**Background**: Evidence on the influence of polysubstance use (PSU) on substance use treatment (SUT) non-completion is limited. Previous studies often exclude patients reporting PSU or with prior treatment histories, restricting applicability to real-world contexts. Therefore, examining the association between reporting PSU and treatment non-completion is crucial for improving treatments.

**Methods**: This retrospective cohort study analyzed records from Chilean National Substance Use Agency (2010–2019), encompassing 13,317 adults with 30,988 treatment episodes. Reporting PSU (yes/no) was the primary exposure and SUT non-completion (vs. completion) was the outcome. Relative risks (RR) and 95% confidence intervals using Poisson generalized estimating equations with inverse intensity weighting were calculated, adjusting for socio-demographics, mental health and substance use patterns. Analyses were stratified by baseline treatment settings, and homogeneity of associations was tested. Weights were obtained through Cox models with fixed lag predictors at baseline (0/1).

**Results**: The association between PSU and non-completion varied across settings (Cochran's Q lag0=14.24, p=.007; Cochran's Q lag1=13.32, p=.010). Non-completion risk was higher in patients reporting PSU in general-population intensive ambulatory (RRlag0=1.04 95%CI 1.01-1.07; RRlag1=1.04 95%CI 1.01-1.08) and in women-only residential settings (RRlag0=1.15 95%CI 1.06-1.25; RRlag1=1.13 95%CI 1.04-1.22) vs. patients not reporting PSU.

**Conclusions**: Reporting PSU was associated with a modest increase in SUT non-completion risk in intensive ambulatory and women-only residential settings. As one of the few studies from outside the Global North, it underscores the need for PSU-focused interventions. These results can guide policies and clinical practices to address complex treatment needs of patients reporting PSU and improve SUT outcomes.

**Keywords**: Polysubstance use; Substance use; Treatment non-completion; Administrative data; Chile.