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Onset, Comorbidity, and Predictors of Nicotine, Alcohol, and Marijuana Use Disorders Among North American Indigenous Adolescents

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Abstract

North American Indigenous (i.e., American Indian and Canadian First Nations) youth experience inequities in rates of substance abuse and dependence. Despite this, few longitudinal studies examine the developmental course of substance use disorders (SUD) among community-based samples of Indigenous youth. The purpose of the study was to examine onset and predictors of nicotine dependence, alcohol use disorders, marijuana use disorders, any SUD, and multiple SUDs across the entire span of adolescence among a longitudinal sample ($N = 744$) of reservation/reserve Indigenous youth in the upper-Midwest of the United States and Ontario, Canada. Using discrete time survival analysis, the results show that rates of meeting criteria for SUDs by late adolescence were 22% for nicotine, 43% for alcohol, and 35% for marijuana. Peak periods of risk for new nicotine dependence and marijuana use disorder cases occurred around 14 years of age, whereas peak periods of risk for new alcohol use disorder cases emerged slightly later around 16 years of age. We found high rates of SUD comorbidity, and the cumulative probability of developing two or more SUDs during adolescence was 31%. Internalizing disorders increased the odds of nicotine dependence and multiple SUDs, while externalizing disorders increased the odds of all outcomes except nicotine dependence. Gender, age, and per capita family income were inconsistently associated with SUD onset. The findings are embedded within broader substance use patterns identified among Indigenous youth, and prevention, intervention, and treatment implications are discussed.

Keywords American Indian · First Nations · Psychiatric comorbidity · Substance abuse · Longitudinal

Although the median age of onset for substance use disorders (SUD) in the United States is around 20 years of age (Kessler et al. 2005), research indicates that onset occurs several years earlier for North American Indigenous adolescents (i.e., American Indian and Canadian First Nations). Problematic substance use (e.g., high quantity and/or high frequency use) has been directly and indirectly linked to leading causes of death among Indigenous youth such as alcohol-involved motor vehicle accidents (West and Naumann 2011), suicide (Harder et al. 2012), and violent victimization (Perry 2004). Moreover, early onset substance use is a key risk factor for negative outcomes in adolescence such as early parenthood and criminal justice involvement (Sittner 2016), which may have reverberating consequences throughout the life course. There is also some evidence of disproportionate prevalence of comorbid alcohol and drug dependence for some Indigenous communities (Falk et al. 2006). This is worrisome because comorbid SUDs can undermine effective treatment and maintenance services (Dutra et al. 2008), and are associated with adverse socioeconomic and psychiatric functioning in early adulthood (Salom et al. 2015). Understanding developmental patterns of SUDs in concert with what we already know about Indigenous adolescent substance use patterns will generate a more holistic epidemiologic profile (e.g., onset, regular use, abuse/ dependence), which can aid in translating basic research science into effective community-based prevention, intervention, and treatment programming.

While earlier age of onset for SUD for many tribal groups is a prominent public health concern, it is critical to highlight the fact that American Indian adults are among the most likely of all racial/ethnic groups in the U.S. to abstain from alcohol use (Cunningham et al. 2016). Such stark contrasts fuel the need to understand the timing, probability, and predictors of

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SUD, and their overlap across life course stages in order to improve health and well-being among Indigenous communities and individuals. The purpose of the paper is to examine the timing of onset and the cumulative probability of developing a nicotine, alcohol, and marijuana use disorder (abuse/dependence) across the span of adolescence among Indigenous young people residing in the upper-Midwest of the U.S. and Ontario, Canada ($N = 744$). In addition, we examine the overlap and prospective associations among these three disorders, and psychiatric functioning and demographic predictors of onset to identify those most at risk for developing a SUD.

Nicotine, Alcohol, and Marijuana Use Patterns Among Indigenous Youth

Although there is heterogeneity across cultural groups, Indigenous youth tend to show earlier onset of substance use (Miller et al. 2008) and move more quickly into regular use (Beauvais 1998; Blum et al. 1992; Herring 1994) compared to other racial/ethnic groups. Nicotine, alcohol, and marijuana are the three most commonly used substances documented among Indigenous youth and often precede use of other "heavy" illicit substances (Novins et al. 2001; Whitesell et al. 2006). Among Indigenous youth, the median age of initiation for nicotine, alcohol, and marijuana use is between the ages of 11–13 years (Novins et al. 2001; Whitbeck and Armenta 2015). Nicotine use precedes both alcohol and marijuana use (Whitbeck and Armenta 2015), but the temporal progression from first alcohol use to first marijuana use is less consistent (Novins et al. 2001; Whitbeck and Armenta 2015). There is evidence that earlier onset substance users may have an accelerated course to dependence with shorter times between onset and dependency than later initiators (Cheadle and Whitbeck 2011; Cheadle and Sittner Hartshorn 2012; Sittner 2016). Moreover, peak periods of risk for abuse/dependence occur within a few years after initiation, with faster transitions from initiation to abuse/dependence for marijuana compared to nicotine and alcohol (Behrendt et al. 2009).

Growth models of Indigenous substance use frequency indicate that daily cigarette smoking and weekly or more binge drinking and marijuana use, which are often precursors of abuse and dependence, increase sharply from ages 10–15, and increase at a slower rate thereafter (Walls et al. 2013; Whitbeck et al. 2012; Whitesell et al. 2014). Taken together with what we know about onset of use, we might expect SUDs to begin to emerge and escalate around mid-adolescence. Support for this pattern would be noteworthy because most large-scale psychiatric epidemiological studies show that few SUD cases occur prior to mid-adolescence (Kessler et al. 2007), and the median age of onset for SUD nationally is around 20 years of age (Kessler et al. 2005).

SUD Comorbidity

Prior research with Indigenous people has typically focused on the development of abuse/dependence on a single substance (e.g., Armenta et al. 2016; Cheadle and Sittner Hartshorn 2012), yet most Indigenous adolescent substance users tend to be polysubstance users (Whitesell et al. 2006), with clear patterns of concurrent alcohol and marijuana use and less conclusive patterns of concurrent use of nicotine with other substances (Whitesell et al. 2014). Early polysubstance use accelerates the transition from initial use to abuse/dependence, compared to use of only one substance (Behrendt et al. 2009). As such, we would also expect there to be a modest overlap in lifetime nicotine, alcohol, and marijuana use disorders across the course of adolescence. Among Indigenous youth, early onset substance users are more likely to proceed to multiple dependencies than are later onset substance users (Sittner 2016). National data indicates that American Indian adults have among the highest rates of comorbid nicotine dependence and alcohol use disorder, and comorbid alcohol use and other drug use disorders, particularly marijuana use disorder (Falk et al. 2006; Falk et al. 2008). Despite these findings, we know very little about SUD comorbidity patterns, timing, or probability among Indigenous youth.

A common liability model of SUD can be used to explain the development of these comorbid disorders, which posits that individual variation in substance abuse and dependence shares substantial commonalities across genetic, psychological, and environmental systems (Vanyukov et al. 2003). Moreover, complex interactions within and between systems cumulatively shape movement along an underlying substance use severity liability axis (Vanyukov et al. 2003). This framework fits within an "alternative forms" model (Neale and Kendler 1995) in which various forms of SUD are a manifestation of a single liability (Rhee et al. 2006). Although SUDs may follow a particular sequence because of differential availability of substances across adolescence and possible cross-tolerance effects (Kandel and Kandel 2015), prior longitudinal research suggests that meeting criteria for any SUD increases the odds of developing a SUD on another substance (Duncan et al. 2015; Palmer et al. 2009). Among Indigenous youth, Whitbeck and colleagues (Whitbeck et al. 2014a) found that meeting criteria for any SUD increased the odds of meeting criteria for a subsequent SUD, but less is known if this association operates for continuity of abuse/dependence on a single substance, or whether this association crosses over to other substances. Support for this model would indicate that substance use prevention and intervention should target early substance use generally, rather than focusing on one specific drug.

Psychiatric Comorbidity

During adolescence, psychiatric disorders are often comorbid with SUD, and accelerate the transition from first use to abuse/dependence (Swendsen et al. 2010). Nationally representative studies of adolescents indicate that various internalizing and externalizing psychiatric disorders often precede SUDs and can be conceptualized as a legitimate risk factor (Swendsen et al. 2010). Reciprocal associations, however, have been noted which necessitates longitudinal data with lagged-predictors to delineate temporal associations been psychiatric disorders and SUD onset (O'Neil et al. 2011). Prior Indigenous research suggests that internalizing symptoms increase the odds of frequent compared to occasional smoking (Yu and Whitbeck 2016) and risk for marijuana dependence (Gilder and Ehlers 2012). Among externalizing disorders, prevalence of conduct disorder, attention deficit hyperactivity disorder, and other disruptive disorders peak by early adolescence (Whitbeck et al. 2008; Whitbeck et al. 2014a), and are highly comorbid with SUDs (Greenfield et al. 2017). We currently do not know whether internalizing and externalizing disorders, rather than symptom scales, prospectively predict SUD onset, or if their effects are consistent across adolescence or conditional upon time. We hypothesize that adolescents who meet criteria for any internalizing or externalizing disorder will have an earlier median age of SUD onset compared to adolescents who do not. Support for this hypothesis would suggest that prevention and intervention should target early psychiatric symptoms to limit secondary disorders such as SUD.

Sociodemographic Factors

In addition to psychiatric disorders, several sociodemographic characteristics may predict onset of SUD. In the National Comorbidity Study-Adolescent Supplement, Merikangas and colleagues (Merikangas et al. 2010) found SUD rates increased faster for males compared to females across age groups. Among Indigenous samples, females have higher odds of early nicotine, alcohol, and marijuana use initiation and regular use than males (Cheadle and Whitbeck 2011; Cheadle and Sittner Hartshorn 2012; Walls 2008; Whitbeck and Armenta 2015; Whitbeck et al. 2014b). By mid-adolescence, rates of Indigenous male substance use onset and misuse overtake that of females and are either significantly higher or no different (Walls et al. 2013). As such, three alternative hypotheses can be derived: (1) there are no gender differences in SUD onset; (2) males have higher odds of developing a SUD than females; or (3) the effect of gender on SUD risk varies as a function of time such that females have higher odds of developing a SUD early in adolescence, while males have higher odds of developing a SUD in late adolescence. Evidence for the latter two hypotheses would suggest that prevention and intervention programming might benefit from gender responsive substance use policy, rather than a universal approach.

Moreover, socioeconomic status is associated with substance use among Indigenous youth. Chronic poverty early in the life course has a deleterious effect on child outcomes and portends behavioral problems into adolescence (Shaw and Shelleby 2014). Socioeconomic status may be considered a "fundamental cause" of disease such that it is intricately linked with multiple reinforcing proximal risk pathways to disease (Link and Phelan 1995), such as stress exposure and negative family relations (Shaw and Shelleby 2014). Within Indigenous communities, poverty and socioeconomic disadvantage are a function and residual effect of historical cultural losses and contemporary marginalization (Evans-Campbell 2008). Financial strain and poverty have been associated with regular binge drinking and marijuana smoking (Walls et al. 2013), and SUDs (Mitchell, Beals, Novins, Spicer, and AI-SUPERPFP Team 2003) among Indigenous youth. We expect that per capita family income will be inversely associated with odds of first SUD diagnosis.

Summary

Initiation of substance use and progression to regular use occur several years earlier for Indigenous youth compared to youth from other racial and ethnic groups. Moreover, epidemiological research shows high rates of SUDs among Indigenous youth. Despite these findings, less is known about the developmental course of SUD onset and how it fits within broader patterns of substance use among Indigenous youth. To address these gaps, the current study centers around three primary research questions: (1) What are the peak periods of risk for nicotine, alcohol, and marijuana use disorder onset, and what is the cumulative probability of developing a SUD across the span of adolescence? (2) How do lifetime nicotine, alcohol, and marijuana use disorders concurrently overlap across time, and do they prospectively predict one another? (3) Who is most at risk for developing nicotine, alcohol, and marijuana use disorders based on psychiatric functioning and demographic factors? To address these questions and the hypotheses presented above, we used discrete time survival analysis to estimate hazard rates and cumulative survival probabilities across four waves of diagnostic data spanning the entire course of adolescence.

Method

Sample

The data come from an eight-year longitudinal study of youth and their caretakers in four U.S. reservations in the upper-Midwest and four Canadian First Nations reserves in

Ontario (see Whitbeck et al. 2014b for more details). Although participants were recruited from different sites, all participants share a common cultural tradition and language. As part of confidentiality agreements, the names of the cultural group and participating reservations/reserves are not provided, nor are any attempts made to make comparisons across communities. At each location, tribal council appointed community research councils (CRCs) advised the research team on all aspects of the research process including recruitment, questionnaire development, and data dissemination. This community-based participatory research design prioritizes tribal sovereignty, collaborative data sharing, and cultural respect. At each wave, participants completed in-person home interviews. The interviewers, as well as the site coordinators, were approved by their respective CRCs and were either enrolled tribal members or, in a very few cases, non-member spouses of enrollees. Interviewers were trained before each wave on personal interviewing guidelines and protection of human subjects.

Prior to the first wave of data collection, each participating reservation/reserve provided a list of all families with tribally-enrolled children aged 10–12 years who lived on or within 50 miles of the reservation/reserve. An attempt to contact all families was made in order to achieve a representative sample of the communities. Families were recruited for the study through personal interviewer visits, during which the families were presented with a culturally traditional gift and an overview of the project. For those families who agreed to participate (79.4% baseline response rate), informed consent/assent was obtained from all individual participants, and both the target adolescent and at least one adult caretaker were interviewed once per year over an eight-year period, beginning in 2002 and ending in 2011. On average, interviews lasted approximately 1.5 h. For each wave of the study, participating families were given $20 for each participant (i.e., adolescent and caregiver[s]) as compensation. Tribally appointed CRCs and the Institutional Review Board at the University of Nebraska-Lincoln approved the protocols of the study.

At the first wave of the study (see Table 1), there were 744 respondents (male – 49.7%; female - 50.3%). All outcome variables and covariates were assessed at waves 1 (M_{age} – 11.08), 4 (M_{age} – 14.25), 6 (M_{age} – 16.23), and 8 (M_{age} – 18.26) of the study, which is when the diagnostic data were collected. At Waves 4, 6, and 8, over three-quarters (87.86%, 87.42%, and 78.05%, respectively) of the original Wave 1 sample remained in the study. A total of 69.48% of the sample completed all waves included in this study, and smaller percentages were missing at one (20.21%), two (4.28%), or three waves (6.02%).

Although wave of the study is not as intuitive of a metric of time as age, restructuring the data by age results in sparse data points and coverage issues. Grouping age into smaller clusters (i.e., 11–12, 13–14, 15–16, and 17–18) also produces time points in which approximately one-third of the sample had no data on at least two time points. Rather than impute SUD event times, we opted to keep the data structured by wave. We accounted for any missing data on covariates by generating 50 imputed datasets in Mplus using the multiple imputation by chained equations method (Asparouhov and Muthen 2010; White et al. 2011). In the survival analysis models, missing data on outcome variables were right censored and handled with robust full-information maximum likelihood estimation. To examine the descriptive overlap in lifetime SUD (see bottom portion of Table 2), SUD estimates were imputed. All subsequent analyses were conducted with the imputed datasets; the results represent the parameter estimates combined across the 50 datasets.

Measures

Substance Use Disorders All substance use and psychiatric disorders were assessed with the Diagnostic Interview Schedule for Children (DISC-IV; Shaffer et al. 2000). The DISC-IV is an interviewer-administered instrument that may be used by trained interviewers with no formal clinical training. Because of their young age, we used combined parent and youth reports at Waves 1 and 4, and only adolescent reports at Waves 6 and 8. Standardized scoring algorithms were used to obtain lifetime diagnoses of nicotine dependence, alcohol abuse and dependence, and marijuana abuse and dependence based on the criteria outlined in the 4th edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV; American Psychiatric Association 2000). In line with the DSM-5 (American Psychiatric Association 2013), alcohol abuse and dependence were combined into a single alcohol use disorder variable and marijuana abuse and dependence were combined into a single marijuana use disorder variable. In addition, we created a variable at each wave which represents meeting lifetime criteria for any of the three SUDs, and a variable that represents meeting criteria for two or more lifetime SUDs. For each outcome, participants were given a score of 1 for the respective disorders if they met criteria for abuse or dependence, or were otherwise given a score of 0 (see Table 1 for raw lifetime estimates at each wave). Raw prevalence rates for separate past year and lifetime abuse and dependence rates can be found in Whitbeck et al. (2014a).

Internalizing Disorders At the aforementioned diagnostic waves, three past year and past month internalizing disorders were assessed: major depressive disorder, dysthymia, and generalized anxiety disorder. At each time point, a dichotomous variable was created with those meeting criteria for any past year internalizing disorder given a score of 1 and those not meeting criteria for any internalizing disorder given a score of 0.

Table 1 Descriptive statistics ($N = 744$)

	% (N) Observed	% (N) Imputed[a]	Percent Missing
Demographics			
Female	50.3 (373)	50.3 (374)	0.3%
Mean age (S.D.)	11.1 (0.82)	11.1 (0.82)	0.1%
Mean per capita family income (S.D.)	5.6 (4.87)	5.6 (4.88)	2.6%
Past year internalizing disorder:			
Wave 1	7.3 (54)	7.3 (54)	0.0%
Wave 4	10.2 (66)	10.2 (76)	12.8%
Wave 6	5.0 (32)	5.1 (38)	13.3%
Wave 8	3.1 (18)	3.2 (24)	22.3%
Past year externalizing disorder:			
Wave 1	19.6 (146)	19.6 (146)	0.0%
Wave 4	26.7 (173)	26.7 (199)	12.8%
Wave 6	10.6 (69)	10.9 (81)	12.6%
Wave 8	3.6 (21)	4.0 (30)	16.3%
Lifetime nicotine dependence:			
Wave 1	1.7 (13)	1.7 (13)	0.0%
Wave 4	10.8 (70)	10.4 (77)	12.5%
Wave 6	18.2 (119)	17.3 (129)	12.1%
Wave 8	23.8 (144)	21.3 (158)	18.5%
Lifetime alcohol use disorder:			
Wave 1	1.3 (10)	1.3 (10)	0.0%
Wave 4	17.5 (114)	17.1 (127)	12.4%
Wave 6	32.9 (217)	32.2 (240)	11.4%
Wave 8	44.3 (275)	41.0 (305)	16.5%
Lifetime marijuana use disorder:			
Wave 1	2.2 (16)	2.2 (16)	0.0%
Wave 4	19.8 (129)	19.1 (142)	12.4%
Wave 6	29.0 (192)	28.0 (208)	11.0%
Wave 8	37.0 (229)	33.8 (251)	16.8%

[a] Results combined across 50 imputed dataset

Externalizing Disorders Similar to internalizing disorders, three lifetime, past year, and past month externalizing disorders were assessed**:** conduct disorder, oppositional defiance disorder, and attention deficit/hyperactivity disorder. Because internalizing disorders were only assessed in past year and month timeframes, past year externalizing disorders were selected to maintain consistency. At each time point, a dichotomous variable was created with those meeting past year criteria for any externalizing disorder given a score of 1 and those not meeting criteria for any externalizing disorder given a score of 0.

Demographic Characteristics We included three variables in our analyses as both predictors of SUD onset and as basic demographic controls. Gender (0 = males, 1 = females), per capita family income (per $1000), and age at baseline were included (Table 1). We also considered residing on vs. off reservation/reserve land, and residing in a remote community vs. non-remote community as covariates; however, because they were not associated with any of the outcomes and did not alter the effects of other covariates, we opted for more statistically parsimonious models and did not include them (they were, however, included as part of the imputation models).

Analytic Strategy

We used discrete time survival analysis (e.g., Allison 2014; Singer and Willett 2003) to examine the probability of meeting lifetime criteria for a SUD and the timing of occurrence. Onset of nicotine dependence, alcohol use disorder, marijuana use disorder, any SUD, and multiple SUDs were examined in separate multivariate models. Data management (i.e., variable recoding and missing data analysis) was conducted in SPSS

Table 2 Unconditional hazard and survival probabilities (top) and comorbidity patterns (bottom) across waves ($N = 744$)

	Wave 1 Probability/ Proportion	Wave 4 Probability/ Proportion	Wave 6 Probability/ Proportion	Wave 8 Probability/ Proportion
Unconditional hazard and survival probabilities:				
Nicotine dependence				
Hazard probability	0.017	0.089	0.084	0.051
Survival probability	0.983	0.895	0.820	0.778
Alcohol use disorder				
Hazard probability	0.013	0.162	0.189	0.144
Survival probability	0.987	0.827	0.671	0.574
Marijuana use disorder				
Hazard probability	0.022	0.178	0.118	0.087
Survival probability	0.978	0.804	0.709	0.647
Any substance use disorder				
Hazard probability	0.035	0.250	0.224	0.181
Survival probability	0.965	0.723	0.562	0.460
Multiple substance use disorders				
Hazard probability	0.013	0.129	0.119	0.087
Survival probability	0.987	0.860	0.757	0.691
Comorbidity:				
No lifetime substance use disorder	0.965	0.725	0.573	0.476
Nicotine dependence only	0.008	0.021	0.030	0.030
Alcohol use disorder only	0.004	0.055	0.097	0.126
Marijuana use disorder only	0.009	0.063	0.063	0.068
Nicotine dependence + Alcohol use disorder	0.001	0.008	0.020	0.031
Nicotine dependence + Marijuana use disorder	0.004	0.021	0.013	0.017
Alcohol use disorder + Marijuana use disorder	0.004	0.053	0.095	0.118
All three substance use disorders	0.004	0.054	0.110	0.135

Hazard and survival probabilities derived from maximum likelihood estimation. Comorbidity estimates were derived from combined estimates across 50 imputed datasets

version 24, and all subsequent analyses were conducted with Mplus Version 8 (Muthen and Muthen 1998–2017). The "*Data Survival*" command was used in Mplus to generate outcome variables suitable for analysis. Using this approach, respondents were coded as zero if they did not experience the target event and one if they experienced the target event (i.e., met diagnostic criteria for a SUD). At subsequent time points, those who have experienced the event are taken out of the risk set and given a value of *. For example, a respondent who first met criteria for SUD at wave 6 would be coded as 0, 0, 1, *, for waves 1, 4, 6, and 8, respectively. Respondents who dropped out of the study and did not have any known SUDs, or those who remained in the study but did not develop a SUD were right-censored, and their event times were assumed to be non-informative (e.g., missing completely at random).

The unconditional (i.e., without covariates) cumulative survival probability was estimated at each wave to assess the probability of not developing a SUD across time. The unconditional hazard rates at each wave were also estimated, which represent the probability at each wave of meeting criteria for a SUD among those who have not already met criteria for a SUD at a prior time point. To estimate the effect of covariates, a multivariate logistic regression path analysis model with a robust maximum likelihood estimator was used, which is statistically equivalent to the approach outlined by Singer and Willett (2003) and other latent variable approaches (Masyn 2014). The hazard function at each time point was regressed on each of the time-invariant and time-varying predictors. Gender, per capita family income, and age were treated as time-invariant covariates because they either change at a constant rate or show little variation across time. For the time-varying predictors, lagged effects were estimated to ensure time ordering such that predictors at wave 1 were used to predict SUD onset at wave 4, predictors at wave 4 were used to predict SUD onset at wave 6, and predictors at wave 6 were used to predict SUD onset at wave 8. For these analyses, past year internalizing, past year externalizing, and non-focal SUDs (e.g., marijuana and alcohol use disorders in the model predicting nicotine dependence) were treated as

lagged time-varying covariates. The hazard functions at each wave were predicted with a logit link-function, and the effect of each covariate is expressed as a hazard odds ratio (*hOR*), which can be interpreted as the odds of meeting SUD criteria for a one-unit increase on a covariate. Values greater than one indicate shorter median survival times to SUD onset, whereas values less than one indicate longer median survival times to onset.

An assumption of discrete time hazard models is that the effect of each predictor has an identical effect in every time period under examination (proportional odds assumption). We examined this assumption by testing a model in which the path coefficients for all of the covariates were constrained to be equal across time points (constrained model), followed by removing the constraints on each covariate individually. A significant drop in model fit (−2 * change in log likelihood) after freeing the constraints indicate that one or more of the associations have different effects at one or more of the waves. A non-significant drop in model fit would indicate a lack of time-based moderation, which would allow us to report a single coefficient for each covariate. In each model, the effect of age varied across time (nicotine dependence: $\chi^2 = 12.38(3)$, $p = 0.01$; alcohol use disorder: $\chi^2 = 10.91(3)$, $p = 0.01$; marijuana use disorder: $\chi^2 = 23.16(3)$, $p = 0.00$; any SUD: $\chi^2 = 16.48(3)$, $p = 0.00$; multiple SUDs: $\chi^2 = 20.18(3)$, $p = 0.00$). Per capita family income was also allowed to vary across time for alcohol use disorder ($\chi^2 = 8.78(3)$, $p = 0.03$) and any SUD ($\chi^2 = 8.67(3)$, $p = 0.03$) models. As a result, the effect of age is freely estimated across each wave, and per capita family income is freely estimated across time in the alcohol use disorder and any SUD models.

Results

Hazard and Cumulative Survival Probabilities

The top portion of Table 2 and Fig. 1 displays the unconditional hazard rates for lifetime nicotine dependence, alcohol use disorder, marijuana use disorder, any of the three SUDs, and two or more SUDs. At the first wave of the study, hazard probabilities were low for all three substances (0.017 for nicotine dependence, 0.013 for alcohol use disorder, and 0.022 for marijuana use disorder). For nicotine dependence and marijuana use disorder, the peak period of risk occurred at wave 4 of the study, when respondents were between the ages of 13 and 15 years. Alcohol use disorder hazard rates peaked at wave 6 of the study, when the respondents were between the ages of 15 and 17 years. By wave 4 of the study, marijuana use disorder hazard rates (0.178) were higher than alcohol use disorder (0.162) and nicotine dependence rates (0.089). By wave 6 of the study, alcohol use disorder rates (0.189) surpassed marijuana use disorder rates (0.118), and were double the rate of nicotine dependence (0.084). By wave 8 of the study, hazard rates declined for each substance, with alcohol use disorder rates (0.144) having the highest probability, followed by marijuana use disorder (0.087) then nicotine dependence (0.051).

The bottom portion of Fig. 1 (see also top portion of Table 2) displays the cumulative survival curves across each time point. Of particular relevance is the survival probability at wave 8 of the study when respondents were between 17 and 19 years old, which marks the end of adolescence and the beginning of early adulthood. The probability of *not* becoming dependent on nicotine was 0.778, while the probability of not developing a marijuana use disorder (0.647) or alcohol use disorder (0.574) were much lower. The survival probability of not developing any SUD was less than half (0.46), which suggests that the median survival time of developing a SUD is somewhere between waves 6 and 8 (ages 16–18).

In addition to the individual substance hazard and survival probabilities, we also assessed concurrent overlaps in lifetime SUD rates for nicotine, alcohol, and marijuana. The bottom portion of Table 2 presents the overlap in lifetime SUDs across each of the four time points. For these analyses, multiple imputation was used to derive prevalence estimates, which were similar to the hazard estimates derived from robust maximum likelihood estimation. The most common single SUD across time was alcohol use disorder, followed by marijuana use disorder and nicotine dependence. The most common two-SUD combination across time points was comorbid alcohol use and marijuana use disorders. Comorbid nicotine dependence and alcohol use disorders, and comorbid nicotine dependence and marijuana use disorders were less common. By waves 6 and 8, lifetime SUD on all three substances were the most common pattern. Hazard and cumulative survival probabilities (see top of Table 1 and Fig. 1) indicate that onset of two or more lifetime SUDs peak at wave 4 of the study and decrease slowly thereafter. The survival curves indicate that 69.1% of respondents either did not develop a SUD or met diagnostic criteria on one substance only.

Multivariate Discrete Time Survival Models

Nicotine Dependence Table 3 presents the multivariate discrete time survival analysis results for each SUD outcome. In the model predicting nicotine dependence, the effect of all covariates were constrained to be equal across time, with the exception of age, which was allowed to vary across time. All three demographic predictors were significant. The odds of meeting criteria for nicotine dependence were higher for females compared to males (*hOR* = 1.52). Increases in per capita family income decreased the odds (*hOR* = 0.95) of nicotine dependence at all waves, whereas increases in age increased the odds at the first two time points only (wave 1 *hOR* = 3.56;

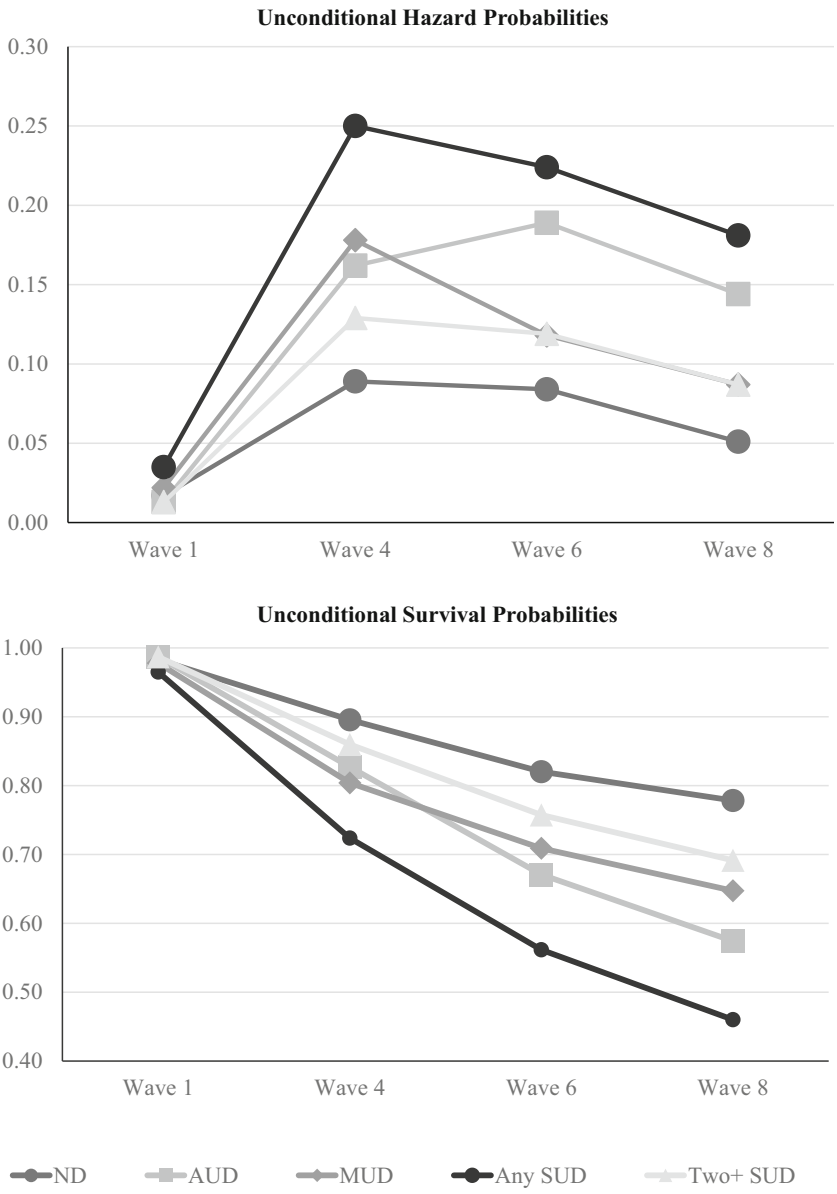

Fig. 1 Unconditional hazard rates (top portion) represent the probability (y-axis) at each wave (x-axis) of meeting criteria for nicotine dependence (ND), alcohol use disorder (AUD), marijuana use disorder (MUD), any substance use disorder (Any SUD), and multiple substance use disorders (Two+ SUD) among those who have not already met criteria at a prior time point. Unconditional survival rates (bottom portion) represent the cumulative probability (y-axis) of *not* meeting criteria for each substance use disorder outcome across each wave (x-axis)

wave 4 *hOR* = 1.52). Of the two psychiatric disorder covariates, only past year internalizing disorders increased the odds of nicotine dependence onset (*hOR* = 2.73). Externalizing disorders did not predict nicotine dependence onset. Neither alcohol use disorder nor marijuana use disorder predicted nicotine dependence onset.

Alcohol Use Disorders For the alcohol use disorder model, per capita family income and age violated the proportional odds assumption and were allowed to vary across time points. Increases in per capita family income decreased the odds of alcohol use disorder onset at wave 4 of the study (*hOR* = 0.93), but not at waves 1, 6, and 8. Similar to the nicotine dependence model, increases in age increased the odds of alcohol use disorder at waves 1 (*hOR* = 4.85) and 4 (*hOR* = 1.50), but not waves 6 and 8. Gender was not associated with alcohol use disorder onset. Of the two psychiatric disorder clusters, only past year externalizing disorders increased the odds of alcohol use disorder onset (hOR = 1.48). Internalizing disorders were not a significant predictor. Prior nicotine dependence (*hOR* = 2.49) and marijuana use disorder (*hOR* = 2.69) each more than doubled the odds of alcohol use disorder onset.

Marijuana Use Disorder For the marijuana use disorder model, all covariates were constrained to be equal, with the exception of age, which was allowed to vary across time. Increases in per capita family income decreased the odds (*hOR* = 0.93) of marijuana use disorder onset at each wave, whereas increases in age increased the odds at waves 1 (*hOR* = 6.84) and 4 (*hOR* = 1.58), but not waves 6 and 8. Gender was not associated with marijuana

Table 3 Discrete time survival analysis models predicting substance use disorder onset ($N = 744$)

	Nicotine dependence hOR 95% CI	Alcohol use disorder hOR 95% CI	Marijuana use disorder hOR 95% CI	Any substance use disorder hOR 95% CI	Multiple disorders hOR 95% CI
Baseline covariates:					
Female	1.52*	1.17	0.99	1.27	1.38*
	[1.06, 2.17]	[0.89, 1.53]	[0.74, 1.33]	[1.00, 1.62]	[1.01, 1.87]
Per capita income[a]					
Wave 1	0.95*	0.89	0.93***	0.92	0.94**
	[0.90, 1.00]	[0.74, 1.09]	[0.89, 0.96]	[0.84, 1.01]	[0.90, 0.98]
Wave 4	0.95*	0.93*	0.93***	0.92**	0.94**
	[0.90, 1.00]	[0.88, 0.99]	[0.89, 0.96]	[0.87, 0.97]	[0.90, 0.98]
Wave 6	0.95*	0.96	0.93***	0.94*	0.94**
	[0.90, 1.00]	[0.90, 1.02]	[0.89, 0.96]	[0.88, 1.00]	[0.90, 0.98]
Wave 8	0.95*	1.03	0.93***	1.02	0.94**
	[0.90, 1.00]	[0.99, 1.07]	[0.89, 0.96]	[0.98, 1.06]	[0.90, 0.98]
Age[b]					
Wave 1	3.56**	4.85*	6.84***	3.75***	10.20***
	[1.46, 8.68]	[1.33, 17.65]	[3.00, 15.58]	[1.95, 7.20]	[2.78, 37.48]
Wave 4	1.52*	1.50**	1.58***	1.70***	1.53**
	[1.09, 2.12]	[1.17, 1.93]	[1.22, 2.04]	[1.34, 2.14]	[1.15, 2.03]
Wave 6	1.03	1.13	1.29	1.18	1.35
	[0.71, 1.49]	[0.86, 1.47]	[0.93, 1.79]	[0.91, 1.55]	[0.98, 1.86]
Wave 8	0.86	1.23	0.92	1.18	1.03
	[0.54, 1.37]	[0.85, 1.79]	[0.62, 1.38]	[0.82, 1.70]	[0.71, 1.49]
Time-varying covariates:					
PY internalizing disorder	2.73**	1.43	1.11	1.57	1.87*
	[1.53, 4.87]	[0.82, 2.48]	[0.58, 2.11]	[0.92, 2.69]	[1.08, 3.25]
PY externalizing disorder	1.39	1.48*	1.52*	1.69**	2.47***
	[0.85, 2.28]	[1.02, 2.15]	[1.01, 2.28]	[1.18, 2.44]	[1.69, 3.61]
LT nicotine dependence		2.49**	2.88*		
		[1.31, 4.72]	[1.27, 6.54]		
LT alcohol use disorder	1.75		3.42***		
	[0.83, 3.68]		[1.91, 6.11]		
LT marijuana use disorder	1.31	2.69***			
	[0.61, 2.80]	[1.64, 4.40]			

hOR Hazard Odds Ratio, *CI* Confidence Interval, *PY* Past Year, *LT* Lifetime

[a] Effects constrained to be equal across time for nicotine dependence, marijuana use disorder, and two or more substance use disorder models (proportional odds assumption holds). Effects were allowed to vary across time points for alcohol use disorder and any substance use disorder (proportional odds assumption not met)

[b] Effects were allowed to vary across time points (proportional odds assumption not met)

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

use disorder onset. Of the two psychiatric disorder clusters, only past year externalizing disorders increased the odds of marijuana use disorder onset across each time period ($OR = 1.52$). Internalizing disorders were not significantly associated with marijuana use disorder onset. Both prior lifetime nicotine dependence ($hOR = 2.88$) and alcohol use disorder ($hOR = 3.42$) increased the odds of marijuana use disorder onset across time points.

Any SUD For the any SUD model, all covariates were constrained to be equal across time points, except for per capita family income and age. Increases in per capita family income decreased the odds of SUD onset at waves 4 ($hOR = 0.92$) and 6 ($hOR = 0.94$), but not waves 1 and 8. Increases in age increased the odds of SUD onset at waves 1 ($hOR = 3.75$) and 4 ($hOR = 1.70$), but not waves 6 and 8. Gender was not a significant

predictor of any SUD onset. Of the two psychiatric disorder clusters, only past year externalizing disorders increased the odds of any SUD onset (*hOR* = 1.69). Internalizing disorders were not a significant predictor.

Multiple SUDs For the multiple SUDs model (meeting criteria for at least two out of the three SUDs), the effect of each covariate was constrained to be equal across time, with the exception of age, which was allowed to vary at each time point. Females had higher odds of multiple SUDs than males (*hOR* = 1.38). Increases in age increased the odds of multiple SUDs at waves 1 (*hOR* = 10.20) and 4 (*hOR* = 1.53), but not waves 6 and 8. Per capita family income was not associated with multiple SUDs. Both psychiatric disorder clusters were significant. Those who met past year criteria for an internalizing (*hOR* = 1.87) or externalizing (*hOR* = 2.47) disorder at a prior time point had increased odds of multiple SUDs at subsequent time points.

Discussion

Research indicates that Indigenous adolescents initiate use of substances earlier than other racial/ethnic groups (Miller et al. 2008) and move more quickly into regular use (Beauvais 1998; Blum et al. 1992; Herring 1994). A modest body of literature examines these two crucial stages of substance use, with far less known about the developmental course of abuse/dependence onset which is qualitatively more deleterious to social and psychological well-being than general use patterns. Moreover, we have a limited understanding of comorbid SUDs, their combinatorial manifestations, and their prevalence within and across various stages of adolescence. To fill this gap in the literature and paint a broader epidemiological picture of substance use patterns among Indigenous youth, the purpose of the study was to examine the timing and probability of SUD onset across the span of adolescence, their concurrent overlap, and psychiatric and demographic predictors of SUD onset.

Before highlighting the implications of the study, four important caveats frame the interpretation of these results. First, SUDs have complex etiologies. Because of statistical power constraints, we were limited in the number of covariates that could be added and opted for a more conceptually and statistically parsimonious model based on SUD and other psychiatric comorbidity. North American Indigenous people experience high rates of collective generational and lifetime trauma, along with ongoing racism, discrimination, and micro-aggressions (Evans-Campbell 2008). These factors are likely fundamental drivers of health disparities, including SUDs, among Indigenous communities (Whitbeck et al. 2014b). The framing and methods of the study reside primarily at the individual level and do not account for these sociohistorical and contemporary factors. With this in mind, future research on SUD etiology among Indigenous youth should shift the focus away from individually-oriented pathology toward social contexts which give rise to these particular patterns of use and abuse across the life course.

Second, there is modest evidence to suggest that substance use rates and patterns vary across tribal and regional communities (Novins and Baron 2004; Novins et al. 2001). Because this research was limited to a single Indigenous cultural group residing on rural reservation/reserves, we caution against generalizing to other Indigenous cultural groups and perhaps to Indigenous youth of the same cultural group residing in urban areas. Although this may be considered a limitation, we believe the cultural and geographic heterogeneity among Indigenous groups necessitates within-culture studies. The accumulated evidence generated from these within-culture studies can be used to make between-culture comparisons, and non-Indigenous comparisons.

Third, when using diagnostic interview schedules cross-culturally in community-based settings there is always the caution that the data collection methods and resulting diagnostic estimates are not culturally appropriate. The entire research approach was informed by the principles of community based participatory research, and almost all of the interviewers were enrolled tribal members from the participating communities. Although the families were given the opportunity to decline particular interviewers if they were related to them or if they were otherwise uncomfortable with the interviewer, local interviewers may have resulted in under reporting and conservative bias in diagnostic estimates. Moreover, some have questioned the validity of using diagnostic instruments in cross-cultural contexts (e.g., O'Nell 1996). Our diagnostic measures, however, were the same as those used in other epidemiological studies of North American Indigenous people (e.g., Whitesell et al. 2006) and previous work suggests that if there is systematic cultural bias in the diagnostic results, it is within estimates of internalizing disorders rather than disorders of externalization and substance use (O'Nell 1996; Whitbeck et al. 2014a).

Fourth, several methodological issues were present. As with any longitudinal dataset, missing data because of attrition is a potential issue. We conducted a thorough attrition analysis using a wide array of Wave 1 variables (e.g., substance use frequency, intentions to use substances in subsequent years, substance using peers, delinquency, depressive symptoms, youth and family demographics) to predict drop out at subsequent waves. The only factor that predicted missingness across outcomes was residing on vs. off reservation/reserve land. Those who reside off reservation/reserve land had higher odds of dropping out of the study. We conducted several sensitivity analyses to examine the effect of various missing data assumptions. The current study right censors participants who drop out and have unknown SUD event times, which are assumed to be missing completely at random, and likely produce conservative SUD estimates. Imputing event times (in this case, assumed to be missing at random) and including auxiliary information from non-diagnostic waves (e.g., substance use frequency, delinquency, depressive symptoms,

anxiety symptoms) to improve model estimation produced similar results to imputing covariates and using right censoring on the outcomes. Although we cannot rule out other unknown factors that may cause selective attrition patterns, our approach to handling missing data appears to be robust to different specifications. Similarly, we were unable to restructure the data by age because of non-uniform missing data patterns, which would have allowed for more precise estimates of SUD onset compared to wave of the study. In addition, because of the young age of the adolescents at the first two diagnostic waves, we relied on combined parent and child reports; however, this likely produces more reliable estimates than using only adolescent-reported data.

Timing and Probability of SUD Onset

With these caveats in mind, the current study provides important insights into the developmental course of nicotine, alcohol, and marijuana use disorders across the span of adolescence. By late-adolescence, the probability of meeting criteria for nicotine dependence, alcohol use disorder, marijuana use disorder, any SUD, and two or more SUDs was 22%, 43%, 35%, 54%, and 31%, respectively. For each outcome, with the exception of alcohol use disorder, periods of new cases in lifetime disorder peaked at Wave 4 of the study (M_{age} = 14.25). For alcohol use disorder, peak periods of risk for new lifetime cases occurred later at Wave 6 of the study (M_{age} = 16.23).

These findings add to a general pattern of Indigenous adolescent substance misuse. Onset of use of nicotine, alcohol, and marijuana typically occurs around the ages of 12–14 years (Novins and Baron 2004; Whitbeck and Armenta 2015), and progression to frequent use of each substance peaks by approximately 15 years of age (Walls et al. 2013; Whitbeck et al. 2012). The peak period for new lifetime cases occurred between the ages of 13 and 17 in this study, which was a few years after initial use and concurrent with peak frequency of use. Compared to substance use patterns found in the general population, these trends for initiation of use and progression to abuse and dependence occur several years earlier (Johnson et al. 2017). Notably, peak risk for SUDs also starts to decline several years prior to that found in the general population, and continuity in abuse/dependence across the life course does not appear to be prevalent. American Indian adults have similar, if not lower, rates of alcohol and marijuana use than whites (Copeland et al. 2017; Cunningham et al. 2016). High rates of lifetime SUDs found among various Indigenous populations may be a function of early and cumulative abuse/dependence cases, rather than sustained risk across the life course (Copeland et al. 2017). Despite this, SUDs in adolescence likely disrupts key developmental processes (e.g., school, family relations) that may portend negative outcomes across the life course such as low educational attainment and criminal justice system involvement (Sittner 2016).

Overlap in SUDs

Just under one-third of the sample was at risk for developing multiple SUDs by the end of adolescence. The prevalence of single SUD declined as a percentage of SUD cases across time for nicotine dependence only and marijuana use disorders only. Alcohol use disorders were the most common single SUD and became more prevalent across time, patterns similar to those found among Colorado adolescents (Palmer et al. 2009). Among those with comorbid SUDs, meeting criteria for abuse/dependence on all three substances was the most common pattern, followed closely by comorbid alcohol use and marijuana use disorders. These patterns suggest that homotypic SUD comorbidity is common and perhaps share common etiologies/liability.

The results of the discrete time survival analysis models showed that nicotine dependence prospectively predicts both alcohol and marijuana use disorders, alcohol and marijuana use disorder prospectively predict one another, and neither alcohol nor marijuana use disorders predict nicotine dependence onset. These finding appear to support a both a general and sequential common liability model. Among Indigenous youth, onset of nicotine use occurs prior to alcohol and marijuana initiation (Whitbeck and Armenta 2015), and is generally the most commonly available substance for adolescents in general (Johnson et al. 2017). Emerging animal models indicate that nicotine tolerance may cross over to other substances such that increasing quantity is needed on other substances to produce the psychoactive effect (Kandel and Kandel 2015). Patterns of use such as this likely magnify addiction liability on other substances and may be why nicotine dependence predicts other SUDs and not the reverse. In such a case, nicotine dependence may be considered a “gateway” addiction. Prevention programming may benefit by focusing on curtailing early nicotine use, followed by a general emphasis on all substances.

Psychiatric Disorders and Demographic Predictors of SUD Onset

Internalizing and externalizing psychiatric disorder clusters often emerge concomitantly with substance use problems, and generally precede onset of SUDs by several years (Swendsen et al. 2010). We found mixed support for these general trends. Internalizing disorders increased the odds of nicotine dependence and multiple SUDs; however, they were not associated with alcohol or marijuana use disorder onset. It may be that specific internalizing disorders have more of an effect on SUD onset than others do (O’Neil et al. 2011). A more plausible explanation is that

internalizing and SUDs are more often comorbid for females than males. Females had higher odds of nicotine dependence than males, and prior research on Indigenous youth shows that internalizing symptoms have more of an effect on smoking rates for females compared to males (Whitbeck et al. 2009). In post-hoc analyses, interactions between gender and internalizing and externalizing disorders were tested, and two significant results emerged. It appears that internalizing disorders have a stronger effect for onset of alcohol use disorder and comorbid SUDs for females than males. Given the small past year prevalence rates for internalizing disorders at each wave, however, we caution against placing too much emphasis on these post-hoc results. These preliminary findings, along with prior research among Indigenous youth, suggest that a more refined gendered-based approach is needed to understand the developmental context of sub stance abuse.

Alternatively, the validity of internalizing disorders among Indigenous groups has been questioned, with somatic complaints and other cultural idioms of distress such as loneliness playing a more prominent part than negative affect and other interpersonal problems (O'Nell 1996). As such, one possibility may be that the association between Western conceptualizations of internalizing disorders and SUD onset are more complex than assumed. Culturally grounded frameworks may provide a fruitful avenue for understanding possible connections between internalizing conditions and SUD development.

Externalizing disorders, on the other hand, were associated with onset of alcohol, marijuana, and multiple SUDs, but not nicotine dependence. Externalizing disorders such as conduct disorder and ADHD share an underlying phenotypic liability with SUDs, and likely share etiology (Vanyukov et al. 2003). These findings also support prior research among Indigenous youth showing that externalizing symptoms tend to precede and overlap with SUD symptoms (Greenfield et al. 2017; Whitbeck et al. 2014a). Taken together with the findings on internalizing disorders, prevention programming may benefit by focusing broadly on mental health promotion and reducing early negative behavioral and emotional symptoms and enhancing personal and communal resilience before secondary (e.g., substance use) problems emerge.

Prior research on the association between gender and substance use risk generally suggests that males have higher odds of substance use problems than females (Merikangas et al. 2010). This trend, however, appears to be declining with female substance use patterns becoming more similar to males for younger age cohorts (Kessler et al. 2005). Among Indigenous youth, females have higher odds of early nicotine, alcohol, and marijuana use than males. By mid-adolescence, however, rates of male substance use surpass that of females (Walls et al. 2013), which may reflect early differences in biosocial maturity. The only gender effect showed that females have higher odds of developing nicotine dependence and multiple SUDs than males. This effect did not vary across the four diagnostic waves, and runs counter to the three alternative hypotheses presented. Moreover, nicotine dependence was highly comorbid with alcohol and marijuana use disorders, and nicotine dependence only was rare. Consequently, the findings showing that females have higher odds of developing multiple SUDs in adolescence are likely driven by nicotine dependence rates. These findings indicate that gender specific prevention and intervention programming may be beneficial during late childhood and early adolescence, particularly centered on curtailing early nicotine use for females.

In addition to gender, per capita family income was associated with onset of each SUD outcome examined. For alcohol and any SUD models, the effect of per capita income was stronger during mid-adolescence compared to early- or late-adolescence. It may be that income has an effect on the early emergence of alcohol use disorder cases; however, given how prevalent alcohol use disorders are over time, alternative factors may become more salient while the role of family income weakens. For each of the other outcomes, increases in income decreased the odds of SUD onset. Although family income does not have a causal effect on substance use, family income may be conceptualized as a proxy for family socioeconomic status and is likely to be associated with adverse health outcomes through its enduring link with multiple proximal risk factors such as stress exposure (Link and Phelan 1995) and family relations (Shaw and Shelleby 2014). Because socioeconomic disadvantage and other ongoing stressors and traumas provide a backdrop for Indigenous community health, understanding the nuanced mechanisms through which income influences substance use is vital for shaping effective community-based substance use policy.

Conclusions

Taken together with what we know about Indigenous adolescent substance use patterns, the current results provide some broad insights for prevention, intervention, and treatment. Because SUDs emerge by mid-adolescence and initiation of use occurs mainly during pre- and early-adolescence, age-appropriate prevention programming should begin during the childhood years. We know that early onset use increases the odds of developing a SUD. Prevention programming aimed at delaying onset of use may reduce rates of abuse/dependence. For youth who do initiate use of substances at an early age, targeted and timely interventions may slow the progression to regular, non-experimental use. Moreover, initiation of nicotine use tends to occur prior to that of other substances, and nicotine dependence generally precedes alcohol and marijuana use disorders. Consequently, a targeted prevention focus on nicotine-based products seems paramount to reducing early abuse and dependence of other substances.

Interventions may also benefit by reducing psychiatric symptoms and focusing on universal and culturally relevant mental health promotion that enhance positive coping responses and resilience. Findings that females initiate use of substances at earlier ages, and are at high risk for developing nicotine dependence and multiple SUDs suggest the need for early gender responsive substance use prevention and intervention programming to adapt to gendered developmental processes. Achieving these policy aims requires a nuanced understanding of the social contexts that give rise to these patterns and the unique cultural and community factors that can be leveraged to adapt and translate basic research science to effective prevention, intervention, and treatment.

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Compliance with Ethical Standards

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Ethical Approval All procedures were approved by the University of Nebraska-Lincoln's Institutional Review Board and tribal council appointed advisory boards.

Informed Consent Informed consent was obtained from all individual participants involved in the study.

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