

## **PROGRESS REPORT**

### **Impact of Poly-substance use on substance use disorder treatment completion between 2010-2019 in Chile**

#### **Research team**

Andrés González Santa Cruz

José Ruiz-Tagle Maturana

Mariel Mateo Piñones

Álvaro Castillo-Carniglia

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## Contents

I. Project Overview .....	3
Current project (modified from original) .....	3
Original project (discarded).....	3
II. Progress milestones.....	4
III. Theoretical Framework.....	6
IV. Preliminary analysis.....	8
V. Next steps.....	10
VI. References .....	11

## **I. 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)?

## II. 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, 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.

#### • 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  $N_i(t)$  (i.e., subsequent SUD treatment episodes and times between them) is static, hence, completely at random and ignorable  $Y_i(t) \perp\!\!\!\perp N_i(t) | Z_i(t)$  (Carrero et al., 2023), based on generalized estimating equations and inverse probability weights given previously observed data  $Z_i(t)$  (Cole & Hernán, 2008). We obtained these stabilized weights from a proportional intensity model in which we adjusted for baseline covariates, previous treatment outcomes, and polysubstance use (if any). The weights are represented through a proportional intensity model as:  $\hat{w}_i(t) = \frac{\exp(-Z_i(t)\tilde{\gamma})}{\hat{\lambda}_0(t)}$ , where  $Z_i(t)$  is a vector of covariates before  $t$ ,  $\tilde{\gamma}$  is a vector of regression coefficients, and the denominator is  $\hat{\lambda}_0(t)$ , a constant baseline hazard to stabilize weights (E. Pullenayegum, 2022). Auxiliary covariates may include confounders of the outcome model. We estimated the relative risk of people with PSU completing at admission (Grafféo et al., 2018) using generalized estimating equations with a logit link function and assuming an independence structure.

- *Weighting process*

Covariates for weights are listed below: Treatment setting, Sex, Substance use onset age, Educational attainment, Primary substance at admission, Primary substance at admission usage frequency, Occupational status, Number of children (binary), Tenure status of households, Macrozone, Psychiatric comorbidity (ICD-10), Substance use severity (dependence status) (ICD-10) Urban/rural municipality of residence, Percentage of poverty of the municipality of residence, Initial substance, Birth year, Cohabitation status.

- *Data and code availability*

Preliminary code & markdowns are available here:  
[https://fondecytacc.github.io/nDP/index\\_prop\\_grant23\\_24.html](https://fondecytacc.github.io/nDP/index_prop_grant23_24.html).

### III. Theoretical Framework

People with substance use disorder (SUD) tend to use more than one substance unintentionally and unnoticed (e.g., due to unregulated and contaminated supplies) or intentionally (Bunting et al., 2023; Quek et al., 2013) 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 (Bhondoeckhan 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). 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.

#### IV. 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 (see Table 1a). 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 (See Table 1b). 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, were less likely to have completed primary education, a higher percentage of them were unemployed, most of them did not have children, and were more likely to be temporarily living with a relative rather than owning a home. Also, people with PSU were more likely to live with their family of origin, rather than alone or with a partner and/or children. Geographically, they seem to be concentrated in the northern macrozone of Chile and in urban municipalities, with fewer residing in the south and rural areas.

Regarding of **substance use** at baseline, people with PSU when compared to people who report single substance use: had an earlier substance use onset, are more likely to report using cocaine paste and hydrochloride cocaine instead of alcohol as the primary substance that led them to treatment. Additionally, there was a higher incidence of diagnosed drug dependence among this population. 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. Also, less patients with PSU were in treatment in public centres, highlighting significant patterns and disparities within this group (See Table 1b).

- Treatment history

In the total sample, 82% had one treatment episode, while 1% had more than 3 treatment episodes. As illustrated in Figure 2, most patients had only one treatment, but some exceptions were noted, such as subject no. 25 with 7 treatments over approximately 83 months, subject no. 21 with 3 treatments in the first 20 months, and subject no. 6 with a second treatment about 80 months after the first follow-up period. 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 non-completion status. According to Figure 3, when considering a bin width of 2% of the gap between treatments, the proportion of patients with two or more admissions was 0.06, decreasing to a proportion of 0.01 when considering a bin width of 6%. An AUC of 0,07 (log-transformed= 20.2) suggest that, although low, there is likely a counting process behind visits rather than perfectly repeated and thus regular measures. Therefore, it seems reasonable to conduct an analysis 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).

- Polysubstance use status, longitudinal patterns



As seen in Figure 4, patients' reporting patterns of PSU show changes over time. Trees of trajectories by treatment setting at baseline are available by treatment setting (<https://rpubs.com/ACCANID/tree>).

- Missing data

The proportion of missing data was 6.8% or less on an item level, with Age of onset of substance use leading the list (6.8%), followed by first substance used (6.6%) and housing situation (5.8%). However, 84% of the observations were complete.

- Modelling of the observation process

Focusing on patients with more than one treatment, we identified 13,317 patients and 30,988 observations. Despite that we tested various weighting schemes for the visiting process, we still must incorporate time as a predictor (in its different parametric shapes), and baseline covariates. Although we are not planning to incorporate actual PSU as it is the focus of the main analysis, we observed that in many specifications, previous PSU had a protective effect when all other lagged covariates were present. This protective effect was exacerbated when we fixed the value of covariates to zero, even when restricting the sample to patients with multiple treatments. Conversely, the actual reported PSU had a risk effect if added (hazard ratio= 1.22, 95% confidence interval: 1.19–1.24). However, we found that predictors of previous treatment trajectories were associated with the outcome. Therefore, to measure the association between reported PSU and dropouts, it is crucial to incorporate the visit process (See Table 2).

## **V. Next steps**

- **Paper:** We have decided to submit our work to Drug and Alcohol Dependence (an International Journal), which is expected in April 2024.
- **Analytic steps:** We aim to select covariates adequately, grouping them according to the hypotheses and behavior. We are still reviewing antecedents and theoretical and empirical convenience of including one or another covariate (e.g., biopsychosocial compromise, treatment admission motive). We are exploring how PSU patterns change longitudinally, depending on previous treatment completion status and months spent in treatment (<3 vs. ≥ 3). These analyses will be stratified by baseline treatment setting due to expected unobserved differences among these groups. Another challenge that remains unexplored is the presence of missing values and imputation methods under Missing-at random. Given the complex longitudinal structure of the data, we will conduct random-forest-based imputation using the *missRanger* package. We will use 200 trees, using 3 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). Lastly, we will conduct separate analyses by baseline treatment modality.
- **Presentation in Scientific meetings:** Our goal is to present this study at least at one international conference such as the National Institute on Drug Abuse International Forum, or in possible scientific community activities organized either by Griffith University (Australia), Universidad de Chile or other national institutions.

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Table 1a. Characteristics of the study sample

Variable	Category	Overall (n= 85,048)	No PSU (n=22,552)	PSU (n=62,496)	Sig.	SMD
Complete status of treatment (binary) (%)						
	Treatment completion	19278 (22.7)	6404 (28.4)	12874 (20.6)	<0.001	0.183
	Treatment non-completion	65761 (77.3)	16148 (71.6)	49613 (79.4)		
	[Missing]	9 (0.0)	0 (0.0)	9 (0.0)		
Age (admission to treatment) (median [Q1, Q3])		34.21 [27.41, 43.17]	41.71 [32.29, 51.21]	32.33 [26.45, 39.90]	<0.001	0.743
Sex (%)	Women	21020 (24.7)	6050 (26.8)	14970 (24.0)	<0.001	0.066
Age of Onset of Substance Use (median [Q1, Q3])		15.00 [14.00, 18.00]	17.00 [14.00, 20.00]	15.00 [13.00, 17.00]	<0.001	0.425
Educational Attainment (%)						
	1-More than high school	14068 (16.5)	3215 (14.3)	10853 (17.4)	<0.001	0.230
	2-Completed high school or less	46653 (54.9)	11143 (49.4)	35510 (56.8)		
	3-Completed primary school or less	23943 (28.2)	8044 (35.7)	15899 (25.4)		
	[Missing]	384 (0.5)	150 (0.7)	234 (0.4)		
Primary Substance (admission to treatment) (%)						
	Alcohol	28859 (33.9)	14212 (63.0)	14647 (23.4)	<0.001	0.890
	Cocaine hydrochloride	16151 (19.0)	2337 (10.4)	13814 (22.1)		
	Cocaine paste	32681 (38.4)	4511 (20.0)	28170 (45.1)		
	Marijuana	5771 (6.8)	972 (4.3)	4799 (7.7)		
	Other	1585 (1.9)	519 (2.3)	1066 (1.7)		
	[Missing]	1 (0.0)	1 (0.0)	0 (0.0)		
Frequency of Substance Use (Primary Substance) (%)						
	1. Less than 1 day a week	4178 (4.9)	1530 (6.8)	2648 (4.2)	<0.001	0.186
	2. 1 day a week or more	5610 (6.6)	1922 (8.5)	3688 (5.9)		
	3. 2 to 3 days a week	23716 (27.9)	6641 (29.4)	17075 (27.3)		
	4. 4 to 6 days a week	13923 (16.4)	3580 (15.9)	10343 (16.5)		
	5. Daily	37200 (43.7)	8744 (38.8)	28456 (45.5)		
	[Missing]	421 (0.5)	135 (0.6)	286 (0.5)		
Corrected Occupational Status (%)						
	Employed	41407 (48.7)	12657 (56.1)	28750 (46.0)	<0.001	0.276
	Inactive	14258 (16.8)	4206 (18.7)	10052 (16.1)		
	Unemployed	29382 (34.5)	5688 (25.2)	23694 (37.9)		
	[Missing]	1 (0.0)	1 (0.0)	0 (0.0)		
Number of Children (dichotomized) (%)						
	One or more	64165 (75.4)	18191 (80.7)	45974 (73.6)	<0.001	0.172
	[Missing]	745 (0.9)	200 (0.9)	545 (0.9)		
Housing Situation (Tenure Status) (%)						
	Others	3260 (3.8)	809 (3.6)	2451 (3.9)	<0.001	0.266
	Owner/Transferred dwellings/Pays					
	Dividends	29934 (35.2)	9863 (43.7)	20071 (32.1)		
	Renting	14566 (17.1)	3835 (17.0)	10731 (17.2)		
	Stays temporarily with a relative	32609 (38.3)	6829 (30.3)	25780 (41.3)		
	[Missing]	4679 (5.5)	1216 (5.4)	3463 (5.5)		
Macro Administrative Zone in Chile (%)						
	Center	64341 (75.7)	16681 (74.0)	47660 (76.3)	<0.001	0.293
	North	12151 (14.3)	2243 (9.9)	9908 (15.9)		
	South	8536 (10.0)	3625 (16.1)	4911 (7.9)		
	[Missing]	20 (0.0)	3 (0.0)	17 (0.0)		
Psychiatric Comorbidity (ICD-10) (%)						
	Without psychiatric comorbidity	32337 (38.0)	10022 (44.4)	22315 (35.7)	<0.001	0.184
	Diagnosis unknown (under study)	16099 (18.9)	3575 (15.9)	12524 (20.0)		
	With psychiatric comorbidity	36612 (43.0)	8955 (39.7)	27657 (44.3)		

SUD Severity (Dependence status) (%)	Drug dependence	61836 (72.7)	13974 (62.0)	47862 (76.6)	<0.001	0.321
	Hazardous consumption	23211 (27.3)	8577 (38.0)	14634 (23.4)		
	[Missing]	1 (0.0)	1 (0.0)	0 (0.0)		
Urbanicity (%)	Mixed	8205 (9.6)	2850 (12.6)	5355 (8.6)	<0.001	0.272
	Rural	7148 (8.4)	2977 (13.2)	4171 (6.7)		
	Urban	69693 (81.9)	16724 (74.2)	52969 (84.8)		
	[Missing]	2 (0.0)	1 (0.0)	1 (0.0)		
Percentage of people in poverty (median [Q1, Q3])		0.11 [0.07, 0.16]	0.11 [0.07, 0.15]	0.12 [0.08, 0.17]	<0.001	0.104
Primary Substance (initial diagnosis) (%)	Alcohol	46623 (54.8)	15574 (69.1)	31049 (49.7)	<0.001	0.505
	Cocaine hydrochloride	3162 (3.7)	957 (4.2)	2205 (3.5)		
	Cocaine paste	3864 (4.5)	1321 (5.9)	2543 (4.1)		
	Marijuana	22991 (27.0)	3083 (13.7)	19908 (31.9)		
	Other	1987 (2.3)	563 (2.5)	1424 (2.3)		
	[Missing]	6421 (7.5)	1054 (4.7)	5367 (8.6)		
Corrected birth year (median [IQR])		1980.00 [1971.00, 1987.00]	1974.00 [1964.00, 1983.00]	1982.00 [1974.00, 1988.00]	<0.001	0.630
Cohabitation status (Recoded) (f) (%)	Alone	8026 (9.4)	2765 (12.3)	5261 (8.4)	<0.001	0.342
	Family of origin	35576 (41.8)	6866 (30.4)	28710 (45.9)		
	Others	7291 (8.6)	1802 (8.0)	5489 (8.8)		
	With couple/children	34154 (40.2)	11118 (49.3)	23036 (36.9)		
	[Missing]	1 (0.0)	1 (0.0)	0 (0.0)		
Physical Comorbidity (ICD-10) (%)	Without physical comorbidity	33609 (39.5)	8363 (37.1)	25246 (40.4)	<0.001	0.084
	Diagnosis unknown (under study)	45892 (54.0)	12457 (55.2)	33435 (53.5)		
	One or more	5547 (6.5)	1732 (7.7)	3815 (6.1)		
Biopsychosocial compromise (%)	1-Mild	7986 (9.4)	3801 (16.9)	4185 (6.7)	<0.001	0.420
	2-Moderate	48355 (56.9)	13544 (60.1)	34811 (55.7)		
	3-Severe	27150 (31.9)	4743 (21.0)	22407 (35.9)		
	[Missing]	1557 (1.8)	464 (2.1)	1093 (1.7)		
Treatment Admission Motive (%)	Spontaneous	38028 (44.7)	10097 (44.8)	27931 (44.7)	<0.001	0.187
	Assisted Referral	7967 (9.4)	1455 (6.5)	6512 (10.4)		
	Other	4514 (5.3)	1184 (5.3)	3330 (5.3)		
	Justice Sector	7976 (9.4)	2787 (12.4)	5189 (8.3)		
	Health Sector	26563 (31.2)	7029 (31.2)	19534 (31.3)	<0.001	
Public treatment center	TRUE	60958 (71.7)	19135 (84.8)	41823 (66.9)	<0.001	0.429
	[Missing]	20 (0.0)	3 (0.0)	17 (0.0)		

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.

Table 1b. Characteristics of the study sample (excluding ongoing treatment episodes or external referrals)

Variable	Category	Overall (n=72,404)	No PSU (n=18,707)	PSU (n=53,697)	Sig.	SMD
Complete status of treatment (binary) (%)	Treatment completion	19278 (26.6)	6404 (34.2)	12874 (24.0)	<0.001	0.228
	Treatment non-completion	53117 (73.4)	12303 (65.8)	40814 (76.0)		
	[Missing]	9 (0.0)	0 (0.0)	9 (0.0)		
Age (admission to treatment) (median [Q1, Q3])		34.04 [27.38, 42.84]	41.40 [32.14, 50.94]	32.27 [26.47, 39.76]	<0.001	0.736
Sex (%)	Women	17342 (24.0)	4793 (25.6)	12549 (23.4)	<0.001	0.052
Age of Onset of Substance Use (median [IQ Q1, Q3R])		15.00 [14.00, 18.00]	17.00 [14.00, 20.00]	15.00 [13.00, 17.00]	<0.001	0.419
Educational Attainment (%)	1-More than high school	11489 (15.9)	2495 (13.3)	8994 (16.7)	<0.001	0.236
	2-Completed high school or less	39904 (55.1)	9289 (49.7)	30615 (57.0)		
	3-Completed primary school or less	20685 (28.6)	6797 (36.3)	13888 (25.9)		
	[Missing]	326 (0.5)	126 (0.7)	200 (0.4)		
Primary Substance (admission to treatment) (%)	Alcohol	24244 (33.5)	11695 (62.5)	12549 (23.4)	<0.001	0.877
	Cocaine hydrochloride	13505 (18.7)	1906 (10.2)	11599 (21.6)		
	Cocaine paste	28563 (39.4)	3922 (21.0)	24641 (45.9)		
	Marijuana	4835 (6.7)	784 (4.2)	4051 (7.5)		
	Other	1256 (1.7)	399 (2.1)	857 (1.6)		
	[Missing]	1 (0.0)	1 (0.0)	0 (0.0)		
Frequency of Substance Use (Primary Substance) (%)	1. Less than 1 day a week	3554 (4.9)	1276 (6.8)	2278 (4.2)	<0.001	0.189
	2. 1 day a week or more	4852 (6.7)	1621 (8.7)	3231 (6.0)		
	3. 2 to 3 days a week	20417 (28.2)	5578 (29.8)	14839 (27.6)		
	4. 4 to 6 days a week	11855 (16.4)	2969 (15.9)	8886 (16.5)		
	5. Daily	31363 (43.3)	7145 (38.2)	24218 (45.1)		
	[Missing]	363 (0.5)	118 (0.6)	245 (0.5)		
Corrected Occupational Status (%)	Employed	35924 (49.6)	10709 (57.2)	25215 (47.0)	<0.001	0.275
	Inactive	11760 (16.2)	3350 (17.9)	8410 (15.7)		
	Unemployed	24719 (34.1)	4647 (24.8)	20072 (37.4)		
	[Missing]	1 (0.0)	1 (0.0)	0 (0.0)		
Number of Children (dichotomized) (%)	One or more	54984 (75.9)	15188 (81.2)	39796 (74.1)	<0.001	0.174
	[Missing]	618 (0.9)	163 (0.9)	455 (0.8)		
Housing Situation (Tenure Status) (%)	Others	2804 (3.9)	689 (3.7)	2115 (3.9)	<0.001	0.268
	Owner/Transferred dwellings/Pays Dividends	25339 (35.0)	8171 (43.7)	17168 (32.0)		
	Renting	12354 (17.1)	3145 (16.8)	9209 (17.1)		
	Stays temporarily with a relative	27759 (38.3)	5637 (30.1)	22122 (41.2)		
	[Missing]	4148 (5.7)	1065 (5.7)	3083 (5.7)		
Macro Administrative Zone in Chile (%)	Center	54864 (75.8)	13988 (74.8)	40876 (76.1)	<0.001	0.292

## Fondo de Investigación Intramural nDP

	North	10690 (14.8)	1882 (10.1)	8808 (16.4)		
	South	6833 (9.4)	2835 (15.2)	3998 (7.4)		
	[Missing]	17 (0.0)	2 (0.0)	15 (0.0)		
Psychiatric Comorbidity (ICD-10) (%)						
	Without psychiatric comorbidity	28308 (39.1)	8542 (45.7)	19766 (36.8)	<0.001	0.187
	Diagnosis unknown (under study)	13616 (18.8)	2918 (15.6)	10698 (19.9)		
	With psychiatric comorbidity	30480 (42.1)	7247 (38.7)	23233 (43.3)		
SUD Severity (Dependence status) (%)	Drug dependence	52416 (72.4)	11498 (61.5)	40918 (76.2)	<0.001	0.322
	[Missing]	1 (0.0)	1 (0.0)	0 (0.0)		
Urbanicity (%)						
	Mixed	6938 (9.6)	2359 (12.6)	4579 (8.5)	<0.001	0.267
	Rural	5861 (8.1)	2382 (12.7)	3479 (6.5)		
	Urban	59603 (82.3)	13965 (74.7)	45638 (85.0)		
	[Missing]	2 (0.0)	1 (0.0)	1 (0.0)		
Percentage of people in poverty (median [Q1, Q3])		0.12 [0.07, 0.17]	0.11 [0.07, 0.16]	0.12 [0.08, 0.17]	<0.001	0.105
Primary Substance (initial diagnosis) (%)						
	Alcohol	39227 (54.2)	12844 (68.7)	26383 (49.1)	<0.001	0.506
	Cocaine hydrochloride	2681 (3.7)	769 (4.1)	1912 (3.6)		
	Cocaine paste	3401 (4.7)	1149 (6.1)	2252 (4.2)		
	Marijuana	19644 (27.1)	2589 (13.8)	17055 (31.8)		
	Other	1648 (2.3)	457 (2.4)	1191 (2.2)		
	[Missing]	5803 (8.0)	899 (4.8)	4904 (9.1)		
Corrected birth year (median [Q1, Q3])		1980.00 [1971.00, 1987.00]	1973.00 [1964.00, 1983.00]	1981.00 [1974.00, 1988.00]	<0.001	0.623
Cohabitation status (Recoded) (f) (%)						
	Alone	6816 (9.4)	2276 (12.2)	4540 (8.5)	<0.001	0.337
	Family of origin	30074 (41.5)	5648 (30.2)	24426 (45.5)		
	Others	6224 (8.6)	1520 (8.1)	4704 (8.8)		
	With couple/children	29289 (40.5)	9262 (49.5)	20027 (37.3)		
	[Missing]	1 (0.0)	1 (0.0)	0 (0.0)		
Physical Comorbidity (ICD-10) (%)						
	Without physical comorbidity	28661 (39.6)	6946 (37.1)	21715 (40.4)	<0.001	0.085
	Diagnosis unknown (under study)	39215 (54.2)	10372 (55.4)	28843 (53.7)		
	One or more	4528 (6.3)	1389 (7.4)	3139 (5.8)		
Biopsychosocial compromise (%)						
	1-Mild	6954 (9.6)	3231 (17.3)	3723 (6.9)	<0.001	0.418
	2-Moderate	41015 (56.6)	11147 (59.6)	29868 (55.6)		
	3-Severe	22998 (31.8)	3909 (20.9)	19089 (35.5)		
	[Missing]	1437 (2.0)	420 (2.2)	1017 (1.9)		
Treatment Admission Motive (%)						
	Spontaneous	32847 (45.4)	8462 (45.2)	24385 (45.4)	<0.001	0.191
	Assisted Referral	6753 (9.3)	1222 (6.5)	5531 (10.3)		
	Other	3935 (5.4)	984 (5.3)	2951 (5.5)		
	Justice Sector	6813 (9.4)	2380 (12.7)	4433 (8.3)		
	Health Sector	22056 (30.5)	5659 (30.3)	16397 (30.5)		
Public treatment center	TRUE	51710 (71.4)	15899 (85.0)	35811 (66.7)	<0.001	0.438

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[Missing]

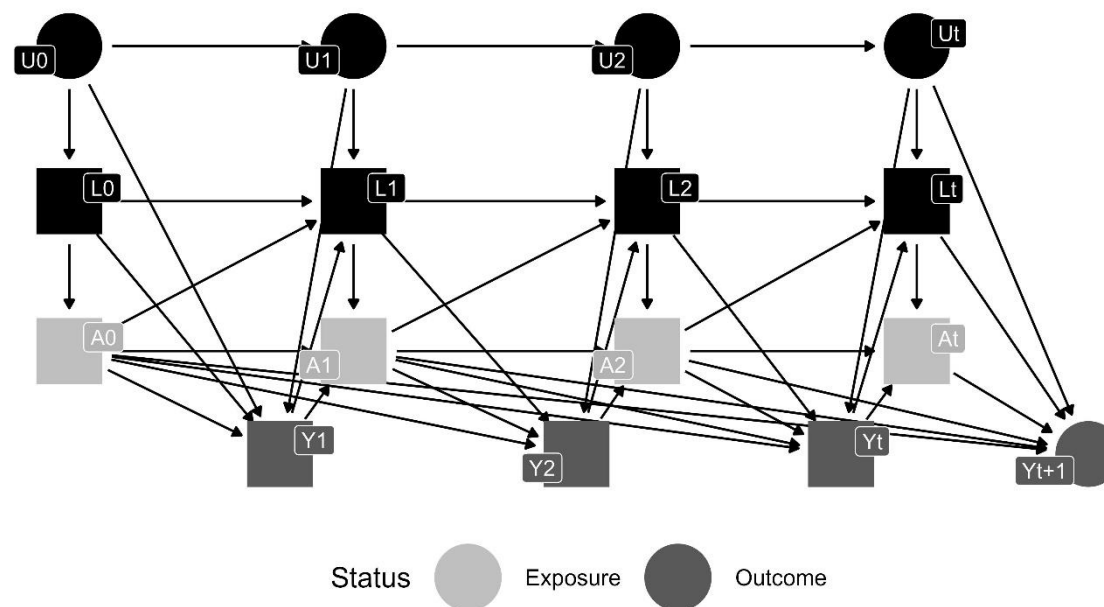
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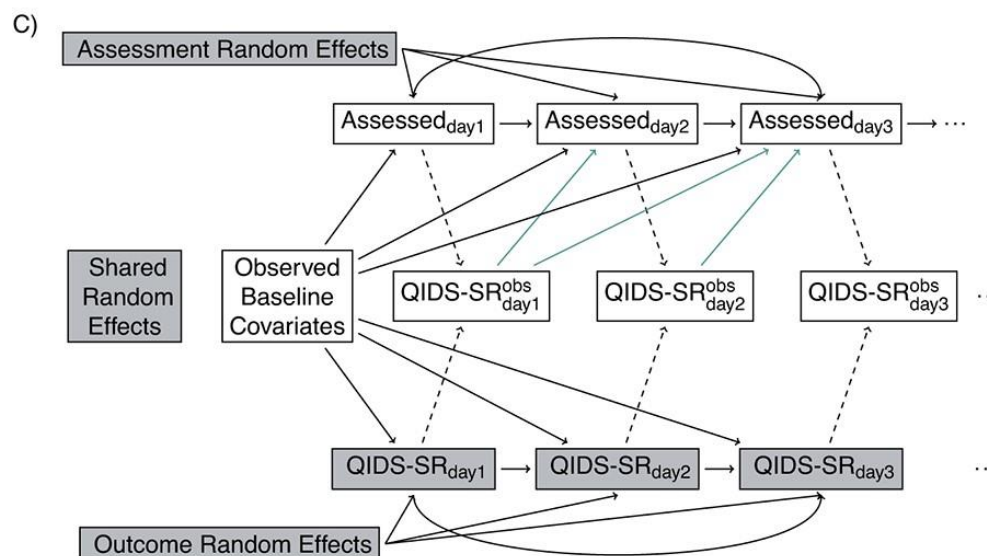
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Figure 1a. Causal diagram as a conceptual reference



Note: A= Reporting PSU at admission; Y= Time to treatment completion status from admission;  $L_0$ =Baseline confounders;  $\{L_1, L_2, \dots, L_t\}$  = time-dependent biopsychosocial; U= Unobserved confounders; t= individual treatments from 2010)

Figure 1b. Causal diagram hypothesized as the observation process

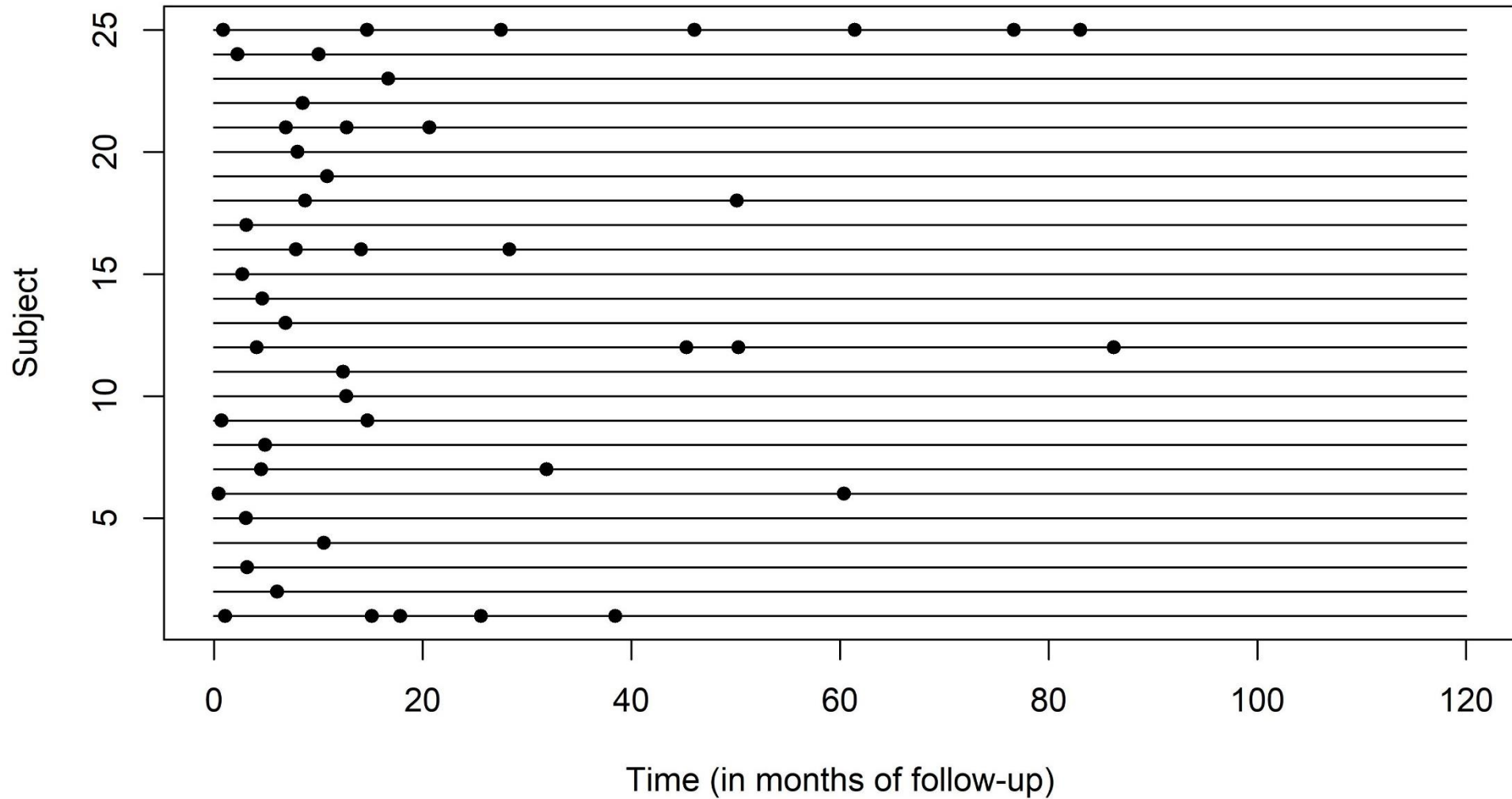


Note. All the backdoors of the month of assessment (admission to treatment), may pass through observed outcomes, history of evolution or baseline covariates to impact on outcomes. If we assume that a proportional intensity model holds, we can search evidence in the data that previous variables are associated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

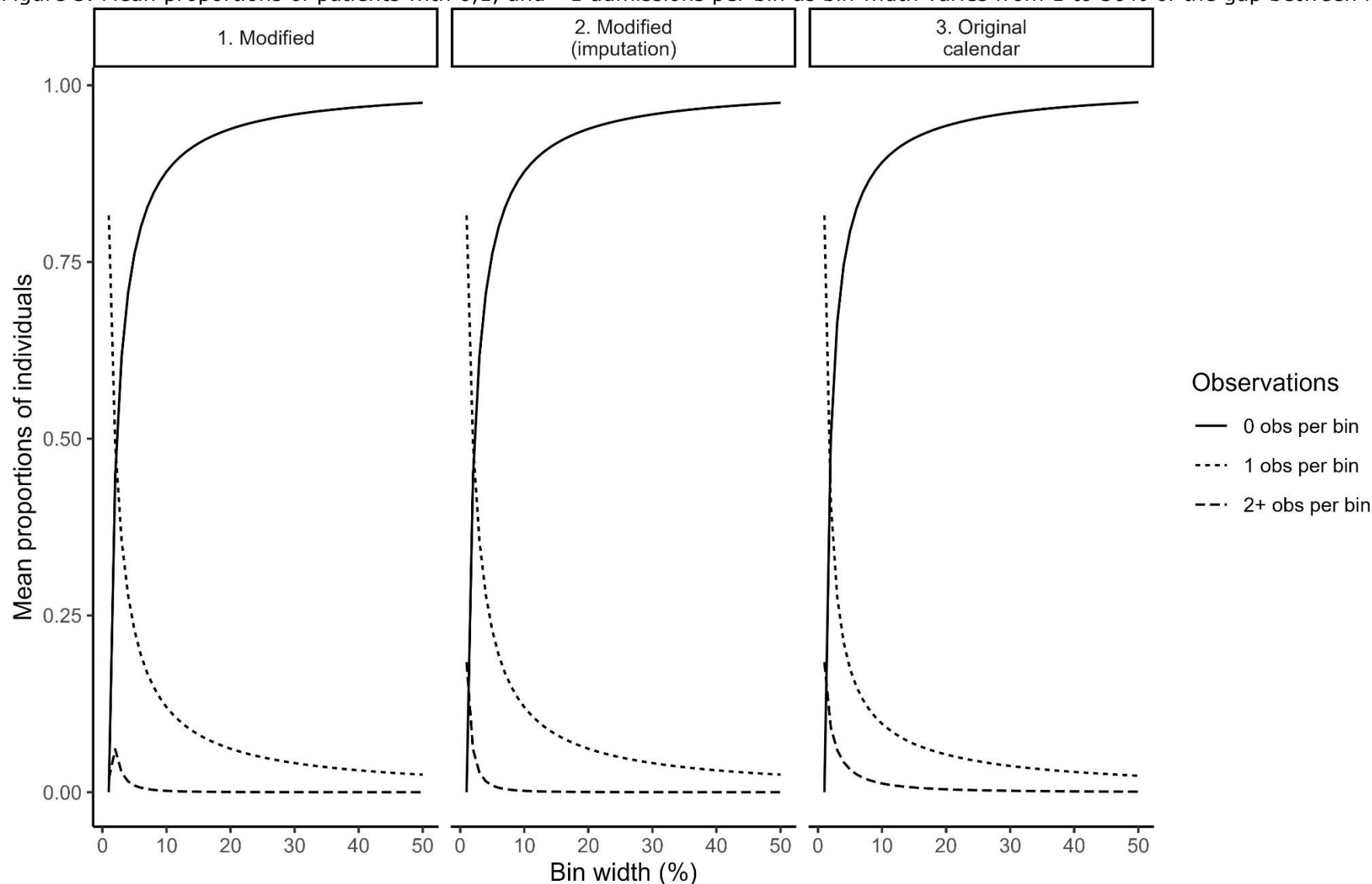


Figure 2. Abacus plot of a random subsample of 25 patients along follow-up period



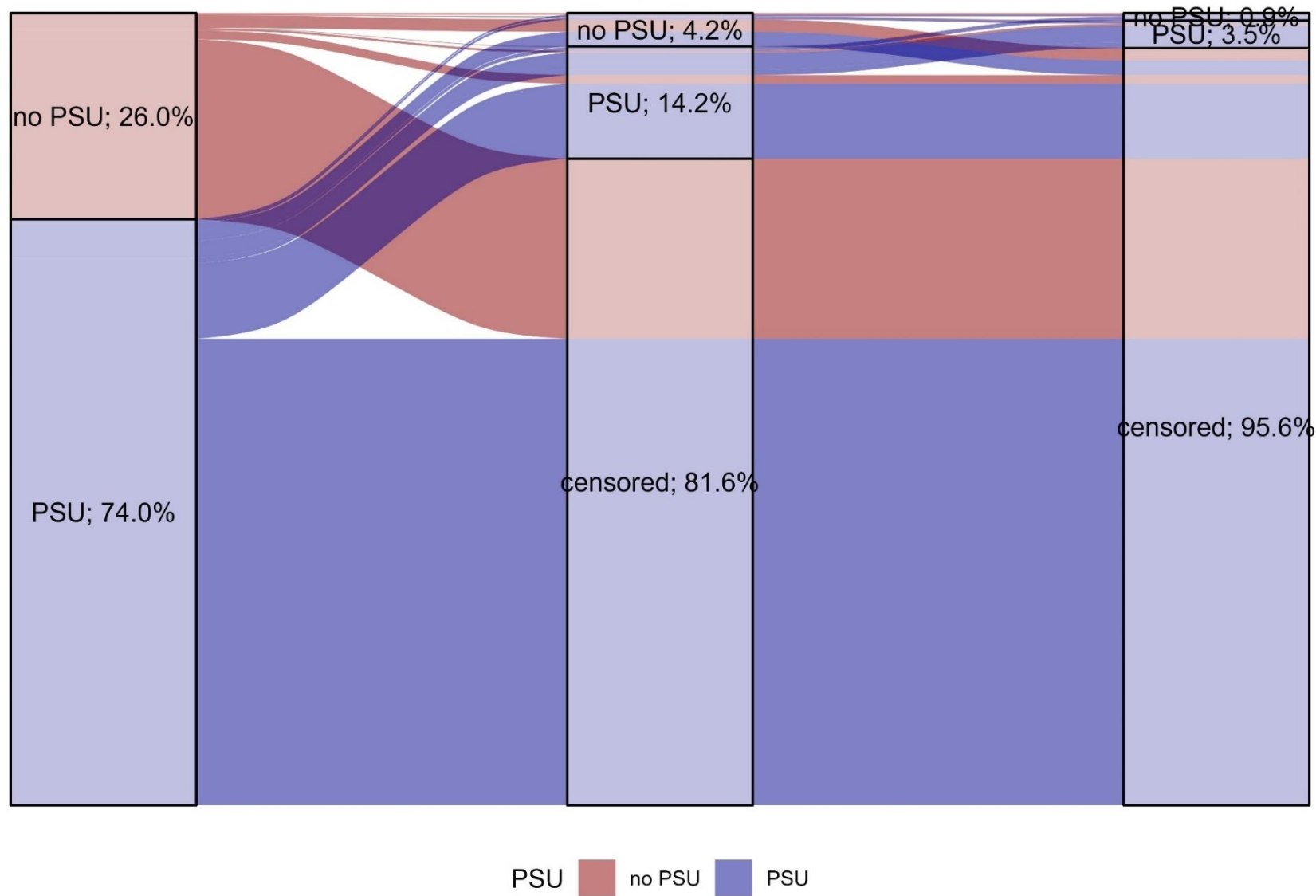
Note. Dot= treatment outcome; horizontal line= patients; seed at number 21251.

Figure 3. 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.

Figure 4. Sankey plot of PSU reported at admission in the total sample , first three treatments.



Note. Patients= 72.404

Table 2. Specifications of the treatment (visit) process

Model	Term	Hazard ratio (95% CI)	Sig.
First model	Previous dropout	1.5 (1.43, 1.57)	<0.001
	Biopsychosocial compromise (moderate)	1.06 (0.99, 1.13)	0.090
	Biopsychosocial compromise (severe)	1.57 (1.46, 1.67)	<0.001
	Less than 90 days in previous treatment	1.71 (1.66, 1.78)	<0.001
	Reported PSU in previous treatment	1.08 (1.04, 1.13)	<0.001
	Count of treatments	0.97 (0.95, 1.00)	0.030
Second model	Previous dropout	1.48 (1.42, 1.55)	<0.001
	Biopsychosocial compromise (moderate)	1.05 (0.98, 1.12)	0.180
	Biopsychosocial compromise (severe)	1.61 (1.5, 1.71)	<0.001
	Less than 90 days in previous treatment	1.77 (1.71, 1.82)	<0.001
	Reported PSU in previous treatment	1.05 (1.00, 1.1)	0.030
	Reported PSU in actual treatment	1.22 (1.19, 1.24)	<0.001

Note. First model= In Andersen-Gill format, restricted to cases with more than one treatment and lag values were fixed to one (excepting on moderate biopsychosocial compromise); In Andersen-Gill format, not restricted to cases with more than one treatment and lag values were fixed to one (excepting on moderate biopsychosocial compromise).