

**Appendix:**

**eTable 1: London Intercommunity Health Centre (LIHC) Safer Opioid Supply (SOS) program description and characteristics**

<b>Program element</b>	<b>Description</b>
<b>Program genesis</b>	<p>- The SOS program was started in 2016 by Dr. Andrea Sereda and was aimed primarily at LIHC clients who were experiencing multiple health conditions due to their injection drug use (i.e. infectious complications, HIV infection, HCV infection), and who were experiencing homelessness, were street-involved, involved in street-based sex work, and were disconnected from traditional models of healthcare delivery. As part of the broader Health Outreach programming offered by LIHC that provides support for people experiencing homelessness or who are heavily street-involved in London, Ontario, the SOS program was informed by the recognition that traditional healthcare, substance use and addiction treatment programs were not meeting the needs of these clients.</p> <p>- The program began with three clients who were heavily street-involved, and who were in a cycle of frequent hospital admissions due to overdose and infectious complications from injection drug use. Traditional OAT treatment programs had not been successful in retaining these clients, despite multiple attempts at treatment.</p> <p>- Following their hospital admissions, these clients were often released with a ‘weaning’ prescription of hydromorphone, and Dr. Sereda observed that while on this weaning prescription they stabilized, were able to engage with healthcare and were not buying from the street supply of opioids. However, when their weaning prescriptions ran out, they would return to buying unregulated opioids on the street, and their health would deteriorate again. So, Dr. Sereda began continuing their hydromorphone prescriptions. By providing these individuals with a prescription for pharmaceutical hydromorphone, they stopped buying opioids from the street and were able to re-engage with healthcare.</p> <p>- Early clinical observations also noted that clients’ hospital admissions decreased dramatically, which informed the choice of outcomes for this study.</p>
<b>Approach to care</b>	<p>- Harm Reduction: The SOS program uses harm reduction as the guiding philosophy of care, and aims to be firmly rooted in the voices of people who use drugs and developed with their guidance.</p> <p>- Primary Care: The SOS program is embedded in a community health centre that provides low threshold primary care. Every client in the SOS program becomes a family practice patient at the community health centre, and receives comprehensive primary care alongside their SOS prescriptions.</p>
<b>Program eligibility criteria</b>	<p>- The SOS program began slowly and was initially offered to people who LIHC physicians believed to be at high risk of imminent death due to unmanaged health conditions associated with their injection drug use (such as recurrent infective endocarditis or untreated HIV).</p>

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	<ul style="list-style-type: none"> <li>- Priority was also given to people who were having difficulty engaging with healthcare or with retention in treatment because their drug use, homelessness or street-involvement could not be accommodated within a traditional healthcare delivery model.</li> <li>- A chart review conducted in 2019 found high levels of medical and social complexity among SOS clients at intake: <ul style="list-style-type: none"> <li>- 40% of clients had been using drugs by injection for over 10 years;</li> <li>- 100% of patients had opioids detected on urine drug screening at intake;</li> <li>- 83% of clients has crystal methamphetamine detected on urine drug screening at intake;</li> <li>- 62% were homeless on intake, with 100% having ever had an experience of homelessness;</li> <li>- 45% reported currently working in sex work;</li> <li>- 99% of clients reported receiving income from income support programs.</li> </ul> </li> <li>- Prior to 2019, many of the clients admitted into the program were internal referrals, with clients of the Health Outreach Team who were experiencing sustained, negative health and social impacts from their drug use being prioritized for admission. As the program expanded, the growing demand for the SOS program from within the community could not be accommodated by LIHC staff. In order to ensure that the people most in need were able to access the SOS program, the following eligibility criteria were developed<sup>1</sup>: <ul style="list-style-type: none"> <li>- Patterns of opioid use consistent with opioid use disorder;</li> <li>- Long term injection drug use (more than two years);</li> <li>- Self-report of regular street-acquired drug use;</li> <li>- Complications of injection drug use (e.g., endocarditis, abscess, HIV);</li> <li>- High risk of death without intervention;</li> <li>- Positive urine drug screen for opioids (to confirm recent use);</li> <li>- Capacity for informed consent (to understand potential risks and benefits of treatment);</li> <li>- Poor psychosocial functioning (e.g. homelessness; disengaged from health care and social services; involvement in criminal activity to support drug use; involvement in sex work).</li> </ul> </li> </ul>
<p><b>Intake process</b></p>	<ul style="list-style-type: none"> <li>- If a client meets the eligibility criteria and there is capacity in the SOS program, they meet with the systems navigator, who helps to assess their individual needs and circumstances. Once their individual needs are identified, clients are referred to both health and social services.</li> <li>- Health services include: comprehensive primary care (including treatment for asthma, diabetes, HIV, hepatitis C); comprehensive sexual health care and screenings; regular preventative health care (cancer screenings and vaccinations). More specialized medical care is also available by referral.</li> <li>- Social services include: harm reduction education and access to equipment and supplies; assistance accessing food programs and other basic needs (e.g., hygiene supplies, clothes); housing support including help finding housing or to prevent housing loss; assistance with transportation to appointments; accompaniment for appointments; advocacy for clients (on issues like accessing income, housing, or in</li> </ul>

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	the justice system); community outreach; counseling and supportive listening for clients.
<b>Program waitlist</b>	<p>- An internal program evaluation with people on the waitlist for the SOS program found that the major reasons for wanting to be part of the program included<sup>2</sup>:</p> <ul style="list-style-type: none"> <li>- A desire to reduce fentanyl use and reduce risk of overdose;</li> <li>- A desire to reduce involvement in criminal activities to acquire drugs, to reduce involvement in street hustles, and to reduce involvement with sex work;</li> <li>- A desire for improved health and stability.</li> </ul>
<b>Medications</b>	<p>- The main medication prescribed in the SOS program is immediate-release hydromorphone tablets (primarily Dilaudid brand, due to this tablet's ease of dissolution into solution). Titration follows the schedule outlined in the SOS guiding document.<sup>3</sup></p> <p>- immediate-release hydromorphone is generally provided as a daily dispensed prescription that may be filled at a local pharmacy of the client's choice. Clients have the choice to use their prescriptions where they are most comfortable, by the route of administration (orally or by injection) that they prefer.</p> <p>- Hydromorphone is typically used by clients to obtain a euphoric effect, though many clients also use hydromorphone to manage withdrawal and cravings on an "as-needed" basis.</p> <p>- Slow-release oral morphine is often prescribed as a long-acting opioid medication "backbone" alongside hydromorphone, in order to suppress withdrawal symptoms. Due to concern about the potential for injection of long-acting opioid formulations to contribute to infective endocarditis<sup>4,5</sup> and HIV transmission<sup>6</sup>, long-acting opioids are generally prescribed as an oral, observed dose to be taken once a day at the pharmacy .</p> <p>- The use of immediate-release hydromorphone and choice of medications are determined primarily by the medications available for coverage on the Ontario Drug Benefit (ODB) formulary. Diacetylmorphine, fentanyl formulations (tablets or injectable) and high-dose injectable formulations of hydromorphone are not covered on the ODB formulary, and are not prescribed within the LIHC program. However, program evaluation results report that SOS program clients were interested in expanded medication options and that the lack of availability of high-dose injectable and other opioid formulations was a major obstacle in meeting client's needs.<sup>2</sup></p>

**eTable 2: Database Definitions**

<b>Database Name</b>	<b>Description</b>	<b>Use in Study</b>
Narcotics Monitoring System	All outpatient dispensing of controlled substances in Ontario, regardless of insurance status.	To define opioid and benzodiazepine dispensing

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Ontario Drug Benefit (ODB) database	All publicly-funded medications dispensed from community pharmacies in Ontario	To determine eligibility for public drug benefits, and to capture publicly-funded medication use and associated costs.
Ontario Health Insurance Plan (OHIP) database	Billing claims for all physician services provided in Ontario	To define patient comorbidities and health services utilization.
OHIP Registered Persons Database	Demographic information, vital status and postal code for all Ontarians with a health card.	To determine age, sex, date of death and geographic variables (e.g. rurality of residence).
Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD)	Diagnostic and procedural data for all inpatient hospital stays in Ontario	To define patient comorbidities and health services utilization
CIHI National Ambulatory Care Reporting System (NACRS)	Diagnostic and procedural data for all emergency department visits in Ontario	To define patient comorbidities and health services utilization
CIHI Ontario Mental Health Reporting System (OMHRS)	Diagnostic and procedural data for all admissions to designated inpatient mental health beds in Ontario	To define patient comorbidities and health services utilization
Ontario HIV Database	A validated administrative data registry of Ontario residents diagnosed with HIV (sensitivity and specificity of 96.2% and 99.6%, respectively).	To determine HIV diagnosis as baseline characteristic and matching variable.
Drug and Drug-Alcohol Related Death Database	Captures all deaths that are investigated by a coroner in Ontario where an opioid was determined to contribute to the cause of death. In Ontario, all sudden and unexpected deaths are required by law to be investigated by a medical coroner, with post-mortem toxicology completed in any cases where drugs are suspected. Therefore, this is considered to be a highly accurate database reflective of opioid-related deaths occurring across the province.	To determine any opioid-related deaths that occurred during follow-up.

**eTable 3: Definition of Opioid Use Disorder**

Data Source	Codes
DAD,	<ul style="list-style-type: none"> <li>DAD/NACRS/OMHRS database:</li> </ul>

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NACRS, OHIP, OMHRS	<ul style="list-style-type: none"> <li>○ ICD-10 code: F11</li> <li>● OMHRS database <ul style="list-style-type: none"> <li>○ DSM-IV/ DSM-V: 304.00, 305.50</li> </ul> </li> <li>● OHIP database <ul style="list-style-type: none"> <li>○ Fee codes: K682, K683, K684</li> </ul> </li> </ul>
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**eTable 4: Clinical characteristics and outcome definitions**

Outcome	Databases Used	Definition	Rationale for Primary vs. Secondary Outcome
<b>Primary Outcomes</b>			
Emergency Department Visits	CIHI NACRS	Any visit recorded in CIHI NACRS (planned and unplanned)	High prevalence, will broadly capture numerous different potential health implications of safer opioid supply programs
Hospital admissions	CIHI DAD	Any visit recorded in CIHI DAD (using admission date)	High prevalence, will broadly capture numerous different potential health implications of safer opioid supply programs
Admissions for incident infections	CIHI DAD	<u>ICD10 Codes:</u> <i>Infective endocarditis</i> I33.0 Acute and sub acute infective endocarditis I33.9 Acute and sub acute endocarditis, unspecified I38 Endocarditis, valve unspecified I39 Endocarditis and heart valve disorders in diseases classified elsewhere B37.6 Candidal endocarditis  <i>Osteomyelitis and septic arthritis</i> M86 Osteomyelitis M00 Osteomyelitis or septic arthritis  <i>Spinal infections/ discitis</i> G06.1 Epidural abscess	Safety outcome of particular debate/concern that warrants particular focus.

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		<p>M46.2 Osteomyelitis of vertebra  M46.3 Infection of intervertebral disc (pyogenic)  M46.4 Discitis, unspecified  M46.5 Osteomyelitis or septic arthritis</p> <p><i>Skin and Soft-tissue infections</i>  L03 Cellulitis  L02 Cutaneous abscess  M76.2 Necrotizing fasciitis</p>	
Non-Primary Care Healthcare costs	DAD, NACRS, OMHRS, OHIP	<p><u>Total Non-Primary Care Healthcare Costs calculated as the sum of costs below, adjusted for inflation (2020 dollars):</u></p> <p><u>Hospitalization Costs:</u> estimated costs of hospitalizations (using resource intensity weights) as well as OHIP costs incurred during inpatient hospital stay</p> <p><u>Emergency Department Costs:</u> estimated costs of emergency department visits (using resource intensity weights) as well as OHIP costs incurred during visit.</p> <p><u>Mental Health Hospitalization Costs:</u> estimated costs of mental health hospitalizations (using resource intensity weights) as well as OHIP costs incurred during mental health hospital stay</p> <p><u>Specialist, lab and non-primary care physician costs:</u>  OHIP costs not occurring during a hospitalization, mental health hospitalization or ED visit, excluding OHIP claims billed by primary care physicians.</p>	Outcome of interest to public funders and policy-makers considering investments in safer opioid supply programs
<b>Secondary Outcomes</b>			
Mental Health Related ED visits and hospital admissions	CIHI OMHRS, NACRS and DAD	<p><u>CIHI OMHRS:</u>  AXIS1_DSM4CODE_DISCH1 = Any OMHRS diagnosis (includes missing; excludes 290.x, 294.x).  Exclude if AXIS1_DSM4CODE_DISCH1 missing and PROVDX_DSM4CODE_ADM1 = 2</p> <p><u>CIHI DAD or NACRS ICD10 Codes:</u>  Admission Diagnosis: F06-F99 or  Any diagnosis: X60-X84, Y10-Y19, Y28 when admission diagnosis ≠ F06-F99</p>	Outcome of interest, but of lower priority to knowledge users

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Opioid-related ED visits or hospital admissions	CIHI DAD and NACRS	<u>ICD10 Codes:</u> T40.0 Poisoning by opium T40.1 Poisoning by heroin T40.2 Poisoning by other opioids T40.3 Poisoning by methadone T40.4 Poisoning by other synthetic narcotics T40.6 Poisoning by other and unspecified narcotics	Outcome of interest, but with low anticipated event rates
ED Visits or hospital admissions related to any substance use disorder	CIHI DAD, NACRS and OMHRS	<u>CIHI OMHRS:</u>  AXIS1_DSM4CODE_DISCH1 = 291.x (all 291 codes, excluding 291.82), 292.x (all 292 codes, excluding 292.85), 303.x (all 303 codes), 304.x (all 304 codes), 305.x (all 305 codes). PROVDX_DSM4CODE_ADM1 = 4  <u>CIHI DAD or NACRS ICD10 Codes:</u> F10 Mental and behavioural disorders due to use of alcohol F11 Mental and behavioural disorders due to use of opioids F12 Mental and behavioural disorders due to use of cannabinoids F13 Mental and behavioural disorders due to use of sedatives or hypnotics F14 Mental and behavioural disorders due to use of cocaine F15 Mental and behavioural disorders due to use of other stimulants, including caffeine F16 Mental and behavioural disorders due to use of hallucinogens F17 Mental and behavioural disorders due to use of tobacco F18 Mental and behavioural disorders due to use of volatile solvents F19 Mental and behavioural disorders due to multiple drug use and use of other psychoactive substances F55 Abuse of non-dependence-producing substances	Outcome of interest, but non-specific, and of lower priority to knowledge users
Opioid-Related Death	DDARD	Defined based on determination of opioid acting as a direct contributor to death by an investigating coroner.	Expected exceedingly low event rates.
Publicly-funded medication costs	ODB	Within the subgroup of individuals eligible for public drug benefits, the total costs reimbursed by the government for	Only available for subgroup of all LIHC clients.

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		all dispensed medications are summed to estimate publicly-funded medication costs. Pharmacy services (e.g. MedsChecks and vaccines) that are provided to all Ontarians regardless of public drug coverage are excluded from these costs.	
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**eTable 5: Characteristics of unmatched LIHC clients**

Characteristics	LIHC clients (N=10)
Age (mean, SD)	40.0 ± 10.4
Male (N, %)	≤5 (≤50%)
Death within 1 year (359 days from index)	0 (0.0%)
Program exit within 1 year (359 days from index)	0 (0.0%)

**eTable 6: Baseline characteristics of matched cohort in sensitivity analysis matched on HIV diagnosis**

Characteristics	LIHC Safer Opioid Supply Clients (N=71)	Matched Unexposed Individuals (N=232)	Weighted Standardized Differences
<b>Age (mean, SD)**</b>	41.0 ± 10.7	41.0 ± 5.9	0.00
<b>Male Sex**</b>	31 (43.7%)	31.0 (43.7%)	0.00
<b>Income Quintile*</b>			
1 (lowest)	49 (69.0%)	49.0 (69.0%)	0.00
2	10 (14.1%)	10.0 (14.1%)	0.00
3	8 (11.3%)	8.0 (11.3%)	0.00
4	≤5	≤5	<0.10‡
5 (highest)	≤5	≤5	<0.10
<b>Eligible for public drug benefits**</b>	62 (87.3%)	62.0 (87.3%)	0.00
<b>Diagnosis of HIV**</b>	17 (23.9%)	17.0 (23.9%)	0.00
<b>Diagnosis of Hepatitis C</b>	46 (64.8%)	19.7 (27.7%)	0.80
<b>Previous mental health-related or substance use hospital admission*** (1 year)</b>	18 (25.4%)	15,4 (21.7%)	0.09
<i>Anxiety disorders</i>	≤5	≤5	>0.10
<i>Deliberate self-harm</i>	≤5	≤5	<0.10
<i>Mood disorder</i>	0	≤5	>0.10
<i>Schizophrenia &amp; other psychotic disorders</i>	≤5	≤5	>0.10
<i>Substance-related disorders</i>	13 (18.3%)	8.9 (12.6%)	0.16
<i>Other</i>	≤5	≤5	<0.10
<b>Hospital admission for opioid toxicity (1 year)**</b>	6 (8.5%)	6.0 (8.5%)	0.00
<b>Hospital admission for any infection (1 year)</b>	19 (26.8%)	7.9 (11.2%)	0.41
<i>Infective Endocarditis</i>	≤5	≤5	<0.10
<i>Skin and soft tissue infection</i>	12 (16.9%)	≤5	>0.10
<i>Osteomyelitis, septic arthritis, or spinal infection</i>	8 (11.3%)	≤5	>0.10
<b>Dispensed Opioid Agonist Therapy (1 year)</b>	45 (63.4%)	45.0 (63.4%)	0.00

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<b>Dispensed Methadone</b>			
Past 30 days	23 (32.4%)	29.0 (40.9%)	0.18
Past 365 days	38 (53.5%)	35.3 (49.7%)	0.08
Past 5 years	56 (78.9%)	54.4 (76.6%)	0.05
<b>Dispensed Buprenorphine/naloxone</b>			
Past 30 days	6 (8.5%)	8.5 (12.0%)	0.12
Past 365 days	14 (19.7%)	11.8 (16.6%)	0.08
Past 5 years	21 (29.6%)	15.8 (22.2%)	0.17
<b>Dispensed Immediate-release Hydromorphone (90 days)</b>	24 (33.8%)	5.8 (8.1%)	0.67
<b>Dispensed Long-Acting Hydromorphone (90 days)</b>	8 (11.3%)	≤5	>0.10
<b>Dispensed any opioid (90 days)</b>	47 (66.2%)	48.5 (68.3%)	0.05
<b>Dispensed benzodiazepines (30 days)</b>	≤5	7.9 (11.2%)	>0.10
<b>Number of physician visits (1 year) (mean, SD)</b>	23.9 ± 21.7	25.6 ± 10.6	0.09
<b>Number of emergency department visits (1 year) (mean, SD)</b>	3.2 ± 3.4	3.0 ± 3.5	0.04
<b>Number of hospital admissions (1 year) (mean, SD)</b>	0.8 ± 1.2	0.62 ± 0.7	0.15

*\*Weighted on number of unexposed individuals matched to each safer opioid supply client*

*\*\*Matching criteria*

*\*\*\* Can be in a mental health hospital or a mental health bed in an acute hospital*

*‡ Censored according to privacy requirements for cell sizes smaller than 6. Accordingly, weighted standardized differences are suppressed to prevent residual disclosure.*

**eTable 7: Unadjusted Comparisons of outcome rates in the 1 year prior to and following cohort entry within sensitivity cohort matched on HIV diagnosis**

Health care Utilization	Safer Opioid Supply Clients (N=71)				Matched Unexposed Individuals (N=232)			
	1 year prior to cohort entry	1 year following cohort entry	Negative Binomial RR (95% CI)	p-value <sup>‡</sup>	1 year prior to cohort entry	1 year following cohort entry	Negative Binomial RR (95% CI)	p-value <sup>‡</sup>
	N (rate per person-year)				N (rate per person-year)			
<b>Primary Outcomes</b>								
Number of Emergency Department Visits	221 (3.16)	146 (2.11)	0.66 (0.48, 0.89)	0.007	599 (2.62)	511 (2.25)	0.86 (0.72, 1.02)	0.08
Number of hospital admissions	59 (0.84)	27 (0.39)	0.44 (0.27, 0.74)	0.002	106 (0.46)	83 (0.37)	0.78 (0.51, 1.18)	0.2
Number of hospital admissions for any Incident Infection	22 (0.31)	11 (0.16)	0.5 (0.24, 1.02)	0.06	20 (0.09)	17 (0.07)	0.83 (0.47, 1.47)	0.5
Incident Infective Endocarditis	≤5*	≤5*	NE	NE	≤5*	≤5*	NE	NE
Incident spinal infection, discitis, osteomyelitis or septic arthritis	9 (0.13)	≤5*	*	>0.05*	7 (0.03)	8 (0.04)	1.13 (0.56, 2.29)	0.7
Incident skin and soft tissue infections	12 (0.17)	6 (0.09)	0.5 (0.21, 1.19)	0.1	12 (0.05)	8 (0.04)	0.66 (0.27, 1.64)	0.4
Total healthcare costs not related to primary care or outpatient medications (\$ per person)	\$13,799	\$6,965	NE	0.03	\$10,006	\$9,435	NE	0.07
<b>Secondary Outcomes</b>								
Mental health ED visits or hospital admissions	30 (0.43)	26 (0.38)	0.87 (0.45, 1.7)	0.7	114 (0.50)	100 (0.44)	0.73 (0.49, 1.08)	0.1
Number of opioid-related ED visits or hospital admissions	9 (0.13)	≤5*	*	>0.05*	10 (0.04)	16 (0.07)	1.56 (0.65, 3.75)	0.3
Number of any substance use disorder-related ED visits or hospital admissions	17 (0.24)	19 (0.28)	1.12 (0.6, 2.1)	0.7	57 (0.25)	45 (0.20)	1.07 (0.62, 1.84)	0.8
All-cause mortality	n/a	≤5*	n/a	--	n/a	≤5*	n/a	--
Opioid-related deaths	n/a	0	n/a	--	n/a	≤5*	n/a	--
Total publicly-funded medication costs (\$ per person) <sup>***</sup>	\$11,569	\$18,126	NE	<0.001	\$8,619	\$8,210	NE	0.1

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Costs for hydromorphone and/or opioid agonist therapy (\$ per person)***	\$1,145	\$3,227	NE	<0.001	\$1,804	\$1,679	NE	0.01
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<sup>†</sup>P-value from Negative Binomial model for all non-cost outcomes. P-value for cost-related outcomes from Wilcoxon signed rank test

\*Censored according to privacy requirements for cell sizes smaller than 6. P-value and RR also suppressed to avoid residual disclosure.

\*\*Note: each year represents the 360 days prior to and following cohort entry to align with the 30-day windows

\*\*\*Among public drug beneficiaries only [N=62 Safer opioid supply clients, and N=199 matched unexposed individuals]

ED: Emergency Department; NE: Not estimable; n/a: not applicable as all individuals were alive on their index date; CI: confidence interval; RR: Rate Ratio

**eTable 8: Unadjusted Comparisons of outcome rates in the 1 year prior to and following cohort entry within subgroup of individuals with high healthcare utilization prior to index date.**

Health care Utilization	Safer Opioid Supply Clients (N=62)				Matched Unexposed Individuals (N=163)			
	1 year** prior to cohort entry	1 year** following cohort entry	Negative Binomial RR (95%CI)	p-value <sup>‡</sup>	1 year** prior to cohort entry	1 year** following cohort entry	Negative Binomial RR (95%CI)	p-value <sup>‡</sup>
	N (rate per person-year)				N (rate per person-year)			
<b>Primary Outcomes</b>								
Number of Emergency Department Visits	224 (3.66)	148 (2.46)	0.67 (0.50, 0.90)	0.009	495 (3.08)	423 (2.68)	0.87 (0.71, 1.07)	0.2
Number of hospital admissions	72 (1.18)	28 (0.46)	0.39 (0.24, 0.66)	0.0004	89 (0.55)	71 (0.45)	0.85 (0.62, 1.17)	0.3
Number of hospital admissions for any Incident Infection	25 (0.41)	11 (0.18)	0.45 (0.23, 0.88)	0.02	27 (0.17)	17 (0.11)	0.66 (0.4, 1.09)	0.1
Incident Infective Endocarditis	≤5*	≤5*	NE	NE	≤5*	0	NE	NE
Incident spinal infection, discitis, osteomyelitis or septic arthritis	10 (0.16)	≤5*	*	>0.05*	14 (0.09)	8 (0.05)	0.59 (0.34, 1.01)	0.06
Incident skin and soft tissue infections	13 (0.21)	≤5*	*	0.04	10 (0.06)	9 (0.06)	0.92 (0.41, 2.06)	0.8
Total healthcare costs not related to primary care or outpatient medications (\$ per person)	\$20,054	\$8,594	NE	0.0001	\$13,542	\$9,178	NE	0.04
<b>Secondary Outcomes</b>								
Mental health ED visits or hospital admissions	32 (0.52)	23 (0.38)	0.73 (0.38, 1.39)	0.3	131 (0.82)	74 (0.47)	0.58 (0.4, 0.84)	0.004
Number of opioid-related ED visits or hospital admissions	7 (0.11)	≤5*	*	>0.05*	17 (0.11)	13 (0.08)	0.78 (0.32, 1.88)	0.6

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Number of any substance use disorder-related ED visits or hospital admissions	18 (0.29)	18 (0.30)	1.02 (0.55, 1.89)	1.0	73 (0.45)	44 (0.28)	0.62 (0.39, 0.98)	0.04
All-cause mortality	n/a	≤5*	n/a	--	n/a	7	n/a	--
Opioid-related deaths	n/a	0	n/a	--	n/a	≤5*	n/a	--
Total publicly-funded medication costs (\$ per person)***	\$14,622	\$23,900	NE	0.0002	\$8,451	\$9,400	NE	0.6
Costs for hydromorphone and/or opioid agonist therapy (\$ per person)***	\$1,100	\$3,154	NE	<0.0001	\$1,556	\$1,526	NE	0.5

†P-value from Negative Binomial model for all non-cost outcomes. P-value for cost-related outcomes from Wilcoxon signed rank test

\*Censored according to privacy requirements for cell sizes smaller than 6. P-value and RR also suppressed to avoid residual disclosure.

\*\*Note: each year represents the 360 days prior to and following cohort entry to align with the 30-day windows

\*\*\*Among public drug beneficiaries only [N=58 Safer opioid supply clients, and N=151 matched unexposed individuals]

NE: Not estimable; n/a: not applicable as all individuals were alive on their index date; CI: confidence interval; RR: Rate Ratio

**eTable 9. Results from ARIMA models using 6 years of data in primary analysis, fitting intervention using ramp function**

Outcome	Group	Model	Ramp Estimate (95% confidence interval) (rate)*	Ramp Function (p-value)
<b>Primary Analysis</b>				
Rate of ED visits	Safer Supply	(0, 1 12, 1)	-1.5 (-3.0, -0.1)	0.04
	Matched Unexposed	(0, 1 12, 1)	0.2 (-0.5, 0.8)	0.6
Rate of Hospital Admissions	Safer Supply	(0, 1 12, 1)	-0.6 (-1.0, -0.2)	0.03
	Matched Unexposed	(0, 1 12, 1)	0.02 (-0.2, 0.2)	0.9
Rate of Hospital Admissions for Infections	Safer Supply	(0, 1 12, 1)	-0.1 (-0.5, 0.2)	0.4
	Matched Unexposed	(0, 1 12, 1)	-0.1 (-0.2, 0.1)	0.3
Healthcare Costs*	Safer Supply	(0, 1 12, 2)	-\$121 (-\$204, -\$38)	0.006
	Matched Unexposed	(2, 1 12, 0)	-\$48 (-\$104, \$7)	0.09

\* Rate reported per 100 individuals for all outcomes except healthcare costs which are reported per person.

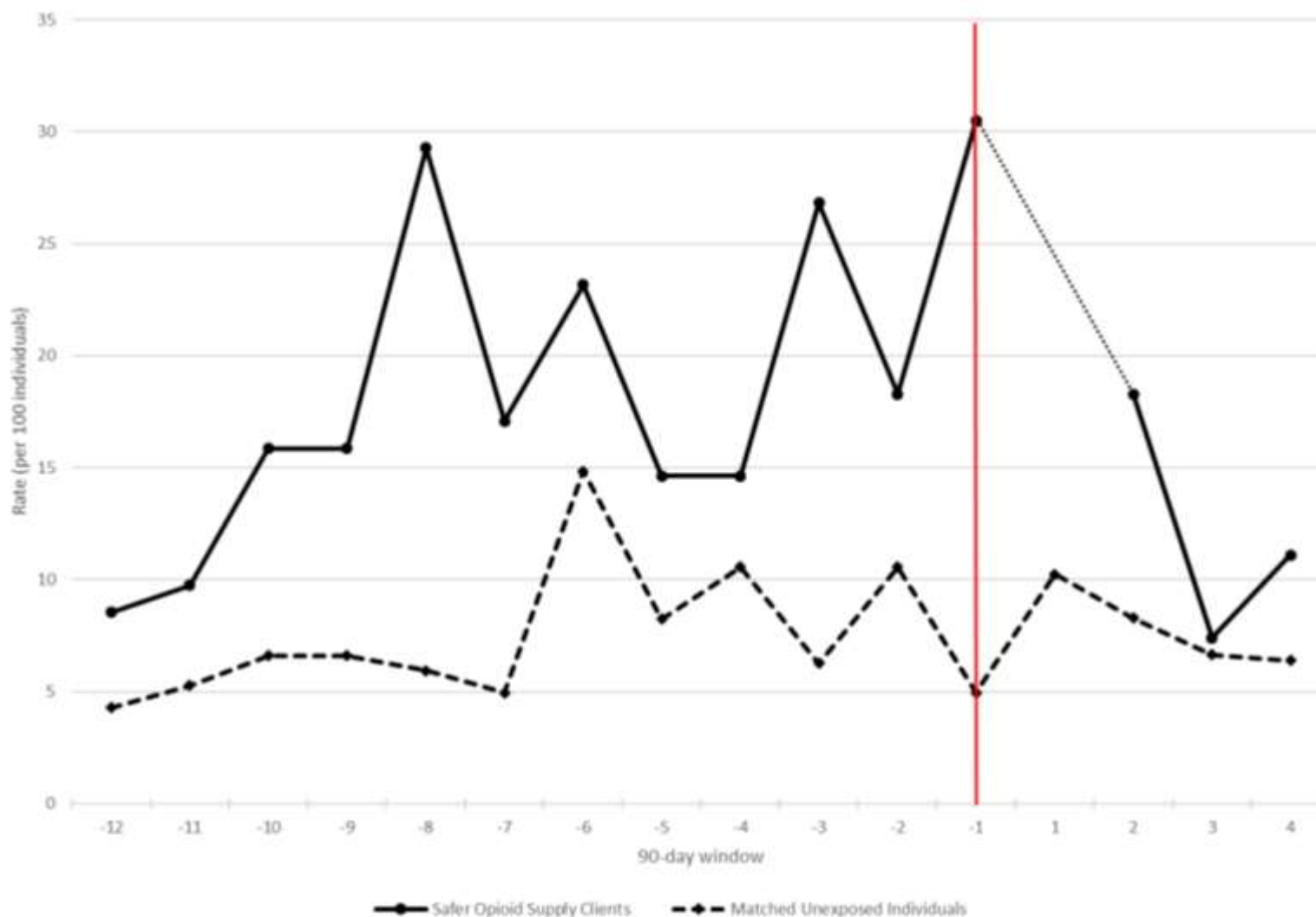
Parameter estimate indicating the slope change in the rate of each outcome as estimated by the ARIMA model.

\*\*Excluding primary care costs and outpatient medication costs

ED: Emergency Department



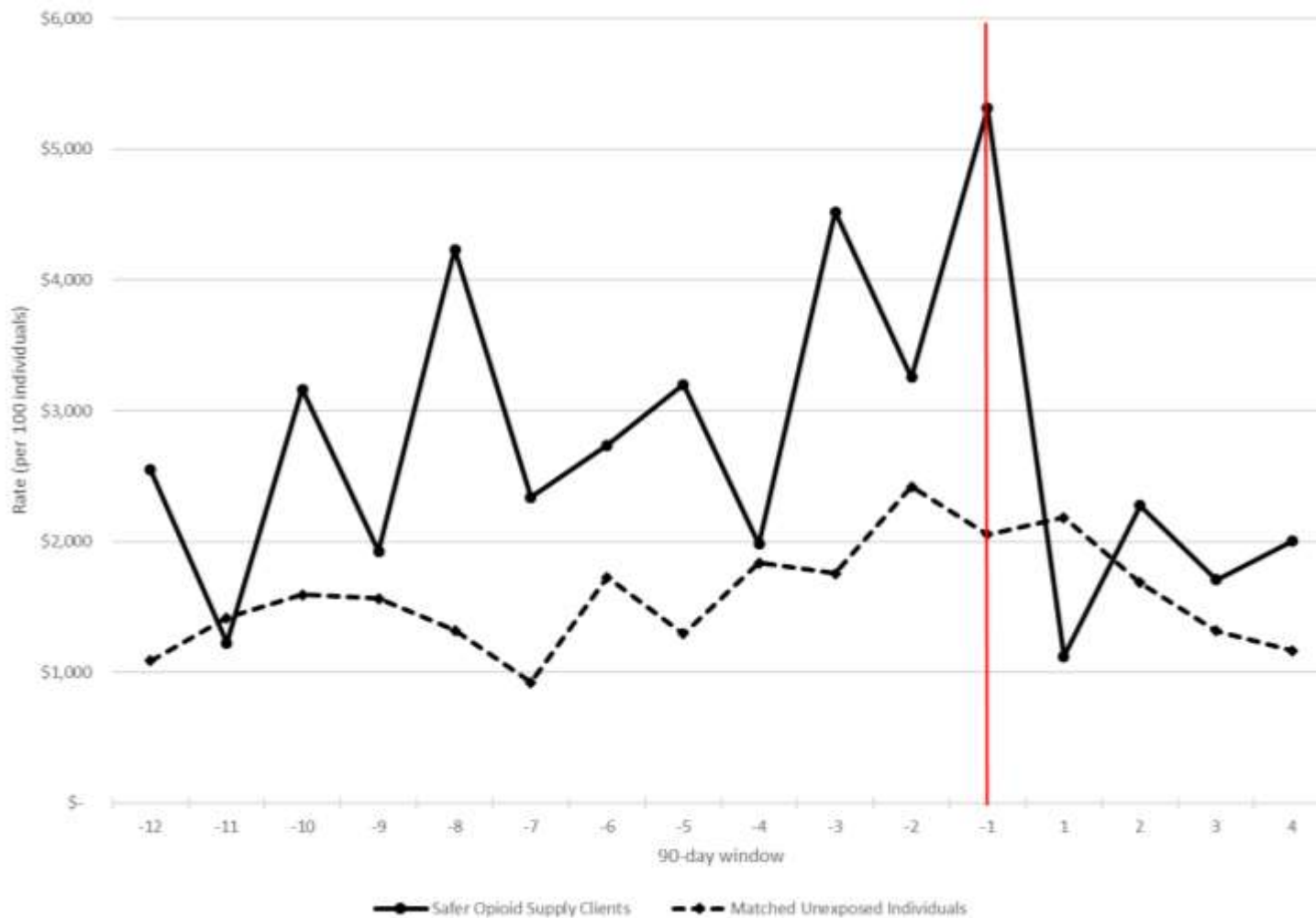
**eFigure 1: Rate of hospital admissions (per 100 individuals), stratified by exposure status**



*Note: Data in the first 90-day window following initiation among Safer Opioid Supply Clients is censored due to an event rate <6. Although rates are reported in this figure in 90 day windows to avoid reporting of small event rates (for privacy reasons), all ARIMA models were fit using event rates in 30-day windows.*

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eFigure 2: Rate of healthcare costs not related to primary care or outpatient medications per capita, stratified by exposure status



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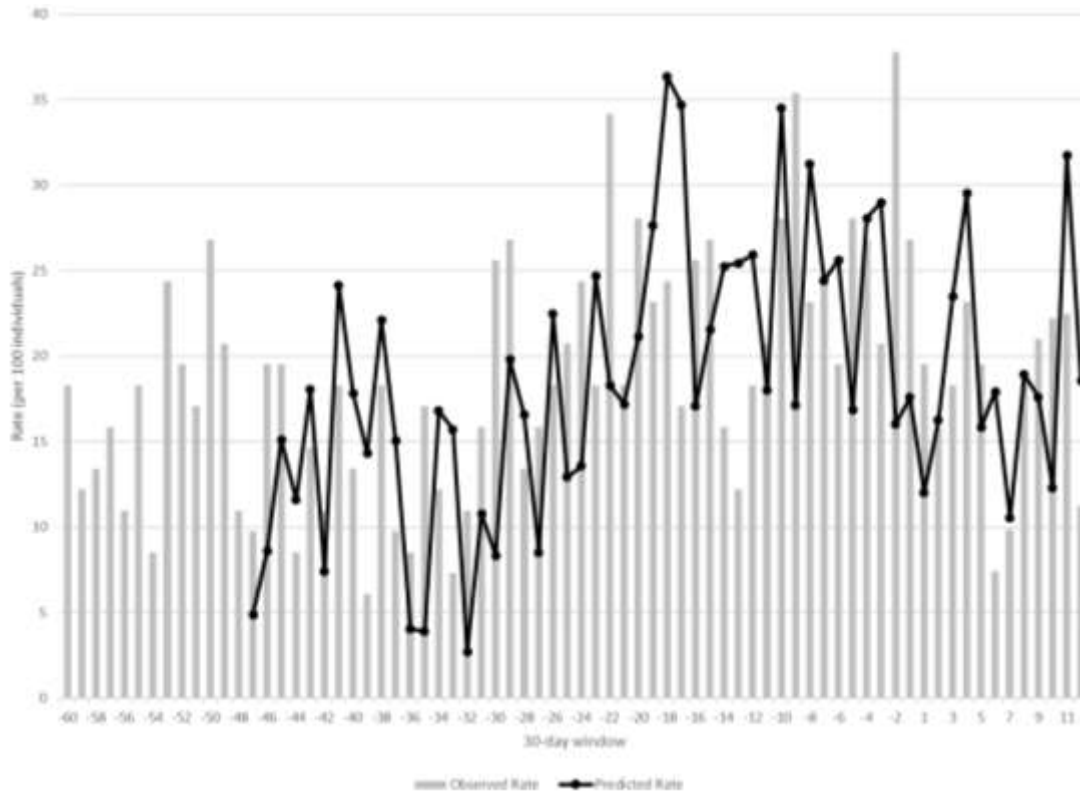


*Note: Although rates are reported in this figure in 90 day windows to avoid reporting of small event rates (for privacy reasons), all ARIMA models were fit using event rates in 30-day windows.*

**Visualization of ARIMA model fit.**

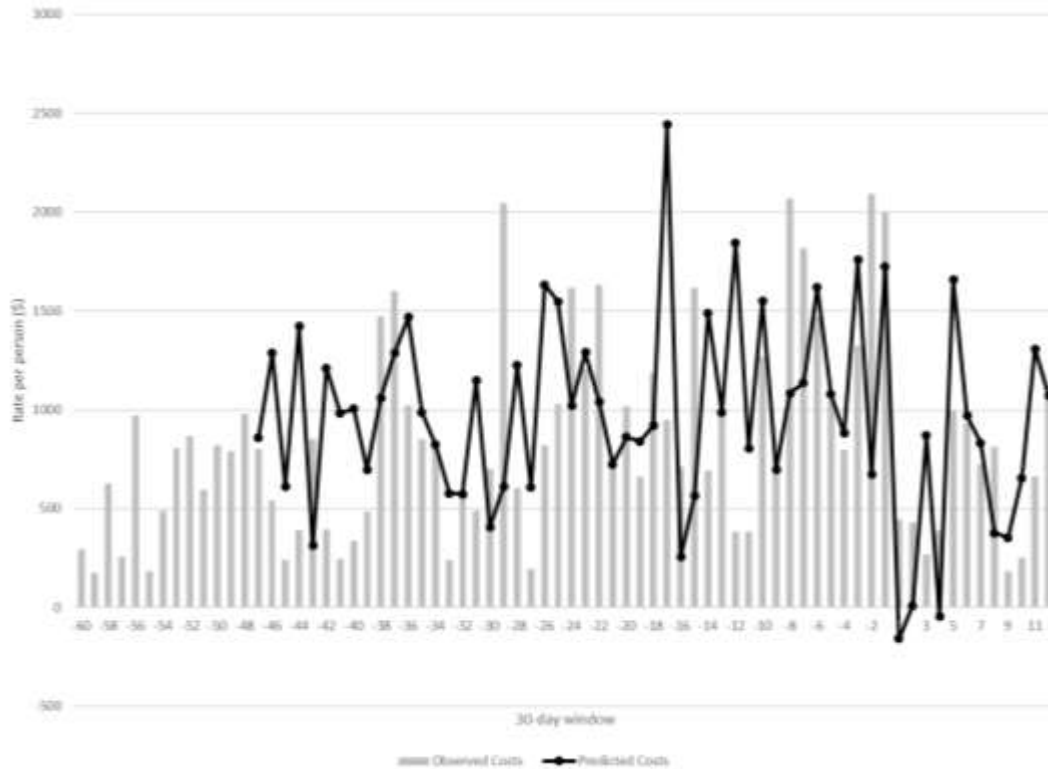
Note: figures could not be reported for hospitalization and infection outcomes due to privacy reasons due to low event rates when measured in 30-day intervals.

**eFigure 3: Observed and Predicted Rates of ED visits among LHC Clients**

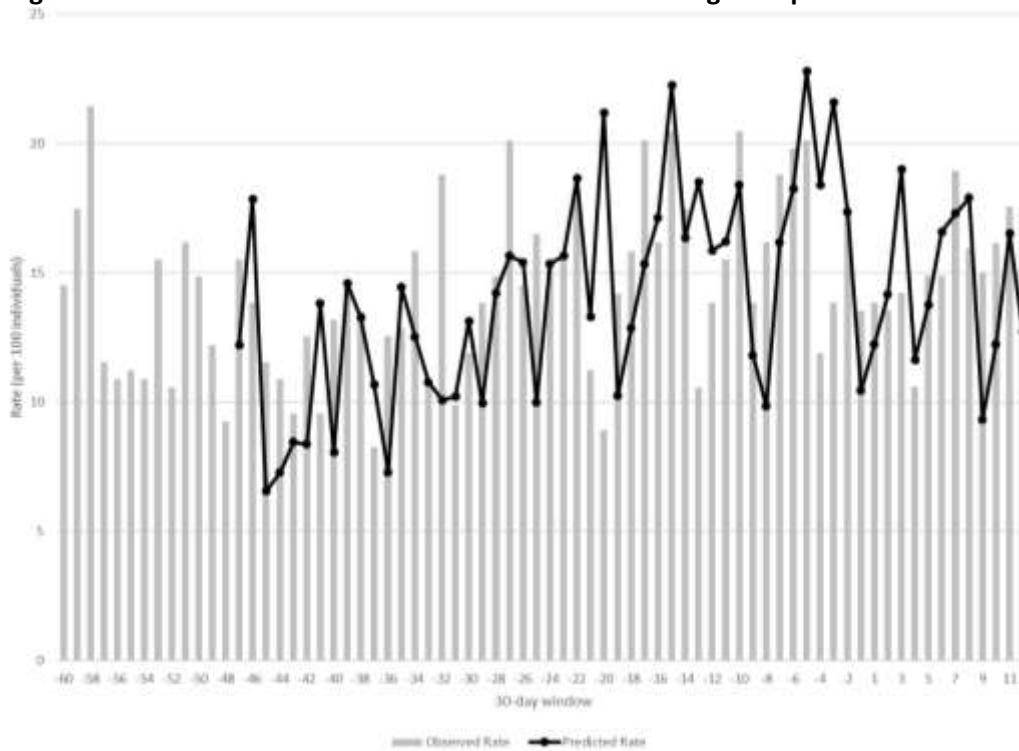


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**eFigure 4: Observed and Predicted Healthcare Costs not related to Primary Care or Outpatient Medications per Person among LIHC Clients**

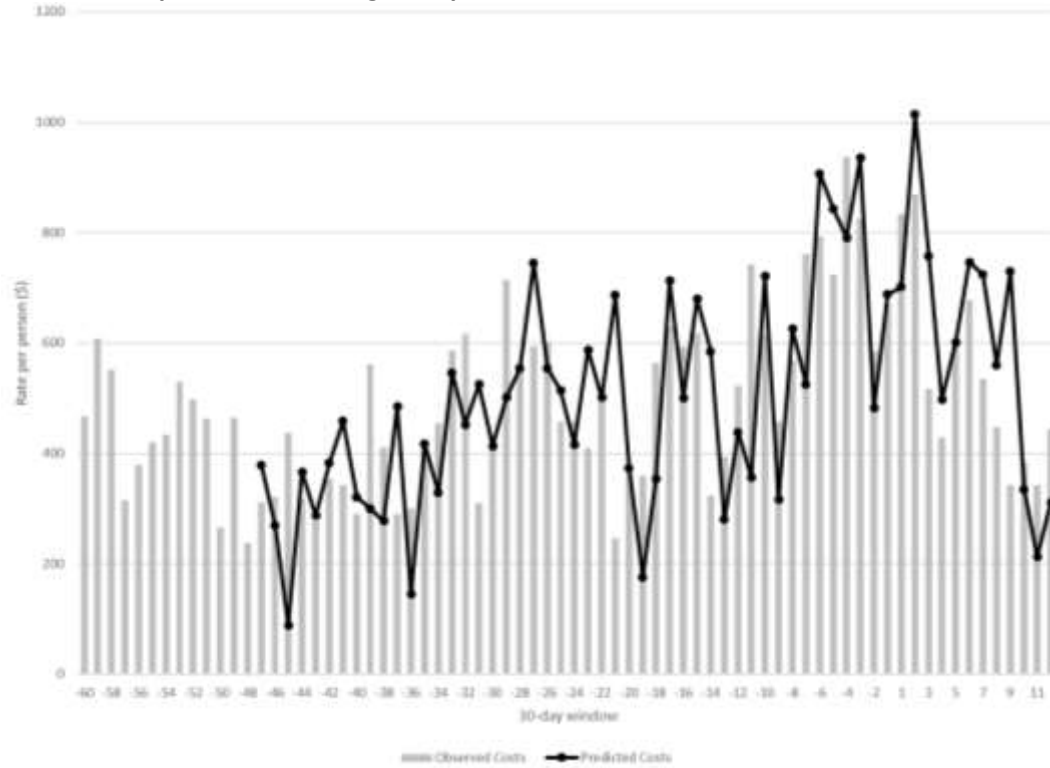


**eFigure 5: Observed and Predicted Rates of ED Visits among Unexposed Individuals**



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**eFigure 6: Observed and Predicted Healthcare Costs not related to Primary Care or Outpatient Medications per Person among Unexposed Individuals**



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