i in hospital h was treated on an outpatient basis, x_i is a vector of patient characteristics plus a constant term, μ_h is a hospital fixed effect, and ϵ_{ih} is an error term. Patient characteristics include age, sex, primary payer (Medicare, Medicaid, private, self), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), whether the visit occurred on a weekend, and comorbidity count indicators (0, 1, 2, ≥3) based on the Elixhauser comorbidity index (Elixhauser et al. 1998). We do not include treatment (operative or non-operative) as a covariate because hospitals' choice of treatment and treatment setting may be driven by the same factors. We constructed an estimate of what outpatient treatment visit rates would be in a hospital if it treated all of the patients in the sample. The predicted outpatient treatment rate for hospital h is then:

$$\frac{1}{N}\sum_i \hat{\beta} x_i + \hat{\mu}_h,$$

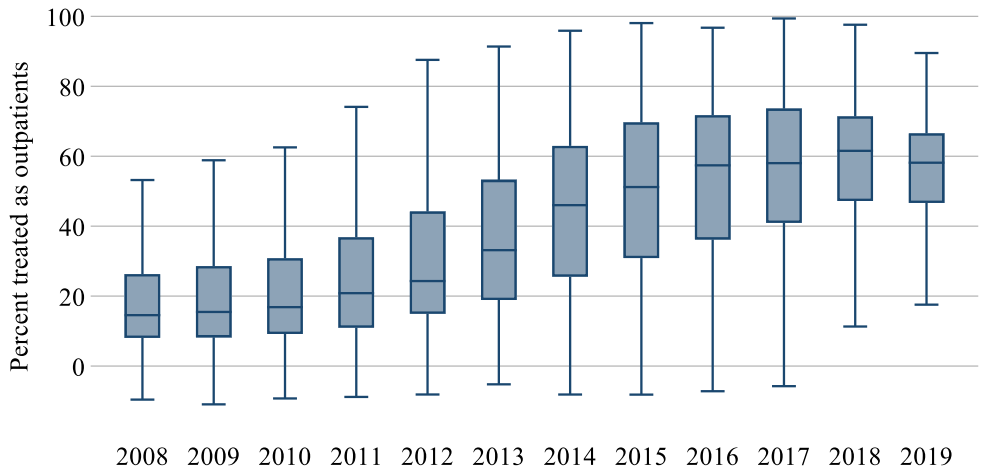
where N is the total sample size. We estimated separate models and predictions for each year.

Figure 2 displays box-and-whisker diagrams of the predicted, hospital-specific outpatient rates for hospitals that treated at least 1,000 appendicitis patients over the study period.[2] The interquartile range increased from 19.6 percentage points in 2008 to a maximum of 36.8 percentage points in 2014 before falling back to 19.2 percentage points in 2019. The experience of outpatient surgery for appendicitis illustrates how hospital-level variation in treatment patterns, a widely-documented phenomenon, increases during periods when there is a lack of consensus about how best to treat patients. Hospital-level variation decreases as outpatient

[2] This minimum volume criteria excludes about one-third of hospitals and 6% of patients.

surgery becomes more established, but there is still substantial variation in the use of outpatient surgery even in the later years of the sample.

Figure 2: Hospital-level trends and variation in the proportion of patients with appendicitis treated on an outpatient basis



The figure displays estimates from fixed-effect models of the percent of appendicitis patients treated as outpatients. Estimates were constructed using models estimated separately by year that included patient charactersitics and hospital fixed effects. The figure displays variation in predictions constructed by summing the predicted values averaged across all patients in a given year and hospital-specific fixed effects.

Laparoscopic surgery was the major innovation that facilitated the shift from inpatient to outpatient care. Figure 3 presents displays box-and-whisker diagrams of the predicted, hospital-specific share of patients undergoing laproscopic versus open (i.e., non-laproscopic) appendectomy for hospitals that treated at least 1,000 appendicitis patients over the study period. The sample excludes patients undergoing non-operative management. (The share of patients managed non-operatively did not change much over the study period, increasing from 12.0% in 2008 to 18.0% in 2019.)

The shift to outpatient surgery over the study period is a combination of two trends: 1) A shift from open to laproscopic surgery and 2) a shift from inpatient to outpatient treatment among patients receiving laproscopic surgery. The results presented in Figure 3 suggests that the shift was mostly driven by the latter. Already by 2008, a substantial share of patients undergoing

surgery, about three-quarters, had laproscopic procedures, and diffusion slowed considerably after 2010. By contrast, the share of patients undergoing laproscopic procedures treated on an outpatient basis increased from 10.7% in 2008 to 32.9% in 2013 to 62.4% in 2019.

Next, we address the question: Does the shift to outpatient treatment represent a true innovation? It is possible that the shift from inpatient to outpatient treatment was simply a relabeling, in the sense that hospitals now file outpatient claims for the same care that used to be provided on an inpatient basis. We evaluate the impact of outpatient care on insurers' costs, patients' length-of-stay, and revisit rates.

We estimate models of the following form

$$y_i = \alpha_i + \beta x_i + \epsilon_i,$$

where y_i is a patient-level outcome, α_i is an indicator for whether the patient was treated on an outpatient basis, and x_i is a vector of patient characteristics, including an intercept term. We also estimate a two-stage least squares model where we instrument for receipt of outpatient treatment with the year of treatment. The instrument is valid under the exclusion restriction that year affects the outcome only via its impact on treatment setting. The restriction would be violated if patients have become healthier or sicker over time, in a way that affects length of stay independent of treatment setting or if hospitals have changed other care processes that affect outcomes in either setting. Coefficients from the first stage are presented in the Appendix. The first stage F-statistic is over 1,000. Change in observables over time. Below we present estimates of the impact of outpatient treatment on each of the three outcomes.

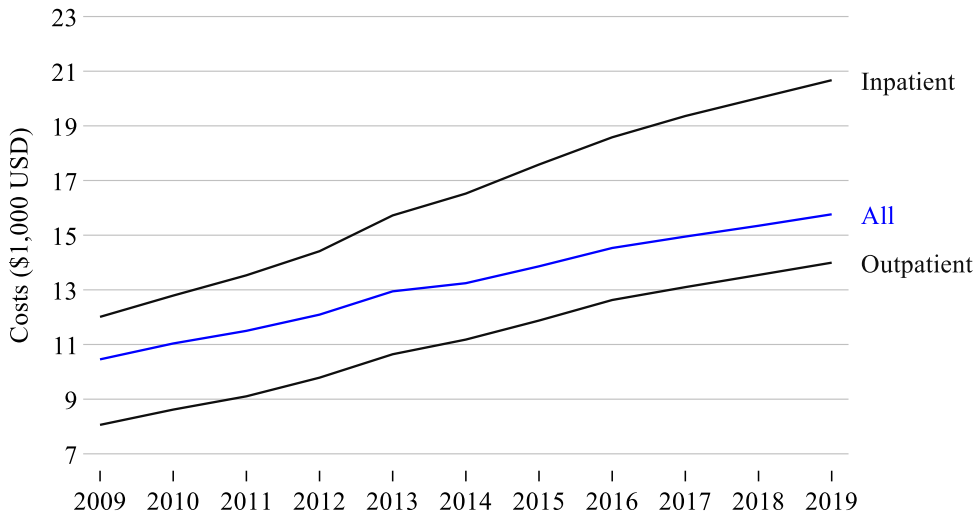
We compared costs, representing insurers' payments to hospitals, between patients treated in an inpatient versus outpatient basis using a large database of private insurers' claims.[3] The advantage of these data is that they report the transaction prices paid by insurers to hospitals. (Our primary data set reports only hospital charges, not insurers' payments.) Using the data from 2009 to 2019, we used diagnosis codes to identify emergency department and inpatient claims for patients with a primary diagnosis of appendicitis. In order to calculate total costs associated with an observation stay for acute appendicitis, we created a grouping variable. Specifically, this variable grouped claims into the same encounter if the claim was from the same enrollee ID on the same or consecutive days and included a diagnosis code of acute appendicitis. For our analysis, we included only the first unique encounter for appendicitis.[4] We excluded encounters for individuals with negative payment amounts and claims without a procedure code for appendectomy. We identified 235,902 inpatient and 282,259 outpatient episodes.

Figure 2 plots average costs, for all encounters and by site of service. Payments for inpatient care increased from $12,012 in 2009 to $20,672 in 2019, and payments for outpatient care increased from $8,059 to $13,994. Average costs in the sample increased from $10,456 to $15,764. The unadjusted difference between average inpatient and outpatient costs increased from $1,556 in 2009 to $4,908 in 2019.

[3] The Merative™ Marketscan ® Research Database includes claims from over 270 million unique individuals. Most of the data are contributed by large firms.

[4] For example, all claims from January 4, 2014, January 5, 2014, and January 6, 2014 including a diagnosis code of acute appendicitis from Enrollee ID 1234 would be grouped together into the same encounter; if there was a claim from January 10, 2014, that would be classified as a separate encounter and not included in the cost analysis.

Figure 3: Payments from insurers to hospitals for patients with appendicitis, by treatment setting



The figure displays average payments from insurers to hospitals.
Costs are not adjusted for inflation.

For the regression model, we de-trended costs, using the same rate for inpatient and outpatient treatment. Regression models adjusted for patient age, sex, Elixhauser comorbidity count (0, 1, 2, 3+). The first two columns of Table 2 display results. Estimates from the least squares and two-stage least squares models are very similar and precisely estimated. They indicate that outpatient treatment reduces insurers' spending $3,400 to $3,700 from a base of $12,600.

Table 2: Impact of outpatient treatment on length of stay and revisit rates

	Insurer spending[a]		LOS in days[b]		Revisits[c]	
	[1]	[2]	[3]	[4]	[5]	[6]
Outpatient	-3,731	-3,398	-2.11*	-1.61*	-0.015*	-0.002
	(18)	(72)	(0.01)	(0.01)	(0.004)	(0.02)
Mean	12,674	12,674	1.99	1.99	0.12	0.12
N	518,161	518,161	632,011	632,011	41,090	41,090
Specification	LS[d]	2SLS[e,f]	Poisson	IV Poisson[e]	LS[d]	2SLS[e,f]

[a]Models estimated using the Marketscan database.

[b]Models estimated using data from all states, 2008 to 2019.

[c]The model is estimated using data from Maryland, the only state that includes variable that permits us to link visits across patients.

[d]LS: Least squares (i.e., linear probability model)

[e]2SLS: Two-stage least squares. The instrument is the year of treatment.

[f]The instrument is the year of treatment.

*p<0.05.

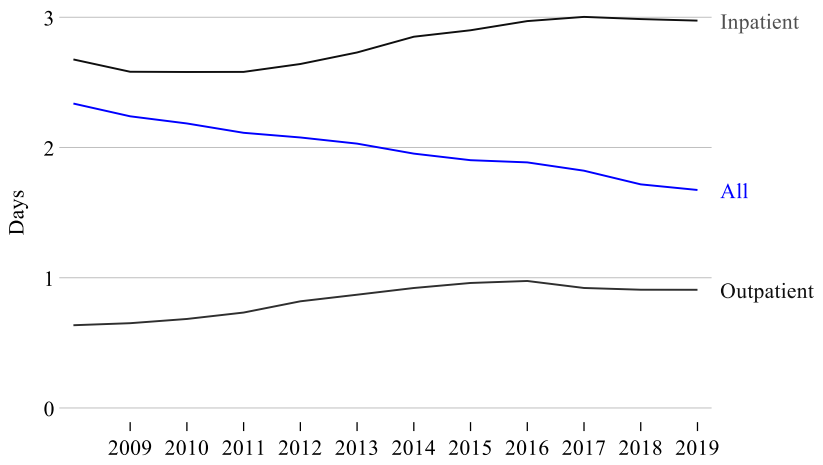
To put these estimates in perspective, we also compared Medicare reimbursements for inpatient and outpatient appendectomy. Medicare reimbursements are established by publicly-available fee schedules. Patients undergoing laproscopic appendectomy may be assigned to one of three Diagnosis Related Groups depending on their comorbidities, and so we calculated a weighted average based on the number of Medicare discharges. In 2018, the national, weighted-average Medicare payment for inpatient care was $9,211, and the payment for outpatient care was $4,488, a difference of $4,722. Medicare payments are substantially lower than private insurers' payments, which is expected, but the difference is larger. These findings show that use of outpatient care leads to substantial savings and suggest that the estimates based on private insurers' claims are not biased by differences in unobserved patient health.

The chief advantage of outpatient care across a range of procedures and conditions is that patients spend less time in the hospital. In addition to freeing up patients' time, outpatient treatment can decrease their exposure to hospital-acquired infections and improve recovery by reducing the time they spend immobilized in bed. In this section, we examine the impact of outpatient treatment of patients' length-of-say.

All states report length-of-stay measured in day increments. Additionally, Arizona reports admission and discharge hour, enabling us to measure length-of-stay in hourly increments. We measured length-of-stay in day increments in all states and in hours in Arizona. In both cases, we Winsorized length-of-stay at the 99th percentile. In all states, the average length-of-stay for patients treated on an inpatient basis is 2.84 days versus 0.86 days for patients treated on an outpatient basis, a difference of about 2 days. The equivalent figures from Arizona are 2.72 days for inpatient treatment and 0.80 days for outpatient treatment.

Figure 3 displays trends in patients' length-of-stay, overall and by treatment setting, in all states. Average length of stay declined from 2.3 to 1.6 days. Average length of stay increased in both the inpatient and outpatient settings, reflecting the progressive shift of less seriously ill patients from the inpatient to the outpatient setting. The difference in average length-of-stay between patients treated on an inpatient versus an outpatient basis is large, around 2 days, but this may reflect differences in patient health status.

Figure 4: Length of stay among patients with appendicitis, by treatment setting



The figure displays average length of stay among patients presenting to the emergency department with a primary diagnosis of appendicitis.

The third and fourth columns of Table 2 displays regression estimates for all states and where length-of-stay is measured in day increments. (Estimates for the Arizona sample with length-of-stay estimated in hourly increments are presented in the Appendix). Coefficients from the least squares and two-stage least squares models are precisely estimated. The coefficient from the two-stage least squares model indicates that outpatient treatment reduces length-of-stay by 1.61 days. The analysis of the Arizona data indicates that outpatient treatment reduces length-of-stay by 1.4 days.

Conclusion

The shift towards outpatient treatment of appendicitis benefited patients, but hospitals lost revenue. Our results indicate that the shift to outpatient treatment was not driven by hospitals' lower unit costs for outpatient treatment or physician and patient preferences. Instead, the positive relationship between hospitals' share of privately-insured patients and use of

outpatient treatment suggests that private insurers promoted adoption. Private insurers commonly require hospitals to seek approval for treating appendicitis patients on an inpatient basis. Private insurers' use of prior authorization has prompted a backlash, and a number of states and the federal government are considering laws and regulations that would limit prior authorization. The implication of our study is that these restrictions may impede the adoption of cost-saving innovations.

References

Asser, Jay. Hospital revenue continues to dip due to shift from inpatient to outpatient care. HealthLeaders. April 4, 2022. https://www.healthleadersmedia.com/finance/hospital-revenue-continues-dip-due-shift-inpatient-outpatient-care

Barnett, Michael L., Andrew Olenski, and Adam Sacarny. 2023. "Common Practice: Spillovers from Medicare on Private Health Care." American Economic Journal: Economic Policy, 15 (3): 65-88.

Byrne, David M., Stephen D. Oliner, Daniel E. Sichel (2018). "How Fast are Semiconductor Prices Falling?" Review of Income and Wealth. 64(3):6790702.

Callison K. (2016). Medicare Managed Care Spillovers and Treatment Intensity. Health economics, 25(7), 873–887.

Chernew, Michael, Dennis Scanlon, Rod Hayward. (1998) Insurance type and choice of hospital for coronary artery bypass graft surgery. Health Services Research 33(3):447-466.

Chernew, M., Decicca, P., & Town, R. (2008). Managed care and medical expenditures of Medicare beneficiaries. Journal of health economics, 27(6), 1451–1461.

Choudhry NK, Fletcher RH, Soumerai SB. (2005) Systematic review: the relationship between clinical experience and quality of health care. Annals of Internal Medicine 142:260-73.

Elixhauser, A., Steiner, C., Harris, D. R., & Coffey, R. M. (1998). Comorbidity measures for use with administrative data. Medical care, 36(1), 8–27.

Einav, L., Finkelstein, A., Ji, Y., & Mahoney, N. (2020). Randomized trial shows healthcare payment reform has equal-sized spillover effects on patients not targeted by reform. Proceedings of the National Academy of Sciences of the United States of America, 117(32), 18939–18947.

Frank, R. G., & Zeckhauser, R. J. (2007). Custom-made versus ready-to-wear treatments: behavioral propensities in physicians' choices. Journal of health economics, 26(6), 1101–1127.

Geruso, M., & Richards, M. R. (2022). Trading spaces: Medicare's regulatory spillovers on treatment setting for non-Medicare patients. Journal of health economics, 84, 102624.

Glied, S., & Zivin, J. G. (2002). How do doctors behave when some (but not all) of their patients are in managed care? Journal of health economics, 21(2), 337–353.

Herman, Bob. 2024. Stat Health Care Inc. Stat+. February 20, 2024. https://www.statnews.com/2024/02/20/medicare-advantages-33-million-club/

Howard DH, David G. (2023). For-profit hospitals and excess inpatient admissions from the emergency department. Health Services Research Published online ahead of print.

Howard DH, Hockenberry J. (2009) Physician age and the abandonment of episiotomy. Health Services Research 54(3):650-657.

Hult, Kristopher J. Sonia Jaffe Thomas J. Phillipson (2018) How Does Technological Change Affect Quality-Adjusted Prices in Health Care? Systematic Evidence from Thousands of Innovations." American Journal of Health Economics. 4(4): 433-453.

Kumar, Pooja, Ramya Parthasarathy. Walking out of the hospital: The continued rise of ambulatory care and how to take advantage of it. September 18, 2020. https://www.mckinsey.com/industries/healthcare/our-insights/walking-out-of-the-hospital-the-continued-rise-of-ambulatory-care-and-how-to-take-advantage-of-it

Leder-Luis, Jason. (Forthcoming). Can Whistleblowers Root Out Public Expenditure Fraud? Evidence from Medicare. Review of Economics and Statistics.

Liu, Yun, Qingxia Kong, Shan Wang, Liwei Zhong, Joris van de Klundert. (2020). “The impact of hospital attributes on patient choice for first visit: evidence from a discrete choice experiment in Shanghai, China” Health Policy and Planning, 35(3):267–278.

Luft, Harold S., Deborah W. Garnick, David H. Mark, Deborah J. Peltzman, Ciaran S. Phibbs, Erik Lichtenberg, Stephen J. McPhee. (1990). Does quality influence choice of hospital? Journal of the American Medical Association 263(21):2899-2906.

Nordhaus, William. “Do Real Output and Real Wage Measures Capture Reality? The History of Light Suggests Not,” Robert J. Gordon and Timothy F. Bresnahan, The Economics of New Goods, University of Chicago Press for National Bureau of Economic Research, 1997, 29-66.

Pearl, Robert. Why major hospitals are losing money by the millions. Forbes. November 7, 2017. https://www.forbes.com/sites/robertpearl/2017/11/07/hospitals-losing-millions/?sh=7634b5687b50

Rebitzer, James B., Robert S. Rebitzer (2023). Why Not Better and Cheaper? Healthcare and Innovation. Oxford University Press.

Sichel, Daniel E. (2022). "The Price of Nails since 1695: A Window into Economic Change." Journal of Economic Perspectives, 36(1):125-50.

Thomson, J. E., Kruger, D., Jann-Kruger, C., Kiss, A., Omoshoro-Jones, J. A., Luvhengo, T., & Brand, M. (2015). Laparoscopic versus open surgery for complicated appendicitis: a randomized controlled trial to prove safety. Surgical endoscopy, 29(7), 2027–2032.

Yang Z, Sun F, Ai S, Wang J, Guan W, Liu S. (2019) Meta-analysis of studies comparing conservative treatment with antibiotics and appendectomy for acute appendicitis in the adult. BMC Surgery. 19(1):110.