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# The long-term relationship between cannabis and heroin use: An 18-20-year follow-up of the Australian Treatment Outcome Study (ATOS)



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**Kathleen T. Brady, M.D., PhD.**

Deputy Editor

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June 15, 2023

Dear Professor Brady,

Thank you for inviting us to revise and resubmit. We wish to thank the authors for their thorough feedback, substantially improving the quality of the manuscript. Please see below the 'clean version' of the manuscript. We have also submitted the 'track changes' version, separate pdf files for the figures, as well as supplementary material.

We have carefully responded to the reviewers within the 'responses to reviewers' file, making changes to the manuscript where appropriate. For instance, as pointed out by numerous reviewers, we have included additional analysis examining the relationship between cannabis and other opioid use.

We look forward to hearing back from you.

Yours sincerely,

Jack Wilson, Katherine L Mills, Matthew Sunderland, Tom P Freeman, Maree Teesson, Paul S Haber, and Christina Marel

**Authorship:** Authors JW, KLM, MS, TPF, and CM conceptualized and designed the study. JW, KLM, MT, and CM collected data and conducted analysis. JW drafted the manuscript. All authors provided critical contribution and revision of the manuscript.

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# The long-term relationship between cannabis and heroin use: An 18-20-year follow-up of the Australian Treatment Outcome Study (ATOS)

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## ABSTRACT

**Objective:** Cannabis use is common among those with opioid use disorders (OUD), but it remains unclear whether cannabis use is associated with an increase or reduction in illicit opioid use. To extend upon previous longitudinal studies with limited follow-ups, the current study examined a within-person reciprocal relationship between cannabis and heroin use at several follow-ups over 18-20-years. **Methods:** The Australian Treatment Outcome Study (ATOS) recruited 615 people with heroin dependence in 2001-2002 and reinterviewed at 3-, 12-, 24-, 36-months, 11 and 18-20-years post-baseline. Heroin and cannabis use

were assessed at each time point using the Opiate Treatment Index (OTI). A random intercept cross-lagged panel model (RI-CLPM) was conducted to identify within-person relationships between cannabis use and heroin use at subsequent follow-ups. **Results:** After accounting for a range of demographic, other substance use, mental and physical health measures, an increase in cannabis use at 24-months was associated with an increase in heroin use at 36-months (Estimate = 0.21, SE = 0.10, $p = 0.03$). Additionally, an increase in heroin use at 3-months and 24-months post-baseline was associated with a decrease in cannabis use at 12-months (Estimate = -0.27, SE = 0.09, $p < 0.01$) and 36-months post-baseline (Estimate = -0.22, SE = 0.08, $p < 0.01$). All other cross-lagged associations were not significant. **Conclusions:** Although there was some evidence of a significant relationship between cannabis and heroin use at earlier follow-ups, this was sparse, and inconsistent across time-points. Overall, there was insufficient evidence to suggest a unidirectional or bidirectional relationship between the use of these substances.

INTRODUCTION

Opioid and cannabis use disorders make up a majority (approx. 77%) of all illicit drug use disorders worldwide (1), and co-occurring use of these drugs is common (2). This is particularly concerning given increasing harms due to opioids in the US, Australia and parts of Europe (3-5), alongside a global shift towards more permissive medical and recreational cannabis policies (3). In the context of the opioid crisis and growing recognition of cannabis as a therapeutic product, there are claims that cannabis use may assist in the reduction of opioid use, although evidence to support or refute this has been limited (6, 7).

US studies utilising state-level data have used cannabis policies (e.g., recreationally legal states vs recreationally illegal states) as a proxy for cannabis use to investigate whether there is a relationship with opioid use. A systematic review of studies examining US state cannabis legislation found that the implementation of medical cannabis laws was associated with a 7.0% reduction in prescription opioids dispensed (95%CI -0.13, -0.01) compared to pre-legalisation (8). It is, however, difficult to infer a causal relationship from such ecological studies, as changes in opioid use may be due to other factors (such as differences in the availability of, and access to, opioid treatment).

Longitudinal studies provide higher quality evidence for investigating the relationship between changing patterns of cannabis and opioid use over time, and to date, findings have been mixed. Within UK and Canadian longitudinal cohort studies of treatment and non-treatment populations with OUD, those reporting cannabis use were around half as likely to report use of opioids at follow-up (9, 10). In contrast with findings of a beneficial effect of cannabis, results from two longitudinal studies in the US showed a substantial increase in illicit opioid use, and prevalence of OUD, given prior cannabis use (11, 12). Adding further uncertainty to the long-term relationship between cannabis and opioid use, studies of patients in pharmacotherapy treatment for OUD found that cannabis use did not predict illicit opioid use (13, 14).

One of the possible reasons for the mixed findings to date is lack of long-term follow up data. Previous longitudinal studies have not extended beyond several years, with most restricted to a single follow-up point. Given that patterns of cannabis and opioids can be heterogenous (15, 16), short-term follow-ups may not have adequately captured the relationship between changing patterns of use over time, which may reflect increases as well as decreases over time. Moreover, distinct patterns of use provide further justification for focusing on within-person differences in use, rather than between-person effects which have predominantly been examined. The current literature has also been limited by a unidirectional approach employed by studies (i.e. cannabis use predicting opioid use), whereas a reciprocal analysis can provide a greater understanding of whether there is a bidirectional relationship between the use of these substances, and how this may be indicative of the mechanisms responsible for an association.

*Current study*

The current study aims to overcome limitations identified in prior research by examining a within-person reciprocal relationship between cannabis and heroin use at several follow-ups over a longer period (i.e., 18-20-years) using random intercept cross-lagged panel modelling.

## METHODS

*Design*

The Australian Treatment Outcome Study (ATOS) is an 18-20-year longitudinal prospective cohort study of people entering treatment for heroin dependence in Sydney, Australia (17). The cohort consisted of 615 participants, made up of 535 (87%) people entering treatment for heroin dependence (201 maintenance therapies, 201 detoxification, and 133 residential rehabilitation), and a comparison group of 80 people who were not in treatment, recruited from

needle and syringe programs (18). Participants were deemed eligible to participate in the study if they: i) had no treatment for heroin dependence in the preceding month, ii) were not a prisoner within a correctional facility in the preceding month, iii) were aged 18-years or over, iv) agreed to provide contact details for follow-ups, and v) were proficient in English. Ethical approval was obtained from the Human Research Ethics Committees of the University of New South Wales and participating area health districts.

Participants were initially recruited and interviewed in 2001-2002 and followed up on six occasions: at 3-months, 12-months, 24-months, 36-months, 10-11-years, and 18-20-years post-baseline. ATOS has maintained remarkable follow-up rates, retaining 549 (89.3%), 495 (80.5%), 469 (76.3%), 429 (69.8%), 431 (70.1%), and 401 (65.2%) of the original sample at each follow up respectively. At 18-20-years, 109 participants were deceased (17.7%; 72 male, 37 female). Although 262 (42.6%) participants completed all waves, 595 (96.7%) completed at least one follow-up, and those retained at each follow-up were broadly similar in baseline characteristics to those not followed-up, including their heroin and cannabis use (19). Participants provided written informed consent for both participation and to be contacted for future follow-ups. Participants were reimbursed $20 AUD for each of the initial five interviews, $40 AUD at 10-11-years, and $50 AUD at 18-20-years. Methods of contacting participants are detailed in (20).



*Measures*

A standardised questionnaire was administered at baseline and at each follow-up. Past month use of cannabis, heroin and other opiates were assessed using the Opiate Treatment Index (OTI) (21) (Supplementary Figure 1). The OTI is a standardised measure that calculates the average consumption of a drug over the past 28 days. A Q-score is calculated from the number of total use episodes (e.g., number of injections or bongs) divided by the total of the two intervals between days of use. For each drug, participants are asked about the most recent three days of use, and the quantity of episodes within each day. Q-scores are interpreted as follows: abstinence, Q=0.00; once a week or less, Q = 0.01-0.13; more than once a week, 0.14-0.99; daily, 1.00-1.99; more than once

a day, >2.00. These categories will be used to describe the prevalence of cannabis and heroin use at each follow-up. Across all drug classes, the OTI has demonstrated good test-retest reliability and (>0.81), and a kappa of 0.65 between self-report and urine analysis (21).

Baseline covariates included the participant's age, sex, county of birth, main source of income during the past month, and their usual form of accommodation (e.g., privately rent, own, or homeless). The criminality scale of the OTI (21) was used to assess past month criminal involvement, and participants were asked about their lifetime prison history. Participants were asked whether they were currently receiving treatment for heroin dependence, including pharmacotherapy (e.g., methadone or buprenorphine), outpatient or inpatient detoxification, residential rehabilitation, rapid opiate detoxification, and outpatient counselling. The OTI was used to assess past month use of other drugs, including prescribed or non-prescribed opiates (e.g., tramadol), alcohol, amphetamines, cocaine, benzodiazepines, antidepressants, hallucinogens, and inhalants (e.g., amyl nitrate), as well as measuring past month injection-related risk-taking behaviours. As per previous work by (22), participants were also asked about lifetime and past 12-month history of heroin overdose. Baseline general physical and mental health were measured using the 12-Item Short Form Health Survey (SF-12) which is composed of a Physical Component Summary (PCS) score and a Mental Component Summary (MCS) score, where greater scores indicate better health (23). The Composite International Diagnostic Interview (CIDI) version 2.1 was used to assess past month diagnosis of DSM-IV major depression, lifetime diagnosis of DSM-IV post-traumatic stress disorder (PTSD) (24), and lifetime suicidal ideation and attempt, while a modified version of the Diagnostic Interview Schedule (DIS) was used to screen for a DSM-IV diagnosis of antisocial personality disorder (ASPD). Baseline ICD-10 borderline personality disorder (BPD) was assessed using the International Personality Disorder Examination Questionnaire (IPDEQ) (25).

*Statistical analysis*

Polychoric correlations were calculated to assess the relationship between cannabis and heroin use within each follow-up. To examine the relationship between cannabis and heroin use between follow-ups, a random intercept cross-lagged panel model (RI-CLPM) was conducted. The RI-CLPM is a method of analysing the degree to which (a) a construct changes over time, where cannabis use at time 1 may influence cannabis use at time 2 (autoregressive term; α2- α7, δ2- δ7), and (b) cross-lagged relations between constructs across time, where cannabis use at time 1 may influence heroin use at time 2 (crossed-lag term; β2- β7, γ2- γ7) (Figure 1) . The RI-CLPM overcomes limitations of the traditional CLPM by accounting for between-unit differences via a random-intercept (e.g., those using cannabis vs not using), so that the remaining autoregressive and crossed-lag terms pertain exclusively to within-unit fluctuations (26). Furthermore, the RI-CLPM typically provides a better fit to the data compared to the traditional CLPM, which is nested within the RI-CLPM.

Structural equation modelling (SEM) in Mplus was used to estimate the RI-CLPM, which has recently been extended for the use of categorical outcomes (27). To determine which covariates would be included in the adjusted RI-CLPM model, a series of univariable regressions were conducted to reveal which baseline characteristics were significantly associated with cannabis or heroin use at any time-point. While the focus is on heroin use, an additional RI-CLPM was conducted to examine the relationship between cannabis and other opioid use. As suggested by Asparouhov and Muthén (28) for categorical outcomes, pairwise deletion is applied to missing data (non-respondents and those deceased), and weighted least square mean and variance adjusted (WLSMV) estimators were used to account for non-normality on the outcome variables.

FIGURE 1 ABOUT HERE

To assess whether the observed values reflected those expected in the model, the following fit indices were evaluated; chi-square goodness of fit, Comparative Fit Index (CFI), Tucker-Lewis Index (TLI), Root Mean Square Error of Approximation (RMSEA), and Standardised Root Mean Square Residual (SRMR). Chi-square goodness of fit values lower than that of the baseline model, CFI and TLI values of ≥ 0.95, SRMR values ≤ 0.08, and RMSEA

vales ≤ 0.06 are indicative of a good model fit (29, 30). Standardised estimates, standard errors and *p*-values are reported for each model. An alpha level of $p<0.05$ was used to determine significance. Multiple comparisons were not adjusted for, and as such, p-values should be considered as nominal.

## RESULTS

### *Sample characteristics*

At baseline, the cohort had a mean age of 29.3 years (SD 7.8), 66.2% were male, and 79.2% were born in Australia. Only 18.4% reported wage, salary, or business as their main source of income, while 40.3% owned or rented accommodation. In terms of criminal history, 40.8% had been in prison, while the majority (54.6%) reported past month criminal activity. Nearly three-quarters (74.3%) experienced recent injection-related problems, and over half (53.7) had a previous overdose. A history of suicide attempt was common (33.0%), and the cohort had high rates of psychopathology; 24.6% met criteria for current major depression, 41.1% lifetime PTSD, 71.5% for ASPD, and 45.5% screened positive for BPD. The general physical and mental health of the cohort was poor with mean SF12 scores of 43.92 (SD 9.81) and 31.65 (SD 11.10), respectively. Further details of the cohort at baseline have been specified elsewhere (18). Relevant participant characteristics at each follow-up are provided in Supplementary Table 1. As previously demonstrated by (19, 20, 31), neither baseline heroin nor cannabis use predicted participant retention at each follow-up.

### *Heroin and cannabis use prevalence*

As seen in

Figure 2, the proportion of participants reporting heroin use more than once a day decreased substantially from baseline (55.3%) to 3-months (14.6%), further declining through to 18-20-years (5.7%). There was also a decline in the proportion of those using heroin daily and more than once a week. At 3-months, almost half (49.3%) had abstained from heroin use in the past month, increasing to 75.6% at 18-20-years. In contrast, there was an increase in the proportion using cannabis more than once a day from baseline (40.8%) to 3-months (45.2%). However, this was followed by a reduction at 12-months (30.1%), and further decline up until 18-20-years (20.4%). Furthermore, the proportion of those abstaining from cannabis use in the past month doubled from baseline (31.9%) to 18-20-years (60.6%).

FIGURE 2 ABOUT HERE

*Correlations between heroin and cannabis use*

Table 1 presents polychoric correlation coefficients between heroin and cannabis use OTI categories at each follow-up. Heroin use was positively correlated with heroin use between all timepoints (r = [.063, .565]), with the weakest correlations occurring between baseline and other timepoints. Cannabis use at different time points was also positively correlated with cannabis use between all other time points (r = [.425, .814]), with weaker correlations observed between cannabis use across greater time intervals (e.g., baseline and 18-20-years). Cannabis and heroin use were negatively correlated at baseline (r = -.108) but positively correlated at subsequent time points (r = [.118, .285]). Between time points, 33 of the 42 cannabis-heroin correlations were positive (r= [.002, .208]). Of the 9 negative correlations between time points (r= [-.012, -.118]), 8 were observed between baseline cannabis/heroin use and other time points. Given that the vast majority of the sample reported past month heroin use at study entry, the distribution was non-normal, and therefore correlation coefficients involving baseline heroin use are limited in their interpretation (32).

TABLE 1 ABOUT HERE

*RI-CLPM*

As seen in Table 2, the following fit indices suggest that the RI-CLPM provided a good fit ($\chi^2(57) = 89.702$, RMSEA = 0.031, SRMR = 0.037, CFI = 0.993, TLI = 0.988).

TABLE 2 ABOUT HERE

All autoregressive parameters were significantly positive, indicating that an increase in heroin and cannabis use relative to a person's average use across time-points predicted an increase in heroin and cannabis use at subsequent follow-ups (Table 3). There were two significant cross-lagged effects, where an increase in heroin use at 3-months relative to their average use across time-points was associated with a decrease in cannabis use at 12-months ($\gamma 3 = -0.21$, SE = 0.08, $p = 0.01$), and an increase in heroin use at 24-months was associated with a decrease in cannabis use at 36-months ($\gamma 5 = -0.23$, SE = 0.08, $p < 0.01$).

TABLE 3 ABOUT HERE

Baseline covariates determined to be significantly associated with the outcomes in the RI-CLPM model included age, sex, country of birth, main source of income, main form of accommodation, past month use of alcohol, cocaine, antidepressants and amphetamines, current form of treatment for heroin dependence, past month criminal behaviour, history of imprisonment, SF 12 PCS score, PTSD and ASPD. The inclusion of significant covariates to the RI-CLPM demonstrated a good fit ($\chi^2(57) = 89.804$, RMSEA = 0.031, SRMR = 0.020, CFI = 0.993, TLI = 0.957), where there was an improvement in model fit according to SRMR, but a worse fit according to TLI. After accounting for covariates, the autoregressive relationships between heroin use at baseline and 3-months, and heroin use at 3-months and 12-months, were no longer significant. However, all other autoregressive effects remained significantly positive. Similar to the previous model, an increase in heroin use at 3-months relative to their average use across time-points was associated with a decrease in cannabis use at 12-months ($\gamma 3 = -0.27$, SE = 0.09, $p < 0.01$), and an increase in heroin use at 24-months was associated with a decrease in cannabis use at 36-months ($\gamma 5 = -0.22$, SE = 0.08, $p < 0.01$). In addition, an increase in cannabis use at 24-months relative to their average use across time-points was associated with an increase in heroin use at 36-months ($\beta 5 = 0.21$, SE = 0.10, $p = 0.03$).

*RI-CLPM examining the relationship between cannabis and other opioid use*

As seen in Supplementary Table 2. the following fit indices suggest that the RI-CLPM examining the relationship between cannabis and other opioid use provided a good fit ($\chi^2(57) = 82.56$, RMSEA = 0.027, SRMR = 0.041, CFI = 0.994, TLI = 0.990). Similar to cannabis and heroin use, all autoregressive parameters were significantly positive (Supplementary Table 3). There were two significant cross-lagged effects, where an increase in cannabis use at 10-11-years relative to their average use across time-points was associated with an increase in other opioid use at 18-20-years ($\beta 7 = 0.25$, SE = 0.12, $p = 0.03$), and an increase in other opioid use at 3-months relative to their average use across time-points was associated with an increase in cannabis use at 12-months ($\gamma 3 = 0.16$, SE = 0.08, $p = 0.03$). As seen in Supplementary Table 2, the inclusion of significant covariates to the model demonstrated a good fit ($\chi^2(57) = 94.98$, RMSEA = 0.033, SRMR = 0.025, CFI = 0.990, TLI = 0.947). After accounting for covariates, all autoregressive parameters remained significant aside from baseline to 3-month other opioid use. There was only one significant cross-lagged effect, where an increase in other opioid use at baseline was associated with reduction in cannabis use at 3-months ($\gamma 3 = -0.17$, SE = 0.08, $p = 0.04$).



## DISCUSSION

The current study aimed to investigate the long-term relationship between cannabis and heroin use over 18-20-years among people with heroin dependence. Consistent with previous findings, cannabis use was highly prevalent within the cohort at baseline, and although rates of use and frequency decreased at each follow-up, over one-third of the participants reported past month cannabis use 18-20-years later. As expected, results of the RI-CLPM suggested that an increase in heroin and cannabis use predicts a further increase in use of the respective substance at subsequent follow-ups. In terms of cross-lagged effects, there were few significant within-person associations

between cannabis and heroin use, indicating little evidence for a consistent relationship. Likewise, there was an absence of an association between cannabis and other opioid use over 18-20-years.

The current findings are somewhat consistent with Proctor, et al. (33) who detected a positive relationship between cannabis and subsequent heroin use among a cohort of methadone prescribed patients, but only between two time-points within the first 6-months since treatment entry. The positive relationship between cannabis and heroin use observed in the current study, however, did not occur until much further into the study period, between 24 and 36-months post-baseline. Nevertheless, these findings are contrary to those of Lake, et al. (10) and Eastwood, et al. (9), who found a negative association between cannabis and opioid use among non-treatment and treatment cohorts over a period of up to 5-years. The RI-CLPM found no evidence to suggest that a within-person increase in cannabis use led to a reduction in heroin use over 18-20-years.

The current study also investigated the impact of heroin on subsequent cannabis use. While previous studies have overlooked this directional relationship, a reciprocal analysis may provide a greater understanding of the potential relationship between these two substances. From 3-months to 12-months, and 24-months to 36-months, cannabis use appeared to decrease following increasing heroin use. It may be argued that this pattern of use resembles an escalation to more harmful use of substances, like that proposed by Kandel and Faust (34). As the severity of heroin use and dependence increases following increased cannabis use, there may be a reduced need to consume cannabis. However, there was a lack of consistent evidence between cannabis and heroin use given that few cross-lag parameters were significant, and none were observed over greater time intervals (10-11-years and 18-years). Overall there is insufficient evidence to conclude that there is either bidirectional or unidirectional relationship between cannabis and heroin use.

There are some potential explanations to consider for why the current findings differ from previous studies. Given that most of the ATOS participants were enrolled in treatment at baseline, it may be argued that participants would be less likely to engage in other substances, and that subsequent treatment episodes could moderate a potential cannabis-heroin relationship. However, studies of people within treatment (9, 33), and not in treatment (10, 12), have both reported

contrasting results, hence it is unclear whether the presence and direction of a cannabis-opioid relationship differs according to treatment status. Further sample characteristics that may contribute to mixed findings include the primary substance being consumed by participants. For instance, participants enrolled in medical cannabis programs for the treatment of pain have reported a reduction in prescription opioid use (35, 36). In such cases, and within the current study, participants may be more likely to maintain their use of the substance for which they were recruited. Furthermore, their reasons for use (e.g., reduce pain, intoxication) must be considered within the context of these findings. Studies such as Lake, et al. (10) that restricted participants to those with chronic pain may have been more likely to observe a substitution effect given the rising use of cannabis as a treatment for pain (3). Overall, there are a range of participant characteristics that may explain why the current findings contrasted with those of other studies.

Alternatively, an inconsistency between the current findings and other studies may be due to differences in outcome measures. Studies have typically used binary self-report/urine drug screen measures of cannabis and opioid use (33), which may not be sensitive to changing patterns of use. Similar to Lions, et al. (37), who reported null findings, the ATOS study used the OTI as a measure of substance use. As a composite of quantity and frequency of use, the measure provides greater specificity, more adequately reflecting changes in cannabis and heroin use at each follow-up and increasing the precision of the estimates in this study.

The present findings may also be explained by an absence of measures assessing the use of different cannabis products which vary in cannabinoid concentration. As seen in Hurd, et al. (38), administration of cannabidiol (CBD), a non-intoxicating cannabinoid, reduced cue induced craving and anxiety relative to placebo in drug abstinent people with heroin use disorder. Hence, future research should explore whether the reciprocal relationship between cannabis and opioid use differs according to the use of different cannabis products and their cannabinoid constituents (e.g. CBD:THC ratio). Moreover, given that concentrations of THC in cannabis products has substantially increased within international markets (39), participant's cannabis potency may have risen over the study period. Hence the current use of THC dominant products with a lack of CBD could have contributed

to the longitudinal relationship between cannabis and heroin use. Nevertheless, this raises broader limitation around the lack of standard THC measurements (40).

This study had some key strengths. To date, this is one of the longest prospective studies to have assessed the relationship between cannabis and opioid use. A study period of 18-20-years provided a unique opportunity to examine long-term patterns of cannabis and opioid use along the life-course, particularly into middle-age, an age group reporting a rise in the prevalence of use for both substances (41, 42). Another major strength of the current study is the use of a RI-CLPM, a recently developed analytical technique that accounts for between-person stable traits, so that the focus is on within-person relationships between variables. Alternative methods of analysis face greater difficulty in accounting for time-varying and time-invariant confounding, which may ultimately inflate the strength of a relationship. To our knowledge, this is the first time that any longitudinal study of opioid use has applied this novel method.

Despite the strengths of the current study, some limitations should be acknowledged. Firstly, caution should be taken in generalising findings from the ATOS cohort to broader populations of those using opioids and cannabis. While the demographic profile and substance use characteristics of this cohort are consistent with other Australian and international studies of people using heroin (43, 44) the cohort may not adequately reflect all people using these substances over the life course. Although around half of all global opioid use is attributed to illicit opioids such as heroin, heroin use disorder accounts for a minority of OUD cases in the US and Australia (3). In response, an additional RI-CLPM was conducted to examine the relationship between cannabis and other opioid use, and similar to the cannabis-heroin findings, there was little evidence to suggests a long-term association. Secondly, population data suggests that only a small portion of those with an OUD ever seek treatment (45). Hence the current study sample may only partially represent a broader population of people with OUD who will use cannabis.

Thirdly, although the RI-CLPM accounts for unequal time intervals, the interpretation of the estimates is relative to the time between follow-ups (e.g. 36 months to 10-11-years), hence different time intervals would provide varying results (46). Fourthly, the analysis was unable to account for

time-varying confounding, as a large proportion of participants missed at least one follow-up (57.4%). Lastly, there may be concerns regarding the validity and reliability of the data given that it was entirely self-report. However, there is now extensive literature demonstrating strong psychometric properties of self-report measures of substance use among those using heroin (21, 47). Furthermore, ATOS aims to maximise recall by utilising a Timeline Follow-Back (TLFB) method (48) and a life-events chart.

Nevertheless, when extrapolating these findings, clinicians should give caution to the relationship between cannabis and opioids. These findings provide further evidence that cannabis use remains common among those with OUD long-term. Clinical services should offer additional support for those aiming to reduce their cannabis use and minimise cannabis-related harms.

In conclusion, cannabis use was shown to be prevalent within a cohort of people with heroin dependence over 18-20-years. However, there was a lack of consistent evidence for the association between cannabis and heroin use over 18-20-years. Nevertheless, caution should be taken given the emergence of cannabis-based interventions for those using opioids.

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Figure 1 Random intercept cross-lagged panel model (RI-CLPM)

Figure 2 Prevalence of past month heroin and cannabis use

Table 1 Polychoric correlations of cannabis and heroin use OTI categories at each follow-up

| | | Cannabis use | | | | | | | Heroin use | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | ***Baseline*** | ***3-month*** | ***12-month*** | ***24-month*** | ***36-month*** | ***10-11-year*** | ***18-20-year*** | ***Baseline*** | ***3-month*** | ***12-month*** | ***24-month*** | ***36-month*** | ***10-11-year*** |
| **Cannabis use** | ***3-month*** | .680 | | | | | | | | | | | | |
| | ***12-month*** | .632 | .786 | | | | | | | | | | | |
| | ***24-month*** | .609 | .754 | .776 | | | | | | | | | | |
| | ***36-month*** | .621 | .676 | .755 | .814 | | | | | | | | | |
| | ***10-11-year*** | .526 | .558 | .624 | .690 | .691 | | | | | | | | |
| | ***18-20-year*** | .425 | .519 | .494 | .500 | .552 | .715 | | | | | | | |
| **Heroin use** | ***Baseline*** | -.108 | -.012 | -.113 | -.075 | -.114 | -.118 | -.024 | | | | | | |
| | ***3-month*** | -.039 | .258 | .200 | .114 | .065 | .093 | .039 | .178 | | | | | |
| | ***12-month*** | .044 | .163 | .285 | .206 | .137 | .116 | .073 | .165 | .434 | | | | |
| | ***24-month*** | -.022 | .029 | .106 | .182 | .052 | .101 | .079 | .067 | .344 | .468 | | | |
| | ***36-month*** | .029 | .208 | .080 | .208 | .209 | .131 | .171 | .174 | .354 | .408 | .512 | | |
| | ***10-11-year*** | .023 | -.015 | .084 | .171 | .162 | .118 | .002 | .082 | .132 | .354 | .340 | .426 | |
| | ***18-20-year*** | .005 | .102 | .095 | .182 | .086 | .147 | .135 | .063 | .197 | .323 | .354 | .443 | .565 |

Table 2 Model fit indices

| Models | df | $\chi^2$ | CFI | TLI | RMSEA | SRMR |
|---|---|---|---|---|---|---|
| ***RI-CLPM*** | 57 | 89.702* | 0.993 | 0.988 | 0.031 | 0.037 |
| ***RI-CLPM with covariates*** | 57 | 89.804* | 0.993 | 0.957 | 0.031 | 0.020 |

*Significant at <0.5

Chi-square goodness of fit values lower than that of the baseline model, Tucker-Lewis Index (TLI), Comparative Fit Index (CFI) and Tucker-Lewis Index (TLI) values of ≥ 0.95, Standardised Root Mean Square Residual (SRMR) values ≤ 0.08, and Root Mean Square Error of Approximation (RMSEA) vales ≤ 0.06, are indicative of a good model fit.

Table 3 Standardised parameter estimates of the RI-CLPM, and RI-CLPM with covariates

| | RI-CLPM | | | RI-CLPM (with covariates[a]) | | |
|---|---|---|---|---|---|---|
| **Parameters** | **Estimate** | **Se** | ***p-value*** | **Estimate** | **Se** | ***p-value*** |
| ***Autoregressive parameters*** | | | | | | |
| Baseline cannabis use > 3-month cannabis use (α2)†‡ | 0.47 | 0.10 | ***<0.01*** | 0.51 | 0.09 | ***<0.01*** |
| 3-month cannabis use > 12-month cannabis use (α3)†‡ | 0.83 | 0.07 | ***<0.01*** | 0.89 | 0.09 | ***<0.01*** |
| 12-month cannabis use > 24-month cannabis use (α4)†‡ | 0.81 | 0.06 | ***<0.01*** | 0.83 | 0.07 | ***<0.01*** |
| 24-month cannabis use > 36-month cannabis use (α5)†‡ | 0.84 | 0.05 | ***<0.01*** | 0.85 | 0.05 | ***<0.01*** |
| 36-month cannabis use > 10-11-year cannabis use(α6)†‡ | 0.60 | 0.09 | ***<0.01*** | 0.57 | 0.09 | ***<0.01*** |
| 10-11-year cannabis use > 18-20-year cannabis use (α7)†‡ | 0.57 | 0.08 | ***<0.01*** | 0.54 | 0.09 | ***<0.01*** |
| Baseline heroin use > 3-month heroin use (δ2)† | 0.24 | 0.07 | ***<0.01*** | 0.08 | 0.06 | *0.20* |
| 3-month heroin use > 12-month heroin use (δ3)† | 0.28 | 0.09 | ***<0.01*** | 0.15 | 0.10 | *0.12* |
| 12-month heroin use > 24-month heroin use (δ4)†‡ | 0.36 | 0.09 | ***<0.01*** | 0.30 | 0.10 | ***<0.01*** |
| 24-month heroin use > 36-month heroin use (δ5)†‡ | 0.31 | 0.09 | ***<0.01*** | 0.29 | 0.09 | ***<0.01*** |
| 36-month heroin use > 10-11-year heroin use (δ6)†‡ | 0.28 | 0.11 | ***0.01*** | 0.28 | 0.10 | ***0.01*** |
| 10-11-year heroin use > 18-20-year heroin use (δ7)†‡ | 0.41 | 0.09 | ***<0.01*** | 0.46 | 0.08 | ***<0.01*** |
| ***Cross-lag parameters*** | | | | | | |
| Baseline cannabis use > 3-month heroin use (β2) | -0.17 | 0.11 | *0.11* | -0.13 | 0.11 | *0.23* |
| 3-month cannabis use > 12-month heroin use (β3) | -0.03 | 0.11 | *0.81* | 0.01 | 0.13 | *0.96* |
| 12-month cannabis use > 24-month heroin use (β4) | -0.16 | 0.11 | *0.16* | -0.09 | 0.11 | *0.41* |
| 24-month cannabis use > 36-month heroin use (β5)‡ | 0.15 | 0.10 | *0.15* | 0.21 | 0.10 | ***0.03*** |
| 36-month cannabis use > 10-11-year heroin use (β6) | 0.04 | 0.12 | *0.75* | 0.09 | 0.11 | *0.45* |
| 10-11-year cannabis use > 18-20-year heroin use (β7) | 0.12 | 0.12 | *0.30* | 0.13 | 0.12 | *0.28* |
| Baseline heroin use > 3-month cannabis use (γ2) | 0.00 | 0.07 | *0.99* | -0.03 | 0.07 | *0.72* |
| 3-month heroin use > 12-month cannabis use (γ3)†‡ | -0.21 | 0.08 | ***0.01*** | -0.27 | 0.09 | ***<0.01*** |
| 12-month heroin use > 24-month cannabis use (γ4) | -0.14 | 0.09 | *0.11* | -0.09 | 0.10 | *0.34* |
| 24-month heroin use > 36-month cannabis use (γ5)†‡ | -0.23 | 0.08 | ***<0.01*** | -0.22 | 0.08 | ***<0.01*** |
| 36-month heroin use > 10-11-year cannabis use (γ6) | 0.10 | 0.11 | *0.37* | 0.12 | 0.10 | *0.26* |
| 10-11-year heroin use > 18-20-year cannabis use (γ7) | -0.11 | 0.11 | *0.30* | -0.10 | 0.09 | *0.29* |

[a] Significant baseline covariates include; age, sex, country of birth, source of income, accommodation, prison history, alcohol use, amphetamine use, cocaine use, antidepressant use, current residential rehabilitation, current maintenance therapy, current detoxification, past month crime, PCS score, PTSD, and ASPD. †Significant relationship in RI-CLPM without covariates (p<.05). ‡Significant relationship in RI-CLPM with covariates (p<.05)

Figure 1 Random intercept cross-lagged panel model (RI-CLPM)

The RI-CLPM decomposes the data into a within-person part and between-person part. The cCAN and cHER represent the within-person fluctuations in cannabis and heroin use, while potentially controlling for covariates. The two random intercepts, riCAN and riHER reflect the between-person differences.

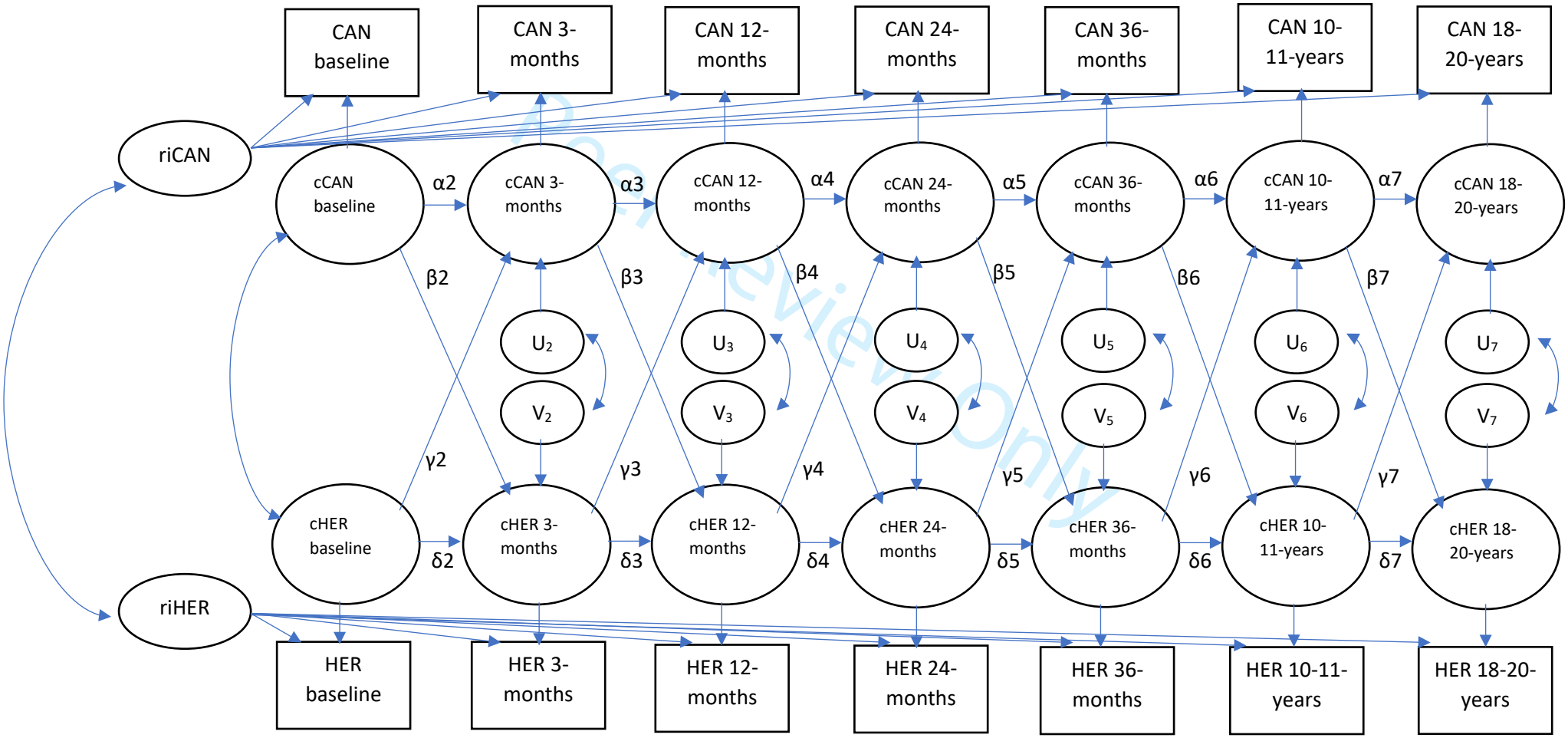
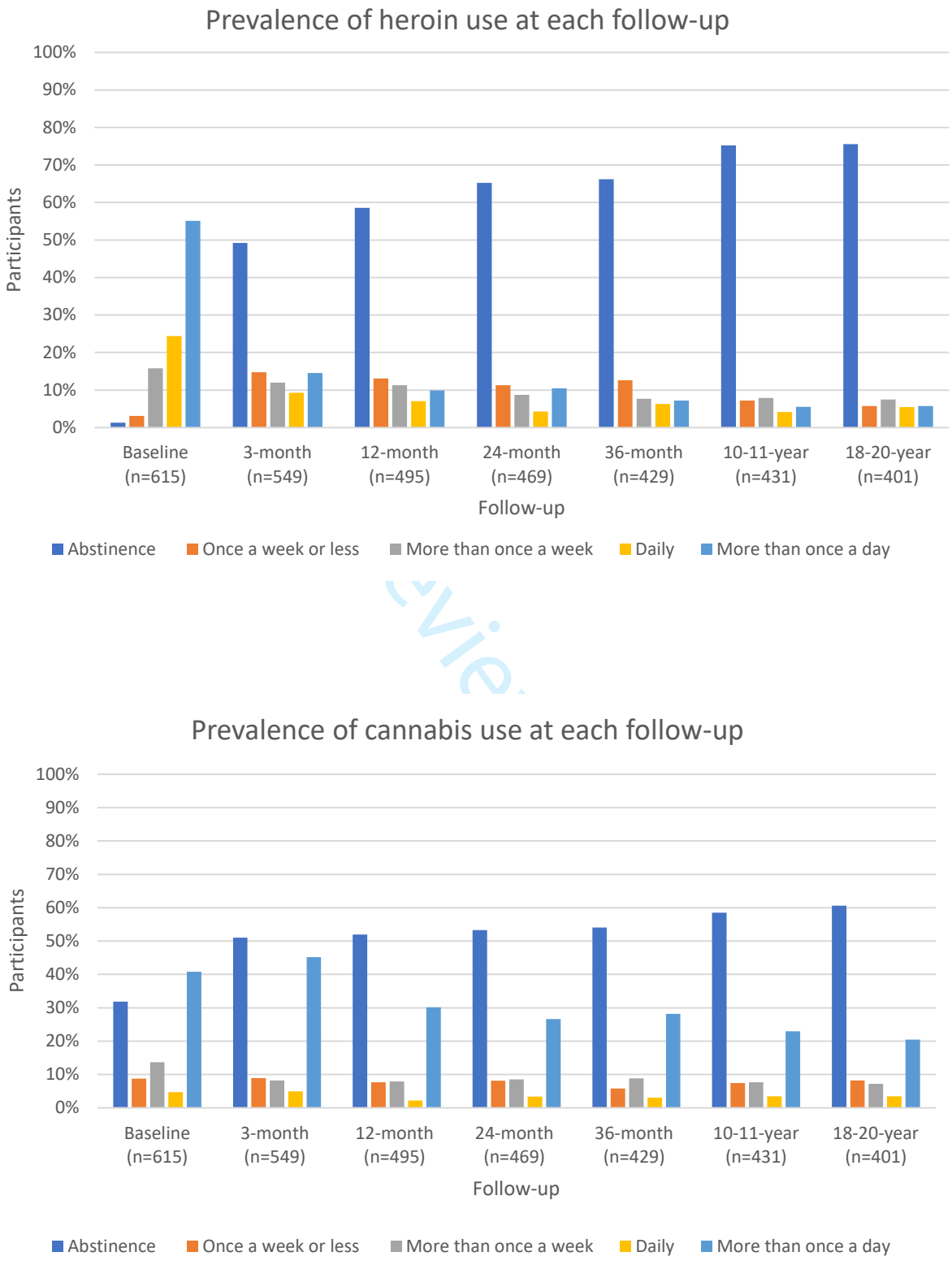


Figure 1 Prevalence of past month heroin and cannabis use



Supplementary Figure 1 Assessment of heroin, other opiate, and cannabis use

## Heroin

**1.** When was the last time you used heroin?
0 – 2 weeks ago.....1
2 weeks – 1 month ago.....2
1 – 6 months ago.....3 Skip to 8
6 – 12 months ago.....4 Skip to 8
More than 12 months ago.....5
***If 5. Record year, month*** _____ **Skip to 8**
**2.** On what day did you last use heroin? *(If 0, skip to 8)*
**3.** How many hits, smokes or snorts did you have on that day?
**4.** On which day before that did you use heroin? *(If 0, skip to 7)*
**5.** And how many hits, smokes or snorts did you have on that day?
**6.** And when was the day before that?
**7.** On how many days in the past 4 weeks have you used any heroin? days

## Other Opiates

These questions are about your use of opiates other than heroin, such as street methadone, fentanyl, oxy, codeine.
**8**. On what day did you last use opiates other than heroin? This does not include methadone or other opiates prescribed to you for the treatment of heroin dependence.
_____ *(If 0, skip to 13)*
**9.** How many pills, doses etc. did you have on that day? _____
**10.** On which day before that did you use opiates other than heroin?
_____ *(If 0, skip to 13)*
**11.** And how many pills, doses etc. did you have on that day? _____
**12.** And when was the day before that? _____

## Cannabis

*These questions are about your use of cannabis (dope, grass, hash, pot)*
**21.** On what day did you last use cannabis? *(if 0, skip to 26)*
**22.** How many joints or cones did you have on that day?
**23.** On which day before that did you use cannabis? *(if 0, skip to 26)*
**24.** And how many joints or cones did you have on that day?
**25.** And when was the day before that?