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Comparative Real-world Effectiveness of Medications for Opioid Use Disorder

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OHDSI Community Call

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Opioid Epidemic

- Opioid epidemic is a complex public health crisis in the US.
- In 2020, 2.7 million people aged 12 or older in the US had an opioid use disorder (OUD).
- Of the 107,622 drug overdose deaths in 2021, about 75% of them involved opioids.

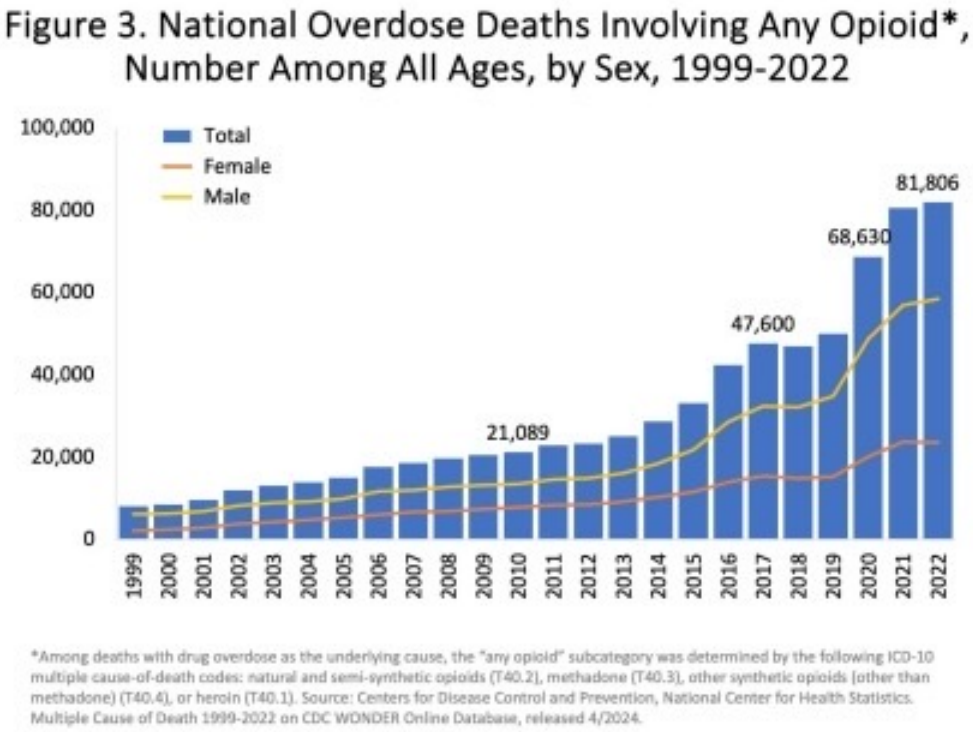


Figure: NIDA; Source: CDC WONDER

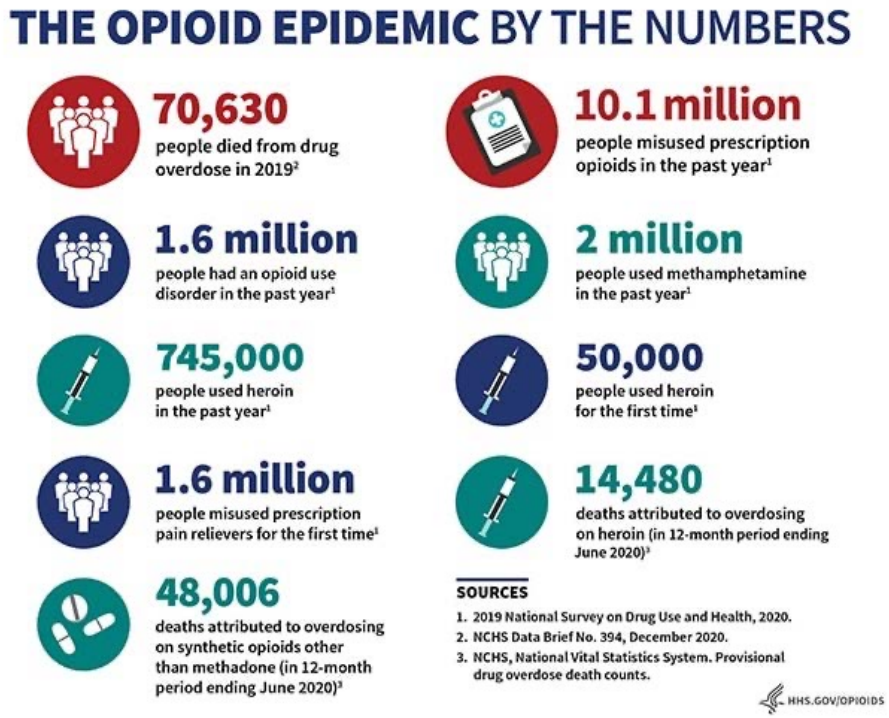


Figure: HHS

Medications for OUD (MOUD)

- 3 FDA-approved medications for opioid use disorder (MOUD) are effective for lowering the risk of OUD and opioid overdose based on trial results.
  - **Methadone**
  - **Buprenorphine**
  - Naltrexone
- Real-world effectiveness can be affected by availability and dosing frequency.

Medication	Mechanism of action	Route of administration	Dosing frequency	Available through
Methadone	Full agonist	Available in pill, liquid, and wafer forms	Daily	Opioid treatment program
Buprenorphine	Partial agonist	Pill or film (placed inside the cheek or under the tongue)	Daily	Any prescriber with the appropriate waiver
		Implant (inserted beneath the skin)	Every six months	
Naltrexone	Antagonist	Oral formulations	Daily	Any health care provider with prescribing authority
		Extended-release injectable formulation	Monthly	

MOUD and Healthcare Visits

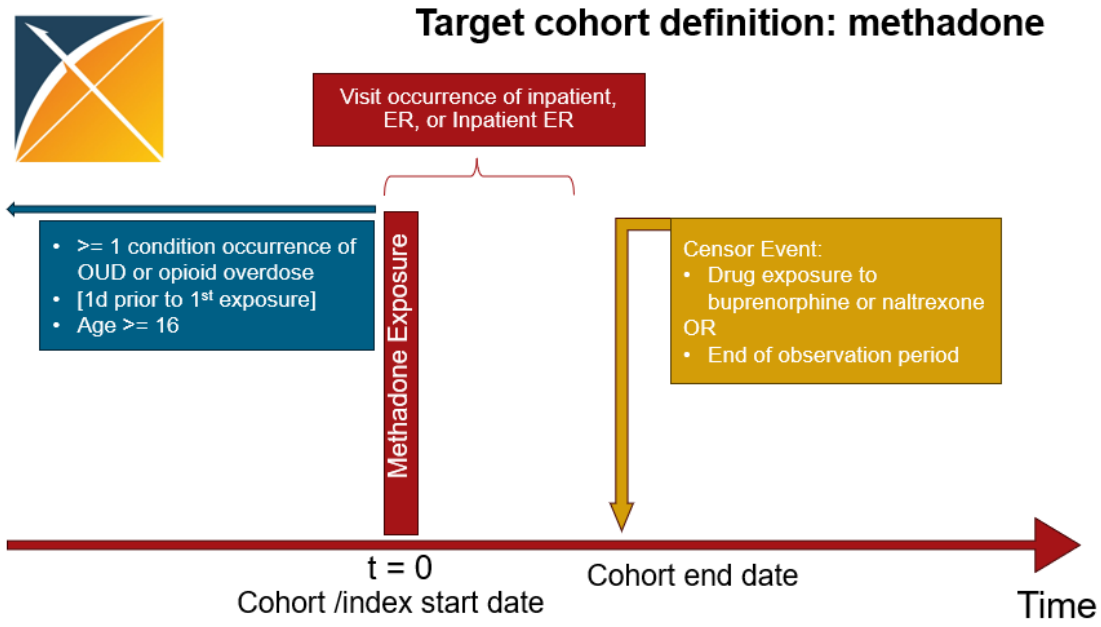
- Goal: Estimating the **comparative effectiveness** of methadone vs buprenorphine in **reducing opioid-related acute care use** (emergency department or inpatient visits) among OUD patients.
- Question: Is methadone more effective in reducing opioid-related acute care use relative to buprenorphine in patients with OUD?
- Design: A retrospective comparative intent-to-treat cohort study

Study design

- Target: Methadone
- Comparator: Buprenorphine
- 3 outcomes: Acute care use defined as inpatient, ER, or inpatient ER visit with a diagnosis of
  - OUD or opioid overdose
  - OUD
  - Opioid overdose

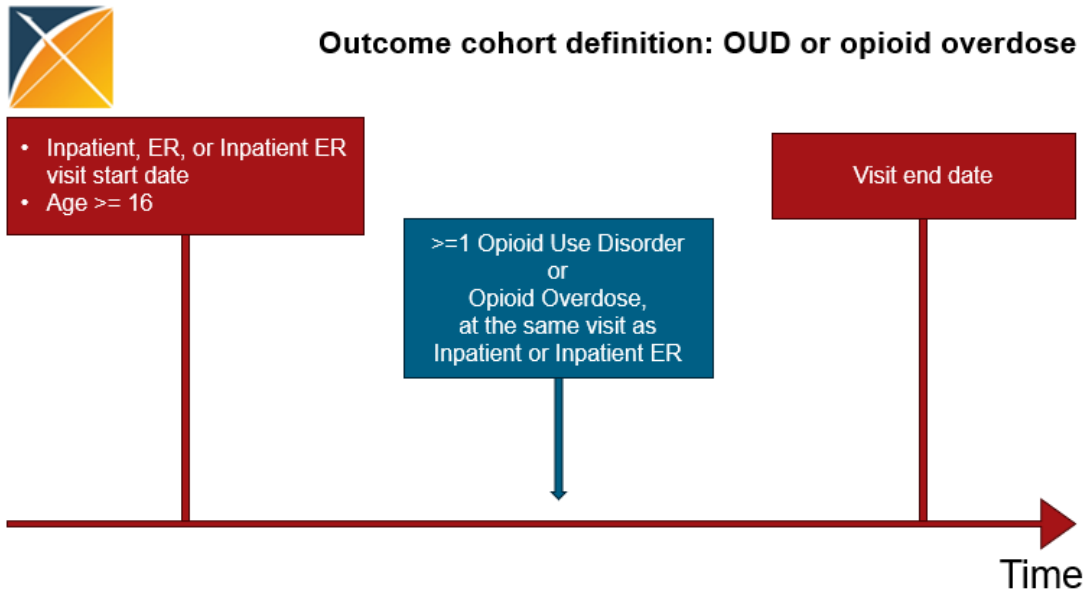
Target / Comparator Cohort Definitions

Cohort name	Entry event / Inclusion criteria	Exit criteria
Methadone (target)	• At least 1 drug exposure to **methadone** during an inpatient, ER, or inpatient ER visit caused by OUD or opioid overdose. • At least 16 years old.	• End of observation period. • Switched drug to buprenorphine or naltrexone.
Buprenorphine (comparator)	• At least 1 drug exposure to **buprenorphine** during an inpatient, ER, or inpatient ER visit caused by OUD or opioid overdose. • At least 16 years old.	• End of observation period. • Switched drug to methadone or naltrexone.



Outcome Cohort Definitions

Cohort name	Cohort size	Entry event / inclusion criteria	Exit criteria
OUD or opioid overdose	36166	• At least 1 inpatient, ER, or inpatient ER visit due to OUD or opioid overdose. • At least 16 years old.	• End of observation period.
OUD	31062	• At least 1 inpatient, ER, or inpatient ER visit due to OUD. • At least 16 years old.	• End of observation period.
Opioid overdose	11580	• At least 1 inpatient, ER, or inpatient ER visit due to opioid overdose. • At least 16 years old.	• End of observation period.



Data

- Type: Electronic health records (EHRs)
- Source: Data are from the BJC HealthCare network
  - 14 hospitals
  - ~2 million patients
- Format: OMOP common data model v5.3

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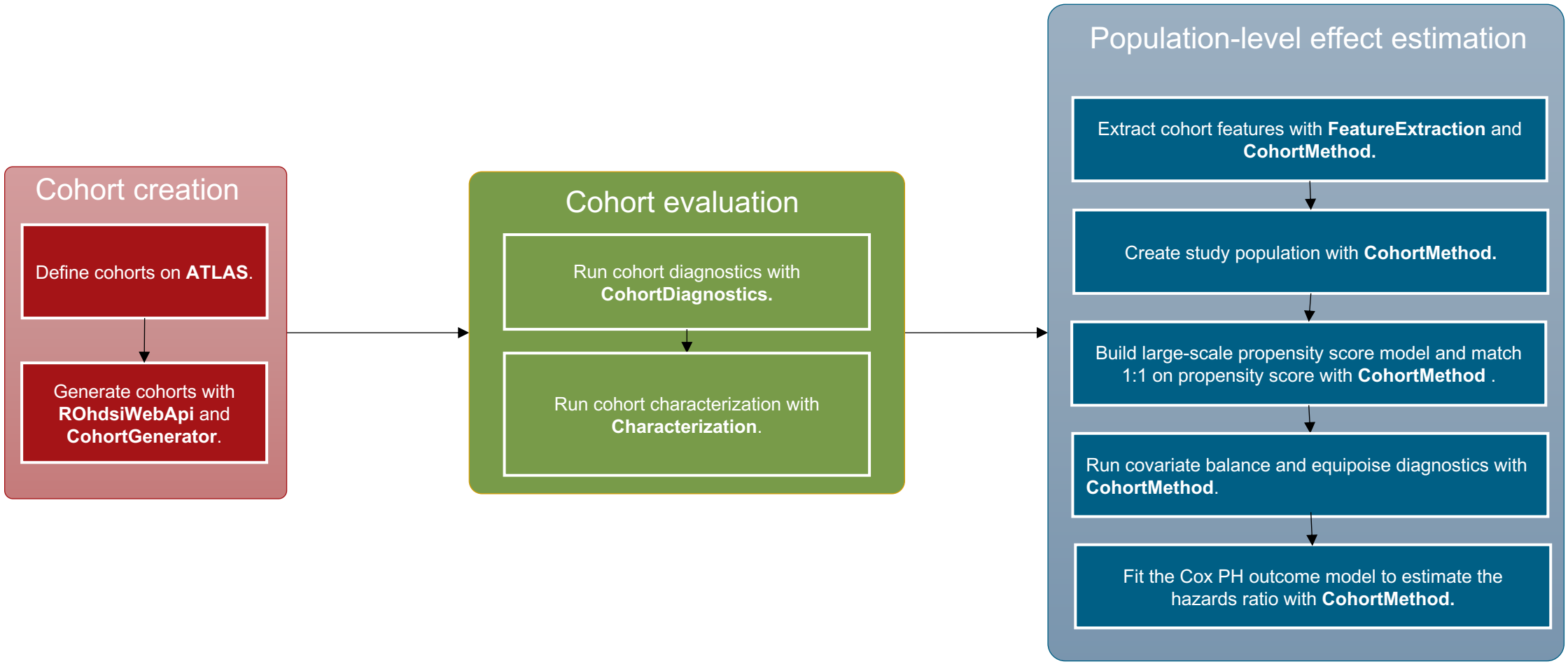
Workflow



Results

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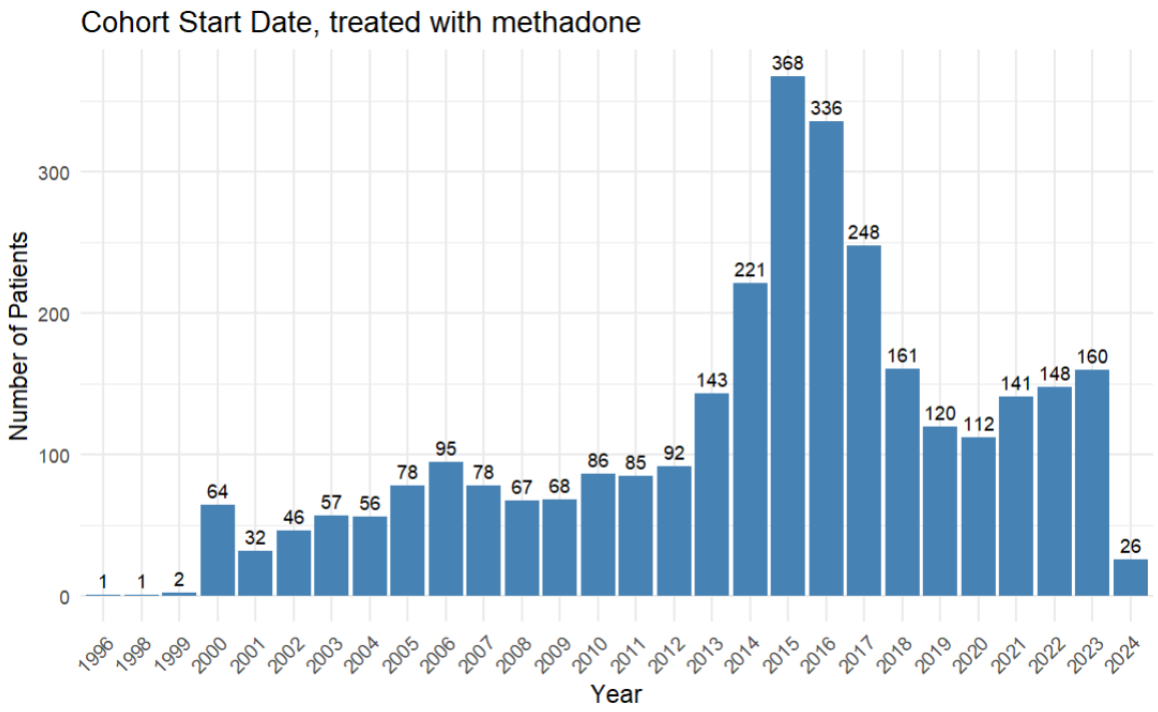
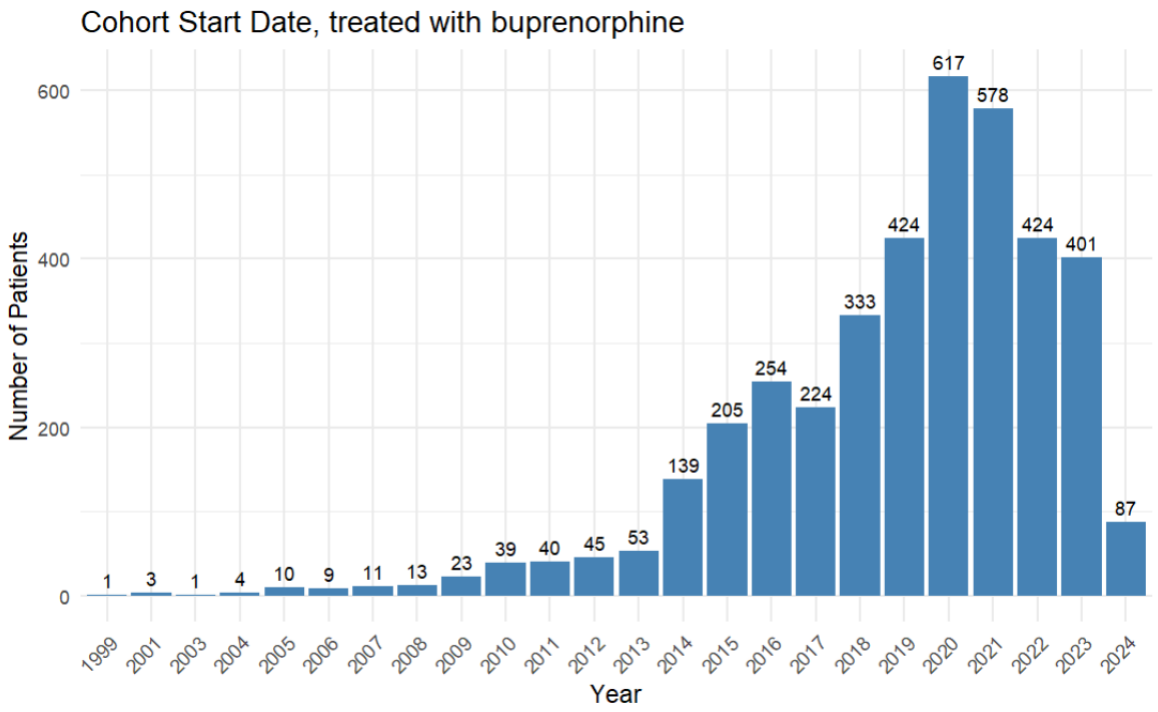
Cohort Characterization by Calendar Year

Methadone



Buprenorphine



Demographics

	Before matching			After matching		
	Target	Comparator		Target	Comparator	
Characteristic	%	%	Std. diff	%	%	Std. diff
Age group						
15 - 19	1	1.1	-0.02	0.2	1.1	**-0.11**
20 - 24	7.6	7.5	0.01	7.4	5.4	0.08
25 - 29	16.5	15.9	0.02	14.8	13.6	0.04
30 - 34	17.3	18	-0.02	17.6	16.6	0.03
35 - 39	14.1	15.5	-0.04	15.6	14.7	0.02
40 - 44	9.8	12.9	-0.1	12.4	12.5	0
45 - 49	8.3	9	-0.02	8.5	7.8	0.03
50 - 54	7.3	6.2	0.04	6.7	7.3	-0.02
55 - 59	7.2	5.3	0.08	6.4	7.8	-0.05
60 - 64	5.6	4.7	0.04	4.8	7	-0.09
65 - 69	3	2.6	0.03	3	4.1	-0.06
70 - 74	1.4	0.8	0.07	1.9	1.1	0.06
75 - 79	0.5	0.3	0.03	0.4	0.5	-0.02
80 - 84	0.3	0.1	0.03	0.4	0.4	0
85 - 89	0.1	0	0.03		0.1	
90 - 94		0				
120 - 124		0				
Gender: female	52	44.1	**0.16**	50.6	51.5	-0.02
Race						
race = Asian	0.2	0.2	0	0.5		
race = Black or African American	28.4	30	-0.04	27.1	26.6	0.01
race = White	65.9	67	-0.02	69.6	69	0.01
race = American Indian or Alaska Native	0.2	0.3	0	0.2		
race = Black	0.9	0	**0.13**		0.1	
race = Other Pacific Islander	0	0.1	-0.04	0.1		
Ethnicity						
ethnicity = Hispanic or Latino	0.9	1.1	-0.02	1.6	1.7	-0.01
ethnicity = Not Hispanic or Latino	72.7	90.5	**-0.47**	88.9	85.5	0.1

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Medical history

	Target	Comparator		Target	Comparator	
	Before matching			After matching		
Characteristic	%	%	Std. diff	%	%	Std. diff
Medical history: General						
Hypertensive disorder	29.4	26.8	0.06	28.8	31.3	-0.05
Depressive disorder	27.1	31.6	-0.1	29.3	31.1	-0.04
Viral hepatitis C	19.4	20	-0.01	22.9	24.4	-0.03
Acute respiratory disease	15.6	14.3	0.04	15.6	15.2	0.01
Osteoarthritis	14.4	10.7	**0.11**	11.1	15.7	**-0.13**
Renal impairment	12.6	10.9	0.05	14.8	14.1	0.02
Gastroesophageal reflux disease	12.3	9.8	0.08	10.9	13.6	-0.08
Urinary tract infectious disease	12.2	7.8	**0.15**	9	10.1	-0.04
Hyperlipidemia	10.6	7.9	0.1	10.9	12.9	-0.06
Pneumonia	10.3	7.3	**0.11**	11.5	12	-0.02
Chronic obstructive lung disease	10.1	8.6	0.05	9.3	10.1	-0.03
Chronic liver disease	10.1	8.1	0.07	11.9	11.5	0.01
Diabetes mellitus	9.7	7.8	0.07	8.9	11.4	-0.08
Obesity	7.9	6.8	0.04	9.4	8	0.05
Lesion of liver	3.7	2.4	0.08	3.3	3.5	-0.01
Gastrointestinal hemorrhage	3.2	2.6	0.04	2.7	3.8	-0.06
Schizophrenia	2.4	5.6	**-0.16**	4.1	3.6	0.03
Rheumatoid arthritis	1.9	1.4	0.04	1.9	1.6	0.02
Attention deficit hyperactivity disorder	1.7	3.7	**-0.12**	2.6	3.3	-0.04
Human immunodeficiency virus infection	1.6	1.3	0.02	1.7	1.1	0.05
Crohn's disease	1.1	0.8	0.03	0.5	1.1	-0.07
Dementia	0.6	0.6	0	0.5	1.2	-0.08
Psoriasis	0.5	0.7	-0.03	0.4	0.9	-0.06
Ulcerative colitis	0.3	0.3	0.01		0.9	

	Target	Comparator		Target	Comparator	
	Before matching			After matching		
Characteristic	%	%	Std. diff	%	%	Std. diff
Medical history: Cardiovascular disease						
Heart disease	24.9	16.7	**0.2**	24	24.7	-0.02
Heart failure	7.1	5	0.09	7.9	8	0
Coronary arteriosclerosis	5.9	3.8	0.1	4.1	6.6	**-0.11**
Ischemic heart disease	5.8	4.1	0.08	5.3	6.8	-0.06
Venous thrombosis	3.5	2.2	0.08	3.2	3.8	-0.03
Pulmonary embolism	3.1	2	0.07	4.2	4.3	-0.01
Cerebrovascular disease	2.8	1.3	**0.11**	1.9	2.6	-0.05
Peripheral vascular disease	2.8	1.9	0.06	2.2	3.2	-0.06
Atrial fibrillation	2.6	2	0.04	2.6	3.3	-0.04

Medical history: Neoplasms						
Malignant neoplastic disease	6.8	2.6	**0.2**	4.3	5.8	-0.07
Malignant tumor of lung	1.3	0.2	**0.14**	0.5	0.7	-0.03
Malignant tumor of breast	0.6	0.3	0.06	0.1	0.5	-0.07
Malignant lymphoma	0.5	0.4	0.03	0.1	0.6	-0.08
Malignant neoplasm of anorectum	0.4	0.1	0.08	0.2	0.1	0.03
Malignant tumor of colon	0.4	0.1	0.07	0.2	0.4	-0.02
Malignant tumor of urinary bladder	0.2	0	0.06	0.1	0.1	0
Primary malignant neoplasm of prostate	0.2	0.1	0.02	0.1	0.1	0

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Medication use

	Target	Comparator		Target	Comparator	
	Before matching			After matching		
Characteristic	%	%	Std. diff	%	%	Std. diff
Medication use						
Psycholeptics	79.4	75.1	0.1	73.4	73.9	-0.01
Drugs for acid related disorders	77.7	63.9	**0.3**	66	69.3	-0.07
Antiinflammatory and antirheumatic products	67.2	64	0.07	63	63.5	-0.01
Antithrombotic agents	58.1	36.7	**0.43**	53.8	59.1	**-0.11**
Opioids	54.1	36.2	**0.36**	49.1	54	-0.1
Antibacterials for systemic use	53.8	44.1	**0.19**	53.4	55.4	-0.04
Antiepileptics	47.7	36	**0.24**	28.9	34.7	**-0.12**
Antidepressants	38.2	46.3	**-0.16**	38.2	37.8	0.01
Drugs for obstructive airway diseases	36.5	29.1	**0.16**	35.2	38.7	-0.07
Beta blocking agents	17.2	13.3	**0.11**	15.9	18.8	-0.08
Diuretics	16.3	11.3	**0.15**	14.3	16.8	-0.07
Drugs used in diabetes	14.5	8.9	**0.18**	11.5	14.2	-0.08
Agents acting on the renin-angiotensin system	13.8	10.6	0.1	13.2	14.5	-0.04
Calcium channel blockers	11.5	10	0.05	11.7	12.9	-0.03
Lipid modifying agents	10.2	9	0.04	10.3	13.2	-0.09
Antineoplastic agents	5.2	2.6	**0.14**	3.8	4.6	-0.04
Psychostimulants, agents used for adhd and nootropics	3	4	-0.05	3.8	3.3	0.03
Immunosuppressants	2.1	1.5	0.05	1.9	2.5	-0.04
Antipsoriatics	1.2	1.4	-0.02	1.5	1.7	-0.02

Incidence rate

Outcome: OUD or opioid overdose

Cohort name	Patients at risk	Number of Outcome	Person-years	Incidence rate (per 1000 person-years)
Methadone	4942	1568	21046.67	74.501092
Buprenorphine	6258	2310	13476.30	171.41198

Outcome: OUD

Cohort name	Patients at risk	Number of Outcome	Person-years	Incidence rate (per 1000 person-years)
Methadone	4942	1613	21046.84	76.6386
Buprenorphine	6258	2416	13476.79	179.2711

Outcome: opioid overdose

Cohort name	Patients at risk	Number of Outcome	Person-years	Incidence rate (per 1000 person-years)
Methadone	4942	430	21046.84	20.43062
Buprenorphine	6258	472	13476.79	35.02317

Population-Level Effect Estimation

- Large-scale propensity score (LSPS) was used to match target and comparator with 1:1 propensity score matching
  - Adjust for 41,202 pre-treatment covariates
- Cox proportional hazards model was used to estimate the risk of inpatient or ED visit because of OUD

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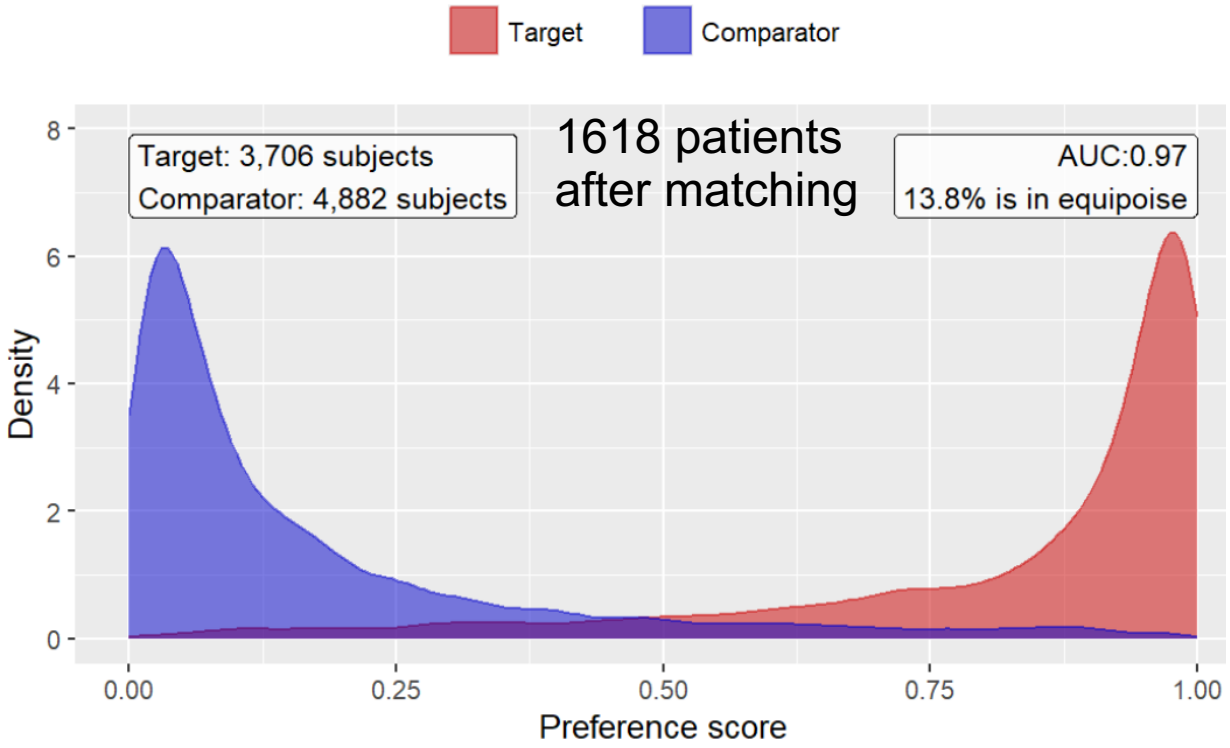
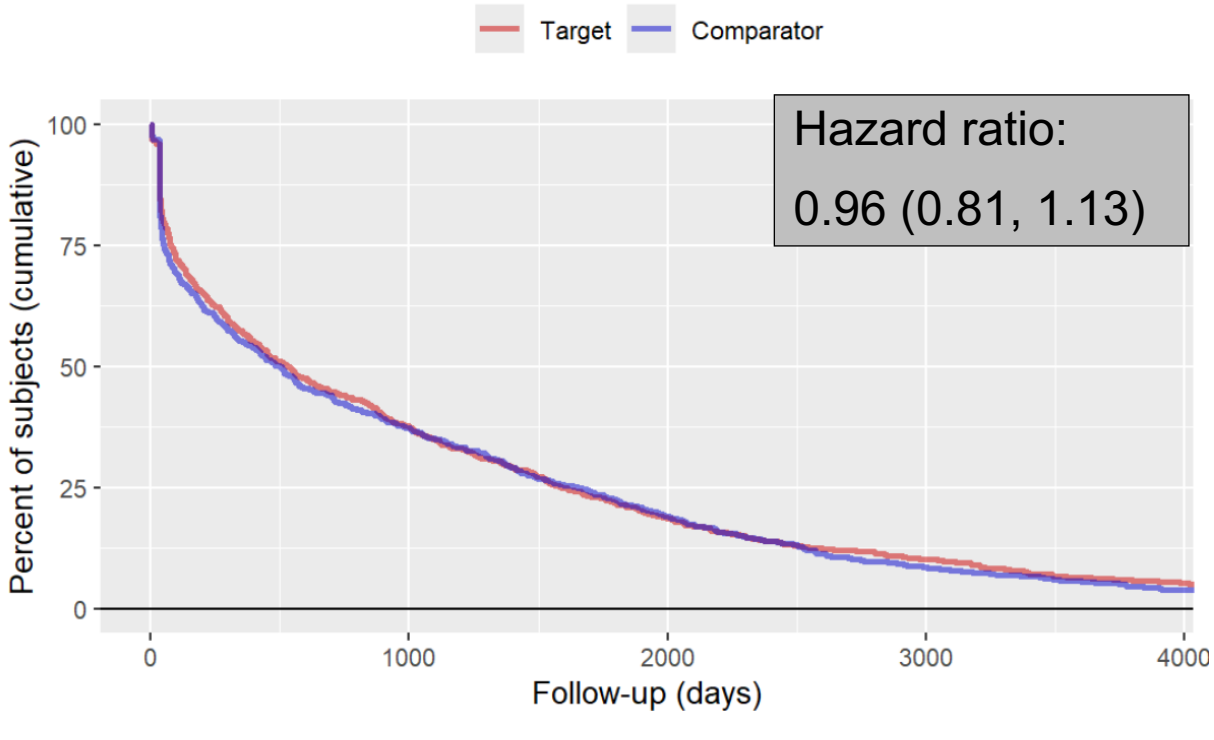
Effect on OUD or Opioid Overdose

Target: methadone
Comparator: buprenorphine
Outcome: **OUD + overdose**





Conclusion: No significant difference between methadone and buprenorphine in reducing OUD or opioid overdose related ER or inpatient visits.

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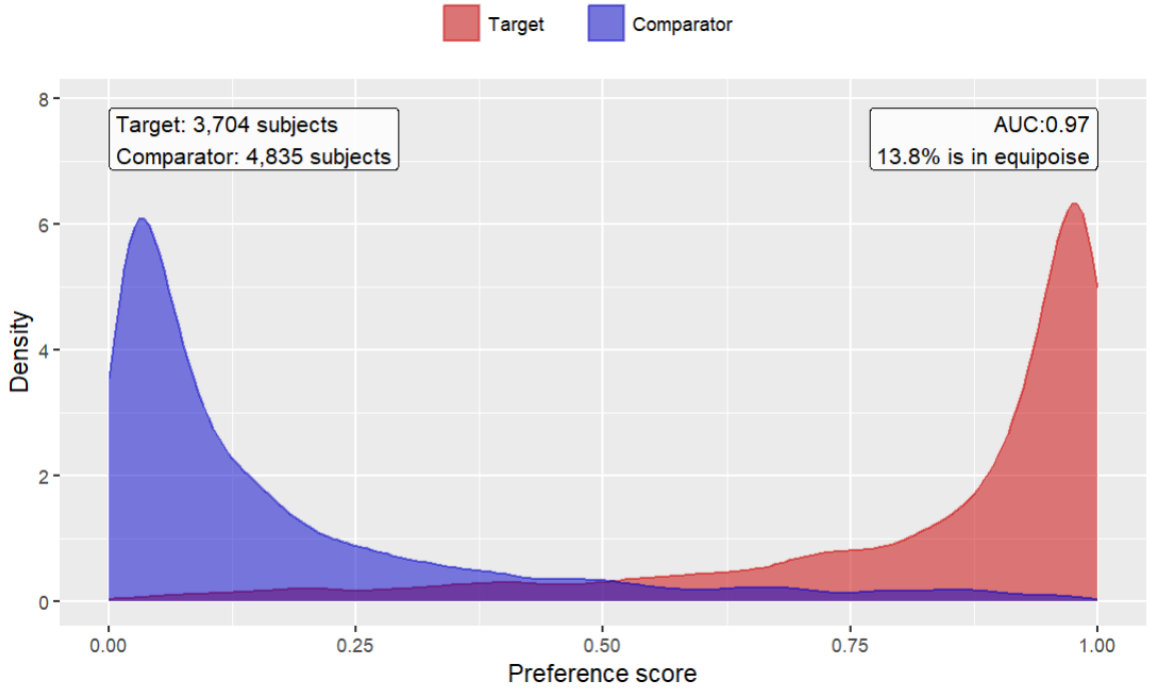
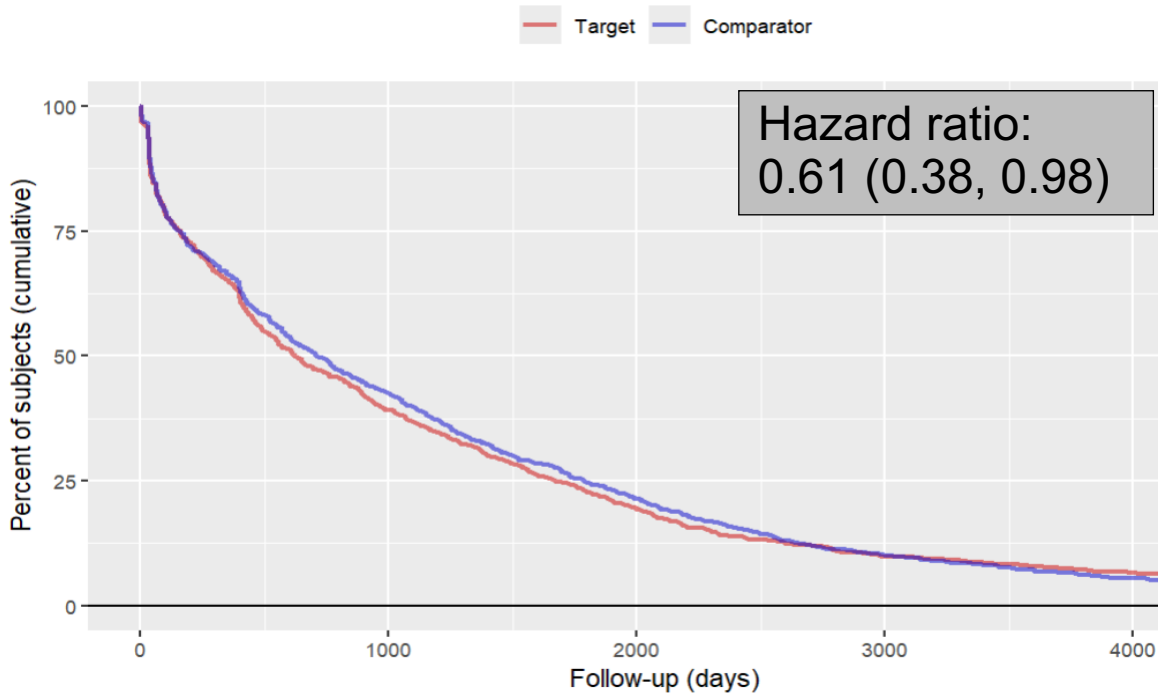
Effect on Opioid Overdose

Target: methadone
Comparator: buprenorphine
Outcome: **overdose**





Conclusion: Methadone was associated with a significantly lower risk of opioid overdose visits compared to buprenorphine.

Results

Outcome	Hazard Ratio with 95% CI
OUD or opioid overdose	0.96 (0.81, 1.13)
OUD	0.95 (0.80, 1.11)
Opioid overdose	0.61 (0.38, 0.98)

Discussion and Conclusion

- Methadone was associated with lower risk of opioid overdose-related acute care visits.
- Methadone and buprenorphine had similar effect on reducing OUD or overdose acute care visits.
- Treatment effect can vary among patients.
  - Individualized effect estimation can reveal the effect heterogeneity.
- Looking for data partner! If interested, please reach out to linyingz [at] wustl.edu

Documentation

- Study GitHub repository: https://github.com/causailab/RWE-MOUD
- Study protocol: https://github.com/causailab/RWE-MOUD/blob/master/Protocol.html

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