What factors predict the transition from methamphetamine use to methamphetamine use disorder over the life course?

Christchurch Health and Development Study (University of Otago Christchurch) – Methamphetamine in New Zealand Research Programme

Professor Joseph M. Boden

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The purpose of this report is to examine the individual, social, family and other life course factors that predict a transition from methamphetamine use to methamphetamine use disorder from late adolescence (age 16) to middle adulthood (age 40), using data from the Christchurch Health and Development Study database. The reported analyses (below) show the estimates of association between a series of predictors related to methamphetamine use measured during childhood, adolescence, and across adulthood. The analyses also show the results of proportional hazard models fit to the data, in order to specify which predictors were most strongly indicative of a transition to methamphetamine use disorder.

Summary

This report describes a series of analyses using data from the Christchurch Health and Development Study, a cohort of approximately 1000 people born in Christchurch in mid-1977 and followed to age 40 in 2017. The analyses examine which of a series of individual, family, and social factors across the life course predicted the transition from methamphetamine use to methamphetamine use disorder, a mental health disorder in which individuals describe personal, social and economic problems arising from their use of methamphetamine. A key feature of the analyses is the use of proportional hazards modelling, which estimates the onset of methamphetamine use disorder as a function of a series of predictors of methamphetamine use. This multivariable approach permits the identification of those factors that play the strongest role in predicting the transition to methamphetamine use disorder. This analytic approach, in turn, allows the identification of those individuals who are at most risk of developing the disorder, and may also point to malleable factors that, if treated or prevented, could reduce this risk.

Previous reports (Report 1 to Report 4) highlighted the life course factors that were associated with the likelihood of using methamphetamine, and using methamphetamine regularly (at least weekly or more often). However, it is important to note that these factors may also play a role in increasing the risk of transitioning from methamphetamine use to meeting criteria for methamphetamine use disorder. The present analyses suggested that while there was a large variety of factors that predicted methamphetamine use/regular use, many fewer factors had a statistically significant association with the transition from methamphetamine use to methamphetamine use disorder after proportional hazards modelling. The factors identified that increased the risk of transitioning to methamphetamine use disorder included male gender, parental history of illicit drug use, paternal overprotectiveness (father's authoritarian parenting), novelty-seeking, adolescent conduct disorder, adult major depression, and adult unemployment. This pattern of results suggests that, while some factors are not particularly malleable (gender and personality, for example), it may be possible to identify individuals at risk of developing methamphetamine use disorder during adolescence and adulthood, in order to target and prioritise intervention and treatment.

Contents

1. Main aim

In the present investigation, we aimed to examine the factors that predict the transition from methamphetamine use to methamphetamine use disorder (previously known as "methamphetamine abuse/dependence", but changed following the publication of the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders [1]). The DSM defines this disorder as a "pattern of amphetamine-type substance… use leading to clinically significant impairment or distress" (p. 561). Symptoms of the disorder include: taking the drug in larger amounts or over a longer period than was intended; a persistent desire or unsuccessful efforts to cut down or control use; spending a great deal of time obtaining, using and recovering from the drug; craving or strong desire to use the drug; use of the drug resulting in a failure to fulfil major role obligations; continued use despite persistent or recurrent social or interpersonal problems caused by the drug; giving up important social, occupational or recreational activities because of the drug; use in situations that are physically hazardous; continued use despite a physical or psychological problem arising from the drug; tolerance (needing to use more for the same effect or diminished effect with the same dose); or withdrawal symptoms. Endorsement of two or more of these symptoms within a 12-month period is the criterion for a diagnosis of methamphetamine use disorder.

Previous reports (Report 1 to Report 4) have shown that there are a range of factors in childhood, adolescence and adulthood that are associated with both casual and regular use of methamphetamine. These factors include childhood family sociodemographic background, childhood family functioning, individual personality and behavioural factors, adolescent mental health and substance use disorders, adult mental health, substance use, life stress, and experience of unemployment. These variables were used in the present analysis to derive a prediction model of the transition from methamphetamine use to methamphetamine use disorder, through use of Cox proportional hazards modelling, which has been used previously in this context to analyse substance use disorder onset [2]. This form of analysis permits the modelling of a hazard function, based on the predictors found to be significantly associated with either increasing or decreasing risk, over several time periods. This is a multivariable modelling approach in which predictors are added and removed from models, with only statistically significant predictors remaining.

Using the data available, we fit a Cox proportional hazards model in which the risk of transitioning from methamphetamine use to methamphetamine use disorder during the period 16-40 years was modelled as a function of the covariate factors described under the 'Measures' section, measured from birth to age 40 years. This analysis included only participants who had reported using methamphetamine at least once during the study.

2. Measures

2.1. Methamphetamine use disorder (16-40 years)

At each assessment from the period covering ages 16-40, participants were asked a series of questions concerning problems associated with the use of illicit drugs other than cannabis (a separate section for problems associated with cannabis was also employed). While we did not query whether cohort members had problems associated with every possible drug, we did ask specifically about four classes of drugs, one of which was methamphetamine. Using this information, we were able to classify cohort members as to whether they met DSM criteria for

illicit drug (methamphetamine) use disorder. The following table displays the percentage of those cohort members who met criteria for the disorder during each assessment period.

Table 1 Percentage of the cohort reporting under each category of methamphetamine use/ disorder

Assessment period	Methamphetamine use	Methamphetamine use disorder	% Using methamphetamine who also met criteria for methamphetamine use disorder
16-18 years	3.3	2.3	69.7
18-21 years	5.5	4.3	78.2
21-25 years	22.4	6.0	26.8
25-30 years	14.4	3.8	26.4
30-35 years	7.8	3.1	39.7
35-40 years	7.4	4.0	54.1

Table 1 shows that those who reported using methamphetamine early (prior to age 21) had relatively high rates of meeting criteria for methamphetamine use disorder, but these rates dropped considerably between ages 21-30. Those using methamphetamine in their 30s again had a relatively high rate of methamphetamine use disorder. These data suggest that those using methamphetamine earlier in life (prior to age 21), and in their 30s, were more likely to have problems arising from their use of methamphetamine.

2.2. Childhood/ adolescent predictors (0-16 years) of methamphetamine use/disorder

We examined the database of the study to determine the variables that would be the most important and useful in examining childhood/ adolescent factors that may predict methamphetamine use (and in turn, methamphetamine use disorder) during the period 16-40 years. This was based in previous literature and research within the Christchurch Health and Development Study [3-6]. Variables in five domains were considered as follows.

2.2.1. Measures of family socio-economic and demographic background

Maternal age. Assessed at the time of the survey child's birth.

Family living standards (0-10 years). At each year, a global assessment of the material living standards of the family was obtained by means of an interviewer rating. These were averaged over the period 0-10 years.

Maternal and paternal education (at birth). Parental education level was assessed at the time of the survey child's birth reflecting the highest level of educational achievement attained, using a

three-level scale. These levels were: no secondary school qualifications; at least one secondary school qualification; tertiary qualification.

Family socio-economic status (SES, at birth). Family SES was assessed at the time of the survey child's birth using the Elley-Irving [7] scale of socio-economic status for New Zealand.

Single parenthood (at birth). Family structure was assessed at the time of the survey child's birth.

Averaged family income (0–10 years). At each year, estimates of the family's gross annual income were obtained from parental report and were recoded into decile [1] categories.

2.2.2. Measures of family functioning

Parental illicit drug use (11 years). At age 11, parents were questioned regarding their history of illicit drug use. The cohort member was classified as having a parent history of illicit drug use if one of his/her parents was reported to have a history of illicit drug use.

Parental alcohol problems (15 years). This was assessed at age 15 years via parental report. These reports were used to form a dichotomous measure of whether or not the young person's parents reported experiencing problems with alcohol.

Parental criminality (15 years). At age 15 years, parents were questioned as to whether any parent had a history of criminal offending. The cohort member was classified as having a parent history of criminality if one of his/her parents was reported to have a history of offending.

Changes of parents (0–15 years). At each assessment from birth to 15 years, information was gathered on changes in the cohort member's family situation since the previous assessment. Using this information, an overall measure of family instability was constructed up to age 15, representing the number of changes in parental figures (due to separation, divorce, death, or re-partnering) in the home during the life of the cohort member to age 15.

Parental Bonding (Maternal and Paternal Care and Protection; 16 years). To measure parental bonding, the maternal care and protection scales of the Parental Bonding Instrument (PBI) [8] were administered to the cohort members at the age of 16 years. The young person was asked to rate their parents on the PBI items describing the quality of care and protection throughout their childhood. The care scale measures the extent to which the parents provide support, affection and nurturing with a high score indicating high levels of care. The protection scale measures the extent to which parents exhibit tendencies to over protection or over control with a high score indicating tendencies to over control. The reliabilities of the resulting scale scores were assessed using coefficient alpha and found to be acceptable: maternal care $\alpha = .89$; paternal care $\alpha = .91$; maternal over protection $\alpha = .85$; paternal over protection $\alpha = .87$.

2.2.3. Individual, personality and behavioural factors

Gender. Recorded at birth.

Child conduct and attention problems, and anxious/withdrawn behaviour (7–9 years). When sample members were aged 7–9 years, information on child behaviour problems was obtained

[1] Decile categories are obtained by ranking income estimates from highest to lowest, and dividing these into groups representing 10% of the overall distribution. Because income is a highly skewed measure, the decile score serves as the income measure.

from parental and teacher report using a behaviour questionnaire combining items from the Rutter et al. [9] and Conners [10] parental questionnaires (α = .97; .93; and .92, respectively).

Neuroticism (14 years). This was assessed using a short form version of the Neuroticism scale of the Eysenck Personality Inventory [11] at age 14 (α = .80).

Novelty-seeking (16 years). Novelty-seeking was assessed at age 16 using the novelty-seeking items from the Tridimensional Personality Questionnaire [12] (α =.76).

Childhood IQ (8-9 years). At ages 8 and 9 years, cohort members were assessed using the revised version of the Wechsler Intelligence Scale for Children (WISC-R [13]) modified for New Zealand conditions. At each age, total IQ scores were computed using the method described in the test manual. The reliabilities of these measures assessed by using split half methods ranged from .93 to .95. The IQ measure used in the present analyses was based on an average of the total IQ score at the two ages.

GPA (11-13 years). School performance was assessed via teachers' ratings in each of five areas of the curriculum (reading, handwriting, written expression, spelling, mathematics) using a 5-point scale ranging from very good to very poor. To provide a global measure of the child's educational achievement over the interval from 11-13 years, the teacher ratings were summed across years and curriculum areas and then averaged to provide a teacher rating grade point average for each child.

2.2.4. Abuse exposure

Childhood sexual abuse (0-16 years). At ages 18 and 21 years, sample members were questioned about their experience of sexual abuse during childhood (<16 years) [4]. Questioning spanned an array of abusive experiences from episodes involving non-contact abuse (e.g. indecent exposure) to episodes involving attempted or completed intercourse. A four-level scale was devised reflecting the most extreme form of sexual abuse reported by the young person at either age. The levels were: no sexual abuse; non-contact sexual abuse; sexual abuse involving physical contact but not penetration; penetrative sexual abuse.

Childhood physical abuse (0-16 years). At ages 18 and 21 years, sample members were questioned about their experience of physical punishment during childhood (<16 years) [14]. Questioning spanned an array of experiences with physical punishment and the frequency with which these occurred during childhood. A four-level scale was devised reflecting the most extreme form of physical punishment reported by the young person at either age. These levels were: no physical punishment; occasional physical punishment; regular physical punishment; harsh and abusive physical punishment.

Exposure to parental intimate partner violence (0-16 years). At the age of 18, sample members were questioned concerning their experience of violence between parental figures during their childhood (prior to age 16 years), with questions derived from the Conflict Tactics Scale [CTS: 15]. The items were chosen on the basis that the behaviours could have been readily observed and reported on by the participant, and also to span the potential range of violent behaviour from verbal abuse to physical assault. Separate questioning was conducted for violence initiated by the father against the mother and for violence initiated by the mother against the father, and combined into a single scale score representing overall exposure across both parents.

2.2.5. Adolescent problem behaviour

Information concerning disruptive childhood behaviour was obtained at two assessments taking place when the sample members were aged 15 and 16 years. At each age, sample members were interviewed on a comprehensive mental health interview that examined aspects of mental health and adjustment over the previous 12 months. A parallel interview was also conducted with the child's mother at each assessment stage.

Conduct disorder, oppositional defiant disorder, attention deficit hyperactivity disorder (14-16 years). As part of the assessments at each age, information was obtained on DSM-III-R [16] symptom criteria for disruptive childhood behaviours, including conduct disorder (CD), oppositional defiant disorder (ODD), and attention deficit hyperactivity disorder (ADHD) [17]. For child self-report, the assessment of ODD and ADHD was based on the relevant sections of the Diagnostic Interview Schedule for Children (DISC) [18], whereas CD was assessed using the Self-Report Early Delinquency (SRED) scale [19]. For parental reports, ODD and ADHD were assessed using items from the Revised Behaviour Problems Checklist (RBPC) [20], and CD was assessed using a parent version of the SRED. The combined symptom data thus comprised information on DSM-III-R symptom criteria for two separate 12-month periods (ages 14-15 and 15-16 years) from two sources (parent, self-report).

Alcohol use disorders (15-16 years). At each interview at ages 15 and 16, cohort members were asked a series of questions concerning whether the individual experienced any problems relating to their drinking. This measure was based on the Diagnostic Interview Schedule for Children (DISC) [21], in order to obtain information pertaining to DSM-III-R [16] symptoms of alcohol abuse/alcohol dependence (alcohol use disorder). These data allowed classification of participants as to whether they meet DSM criteria for an alcohol use disorder; during the period following the previous assessment.

Internalizing disorders (14-16 years). Parallel to the assessment of disruptive behaviour disorders, ages 15 and 16 years cohort members and their parents were questioned about symptoms of major depression and anxiety disorders (generalized anxiety disorder; over-anxious disorder; social phobia; simple phobia) occurring in the previous 12 months using the relevant sections of the Diagnostic Interview Schedule for Children [DISC: 18]. These items were used to classify participants according to DSM-III-R [16] symptom criteria for major depression and anxiety disorders. Participants were classified as having major depression or an anxiety disorder during the period 14-16 years if they met criteria for disorder on the basis of either self or parental report over the period 14-16 years.

Deviant peer affiliation (age 15). At the assessment at age 15, cohort members and their parents were asked to indicate how many of the child's friends were "deviant", defined as smoking cigarettes, drinking alcohol, using illicit drugs, or who committed crimes. The larger of the two answers (child; parent) was used as the measure.

2.3. Contemporaneous predictors (16-40 years) of methamphetamine use/disorder

Several variables, measured contemporaneously with methamphetamine use, will also be employed as factors that potentially predict methamphetamine use (and therefore also methamphetamine use disorder) from age 16-40. Previous CHDS analyses have shown that substance use in adulthood tends to "cluster" particularly in early adulthood, and specifically for illicit drugs in early and later adulthood [2, 22]. In addition, mental health disorders such as depression and anxiety [23, 24], as well as life stress [25] and unemployment [26, 27] have also been shown to be associated with substance use outcomes in analyses of CHDS data. Finally,

it is clear that factors such as substance use, life stress and unemployment are associated with psychosocial outcomes in adulthood [26, 27]. The variables considered include:

Alcohol use disorders (16-40 years). At each interview from age 18 years, cohort members were asked a series of questions concerning whether the individual experienced any problems relating to their drinking. This measure was based on the Composite International Diagnostic Interview (CIDI) [28] at ages 18 , 21, 25, 30, 35 and 40 years, in order to obtain information pertaining to DSM-IV (age 18 and above) [29] symptoms of alcohol abuse/alcohol dependence (alcohol use disorder). These data allow classification of participants as to whether they meet DSM criteria for an alcohol use disorder at any time during the period 16-40 years.

Major depression (15-40 years). Cohort members completed the CIDI at ages 18, 21, 25, 30, 35, and 40 years. These data were used to classify individuals as to whether they met DSM-IV criteria for major depression over the intervals 15-18 years, 18-21 years, 21-25 years, 25-30 years, 30-35 years, and 35-40 years. In turn, any participant who met criteria for major depression during at least one assessment period was classified as having major depression during the period 15-40 years.

Other substance use disorders (15-40 years). At ages 18, 21, 25, 30, 35 and 40 years, cohort members were questioned about their substance use behaviours and problems associated with substance use since the previous assessment (tobacco, cannabis), based on the CIDI (items for cigarette smoking were custom written). Using this information cohort members were classified as meeting DSM-IV criteria for nicotine dependence and cannabis dependence over the intervals 15-18 years, 18-21 years, 21-25 years, 25-30 years, 30-35 years, and 35-40 years (for nicotine dependence, the measure refers to current ND at ages 18, 21, 25, 30, 35 and 40 years). These reports were combined over the period 15-40 years to create a single classification of whether participants met criteria for a tobacco or cannabis use disorder at any point during the period 15-40 years.

Unemployment (18-40 years). At each assessment, starting at age 21, cohort members were asked whether they had been unemployed and looking for work for three or more months during any calendar year since the previous assessment (ages 18–21, 21–25, 25–30, 30–35, and 35-40 years). These reports were combined over the period 21-40 years to create an overall classification of unemployment status over the period 18 to 40 years.

Stressful life events other than unemployment (18-40 years). Life events were assessed for each 12-month period during ages 18–40 years using a 30-item inventory based on the Social Readjustment Rating Scale [30] supplemented by custom-written survey items. These items spanned several domains, including, for example, death and illness, relationship problems and difficulties, and crime victimization. All items were scored on a 0 to 4 scale (0 = *no event*, 1 = *not upset or distressed*, 2 = *a little upset or distressed*, 3 = *moderately upset or distressed*, and 4 = *very distressed*). Using this information, a measure of exposure to stressful life events was created by summing the scores for each item for each 12-month period, and then summing over each assessment period and across periods, resulting in a total life events distress score for the periods 18-40 years.

3. Preliminary findings

3.1. Association between childhood/ adolescent predictors and lifetime methamphetamine use/ disorder

Below are illustrated the associations between each of the childhood/ adolescent predictors (confounding factors) detailed previously, and lifetime methamphetamine use (ages 16-40) and methamphetamine use disorder. Spearman's *r* was used as the measure of association as lifetime methamphetamine use and methamphetamine use disorder were dichotomous variables (i.e. participants were categorised as either using or not using methamphetamine and as either having or not having a methamphetamine use disorder at different time points), and many of the measures reported were also categorical in nature (Spearman's *r* is a non-parametric statistic, which therefore does not require an underlying assumption of a normal distribution of the two variables for which a correlation is being estimated). An important assumption for the evaluation of confounding factors in observational data is that the fixed (time-invariant) confounding factors must be associated with the exposure (in this case, methamphetamine use/disorder).

For social research data such as that reported below, a correlation with an absolute value of 0 to 0.9 is considered "weak" in magnitude, 0.10 to 0.19 is considered "moderate", and 0.20 or higher is considered "strong". Significant associations are presented in the table below in bold (p-value). P-values refer to "probability values", which refer to the likelihood of error in conclusions drawn using the analysed data. Our maximum acceptable likelihood of error is set at 5% as a matter of convention. P-values larger than this are referred to as "non-significant", while p-values smaller than this are referred to as "significant" (with significance level noted at the foot of Table 2).

Table 2: Associations between childhood/adolescent predictors and lifetime methamphetamine use/disorder

Measure	Methamphetamine use	Methamphetamine use disorder
Measures of family socio-economic and demographic background		
Maternal age (at birth)	-.03	-.02
Family living standards (0-10 years)	-.06	-.05
Maternal education (at birth)	.00	.05
Paternal education (at birth)	-.06	-.00
Family socio-economic status (at birth)	-.00	-.03
Single parenthood (at birth)	.02	.03
Averaged family income (0-10 years)	-.04	-.02
Measures of family functioning		

Parental illicit drug use (11 years)	.06	**.07***
Parental alcohol problems (15 years)	.02	.06
Parental criminality (15 years)	.05	**.09****
Changes of parents (0-15 years)	**.07***	**.**06
Maternal care (16 years)	-.04	**-.08***
Paternal care (16 years)	**-.09***	**-.10****
Maternal over-protection (16 years)	**.07***	**.08****
Paternal over-protection (16 years)	**.10****	**.11****
Individual, personality and behavioural factors		
Gender (at birth)	**-.14*****	**-.07***
Child conduct problems (7-9 years)	**.09****	**.09****
Child attention problems (7-9 years)	**.07***	**.09****
Anxious/ withdrawn behaviour (7-9 years)	**-.09****	-.02
Neuroticism (14 years)	-.06	**-.07***
Novelty-seeking (16 years)	**.22*****	**.14*****
Childhood IQ (8-9 years)	.06	-.01
GPA (11-13 years)	-.00	.03
Abuse exposure		
Exposure to childhood sexual abuse (0-16 years)	-.02	.04
Exposure to childhood physical punishment (0-16 years)	.04	**.09****
Exposure to parental IPV (0-16 years)	.03	.04
Adolescent problem behaviour and mental health		
Conduct disorder (14-16 years)	**.19*****	**.15*****
Oppositional defiant disorder (14-16 years)	**.17*****	**.09****
Attention deficit hyperactivity disorder (14-16 years)	**.11*****	**.08***
Alcohol use disorder (15-16 years)	**.10****	**.07***
Major depression (14-16 years)	-.06	-.01
Anxiety disorder (14-16 years)	-.05	.02
Deviant peer affiliation (15 years)	**.16*****	**.15*****

* p < .05; ** p < .01; *** p < .001

As can be seen from Table 2, childhood, family functioning and abuse exposure variables were for the most part weakly associated (or not significantly associated) with later methamphetamine use/methamphetamine use disorder. On the other hand, behaviour problems (externalizing) in adolescence (and association with deviant peers) were moderately associated with later methamphetamine use/disorder. In terms of personality, novelty-seeking was strongly associated with methamphetamine use (and moderately with methamphetamine use disorder). The focus of the model detailed below will be the statistically significant ($p < .05$) variables noted above.

It is also worth noting that the profile of potential confounding variables differs with respect to whether a person used methamphetamine, or met criteria for a methamphetamine use disorder at some point. Predictors varied both in their strength of association with the methamphetamine variables, and whether they reached statistical significance.

3.2. Association between contemporaneous predictors and lifetime methamphetamine use/ disorder

The associations between contemporaneous predictors and lifetime methamphetamine use (ages 16-40 years) and methamphetamine use disorder are shown in Table 3 below. As per previous section, Spearman's *r* and p-values are used to assess the relationship between factors.

Table 3: Associations between contemporaneous predictors and lifetime methamphetamine use

Measure	Methamphetamine use	Methamphetamine use disorder
Alcohol use disorder (ages 16-40)	**.18*** **	**.19*** **
Major depression (ages 15-40)	**.07***	**.12*** **
Nicotine dependence (ages 16-40)	**.24*** **	**.18*** **
Cannabis use disorder (ages 16-40)	**.26*** **	**.35*** **
Unemployment (ages 18-40)	**.18*** **	**.16*** **
Life stress (ages 18-40)	**.22*** **	**.17*** **

* $p < .05$; ** $p < .01$; *** $p < .001$

As can be seen in Table 3, the contemporaneous measures are significantly associated with methamphetamine use and methamphetamine use disorder, although the magnitude of association varied. Therefore each of these will be considered in the analyses.

4. Main findings

To model the data on the predictors of the transition from methamphetamine use to methamphetamine use disorder, a Cox proportional hazards was fitted. This model estimated the hazard function (the likelihood of meeting criteria for methamphetamine use disorder) as a function of the set of predictors shown in Tables 2 and 3.

The model was fitted in steps, as follows.

- In the first model, the predictors presented in Table 2 (i.e. measures of family socio-economic and demographic background; measures of family functioning; individual, personality and behavioural factors; abuse exposure; and adolescent problem behaviour) were entered in blocks, with forward and backward elimination of variables to identify a stable and parsimonious set of predictors.
- The second model extended the first model by including the contemporaneous factors listed in Table 3 (i.e. alcohol use disorder; major depression; nicotine dependence; cannabis use disorder; unemployment; and life stress), with the factors being entered into the models simultaneously, with forward and backward elimination of variables to identify a stable and parsimonious set of predictors.

All models were fitted using Stata 16 [31].

4.1. Cox proportional hazards modelling of the transition from methamphetamine use to methamphetamine use disorder

Table 4 shows the parameter estimates (given as the hazard ratio), standard errors of estimate, and probability values for the statistically significant predictors of the transition from methamphetamine use to methamphetamine use disorder. During the model fitting process, it was discovered that two predictors were causing model pathology (model misspecification, which refers to an incorrectly fitting model). These two predictors were strongly associated with methamphetamine use disorder (nicotine use disorder; cannabis use disorder), and in the process of model fitting, it was discovered that the inclusion of these predictors would not permit a statistically significant association for the transition to methamphetamine use disorder with any other predictors. We judged that this pattern of results reflected model misspecification, and chose to omit these from the final model. After the process of model fitting, only seven predictors remained statistically significant. These included: male gender; parental history of illicit drug use; paternal overprotectiveness; novelty-seeking; adolescent conduct disorder; adult major depression; and adult unemployment.

All other predictors that were removed from the model (apart from the two noted above) were not statistically significantly associated with the transition to methamphetamine use disorder.

Table 4. Cox proportional hazards model of the transition from methamphetamine use to methamphetamine use disorder

Predictor	Hazard ratio	Standard error	p-value
Male gender (at birth)	2.34	.45	<.0001
Parental illicit drug use (11 years)	1.48	.28	.023
Paternal over-protection (16 years)	1.04	.01	.004
Novelty-seeking (16 years)	1.13	.02	<.0001
Conduct disorder (14-16 years)	2.43	.56	<.0001
Major depression (15-40 years)	2.39	.40	<.0001
Unemployment (18-40 years)	2.01	.18	<.0001

5. Discussion

There has been consistent evidence that substance use disorders, including methamphetamine use disorder, is associated with exposure to adversity over the life course, as well as familial, individual, and mental health factors, and the experience of severe stressors [26, 27, 32-40]. Much of the previous research in this area, however, has been limited by the use of selected samples or special populations (such as drug treatment patients), and relies primarily on the use of cross-sectional data [41]. The strength of the present study is that it draws on prospective longitudinal data from a representative birth cohort, born in 1977 and followed to age 40, covering the entire life course of the cohort to this point. In addition, the repeated measure of methamphetamine use and methamphetamine use disorder allowed us to model the timing of the transition more effectively from methamphetamine use to methamphetamine use disorder. Finally, the wide range of prospectively collected measures of factors predicting the transition to methamphetamine use disorder over the life course allowed us to specify a risk profile describing the factors that increased the risk of transition.

The results of this analysis show that individual “fixed” factors such as being male and having higher levels of novelty-seeking generally increased the risk of transitioning from methamphetamine use to methamphetamine use disorder. These findings are consistent with the literature, and previous analyses of CHDS data [2, 42-48]. Childhood and adolescent family factors also played a role with parental illicit drug use increasing the risk of developing methamphetamine use disorder, which is also consistent with previous literature [32, 49, 50]. Paternal overprotectiveness, and conduct disorder in adolescence (a severe mental health disorder) also increased the risk of this transition, but it may be possible that these factors are closely related (over-protection, or surveillance, is a common parental reaction to conduct disorder) [51, 52]. Conduct disorder itself is known to be strongly comorbid with substance use disorders [53-57]. Finally, major depression and the experience of unemployment in late adolescence and early adulthood also contributed to increasing the risk of transitioning from methamphetamine use to methamphetamine use disorder. Internalizing disorders and life stress

have both been shown previously to be associated with increased risk of substance use disorder, both within the cohort and in the literature generally [24, 26, 27, 37, 58, 59].

It is also notable that major depression, one of the factors found in prior reports (e.g. Report 2 in the present series) to not predict significantly casual or regular methamphetamine use, did in fact predict the transition to methamphetamine use disorder in the present analysis. This pattern of results may reflect a kind of "clustering" of mental disorders, in which meeting criteria for one disorder increases the likelihood of meeting criteria for another disorder [60]. This has been observed previously in CHDS data, but the reasons for this apparent clustering are not clear. It could be argued that people who view themselves as having a mental disorder may tend to respond positively to items measuring mental disorder more generally, but further research is required to examine this issue.

One limitation of the present approach is that we were required to exercise judgement regarding the inclusion of two factors as predictors (nicotine use disorder and cannabis use disorder). The reason for this issue is that while both were strongly associated with the transition to methamphetamine use disorder, their inclusion in the model effectively "swamped" the analysis by consuming variance, and fully "outcompeting" any other predictors which reduced the overall predictive value of the model. Given that there is very little theoretical rationale for "cause" in this case (substance use disorders are highly comorbid as regular substance users tend to use multiple substances [38, 39, 56, 61], although there is little evidence for causality among disorders), we chose to omit these predictors from the model, which increased the number of predictors that were statistically significantly associated with the transition from methamphetamine use to methamphetamine use disorder.

Another limitation of this approach was that, because we used a prospectively measured population sample, the number of methamphetamine users, and in particular methamphetamine users who met criteria for disorder, was relatively small which could reduce the reliability of modelling. This limitation shows the importance of replicating the present findings with other cohorts and in other settings, with one possible example being the use of a multi-cohort design [62] to increase power.

The implications of the present findings are that it may be possible to identify those at greater risk of methamphetamine use disorder (males, and those with high novelty-seeking). It is also clear that addressing adverse life circumstances earlier in the life course (childhood and adolescence) has the potential to help reduce methamphetamine use disorder. Finally, depression and life stress (in the form of unemployment) were related to the transition to methamphetamine use disorder which may be useful in identifying those at risk, and employing interventions to reduce the risk among those receiving counselling or treatment.

6. References

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