PLOS Mental Health

RESEARCH ARTICLE

Subgroup identification of disparities in buprenorphine discontinuation in opioid-use disorder: A Virtual Twins machine learning approach using nationwide United States claims data, 2006–2022

Kehe Zhang[1,2], **Paula A. Jaimes-Buitron**[3], **Wanru Guo**[1], **Yanmin Gong**[4], **Yuanxiong Guo**[5], **Carolina Vivas Valencia**[3], **Cici Bauer**[1,2]*

1 Department of Biostatistics and Data Science, School of Public Health, The University of Texas Health Science Center at Houston, Houston, Texas, United States of America, **2** Center for Spatial-Temporal Modeling for Applications in Population Sciences, School of Public Health, The University of Texas Health Science Center at Houston, Houston, Texas, United States of America, **3** Department of Biomedical Engineering and Chemical Engineering, The University of Texas at San Antonio, San Antonio, Texas, United States of America, **4** School of Engineering Medicine, Texas A&M University, Houston, Texas, United States of America, **5** Department of Information Systems and Cybersecurity, The University of Texas at San Antonio, San Antonio, Texas, United States of America

* cici.x.bauer@uth.tmc.edu

Check for updates

OPEN ACCESS

Citation: Zhang K, Jaimes-Buitron PA, Guo W, Gong Y, Guo Y, Valencia CV, et al. (2026) Subgroup identification of disparities in buprenorphine discontinuation in opioid-use disorder: A Virtual Twins machine learning approach using nationwide United States claims data, 2006–2022. PLOS Ment Health 3(4): e0000469. https://doi.org/10.1371/journal.pmen.0000469

Editor: Kristen A. Morin, Northern Ontario School of Medicine: NOSM University, CANADA

Received: September 23, 2025

Accepted: March 18, 2026

Published: April 9, 2026

Copyright: © 2026 Zhang et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data availability statement: The individual-level claims data are from the IQVIA PharMetrics Plus for Academics database (2006–2023). Because of licensing and HIPAA

Abstract

Buprenorphine retention is crucial for effective treatment of opioid use disorder (OUD), yet disparities in treatment discontinuation persist. This study aims to identify and quantify disparities in buprenorphine treatment retention using a machine learning framework adapted from Virtual Twins approach focusing on disparities related to sex, age, insurance type, geographic region, mental health status and community-level Social Vulnerability Index (SVI). Using a nationwide longitudinal cohort, we applied a two-stage machine learning approach. In Stage one, we trained classification models to estimate the counterfactual differences in treatment discontinuation across disparity types. Model performance was assessed using C-statistics and precision-recall curve. In Stage two, we employed regression models, decision trees and neural networks with Shapley Additive Explanations, to identify subgroups most vulnerable to the disparities and key contributing factors. Among 303,528 treatment episodes from 131,169 patients aged 18–85, 71% discontinued treatment within 180 days. Early medication adherence (3-month proportion of days covered) was the strongest predictor. Significant disparities emerged based on insurance, region, mental health status, age, and SVI. Higher discontinuation risk was observed among privately insured older adults, patients from high-SVI areas in the South without mental health diagnoses, and younger publicly insured individuals lacking psychiatric services. Psychiatric service utilization consistently mitigated discontinuation risks across subgroups. Limitations include the absence of race/ethnicity in the

restrictions, these data cannot be shared publicly. Qualified researchers can obtain access via a data use agreement with IQVIA or by submitting a request through the UTHealth Center for Health Care Data: https://sph.uth.edu/research/centers/center-for-health-care-data/data-request.

Funding: This research was, in part, funded by the National Institutes of Health (NIH) Agreement No. 1OT2OD032581 (to Y.G., C.B., C.V.V. and Y.G.). The views and conclusions contained in this document are those of the authors and should not be interpreted as representing the official policies, either expressed or implied, of the NIH. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

claims data, the inability to capture concurrent medications and initial buprenorphine dose, and lack of formal uncertainty estimates for the quantified disparities. The Virtual Twins analytical framework enabled identification of vulnerable subgroups and quantification of disparities attributable to specific risk factors. Interventions that prioritize early adherence, expand access to psychiatric services, and address structural barriers in high-SVI Southern communities and insurance-defined risk groups may improve equity in buprenorphine retention.

Introduction

Opioid use disorder (OUD) is a major public health crisis, affecting millions globally and imposing substantial social and economic burdens. In 2022, there were nearly 110,000 deaths attributed to drug overdose in the US, with over 81,000 involving opioids – a 400% increase over the past decade [1]. From 2013 to 2022, the age-adjusted overdose death rates from synthetic opioids other than methadone increased significantly from 1.0 to 22.7 per 100,000 population [2]. Effective treatment strategies are needed to mitigate these consequences [3]. In the United States, opioid agonist treatment is delivered within a highly regulated system in which methadone is dispensed only through federally certified opioid treatment programs and buprenorphine has historically been prescribed in office-based settings under separate regulatory requirements [4], in contrast to more integrated models such as Canada where both medications are available within routine care [5]. Buprenorphine, an FDA-approved medication for opioid use disorder (MOUD) in the U.S., is one of the most effective treatments [6]. Studies have demonstrated its efficacy in reducing opioid cravings, overdose risk, and mortality, particularly when maintained for at least six months [7].

The utilization of buprenorphine for at least 180 days is recognized as a benchmark of treatment quality, as extended durations are associated with improved outcomes [8–13]. In addition, prior studies have demonstrated that retention at one year is strongly associated with sustained clinical benefit, including reduced substance use, lower relapse risk, and improved psychosocial functioning [14,15]. However, the optimal length of treatment has not been empirically established. Despite its effectiveness, maintaining consistent treatment and ensuring patient retention continue to be significant challenges. In 2022, only approximately 25% of the estimated 4% of U.S. adults requiring OUD treatment received recommended medications [16]. Recent studies have shown substantial variability in buprenorphine retention rates, with many reporting rates below 50% across different populations and treatment settings [17–19]. For example, an analysis of 2011–2015 Health Care Cost Institute commercial claims data showed that over 55% of patients discontinued buprenorphine treatment within the first six months [19]. Similarly, a study examining an all-payer pharmacy claims database found that only 41% of individuals had treatment lasting for at least 6 months [18]. Additionally, in a retrospective cohort study utilizing multi-state claims data, 50.6% patients discontinued their treatments within 180 days [20]. Importantly, treatment discontinuation increases the risk of opioid overdose mortality,

suicide, and all-cause mortality [21–23]. Therefore, identifying factors associated with treatment discontinuation is essential for improving treatment retention and optimizing the impact of OUD treatment programs.

Existing research has documented disparities in access to and retention in MOUD treatment at both the individual and community level. These disparities include socioeconomic factors [24–26], geographic variation [27,28], race/ethnicity [29], insurance status [18], gender [30], and mental health comorbidities [31]. Studies have also identified key risk and protective factors for treatment discontinuation, such as demographic characteristics (sex, region, insurance type) [32,33], medical comorbidities (HIV, Hepatitis C, chronic pain) [17], and health services utilization [34–36]. In addition to individual-level risk factors, contextual community factors, including provider access [37], urban versus rural settings [38–40] and social vulnerability [41,42], have also been shown to impact MOUD treatment.

Despite these findings, several important gaps exist. First, most studies only examine a limited set of risk factors and neglect critical healthcare utilization factors. For example, Faysal et al. developed an explainable machine learning model incorporating key demographic and clinical factors along with early treatment adherence, but failed to account for health services utilization factors such as outpatient treatment services, medication management, group psychotherapy, and counselling, which are known to impact retention [43]. Studies have also been constrained to specific insurance types, geographic regions, or treatment settings, making their findings difficult to generalize. For example, Chan et al. (2024) [44], Sweeney et al. (2022) [35], and Vakkalanka et al. (2022) [34] focused exclusively on commercially insured patients or specific treatment modalities, such as telehealth- or primary care-based settings. Similarly, studies that relied solely on surveys [29] or interviews [30] may introduce potential bias and limit generalizability.

Recently, machine learning methods have increasingly been applied in MOUD research to identify risk factors and predict treatment outcomes, as demonstrated by Faysal et al. (2024) [45], Hasan et al. (2021) [46], and Warren et al. (2022) [8]. The Virtual Twins framework, originally introduced by Foster et al. in randomized clinical trial settings, provides a novel machine learning-based approach for identifying heterogeneity in treatment responses across subgroups [47]. In this framework, individual-level counterfactual outcomes under alternative treatment or exposure conditions are first estimated, and the resulting differences in predicted outcomes are subsequently modeled to identify subgroups with differential treatment responses [48]. This approach has since been adapted to examine disparities in substance use disorder treatment, which enables identification of subgroups with heterogeneous treatment effects and the factors contributing to these disparities [49,50]. However, prior applications were constrained by limited data coverage in terms of population, temporality, and geography, and none were focused on MOUD retention.

To address these gaps, we conducted a nationwide, longitudinal analysis leveraging the IQVIA PharMetrics Plus for Academics Closed Health Plan Claims database (2006–2023). Our objective was to quantify disparities in buprenorphine treatment discontinuation across key dimensions (sex, age, insurance type, region of residence, mental health status, and community-level social vulnerability) and to identify the subgroups and risk factors driving these disparities using a two-stage Virtual Twins framework with a counterfactual design [47]. Leveraging a large national dataset and both individual and community level factors, this study proposes a novel approach to identifying disparities in OUD treatment from multiple lenses, to inform policies aimed at promoting equitable access and retention.

Methods

Ethical statement

The study was reviewed and approved by the UTHealth Committee for the Protection of Human Subjects (CPHS; HSC-SPH-23-1114), with a waiver of informed consent for use of de-identified secondary data and no direct participant contact. IQVIA longitudinal prescription claims data (2006–2022) were accessed within the UTHealth Center for Health Care Data's secure, access-controlled environment under a data-use agreement. Data were initially extracted and accessed on March 27th, 2024. The analytic dataset was de-identified; investigators had no access to direct identifiers or re-identification keys at any time.

Data sources

We used IQVIA PharMetrics Plus for Academics Closed Health Plan Claims, a nationwide longitudinal claims database capturing prescription records in the U.S. from January 2006 to April 2023, with a total of 90,327,620 records for 256,737 individual patients. Each prescription record contains patient demographics (sex, age), geographic locations (from latest enrollment record), prescription claims details (e.g., National Drug Code [NDC], procedure and diagnostic codes, days and quantity of supply), prescription information (drug name, generic name, dosage form, strengths), diagnosis information for coexisting conditions (ICD-9/ ICD-10 codes and diagnosis description), procedures performed (CPT/ HCPCS and procedure description), and patient enrollment information (health insurance type, months of coverage). Geographic location measures available in IQVIA include region of residence (Northeast, Midwest, South, West, based on U.S. Census definitions) and 3-digit ZIP codes, which represent the first three digits of the standard 5-digit ZIP code and capture broader geographic areas while preserving confidentiality. We refer to patient-level variables as time-invariant information (e.g., demographics and geographic location), while episode-level variables characterize each treatment episode (e.g., duration in days). Details of the variable definitions are in Table A in S1 Appendix. In addition, we incorporate area-level socioeconomic variables based on the patients' 3-digit ZIP code. Specifically, we used the Social Vulnerability Index (SVI) developed by the U.S. Centers for Disease Control and Prevention (CDC) for year 2022 [51]. The CDC SVI ranks 16 socioeconomic and demographic variables from the American Community Survey conducted by U.S. Census Bureau, including measures of socioeconomic status, racial and ethnic minority status, household characteristics and housing type and transportation. The SVI is a score ranging from 0 and 1, with higher values indicating greater vulnerability. Since the CDC SVI is reported by census tracts, it was mapped to 3-digit ZIP Code Tabulated Areas using population-weighted aggregation. The resulting values were rescaled to a 0–1 range and classified into four vulnerability levels based on quartiles: Low (0 - < 0.25), Medium-Low (0.25 - < 0.5), Medium-High (0.5 - < 0.75), and High (0.75 - 1.0).

Study design and analytical cohort

This retrospective cohort study leveraged U.S. nationwide longitudinal claims data to construct buprenorphine treatment episodes and evaluate discontinuation among adult population. **Fig 1** summarizes the inclusion/exclusion criteria and procedures used to construct the analytical cohort. Buprenorphine claims for OUD were identified using the Uniform System of Classification (USC) code 78340 and refined by selecting prescriptions with buprenorphine-related product names and excluding exact duplicates. Buprenorphine treatment was defined to include all major formulations, including buprenorphine monoproducts, buprenorphine-naloxone combination products, and extended-release formulations (e.g., SUBLOCADE and PROBUPHINE), consistent with prior literature [52,53]. Sublingual products accounted for the vast majority of prescriptions (99.65%), whereas long-acting injectable formulations comprised a small proportion (0.35%). The initial screening yielded 4,487,146 records across 256,737 unique patients. Records with missing, zero, or negative values for "days of supply" (N = 24,947; 0.56%) were imputed using the population median, and extreme values were truncated at 90 days (N = 88; 0.002%), following the prior reports on prescribing practices [52,54,55]. Buprenorphine treatment episodes were constructed from prescription records, with a new episode defined as a prescription filled after a > 14-day gap in supply. This threshold was chosen based on a sensitivity analysis comparing alternative gaps of 7, 21, 30, and 60 days (Supplemental Results in S1 Appendix). For overlapping prescriptions, excess days were added to the end of the last prescription to calculate episode duration [52]. Episode construction was performed using the *AdhereR* package (version 0.8.1) in R [56,57]. We further excluded patients with missing demographic information (age, sex, and health insurance; N = 2,097) or invalid/missing 3-digit Zip Codes (N = 73,243). The primary outcome was buprenorphine treatment discontinuation, defined as a treatment episode lasting fewer than 180 days [52,58]. Episodes with a duration of <180 days were coded as discontinued (1), whereas episodes lasting ≥180 days were coded as continued (0).

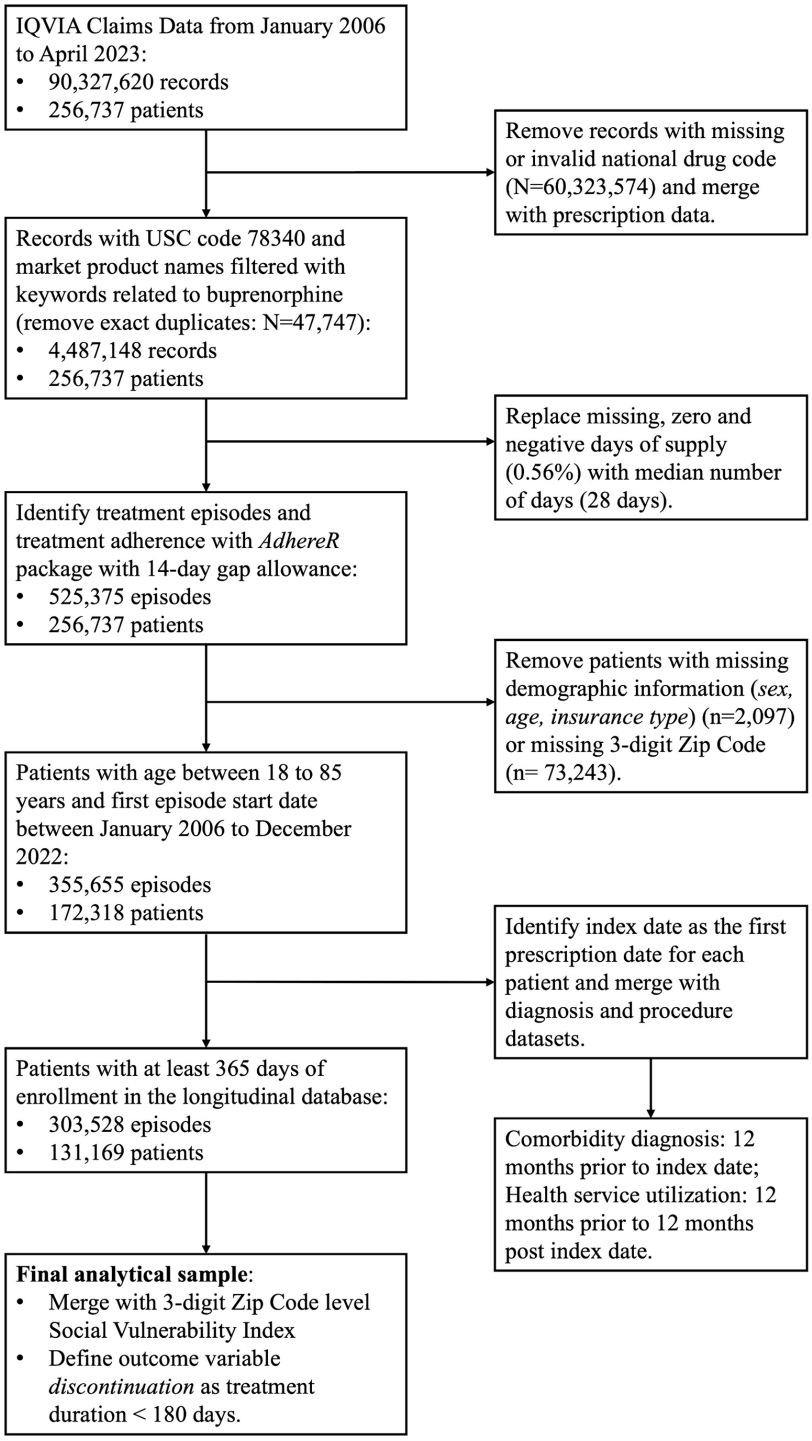


Fig 1. Flowchart of data processing and analytical cohort generation. N refers to the number of episodes and n refers to the number of patients.

https://doi.org/10.1371/journal.pmen.0000469.g001

Patient-level comorbidities were identified using ICD-10 and ICD-9 diagnostic codes present within the 12 months preceding the start date of the initial treatment episode, defined as the index date. Comorbidities conditions included alcohol use disorder, non-opioid substance use disorders, schizophrenia, bipolar disorder, anxiety disorder, posttraumatic stress disorder, depressive disorders, and HIV. Each comorbidity was coded as a binary indicator. Health service utilization was captured through CPT/HCPCS procedure codes occurring from 12 months before to 12 months after the index episode. These included outpatient medical services for general evaluations, outpatient psychiatric services, medication-assisted treatment counseling, telehealth services, induction and maintenance services, and in-clinic OUD services [59–61]. These variables captured the types of healthcare engagement that may influence adherence and treatment continuity. Detailed diagnostic and procedure codes are provided in Tables B and C in S1 Appendix.

To evaluate the early treatment adherence, we calculated the patient-level proportion of days covered (PDC), defined as the number of days covered by buprenorphine divided by the observation window [43]. PDC is a validated claims-based metric that quantifies the proportion of days a patient has medication available over a specified period [62,63]. PDC has been commonly used in prior studies of substance use disorder to assess early adherence and predict treatment retention and outcomes [43,46]. We compared 1-month and 3-month PDC measures and found that the 3-month PDC was more predictive of treatment discontinuation (Supplemental Results in S1 Appendix). Therefore, we used the 3-month PDC, defined as the number of days covered within the initial 90 days after treatment initiation divided by 90, in our final models. The final analytical cohort included 303,528 episodes from 131,169 patients aged between 18 and 85 who had at least one year of enrollment.

Virtual twins machine learning model

We employed a two-stage machine learning framework adapted from Virtual Twins approach to investigate the impact of disparities on treatment discontinuation risk. The modeling design and analytical workflow are illustrated in **Fig 2**. In Stage one, we trained a classification model to generate counterfactual predictions by toggling disparity variables (e.g., sex, age, health insurance) while holding other covariates constant, and computed the resulting individual-level disparity effects as differences in predicted discontinuation risk. In Stage two, we applied interpretable machine learning algorithms, including decision trees [64] and shallow neural network, to regress these disparity effects on patient characteristics, identifying subgroups most vulnerable to disparities. This two-stage approach separates disparity-effect estimation from subgroup identification and explanation, enhancing the interpretability of disparity-driven risk stratification. The coding and categorization of disparity variables used as predictors and as binary outcomes are summarized in Table A in S1 Appendix.

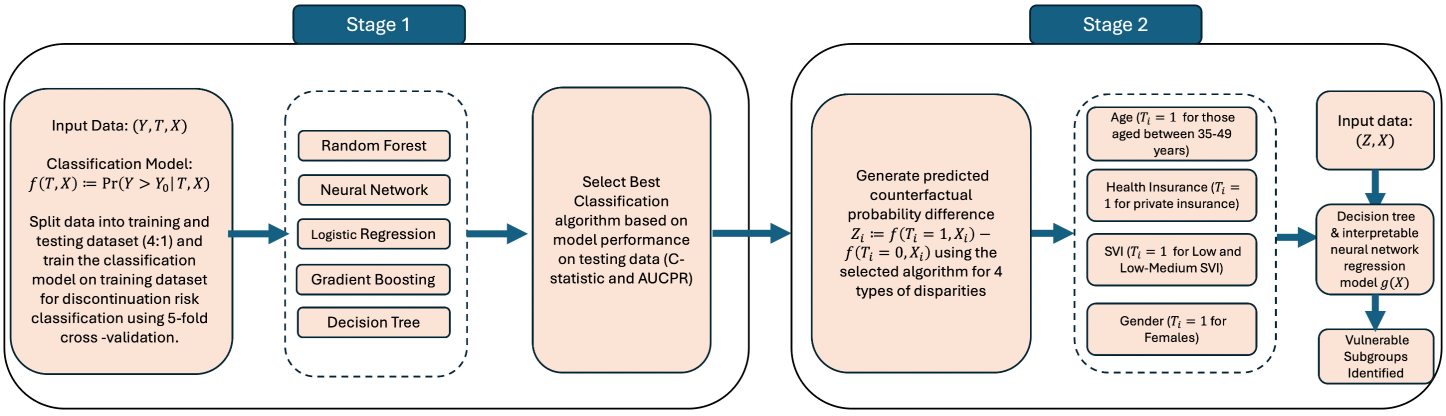


Fig 2. Two-stage Virtual Twins machine learning model diagram.

https://doi.org/10.1371/journal.pmen.0000469.g002

Let $\{(Y_i,\ T_i,\ \boldsymbol{X}_i)\}_{i\in\{1,\,2,\,\ldots,\,n\}}$ represent the treatment episode dataset, where Y_i is the outcome variable - treatment discontinuation, T_i is the disparity variable of interest (e.g., $T_i = 1$ for females and $T_i = 0$ for males), and $\boldsymbol{X}_i$ is a vector of all other covariates for the i-th episode. In the first stage, we trained predictive models to estimate the probability of treatment discontinuation given the disparity type and all other covariates $f(T_i,\ \boldsymbol{X}_i) = \Pr(Y_i = 1 \mid T_i = 1,\ \boldsymbol{X}_i)$. We considered different machine learning algorithms, including logistic regression, decision trees, random forest, gradient boosted machine (GBM) and neural network models. Three nested models were developed: Model 1 included baseline characteristics (sex, age, insurance type, geographic region, comorbidities, healthcare utilization); Model 2 added the SVI; and Model 3 further included the 3-month PDC variable. A complete list of variables included in each model is presented in Table D in S1 Appendix.

We randomly split the dataset into 80% training and 20% testing. Within the training data, five-fold cross-validation and grid search were used for model tuning. To address class imbalance, Synthetic Minority Oversampling Technique (SMOTE) was applied within training dataset. The optimal model was selected based on the highest C-statistic, defined as the area under the receiver-operating characteristic curve (AUC-ROC). Model performance was further evaluated using accuracy, precision, recall, and the area under the precision-recall curve (AUC-PR). For each observation, we computed a virtual difference $Z_i = f(T_i = 1,\ X_i) - f(T_i = 0,\ X_i)$, which captures the counterfactual probability change had the individual belonged to the alternative group (e.g., female vs. male) when all other covariates remained the same. We calculated the probability differences for sex (females vs. males), age group (35–49 vs. 18–34 and 50–85 combined), health insurance type (private vs. public insurance), SVI (low and low-medium vs. medium-high and high), region of residence (West vs. other regions), and mental health status (Yes vs. No). Mental health diagnosis refers to any diagnosis related to anxiety, depression, bipolar disorder, PTSD, and schizophrenia. Details on grid search for parameter tuning are included in Supplemental Methods in S1 Appendix.

In the second stage, the estimated virtual probability difference Z_i from Stage one was treated as the primary outcome, and we fit regression models $g(\boldsymbol{X}_i)$ adjusting all other covariates $\boldsymbol{X}_i$, excluding the disparity variable. The covariates included in the model are healthcare services utilization, alcohol disorder, and non-opioid drug use 12 months prior to the index date. We considered interpretable machine learning methods such as decision trees and shallow neural network models to identify key factors contributing to disparities. Decision trees were used to define subgroups most vulnerable to discontinuation disparities, while neural networks were paired with SHAP (Shapley Additive Explanations) [65] values to quantify global and local feature importance. SHAP is a model-agnostic approach that attributes each feature's contribution to a given model prediction, based on its marginal effect across all possible feature combinations [65]. In our application, SHAP values reflect the relative importance of each feature in explaining the variance in predicted counterfactual differences. To maintain interpretability, we limited decision trees to three layers and neural networks to five hidden units per layer.

All analyses were conducted using R (version 4.3.1) [66] and RStudio (version 2023.06.0) [67]. We used the R package *tidymodels* to implement all the machine learning models [68]. The R code used for analytical cohort construction, model development, and data visualization is publicly available at https://github.com/kehezhang12/MOUD_Disparity_DigitalTwins.

Results

Patient and episodes characteristics

Table 1 summarizes the demographic, clinical, and treatment episode characteristics of the analytical cohort. Most of the patients were male (60.8%), residing in the South (34.2%), aged 25–34 years (33.7%) and were covered under commercial insurance (76.0%). Approximately 7.2% had a history of alcohol disorder, and 31.2% reported non-opioid drug use 12 months preceding the first buprenorphine prescription. Mental health conditions were prevalent, with anxiety (22.6%) and depression (22.3%) being the most common diagnoses. Outpatient services were utilized by 90.6% of patients, while

Table 1. Baseline patient demographic and clinical characteristics at patient-level and episode-level.

	Episode-level			Individual-level (N = 131,169)
	Discontinued (N = 215,921)	Continued (N = 87,607)	Overall (N = 303,528)	
Sex				
Female	82,335 (38.1%)	32,592 (37.2%)	114,927 (37.9%)	51,426 (39.2%)
Male	133,586 (61.9%)	55,015 (62.8%)	188,601 (62.1%)	79,743 (60.8%)
Age group				
18-24	28,820 (13.3%)	7,315 (8.3%)	36,135 (11.9%)	18,409 (14.0%)
25-34	69,623 (32.2%)	28,514 (32.5%)	98,137 (32.3%)	44,174 (33.7%)
35-44	52,218 (24.2%)	24,312 (27.8%)	76,530 (25.2%)	32,054 (24.4%)
45-54	36,296 (16.8%)	15,585 (17.8%)	51,881 (17.1%)	20,701 (15.8%)
55-64	22,953 (10.6%)	9,378 (10.7%)	32,331 (10.7%)	12,357 (9.4%)
65-85	6,011 (2.8%)	2,503 (2.9%)	8,514 (2.8%)	3,474 (2.6%)
Insurance type				
Medicaid	24,463 (11.3%)	9,588 (10.9%)	34,051 (11.2%)	19,277 (14.7%)
Medicare	15,330 (7.1%)	8,959 (10.2%)	24,289 (8.0%)	11,973 (9.1%)
Commercial	175,872 (81.5%)	68,956 (78.7%)	244,828 (80.7%)	99,735 (76.0%)
Self-insured	256 (0.1%)	104 (0.1%)	360 (0.1%)	184 (0.1%)
Region of residence				
Northeast	38,522 (17.8%)	16,666 (19.0%)	55,188 (18.2%)	22,388 (17.1%)
Midwest	49,310 (22.8%)	22,456 (25.6%)	71,766 (23.6%)	35,610 (27.1%)
South	70,034 (32.4%)	32,639 (37.3%)	102,673 (33.8%)	44,882 (34.2%)
West	58,055 (26.9%)	15,846 (18.1%)	73,901 (24.3%)	28,289 (21.6%)
Alcohol disorder				
No	200,718 (93.0%)	83,458 (95.3%)	284,176 (93.6%)	121,771 (92.8%)
Yes	15,203 (7.0%)	4,149 (4.7%)	19,352 (6.4%)	9,398 (7.2%)
Non-opioid drug use				
No	152,122 (70.5%)	67,179 (76.7%)	219,301 (72.3%)	90,215 (68.8%)
Yes	63,799 (29.5%)	20,428 (23.3%)	84,227 (27.7%)	40,954 (31.2%)
Schizophrenia				
No	214,407 (99.3%)	87,236 (99.6%)	301,643 (99.4%)	130,130 (99.2%)
Yes	1,514 (0.7%)	371 (0.4%)	1,885 (0.6%)	1,039 (0.8%)
Bipolar disorder				
No	203,693 (94.3%)	84,258 (96.2%)	287,951 (94.9%)	123,745 (94.3%)
Yes	12,228 (5.7%)	3,349 (3.8%)	15,577 (5.1%)	7,424 (5.7%)
Anxiety				
No	167,622 (77.6%)	72,625 (82.9%)	240,247 (79.2%)	101,581 (77.4%)
Yes	48,299 (22.4%)	14,982 (17.1%)	63,281 (20.8%)	29,588 (22.6%)
Post-traumatic stress disorder				
No	209,884 (97.2%)	85,837 (98.0%)	295,721 (97.4%)	127,079 (96.9%)
Yes	6,037 (2.8%)	1,770 (2.0%)	7,807 (2.6%)	4,090 (3.1%)
Depressive disorder				
No	166,752 (77.2%)	72,437 (82.7%)	239,189 (78.8%)	101,863 (77.7%)
Yes	49,169 (22.8%)	15,170 (17.3%)	64,339 (21.2%)	29,306 (22.3%)
Outpatient visits				
No	19,112 (8.9%)	8,364 (9.5%)	27,476 (9.1%)	12,387 (9.4%)
Yes	196,809 (91.1%)	79,243 (90.5%)	276,052 (90.9%)	118,782 (90.6%)

(Continued)

Table 1. (Continued)

	Episode-level			Individual-level (N = 131,169)
	Discontinued (N = 215,921)	Continued (N = 87,607)	Overall (N = 303,528)	
Psychiatric visits				
No	164,204 (76.0%)	70,048 (80.0%)	234,252 (77.2%)	105,697 (80.6%)
Yes	51,717 (24.0%)	17,559 (20.0%)	69,276 (22.8%)	25,472 (19.4%)
Medication-assisted treatment				
No	215,917 (100.0%)	87,606 (100.0%)	303,523 (100.0%)	131,166 (100.0%)
Yes	4 (0.0%)	1 (0.0%)	5 (0.0%)	3 (0.0%)
Telehealth visits				
No	212,541 (98.4%)	85,557 (97.7%)	298,098 (98.2%)	128,108 (97.7%)
Yes	3,380 (1.6%)	2,050 (2.3%)	5,430 (1.8%)	3,061 (2.3%)
Induction visit				
No	211,479 (97.9%)	86,282 (98.5%)	297,761 (98.1%)	129,026 (98.4%)
Yes	4,442 (2.1%)	1,325 (1.5%)	5,767 (1.9%)	2,143 (1.6%)
Buprenorphine treatment				
No	214,566 (99.4%)	86,925 (99.2%)	301,491 (99.3%)	129,981 (99.1%)
Yes	1,355 (0.6%)	682 (0.8%)	2,037 (0.7%)	1,188 (0.9%)
Social Vulnerability Index				
Low	24,013 (11.1%)	12,749 (14.6%)	36,762 (12.1%)	17,506 (13.3%)
Low-Medium	62,960 (29.2%)	30,480 (34.8%)	93,440 (30.8%)	42,281 (32.2%)
Medium-High	62,135 (28.8%)	24,729 (28.2%)	86,864 (28.6%)	38,118 (29.1%)
High	66,813 (30.9%)	19,649 (22.4%)	86,462 (28.5%)	33,264 (25.4%)
Episode duration (days)				
Mean (SD)	51.1 (43.7)	588 (512)	206 (369)	–
Median [Min, Max]	30.0 [1.00, 179]	419 [180, 7,010]	63.0 [1.00, 7,010]	–
3-month PDC*				
Mean (SD)	0.65 (0.33)	0.92 (0.21)	0.73 (0.32)	0.73 (0.34)
Median [Min, Max]	0.70 [0.01, 1.00]	1.00 [0.01, 1.00]	0.86 [0.01, 1.00]	1.00 [0.01, 1.00]

Abbreviations: SD – standard deviation; Min – minimum; Max- maximum.

* The 3-month PDC is defined at episode level to assess adherence over a 90-day period by calculating the proportion of the 90-day interval that is covered by the episode duration.

https://doi.org/10.1371/journal.pmen.0000469.t001

19.4% accessed psychiatric services. Patients had an average of 2.3 treatment episodes, with a median duration of 63 days. Most episodes are discontinued with buprenorphine treatment (N = 215,921; 71.1%), while only 28.9% episodes lasted 180 days or longer. The average 3-month PDC across all episodes is 73%, with continued episodes having averaged 3-month PDC greater than 90%, compared to 65% for discontinued episodes. Discontinuation was significantly more common among patients aged 18–24 (13.3% vs. 8.3%), those residing in the West (26.9% vs. 18.1%), and those with alcohol use disorder (7.0% vs. 4.7%), non-opioid drug use (29.5% vs. 23.3%), or any mental health diagnosis within 12 months before the index date (all comparisons $p < 0.001$, chi-square tests).

First-stage Virtual Twins: Classification model

Table 2 presents the predictive performance of different machine learning models on the testing dataset, including C-statistics and AUC-PR. The initial evaluation with the baseline predictors achieved the following C-statistics: logistic

Table 2. Model predictive performance from Stage-one classification model by different machine learning algorithms.

Algorithms	Model 1		Model 2		Model 3	
	AUC-ROC	AUC-PR	AUC-ROC	AUC-PR	AUC-ROC	AUC-PR
Logistic regression	0.595	0.360	0.608	0.372	0.767	0.527
Random Forest	0.608	0.375	0.632	0.398	0.785	0.559
Gradient Boosted Machine	0.604	0.371	0.643	0.408	0.789	0.572
Decision Tree	0.567	0.539	0.577	0.520	0.733	0.677
Neural Network	0.605	0.370	0.616	0.379	0.773	0.535

https://doi.org/10.1371/journal.pmen.0000469.t002

regression (0.595), decision tree (0.567), random forest (0.608), gradient boosting machine (0.604), and neural network (0.605). Performance improved with the inclusion of contextual SVI, particularly for random forest (0.632) and gradient boosting tree (0.643), suggesting the importance of contextual SDOH in predicting discontinuation risk. Substantial improvements were observed after including the 3-month PDC, known to be highly predictive of treatment adherence. With PDC, C-statistics increased significantly: logistic regression (0.767), decision tree (0.733), random forest (0.785), GBM (0.789), and neural network (0.773). ROC and Precision-recall curves are shown in the Figure A in S1 Appendix, and additional metrics including accuracy, precision, recall and F1 score are available in Tables E-G in S1 Appendix. GBM demonstrated the best performance in Models 2 and 3 and was selected for estimating counterfactual probabilities for Stage-two analysis.

Variable importance plots from the random forest models across all three settings are displayed in **Fig 3**. When using only baseline characteristics, region of residence was the most influential predictor, followed by depression disorder and non-opioid drug use. After incorporating SVI, it became the top predictor, confirming that community-level SDOH factors significantly affect treatment duration. However, with the addition of 3-month PDC, SVI's importance reduced substantially, as PDC accounted for a large proportion of the variance in treatment discontinuation in this cohort.

Second-stage Virtual Twins: Regression model

For the second-stage analysis, we examined six types of disparities that have been documented in prior research: sex, age, SVI, health insurance, geographic region, and mental health diagnosis. The decision tree for sex disparity (**Fig 4A**) showed overall minimum differences between females and males, with the largest observed among older adults (aged 65–85) with private insurance (commercial or self-insured). Females in this subgroup had a 6.3% lower probability of treatment discontinuation (1% of the episodes; N = 3035). The SVI disparity tree (**Fig 4B**) showed greater discontinuation

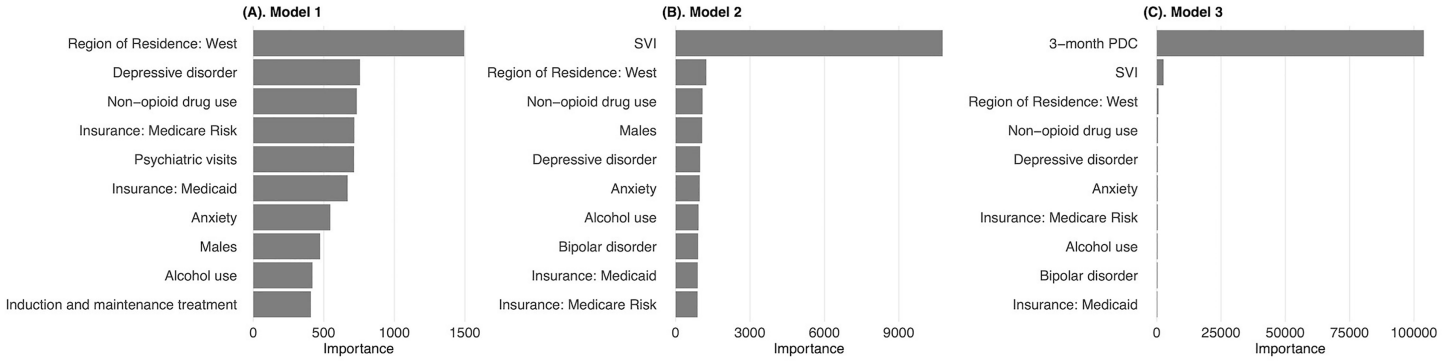


Fig 3. Variable importance plots from the random forest models for Stage-one classification model.

https://doi.org/10.1371/journal.pmen.0000469.g003

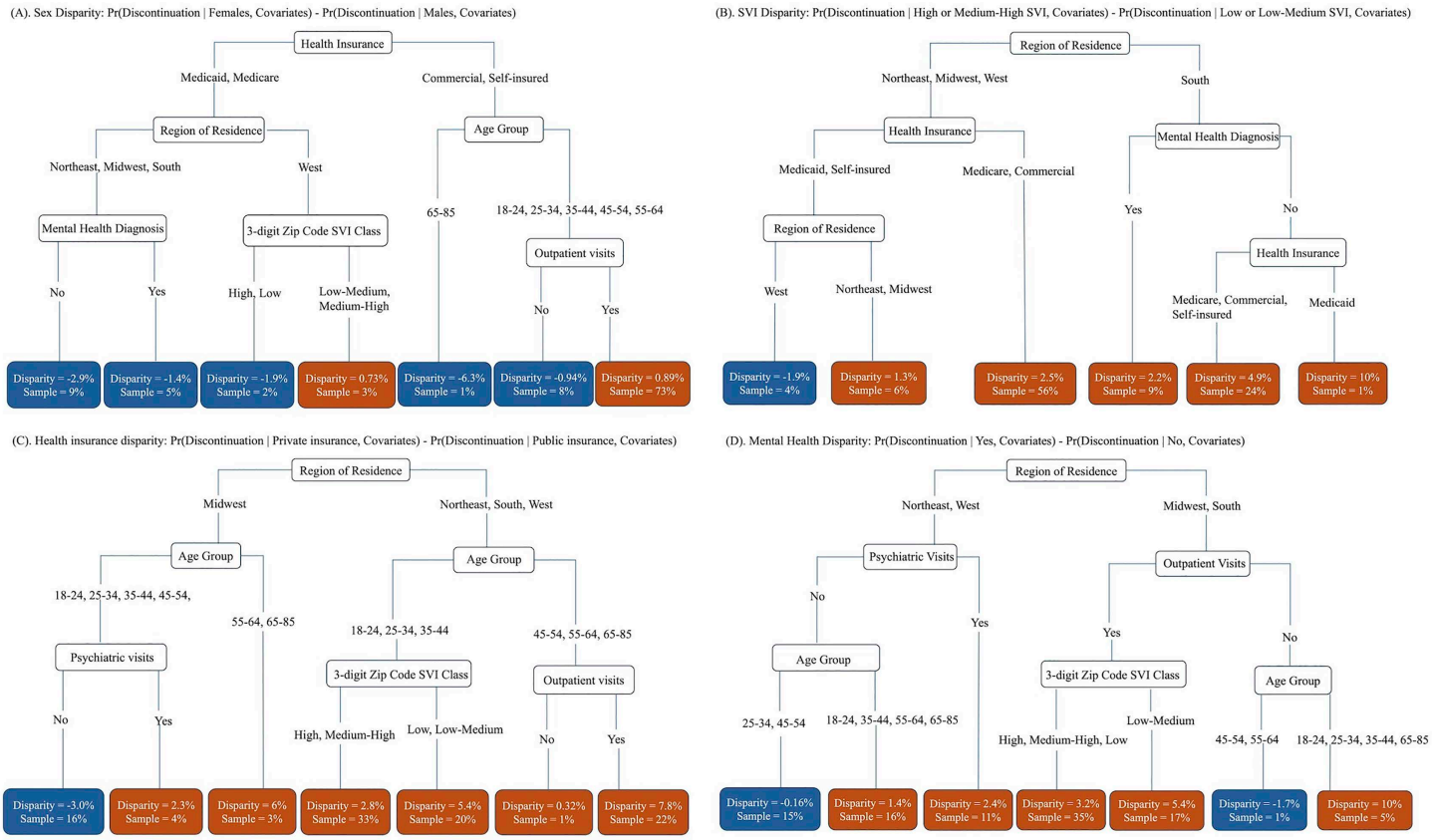


Fig 4. Decision tree diagram from the Stage-two regression model for different types of disparity: (A). Sex Disparity; (B). SVI Disparity; (C). Health Insurance Disparity (D). Mental Health Disparity.

https://doi.org/10.1371/journal.pmen.0000469.g004

risks for patients from high-SVI areas, particularly those living in the South without recent mental health diagnoses. Specifically, discontinuation probability increased by 10% for Medicaid patients (1% of the episodes) and by 4.9% for patients with other insurance (24% of the episodes) in this subgroup. Patients with private insurance (commercial or self-insured) generally had higher risks of discontinuation than those with public insurance (Fig 4C). Among adults residing in the South, West or Northeast aged 45–85 with recent outpatient visits, having private insurance increased discontinuation risk by 7.8% (22% of the episodes). Mental health diagnosis also contributed to substantial disparities (Fig 4D) but varied geographically. In the Midwest and South regions, patients aged 18–44 or 65–85 with no recent outpatient visits, having mental health diagnosis increased the risk of discontinuation by 10% (5% of the episodes). Even among patients with recent outpatient visits, mental health diagnosis increased the risk by 5.4% for those living in low-to-medium SVI areas from Midwest or South (17% of the episodes).

To validate the decision tree findings, we then examined variable importance using SHAP values derived from neural network regression models, which quantifies how much each predictor contributes to the estimated disparity in treatment discontinuation risk between groups. Positive SHAP values indicate predictors associated with increased disparity, that is, a larger difference in discontinuation risk between the comparison groups, while negative values indicate reduced disparity. As shown in Fig 5, SVI and region of residence consistently ranked among the most influential contributors to disparities. Insurance type, psychiatric service utilization, and age are also key predictors, highlighting the role of both sociodemographic and behavioral health factors in shaping subgroup differences in treatment duration.

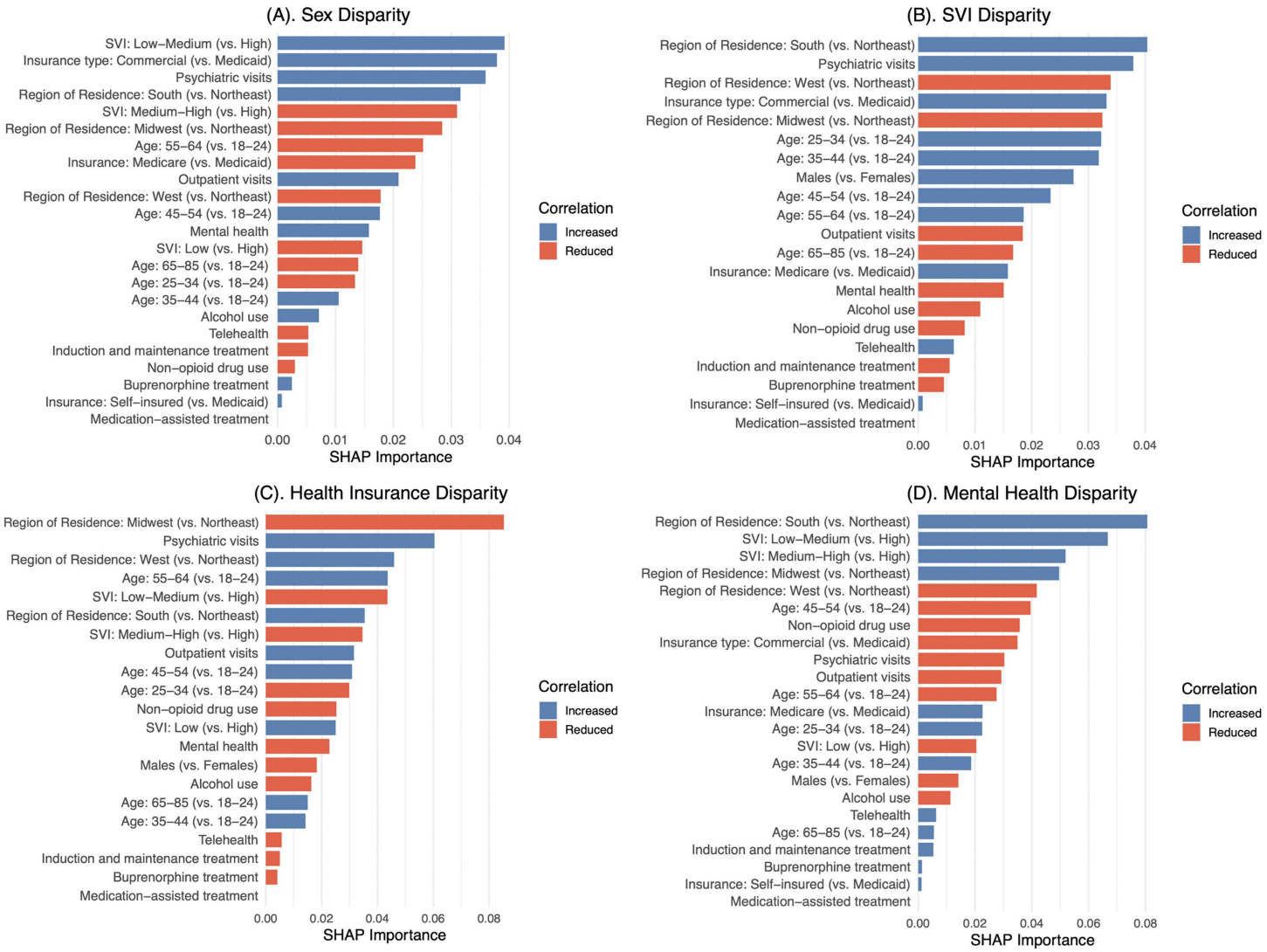


Fig 5. SHAP variable importance plots from the Stage-two neural network regression model: (A). Sex Disparity; (B). SVI Disparity; (C). Health Insurance Disparity (D). Mental Health Disparity.

https://doi.org/10.1371/journal.pmen.0000469.g005

Results for age and geographic region disparities are provided in Figures B and C in S1 Appendix. Overall, patients aged 35–49 had lower discontinuation risk compared to younger (18–34) and older adults (50–85). Additionally, patients in the Western region, particularly older adults (65–85) covered by Medicare or commercial insurance and living in areas with high social vulnerability, experienced notably higher discontinuation risks.

Discussion

In this nationwide, longitudinal cohort study of OUD patients, approximately 57% treatment episodes were discontinued within 90 days of buprenorphine initiation, and 71% discontinued by 180 days, resulting in a retention rate of only 29%. These findings highlight the challenges of retaining patients in buprenorphine treatment. The Stage-one analysis identified the 3-month PDC as the strongest predictor of treatment discontinuation, underscoring the importance of medication

adherence in early treatment stages to promote long-term treatment retention. These findings align closely with previous studies by Faysal et al. (2024) [45] and Hasan et al. (2021) [46], suggesting that interventions focused on improving adherence during the initial treatment phase may be beneficial to improve the overall retention rate.

Our second-stage analysis revealed significant disparities in buprenorphine discontinuation related to SVI, insurance type, region of residence, mental health status, and age. Although prior studies have identified gender-based disparities in OUD treatment retention, citing barriers faced by women such as caregiving responsibilities, financial instability, and limited access to gender-responsive services [69,70], our analysis showed minimum differences in discontinuation risk between females and males. In contrast, disparities related to social vulnerability were more pronounced, especially among patients in high-SVI areas in the South, enrolled in Medicaid, and without a mental health diagnosis. Yet, SVI disparities were mitigated among Southern patients with mental health diagnoses, potentially reflecting the protective effects of psychiatric services. These findings suggest structural barriers, such as inadequate healthcare infrastructure, may disproportionately affect vulnerable populations. Federally Qualified Health Centers, primarily located in underserved communities, could play a key role in addressing these disparities by offering integrated primary care, behavioral health, and substance use services [71].

Mental health diagnosis itself was associated with higher discontinuation risk, especially among younger (18–44) and older (65–85) adults in the Midwest or South without recent outpatient visits. This aligns with previous research showing lower adherence among patients with psychiatric conditions [72–74], possibly reflecting prioritization of mental health treatment over substance use treatment [75]. These findings indicate an urgent need for integrated care models to concurrently address mental health and substance use disorders.

Regarding insurance type, patients with public insurance had lower discontinuation risk overall. This may reflect broader and more stable coverage in Medicaid for both immediate- and extended- release buprenorphine, with minimal prior authorization and quantity limits [76]. Yet, privately insured individuals, especially those aged 45 and older with outpatient visits in the West, South, or Northeast, had a significantly higher discontinuation risk (7.8%). This difference may be attributed to higher cost-sharing and more frequent utilization management in private plans, which can delay or interrupt treatment [77]. In addition, Medicaid expansion has been associated with increased receipt of medications for OUD in outpatient settings [78], and removal of prior authorization requirements has been linked to increased buprenorphine prescribing in Medicaid populations [79], underscoring the role of administrative barriers in treatment retention. Among publicly insured individuals, younger patients (18–54) in the Midwest who lacked psychiatric service utilization showed elevated discontinuation risks, highlighting the potential protective effects of psychiatric services. Integrating behavioral health care, particularly for younger publicly insured patients, may significantly enhance treatment continuity, consistent with evidence supporting the benefits of concurrent behavioral therapies [80]. Tailored approaches that address psychiatric care access and insurance-related barriers are critical for MOUD treatment retention.

We observed age-related disparities in buprenorphine treatment discontinuation. Patients aged 35–49 years showed a lower risk of discontinuation compared to rest of the adult population (those aged 18–34 and 50 + combined). Previous studies similarly report age gradients in buprenorphine retention, with younger adults (18–49) generally exhibiting lower retention compared with those aged ≥50, and a pattern suggesting decreasing retention with decreasing age [81,82]. Although our findings are directionally consistent with this literature, direct comparison remains challenging given the heterogeneous and nonstandardized age categorizations used across studies. We were particularly interested in the 35–49 age group because national surveillance data indicate that adults in this age range account for a substantial proportion of individuals actively receiving OUD treatment [16]. Considered alongside our finding of lower discontinuation risk in this group, their greater representation in treatment may reflect stronger engagement in care, which could contribute to the lower discontinuation risk observed in our analysis.

In addition, we also observed notable regional differences. Individuals in the Western U.S., especially older adults enrolled in Medicare or commercial insurance in high-SVI areas, had the highest discontinuation risks. These findings

may reflect geographic disparities in provider availability, restrictive Medicaid policies, and infrastructure barriers such as limited access to waivered prescribers and longer travel distances in rural or socially vulnerable regions [83]. Tailored strategies addressing regional healthcare access gaps and age-specific needs are essential to improve buprenorphine treatment retention.

Our study has several strengths. First, we integrate a geographically referenced contextual measure of social vulnerability, which provided insights beyond individual-level predictors and significantly improved the predictive accuracy. Second, unlike previous studies that were limited by data coverage and demographics, our study utilizes a nationwide, longitudinal cohort, providing more generalizable findings. Third, our use of episode-level data, rather than patient-level data, enables a more granular capture of treatment episode discontinuation. Fourth, our application of a two-stage Virtual Twins analytical framework enables identification of vulnerable subgroups and quantification of disparities attributable to specific risk factors. This approach, while previously applied in substance abuse research [49,50], is the first in MOUD treatment retention, addressing the limitations of single prediction models that fail to capture heterogeneous effects across diverse populations [45,46].

Despite the strengths, we should also acknowledge the limitations. First, our demographic data lacked patient race and ethnicity, a key disparity reported by many other studies [52,84]. Second, due to the limitation of the dataset, we could not account for concurrent medications taken by patients [45] or their initial amount of dosage, despite the evidence that a low initial dose of buprenorphine (4mg or less) was seen as the strongest risk factor driving discontinuation [17]. In addition, although all major buprenorphine formulations were included, long-acting injectable products accounted for only 0.35% of prescriptions, which precluded meaningful comparisons between short- and long-acting formulations. Future studies with greater uptake of extended-release formulations are needed to evaluate formulation-specific retention patterns. Third, geographic location was derived from each patient's most recent enrollment record and treated as time-invariant. Therefore, we were unable to capture residential changes over time, which may introduce some misclassification if patients relocated during the study period. Finally, although the use of the Virtual Twins framework is a novel approach to quantifying OUD disparities, it currently lacks uncertainty assessment, which warrants investigation in future studies.

Conclusion

Leveraging a nationwide longitudinal cohort and a two-stage Virtual Twins model, our study identified and quantified vulnerable subgroups with pronounced disparities in sex, age, insurance, region of residence, mental health status, and SVI. Our key innovation is the incorporation of contextual SDOH, allowing us to capture key risk and protective factors and providing actionable insights for tailored policy interventions. This study has shown that different disparities exist and persist in MOUD treatment retention, and psychiatric service utilization consistently emerged as protective against treatment discontinuation across various disparities. These findings highlight the importance of targeted interventions, including enhanced psychiatric care, region-specific programs, and strengthened community support, to address structural barriers and improve equitable access and retention in medication for OUD treatment.

Supporting information

S1 Appendix. Supplemental materials including supplemental figures, tables, and method descriptions. Table A. List of variables defined at patient, episode and community level. Each variable may be coded differently for Stage-one and Stage-two analysis. **Table B.** List of Diagnosis and Healthcare utilization. **Table C.** Healthcare utilization identified using CPT/HCPCS codes. **Table D.** List of variables included in each model. **Supplemental Methods:** Stage-one Model Training and Parameter Tuning. **Figure A.** AUC-ROC and AUC-PR Curve for Stage-one digital twin analysis: (A). Model 1; (B). Model 2; (C). Model 3. **Table E.** Results from Stage-one model 1: baseline predictors only. **Table F.** Results from Stage-one model 2: baseline predictors + SVI. **Table G.** Results from Stage-one model 3: baseline predictors + SVI + PDC. **Figure B.** Decision tree results for (A). Geographic region disparity and (B). Age disparity. **Figure C.** SHAP importance

from neural network model for (A). Geographic region disparity and (B). Age disparity. **Supplemental Results:** Sensitivity Analysis on Gaps of Supply, Sensitivity Analysis on PDC 30 vs. PDC 90.
(DOCX)

Author contributions

Conceptualization: Yanmin Gong, Cici Bauer.

Data curation: Kehe Zhang, Paula A. Jaimes-Buitron, Wanru Guo, Cici Bauer.

Formal analysis: Kehe Zhang, Cici Bauer.

Funding acquisition: Yanmin Gong, Yuanxiong Guo, Carolina Vivas Valencia, Cici Bauer.

Methodology: Yanmin Gong, Yuanxiong Guo, Carolina Vivas Valencia, Cici Bauer.

Software: Kehe Zhang, Paula A. Jaimes-Buitron, Cici Bauer.

Supervision: Cici Bauer.

Visualization: Kehe Zhang.

Writing – original draft: Kehe Zhang, Wanru Guo, Cici Bauer.

Writing – review & editing: Kehe Zhang, Paula A. Jaimes-Buitron, Yanmin Gong, Yuanxiong Guo, Carolina Vivas Valencia, Cici Bauer.

References

1. National Institute on Drug Abuse website. NIDA. Drug Overdose Deaths: Facts and Figures [Internet]. 2024 [cited 2025 Jul 15]. Available from: https://nida.nih.gov/research-topics/trends-statistics/overdose-death-rates
2. Spencer MR, Garnett MF, Miniño AM. Drug Overdose Deaths in the United States, 2002-2022 [Internet]. [cited 2025 Jul 24]. Available from: https://stacks.cdc.gov/view/cdc/135849
3. Increases in Drug and Opioid Overdose Deaths — United States, 2000–2014 [Internet]. [cited 2025 Jul 23]. Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6450a3.htm
4. SAMHSA. Substance Abuse and Mental Health Services Administration [Internet]. Substance Use Disorders Treatment - Statutes, Regulations, and Guidelines. 2024. [cited 2026 Feb 20]. Available from: https://www.samhsa.gov/substance-use/treatment/statutes-regulations-guidelines
5. Priest KC, Gorfinkel L, Klimas J, Jones AA, Fairbairn N, McCarty D. Comparing Canadian and United States opioid agonist therapy policies. Int J Drug Policy. 2019;74:257–65. https://doi.org/10.1016/j.drugpo.2019.01.020 PMID: 30765118
6. Kampman K, Jarvis M. American Society of Addiction Medicine (ASAM) National Practice Guideline for the use of medications in the treatment of addiction involving opioid use. J Addict Med. 2015;9(5):358–67. https://doi.org/10.1097/ADM.0000000000000166 PMID: 26406300
7. Volkow ND, Frieden TR, Hyde PS, Cha SS. Medication-assisted therapies — tackling the opioid-overdose epidemic. N Engl J Med. 2014;370(22):2063–6. https://doi.org/10.1056/NEJMp1402780
8. Warren D, Marashi A, Siddiqui A, Eijaz AA, Pradhan P, Lim D, et al. Using machine learning to study the effect of medication adherence in opioid use disorder. PLoS One. 2022;17(12):e0278988. https://doi.org/10.1371/journal.pone.0278988 PMID: 36520864
9. Williams AR, Samples H, Crystal S, Olfson M. Acute care, prescription opioid use, and overdose following discontinuation of long-term buprenorphine treatment for opioid use disorder. Am J Psychiatry. 2020;177(2):117–24. https://doi.org/10.1176/appi.ajp.2019.19060612 PMID: 31786933
10. Ma J, Bao Y-P, Wang R-J, Su M-F, Liu M-X, Li J-Q, et al. Effects of medication-assisted treatment on mortality among opioids users: a systematic review and meta-analysis. Mol Psychiatry. 2019;24(12):1868–83. https://doi.org/10.1038/s41380-018-0094-5 PMID: 29934549
11. Sordo L, Barrio G, Bravo MJ, Indave BI, Degenhardt L, Wiessing L, et al. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. 2017. https://doi.org/10.1136/bmj.j1550
12. Landis RK, Opper I, Saloner B, Gordon AJ, Leslie DL, Sorbero M, et al. Buprenorphine treatment episode duration, dosage, and concurrent prescribing of benzodiazepines and opioid analgesics: the effects of Medicaid prior authorization policies. Drug Alcohol Depend. 2022;241:109669. https://doi.org/10.1016/j.drugalcdep.2022.109669 PMID: 36332589
13. National Quality Forum. Quality positioning system TM: Continuity of pharmacotherapy for opioid use disorder [Internet]. 2022. Available from: https://qpp.cms.gov/docs/QPP_quality_measure_specifications/CQM-Measures/2022_Measure_468_MIPSCQM.pdf
14. Peles E, Linzy S, Kreek M, Adelson M. One-year and cumulative retention as predictors of success in methadone maintenance treatment: a comparison of two clinics in the United States and Israel. J Addict Dis. 2008;27(4):11–25. https://doi.org/10.1080/10550880802324382 PMID: 19042587

15. Weisner C, Matzger H, Kaskutas LA. How important is treatment? One-year outcomes of treated and untreated alcohol-dependent individuals. Addiction. 2003;98(7):901–11. https://doi.org/10.1046/j.1360-0443.2003.00438.x PMID: 12814496
16. Dowell D. Treatment for opioid use disorder: population estimates — United States, 2022. MMWR Morb Mortal Wkly Rep. 2024;73. https://doi.org/10.15585/mmwr.mm7325a1
17. Samples H, Williams AR, Olfson M, Crystal S. Risk factors for discontinuation of buprenorphine treatment for opioid use disorders in a multi-state sample of Medicaid enrollees. J Subst Abuse Treat. 2018;95:9–17. https://doi.org/10.1016/j.jsat.2018.09.001 PMID: 30352671
18. Saloner B, Daubresse M, Caleb Alexander G. Patterns of buprenorphine-naloxone treatment for opioid use disorder in a multistate population. Med Care. 2017;55(7):669–76. https://doi.org/10.1097/MLR.0000000000000727 PMID: 28410339
19. Meinhofer A, Williams AR, Johnson P, Schackman BR, Bao Y. Prescribing decisions at buprenorphine treatment initiation: do they matter for treatment discontinuation and adverse opioid-related events? J Subst Abuse Treat. 2019;105:37–43. https://doi.org/10.1016/j.jsat.2019.07.010 PMID: 31443889
20. Xu KY, Gertner AK, Greenfield SF, Williams AR, Grucza RA. Treatment setting and buprenorphine discontinuation: an analysis of multi-state insurance claims. Addict Sci Clin Pract. 2024;19(1):17. https://doi.org/10.1186/s13722-024-00450-0 PMID: 38493109
21. Santo T Jr, Clark B, Hickman M, Grebely J, Campbell G, Sordo L, et al. Association of opioid agonist treatment with all-cause mortality and specific causes of death among people with opioid dependence: a systematic review and meta-analysis. JAMA Psychiatry. 2021;78(9):979–93. https://doi.org/10.1001/jamapsychiatry.2021.0976 PMID: 34076676
22. Glanz JM, Binswanger IA, Clarke CL, Nguyen AP, Ford MA, Ray GT, et al. The association between buprenorphine treatment duration and mortality: a multi-site cohort study of people who discontinued treatment. Addiction. 2023;118(1):97–107. https://doi.org/10.1111/add.15998 PMID: 35815386
23. Vakkalanka P, Lund BC, Arndt S, Field W, Charlton M, Ward MM. Association between buprenorphine for opioid use disorder and mortality risk. [cited 2025 Jul 29]. Available from: https://stacks.cdc.gov/view/cdc/109552
24. Alyssa S. Social determinants associated with retention in buprenorphine treatment for opioid use disorder in US adults: A systematic review [Internet]. The University of North Carolina. 2022. Available from: https://doi.org/10.17615/ebx6-v411
25. Pilarinos A, Bromberg DJ, Karamouzian M. Access to medications for opioid use disorder and associated factors among adolescents and young adults: a systematic review. JAMA Pediatr. 2022;176(3):304–11. https://doi.org/10.1001/jamapediatrics.2021.4606 PMID: 34870707
26. Biondi BE, Vander Wyk B, Schlossberg EF, Shaw A, Springer SA. Factors associated with retention on medications for opioid use disorder among a cohort of adults seeking treatment in the community. Addict Sci Clin Pract. 2022;17(1):15. https://doi.org/10.1186/s13722-022-00299-1 PMID: 35255967
27. Stein MD, Cioe P, Friedmann PD. Buprenorphine retention in primary care. J Gen Intern Med. 2005;20(11):1038–41. https://doi.org/10.1111/j.1525-1497.2005.0228.x PMID: 16307630
28. Rigg KK, Monnat SM. Urban vs. rural differences in prescription opioid misuse among adults in the United States: informing region specific drug policies and interventions. Int J Drug Policy. 2015;26(5):484–91. https://doi.org/10.1016/j.drugpo.2014.10.001 PMID: 25458403
29. Lagisetty PA, Ross R, Bohnert A, Clay M, Maust DT. Buprenorphine treatment divide by race/ethnicity and payment. JAMA Psychiatry. 2019;76(9):979–81. https://doi.org/10.1001/jamapsychiatry.2019.0876 PMID: 31066881
30. Öhlin L, Fridell M, Nyhlén A. Buprenorphine maintenance program with contracted work/education and low tolerance for non-prescribed drug use: a cohort study of outcome for women and men after seven years. BMC Psychiatry. 2015;15:56. https://doi.org/10.1186/s12888-015-0415-z PMID: 25881164
31. Xu KY, Huang V, Williams AR, Martin CE, Bazazi AR, Grucza RA. Co-occurring psychiatric disorders and disparities in buprenorphine utilization in opioid use disorder: an analysis of insurance claims. Drug Alcohol Depend Rep. 2023;9:100195. https://doi.org/10.1016/j.dadr.2023.100195 PMID: 38023343
32. Bhatraju EP, Grossman E, Tofighi B, McNeely J, DiRocco D, Flannery M, et al. Public sector low threshold office-based buprenorphine treatment: outcomes at year 7. Addict Sci Clin Pract. 2017;12(1):7. https://doi.org/10.1186/s13722-017-0072-2 PMID: 28245872
33. Whitley SD, Kunins HV, Arnsten JH, Gourevitch MN. Colocating buprenorphine with methadone maintenance and outpatient chemical dependency services. J Subst Abuse Treat. 2007;33(1):85–90. https://doi.org/10.1016/j.jsat.2006.11.003 PMID: 17588493
34. Vakkalanka JP, Lund BC, Ward MM, Arndt S, Field RW, Charlton M, et al. Telehealth utilization is associated with lower risk of discontinuation of buprenorphine: a retrospective cohort study of US veterans. J Gen Intern Med. 2022;37(7):1610–8. https://doi.org/10.1007/s11606-021-06969-1 PMID: 34159547
35. Sweeney MM, Prichett L, Fingerhood MI, Antoine D, Umbricht A, Dunn KE, et al. Buprenorphine treatment retention and comorbidities among patients with opioid use disorder in a primary care setting. Am J Addict. 2022;31(3):256–60. https://doi.org/10.1111/ajad.13268 PMID: 35385169
36. Francis AG, Croll J, Vaishnav H, Langdon K, Beaudoin FL. Treatment retention in older versus younger adults with opioid use disorder: a retrospective cohort analysis from a large single center treatment program. R I Med J (2013). 2021;104(1):51–4. PMID: 33517601
37. Langabeer JR, Stotts AL, Cortez A, Tortolero G, Champagne-Langabeer T. Geographic proximity to buprenorphine treatment providers in the U.S. Drug Alcohol Depend. 2020;213:108131. https://doi.org/10.1016/j.drugalcdep.2020.108131

38. Amiri S, McDonell MG, Denney JT, Buchwald D, Amram O. Disparities in access to opioid treatment programs and office-based buprenorphine treatment across the rural-urban and area deprivation continua: A US Nationwide small area analysis. Value Health. 2021;24(2):188–95. https://doi.org/10.1016/j.jval.2020.08.2098 PMID: 33518025
39. Conway KP, Khoury D, Hilscher R, Aldridge AP, Parker SJ, Zarkin GA. Rural and urban differences in undersupply of buprenorphine provider availability in the United States, 2018. Addict Sci Clin Pract. 2022;17(1):5. https://doi.org/10.1186/s13722-021-00282-2 PMID: 35101112
40. Franz B, Cronin CE, Lindenfeld Z, Pagan JA, Lai AY, Krawczyk N, et al. Rural-urban disparities in the availability of hospital-based screening, medications for opioid use disorder, and addiction consult services. J Subst Use Addict Treat. 2024;160:209280. https://doi.org/10.1016/j.josat.2023.209280 PMID: 38142042
41. Joudrey PJ, Kolak M, Lin Q, Paykin S, Anguiano V Jr, Wang EA. Assessment of community-level vulnerability and access to medications for opioid use disorder. JAMA Netw Open. 2022;5(4):e227028. https://doi.org/10.1001/jamanetworkopen.2022.7028 PMID: 35438757
42. Landis RK, Levin JS, Saloner B, Gordon AJ, Dick AW, Sherry TB, et al. Sociodemographic differences in quality of treatment to Medicaid enrollees receiving buprenorphine. Subst Abus. 2022;43(1):1057–71. https://doi.org/10.1080/08897077.2022.2060424 PMID: 35442178
43. Al Faysal J, Noor-E-Alam M, Young GJ, Lo-Ciganic W-H, Goodin AJ, Huang JL, et al. An explainable machine learning framework for predicting the risk of buprenorphine treatment discontinuation for opioid use disorder among commercially insured individuals. Comput Biol Med. 2024;177:108493. https://doi.org/10.1016/j.compbiomed.2024.108493 PMID: 38833799
44. Chan B, Cook R, Levander X, Wiest K, Hoffman K, Pertl K, et al. Buprenorphine discontinuation in telehealth-only treatment for opioid use disorder: a longitudinal cohort analysis. J Subst Use Addict Treat. 2024;167:209511. https://doi.org/10.1016/j.josat.2024.209511 PMID: 39243979
45. Al Faysal J, Noor-E-Alam M, Young GJ, Lo-Ciganic W-H, Goodin AJ, Huang JL, et al. An explainable machine learning framework for predicting the risk of buprenorphine treatment discontinuation for opioid use disorder among commercially insured individuals. Comput Biol Med. 2024;177:108493. https://doi.org/10.1016/j.compbiomed.2024.108493 PMID: 38833799
46. Hasan MM, Young GJ, Shi J, Mohite P, Young LD, Weiner SG, et al. A machine learning based two-stage clinical decision support system for predicting patients' discontinuation from opioid use disorder treatment: retrospective observational study. BMC Med Inform Decis Mak. 2021;21(1):331. https://doi.org/10.1186/s12911-021-01692-7 PMID: 34836524
47. Foster JC, Taylor JMG, Ruberg SJ. Subgroup identification from randomized clinical trial data. Stat Med. 2011;30(24):2867–80. https://doi.org/10.1002/sim.4322 PMID: 21815180
48. Wilcox KE. Foundational Research Gaps and Future Directions for Digital Twins. Washington (DC): National Academies Press (US); 2024 [cited 2026 Feb 20]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK605515/
49. Baird A, Cheng Y, Xia Y. Use of machine learning to examine disparities in completion of substance use disorder treatment. PLoS One. 2022;17(9):e0275054. https://doi.org/10.1371/journal.pone.0275054 PMID: 36149868
50. Kong Y, Zhou J, Zheng Z, Amaro H, Guerrero EG. Using machine learning to advance disparities research: Subgroup analyses of access to opioid treatment. Health Serv Res. 2022;57(2):411–21. https://doi.org/10.1111/1475-6773.13896 PMID: 34657287
51. The Centers for Disease Control, Prevention and Agency for Toxic Substances and Disease Registry. Social Vulnerability Index [Internet]. 2024 [cited 2025 Jul 25]. Available from: https://www.atsdr.cdc.gov/place-health/php/svi/index.html
52. Dong H, Stringfellow EJ, Russell WA, Jalali MS. Racial and ethnic disparities in buprenorphine treatment duration in the US. JAMA Psychiatry. 2023;80(1):93–5. https://doi.org/10.1001/jamapsychiatry.2022.3673 PMID: 36350592
53. Stringfellow EJ, Lim TY, Dong H, Zhang Z, Jalali MS. The association between longitudinal trends in receipt of buprenorphine for opioid use disorder and buprenorphine-waivered providers in the United States. Addiction. 2023;118(11):2215–9. https://doi.org/10.1111/add.16291 PMID: 37434347
54. Sikka R, Xia F, Aubert RE. Estimating medication persistency using administrative claims data. Am J Manag Care. 2005;11(7):449–57. PMID: 16044982
55. Hansen RA, Dusetzina SB, Dominik RC, Gaynes BN. Prescription refill records as a screening tool to identify antidepressant non-adherence. Pharmacoepidemiol Drug Saf. 2010;19(1):33–7. https://doi.org/10.1002/pds.1881 PMID: 19998397
56. Dima AL, Dediu D. Computation of adherence to medication and visualization of medication histories in R with AdhereR: Towards transparent and reproducible use of electronic healthcare data. PLoS One. 2017;12(4):e0174426. https://doi.org/10.1371/journal.pone.0174426 PMID: 28445530
57. Dediu D, Allemann S, Dima A. AdhereR: Computation and visualisation of adherence to medications from Electronic Health care Data. 2025.
58. Chua KP, Nguyen TD, Zhang J, Conti RM, Lagisetty P, Bohnert AS. Trends in buprenorphine initiation and retention in the United States, 2016-2022. JAMA. 2023;329(16):1402–4. https://doi.org/10.1001/jama.2023.1207
59. Baxter JD, Clark RE, Samnaliev M, Aweh G, O'Connell E. Adherence to Buprenorphine Treatment Guidelines in a Medicaid Program. Subst Abus. 2015;36(2):174–82. https://doi.org/10.1080/08897077.2014.991469 PMID: 25706332
60. Center for Medicare and Medicaid Services. Office-Based Substance Use Disorder (SUD) Treatment Billing [Internet]. [cited 2025 Jul 28]. Available from: https://www.cms.gov/medicare/payment/opioid-treatment-programs-otp/billing-payment/office-based-substance-use-disorder-sud-treatment-billing
61. Lin LA, Casteel D, Shigekawa E, Weyrich MS, Roby DH, McMenamin SB. Telemedicine-delivered treatment interventions for substance use disorders: a systematic review. J Subst Abuse Treat. 2019;101:38–49. https://doi.org/10.1016/j.jsat.2019.03.007 PMID: 31006553

62. Dalli LL, Kilkenny MF, Arnet I, Sanfilippo FM, Cummings DM, Kapral MK, et al. Towards better reporting of the proportion of days covered method in cardiovascular medication adherence: a scoping review and new tool TEN-SPIDERS. Br J Clin Pharmacol. 2022;88(10):4427–42. https://doi.org/10.1111/bcp.15391 PMID: 35524398

63. Canfield SL, Zuckerman A, Anguiano RH, Jolly JA, DeClercq J, Wascher M, et al. Navigating the wild west of medication adherence reporting in specialty pharmacy. J Manag Care Spec Pharm. 2019;25(10):1073–7. https://doi.org/10.18553/jmcp.2019.25.10.1073 PMID: 31556829

64. Doshi-Velez F, Kim B. Towards A Rigorous Science of Interpretable Machine Learning [Internet]. arXiv; 2017 [cited 2025 Jul 30]. Available from: https://doi.org/10.48550/arXiv.1702.08608

65. Lundberg SM, Lee SI. A Unified Approach to Interpreting Model Predictions. In: Advances in Neural Information Processing Systems [Internet]. Curran Associates, Inc.; 2017 [cited 2025 Aug 12]. Available from: https://papers.nips.cc/paper_files/paper/2017/hash/8a20a8621978632d-76c43dfd28b67767-Abstract.html

66. R Core Team. R: A language and environment for statistical computing [Internet]. Vienna, Austria: R Foundation for Statistical Computing. Available from: https://www.R-project.org/

67. Posit team. RStudio: Integrated Development Environment for R [Internet]. Boston, MA: Posit Software, PBC; 2025. Available from: http://www.posit.co/

68. Kuhn M, Wickham H. Tidymodels: a collection of packages for modeling and machine learning using tidyverse principles [Internet]. 2020. Available from: https://www.tidymodels.org

69. Apsley HB, Brant K, Brothers S, Harrison E, Skogseth E, Schwartz RP, et al. Pregnancy- and parenting-related barriers to receiving medication for opioid use disorder: A multi-paneled qualitative study of women in treatment, women who terminated treatment, and the professionals who serve them. Womens Health (Lond). 2024;20. https://doi.org/10.1177/17455057231224181 PMID: 38362719

70. Crawford AD, McGlothen-Bell K, Recto P, McGrath JM, Scott L, Brownell EA, et al. Stigmatization of pregnant individuals with opioid use disorder. Womens Health Rep (New Rochelle). 2022;3(1):172–9. https://doi.org/10.1089/whr.2021.0112 PMID: 35262054

71. Schulman M, Asko AJ, Center for Health Care Strategies. Opportunities to Promote Medications for Opioid Use Disorder in Federally Qualified Health Centers [Internet]. 2024 [cited 2025 Aug 1]. Available from: https://www.chcs.org/resource/opportunities-to-promote-medications-for-opioid-use-disorder-in-federally-qualified-health-centers/

72. Litz M, Leslie D. The impact of mental health comorbidities on adherence to buprenorphine: a claims based analysis. Am J Addict. 2017;26(8):859–63. https://doi.org/10.1111/ajad.12644 PMID: 29143483

73. Bailey SR, Lucas JA, Angier H, Cantone RE, Fleishman J, Garvey B, et al. Associations of retention on buprenorphine for opioid use disorder with patient characteristics and models of care in the primary care setting. J Subst Abuse Treat. 2021;131:108548. https://doi.org/10.1016/j.jsat.2021.108548 PMID: 34244013

74. Tran LT, McKetin R, Clark B, Macdonald C, Zahra E, Arunogiri S, et al. The association between mental disorders and treatment retention among people with opioid use disorder receiving opioid agonist treatment: a systematic review and meta-analysis. Drug Alcohol Depend. 2025;274:112768. https://doi.org/10.1016/j.drugalcdep.2025.112768 PMID: 40582093

75. Jones CM, McCance-Katz EF. Co-occurring substance use and mental disorders among adults with opioid use disorder. Drug Alcohol Depend. 2019;197:78–82. https://doi.org/10.1016/j.drugalcdep.2018.12.030 PMID: 30784952

76. Andraka-Christou B, Simon KI, Bradford WD, Nguyen T. Buprenorphine treatment for opioid use disorder: comparison of insurance restrictions, 2017-21. Health Aff (Millwood). 2023;42(5):658–64. https://doi.org/10.1377/hlthaff.2022.01513 PMID: 37126752

77. Martin K. Is Treatment for Opioid Use Disorder Affordable for Those with Public or Private Health Coverage? Foundations for Opioid Response Effects. 2021.

78. Presskreischer R, Mojtabai R, Mauro C, Zhang Z, Wall M, Olfson M. Medicaid expansion and medications to treat opioid use disorder in outpatient specialty care from 2010 to 2020. J Subst Use Addict Treat. 2025;168:209568. https://doi.org/10.1016/j.josat.2024.209568 PMID: 39505113

79. Keshwani S, Maguire M, Goodin A, Lo-Ciganic W-H, Wilson DL, Hincapie-Castillo JM. Buprenorphine use trends following removal of prior authorization policies for the treatment of opioid use disorder in 2 state medicaid programs. JAMA Health Forum. 2022;3(6):e221757. https://doi.org/10.1001/jamahealthforum.2022.1757 PMID: 35977240

80. Samples H, Williams AR, Crystal S, Olfson M. Psychosocial and behavioral therapy in conjunction with medication for opioid use disorder: patterns, predictors, and association with buprenorphine treatment outcomes. J Subst Abuse Treat. 2022;139:108774. https://doi.org/10.1016/j.jsat.2022.108774 PMID: 35337716

81. Krawczyk N, Williams AR, Saloner B, Cerdá M. Who stays in medication treatment for opioid use disorder? A national study of outpatient specialty treatment settings. J Subst Abuse Treat. 2021;126:108329. https://doi.org/10.1016/j.jsat.2021.108329 PMID: 34116820

82. Groeger JL, Lu T, Jakubowski A, Zhang C, Deng Y, Perez H. Older age is associated with long-term retention in buprenorphine treatment for opioid use disorder. J Am Geriatr Soc. 2026. https://doi.org/10.1111/jgs.70274 PMID: 41579867

83. Andrilla CHA, Coulthard C, Larson EH. Barriers rural physicians face prescribing buprenorphine for opioid use disorder. Ann Fam Med. 2017;15(4):359–62. https://doi.org/10.1370/afm.2099 PMID: 28694273

84. Hollander MAG, Chang C-CH, Douaihy AB, Hulsey E, Donohue JM. Racial inequity in medication treatment for opioid use disorder: exploring potential facilitators and barriers to use. Drug Alcohol Depend. 2021;227:108927. https://doi.org/10.1016/j.drugalcdep.2021.108927 PMID: 34358766