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Multi-level patterns predict cannabis use onset among youth

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ABSTRACT

Early cannabis initiation during youth is associated with elevated risk for harmful substance use, mental disorders, and cognitive impairments. To account for the complexity behind cannabis use initiation, we performed a data-driven analysis across 151 measurements spanning seven domains from the individual, microsystem, and exosystem level of influences: biobehavior, cognition, brain MRI, family, peer, neighborhood and legal factors. Data were from 450 cannabis-naïve youths from the National Consortium on Alcohol and NeuroDevelopment in Adolescence (NCANDA) (baseline age: 12–21 years). Within an 8-year period, 292 transitioned to first use and 163 to weekly use of cannabis. Random Survival Forest predicted age of first onset (C-index = 0.68; 95 % CI: [0.65,0.71]) and weekly onset (C-index = 0.69; 95 % CI: [0.67–0.71]) with an accuracy significantly higher than chance (i.e., C-index = 0.5). Its prediction patterns consisted of factors from all three levels of influence. The predictive pattern of first onset comprised 13 factors across six domains including lower positive thinking during stress coping, which correlated with earlier use (R^2=0.023, $p = 0.0090$). Three variables were shared with the predictive pattern of weekly use onset: cannabis outlet density, access to alcohol at home, and more positive social expectations of alcohol use forecasting earlier onset (Initial Use: R^2=0.031, $p = 0.0027$; Weekly Use: R^2=0.023, $p = 0.0090$). Weekly use onset was predicted by only four factors suggesting that while many influences contribute to a youth trying cannabis, only a few key factors appear to facilitate escalation to habitual use, some of which represent promising targets for prevention programs.

1. Introduction

Cannabis (marijuana) is widely used by youth in the United States. In 2024, 26 % of 12th graders reported cannabis use in the past 12 months (Abuse, National Institute on Drug, 2024). While youth drinking has trended downwards in recent decades, cannabis use has increased: 3 % of youth report using cannabis daily, compared to < 1 % for alcohol and cigarettes (Miech et al., 2023). This parallels decreased perception of harm, as only 28 % of 12th graders perceived cannabis use to be risky (Miech et al., 2023).

This trend is concerning given the deleterious effects of early cannabis use on youth neurological and psychosocial development (Fischer et al., 2020; Hammond et al., 2020a; Jacobus and Tapert, 2014; Scheier and Griffin, 2021; Wade et al., 2024). Both recent and lifetime marijuana use in youth are associated with poorer performance on tests of attention, learning and memory (Gowin et al., 2025; Venero Hidalgo et al., 2022), psychomotor speed and executive functioning (Scott et al., 2018), and sleep disruptions (Furer, Nayak, and Shatkin, 2018). Also reported are divergence in brain development (Albaugh et al., 2021), such a reduction in white matter coherence (Burggren et al., 2019; Jacobus et al., 2013; Orr, Paschall, and Banich, 2016) and macro structural variability (Battistella et al., 2014; Soleimani et al., 2023). Even when the criteria for cannabis use disorder are not met (American Psychiatric Association, 2013), cannabis use (between aged 12 – 17 years) (American Psychiatric Association, 2013) is associated with increased likelihood of major depressive episodes, poorer processing speed, truancy, low academic performance, and delinquent behavior (Sultan et al., 2023). Furthermore, earlier ages of cannabis use onset

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have been linked to increased risk of subsequent cannabis use disorder (Gruber et al., 2012; Hamaoui et al., 2025).

Inspired by Bronfenbrenner's Bioecological Theory (Bronfenbrenner, Pamela, 2006; Trucco, 2020), cannabis use onset in adolescents can be conceptualized as emerging from a pattern of nested and interacting influences that range from individual characteristics to broader environmental factors (Fig. 1). These levels of influence have been largely studied in isolation with respect to cannabis use initiation (Zimmerman and Farrell, 2017). At the individual level, examples of early predictors include male sex (Guxensa et al., 2007), neurobiological vulnerability [including in brain function and cortical gray matter (Spechler et al., 2019)], cognitive functioning (Debenham et al., 2021), and biobehavioral characteristics, such as increased novelty seeking (LaSpada et al., 2020; Wasserman et al., 2021) and externalizing behaviors (Hayatbakhsh et al., 2009, 2013; Merrin et al., 2022). On the microsystem level, key predictors include the immediate family environment [e.g., poor parental monitoring and strained family relationships (Guxensa et al., 2007; Merrin et al., 2022; Scholes-Balog et al., 2020; Wellman et al., 2023)] and peers, such as peer cannabis use and the quality of peer relationships (Wellman et al., 2023). Interactions between factors of the microsystem that shape risk for cannabis use are modelled on the mesosystem level. For example, poor parental monitoring or strained family relationships may amplify the influence of deviant peer affiliations, increasing the risk for cannabis use (Van Ryzin et al., 2012). The exosystem level models indirect environmental influences such as neighborhood and [like the density of local cannabis outlets (Hayatbakhsh et al., 2013)] and broader legal policies, included the legal status of cannabis (Vuolo et al., 2025). Omitted from the framework outlined in Fig. 1 are the macrosystem level, which captures risk factors associated with cultural environment [such as cultural acceptance of cannabis use (Wanke et al., 2022)], and the chronosystem level encoding the effect of temporal changes in the environment (such as changes in cannabis legalization during ones up brining). Furthermore, the framework replaces the mesosystem level with the *mesosystemic processes* to account for interactions among factors from all levels.

We do so as examining these levels in isolation may help explain why predictors identified in prior studies have rarely translated into reliable risk assessments for cannabis use in individuals, an important principle in advancing precision prevention (Olthof et al., 2024; Rajapaksha et al., 2020; Spechler et al., 2019). For example, (Rajapaksha et al., 2020) identified individuals with cannabis use disorder from 14 predictors limited to biobehavioral and cognitive domains. Also confined to domains at the individual level, Spechler et al. (2019) prospectively examined neurobiological and psychodevelopmental risk factors for

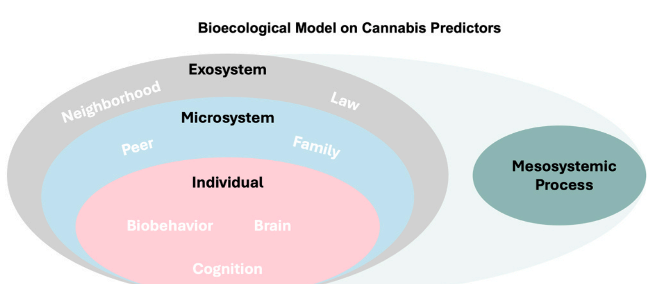

Fig. 1. A Bioecological Framework of Cannabis Use Onset with Multilevel Predictors. Influences on adolescent cannabis use onset are structured across three nested levels: individual, microsystem, and exosystem. The individual level includes biobehavioral characteristics, cognition and brain MRI measures. The microsystem level comprises proximal social environments (peer and family context). The exosystem level reflects broader contextual exposures (neighborhood and state-level cannabis laws). Finally, the *mesosystemic processes* capture interactions across factors from all three levels that influence cannabis use.

cannabis use onset by age 16 years. Here, we hypothesized that factors (and their interactions) from all three levels are important for predicting cannabis initiation and weekly use in individuals.

To test this hypothesis, we performed a machine learning based search across multi-level data acquired from 450 participants of the National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA). Inspired by Nguyen-Louie et al. (2024), NCANDA data were confined to 151 predictors across seven domains that span all three levels: biobehavioral characteristics, cognitive functioning, and brain MRI measures of the individual level, family environment and peer context of the microsystem level, and neighborhood exposures and cannabis law of the exosystem level. Across the seven domains, we developed two separate machine learning models: one to predict age of first use onset and another to predict onset of weekly use. Each model identified a distinct multivariate pattern of predictors, which we interpreted as a *mesosystemic process*. For each pattern, we identified their significant predictors to assess whether they spanned all three bioecological levels. To gain a deeper understanding into their relevance, we computed their effect sizes and directionalities with respect to onset age.

1.1. Participants

The present study drew from the ongoing NCANDA data (Baseline to Year 8 Data Release of National Institute of Mental Health Data Archive Collection C4513), representing baseline (i.e., study entry) through year 8 follow-up of the National Institute on Alcohol Abuse and Alcoholism Data Archive ($NIAAA_{DA}$, Collection C4513). Participants were recruited using a cohort sequential design between 2013 and 2014 at five sites: Oregon Health & Science University, SRI International, University of California San Diego, University of Pittsburgh Medical Center, and Duke University Medical Center. Participants were followed annually for 8 years and administered assessments of sociodemographic, peer relations, parental relations, substance use, and psychological functioning. NCANDA participants underwent neuroimaging and neuropsychological assessment annually until age 22 years, then at ages 24, 27, and 30 years. Parent/legal guardian reports were used to assess family history of substance use and parental education, while all other measures in this study were based on youth self-reports.

Informed consent was obtained from adult participants and parents/legal guardians for minor participants under 18 years old, who provided written assent. Study protocol and procedures were approved by each study site's Institutional Review Board. Documented informed consent was obtained from adult participants (18 + years old) and parents/legal guardians, and written assent was obtained from participants under 18 years old. Exclusion criteria included age younger than 12 years or older than 21 years at study entry, limited English fluency, MRI contraindications, current psychotropic medication use, non-correctable sensory problems, history of serious medical conditions that may affect MRI, early developmental problems (e.g., prenatal alcohol or illicit drug exposure); persistent Axis I mental health disorder, head trauma or loss of consciousness (>2 min), and severe learning or other pervasive developmental disorder. Of 831 youth who enrolled in the NCANDA study, 88 participants were excluded due to missing baseline

Table 1
Participant baseline characteristics at study entry (N = 450, recruited in 2013–2014).

Characteristic at Baseline	M (SD) [Range] or n (%)
Age at study entry	15.12 (2.11) [12.00–21.08]
Sex (female)	227 (50.4 %)
White	323 (71.8 %)
Hispanic	49 (10.9 %)
Socioeconomic Status	90.91 (14.00) [35.00–110.00]
Age of first cannabis use onset	17.85 (2.29) [13.25–27.50], 292 (64.9 %)
Age of weekly cannabis use onset	19.06 (2.26) [13.25–28.00], 163 (36.2 %)

Table 2
Model predictors for initial and weekly cannabis use onset.

Metric of interest	Measure	Source
INDIVIDUAL LEVEL		
BIOBEHAVIORAL CHARACTERISTICS		
Academic functioning	Grade point average; future career intentions	(Brown et al. 2015)
Personality traits	Ten Item Personality Inventory (TIPI)[a]	(Gosling, Rentfrow, and Swann, 2003)
	Urgency-Premeditation-Perseverance-Sensation Seeking-Positive Urgency (UPPS-P) Impulsive Behavior Scale[b]	(Cyders et al. 2007; Lynam et al. 2006)
	Behavior Rating Inventory of Executive Function – Self-Report Version (BRIEF-SR)[c]	(Gioia et al. 2002)
	Alcohol Expectancies Questionnaire (AEQ)[d]	(Brown, Christiansen, and Goldman, 1987)
	Youth Self-Report (17 years) and Adult Self-report (18 years) Internalizing and Externalizing scores	(Achenbach, 1991; Achenbach and Rescorla, 2003)
	Responses to Stress Questionnaire (RSQ)	(Connor-Smith et al. 2000)
Sleep patterns	Sleep Habits Questionnaire	(Buysse et al. 1989; Smith, Reilly, and Midkiff, 1989; Wolfson and Carskadon, 1998)
Other substance use	Cigarette use status at study entry	(Brown et al. 2015)
COGNITION		
Working memory	Penn Continuous Performance Test-Number Letter Version	(Gur et al. 2010)
Visual learning and memory	Penn Short Visual Object Learning Test (immediate and delayed)	
	Penn Facial Memory Test (immediate and delayed)	
	Penn Word Memory Test (immediate and delayed)	
Executive functioning	Penn Conditional Exclusion Task	
	Penn Matrix Analysis Test	
	Penn Logical Reasoning Task	
Affect processing	Penn Measured Emotion Differentiation Task	
	Penn Emotion Recognition Test	
BRAIN MRI MEASURES		
Structural MRI	Volume scores of 32 regions of interest defined by SRI24 atlas	(Rohlfing et al., 2010)
Diffusion MRI	Fractional anisotropy values of 21 bilateral and 6 midline white matter regions defined by the JHU DTI atlas	(Mori et al. 2005)
MICROSYSTEM LEVEL		
FAMILY FACTORS		
Family history	Family history density of alcohol related problems	(Rice et al. 1995)
Access to substances	Access to drugs & alcohol at home	(Komro et al. 2007; Tobler et al. 2009)
Youth-parent relations	Parental warmth, solicitation, knowledge, control, and supervision	(Fletcher, Steinberg, and Williams-Wheeler, 2004)
PEER FACTORS		
Social network	Number of same sex friends & opposite sex friends	(Brown et al. 2015)
Peer influence	Number of friends who drink alcohol, get drunk, or have problems with alcohol	(Bachman, 1981)
Romantic relationships	Dating history	(Brown et al. 2015)
EXOSYSTEM LEVEL		
NEIGHBORHOOD FACTORS		
Population-level socioeconomic factors	ZIP code-based population metrics on median household income, poverty, educational attainment, public assistance recipients, and unemployment	(U.S. Census Bureau 2023a, 2023b)
Cannabis outlet density	ZIP code-based quantity of cannabis-related establishments	(U.S. Census Bureau 2023c)
Alcohol outlet density	ZIP code-based quantity of alcohol-related establishments (beer/wine/liquor stores, bars)	(U.S. Census Bureau 2023c)
Self-reported neighborhood access to substances	Access to drugs & alcohol in neighborhood, and outside neighborhood	(Komro et al. 2007; Tobler et al. 2009)
LAW		
Statewide legal status of cannabis	State-based metric on legality of cannabis use (e.g., medical or recreational) in the participant's state of residence	(Rahal et al. 2023; Hammond et al. 2020b)

[a]TIPI subscales examined: Agreeableness, Conscientiousness, Emotional Stability, Extraversion, and Openness to Experiences;
[b]UPPS subscales examined: Negative Urgency, Lack of Premeditation, Lack of Perseverance, Positive Urgency, and Sensation Seeking;
[c]BRIEF-SR scales examined: Inhibitory Control, Flexibility, Emotional Control, Monitoring, Working Memory, Planning, Organization, and Task-Completion;
[d]AEQ scales examined: Changes in Social Behavior, Increased Arousal, Improved Cognitive and Motor Ability, Relaxation and Tension Reduction, and Global Positive Change.

questionnaire data on one or more predictors of interest, which is considered a more rigorous approach over imputing missing measures. To examine predictors of cannabis onset without confounding effects of prior substance exposure, 277 participants were excluded as they initiated substance use (alcohol or cannabis) at or prior to study enrollment. Additionally, 16 participants were excluded due to structural brain anomalies detected on neuroimaging at baseline, which precluded automated quantification. Of the remaining N = 450 cannabis naïve individuals at baseline, N = 292 had transitioned into cannabis use and of those N = 163 initiated weekly use of cannabis by the Year 8 follow-up, when participants were approximately 20–29 years old (Table 1).

1.2. Measures

This study aims to identify predictors of two key outcomes: age of first cannabis use and age of weekly cannabis use. A total of 151 predictor variables were drawn across seven major domains aligned, spanning three levels of the Bronfenbrenner's bioecological framework (Fig. 1): biobehavioral characteristics, cognition, brain MRI measures, family, peer, neighborhood and cannabis law factors (see Table 2 for a list of variables). This multilevel structure reflects our interest in identifying patterns of risk that operate both within and across bioecological levels. Predictors were assessed at the baseline visit (i.e., prior to cannabis initiation) with the exception of the zip code related factors and legal status of cannabis. Those objective predictors were assessed the year prior initiation to capture exosystem-level characteristics proximally preceding transition (see Nguyen-Louie et al., 2024 for details).

1.2.1. Outcomes

Cannabis use patterns were assessed using the Customary Drinking and Drug Use Record (CDDR; Brown et al., 1998). Two outcomes of interest were examined: (1) age of first use (when youth first "used marijuana in any form [pot, hash, edibles, vape, wax, budder, dabs, shatter], even a puff or small amount") and (2) age of weekly use (Brown et al., 1998), i.e., when youth first used marijuana in any form at least once a week for three consecutive months.

1.2.2. Predictors

Potential risk factors from domains other than brain development were drawn from a literature review conducted as part of a recent study with NCANDA data looking at alcohol use among youth (see Nguyen-Louie et al., 2024 for further details). Measures of response to stress (Responses to Stress Questionnaire (RSQ); Connor-Smith et al., 2000) and statewide legal status of cannabis were added, which have both been linked to substance use vulnerability and access (Rahal et al., 2023; Hammond et al., 2020b). A total of 92 predictor variables were used (see Table 2 for further details), with details about measures in the Supplementary Method.

1.2.3. MRI variables and data acquisition

High-resolution structural and diffusion MRI images were acquired at all sites; two sites (UMPC, OHSU) used a Siemens 3 T TIM TRIO scanner and three sites (UCSD, SRI International, and DUMC) used General Electric (GE) 3 T Discovery MR750 scanners. T1- and T2-weighted 3D structural images were acquired in the sagittal plane. GE sites used an 8-channel head coil and acquired an Inversion Recovery-SPoiled Gradient Recalled (IR-SPGR) echo sequence; Siemens scanners employed a 12-channel head coil and acquired an MPRAGE sequence (for detailed acquisition methodology, see Pfefferbaum et al., 2016, 2018).

Image processing was based on the SIBIS pipeline (Park et al., 2018) (SIBIS pipeline, https://github.com/sibis-platform). Briefly, preprocessing included noise removal, field inhomogeneity correction, T2-to-T1-weighted image registration, and non-rigid registration of the SRI24 atlas (Rohlfing et al., 2010). Based on the atlas, volume scores of 32 Regions of Interest (ROI) were computed and used as brain structural measures. Diffusion-weighted images were acquired with 60 directions (b = 1000 s/mm^2) at 2.5 mm isotropic resolution. Quality control and imaging processing were detailed in a previous paper by Pohl and colleagues (Pohl et al., 2016). Fractional anisotropy (FA) values were extracted from 21 bilateral and 6 midline white matter regions defined by the JHU DTI atlas (Mori et al., 2005), with left/right values averaged, resulting in an additional 27 brain measures on white matter integrity.

To account for potential confounding effects, sex, age, race, and socioeconomic status were regressed out by applying a generalized linear model (GLM) separately to each of the 92 non-MRI and 59 brain ROI predictors. In addition, study site and intracranial vault size were regressed out from the ROI measurements to account for scanner-related variability and individual differences in head size (Pfefferbaum et al., 2016). All residualized measures were subsequently considered candidate predictors.

1.3. Survival analyses

Based on the 151 residualized measurements (assessed at baseline except zip-code related factors and legal status of cannabis), a Random Survival Forest algorithm (RSF; python package scikit-survival (v0.25.1); Ishwaran et al., 2008; Kurt Omurlu et al., 2009) identified the age of first onset for each of the 450 subjects. RSF extends random forests from binary classification to 'right-censored' samples, i.e., to participants that are cannabis-naïve by the 8-year follow-up visit so that their onset age is unknown. For right-censored samples, the censoring point is the last recorded visit and the prior year of that visit is used for determining zip-code values and legal status of cannabis.

RSF was trained and tested using five-fold nested cross-validation as an internal validation strategy across all 450 participants. Specifically, the data were split into five outer folds, with each fold serving once as a test set (90 participants) while the remaining 360 participants were used for training. During training, the optimal key hyperparameters [such as the number of trees (ranging from 100 to 3000) and the minimum leaf size (ranging from 5 to 60)] were determined via inner-loop cross-validation. In other words, the model was trained on 3 folds for each hyperparameter setting and the optimal setting for the test fold was then chosen based on the accuracy of that model on the fourth fold (validation set). The accuracy was assessed using the Concordance index (C-index) (Harrell et al., 1982), where a value of 0.5 is interpreted as random guessing and 1.0 indicates perfect prediction. Based on that assessment, the optimal hyperparameter setting was always 'inside' the search space indicating that the search space was appropriately chosen. Finally, the trained model with these optimized parameters was applied to the held-out test fold set and its C-index was recorded.

Based on the onset predictions, we estimated survival probabilities (Ishwaran et al., 2008; Lillelund, Harbo, and Pedersen, 2024) for each subject, representing the likelihood that the onset of first or weekly cannabis use has not yet occurred by a given age. We plotted the cumulative/dynamic area under the receiver operating characteristic (ROC) curve (AUC) (Lambert and Chevret, 2016; Uno et al., 2007) to evaluate the model's ability to distinguish participants who started cannabis use by a specific time point from those who remain cannabis-naïve after that time.

The entire analysis was repeated for predicting age of weekly cannabis use onset. The event time was now the age at weekly use onset. For right censored subject (i.e., those that were cannabis naïve or had used cannabis but not meet the weekly use criteria), the age at their last recorded visit was used for event time and the year prior for recoding zip code and legal status factors.

1.4. Identifying significant predictors

For each RSF model, we identified significant predictors using permutation importance [python package scikit-learn (v1.7.1); (Breiman,

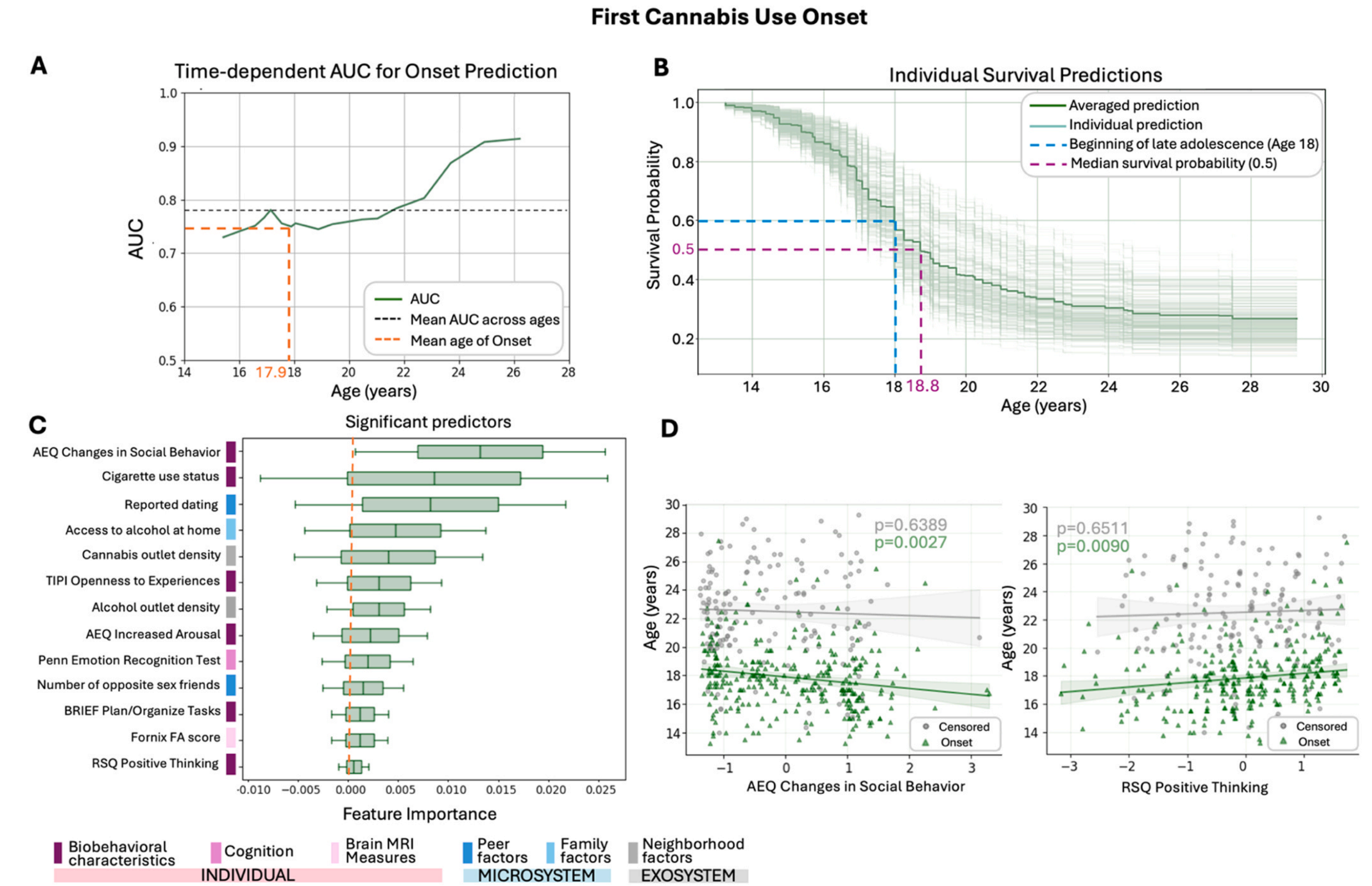

Fig. 2. Predictors of First Cannabis Use Onset Identified via Random Survival Forest. (A) The time-dependent AUC curve assessing the RSF model's predictive performance at the cohort's mean cannabis-onset age of 17.9 years (orange dashed line) yielded an AUC of 0.74 (95 % CI 0.72–0.76). (B) Individual-level survival curves predicted by the RSF model, showing the probability of remaining free of cannabis over time. The dark green line indicates the average predicted survival, with a probability of 0.6 at entering late adolescence (age 18 years) and a median survival probability (0.5) occurring at age 18.8. (C) Permutation-based feature importance analysis identified 13 significant predictors of first cannabis use onset, spanning all six domains across all three levels. (D) Follow-up univariate analyses showed that expectations on alcohol's greater changes in social behavior ($p = 0.0027$) and lower RSQ Positive Thinking scores ($p = 0.0090$) were associated with earlier onset.

2001)]. Predictors were considered important if their importance scores differed significantly ($p < 0.05$) from the zero-centered null distribution. For each significant predictor, we quantified their associations with age of onset via a univariate analysis, i.e., linear regression for continuous predictors, two-sample *t*-tests for binary variables, or one-way ANOVA for categorical factors.

2. Results

2.1. Prediction accuracy

The model recorded a C-index for predicting first cannabis use onset of 0.68 (*95 % CI 0.65–0.71*) and an average AUC of 0.78. The mean age of first use onset was 17.9 years, and the mean time-dependent AUC progressively increased with age after 19 years (see Fig. 2A). For predicting weekly cannabis use onset, the model recorded a similar C-index of 0.69 (*95 % CI 0.67–0.71*) and mean time-dependent AUC of 0.79, the mean age of weekly use onset was 19.1 years, and accuracy improved with age after around age 21 years (Fig. 3A).

2.2. Survival probability

The average survival probability for first cannabis use (dark green line, Fig. 2**B**) declined from 60 % at age 18 years [beginning of late adolescence (Fleming, 2005)] to 50 % (median survival probability) just eight months later. In comparison, the survival probability for weekly use was 90 % at age 18 years and dropped to 65 % by age 21 years.

2.3. Predictors of first cannabis onset

The predictive pattern of first cannabis use onset consisted of 13 significant variables (Fig. 2**C**). Significant factors and their domains of the individual level were the biobehavioral characteristics "Alcohol Expectancy Questionnaire (AEQ) changes in social behavior", "AEQ increased arousal", "Cigarette use status", "Ten Item Personality Inventory (TIPI) Openness to Experiences", "Behavior Rating Inventory of Executive Function (BRIEF) Plan/Organize task" and "Responses to Stress Questionnaire (RSQ) Positive Thinking score". In addition, predictive were the cognition factors "Penn Emotional Recognition Test" and the brain MRI measure "Fornix FA score". Significant domains and factors of the microsystem level were the family factor "Access to alcohol at home" and the peer factors "Reported dating" and "Number of opposite sex friends". Finally, on the exosystem level, the neighborhood factors, including local density of cannabis and alcohol outlets, were significant predictors. Robust linear regression (Fig. 2**D**) revealed that higher levels of expected change in social behavior ($R^2 = 0.031$, $p = 0.0027$) and lower RSQ Positive Thinking scores ($R^2 = 0.023$, $p = 0.0090$) were associated with earlier cannabis onset.

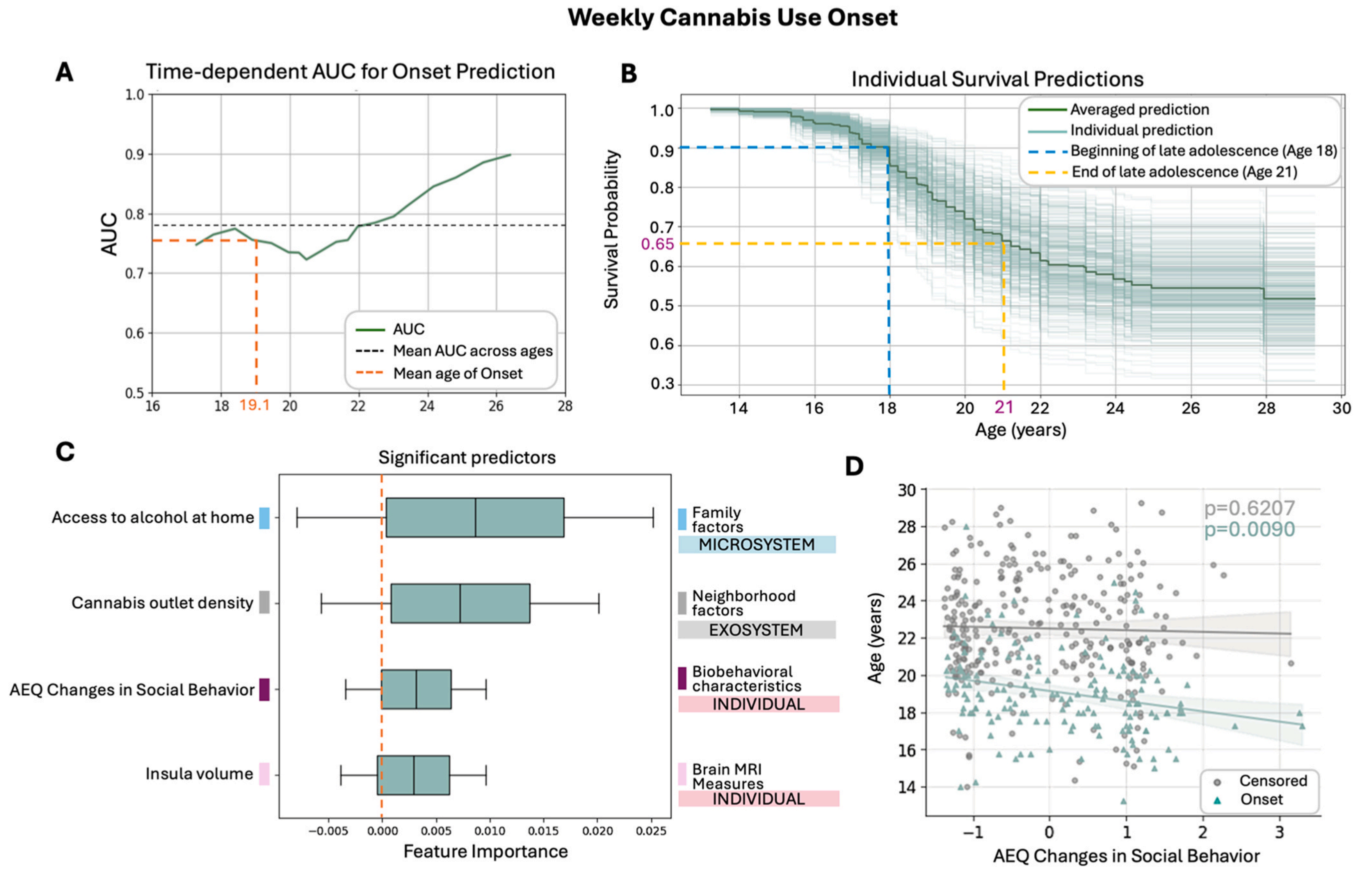

Fig. 3. Predictors of Weekly Cannabis Use Onset Identified via Random Survival Forest. (A) The time-dependent AUC curve evaluating the RSF model's performance at the cohort's mean age of weekly cannabis onset (19.1 years) yielded an AUC of 0.75 (95 % CI 0.74–0.76). (B) Predicted survival curves for weekly cannabis use onset; the average survival probability at the beginning of late adolescence (age 18 years) was 0.9, which declined to below 0.6 by the end of late adolescence (age 21 years). (C) Feature importance analysis identified four significant predictors: access to alcohol at home, local cannabis outlet density, AEQ Changes in Social Behavior, and insula gray matter volume. (D) More positive expectations of alcohol on social behavior change ($p = 0.0090$) were associated with earlier onset of weekly cannabis use.

2.4. Prediction of onset of weekly cannabis use

The predictive pattern of weekly cannabis use onset consisted of four significant factors (Fig. 3C). Significant factors of the individual level were the biobehavioral characteristics "AEQ Changes in Social Behavior" and the brain MRI measure "volume of the insula". Predictive of the microsystem was the family factor "access to alcohol at home" and on the exosystem the neighborhood factor "local cannabis outlet density". Further univariate analyses revealed associations between key predictors and age of weekly use onset (Fig. 3D). Higher levels of expected changes in social behavior were associated with earlier weekly cannabis use initiation (R^2=*0.023, p* = *0.0090*).

3. Discussion

Consisting primarily of baseline data from 450 NCANDA youths, the machine learning model confirmed our hypothesis that predicting first and weekly onset on a subject level relies on factors from the individual, microsystem, and exosystem levels, consistent with Bronfenbrenner's bioecological theory. Of those, only factors from the individual level were significantly correlated by themselves with age of first and weekly use onset. Specifically, having more negative thoughts during stress coping and higher expectations towards social changes from alcohol use correlated with earlier age of first use onset. Social expectation was also the only factor by itself correlating with the onset age of weekly use, indicating that when the expectations are initially met, weekly use is more likely. The other two factors of the prediction pattern of weekly onset shared with the first-use pattern were access to alcohol at home (a microsystem influence) and local cannabis outlet density (an exosystem level influence). In total, the pattern of weekly onset consisted of 4 significant factors, suggesting that while many influences (i.e., 13 predictors across six domains from all three levels) contribute to a youth trying cannabis, only a few key factors may facilitate escalation to habitual use.

The strongest predictive factors for onset of weekly use and among the strongest for onset of first use were linked to access to substances on a micro and exosystem level, i.e., access to alcohol at home and living in an area with a high density of cannabis outlets. Access to alcohol at home also significantly co-occurred with alcohol outlets density and access to other drugs at home ($p < 0.001$ according to Pearson correlation, Supplementary Figure S1). These strong predictive factors likely reflect a permissive substance environment that lowers barriers to trying cannabis (Komro et al., 2007; Tucker, Ellickson, and Klein, 2008). Easy access to substances at home (often via parents or siblings) may implicitly normalize use or make it logistically easier to initiate (Komro et al., 2007; Tobler, Komro, and Maldonado-Molina, 2009). Likewise, the association between onset and the density of cannabis retailers near one's residence aligns with emerging evidence that when cannabis outlets are numerous and visible, young people may develop more positive attitudes and intentions toward use (Shih et al., 2019). Even if underage youth cannot purchase from local dispensaries, the presence of many of them may increase social exposure to cannabis and reduce the perceived risk, thereby hastening use (Shih et al., 2019; Roditis et al., 2016; Pacula et al., 2014).

Key contributors to favorable views of substance use and significant predictors in our experiments were the expectation that alcohol would lead to arousal (i.e., AEQ Increased Arousal Fig. 2C) and enhance social experiences (i.e., AEQ Changes in Social Behavior of the biobehavioral domain; Fig. 2C & 3 C). Expecting enhanced social experiences from alcohol was the only baseline factor correlated with earlier onset of first and weekly cannabis use (Fig. 2D & 3D). This finding is in line with youth anticipating social benefits from substance use may not only experiment sooner but also progress to weekly use if those expectations are met or reinforced (Doran et al., 2013; Montes et al., 2019). Furthermore, while NCANDA participants were not asked about cannabis-specific expectancies, prior research has documented a positive correlation between alcohol- and cannabis-related expectancies (Willner, 2001). This association may help explain the high rate of concurrent alcohol and cannabis use observed in our cohort. While none of the individuals were using either substance at baseline, 53.7 % of cannabis users had already consumed alcohol prior to initiating cannabis use. In our study, cigarette smoking at baseline (independent of age) was also part of the predictive pattern for cannabis onset, which is consistent with the finding that alcohol and cigarette use during adolescence often precede and predict cannabis initiation (Hayatbakhsh et al., 2009; Evans-Polce et al., 2024; Brennan et al., 2025). Substance co-use is quite frequent in adolescents, which suggests that early exposure to alcohol may sensitize youth to the rewarding effects of other substances, including cannabis (Volkow et al., 2019).

Alcohol and cannabis share overlapping neurobiological pathways (e.g., dopaminergic reward circuits) (Hayes et al., 2020) and often co-occur in similar social contexts, such as peer gatherings (Lisha, Crano, and Delucchi, 2014; Yurasek, Aston, and Metrik, 2017). Key factors driving experimentation with these substances at this age are curiosity and a tendency toward novelty-seeking (Zhao et al., 2024; Kang, 2022). This was reflected in the pattern for first onset, which included openness to new experiences as predictor. Collectively, all these factors may prime youth for subsequent cannabis use. On the upside, prior work has shown that reducing substance-related expectancies can decrease intentions to use, highlighting expectancy as a potentially malleable target for prevention (Skenderian et al., 2008; Wood et al., 2007).

Positive Thinking of the biobehavioral domain was identified as another key predictor for first cannabis use onset, and a lower score was associated with earlier onset of first cannabis use. Positive thinking, a form of adaptive cognitive coping, involves reframing stressful experiences in constructive ways and generating optimistic thoughts about future outcomes (Compas et al., 2001). This coping strategy is associated with greater emotional resilience and reduced risk for internalizing symptoms, such as anxiety and depression (Garnefski and Kraaij, 2006). Youth lacking positive cognitive reframing skills may be more susceptible to stress and negative affect, which could, in turn, increase the likelihood of engaging in substance use as a form of emotional escape or regulation (Wills et al., 2001).

Beyond expectations and personality traits, the cognitive factors of emotion recognition abilities and planning skills were key factors in forecasting the timing of cannabis onset. These domains are closely tied to executive function and social cognition, which support the development of effective behavioral regulation strategies (Karbach and Unger, 2014; Fishbein et al., 2016). Difficulties in interpreting emotional cues, maintaining attentional control, and exercising cognitive flexibility have been shown to lead to maladaptive responses in social contexts (Powell et al., 2024), including poorer emotion regulation and increased vulnerability to risk behaviors such as substance initiation (Luciana, 2020; McKee et al., 2020). Prior findings have also suggested that cannabis use may be specifically related to a decline in emotion recognition (Ren and Fishbein, 2023), aligning with the results of our study.

Cognitive differences are often associated with underlying neurobiological markers. In our analysis, the fractional anisotropy of the fornix, a key frontolimbic tract involved in memory and emotion regulation (Hinton et al., 2019; Aggleton et al., 2010), emerged as part of the predictive pattern of initial cannabis use onset. This finding suggests that alterations in limbic pathways may influence vulnerability to early cannabis initiation, which is consistent with evidence that reduced integrity in frontolimbic white matter tracts is associated with greater risk-taking behavior and earlier initiation of heavy substance use (Jacobus et al., 2013; Mandelbaum and de la Monte, 2017). Interestingly, in our cohort, the onset of weekly substance use was partly forecasted by the volume of the insular cortex. While reduced thickness of the insula was observed in cannabis using youth (Lopez-Larson et al., 2011), it is important to note that in our study, these brain measures were taken before cannabis onset (in our longitudinal design), supporting the interpretation that they are likely risk factors of future cannabis use. Nevertheless, future research should confirm these relationships and the causal pathways by, for example, investigating whether youth with specific neural profiles are more prone to sensation-seeking or peer influence, which in turn leads to earlier use.

It is important to note that each individual factor contributing to the patterns did not predict the age of first and weekly cannabis onset on a subject-level by itself (see Supplementary Table S2). Doing so requires a pattern, which was also reported by (Spechler et al., 2019) and was inline with the *mesosystemic processes* shown in Fig. 1. Confined to predictors of the biobehavioral and brain MRI domain of the individual level, their predictive pattern consisted of novelty-seeking traits, less negative feelings to deviant behaviors, and cigarette use, which was in line with our findings. Interestingly, our patterns consisted of predictors from four domains (for weekly onset) and six domains (for first onset) across all three levels, which confirmed our overall hypothesis and implies that although numerous influences may lead an adolescent to try cannabis, only a few key factors are likely to facilitate escalation to habitual use.

To ensure that these patterns were actually specific to cannabis onset and not substance use in general, we recoded the accuracy of the patterns to forecast the timing of first and weekly alcohol use, i.e., the substance with the highest percentage of co-use with cannabis in our cohort. The C-index values (first drink: 0.62, weekly drinking: 0.61) of the models were now below the 95 % confidence intervals recorded for cannabis use outcomes (first use: 0.65–0.71; weekly use: 0.67–0.71). This was not the case when recomputing the score for cannabis onset confined to those without prior (weekly) alcohol use. The C-index value was now inside the 95 % confidence intervals for first onset cannabis use (C-Index: 0.65) and above for weekly onset (C-index: 0.72). These results reinforce the idea that the derived patterns are predictive of cannabis use onset, rather than simply reflecting a generalized vulnerability to substance initiation.

4. Limitations

However, only a small number of individual factors demonstrated a statistically significant standalone effect, which complicates the interpretation of their unique directional influence on cannabis initiation. When analyzing the importance of individual factors, the issue of polysubstance use among youth presents a significant challenge. Further complicating the issue is that the NCANDA study collected more detailed information related to alcohol drinking than cannabis use, such as recording the alcohol expectancy questionnaire, but not the cannabis counterpart. Thus, many of the individual factors of these predictive patterns may indicate a general tendency towards substance use rather than being unique to cannabis. For example, a prior study on NCANDA data found that access to alcohol at home, novelty-seeking traits, insular cortex volume, and positive usage expectancies were also predictive of alcohol use onset (Nguyen-Louie et al., 2024). While our predictive model did not explicitly account for alcohol use in parallel, we attempted to mitigate this issue by excluding individuals who reported alcohol use at baseline, i.e., predictions were based on alcohol and cannabis-naïve individuals.

Although modeling developmental variation was not a primary aim, we recognize its potential influence on predictive accuracy and predictors. Thus, we investigated this topic by separately performing predictions confined to the younger and older cohort at baseline and the younger and older cohort with respect to cannabis onset age. According to the Supplementary Table S1, the prediction accuracies did not significantly differ by age suggesting that our predictive patterns generalize well across different age ranges and onset timing groups.

While we accounted for neighborhood outlet density at the time of cannabis use onset, we did not model the time-varying nature of state cannabis legalization. The statewide legal status of cannabis one year prior to onset was included as one of the predictors in our model but was not a significant contributor to either predictive pattern. Given that legal status evolved over the course of the study and potentially influenced both access and behavior, this remains an important area of research.

Finally, our modeling approach treated predictors from diverse modalities as independent inputs, thereby potentially neglecting the complex mediating role of neural mechanisms in the pathway from environmental influences to behavior and cognition. This limitation in causal modeling may partially explain why neuroimaging measures, despite their potential to identify relevant mechanisms, contributed relatively little to prediction in our current mode.

5. Conclusion

Leveraging a large, longitudinal youth data set collected by NCANDA, this study applied machine learning survival models to prospectively identify patterns predictive of first and weekly cannabis use onset by searching across 151 factors across individual, microsystem, and exosystem levels, as conceptualized within Bronfenbrenner's bioecological theory. While negative thoughts and higher expectations towards social changes from alcohol use exert a standalone influence, none of the factors from each pattern forecasted cannabis use onset on a subject level. Both initial and weekly onset were predicted by patterns containing factors from all three levels and thus modelling a *mesosystemic process*. While the pattern of initial onset contained a broad, heterogeneous set of factors, progression to habitual use was driven by a small subset, including social expectations and access to substances. The findings provide foundational work for prevention efforts focusing on reducing youth cannabis use initiation at multiple bioecological levels.

CRediT authorship contribution statement

Laika Aguinaldo: Writing – review & editing, Methodology, Data curation. **Robbie Fraser:** Writing – original draft, Formal analysis, Data curation. **Kilian M. Pohl:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Susan F. Tapert:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Funding acquisition, Data curation, Conceptualization. **Fiona C. Baker:** Writing – review & editing. **Tam T. Nguyen-Louie:** Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Yixin Wang:** Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Kilian M. Pohl reports financial support was provided by National Institutes of Health. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.dcn.2025.101639.

Data availability

Data will be made available on request.

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