

Effects of sleep on substance use in adolescents: a longitudinal perspective

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ABSTRACT

Substance use (SU) and sleep problems appear interrelated, but few studies have examined the influence of adolescent sleep patterns on development of SU disorders. This study prospectively examined the influence of sleep habits on subsequent SU in youth who later transitioned into heavy drinking. At time 1 (T1), participants ($n = 95$) were substance-naïve 12- to 14-year-olds. Path-analytic models examined whether the effects of T1 risk factors (familial SU disorder, inhibition control, and externalizing and internalizing traits) on time 3 ($M = 19.8$ years old) tobacco, alcohol, and cannabis were mediated by time 2 ($M = 15.1$ years old) sleep chronotype, daytime sleepiness, and erratic sleep/wake behaviors. Significant direct path effects of T1 risk factors and time 2 sleep behaviors on time 3 SU were found, $P_s < 0.05$. In models that examined the effect of each individual sleep behavior separately on SU, more erratic sleep/wake and greater daytime sleepiness predicted higher lifetime use events for all substances ($P_s < 0.01$). Higher evening chronotype tendencies predicted lower tobacco and higher but lower alcohol and cannabis lifetime use events ($P_s < 0.01$). Erratic sleep/wake behaviors mediated the effect of inhibitory control on subsequent SU; less erratic sleep/wake behaviors predicted better inhibition control ($\hat{\beta} = -0.20$, $P < 0.05$). Early-mid adolescent psychiatric health and sleep behaviors prior to drinking onset predicted greater SU 5 years later. Participants were substance-naïve at baseline, allowing for the examination of temporal order in the relationship between sleep problems and alcohol use. Early adolescent sleep problems may be an important risk factor for SU in later life.

Keywords adolescence, sleep, substance use.

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INTRODUCTION

Adolescence is a period characterized by marked physiological, social, and neurocognitive changes and maturation. During puberty, youth begin to display a preference for later sleep and wake times (Wolfson & Carskadon 1998), even after accounting for the influence of other social factors (e.g. home illumination and extracurricular involvement; National Sleep Foundation 2014). Similar findings in other countries suggest that this phenomenon is not culturally bound but may reflect underlying biological changes (Yang *et al.* 2005). Shifts in sleep patterns during adolescence often negatively affect sleep duration and quality, leaving many

adolescents sleep deprived. Between ages 13 and 19, there is an overall decrease in weekend and weekday sleep duration (Wolfson & Carskadon 1998). The proportion of youth who obtain at least 8 hours of sleep decreases from 40 to 23 percent between 9th and 12th grade (Kann *et al.* 2014).

Concomitant with changes in sleep increases and in substance use (SU) during adolescence (McKnight-Eily *et al.* 2011). Alcohol, marijuana, and tobacco are the most commonly used substances among youth (Johnston *et al.* 2016). There is a threefold increase in the prevalence of cigarette, smokeless tobacco, and cannabis use from eighth grade (13, 9, and 16 percent, respectively) to the end of high school (Johnston *et al.*

2016). Teens 12–18 years old who experience problems with falling or staying asleep are more likely to endorse SU (O'Brien & Mindell 2005; Roane & Taylor 2008). Among students, decreased school night sleep duration, increased differences between weekday and weekend sleep onset time, and lowered sleep quality have been associated with increased SU and related consequences (O'Brien & Mindell 2005). Sleep timing propensity, or chronotype, has been consistently associated with SU (Hasler *et al.* 2013). Morning chronotypes tend to have an earlier sleep onset and offset (i.e. wake-up) time. In comparison, evening chronotypes are more active later in the day and have a later pattern of sleep onset and offset. Compared with their morning chronotype counterparts, evening chronotypes engage in significantly more SU behaviors (Pieters *et al.* 2010).

It is important to understand the possible contributions of environmental and psychosocial influences on why sleep problems may precede SU. This will further aid in efforts to better identify sleep as a possible risk factor and address the alarming trend of using alcohol and tobacco as sleep aids among students (Noland *et al.* 2009). The relationship between SU and sleep has been well studied in adults and, to a lesser extent, in adolescents. Two key criteria must be considered in understanding the effects of sleep problems on adolescent SU. First, to ascertain whether alcohol use precedes or follows sleep disturbance, it is important to examine the onset of sleep problems prior to SU initiation. To date, there have been few studies examining this issue longitudinally. Children with daytime over-tiredness and trouble sleeping are twice as likely to begin drinking in adolescence and experience alcohol-related consequences compared with same-aged peers without early life sleep problems (Wong *et al.* 2010). Recently, further evidence emerged to suggest that sleep problems precede, and are predictive of, future adolescent SU (Hasler *et al.* 2016). Importantly, youth were substance-naïve at baseline in these studies, decreasing possible confounding effects of concomitant alcohol use and sleep problems.

The relationship between sleep patterns and SU has yet to be characterized in the context of a broader array of other age-appropriate psychological and environmental factors associated with these constructs. Such factors include psychiatric functioning, impulsivity, and family history (FH) of SU disorder (SUD). One study found that daytime sleepiness predicted alcohol use above and beyond internalizing and externalizing symptomatology (Miller *et al.* 2016), while another reported that the association between insomnia and use initiation decreased after controlling for them (Johnson & Breslau 2001). The effect of FH on the development and maintenance of SU has been well documented

(Barnow *et al.* 2002). However, if and how familial SUD affects sleep patterns is less clear. Healthy adults with FH of parental alcohol use disorder take longer to fall asleep than those without (Rupp *et al.* 2007). Substance-naïve 9- to 10-year-olds with parental history of alcoholism displayed lower delta power during non-rapid eye movement sleep than in negative FH children (Tarokh & Carskadon 2010). Poor response inhibition has been associated with increased SU and poor sleep in adolescents (Beebe 2011). Together, these findings suggest that the relationship between sleep and SU in adolescents interacts with other psychological and environmental factors. Yet few studies have examined them together in a comprehensive prospective model.

The present study utilized a longitudinal design with three timepoints spanning 8 years to test whether the effects of environmental and psychiatric risk factors at project entry [i.e. time 1 (T1) inhibitory control, externalizing and internalizing traits, and SUD FH] on subsequent lifetime SU events measured at time 3 (i.e. cumulative use of alcohol, tobacco, and cannabis; T3) are influenced by sleep behaviors at time 2 (i.e. chronotype, daytime sleepiness, and erratic sleep/wake behaviors; T2) in adolescents. T1 factors were chosen owing to associations with sleep and SU in prior studies. Importantly, participants had not initiated SU at the time their sleep behaviors were assessed, allowing for the question of whether sleep in mid-adolescence predicts subsequent SU quantity. On the basis of previously reported cross-sectional findings, it was hypothesized that youth with poorer inhibitory control, increased internalizing and externalizing symptomatology, and greater SUD FH density at T1 will have greater lifetime use events of alcohol, tobacco, and marijuana by T3 (Johnson & Breslau 2001). Further, we propose that this relationship between risk factors and SU is mediated by sleep patterns in mid-adolescence. Youth with more T1 risk factors will have greater T2 evening chronotype tendencies and T2 sleep problems (i.e. greater daytime sleepiness and more erratic sleep/wake behaviors), which will in turn lead to greater lifetime SU events at T3 (Nicholson *et al.* 2004). It was theorized that sleep problems influence SU outcomes through negative effects on basic biological functions (i.e. autonomic nervous system and circadian rhythms) associated with decreased capacity for self-regulation and impulse control (Hasler & Clark 2013; Hasler *et al.* 2016).

MATERIALS AND METHODS

Participants

This study is part of an ongoing longitudinal neuroimaging project on adolescent SU (R01-

AA13419). At T1, participants were healthy 12–14 year-old San Diego middle school students with minimal SU experience. Potential participants were recruited through fliers and screened by bachelor's or master's level psychometrists. Parents provided verbal consent for a telephone screening to assess inclusion and exclusion criteria. Eligible participants were assessed using in-person detailed youth screening; parents underwent a parallel parent screen. Youth and parents were then followed annually following T1 at approximately the same time each year (within 3 months). At each annual follow-up, youth were administered the same detailed interview and questionnaires described later. The study protocol was approved by the University of California San Diego Human Research Protections Program.

Agers 12–14 years are an important time for neurodevelopment. During this period, development of frontal brain regions intensifies but the brain is mature enough to allow for longitudinal comparisons without gross structural changes (Giedd 2004). Rapid psychosocial developments also occur in this age range and are reflected in increased rates of SU. Fifteen to 26 percent of students try alcohol by eighth grade (SAMHSA 2013). Further, sleep changes generally emerge in adolescence around age 11–12 years (Colrain *et al.* 2014), in part owing to puberty-related changes in circadian rhythms and environment (e.g. earlier school times). The 12–14 years age range is early enough to capture SU initiation and sleep pattern changes, but structural neurodevelopment has stabilized to allow for the examination of long-term changes throughout adolescence. To account for developmental variation within this age range, age and pubertal development were included as covariates in all analyses.

Exclusionary criteria at T1 included: prenatal alcohol (greater than two drinks in a week) or illicit drug exposure; born before 35th gestational week; history of DSM-IV (American Psychiatric Association 2000) Axis I disorder, traumatic brain injury or loss of consciousness (>2 min), neurological or chronic medical illness, learning disability or mental retardation, or use of psychoactive medications; significant experience with substances; inadequate comprehension of English; and non-correctable sensory problems.

The parent study enrolled a total of $n = 295$ participants (six withdrew from the study by T3). The Sleep Habits Questionnaire was added to the parent study protocol at a later time period; thus, not all 295 participants were administered this measure prior to alcohol use initiation. For the present analysis, no participant had consumed a full drink of alcohol or tried any other drug at T1 or T2 or had a history of Axis I disorder at T3 (measured by annual follow-up diagnostic

interview; $n = 95$; see Table 1). The study took place over 8.2 years, such that T1 data were collected at project entry, T2 data were collected 1.5 (SD = 0.7, range: 0.9–3.5) years later, and T3 data 4.6 (SD = 0.5, range: 2.6–5.9) years after time 2. Participants were, on average, 13.4 (SD = 0.7), 15.1 (SD = 0.9), and 19.8 (SD = 0.9) years old at T1, T2, and T3, respectively.

At T3, youth must have at least initiated alcohol use and been between ages 17 and 21 years. This age range was selected for two reasons. It coincides with the social event of transitioning out of high school and into college (all participants attended post high school education). Alcohol and other SU behaviors also change at this time, with college students more likely to be engaged in risky

Table 1 Sample characteristic at time 1 and follow-ups ($n = 95$).

	Baseline Time 1	Follow-up Time 2	Follow-up Time 3
	M (SD) or %		
Age	13.4 (0.7)	15.1 (0.9)	19.8 (0.9)
Female (%)	47.4%		
Hollingshead Index (SES)	22.1 (12.7)		
Family History			
Negative	43.6%		
Mild	34.0%		
Positive	22.3%		
Race			
Latino/a	20.0%		
Caucasian	68.4%		
African-American	3.2%		
Asian	6.3%		
Other	5.3%		
Multiple races	16.8%		
Conduct disorder (%)	3.2%		
Sleepiness ^a		13.2 (2.9)	
Erratic sleep/wake behaviors ^a		14.6 (4.0)	
Chronotype ^a		28.2 (4.9)	
Lifetime tobacco users (%)	0%		54.7%
Lifetime drinkers (%)	0%		100%
Lifetime cannabis users (%)	0%		57.9%
Other recreational drug users (%) ^b	0%		22.1%
Past year drinking days	0 (0.0)		43.6 (55.3)
Past year HED days	0 (0.0)		17.9 (35.6)
Average monthly drinking days ^c	0 (0.0)		3.6 (4.5)

HED = Heavy episodic drinking; SES = socioeconomic status. ^aSleep Habits Questionnaire scale score, higher values indicate more sleepiness, more erratic sleep/wake behaviors, and greater morning chronotype tendency. ^bAmphetamines, barbiturates, hallucinogens, cocaine, inhalants, opiates, benzodiazepines, ecstasy, ketamine, gamma-hydroxybutyric acid [GHB], and Phencyclidine [PCP]. ^cPast 3 months.

drinking behaviors than high school students. Epidemiologically, tobacco and illicit drug use peaks during this time (SAHMSA 2013). Further, age 17–21 years marks a range and developmental period that is arguably distinct from younger (i.e. high school students) and older (i.e. post-college young adults) ages. Thus, T3 outcome data were confined to this age range to decrease heterogeneity in the outcome variables of interest (i.e. SU) owing to environmental factors unrelated to T2 sleep.

Procedures

After initial screen at T1, eligible youth were administered a comprehensive interview assessing SUD, FH and psychopathology, SU, and general background information. A different psychometrist interviewed the parent on background and FH. Participants were assured that responses are not shared with parents or schools. To maintain a high follow-up rate (>95 percent), participants were contacted quarterly and with brief interviews, newsletters, and birthday cards (Twitchell *et al.* 1992).

Measures

Structured clinical interview

The Structured Clinical Interview (Brown *et al.* 1994) was administered by trained bachelor-level and masters-level psychometricians to youth at baseline and annual follow-ups to assess academic functioning, major medical illnesses, and activities involved (e.g. extracurricular).

Sleep

At T2, prior to any SU, participants were administered the self-report Sleep Habits Questionnaire, adapted from the School Sleep Habits Survey (Wolfson & Carskadon 1998; <http://www.sleepforscience.org>). Three aspects of sleep were assessed. The Sleepiness Scale sums items asking about past 2-week degree of daytime sleepiness (i.e. fought sleep) experienced in 10 common situations; higher scores indicated greater sleepiness during wake-hour activities. The Sleep/Wake Problems Behavior Scale asked the past 2-week frequency of erratic behaviors related to sleeping and waking (e.g. stayed up all night); higher scores indicated greater frequency of problematic behaviors owing to poor sleep/wake habits. The Superscience Morningness/Eveningness Scale assessed chronotype; higher scores indicated a greater tendency towards a morning chronotype, and lower scores indicating a greater tendency towards an evening chronotype.

Substance use measures

The Customary Drinking and Drug Use Record (Brown *et al.* 1998), an interview-based assessment, was administered to assess the pattern and severity of SU for each year beginning at T1. Lifetime SU events were defined as the cumulative total use occasions for each substance after T2 up to, and including, T3. The total number of SU occasions in the past year was assessed annually, summed, and recoded by the psychometrician. Parent or other informant (sibling, friend, and roommate) report of youth SU was collected at approximately the same time to confirm youth reports. There were no gross discrepancies between the two sources in the current study ($n = 95$).

Time 1 risk factors

At T1, prior to any SU, parents were administered the Child Behavior Checklist to obtain T-scores of internalizing and externalizing symptoms on the basis of an age-normed and gender-normed national sample (Achenbach 1991). Higher scores indicated greater symptomology. T1 inhibitory control was measured using the Delis–Kaplan Executive Function System (Delis *et al.*, 2001) Color-word Interference Condition 3 (Inhibition) subtest raw scores (i.e. time to completion). To better understand the effect of inhibitory control on sleep and SU, independent of general processing speed, analyses were also conducted using the difference between conditions 1 and 2 average (Word and Color Naming) and Color-word Interference Condition 3. Significance and directionality of the findings reported later were unchanged when using this index.

Pubertal development

The Pubertal Development Scale (Petersen *et al.* 1988), a valid and reliable self-assessment measure of pubertal maturational stage, was administered at T2 when sleep behaviors were assessed.

Demographics

The Hollingshead Index of Social Position score (Hollingshead 1965), an index of socioeconomic status (SES), was calculated for each subject using parental socioeconomic information (i.e. educational attainment, occupation, and salary of each parent) to characterize the youth's home environment. Higher values indicate lower SES. The Family History Assessment Module (Rice *et al.* 1995) was administered to youth and both parents to assess familial density of alcohol and other SUD. Familial density was calculated as the weighted sum of biological parents (weighted 0.5) and biological

grandparents (weighted 0.25) who endorsed two or more SUD symptoms.

Data analysis

A path-analytic model was tested in MPLUS (Muthén & Muthén 2012) to explore the mediator role of T2 sleep behaviors on the relationship between T1 risk factors and T3 lifetime SU events. On the basis of the literature, a comprehensive a priori model was conceptualized (Fig. 1). Four psychiatric and environmental T1 risk factors were examined: FH density of SUD, inhibitory control, and internalizing and externalizing traits. Three T2 sleep behaviors were examined as possible mediators: chronotype, daytime sleepiness, and erratic sleep/wake behaviors. Three T3 outcome measures of SU were examined: lifetime use events of alcohol, cannabis, and tobacco. In an initial model, all three sleep behavior predictors were entered into the same path-analytic model to understand the unique effects of each sleep behavior, controlling for the other two. Daytime sleepiness, erratic sleep/wake behaviors, and evening chronotype tendencies were significantly intercorrelated

($r = -0.51$ to 0.40 ; $P_s < 0.05$), and tests of multicollinearity showed minimal variance inflation. However, owing to their shared variance, a single model with all three sleep behaviors entered simultaneously may overlook a common risk factor for SU. Thus, follow-up analyses were conducted with only one sleep predictor examined at a time to better understand the effects of each on SU outcome. Other recreational drugs were not examined owing to small sample size (i.e. 21 participants have tried other drugs, of whom 10 had one lifetime use event).

As expected, outcome SU variables were not normally distributed. Lifetime alcohol use events ranged from 1 to 2154 times ($M = 294.0$, $SD = 379.4$, $Mdn = 191$, first quartile = 29, third quartile = 427, skewness = 2.4, and kurtosis = 9.8). Lifetime tobacco use events ranged from 0 to 5010 ($M = 199.0$, $SD = 641.8$, $Mdn = 6$, first quartile = 0, third quartile = 50, skewness = 5.3, kurtosis = 36.0). Lifetime marijuana use events ranged from 0 to 380 ($M = 37.6$, $SD = 87.6$, $Mdn = 2$, first quartile = 0, third quartile = 23, skewness = 2.8, and kurtosis = 9.5). A Poisson distribution was used for lifetime alcohol use events outcome. Other outcome

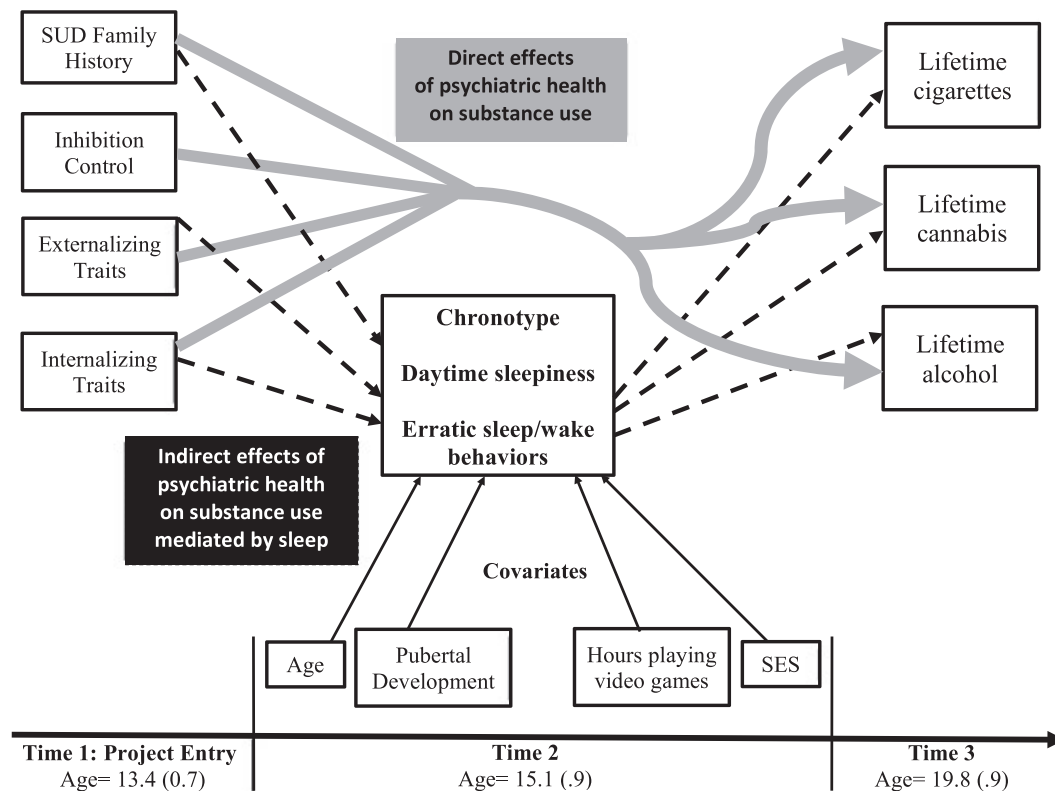


Figure 1 Conceptual path-analytic model. Paths indicate hypothesized direct effects of time 1 (T1) risk factors (substance use disorder family history, inhibition control, and internalizing and externalizing traits) to outcome substance use. Dashed black lines indicate hypothesized indirect effects of T1 risk factors, mediated by sleep behaviors (chronotype, daytime sleepiness, and erratic sleep/wake behaviors), on outcome substance use. Solid black lines indicate biological (age and pubertal development) and environmental (hours playing video games and SES) factors that may influence and covary with sleep behaviors. All T1 risk factors were assessed at time 1, project entry; all sleep behaviors and covariates were assessed at time 2, and all outcome substance use measures were assessed at time 3

measures were modeled using a zero-inflated Poisson distribution to more accurately capture excessive zeros in the data from youth who have not tried tobacco or marijuana.

Four biological and environmental aspects of adolescent development hypothesized to affect sleep and SU behaviors were tested as covariates in the model: SES, T2 age, pubertal development stage, and weekly hours playing video games. Higher SES youth may be at greater risk for developing SU but decreased risk of tobacco use (Patrick *et al.* 2012). Sleep patterns change as a function of age and pubertal stage throughout young adulthood, in which pubertal development may exert a positive indirect effect on alcohol use via sleep problems and chronotype (Pieters *et al.* 2010). Thus, age and pubertal developmental stage were included as covariates in the model to examine the relationship among T1 risk factors on T2 sleep, and in turn, T3 SU, independent of possible effects of age and maturation. The use of electronic media negatively impacts sleep (Cain & Gradisar 2010), yet 24 percent of American adolescents play video games before bed (Calamaro *et al.* 2009). Youth who play video games before bed tend to go to sleep later, have shorter sleep durations, and report more daytime tiredness and poorer sleep quality (Cain & Gradisar 2010). Weekly number of hours spent playing videos was included as a covariate to reduce possible confounding effects of electronic games on sleep patterns. All reported path coefficients ($\hat{\beta}$) are standardized betas.

RESULTS

Description of sample

At T1 and T2, all participants ($n = 95$) were substance naive. As the aim of this study was to understand the effects of biological and environmental risk factors and sleep behaviors on subsequent SU, only youth who at least tried alcohol by T3 were included in the analysis. Participants were 12–14 years old at T1, 14–17 at T2, and 17–21 years old at T3. Forty-seven percent of participants were female, and no significant differences in the distribution of gender were found among age groups. Further, youth did not differ in T1 familial density, internalizing and externalizing symptomology, and lifetime SU events by age. Unsurprisingly, older adolescents performed better on a measure of inhibitory control than younger adolescents. However, this is likely a reflection of enhanced neural maturation among older participants at T1 and that including age as a covariate in path models as described adequately accounted for this effect. Overall, these findings suggest that effects of the current study are unlikely attributable to participant age at T1. On average (SD), youth drank 3.6 days a

month (4.5) and in total, 44 days (SD = 55.3, *Mdn* = 24.1) in the past year. Sixty percent initiated cannabis use, 55 percent tried tobacco products, and 22 percent tried other recreational drugs at least once in their lifetime. Transitioners (i.e. youth who have tried at least one standard alcoholic drink and any tobacco, cannabis, or other drug at least once in their lifetime) used tobacco products at least once in the past month (range: 1–30 days), cannabis on 27.5 days (85.7; range: 0–365), and other drugs on 29.7 days (71.8; range: 0–365) out of the year (Table 1). In the subsample of the parent study used for this analysis, no participant met DSM-5 (APA 2013) diagnostic criteria for SUD at T3.

Path analysis

Of the four covariates tested, only age was significantly associated with daytime sleepiness. As age increased, daytime sleepiness also increased, $P < 0.05$. Pubertal development, weekly video game hours, and SES were not associated with chronotype, daytime sleepiness, or erratic sleep/wake behaviors ($P > 0.05$) and were excluded from analyses.

Direct effects of time 1 risk factors

The direct effects of T1 internalizing symptoms on lifetime use events of tobacco ($\hat{\beta} = 0.04$), alcohol ($\hat{\beta} = -0.35$), and cannabis ($\hat{\beta} = 0.36$) were statistically significant, $P_s < 0.0001$ (Fig. 2). Those individuals who reported higher levels of T1 internalizing symptoms had greater lifetime events of tobacco and cannabis but lower lifetime alcohol use. The direct effects of T1 externalizing traits on subsequent SU were significant; higher levels of T1 externalizing traits predicted significantly lower lifetime events of tobacco use ($\hat{\beta} = -0.05$) but higher lifetime events of alcohol ($\hat{\beta} = 0.70$), $P_s < 0.0001$. The direct effects of T1 inhibitory control on subsequent SU were significant; better inhibition control predicted lower lifetime events of cigarette ($\hat{\beta} = -0.70$) and cannabis ($\hat{\beta} = -0.64$), $P_s < 0.0001$. The direct effects of SUD FH density on subsequent SU were significant; higher SUD FH density predicted lower cigarettes ($\hat{\beta} = -0.10$) but higher alcohol ($\hat{\beta} = 0.57$) and cannabis ($\hat{\beta} = 0.08$) lifetime events, $P_s < 0.05$.

Direct effects of time 2 sleep behaviors

The direct effects of T2 erratic sleep/wake behaviors, daytime sleepiness, and chronotype on subsequent SU were significant. When controlling for daytime sleepiness and chronotype, more erratic sleep/wake behaviors predicted significantly higher tobacco ($\hat{\beta} = 0.60$) and cannabis ($\hat{\beta} = 0.67$), but lower alcohol ($\hat{\beta} = -0.27$)

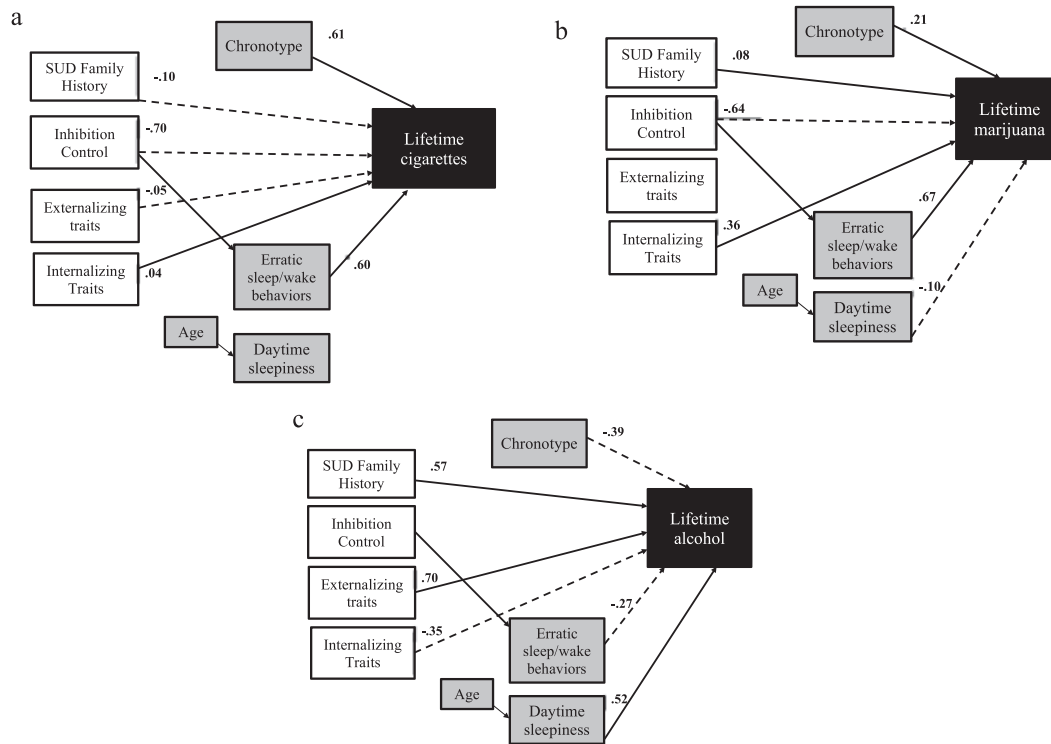


Figure 2 Results of path-analytic model. Note: SUD = Substance use disorder All paths shown are significant effects, $P_s < .05$. Solid lines indicate significant positive effects of time 1 (T1) risk factors and time 3 sleep behaviors on outcome lifetime SU events and dashed lines indicate significant negative effects of T1 risk factors and time 3 sleep behaviors on T3 lifetime SU events. Unshaded boxes are indices measured at time 1 (age = 13.4 [0.7]) grey boxes are indices measured at time 2 (age = 15.1 [.9]), and black-shaded boxes are indices measured at time 3 (19.8 [.9]). In all models, better inhibitory control (lower time to completion score) predicted less erratic sleep/wake behaviors ($\hat{\beta} = .20$). Note that higher Chronotype score indicates greater morningness tendency and higher SUD Family History indicates greater familial density of SUD. Shown are standardized path coefficients

lifetime use events, $P_s < .0001$. When controlling for erratic sleep/wake behaviors and chronotype, greater daytime sleepiness predicted significantly lower cannabis ($\hat{\beta} = -0.10$) but higher alcohol ($\hat{\beta} = 0.52$; $P < 0.0001$) lifetime use events. When controlling for daytime sleepiness and erratic sleep/wake behaviors, higher evening chronotype tendencies predicted significantly lower tobacco ($\hat{\beta} = 0.61$) and cannabis ($\hat{\beta} = 0.21$) but higher alcohol ($\hat{\beta} = -0.39$) lifetime use events, $P_s < 0.0001$.

In follow-up analyses that examined the effects of each sleep behavior in its own path-analytic model, more erratic sleep/wake behaviors predicted significantly higher tobacco ($\hat{\beta} = 0.41$), cannabis ($\hat{\beta} = 0.54$), and alcohol ($\hat{\beta} = 0.27$) lifetime use events, $P_s < 0.0001$. Greater daytime sleepiness predicted significantly higher tobacco ($\hat{\beta} = 0.22$; $P < 0.0001$), cannabis ($\hat{\beta} = 0.12$; $P < 0.01$), and alcohol ($\hat{\beta} = 0.57$; $P < 0.0001$) lifetime use events. Higher evening chronotype tendencies predicted significantly lower tobacco ($\hat{\beta} = .28$; $P < 0.0001$) and higher cannabis ($\hat{\beta} = -0.12$; $P < 0.01$) and alcohol ($\hat{\beta} = -0.40$; $P < 0.0001$) lifetime use events.

Mediation effects of time 2 sleep behaviors

Erratic T2 sleep/wake behavior was a significant mediator of the effect of T1 inhibitory control on subsequent lifetime SU events. Better inhibitory control (i.e. lower time to completion score) predicted less erratic sleep/wake behaviors ($\hat{\beta} = 0.20$) in all models, which, in follow-up analyses examining the effects of individual sleep behaviors in separate path-analytic models, in turn predicted lower lifetime tobacco ($\hat{\beta} = 0.41$), cannabis ($\hat{\beta} = 0.54$), and alcohol use ($\hat{\beta} = 0.27$) events, $P_s < 0.05$. No significant mediating effects of chronotype and daytime sleepiness were found.

DISCUSSION

While SU and sleep behaviors have been examined extensively in adults (for review, see Colrain *et al.* 2014), their relationships in adolescents are less clear. Longitudinal designs, like that of the present study, allow for the consideration of temporal precedence, above and beyond a cross-sectional examination of the bidirectional association between sleep and alcohol

use. We further extend previous findings with the inclusion of other substances commonly used by adolescents (e.g. cannabis). Results support the hypothesis that psychiatric and environmental risk factors and sleep behaviors in substance-naïve youth prospectively predict level of substance involvement in later life (Hasler *et al.* 2016; Miller *et al.* 2016; Roane & Taylor 2008; Wong *et al.* 2010). T1 risk factors (i.e. internalizing and externalizing traits, inhibitory control, and familial density) and sleep behaviors (i.e. daytime sleepiness, erratic sleep/wake behaviors, and chronotype) were all unique predictors of subsequent alcohol, cannabis, and tobacco use. Further, erratic sleep/wake behavior was a significant mediator in the effect of T1 risk factors on lifetime SU events.

The relationship between SU and sleep is often described as bidirectional. Some studies suggest that alcohol facilitates sleep onset but interferes with sleep maintenance throughout the night (Van Reen *et al.* 2013) depending on the circadian phase during acute administration. Alcohol's effects on sleep appear to operate, in part, by enhancing the major inhibitory neurotransmitter gamma-aminobutyric acid and suppressing the activities of N-methyl-D-aspartate glutamate receptors, leading to easier sleep onset but less restful sleep (Koob *et al.* 1998). Moderate to high doses of alcohol delay the onset of, and decrease overall, rapid eye movement (REM) sleep (Ebrahim *et al.* 2013; Pressman 2012). On the other hand, nicotine binds to the nicotinic acetylcholine receptor neural pathways implicated in sleep regulation to produce the pleasurable effects reported by tobacco users (Jones *et al.* 1999). Continued tobacco use leads to sleep disruption, manifested through increased sleep latency and REM sleep and decreased total sleep time (Jaehne *et al.* 2009). Δ -9-Tetrahydrocannabinol, a psychotropically active cannabis compound, diffusely affects cannabinoid CB₁-receptors in the brain throughout frontal, cerebellar, and basal ganglia regions. Acute administration of Δ -9-tetrahydrocannabinol may decrease sleep latency, promote sleep onset, and decrease total REM sleep time (Nicholson *et al.* 2004). However, similar to nicotine and alcohol, prolonged cannabis use and withdrawal has been associated with increased dreams and sleep problems (Vandrey *et al.* 2005).

Models showed significant main and mediating effects of T1 and T2 predictors on SU outcome. Controlling for the other two sleep behaviors, each sleep behavior appeared to have an opposite effect on lifetime SU events. For example, controlling for daytime sleepiness and chronotype, more erratic sleep/wake behaviors predicted higher tobacco and cannabis but lower alcohol lifetime use events. In follow-up models examining each sleep behavior separately, the effects of sleep on SU outcomes

operated in a more consistent directionality, perhaps owing to avoiding suppression effects. For example, greater early adolescent erratic sleep/wake behaviors predicted more use of all three substances by later adolescence. Because the three sleep behaviors were significantly and moderately intercorrelated, analyses that examined each sleep behavior while holding the other constant may decrease the influence of a common risk factor for SU that daytime sleepiness, erratic sleep/wake behavior, and evening chronotype tendencies share. Thus, the results of follow-up analyses likely better reflect clinical observations of sleep behaviors in adolescents, because individuals with greater daytime sleepiness are also more likely to experience erratic sleep/wake behaviors and evening chronotype tendencies (Giannotti *et al.* 2002).

In general, analyses modeling all sleep parameters simultaneously suggested that the influence of T1 risk factors on tobacco and marijuana use operated in the reverse direction as its effect on alcohol. For example, greater internalizing symptomology predicted increased T3 tobacco and marijuana but decreased alcohol use. The distinct psychopharmacological profiles of each substance may offer insight into a possible reason for the observed difference in directionality. Use patterns of alcohol (both a stimulant and relaxant) and cigarettes and marijuana (generally used as relaxants) may differ owing to their psychopharmacological and social functions. Youth with high sensation seeking and low anxiety sensitivity prefer alcohol over marijuana and cigarettes (Comeau *et al.* 2001). Six percent of 12th graders reported using alcohol to sleep, while less than 1 percent reported the same reasons for marijuana (Terry-McElrath *et al.* 2009). The primary reason reported for alcohol use within this age group was 'to have a good time' and 'get intoxicated'. For marijuana, it was 'to get high' and 'relax' (Boys *et al.* 2001; Terry-McElrath *et al.* 2009). Examining reasons for use and how this may interact with the relationship between risk factors, sleep, and SU patterns is beyond the scope of the current study. Nevertheless, it is an important area to explore in future studies and may offer insight into mechanisms by which the current results operate.

There are several limitations in this study. Importantly, because T1 sleep data were not available, analyses did not control for prior sleep as a potential confounding factor, which limits the causal interpretations drawn regarding the relationship between inhibition control/others and sleep behaviors. Efforts were taken to account for other confounding factors often associated with SU (i.e. SES, conduct disorder, and age), but environmental features that may affect sleep such as room ambience were not measured in this study. Another limitation of the study is the lack of power to

examine T1 risk factors in 12-, 13-, and 14-year-olds separately. By examining all individuals in this age group together, it was assumed that age was not a significant moderator in the relationship among T1 risk factors, T2 sleep patterns, and T3 lifetime SU events. It is possible that future studies with larger sample sizes may be able to fill in this gap of the results reported here. Several unexpected results are of note. First, we tested biological and environmental factors as covariates in the model. On the basis of previous reports (Pieters *et al.* 2010) and results of large epidemiological surveys (National Sleep Foundation 2014), we expected pubertal stage, age, increased video game playing, and lower SES to be associated with the sleep behaviors examined. However, only age was related to sleep (i.e. older youth reported more daytime sleepiness). Null findings for other covariates may be due to insufficient power to detect such effects.

Epidemiologically, a small proportion of teens with sleep problems use tobacco (6 percent) and alcohol (3 percent) as sleep aids (Noland *et al.* 2009). A possible reason for the onset of sleep problems in adolescence is the increased tendency for youth to go to sleep later, resulting in decreased total sleep time when coupled with earlier school hours (Owens *et al.* 2010). Considering the high comorbidity between sleep problems and SUDs (Wong *et al.* 2015), targeting sleep improvements may be a useful tool in the prevention and treatment of SU. For example, later school start time has been recommended as one way to mitigate daytime sleepiness, fatigue, and negative mood (Owens *et al.* 2010). Adolescents in an SUD outpatient program who reported sleep disturbances showed significant improvements in sleep hygiene, daytime sleepiness, and rate of relapse after completing a multi-component sleep treatment program, compared with non-completers (Bootzin & Stevens 2005). Nevertheless, further studies are needed to comprehensively assess healthy early adolescent sleep as protection from late adolescent SU.

In summary, by including only youth who have not initiated SU when psychiatric health and sleep behaviors were assessed, we were able to better understand temporal precedence in the interaction of these factors. Considering the multi-faceted effects of tobacco, alcohol, and cannabis on sleep, a longitudinal examination of this relationship was necessary to ascertain whether problematic sleep behaviors precede initiation of SU. However, as this study focused on SU in adolescents aged 17–24, it is unclear if and how results can be generalized to young adults and adults. Heavy alcohol, tobacco, and illicit drug use peak at 21–25, 21–34, and 18–25, respectively (SAMHSA 2013). Thus, the examination of the interplay between sleep and SU in these older ages

is an important topic of consideration in future directions.

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Authors Contribution

T.T.N. performed the analysis and interpretation of data, and drafting and revising of the manuscript for submission. I.M.C., G.E.M., and M.J.W. provided consultations on data analysis and interpretation of findings. All authors provided critical revision of the manuscript for intellectual content and approved the content of the final version for publication.

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