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Predictors of transitions across stages of heroin use and dependence prior to treatment-seeking among people in treatment for opioid dependence

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Abstract

Background and Aims: Little is known about transition pathways among heroin users prior to treatment. This study examined the demographic and clinical predictors of transition speed from heroin use, to dependence, to first treatment episode.

Methods: 1149 heroin-dependent participants recruited from opioid agonist treatment clinics in Sydney, Australia, underwent a structured interview. Age of onset (AOO) was collected for heroin use, dependence and treatment-seeking, childhood maltreatment, psychiatric history and other substance dependence. Discrete-time survival analyses modelled years from onset of use to dependence, and from dependence to treatment-seeking, including demographic and clinical covariates.

Findings: Median AOO for first heroin use, dependence and treatment-seeking was 18 years (inter-quartile range, or IQR=6), 21 years (IQR=7), and 24 years (IQR=10) respectively. In adjusted models, younger birth cohorts (vs. born <1960), greater childhood maltreatment and later AAO of first heroin use were associated with more rapid transitions from heroin use to dependence. Living independently, parental violence, and alcohol dependence were associated with slower transitions. Earlier treatment-seeking was associated with younger birth cohorts, having dependent children and later AOO of dependence. Delayed treatment-seeking was associated with <10 years school education, living independently, depression and alcohol dependence.

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Contributors

Authors LD and EN contributed to the development of the CATS study, obtained funding and oversaw the data collection. Authors BL, EC and NG led the writing of the first draft of this report. All authors (BL, NG, EC, EN, SD, SL, and LD) contributed to the following iterations of this report and have read and approved the final manuscript.

Conflict of Interest

BL, SL and LD have received investigator-driven untied educational grants from Reckitt Benckiser/Indivior, and BL and LD have received an untied grant from MundiPharma, for unrelated work. Neither company had input into the design, conduct, data collection, analyses or publication of these studies' findings.

Conclusions: In this treatment sample, onset of heroin use occurred during late adolescence, suggesting the need for targeted interventions in mid-adolescence. Transitions to heroin dependence, then treatment-seeking, occurred during early adulthood. Rapid transitions from use to dependence were associated with younger birth cohorts, greater exposure to childhood maltreatment, and later onset of use.

Keywords

heroin; opioid dependence; opioid use disorders; treatment-seeking

1.0 INTRODUCTION

Despite heroin dependence being documented as a major clinical and public health concern, little is known about the specific risk factors associated with the transitions from heroin use to dependence to treatment-seeking. These important transitions, and their demographic and clinical predictors, have been well-documented for nicotine (Agrawal et al. 2006, Agrawal et al. 2008, Behrendt et al. 2009, Lopez-Quintero et al. 2011), alcohol (Wagner and Anthony 2002, Agrawal et al. 2006, Sartor et al. 2007, Behrendt et al. 2009, Kalaydjian et al. 2009, Kalaydjian et al. 2009, Lee et al. 2009, Suliman et al. 2010, Lopez-Quintero et al. 2011, Silveira et al. 2011, Florez-Salamanca et al. 2013) and cannabis (Van Etten et al. 1997, Wagner and Anthony 2002, Chen et al. 2005, Agrawal et al. 2006, Agrawal et al. 2008, Behrendt et al. 2009, Lopez-Quintero et al. 2011, Florez-Salamanca et al. 2013), typically analyses of data from large population-based cohorts. Such population-level data, however, are limited in their ability to characterise heroin transitions. The relatively low population prevalence of heroin use (between 0.2% and 0.5% of the global population (Degenhardt et al. 2014), means these studies identify few heroin-dependent people.

It is widely accepted that heroin has a high “dependence liability” (the propensity of a substance to give rise to dependence as a result of its intrinsic pharmacological properties) (Darke 2011; World Health Organization, 2017). Although likely under-estimating the overall size of the heroin-using population, general population surveys from the United States (US) (e.g., Anthony et al. 1994, Van Etten and Anthony 1999) indicate that approximately one in five people who have the opportunity to use heroin, choose to do so (and men are twice as likely as women to be exposed to heroin) (Van Etten and Anthony 1999). Of those who commence heroin use, one in six do so within twelve months of the first offer (Van Etten and Anthony 1999). An often-quoted estimate suggests that approximately one in four people who use heroin become dependent (with no differences by sex and second in dependence liability only to tobacco) (Anthony et al. 1994, Darke 2011). Many of these studies were conducted prior to recent shifts in the demographics associated with opioid use in the US, where opioid use has changed from an inner-city, minority-centred problem to one involving predominantly white men and women in their late 20s living in less urban areas who report prior prescription opioid use (Cicero et al. 2014). Combined with the recent changes in the availability of heroin and other synthetic opioids (Ciccarone et al. 2017, Cicero et al. 2017), it is possible that the progression through these key milestones may be changing. Once established, however, opioid dependence is a lifelong concern associated with severe health and social consequences (Hser et al. 2001, Teesson et

al. 2015). Prospective cohort studies of dependent opioid users spanning decades in the United Kingdom (UK) and the US indicate that many dependent heroin users, who seek treatment or are identified in the criminal justice system, continue to use heroin for decades (Goldstein and Herrera 1995, Hser et al. 2001, Hser et al. 2007, Hser et al. 2008). 'Remission' rates for heroin dependence are half those for other illicit drugs (Calabria et al. 2010).

A range of demographic and clinical correlates have been identified as being associated with transitions from heroin use, to dependence and treatment-seeking. An earlier onset of heroin use is associated with poorer outcomes, including more rapid progression from heroin use to dependence (Chen et al. 2009, Woodcock et al. 2015), and a longer heroin use career (Best et al. 2008). Childhood trauma and maltreatment have been found to be strongly associated with an earlier onset of heroin use and dependence (Khoury et al. 2010, Li et al. 2012, Tomassi et al. 2017). More recent birth cohorts have higher rates of psychiatric comorbidity such as depression (Mills et al. 2004) and report more rapid transitions from first heroin use, to regular use and treatment-seeking compared to older birth cohorts (Kessler et al. 2001, Kessler et al. 2001, Mills et al. 2004, Woodcock et al. 2015).

There are marked sex differences in the clinical profiles of heroin users, with women more likely to experience most forms of childhood maltreatment and more problematic psychiatric histories, and men reporting more lifetime substance dependence diagnoses, criminal behaviour and anti-social personality disorder (Shand et al. 2011). It is possible that women progress more rapidly through usage milestones (referred to as 'telescoping'), but research findings are mixed. Some studies found women transitioned more rapidly from use to dependence (Ridenour et al. 2005), and sought treatment earlier (Hernandez-Avila et al. 2004); however, more recent studies failed to find evidence of gender-related telescoping for heroin transitions (Lewis et al. 2014, Stoltman et al. 2015), with one study identifying more rapid transitions among women who use pharmaceutical opioids (Lewis et al. 2014). Parental responsibilities may be an important facilitator of treatment-seeking among women (McMahon et al. 2002, VanDeMark 2007). Sex differences may lead to different pathways to heroin dependence and different treatment needs for men and women.

A major limitation of previous studies is that they have examined these risk factors for key heroin transitions in isolation, and could not control for the full range of demographic and clinical predictors. To our knowledge, no prior study has undertaken a detailed examination of the demographic and clinical predictors associated with speed of the key heroin use transitions prior to treatment seeking. The current study examines transitions from onset of heroin use to dependence to first treatment episode among a large heroin-dependent sample receiving opioid agonist treatment. The specific aims of this study are to: (a) examine the age of onset of first exposure to heroin, first heroin use, heroin dependence and treatment-seeking, and the time to each of these events, by sex; and (b) examine the demographic and clinical predictors of time to transition from onset of heroin use to dependence, and from onset of dependence to treatment seeking.

2.0 METHODS

2.1. Participants and procedure

The sample consisted of participants receiving opioid agonist treatment who took part in a face-to-face structured psychiatric interview between 2004 and 2008. Participants were part of a broader retrospective case-control study, the Comorbidity and Trauma Study (CATS) which examined factors contributing to heroin dependence (Shand et al. 2011). A total of 1,487 heroin-dependent participants were recruited primarily from 34 of the 35 public and private heroin agonist treatment clinics in the greater Sydney region, as well as through word-of-mouth and snowballing. To be eligible, participants were over 18 years of age, English-language proficient, and were receiving either methadone or buprenorphine for the treatment of heroin dependence. Participants reporting psychotic behaviours or suicidal intent were excluded from the study. Participants received AUD\$50 as reimbursement for time and out-of-pocket expenses. This study received approval from the following ethics boards: University of New South Wales Human Research Ethics Committee, the Washington University School of Medicine Human Subjects Committee, the Queensland Institute of Molecular Research Ethics Committee and local area health ethics boards governing public opioid agonist treatment clinic sites in Sydney.

2.2. Measures

Interviews took between 1.5 and 2.5 hours, covering substance use, mental health and family background. Socio-demographic data were also collected, including age, sex, educational attainment and parental status/dependent children. Childhood maltreatment (specifically, physical abuse resulting in injury and any sexual abuse) was assessed using an assessment from the Christchurch Health and Development Study (Fergusson et al. 1989); the interview included additional questions on emotional abuse and neglect by parents/caregivers (i.e. a total of four types of childhood maltreatment). Clinical characteristics of the sample were determined using the Semi-Structured Assessment of the Genetics of Alcoholism-Australia (SSAGA-OZ) (Bucholz et al. 1994, Hesselbrock et al. 1999). The SSAGA-OZ allowed for DSM-IV diagnoses to be made for substance dependence (alcohol, cannabis, cocaine, heroin, sedative and stimulant) and psychiatric disorders (conduct disorder, depression and post-traumatic stress disorder (PTSD)). Heroin exposure and use was assessed in a separate section of the interview. Age of onset data was collected for the following variables: first observing someone else using heroin, first being offered heroin, first heroin use, first heroin dependence and first sought heroin treatment. Although the questionnaire wording for two outcome variables was specific to 'opioids' and not 'heroin' (age of onset for first opioid use and onset of opioid dependence), all participants had used heroin. Borderline personality disorder (BPD) was assessed using a screening tool (Loranger et al. 1994). Detailed information about the interview content have been reported elsewhere (Shand et al. 2011).

2.3. Data analysis

For descriptive comparisons between groups, differences between proportions were examined using odds ratios (OR) with 95% confidence intervals (95% CI). For normally-distributed continuous data (e.g. age), means, standard deviation (SD) and parametric tests of significance (independent samples *t* test) are reported. For skewed data, medians, inter-

quartile range (IQR; a measure of statistical dispersion equal to the difference between the 25th and 75th percentiles) and non-parametric tests of significance (Mann-Whitney U) are reported.

The primary outcomes in this study were the transitions from first heroin use to heroin dependence, and from heroin dependence to treatment seeking. Outcomes were modelled as a time-to-event measure, defined in years from onset of heroin use to onset of dependence, and from onset of dependence to onset of first seeking treatment for dependence. Univariate and multivariate discrete-time survival analyses were used to examine predictors of time to dependence and time to treatment seeking (Singer and Willett 1993). Covariates examined in the models included: birth cohort (with those born prior to 1960 as the referent category), male gender, low educational attainment (less than 10 years school education), living independently, dependent children, childhood maltreatment (measured as the number of different types of maltreatment from zero to four), witnessing parental violence, depression, PTSD, alcohol and other drug (cannabis, cocaine, sedative and stimulant) dependence, age of onset of heroin use (for the model examining predictors of time from heroin use to dependence), and age of onset of heroin dependence (for the model examining predictors of time from dependence to treatment-seeking).

To maximise inferences about temporality, only characteristics occurring in the same year or prior to each outcome were included in the models. Given its clinical importance, this study assumed that onset of childhood maltreatment occurred in early childhood, prior to the onset of heroin use (no age of onset was collected for the childhood maltreatment variables).

Assumptions of proportionality were examined by testing interactions between each of the main covariates and log(time) in the models. If the interaction was significant at $p < 0.05$, the predictor was considered to violate the assumption of proportionality, and both the predictor variable and its log(time) interaction with the time-varying predictor were retained in the multivariate models. Odds ratios (ORs) and 95% confidence intervals (95% CI) are reported.

A total of 1,149 participants with complete data for all dependent and independent variables were included in analyses (out of a total of 1,487 heroin-dependent participants interviewed for the CATS).

3.0 RESULTS

3.1. Sample characteristics

The sample comprised 1,149 participants with complete data. Table 1 presents the demographic characteristics, clinical profiles and family histories of the sample. Overall, the sample reported high levels of social disadvantage, including low educational attainment, problematic family environments during childhood or early adolescence and high levels of childhood maltreatment.

Participants also reported high levels of lifetime comorbid mental health disorders including depression and PTSD. There were complex patterns of substance use and risk; including high levels of overdose and multiple drug dependencies (Table 1). A substantial minority of participants reported the onset of comorbid mental health disorders prior to age 18: one in

three reported early onset of cannabis dependence (32.3%); one in four reported early onset of PTSD (26.9%); and one in five reported early onset of alcohol dependence (22.8%) (Supplementary Appendix S1).

3.2. Heroin use transitions

Participants first observed someone else using heroin at median age 16 (IQR=5) and were first offered heroin at median age 17 (IQR=5). Approximately three in five participants (61%) reported being offered heroin within one year of first observing someone else using, and 58% reported less than a year between being first offered heroin and first using heroin. There were no differences by gender (Supplementary Appendix S2).

Participants first used heroin at median age 18 (IQR=6); there were no significant associations between age of first heroin use and birth cohort, gender or years of education (Supplementary Appendix S3). On average, participants reporting onset of heroin dependence at age 21 (IQR=7). Women had a younger age of onset of dependence (median 20 years) than men (median 21 years; $Z=2.82$, $p=0.005$). Men had significantly lower odds of developing heroin dependence within one year of first heroin use, compared to women (OR 0.68, 95% CI: 0.52–0.88); and inversely, men reported significantly higher odds of reporting a period of greater than 3 years between first heroin use and heroin dependence, compared to women (OR 1.41, 95% CI: 1.10–1.82) (See Supplementary Appendix S2). This faster transition from heroin use to dependence among women is illustrated in the unadjusted survival curve in Figure 1a (log-rank test, $p=0.003$).

Participants first sought heroin treatment a median of 2 years following the onset of heroin dependence, at median age 24 (IQR=10). Women reported a younger age of onset for treatment-seeking (median 23 years) than men (median 25 years; $Z=4.33$, $p<0.001$). Men were more likely to report slower treatment-seeking than women, with 44% of men seeking treatment more than three years following the onset of heroin dependence, compared to 35% of women (OR 1.48, 95% CI: 1.16–1.89). The faster transition from dependence to treatment-seeking for women is illustrated in the unadjusted survival curve in Figure 1b (log-rank test, $p<0.001$).

3.3. Predictors of time to transition across stages

3.3.1. First heroin use to heroin dependence—Men had 20% lower odds than women of transitioning to dependence in any given year, though this did not remain significant in the multivariate model (see Table 2). Participants in more recent birth cohorts (vs. being born prior to 1960), who had experienced more forms of childhood maltreatment and had an older age of onset of heroin use had significantly higher odds of transitioning from heroin use to dependence in any given year. Living independently of family, witnessing parental violence, depression and alcohol dependence significantly lowered the odds of transitioning from heroin use to dependence in a given year (Table 2).

3.3.2. Heroin dependence to first sought heroin treatment—In the unadjusted model, men had 22% lower odds of transitioning from heroin dependence to heroin treatment seeking in any given year (see Table 2 and Figure 1b); this did not remain

significant in the multivariate model. Significant predictors of a higher odds of transitioning from dependence to treatment-seeking in a given year included being born 1960–69, 1970–79, and 1980–89 (vs. being born prior to 1960), having dependent children and having an older age of onset of dependence. Factors that lowered the odds of transitioning to treatment seeking were having fewer than 10 years school education, living independently from family, depression and alcohol dependence (Table 2).

4.0 DISCUSSION

This is the first study to undertake a detailed examination of the demographic and clinical predictors of transitions across stages of first heroin use, dependence to treatment-seeking, among people in treatment for heroin dependence. Previous population-level studies have been limited in sample size and statistical power because of low overall population prevalence of heroin use and dependence. The current report took advantage of a large, heroin-dependent sample who participated in detailed structured interviews including sociodemographic, family history, and clinical profile data.

This study identified characteristics that conferred differential risk across the stages of transition. Telescoping effects (where women transitioned from first heroin use to heroin dependence, and from heroin dependence to treatment-seeking, more rapidly than men) were observed in unadjusted models, but not in multivariate analyses. After controlling for a range of confounders, being in younger birth cohorts (vs. being born prior to 1960), having experienced more forms of childhood maltreatment, having dependent children and having a later onset of heroin use predicted more rapid transitions from first heroin use to dependence. Inversely, living independently of family, witnessing parental violence, and alcohol dependence were significantly associated with lower odds of transitioning. Many of these sociocultural variables have not been previously examined, and they shed light on the importance of adverse early life experiences, regardless of sex, in the progression of heroin use to dependence.

Childhood and adolescent experiences were important predictors of risk in this sample. Many participants reported pre-existing adverse childhood events and psychopathology, highlighting the convergence of multiple risk factors during adolescence. Being a young parent may also be a marker for increased risk, and other studies have confirmed early sexual intercourse as a predictor of substance use disorders (Cornelius et al. 2007). Commencing heroin use in adolescence additionally exposes young people to the risks of overdose, blood-borne viruses, crime and psychological distress (Darke 2011), which are likely to have lasting effects on health and wellbeing into adulthood. We found that heroin dependence was established rapidly – by the early 20s – a finding that is remarkably consistent with a number of other studies that have examined the onset of heroin dependence (Darke 2011).

Although participants in the younger birth cohorts (vs. being born prior to 1960) reported faster transitions to heroin dependence, they also sought treatment earlier (after controlling for a range of demographic and clinical characteristics). Having dependent children and being older at the onset of dependence were also significantly associated with earlier

treatment-seeking. The finding that having dependent children may be an important catalyst to seeking treatment for heroin dependence has important implications for treatment services, which typically do not provide family-centred services (Taplin and Mattick 2015). In contrast, delayed treatment seeking was associated with poorer educational attainment, living independently of family, depression and alcohol dependence. Previous research has identified depression and heavy drinking are associated with more complex clinical profiles, ongoing heroin use and poorer treatment outcomes in longitudinal studies (Teesson et al. 2015, Darke et al. 2015).

The speed of the typical transition from first heroin use, to dependence and treatment-seeking was rapid (<5 years in total), and likely reflects the high dependence liability of heroin. Attractive and accessible treatments for heroin dependence are essential strategies in reducing the health and social burdens associated with heroin dependence. There is strong evidence that treatments, such as opioid agonist treatment, are effective in reducing drug use (Mattick et al. 2003, Amato et al. 2005, Mattick et al. 2014, Mattick et al. 2009), HIV (Gowing et al. 2013, Gowing et al. 2011) and crime (Marsch 1998, Amato et al. 2005, Mattick et al. 2009). Longer durations of treatment with fewer treatment episodes are associated with better outcomes (Darke et al. 2005, Darke et al. 2007, Burns et al. 2015, Teesson et al. 2015, Xia et al. 2015). Global demand for treatment, however, typically far exceeds the number of treatment places that are needed (Mathers et al. 2010).

This study is subject to limitations. Although the structured interview collected age of onset data for key heroin transitions (i.e., first saw someone use heroin, first offered heroin, first treatment for heroin dependence), two variables were specific to ‘opioids’ (first opioid use and onset of opioid dependence). This sample had long heroin use histories at the time of interview, and the use of illicit opioids other than heroin (such as pharmaceutical opioids) among was rare in Australia prior to 2000. We thus assumed that reports of opioid use and dependence equate to heroin use and dependence. All age of onset variables were collected through retrospective assessment, and may therefore be biased by the tendency to report events closer to the time of interview than is accurate (Shillington et al. 2012).

Our finding that being in the younger birth cohorts (vs. being born prior to 1960) was a significant predictor of transition from heroin use to dependence may possibly be biased by higher mortality among those with more clinically severe profiles in the older cohorts. An alternative explanation may be that high-purity heroin was more available in Australia in the decade prior to 2000 (when the younger birth cohorts were initiating heroin use; Darke et al. 2000), though we are unable to determine this in the current study. Given the study sample was interviewed between 2004 and 2008, it is also possible that more recent birth cohorts not captured in this study may display different use trajectories. Australia has documented increases in pharmaceutical opioid utilisation in the last decade (Karanges et al. 2017) paralleled by increases in opioid-related hospitalisations, treatment-seeking and deaths (Roxburgh et al. 2011, Roxburgh et al. 2017, Larance et al. 2017). Unlike the US, to date Australia has not observed population-level shifts in new opioid dependent populations transitioning from pharmaceutical opioid use to heroin use and injecting (e.g. Banerjee et al. 2016), nor the same rapid escalation in problematic opioid use and harm (Larance et al. 2017). Replication of this study in more recent birth cohorts would be useful. Finally, the

current report focused on heroin dependent individuals in treatment at the time of interview. Accordingly, this report did not characterise transitions among people who have used heroin but have never become dependent, nor among people who were heroin-dependent and have never sought treatment. Despite these limitations, this is a large study of heroin-dependent people that benefits from rich data on clinical profiles.

These findings have important clinical implications, with regard to the design of early, targeted interventions. Multi-faceted individual, family and community-level interventions are needed to prevent or delay heroin use and subsequent transitions to dependence. Although the wider literature suggests the predominant trajectory is long-term dependence, treatment presents unique opportunities. Making treatment more attractive and accessible to young people early in their heroin use career, and retaining them for longer treatment episodes, may disrupt long-term trajectories.

4.1. Conclusions

Onset of heroin use occurred during late adolescence and transitions to heroin dependence, then treatment-seeking, occurred during early adulthood. Factors associated with more rapid transitions from use to dependence were largely static, suggesting the importance of intervening prior to onset of use. In particular, targeted interventions during mid-adolescence may assist in improving outcomes for at-risk youth.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1a:
Unadjusted survival curve of years to transition from heroin use to dependence, by sex.

Figure 1b:
Unadjusted survival curve of years to transition from heroin dependence to treatment seeking, by sex.

Table 1:
Socio-demographic and clinical characteristics of the sample

N = 1149	
Mean age in years at interview [SD]	36.34 [8.54]
Birth cohort, n (%)	
>1960	174 (15)
1960–1969	380 (33)
1970–1979	452 (39)
1980–1989	143 (12)
Male sex, n (%)	705 (61)
Education, n (%)	
< 10 years school education	590 (51)
11–12 years school education	222 (19)
Technical college or diploma	269 (23)
University graduate	68 (6)
Family history n (%)	
Childhood maltreatment (any)	873 (76)
Emotional abuse	597 (52)
Physical abuse	563 (49)
Sexual abuse	552 (48)
Neglect	471 (41)
No. types of childhood maltreatment	
None	273 (24)
One type	270 (24)
Two types	247 (22)
Three types	222 (19)
Four types	137 (12)
Witnessed parental violence	797 (69)
Lived with biological parents until age 16	486 (42)
Median age began living independently in years [IQR]	16.00 [3.00]
Had a child prior to age 18, n (%)	77 (7)
Among men	29 (4)
Among women	48 (11)
Dependent children at interview, n (%)	660 (57)
Among men	360 (51)
Among women	297 (67)
Lifetime psychiatric disorders, n (%)	
PTSD	439 (44)
Depression	695 (61)
Lifetime substance use disorders, n (%)	
Experienced an opioid overdose	673 (59)
3+ opioid overdoses requiring medical treatment	261 (39)

	N = 1149
Alcohol dependence	473 (41)
Other drug dependence [/]	971 (85)
Cannabis dependence	668 (58)
Cocaine dependence	356 (31)
Stimulant dependence	599 (52)
Sedative dependence	415 (36)

[/]Other drug dependence includes cannabis, cocaine, sedative or stimulant dependence

Table 2:

Demographic and clinical correlates of time (in years) from use to dependence, and dependence to treatment-seeking (N=1,149)

	Use to dependence (years) ¹				Dependence to treatment seeking (years) ²			
	Unadjusted		Multivariate		Unadjusted		Multivariate	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Demographics								
Birth cohort								
Prior to 1960								
1960–1969	1.31 (1.07–1.60)	0.009	1.54 (1.25–1.91)	<0.001	1.63 (1.34–1.98)	<0.001	2.35 (1.90–2.92)	<0.001
1970–1979	2.26 (1.84–2.78)	<0.001	3.35 (2.68–4.20)	<0.001	2.28 (1.87–2.79)	<0.001	4.49 (3.53–5.71)	<0.001
1980–1989	2.93 (2.23–3.87)	<0.001	5.33 (3.90–7.27)	<0.001	3.51 (2.67–4.61)	<0.001	9.32 (6.68–13.0)	<0.001
Male	0.81 (0.70–0.93)	0.003	0.90 (0.78–1.05)	0.194	0.78 (0.68–0.89)	<0.001	0.85 (0.73–1.00)	0.044
<10 years education	0.98 (0.86–1.12)	0.789	1.06 (0.92–1.23)	0.422	0.78 (0.68–0.89)	<0.001	0.79 (0.68–0.91)	0.001
Adverse events in childhood								
No. of types of childhood maltreatment ³	1.01 (0.96–1.07)	0.605	1.11 (1.04–1.18)	0.001	0.96 (0.92–1.01)	0.101	1.01 (0.95–1.07)	0.813
Witnessing parental violence	0.90 (0.78–1.04)	0.159	0.85 (0.72–0.99)	0.038	1.05 (0.91–1.21)	0.493	1.01 (0.86–1.18)	0.947
Living independently of family	0.54 (0.43–0.69)	<0.001	0.47 (0.37–0.61)	<0.001	0.45 (0.33–0.61)	<0.001	0.46 (0.34–0.64)	<0.001
Mental health/substance use disorders								
Depression	0.81 (0.69–0.95)	0.012	0.71 (0.60–0.85)	0.002	0.93 (0.80–1.08)	0.348	0.76 (0.65–0.90)	0.001
PTSD	1.00 (0.87–1.16)	0.982	0.95 (0.80–1.12)	0.539	0.97 (0.84–1.11)	0.619	0.95 (0.81–1.12)	0.536
Alcohol dependence	0.78 (0.67–0.90)	<0.001	0.76 (0.65–0.89)	<0.001	0.73 (0.63–0.83)	<0.001	0.74 (0.64–0.86)	<0.001
Cannabis dependence	0.95 (0.83–1.09)	0.478	0.91 (0.79–1.05)	0.201	1.01 (0.89–1.16)	0.861	1.00 (0.87–1.16)	0.997
Sedative dependence	1.12 (0.91–1.39)	0.282	1.18 (0.94–1.47)	0.153	1.04 (0.87–1.24)	0.684	1.03 (0.85–1.25)	0.774
Psychostimulant dependence ⁴	1.04 (0.90–1.20)	0.618	0.97 (0.83–1.13)	0.134	1.12 (0.98–1.29)	0.093	1.07 (0.92–1.24)	0.395
Age of onset of opioid use (years)	1.06 (1.04–1.07)	<0.001	1.12 (1.10–1.14)	<0.001	-	-	-	-
Age of onset of use*log(time)	-	-	0.95 (0.93–0.97)	<0.001	-	-	-	-
Age of onset of opioid dependence (years)	-	-	-	-	1.03 (1.02–1.04)	<0.001	1.10 (1.09–1.12)	<0.001
Parenting responsibilities								

	Use to dependence (years) ¹				Dependence to treatment seeking (years) ²			
	Unadjusted		Multivariate		Unadjusted		Multivariate	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Dependent children	1.23 (1.07–1.41)	0.003	1.68 (1.44–1.96)	<0.001	1.42 (1.23–1.64)	<0.001	2.01 (1.71–2.35)	<0.001

Significant estimates are in bold (p<0.05). All models were determined using discrete-time survival analyses.

¹ Only those clinical characteristics occurring prior to onset of dependence were included in the 'Use to dependence' model

² Only those clinical characteristics occurring prior to onset of treatment seeking were included in the 'Dependence to treatment seeking' model

³ No age of onset was collected for this variable (i.e. all incidents occurred prior to age 18, but cannot determine whether childhood maltreatment occurred prior to onset of use/dependence).

⁴ Psychostimulant dependence: cocaine and/or other stimulant dependence