**PROGRESS REPORT**

**Association between poly-substance use and substance use disorder treatment noncompletion admitted to multiple treatments between 2010-2019 in Chile**

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# Abstract

**Aim**: (1) To describe the incidence of polysubstance use (PSU) reports and treatment completion in the sample, (2) to compare the association of treatment completion rates between individuals reporting polysubstance use and single-substance use, and (3) to estimate the association between reporting PSU at admission and treatment completion, accounting for irregular and informative observation times.

**Design**: Retrospective cohort study based on adult treatment records from the Chilean National Service for the Prevention and Rehabilitation of Drug and Alcohol Use (SENDA) from 2010 to 2019.

**Setting**: Substance use treatment (SUT) is available at no cost through Chile’s publicly funded healthcare and is provided in ambulatory and residential modalities in public and private centers.

**Participants**: A total of 13,317 individuals with multiple treatment episodes were analyzed from the 70,854 individuals who received their first SUT between 2010 and 2019.

**Measurements**: SUT completion status was categorized as completed or noncompleted. Primary outcomes focused on treatment noncompletion.

**Findings**: Higher rates of treatment noncompletion were observed in patients who reported PSU at admission. The risk of noncompletion was significantly higher in intensive ambulatory settings for the general population and in women-only residential settings, with relative risk (RR) values around 1.04 and 1.13-1.15, respectively. However, the association was not consistent across all treatment settings.

**Conclusions**: Reporting PSU at admission was modestly associated with a higher risk of treatment noncompletion. The analysis, adjusted for various covariates and accounting for irregular observation times, highlights the association between PSU reporting and treatment outcomes in specific settings. This underscore the necessity for strategies tailored to different patients in treatment settings, paving the way for more personalized interventions.

**Key Terms**: Substance use treatment noncompletion; Irregular assessment; Polysubstance use; Chile.

# Project Overview

The research question and design of this project has been modified due to administrative constraints. Therefore, below is presented the current and original (discarded) project designs.

## Current project (modified from original)

* **Research question:** What are the effects of having reported polysubstance use (PSU) at admission to substance use disorder (SUD) treatments on treatment completion in Chile?
* **Specific Aims:** (1) To describe the incidence of PSU reports and treatment completion in the sample, (2) to compare the occurrence rate of treatment completion between people with reporting poly and single-substance use, and (3) to estimate the association between reporting PSU at admission and treatment completion, accounting for irregular and informative observation times.
* **Hypothesis:** Reporting PSU at admission to SUD treatment is related to lower treatment completion rates.

## Original project (discarded)

* **Research question:** What are the mediating effects of completing SUD treatment on the relationship between baseline PSU and contact with CJS in Chile in the short (six months), middle (one year), and long term (three years)?

# Progress milestones

In this section we described the main milestones achieved so far.

* **Data wrangling**

This research relies on a population-based record-linkage retrospective cohort design. The data wrangling includes managing an administrative database that contains information of patients receiving substance use treatment financed by the National Service for the Prevention and Rehabilitation of Drug and Alcohol Use (SENDA).

* *Data exploration and cleaning:* Considering all the variables available in the database, we explored the data focusing on missing data, variance, and other descriptive measures.
* *Data normalization:* We standardised variables, labelled fields, and corrected data integrity issues (e.g., typographical errors in dates, automation bias, or variations in name spelling or form). We also modified the time (in months) from the first admission for each subject and formatted to avoid overlapping between treatments.
* **Ethics application**

The study was approved by the Griffith University Human Research Ethics Committee (GUHREC GU Ref No: 2022/919).

* **Theoretical framework**

We have conducted a literature review according to the project design and the selected outcome variables. The theoretical framework progress is exposed in the next section (III). Changes to the theoretical framework will be introduced after concluding the analysis.

* **Preliminary analysis**
* *Data structure*

Patients’ entry to the retrospective cohort starts at the time they were admitted to a SUD treatment listed in the SENDAs yearly databases with information on treatments between 2010-2019. We considered patients who had ongoing treatments from 2010 until 2019. Censoring occurred after the date of data retrieving (November 13, 2019), after an outcome event occurred, or when a patient left the cohort with no other outcomes. We excluded from the sample patients with only one treatment episode. The degree of irregularity of assessment times (times in which reported PSU was measured), in this case, in admission processes, is measured through the area under the curve (AUC) and log-transformed area under the curve. To inspect the degree of visit irregularity, the entire follow-up period was divided into adjacent and equally sized timeframes, and the number of bins changed. The AUC was obtained by plotting the mean proportions of individuals with 0 visits per bin against the mean proportions of individuals with > 1 visit per bin. AUC was log-transformed for better interpretation, in which 100 is very irregular, and 0 is equivalent to a repeated measures design.

* *Measures*

The exposure variable will be PSU at admission (self-report of using more than one main substance among alcohol and illicit drugs at admission to SUD treatment, whether sequential or concurrent) (Crummy et al., 2020; Font-Mayolas & Calvo, 2022).

The outcome variable will be SUD treatment outcome/completion status (1=dropout or spelled by misconduct; 0= completed treatments).

Additionally, the models adjust for various baseline and time-varying confounding variables related to substance use, demographics, and social factors mainly to correct irregular observation times that may be related to the outcomes.

Covariates:

Covariates for weights are listed below: Treatment outcome of the previous treatment, previous biopsychosocial compromise (severe status), previous treatment duration (<90 days), previous treatment duration (in logarithmic scaled days), polysubstance use status of the previous treatment, age at admission to treatment, birth year, primary Substance (initial diagnosis; alcohol, cocaine hydrochloride, cocaine base paste, marijuana), Psychiatric comorbidity under the International Classification of Diseases, 10th Revision (ICD-10) (diagnosis unknown or under study and with confirmed comorbidity), daily frequence of primary substance use at admission, occupational status (inactive or unemployed), and primary substance at admission to treatment (alcohol, cocaine hydrochloride, cocaine base paste, and marijuana).

Covariates for the outcome model of the association between reported substance use and treatment outcome: biopsychosocial compromise (severe status) at admission to treatment, age at admission to treatment, birth year, primary substance of the initial diagnosis (alcohol, cocaine hydrochloride, cocaine base paste, marijuana), psychiatric comorbidity (diagnosis unknown or under study and With confirmed comorbidity), daily frequence of primary substance use at admission, occupational status (inactive and unemployed), primary substance at admission to treatment (cocaine hydrochloride, cocaine base paste, marijuana, alcohol). For further information, please review Supplemental Section 1.

To account for variability by treatment setting, we stratified the analysis by setting at baseline treatment: basic ambulatory (n= 4,360) GP intensive ambulatory (n= 4,998) GP residential (n= 2,178) WO intensive ambulatory (n= 745) WO residential (n= 1,036).

* *Missing data*

Given the complex longitudinal structure of the data, we conducted random-forest-based imputation using the *missRanger* package. We will use 300 trees, using 5 candidate values of predictive matching (thus, aiming for plausible imputations given predictor values), with a maximum of 50 iterations per chaining steps. This imputation procedure may circumvent specification of interactions or nonparametric relationships and can handle collinearity between imputation variables (Hong & Lynn, 2020; Sheetal et al., 2023).

* *Model adjustment*

Models such as marginal structural models, g-computation, and targeted maximum likelihood estimation assume that observation times and gaps between them are not informative of the outcome of interest (E. M. Pullenayegum et al., 2023). The models adjust for the mentioned confounding variables. The study sample is based on a pseudo population in which the counting process (i.e., subsequent SUD treatment episodes and times between them) is static, hence, completely at random and ignorable (Carrero et al., 2023), based on generalized estimating equations and inverse probability weights given previously observed data (Cole & Hernán, 2008). We obtained these stabilized weights from a proportional intensity model in which we adjusted for baseline covariates, previous treatment outcomes, and previous polysubstance use (if any). The weights are represented through a proportional intensity model as: , where is a vector of covariates before , is a vector of regression coefficients, and the denominator is , a constant baseline hazard to stabilize weights (E. Pullenayegum, 2022). Auxiliary covariates may include confounders of the outcome model. Here, time is defined since the first individual admission in the study period (2010-2019), followed and divided by months (30.1 days). Inverse intensity weights to adjust for irregularity in the observation of treatment outcomes due to irregular admission to treatment patterns, were truncated at the 2.5th and 97.5th percentiles to mitigate the influence of extreme weights, thus, aiming for a more stable and reliable analysis. Sensitivity analyses to the potential violations of proportional hazards assumption for the intensity model were tested (See Supplemental Section 2).

Posteriorly, we fit marginal regression models to estimate the relative risk of people with or without PSU at admission completing treatment (Grafféo et al., 2018) through generalized estimating equations (GEE) assuming a Poisson distributions with a log link function and an independence structure. Additionally, GEE models were weighted using IIWs to account for irregular patterns of admission to treatment. Sensitivity analyses due to differences between variance and the mean of PSU reports using Negative Binomial distributions were tested using Quasi-likelihood Information criterion for model selection (See Supplemental Section 3).

* *Data and code availability*

Preliminary code & markdowns are available here: <https://fondecytacc.github.io/nDP/index_prop_grant23_24.html>.

# Theoretical Framework

People with substance use disorder (SUD) tend to use more than one substance unintentionally and unnoticedly (e.g., due to unregulated and contaminated supplies) or intentionally [(Bunting et al., 2023; Quek et al., 2013)](https://www.zotero.org/google-docs/?46rrTq) during active use in their lifetime (Connor et al., 2014). Some reasons for intentional polysubstance use (PSU) include additive or synergistic reward, compensation for undesired effects or negative internal states, predisposition, or related to supply (e.g., due to shortages of the main substance)(Karamouzian et al., 2024). Importantly, people with PSU are a high-risk population because it is related to a higher mortality rate (Gjersing & Bretteville-Jensen, 2018), a higher risk of relapse (Chen et al., 2019; Hassan & Le Foll, 2019), less responsive to substance use treatment (Bonfiglio et al., 2022), and other detrimental features such as risky sexual behavior (Daskalopoulou et al., 2014; Sewell et al., 2017), violence (H. J. Choi et al., 2022; Steele & Peralta, 2020), and psychiatric comorbidities (Mefodeva et al., 2022). Over the last three decades, evidence has shown that the rate of people with PSU has significantly increased, at least in high-income countries from North America, Europe, and Australia (Bonfiglio et al., 2022), highlighting the relevance of studying this topic.

Despite the association between completing SUD treatment and long-term benefits, such as lower risk of readmission to treatment (Ruiz-Tagle Maturana et al., 2023), lower risk of relapse (Andersson et al., 2019), abstinence (McPherson et al., 2017), and better quality of life (N. G. Choi & DiNitto, 2020) is well known, evidence regarding the long-term consequences of reporting PSU on treatment outcomes is limited and mixed. The lack of research on PSU is partly because most studies have focused on individual substances in isolation and have considered a multiple substance use history as an exclusion criterion for clinical studies on treatment effectiveness, which raises the problem of its translatability to real health contexts (Bonfiglio et al., 2022). Regarding the treatment outcomes, some studies report a lower likelihood of treatment completion among people with PSU (Andersson et al., 2021; Levola et al., 2021), while others found no association (Andersson et al., 2018) or higher completion rates (Basu et al., 2017). In any case, it is crucial to determine the role of reporting PSU in treatment completion to improve treatment effectiveness and research translatability (Crummy et al., 2020).

However, this role must be understood in a context of patients who experience multiple and recursive treatments (Bórquez et al., 2024). Treatments are expected to change behavior relative to no treatment. Patients not benefiting from treatments often switch to other alternatives. Those facing adverse effects or resistance to change might quit, while some persevere and follow other recommendations, such as lifestyle changes that affect their prognosis. Hence, treatment outcomes such as dropout or treatment completion are linked to subsequent exposures such as a readmission(Ruiz-Tagle Maturana et al., 2023) to a posterior treatment, what is known as “feedback loop”(Hernan & Robins, 2020). Given that SUD is understood as a chronic condition, the association between reporting PSU and treatment completion on first SUD treatment alone requires accounting that some patients may be readmitted to treatment through the follow-up period (See Figure 1a). Thus, checking for group biases and adjusting for confounders is needed (Griffin et al., 2014; Hansen et al., 2020). Additionally, these treatments are irregularly spaced, nevertheless, not at random, as the time between treatments might be related to biopsychosocial and treatment-related factors (See Figure 1b). Thus, patients with worst outcomes in a previous treatment might have more or less intense frequency of treatments in the future, that may also explain treatment outcomes such as completion or dropout (Hansen et al., 2020; Vázquez-Real et al., 2022).

Additionally, the relationship between people reporting PSU and treatment completion can be affected by various factors, such as heterogeneous PSU patterns (Bhondoekhan et al., 2023; Price et al., 2023), treatment goals, patient characteristics, resource availability, and SUD severity profiles. In turn, these characteristics are highly dependent on treatment settings (Fiestas & Ponce, 2012; Reif et al., 2021; Tiet et al., 2007). In Chile, Olivari and colleagues found that women-specific treatment settings had different readmission and treatment completion than the general population. In a similar vein, Ruiz-Tagle et al. found that completion was less likely among ambulatory settings . Most research on PSU comes from the Global North, where the treatment settings are usually specialized on particular substances (Babor, 2021; Körkel, 2021). This is not the reality of other contexts, such as Latin America, due to scarce resources and a shortage of mental health workforce, in which treatment is mostly delivered in non-specialized settings. However, studying the role of PSU on treatment outcomes in Latin America is challenging due to limited local data (Lalwani et al., 2022). Furthermore, using evidence from the Global North is not straightforward, as it focuses on opioids and injecting drug use, which are epidemiologic features that are not prevalent in the Latin American context (Castaldelli-Maia et al., 2023).

Moreover, as many studies in the Global North have often overlooked high-risk populations, there are reasons to believe that is also the case in Latin America, where the prevalence of individuals with PSU is notably high (Reyes et al., 2013). A meta-analysis focusing on Global North studies on cocaine found that more than 70% of people who use cocaine have concurrent alcohol consumption. In addition, between 38% and 64% of the participants had concurrent marijuana use (Liu et al., 2018). A recent study conducted in a Chilean hard-to-reach population that used cocaine base paste found that between 47% and 66% of users had simultaneous substance use (Olivari et al., 2022). Similarly, an analysis of data from studies conducted in six Latin American countries found that 21% of the participants reported PSU (Vilugrón et al., 2022), which was more frequent among males and young adults( 18-34) from Chile, Uruguay, and Argentina. In addition, PSU is related to school dropout, unemployment, sexual and antisocial risk behaviors (Olivari et al., 2022; Santis B et al., 2007; Vilugrón et al., 2022).

Chile has a robust public treatment system that produces a large and high-quality dataset that includes all treatment episodes of people with public health insurance (~80% of the population) since its creation in 2010 (Mateo Pinones et al., 2022). Annually, nearly 15,000 individuals are admitted for treatment. Each patient identifies the primary substance that prompted them to seek treatment, as well as any additional substances that may have contributed to their decision. However, findings from the Chilean Budgetary Office study substantiate the need for further research to determine whether treatments address characteristics such as PSU behaviors effectively in a context where 2 out of 3 reported PSU (DIPRES, 2017). Understanding the PSU-treatment completion relationship could inform effective prevention and intervention strategies for people with PSU. Moreover, expanding the knowledge about patterns of social inequalities and vulnerabilities in access to health services can serve as input to raise awareness among society and decision-makers and as a guide for developing policies and actions to reduce health inequities. Thus, this study aims to address this gap by estimating the effect of having reported PSU on treatment completion among adult patients admitted to SUD treatment programs in Chile from 2010-2019.

# Preliminary analysis

The preliminary analysis is structured with a summary of covariate baseline characteristics by polysubstance use status reported at admission. Then, we formatted the database and structured it by patient id and treatment number. Also, we provide a summary of the trajectories of patients by polysubstance use status and treatment outcome. Finally, we show a glimpse of missingness patterns.

* Characteristics of the study sample at treatment admission

After excluding records of ongoing treatments and referred outside the treatment network, 72,404 patients with 90,075 treatments were selected. In the total sample, 82% had one treatment episode, while 1% had more than 3 treatment episodes. We focused on patients with more than one treatment, identifying 13,317 patients and 30,988 observations. Several key differences were notable among individuals reporting polysubstance use.

In terms of **demographics** at baseline, people with PSU, when compared to people who report single substance use had their first admission to treatment earlier in life. Also, a higher percentage of them were unemployed. Regarding of **substance use** at baseline, people with PSU when compared to people who report single substance use: were more likely to report using cocaine paste and hydrochloride cocaine instead of alcohol as the primary substance that led them to treatment. In terms of the type of initiation substance, fewer started with alcohol, while more began with marijuana. In terms of other **health** information at baseline, severe biopsychosocial compromise was more frequent among people with PSU (See Table 1).

* Treatment history

Interestingly, among patients with only one treatment, 72% reported PSU. However, when examining patients with multiple treatment episodes, between 80% and 88% reported PSU. This suggest that exposure to PSU could be overrepresented in the sample, as readmission is associated with PSU. This association is also evident when comparing the number of treatments to the proportion of non-complete treatments. Specifically, 71% of patients with only one treatment did not complete it, while 79%, 81% and 85% of the treatment episodes of patients with two, three or four and more, respectively, correspond to noncompletion status. According to Figure 2, when considering a bin width of 2% of the gap between treatments, the proportion of patients with two or more admissions was 0.33, decreasing to a proportion of 0.04 when considering a bin width of 6%. An AUC of 0.21 (log-transformed= 80) suggest there is likely a counting process behind visits rather than perfectly repeated and thus regular measures. Therefore, it seems reasonable to conduct an analysis to measure the association between reported PSU and dropouts that considers irregularity in observations and an extent of informative assessment times, conditional on several covariates, including past observed outcomes, past assessment history, and baseline covariates (Lokku et al., 2020).

A higher incidence of noncompletion was observed in patients who reported PSU at admission, without the need to distinguish whether it was the first event or occurred later during the study period (See Table 2).

* Modelling of the observation process

We analysed the visiting process of the patients readmitted to treatment as a function of several predictors. The intensity model identifies several significant factors of treatment visits. Previous treatment dropout or misspelling (HR[Hazard ratio]= 1.17, 95% CI 1.13, 1.21), severe biopsychosocial compromise diagnosed in the previous treatment (HR= 1.06 95%CI 1.03, 1.10), less than 90 days in the previous treatment (HR= 1.11 95%CI 1.06, 1.16) a reduction of one unit in the log scale of days in the previous treatment (HR= 0.98 95%CI 0.96, 1.00), a one unit increase in age at admission to the initial treatment (HR= 1.26 95%CI 1.25, 1.27), and one unit increase in birth year (HR= 1.27 95%CI 1.26, 1.28) are associated with an increased likelihood of subsequent treatment visits. Specific substances at initial diagnosis such as cocaine base paste (HR= 1.17 95%CI 1.06, 1.30) and marijuana (HR= 1.17 95%CI 1.07, 1.29) (vs. other) and inactive (HR= 1.06 95%CI 1.02, 1.11) or unemployed (HR= 1.06 95%CI 1.03, 1.10) occupational status (vs. employed) also influence the time to returning for treatment, thus, being observed again in the database (See Table 2). Inverse intensity weights are shown in Supplemental Table 1 and models by .

* Marginal longitudinal association between Polysubstance use at admission and treatment outcome

According to the Table 4, we found a modest association between polysubstance use at any admission to treatment among users in intensive ambulatory settings for the general population (RR[*relative risk*]= 1.04, 95% CI 1.01, 1.07). Also, the risk is higher for residential settings exclusive to women, with RR values around 1.13-1.15 with intervals not including the null across all models and lag scenarios.

* Sensitivity analyses

The magnitude and direction of the associations presented in the main analysis remained stable despite different weighting schemes and different distributions used (See Table S.

# Discussion

This study is focused on people who probably had a persistent pattern of substance use disorder rather than transient substance use disorder. These patients are characterized by repeated treatment episodes, varying periods of abstinence, and relapses leading to the resumption of moderate or problematic substance use as highlighted in the literature. The results of the inverse intensity model also provide unique insights into patient characteristics associated with increased readmissions to SUD treatments. Age at admission to treatment and recent birth years may suggest the presence of an age-cohort effect, where younger individuals might be less reluctant to seek subsequent treatment. Additionally, the expansion of treatment offerings, the broader reach of SENDA into more sectors and the healthcare network, or a gradual reduction in the stigma associated with returning to treatment could also contribute to this pattern. Interestingly, some factors that we expected to be influential, such as polysubstance use in the previous treatment, specific primary substances at admission, and certain psychiatric comorbidities, were found to have negligible or non-significant effects on treatment return rates. Possibly, the fact of being adjusting for biopsychosocial compromise and stratifying by treatment settings would have capture the variability attributed to these factors.

Nonetheless, regarding the association between polysubstance use reported at admission and treatment noncompletion is restricted to intensive ambulatory settings and women-specific residential treatments.

Limitations

The proportional intensity model to calculate IIWs impose a proportional hazards assumption on the assessment intensity. However, this assumption is debatable. Diagnosing proportionality in a Cox model with recurrent events can be quite challenging and statistical tools might not account for changes in the intensities due to possible changes in baseline risks for cumulative events, making interpretations of nonproportionality less straightforward. Tests such based on Schoenfeld residuals are insufficient as contrasting for the null for changes as a function of time may not be fully indicative of nonproportional hazards. Even small violations can become apparent due to the sample size. Additionally, given that the intensity model has prediction purposes (i.e., readmission), it can still be used effectively even if hazards might not be proportional.

Although, the association described here lacks a causal interpretation given that the recurrent event process might be associated with right censoring mechanism. For example, patients admitted to treatment in dates closer to administrative censorship or in ongoing treatments might had different characteristics that may change the inverse of the susceptibility of having recurrent treatments.

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Table 1. Characteristics of the study sample

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Variable** | **Category** | **No PSU (n=2,383)** | **PSU (n=10,934)** | **Overall (n= 13,317)** | **SMD** |
| Complete status of treatment (Dropout / Misspelled) (%) | 1 | 1833 (76.9) | 8615 (78.8) | 10448 (78.5) | 0.045 |
| Biopsychosocial compromise (Severe) (%) | 1 | 690 (29.0) | 4806 (44.0) | 5496 (41.3) | 0.315 |
| Treatment duration (binary) (<90 days) (%) | 1 | 567 (23.8) | 2702 (24.7) | 3269 (24.5) | 0.021 |
| Treatment duration (log-scaled days) (median [IQR]) |  | 5.1 [4.5, 5.6] | 5.1 [4.5, 5.7] | 5.11 [4.5, 5.7] | 0.043 |
| Age at admission to treatment (median [IQR]) |  | 37.1 [29.4, 46.2] | 31.4 [26.1, 38.1] | 32.18 [26.5, 39.6] | 0.542 |
| Birth year (median [IQR]) |  | 1976.0 [1968.0, 1984.0] | 1981.0 [1974.0, 1987.0] | 1981.0 [1973.0, 1986.0] | 0.446 |
| Primary substance (initial diagnosis): alcohol (%) | 1 | 1484 (62.3) | 5440 (49.8) | 6924 (52.0) | 0.254 |
| Primary substance (initial diagnosis): cocaine hydrochloride (%) | 1 | 108 (4.5) | 519 (4.7) | 627 (4.7) | 0.010 |
| Primary substance (initial diagnosis): cocaine base paste (%) | 1 | 251 (10.5) | 872 (8.0) | 1123 (8.4) | 0.088 |
| Primary substance (initial diagnosis): marijuana (%) | 1 | 483 (20.3) | 3865 (35.3) | 4348 (32.6) | 0.341 |
| Psychiatric comorbidity (ICD-10): In study (%) | 1 | 420 (17.6) | 2233 (20.4) | 2653 (19.9) | 0.071 |
| Psychiatric comorbidity (ICD-10): Diagnosis (%) | 1 | 986 (41.4) | 4850 (44.4) | 5836 (43.8) | 0.060 |
| Daily frequence of primary substance use at admission (%) | 1 | 1013 (42.5) | 5229 (47.8) | 6242 (46.9) | 0.107 |
| Occupational Status: Inactive (%) | 1 | 468 (19.6) | 1942 (17.8) | 2410 (18.1) | 0.048 |
| Occupational Status: Unemployed (%) | 1 | 764 (32.1) | 4507 (41.2) | 5271 (39.6) | 0.191 |
| Primary substance at admission to treatment: cocaine hydrochloride (%) | 1 | 292 (12.3) | 2078 (19.0) | 2370 (17.8) | 0.187 |
| Primary substance at admission to treatment: cocaine base paste (%) | 1 | 902 (37.9) | 5996 (54.8) | 6898 (51.8) | 0.346 |
| Primary substance at admission to treatment: marijuana (%) | 1 | 64 (2.7) | 653 (6.0) | 717 (5.4) | 0.162 |
| Primary substance at admission to treatment: alcohol (%) | 1 | 1082 (45.4) | 2062 (18.9) | 3144 (23.6) | 0.593 |
| Treatment setting (%) | Basic ambulatory | 1040 (43.6) | 3320 (30.4) | 4360 (32.7) | 0.298 |
|  | GP intensive ambulatory | 786 (33.0) | 4212 (38.5) | 4998 (37.5) |  |
|  | GP residential | 272 (11.4) | 1906 (17.4) | 2178 (16.4) |  |
|  | WO intensive ambulatory | 138 (5.8) | 607 (5.6) | 745 (5.6) |  |
|  | WO residential | 147 (6.2) | 889 (8.1) | 1036 (7.8) |  |

Note. n= frequency of patients; descriptive statistics of baseline characteristics used the median (Q2) and percentiles 25 and 75 in brackets for continuous variables. Furthermore, categorical variables are represented in frequencies and percentages (%) in parenthesis.

Figure 1a. Causal diagram as a conceptual reference

Diagrama

Descripción generada automáticamente

Note: A= Reporting PSU at admission; Y= Time to treatment completion status from admission; L0=Baseline confounders; {L1, L2, ..., Lt} = time-dependent biopsychosocial; U= Unobserved confounders; t= individual treatments from 2010)

Figure 1b. Causal diagram hypothesized as the observation process

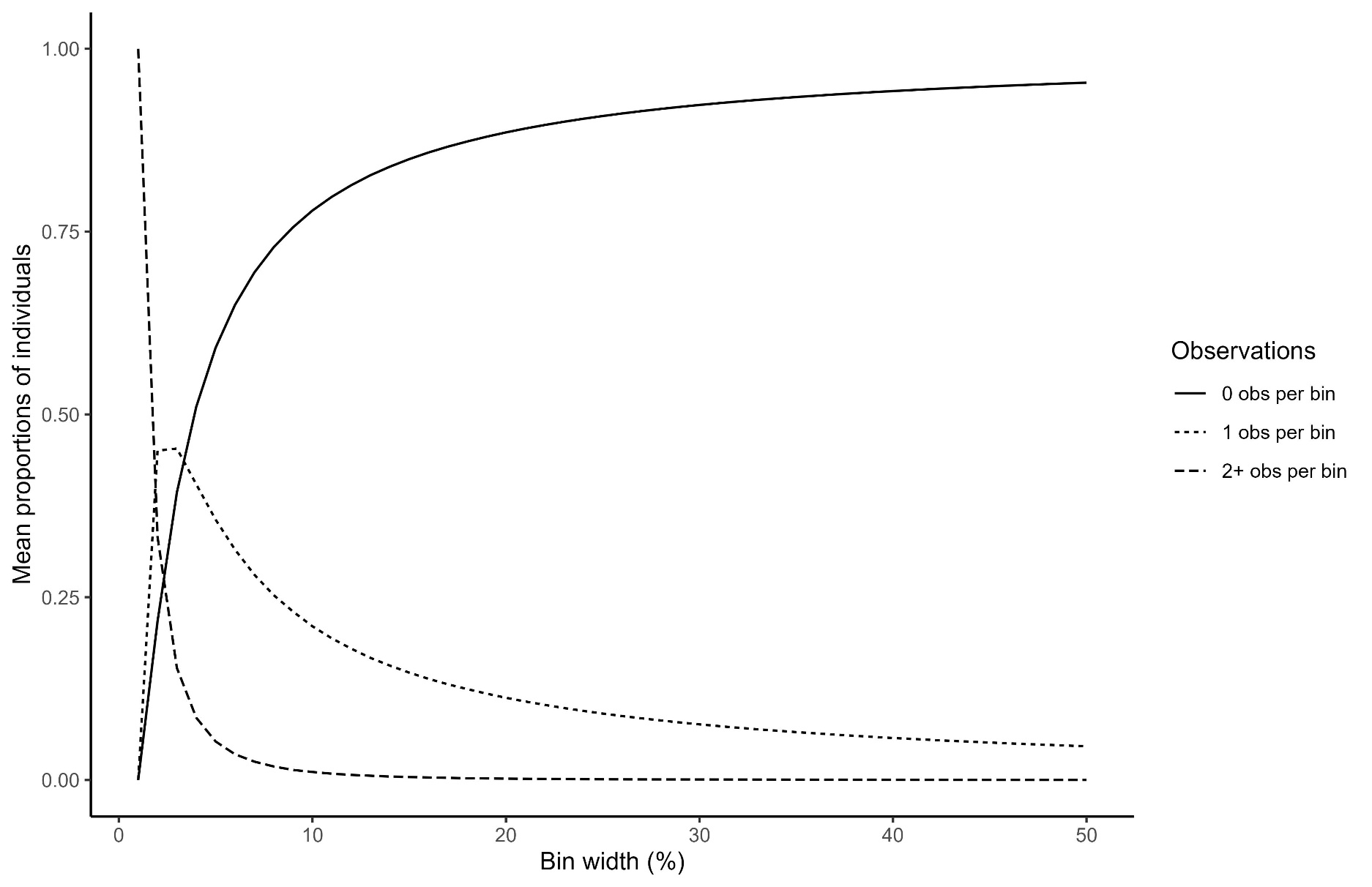
Diagrama

Descripción generada automáticamente

Note. All the backdoors of the month of assessment (admission to treatment), may pass through observed outcomes, history of evolution or baseline covariates to impact on outcomes. If we assume that is a proportional intensity model holds, we can search evidence in the data that previous variables are associated with outcomes.

Source: Pullenayegum, E. M., & Scharfstein, D. O. (2022). Randomized Trials With Repeatedly Measured Outcomes: Handling Irregular and Potentially Informative Assessment Times. Epidemiologic Reviews, 44(1), 121-137. https://doi.org/10.1093/epirev/mxac010

Figure 2. Mean proportions of patients with 0,1, and >1 admissions per bin as bin width varies from 1 to 50% of the gap between readmissions.



Note. Modified= Time in months from the first admission, and formatted to avoid overlapping between treatments, complete cases; Modified (imputation)= Time in months from the first admission, and formatted to avoid overlapping between treatments, imputed missing values; Original calendar= Formatted in calendar date, no further format.

**Table 2. Incidence rates (per 1.000 person days)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **type** | **Polysubstance use** | **Follow-up time** | **Events** | **IR (95% CI)** |
| PSU at admission and at least one dropout from the first admission | Not reported | 161,852.30 | 2,135 | 13.19 (12.64, 13.76) |
|  | Reported | 872,863.25 | 10,085 | 11.55 (11.33, 11.78) |
| PSU at admission and first dropout | Not reported | 161,852.30 | 1,833 | 11.33 (10.81, 11.86) |
|  | Reported | 872,863.25 | 8,615 | 9.87 (9.66, 10.08) |
| At least one treatment reporting PSU and at least one dropout from the first admission | Not reported | 78,926.85 | 1,099 | 13.92 (13.11, 14.77) |
|  | Reported | 955,788.69 | 11,121 | 11.64 (11.42, 11.85) |
| At least one treatment reporting PSU and first dropout | Not reported | 78,926.85 | 936 | 11.86 (11.11, 12.64) |
|  | Reported | 955,788.69 | 9,512 | 9.95 (9.75, 10.15) |

Note. incidence rate (IR) along with the 95% confidence interval (95% CI).

**Table 3. Specifications of the treatment (visit) process**

|  |  |
| --- | --- |
| **Term** | **Hazard ratio (95% CI)** |
| Treatment outcome of the previous treatment | 1.17 (1.13, 1.21) |
| Previous biopsychosocial compromise (severe) | 1.06 (1.03, 1.10) |
| Previous treatment duration (<90 days) | 1.11 (1.06, 1.16) |
| Previous treatment duration (in logarithmic scaled days) | 0.98 (0.96, 1.00) |
| Polysubstance use status of the previous treatment | 0.98 (0.95, 1.02) |
| Age at admission to treatment | 1.26 (1.25, 1.27) |
| Birth year | 1.27 (1.26, 1.28) |
| Primary substance (initial diagnosis), alcohol | 1.05 (0.95, 1.14) |
| Primary substance (initial diagnosis), cocaine | 1.12 (1.00, 1.25) |
| Primary substance (initial diagnosis), cocaine base paste | 1.17 (1.06, 1.30) |
| Primary substance (initial diagnosis), marijuana | 1.17 (1.07, 1.29) |
| Psychiatric comorbidity (diagnosis unknown or under study) | 1.03 (0.99, 1.08) |
| Psychiatric comorbidity (confirmed comorbidity) | 1.02 (0.99, 1.05) |
| Daily frequence of primary substance use at admission | 1.01 (0.98, 1.05) |
| Occupational status (inactive) | 1.06 (1.02, 1.11) |
| Occupational status (unemployed) | 1.06 (1.03, 1.10) |
| Primary substance at admission to treatment (alcohol) | 0.90 (0.80, 1.02) |
| Primary substance at admission to treatment (cocaine hydrochloride) | 0.90 (0.79, 1.01) |
| Primary substance at admission to treatment (cocaine base paste) | 0.91 (0.81, 1.03) |
| Primary substance at admission to treatment (marijuana) | 0.89 (0.78, 1.02) |

Note. 95%CI= 95% confidence intervals in parenthesis; Intensity model, in Andersen-Gill format Clustered by ID and stratified by treatment setting.

**Table 4. Association between Polysubstance use at admission and Treatment noncompletion** **status (dropout or spelled by misconduct) from Poisson Regression Multivariable Model with independence structure**

|  |  |  |  |
| --- | --- | --- | --- |
| **Treatment setting** | **RR (95%CI)** | **Inverse intensity weighted RR (95%CI) (lag=0)** | **Inverse intensity weighted RR (95%CI) (lag=1)** |
| Basic ambulatory |  |  |  |
|  | 1.02 (1.00, 1.05) | 1.02 (0.99, 1.05) | 1.02 (1.00, 1.05) |
| General-population, intensive ambulatory |  |  |  |
|  | 1.04 (1.01, 1.07) | 1.04 (1.01, 1.08) | 1.04 (1.01, 1.07) |
| General-population, residential |  |  |  |
|  | 0.97 (0.92, 1.02) | 0.97 (0.92, 1.02) | 0.95 (0.90, 1.01) |
| Women-only, intensive ambulatory |  |  |  |
|  | 0.99 (0.92, 1.05) | 0.99 (0.92, 1.07) | 0.99 (0.92, 1.07) |
| Women-only, residential |  |  |  |
|  | 1.14 (1.06, 1.23) | 1.15 (1.06, 1.26) | 1.13 (1.04, 1.22) |

Note. RR= Relative risk; 95%CI= 95% confidence intervals in parenthesis; lag=0: Lagged covariates were fixed to 0 for binary variables and natural logarithm of 45 days; lag=1: Lagged covariates were fixed to 1 for binary variables and natural logarithm of 90 days.

All models adjusted for the following covariates: biopsychosocial compromise (severe status) at admission to treatment, Age at admission to treatment, Birth year, Primary substance of the initial diagnosis (alcohol, cocaine hydrochloride, cocaine base paste, marijuana), Psychiatric comorbidity (in study and with comorbidity), Daily frequence of primary substance use at admission, Occupational status (inactive and unemployed), Primary substance at admission to treatment (Cocaine hydrochloride, cocaine base paste, marijuana, alcohol).