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Disparities in Adherence and Emergency Department Utilization Among People with Epilepsy: A Machine Learning Approach

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Abstract

Purpose: We used a machine learning approach to identify the *combinations* of factors that contribute to lower adherence and high emergency department (ED) utilization.

Methods: Using Medicaid claims, we identified adherence to anti-seizure medications and the number of ED visits for people with epilepsy in a 2-year follow up period. We used three years of baseline data to identify demographics, disease severity and management, comorbidities, and county-level social factors. Using Classification and Regression Tree (CART) and random forest we identified combinations of baseline factors that predicted lower adherence and ED visits. We further stratified these models by race and ethnicity.

Results: From 52,175 people with epilepsy, the CART model identified developmental disabilities, age, race and ethnicity, and utilization as top predictors of adherence. When stratified by race and ethnicity, there was variation in the combinations of comorbidities including developmental disabilities, hypertension, and psychiatric comorbidities. Our CART model for

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ED utilization included a primary split among those with previous injuries, followed by anxiety and mood disorders, headache, back problems, and urinary tract infections. When stratified by race and ethnicity we saw that for Black individuals headache was a top predictor of future ED utilization although this did not appear in other racial and ethnic groups.

Conclusions: ASM adherence differed by race and ethnicity, with different combinations of comorbidities predicting lower adherence across racial and ethnic groups. While there were not differences in ED use across races and ethnicity, we observed different combinations of comorbidities that predicted high ED utilization.

Keywords

Disparities; Adherence; Emergency Department Utilization; Machine Learning

Introduction

Epilepsy is a complex neurological condition with a wide array of health and social complications including several comorbid health conditions, lower education and income, and an overall lower reported quality of life.¹⁻⁷ Ultimately, these complications contribute to an increased risk for poor health outcomes.⁸⁻¹⁷ While these outcomes are documented across all people living with epilepsy, there are also disparities for specific populations of people with epilepsy, including racial and ethnic minoritized populations.^{1,6-8,18-23} It is known that there are complex cultural barriers and social factors that contribute to stigmatization and care seeking behavior.²⁴⁻²⁸ While some disparities are inequities driven by systemic factors and the social determinants of health²³, there are likely intermediary and more specific factors that could be targeted for intervention.

Two important and commonly used health outcomes for people with epilepsy include adherence to anti-seizure medications (ASMs) and utilization of the emergency department (ED). There have been numerous studies underscoring the importance of ASM adherence to prevent seizures and improve quality of life, as well as identifying important racial and ethnic disparities in adherence.^{8,29-36} Additionally, there has been substantial attention to ED visits as an important outcome of interest to understand quality of care for people with epilepsy. Several studies have sought to identify specific risk factors for high ED utilization as potential points of intervention.³⁷⁻⁴⁰ However, prior work remains limited.^{41,42} These outcomes are not just driven by clinical care factors, as commonly examined, but the combination of clinical and social factors.^{35,41,43}

Traditionally, disparities research has relied on comparing rates or ratios of outcomes between two groups and conducting multivariable analyses to identify the most important correlates of poor outcomes, one risk factor at a time.^{44,45} By examining multilevel factors *in combination*, rather than independently, it is possible to better understand these disparities. In real-life, risk factors undoubtedly cooccur and act in concert to impact outcomes. Therefore, in this study we sought to use supervised machine-learning, that can identify this co-occurrence, to investigate the impact of individual, treatment, and community-level factors on non-adherence to anti-seizure medications and ED visits.

Methods

Data Source and Inclusion Criteria

The data used in this study have been previously described.^{22,29} Briefly, we used Medicaid Analytic Extract (MAX) claims data from 2010 – 2014 for 16 geographically diverse states, that were available at the time the initial study was initiated. The 16 states include California, Georgia, Iowa, Louisiana, Michigan, Minnesota, Missouri, Mississippi, New Jersey, Pennsylvania, South Dakota, Tennessee, Utah, Vermont, West Virginia, and Wyoming. Medicaid is a state-administered public health insurance program in the United States that is focused on providing health insurance coverage for some low-income individuals and individuals with disabilities. Given this, those who are insured through Medicaid often have greater social and clinical complexity influencing health outcomes. We followed published guidelines to identify people with epilepsy: requiring at least two claims for epilepsy or seizure (at least 30-days apart), as well as at least 2 pharmacy claims for an ASM.⁴⁶

Of the initial 408,526 individuals in the claims data, we excluded those from Louisiana due to missing provider information (new n = 385,052). We included only those who met full epilepsy inclusion criteria (283,685), who were covered by Medicaid the entire study period (n = 156,053), those who were never dually enrolled in both Medicare and Medicaid (n = 139,186), those who were between 18 and 64 (n = 88,782), and those who were prevalent cases (n = 76,526). Due to small numbers, we also only included White, Black, Hispanic, and a combined Asian and Native Hawaiian Other Pacific Islander (NHOPI) individuals with adherence data (n = 67,576), and complete data for all our covariates (n = 52,175). Missingness in the covariates included only county-levels variables, with 15,401 missing percent of good quality air days, and a small number across the others. A comparison between those with/without complete data can be found in Supplemental Table 1.

Outcomes

We chose two outcomes that represent various points of epilepsy care and sequelae. The first outcome of interest was adherence to ASMs assessed via the average proportion of days covered (PDC; < 0.8 represents non-adherent) for all ASMs. This measure of adherence is based on the recorded date of dispensing and days supply of medication. It estimates the overall proportion of days that an individual is covered with their medication from these dispensing claims and is averaged across all ASMs.⁴⁷ Importantly, this measure and these data are unable to assess if an individual is taking their medication as prescribed. The second outcome was being in the top quartile of the number of all-cause ED visits – identified via the revenue center code, place of service codes, and procedure codes. These outcomes result from combination of individual- and community-level factors and therefore represent varied levels of interventions and therefore are well positioned to benefit from advanced statistical techniques. We identified these outcomes across years 4 and 5 of our data (2013 and 2014), to use baseline covariates to predict future adherence and ED utilization.

Covariates of Interest

A full justification of all included covariates can be found in Supplemental Table 2. From the Medicaid data we obtained the following variables: sex (male/female), race and ethnicity (White, Black, American Indian or Alaskan Native (AIAN), Asian Pacific Islander (API) or Native Hawaiian or Other Pacific Islanders (NHOPI), and Hispanic), age, index year, undergoing a video-correlated electroencephalogram (vEEG), undergoing surgery, and seeing a neurologist. We also captured an overall measure of healthcare utilization – the number of hospitalizations and ED visits termed “negative health events” or NHEs. We further identified nursing home status.^{48,49} In the model predicting future ED utilization, we did not include previous ED utilization due to its outsized and well-known influence on future utilization. Indeed, in a supplemental analysis ED utilization in the three-year baseline period was the only included variable predicting future ED utilization (Supplemental Figure 1). Elixhauser comorbidities as well as the top combinations of empirically emerging conditions – aimed at capturing the multimorbidity burden – that have been described in a previous manuscript.²² We included the top 10 single conditions, the top 5 combinations of two, and the top 5 combinations of 3. In addition to those individual-level factors obtained from the Medicaid data, we included several structural-level variables. This included rurality (via the Rural-Urban Continuum Code), and several from the publicly available Area Health Resources File (AHRF). Some of these were directly related to healthcare and epilepsy care, while others focused more broadly on the nature of the county. These included: the number of neurologists (per 100,000 individuals), the number of primary care physicians (per 100,000 individuals), the number of individuals eligible for Medicaid (per 100,000 individuals), the percent of individuals in poverty, the median household income, the percent of the population under 65 years old who are uninsured, the percent of good air days (of those measured), and the percent of individuals with a 4-year college degree. Importantly, the measures of disease severity and comorbidities were identified during a 3-year baseline period (2010 – 2012).

Supervised Machine Using Classification and Regression Tree (CART) and Random Forest

The primary analytic technique used in this study was a non-parametric (distribution-free) supervised machine-learning approach known as Classification and Regression Tree (CART) analysis. With CART, we can *see what the data say* are the most important factors contributing to specific outcomes, and how these factors work in *combination*. Notably, this ability to identify the combinations of factors, rather than simply when controlling for all others, extends beyond traditional regression approaches. This approach acknowledges that risk factors for patients do not exist in isolation, but rather work in concert to contribute to health and health outcomes – and provides a clear look at the specific combinations of variables that could be targeted for an intervention. This is accomplished through recursive partitioning that splits the population into mutually exclusive groups, aiming to make the outcome of interest in that group as homogenous as possible.^{50–52} Statistically, the Gini impurity measure is used to assess the estimated probability of misclassification of the outcome given a split at that variable.⁵⁰ The algorithm seeks to minimize the Gini impurity measure when splitting nodes. When using a CART approach, there are a number of parameters that can be specified when building the tree: complexity parameter is the amount that a split must reduce the error to be used in the model, the minimum bucket size is

the minimum number of individuals in a terminal node, and the maximum depth is the maximum depth of any terminal node.^{50–52} The final step when constructing a CART model is to “prune” the tree, via the complexity parameter, to reduce overfitting of the data while reducing the crossvalidated misclassification error.⁵² By “pruning” the tree we are taking the overly large initial CART model and reducing the number of splits while maintaining a low misclassification rate. This combination of number of splits and the misclassification rate determines the overall complexity parameter of the tree size.

Recognizing that CART models have inherent limitations with stability (i.e., when the data is changed the model may change substantially), we also employed random forest to validate our resulting CART model. Simply, random forest creates multiple individual decision trees from bootstrapped samples of the data.⁵³ These trees and the variables are then combined by selecting the most common outputs and result in a model that, while not giving a singular tree, can inform of the relative importance of specific variables (across all trees). We report the variables with a relative importance, that is a mean Gini coefficient decrease, of 50% or higher. By using the relative importance, we scale all measures to be a percent of the most important variable.

Analytic Approach

In addition to descriptive statistics, we used CART analysis and random forest to explore factors that associate with outcomes for people with epilepsy on Medicaid. Used in combination, these methods complement each other while also triangulating to the most critical point(s) of intervention. In our main analysis, we used a 70% random sample of the data as the training sample to build the CART model using a minimum bucket size of 1% of the training data size, and a maximum depth of seven, with 10-fold cross validation. The model was then pruned to select the most appropriate complexity parameter. While our main goal was to use these models for descriptive purposes, we tested their predictive ability on the remaining 30%. In addition to including race and ethnicity in the CART model, as is traditionally done, we were interested to see if stratified models would yield different trees across race/ethnicities. These stratified models were just for descriptive comparisons, and thus did not have a training and test sample. We varied the minimum bucket to 1% of the sample size for that race and ethnicity, while keeping a maximum depth of five. If there was one, or fewer, splits we lowered the minimum bucket to 20. This was done for predicting ED utilization among Asian/NHOPI. We similarly employed 10-fold cross validation and the model was similarly pruned. We also performed random forest analyses, with 1,000 trees, on the full dataset to further validate the CART models. SAS version 9.3 was used for data cleaning, while R version 3.6.3 and the following packages were used for analyses: “tidyverse”, “rpart”, “rpart.plot”, “party”, “partykit”, and “randomForest”.^{54–59}

This study was approved by the Institutional Review Board of Case Western Reserve University (Protocol #2018–0780), and the Privacy Board of the Centers for Medicare and Medicaid Services (Data Users Agreement #52636).

Results

Among the 52,175 adult people with epilepsy who met inclusion criteria, 44.4% were male, 19.7% were between 18 and 24 years old, and 25.0% were between 25 and 34 years old, with 20.2%, 23.8% and 11.3% between 35 – 44, 45 – 54, and 55+ years old, respectively. While just over half (51.2%) were White, there were 14,607 (28.0%) Black individuals, 2,263 (4.3%) Asian or Native Hawaiian or Other Pacific Islanders (NHOPI), and 8,615 (16.5%) Hispanic individuals. See Supplemental Table 1 for full study cohort characteristics.

Adherence

Over half (57.9%) of patients were adherent to their anti-seizure medications (ASMs) during the 2-year follow-up period. While 63.2% of White individuals were adherent, only 51.4% of Black individuals, 58.5% of Asian/NHOPI, and 52.5% of Hispanic individuals were (Table 1). Our main CART model identified that people with epilepsy without developmental disabilities, who were less than 45 years old, and were Black or Hispanic had the lowest adherence, compared to those with developmental disabilities (Figure 1). Among younger White or Asian/NHOPI individuals without developmental disabilities, high health care utilizers (top quartile) had lower adherence. The accuracy, sensitivity, and specificity of the model using these four variables is shown in Table 2. When stratified by race and ethnicity, for White individuals we observed that only the absence of developmental disabilities, younger age, and high utilization predicted lower adherence (Figure 1). Meanwhile, for Black individuals, having hypertension was identified as an additional predictor of lower adherence, while evidence of nursing home stay was a predictor of higher adherence perhaps due to greater epilepsy severity and/or clinical complexity. These variables were in addition to not having developmental disabilities and high utilization predicting lower adherence (Figure 1). Similarly, for Hispanic individuals, not having hypertension was a predictor of lower adherence, as was being younger (Figure 1). Finally, among Asian/NHOPI not having psychiatric comorbidities was the top predictor of lower adherence, followed by not having hypertension (Figure 1). Interestingly, county-level variables were predictors of lower adherence (Figure 1). For example, more Medicaid eligible individuals per capita at the county-level was associated with lower adherence. In our random forest, we saw that the variables with the most importance included age, county-level characteristics, and race and ethnicity with an error of 36.6% (Table 3).

Emergency Department

The median number of ED visits was two, with an interquartile range of zero to five. Overall, Black individuals had higher ED utilization than White individuals with an outsized number of these individuals being in the top quartile of ED visits (Table 1). Our CART model predicted that a history of injuries was the top predictor of future emergency department utilization, with 76% of those patients who had a history of injuries and anxiety and mood disorders and back problems being in the top quartile of future ED utilization (Figure 2). On the other hand, among those without a history of injuries and without anxiety and mood disorders and headache (as a combination) in the preceding three years only 20% were in the top quartile of ED visits (Figure 2). Further splits in the prediction model included urinary tract infections and headache, with those patients having either being

higher ED utilizers (Figure 2). The model's accuracy, sensitivity, and specificity in the 30% test data are reported in Table 2. The CART models stratified by race and ethnicity showed less separation for ED utilization than the models for adherence (Figure 2). Interestingly, in addition to a history of injuries, headaches and back problems, a lower density of neurologists in the county predicted higher ED utilization. Only a single variable was included for Hispanic (back problems and injury) and White (anxiety and mood disorders and injury) individuals (Figure 2). Meanwhile, for Black individual, injuries, headache, urinary tract infections, and anxiety and mood disorders all predicted higher utilization (Figure 2). In supplemental analyses for Hispanic and White patients, we reduced the threshold for overall model improvement to generate expanded, but less reliable, models to identify any meaningful differences. We observed similar variables as the larger models for the other race/ethnicities, with the addition of chronic lung disease and drug abuse among Hispanic individuals (Supplemental Figures 2 and 3). The random forest model had an error of 23.2% and included age, county-level characteristics, injury, and race and ethnicity (Table 3). The most common primary diagnoses for ED visits included other convulsions, chest pain (unspecified), epilepsy (unspecified), abdominal pain (unspecified), and headache (Supplemental Table 3).

Discussion

We used a supervised machine learning approach to examine potential racial and ethnic disparities in two important outcomes for people with epilepsy: ASM adherence and ED utilization. Overall, race and ethnicity were important predictors of lower adherence. Unsurprisingly, comorbidities were the strongest predictors of ED utilization; however, there was variation by racial and ethnic group. Developmental disabilities and a history of injuries emerged as the top predictors of future adherence and ED utilization, respectively. This suggests the need for an expanded view of co-occurring conditions among people with epilepsy that are associated with poor health outcomes.

There was substantial variation in model performance, with the model predicting lower adherence performing poorly, only classifying 62.5% correctly, whereas the model for ED utilization correctly classified 76% of patients. This variation may be due, in part, to the complexity of each of these outcomes. Lower adherence, specifically, is driven by a multitude of structural, cultural, and physiological factors. Both models had a low sensitivity and high specificity – resulting in a high number of false negatives. In other words, if used for prediction the models would miss many individuals who could benefit from intervention. These indicate that while these models may be helpful in characterizing patients, they have serious limitations as predictive models at the individual level. Importantly, our measure of adherence is potentially an over-estimation, given that filling a medication does not correlate completely with taking the medication. Meanwhile, ED visits were derived directly from claims but nonetheless lack the ability to contextualize the incident precipitating the ED visit.

There is often great heterogeneity within groups that experience disparities in health outcomes, and there is a need to understand the complex interplay of individual, treatment, and community level factors that work in combination to contribute to health

disparities.^{60–63} This is a particular area where using tree-based approaches, such as CART, can elucidate this complex interplay. In the epilepsy field, there have been several machine-learning approaches for seizure detection and classification, but work using these statistical tools to examine outcomes has remained limited.⁶⁴ For example, just one study used this approach to predict ED utilization, but did not do so from a disparities or equity perspective.³⁸ Additionally, these models have been used to develop and refine screening tools for depression among people with epilepsy.⁶⁵ Outside of the epilepsy literature, CART has been used to examine disparities in people living with HIV, risk stratification for heart failure, combinations of chronic conditions, geriatric syndromes, and functional limitations that associate with health outcomes, as well as combinations of conditions constituting multimorbidity.^{66–69} The approach of classifying patients based on a common set of characteristics, with respect to an outcome, is also complementary to recent work that focused on identifying groups with common trajectories in ASM adherence.⁷⁰ The CART approach has several substantial strengths when compared to traditional regression-based approaches. When we examine the combinations in CART models, we can overcome limitations of interpretability and the use of numerous interaction terms in a regression model. Additionally, our analytic approach has extended previous uses of CART analyses by stratifying by race and ethnicity. While most models simply include a race and ethnicity variable, our additional step of stratification allowed us to examine how the most important factors differ across races and ethnicities. While the variables we chose to include were based on previous literature, we did not hypothesize any specific interactions that may emerge. What we did observe, however, confirmed how it is the complex interplay of demographic factors (e.g., race/ethnicity), social factors (e.g., evidence of a nursing home stay), and clinical complexity (e.g., co-occurring conditions) that result in differences in adherence and ED utilization.

With this approach, we were able to identify racial and ethnic differences that are often masked by traditional approaches. For example, when we examined adherence, we saw race and ethnicity appear in the top three predictors such that Black and Hispanic individuals were in a group with lower adherence. When stratified, there were notable differences between racial and ethnic groups. On the other hand, we did not see race and ethnicity as a top predictor of ED utilization. However, there are again slightly different combinations of comorbidities that were most important across races and ethnicities. These findings highlight that even when a clear disparity may not emerge, the difference in comorbidities suggests the need for more tailored interventions to improve adherence and reduce ED utilization.

Interestingly, our findings identified several county-level factors that are strongly associated with lower adherence and ED utilization. We do not suggest here that these specific factors are what directly cause these poor outcomes, but rather they reflect the importance of structural and social determinants of health. We included these measures to broadly characterize the counties in which our patients live, and, across both outcomes, we observed that individuals residing in counties with a higher proportion of individuals eligible for Medicaid, lower density of primary care physicians, lower median income, and higher poverty, tended to have worse outcomes. Simply, these variables reflect counties where healthpromoting resources are limited and where adverse social determinants of health create a greater magnitude of social risks and social needs. These findings are consistent

with other work highlighting that people with epilepsy with social needs, have increased utilization compared to those people with epilepsy without social needs.⁷¹ This also provides a clear direction for future work to examine the mechanism(s) by which these social drivers of health affect outcomes for people with epilepsy, including identifying factors at a smaller geographic region. Finally, we found that individuals with developmental disabilities and psychiatric comorbidities had higher adherence. This finding may suggest that certain individuals, with these comorbidities, have greater social support in refilling and taking their medications. While our data were unable to assess this potential mechanism, this finding provides a direction for future studies.

Prominent limitations of this work include the use of county-level measures, limitations in CART approaches, limitations in understanding medication burden, and the overall predictive accuracy of these models. First, county-level measures are generally too geographically broad to understand the role of social determinants of health on outcomes. However, due to data privacy we were restricted to county-level data elements, and they nonetheless provided a broad view of how community-level factors associate with health outcomes. Next, there are inherent limitations to CART analyses. First, CART models tend to overfit and experience drastic changes with minor differences in the data (e.g., adding new patients or a new variable). This limitation was partially addressed by comparing our CART models to random forest results. Additionally, we focused our study on adherence to ASMs and did not evaluate the role of polypharmacy, for both ASMs and other comorbidities, that may affect adherence and outcomes – a direction for future work. Finally, our models' accuracy, sensitivity, and specificity were relatively low when used for prediction in the test data. This indicates that such simple models may not perfectly predict an individual's outcome trajectory, but nonetheless provide important characteristics to consider. Future work could incorporate additional variables that were unavailable for this study, such as seizure semiology and frequency, that may result in improved predictions.

Conclusion

In conclusion, we used supervised machine learning to identify combinations of factors that are associated with two important health outcomes. We found that specific combinations of comorbidities were strong predictors of both lower adherence and ED utilization. Our study highlights the possibility of using machine-learning approaches to extend previous work to better identify disparities, refine interventions and improve the quality of life for people with epilepsy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Declaration of Competing Interest

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Highlights

- Traditional approaches to disparities research have not fully considered how *combinations* of factors are associated with outcomes
- Using Classification and Regression Trees, we identified developmental disabilities, age, race and ethnicity, and utilization as top predictors of adherence/
- Top predictors of emergency department utilization included a history of injuries, anxiety and mood disorders, headache, back problems, and urinary tract infections.
- Even when race and ethnicity did not appear as a top predictor of poor outcomes, there was variation in the clinical and social factors that contribute to poor adherence and high utilization.

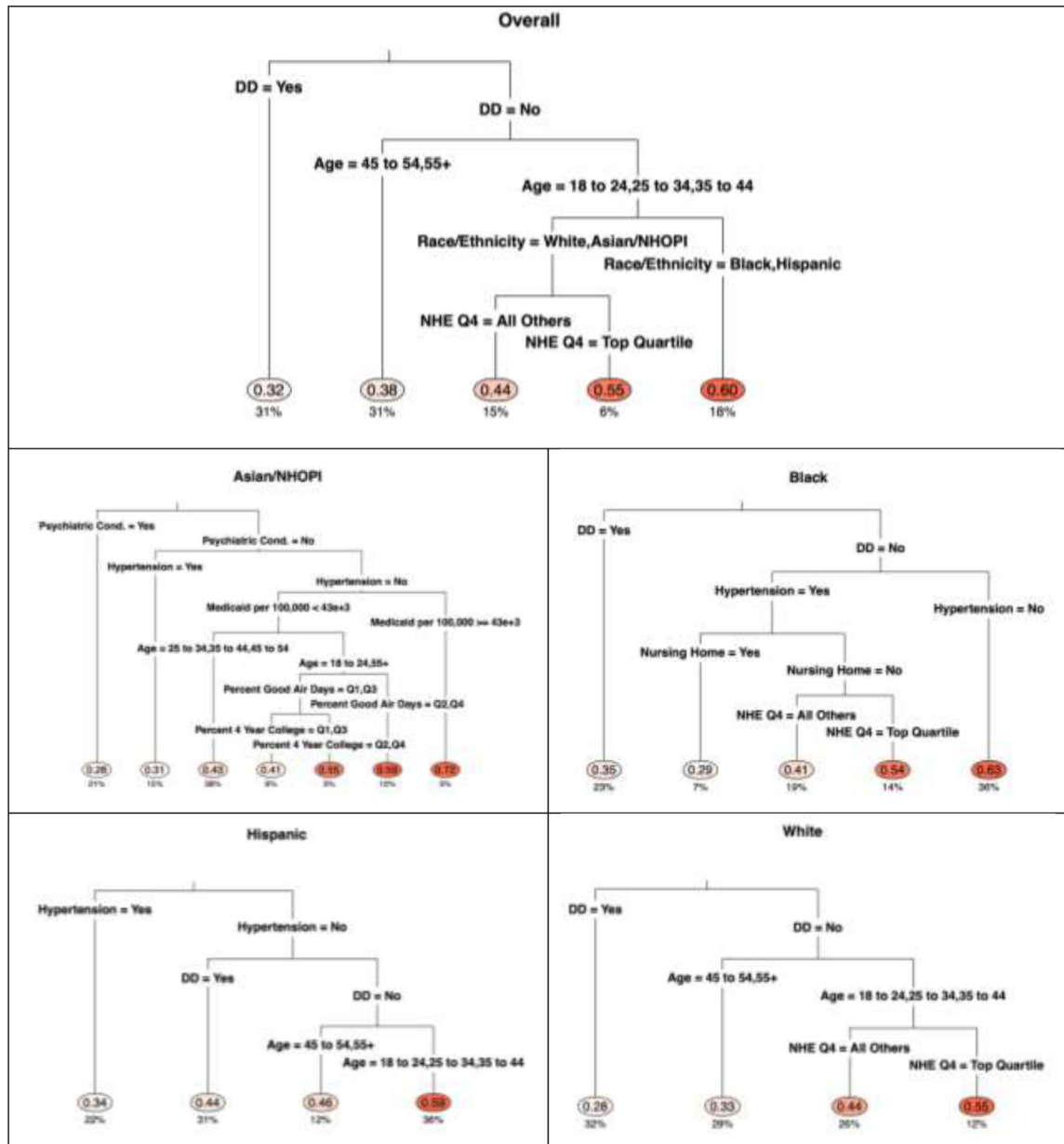


Figure 1. CART Models for Lower Adherence
 The number in the oval is the percent of patients who are not adherent, while the number below the oval is the percent of patients in that group. For example, among those with developmental disabilities, 32% are not adherent and this represents 31% of our study cohort. NHE: negative health event; DD: Developmental disabilities

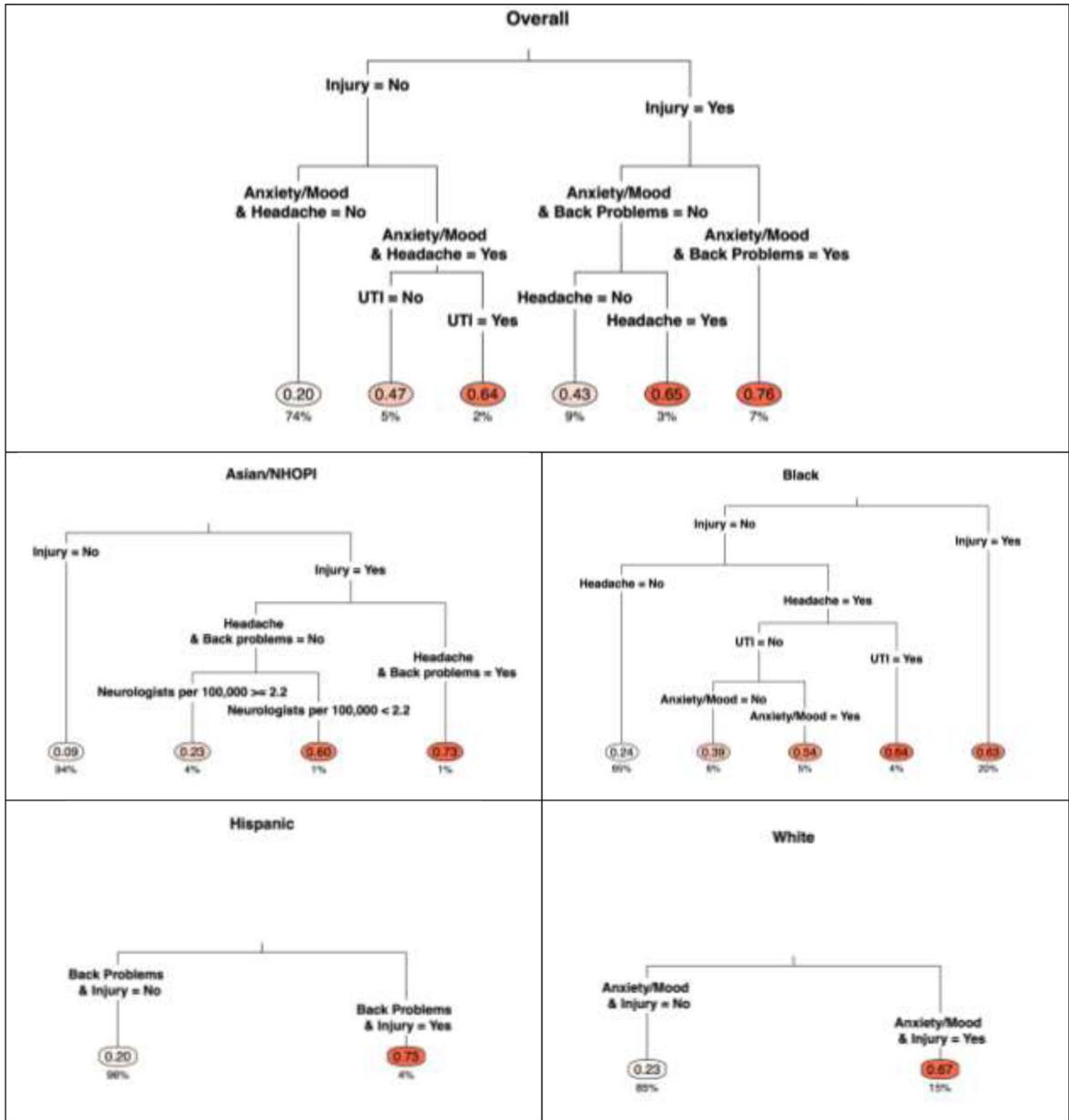


Figure 2. CART Models for Emergency Department Utilization
 The number in the oval is the percent of patients who are in the top quartile of emergency department visits, while the number below the oval is the percent of patients in that group. For example, among those patients with injuries, and anxiety/mood disorders & back problems, 76% are in the top quartile of ED visits and this represents 7% of our study population. The models for Asian/NHOPI, Hispanic, and White had a reduced minimum bucket of 20. UTI: urinary tract infection

Table 1.

Outcomes stratified by race and ethnicity.

N (%) or median [IQR]	White, n = 26,690	Black, n = 14,607	Asian/NHOPI, n = 2,263	Hispanic, n = 8,615
Adherent	16,875 (63.2)	7,505 (51.4)	1,323 (58.5)	4,522 (52.5)
Emergency Department Visits	2.00 [0.00, 6.00]	3.00 [1.00, 7.00]	0.00 [0.00, 2.00]	1.00 [0.00, 4.00]
Emergency Department, Q4	7,920 (29.7)	5,243 (35.9)	235 (10.4)	1,935 (22.5)

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Table 2.

Accuracy, sensitivity, and specificity of our CART models in the 30% test sample.

	Adherence	ED Visits
Accuracy	62.5% (95% CI: 61.7, 63.2)	76% (95% CI: 75.3, 76.7)
Sensitivity	33.6%	30.3%
Specificity	83.3%	94.4%

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Table 3.

Random Forest results, variables above 50% relative importance

Variable	% Relative Importance
<i>Lower Adherence</i>	
Age	100
Medicaid Eligible per 100,000	88.5
Primary Care Physicians per 100,000	87.0
Median Household Income	86.4
Percent in Poverty	85.5
Neurologists per 100,000	83.7
Race	64.4
Index Year	57.9
<i>Emergency Department Visits</i>	
Age	100
Median Household Income	87.6
Primary Care Physicians per 100,000	86.9
Medicaid Eligible per 100,000	85.0
Neurologists per 100,000	84.8
Percent in Poverty	84.0
Injury	70.6
Race	58.0
Index Year	51.8

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