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Authors

Kiss, Orsolya

Goldstone, Aimée

de Zambotti, Massimiliano

et al.

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Original Article

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Effects of emerging alcohol use on developmental trajectories of functional sleep measures in adolescents

Orsolya Kiss[1], Aimée Goldstone[1], Massimiliano de Zambotti[1], Dilara Yüksel[1], Brant P. Hasler[2], Peter L. Franzen[2], Sandra A. Brown[3], Michael D. De Bellis[4], Bonnie J. Nagel[5], Kate B. Nooner[6], Susan F. Tapert[3], Ian M. Colrain[1], Duncan B. Clark[2] and Fiona C. Baker[1,7,*]

[1]Center for Health Sciences, Bioscience Division, SRI International, Menlo Park, CA, USA,
[2]Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA,
[3]Department of Psychiatry, University of California, San Diego, San Diego, CA, USA,
[4]Department of Psychiatry and Behavioral Sciences, Duke University School of Medicine, Durham, NC, USA,
[5]School of Medicine, Division of Clinical Psychology, Oregon Health and Sciences University, Portland, OR, USA,
[6]Psychology Department, University of North Carolina Wilmington, Wilmington, NC, USA and
[7]Brain Function Research Group, School of Physiology, University of the Witwatersrand, Johannesburg, South Africa

*Corresponding author. Fiona C. Baker, Center for Health Sciences, SRI International, Menlo Park, CA 94025, USA. Email: Fiona.baker@sri.com.

Abstract

Study Objectives: Adolescence is characterized by significant brain development, accompanied by changes in sleep timing and architecture. It also is a period of profound psychosocial changes, including the initiation of alcohol use; however, it is unknown how alcohol use affects sleep architecture in the context of adolescent development. We tracked developmental changes in polysomnographic (PSG) and electroencephalographic (EEG) sleep measures and their relationship with emergent alcohol use in adolescents considering confounding effects (e.g. cannabis use).

Methods: Adolescents (n = 94, 43% female, age: 12–21 years) in the National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA) study had annual laboratory PSG recordings across 4-years. Participants were no/low drinkers at baseline.

Results: Linear mixed effect models showed developmental changes in sleep macrostructure and EEG, including a decrease in slow wave sleep and slow wave (delta) EEG activity with advancing age. Emergent moderate/heavy alcohol use across three follow-up years was associated with a decline in percentage rapid eye movement (REM) sleep over time, a longer sleep onset latency (SOL) and shorter total sleep time (TST) in older adolescents, and lower non-REM delta and theta power in males.

Conclusions: These longitudinal data show substantial developmental changes in sleep architecture. Emergent alcohol use during this period was associated with altered sleep continuity, architecture, and EEG measures, with some effects dependent on age and sex. These effects, in part, could be attributed to the effects of alcohol on underlying brain maturation processes involved in sleep–wake regulation.

Key words: adolescence; alcohol use; slow wave activity; REM sleep; electroencephalogram; longitudinal; sex differences

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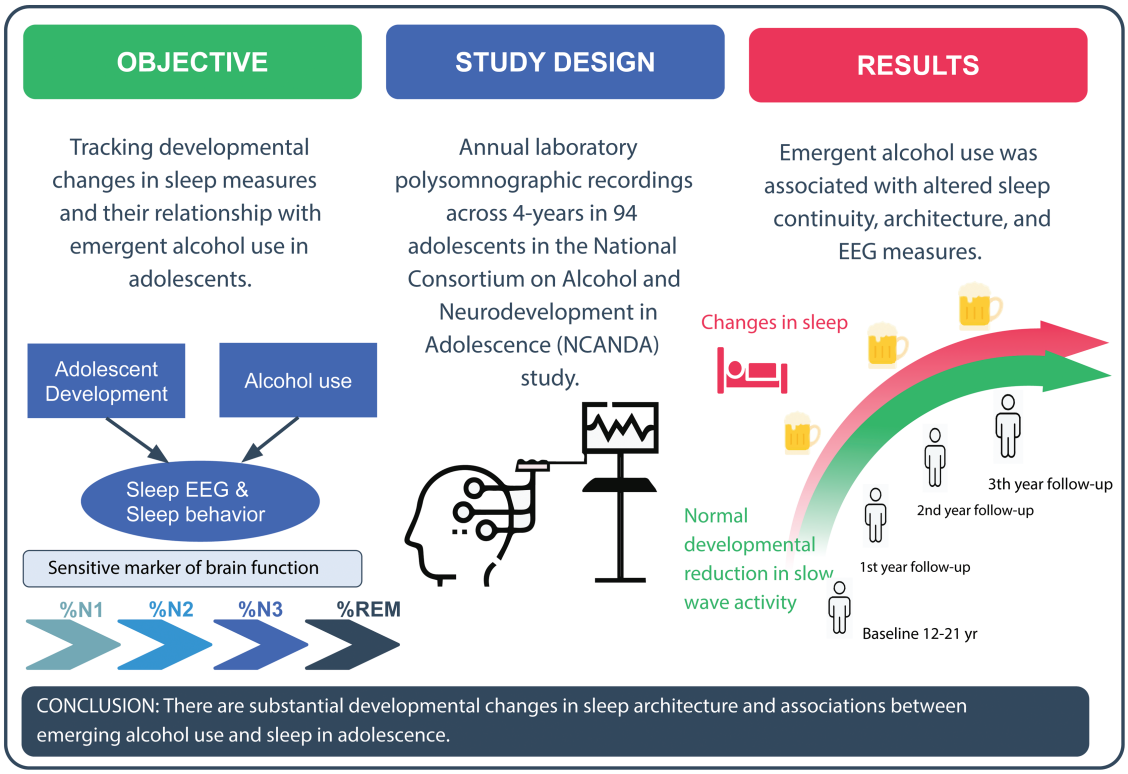
Graphical Abstract



Statement of Significance

Longitudinal, multi-year polysomnographic data from a large sample of adolescents show changes in sleep architecture and the electroencephalogram across adolescence and, for the first time, how the emergence of alcohol use is associated with altered sleep measures. Slow wave sleep and delta power declined with age, likely reflecting underlying brain maturation. Participants who emerged as moderate/heavy drinkers differed from those who stayed as no/low drinkers, with a decline in rapid eye movement sleep over time, lower delta and theta power in male moderate/heavy drinkers, and more indicators of poor sleep (longer sleep onset latency, shorter total sleep time) in older drinkers. Emergent alcohol use in adolescents is associated with altered sleep architecture, possibly reflecting alcohol's effects on sleep–wake maturational processes.

Introduction

Adolescence is a dynamic maturational period, critical for social development, and integration into society, characterized by marked physiological, and neurocognitive changes, increased risk-taking, and the transition from dependence to the relative independence of adulthood [1]. The Bright Futures guidelines from the American Academy of Pediatrics identifies adolescence as 11–21 years of age, which can be further categorized into early (ages 11–14 years), middle (ages 15–17 years), and late (ages 18–21 years) adolescence [2]. Profound changes in sleep behavior and architecture occur across these stages [3–8]. One of the most obvious changes is the shift towards later bedtimes, leading to shorter sleep duration on weekdays [9], as wake times are highly restricted by school schedules [10]. These sleep timing changes are thought to be partially driven by the progressively slower build-up in homeostatic sleep pressure during wakefulness [11] and by altered circadian regulation during puberty [7].

The changes impact not only the timing and duration of sleep, but also sleep microstructure reflected in the EEG signals. Scalp electroencephalogram (EEG) recordings are the primary objective method to study human sleep architecture. After visual sleep stage scoring by an expert, the Fast Fourier transform (FFT) computational method can be applied to convert time-domain EEG signals into frequency domain intervals. For example, slow wave (delta power) brain activity (between 1 and 4 Hz) reflects the slow oscillation of cortical neurons [12] and is a marker of homeostatic sleep need [13], and important for several brain-related functions including memory consolidation [14]. The most dramatic change in sleep architecture across adolescence is in N3 (slow wave) non-rapid eye movement (NREM) sleep: older adolescents have over 40% less N3 sleep than younger adolescents, or children [15]. Cross-sectional studies have also shown profound age-related differences in the sleep EEG across childhood and adolescence, with prepubertal children (~11 years old) having more NREM and REM sleep EEG spectral power, particularly delta power (slow wave activity), that increases steeply during the first years of life, reaches a maximum in early childhood, then declines markedly across adolescence [16, 17]. Children have five or six sleep cycles each night [18] and the number of stage shifts from sleep to wake is slightly lower in adolescents than in children [19]. A cross-sectional analysis of data from the US National Consortium

on Alcohol and Neurodevelopment in Adolescence (NCANDA), also showed that delta (0.3–4 Hz) EEG power in non-REM sleep was lower in older than younger adolescents at all electrode sites, with a larger age-related difference at the occipital site [4].

In their longitudinal studies that tracked pre-adolescent and adolescent cohorts studied at 6-month intervals spanning ages 9–18 years, Feinberg, Campbell, and colleagues were able to show the temporal developmental patterns of NREM and REM sleep EEG, with a steep decline in delta power (1–4 Hz) starting at ages 11–12 years, falling over 60% by age 17 years [20] however, the maturational patterns differed for NREM and REM sleep EEG [6]. Theta power (4–8 Hz) showed a similar trajectory, with an earlier onset of decline (starting at age 7.5 years) not only in NREM, but also in REM sleep [6]. The rate of decline in delta power across adolescence varied according to scalp measurement site, with the steepest decline at occipital electrodes [20]. The authors argue that these developmental changes in the sleep EEG reflect synaptic pruning in different brain circuits [21]. Age-related differences in EEG power across adolescence are evident in higher frequency bands during sleep (alpha, sigma, and beta power) [4, 16, 22] as well as during waking, again with differences becoming evident initially at posterior occipital electrodes and progressing towards the frontal regions with age [23, 24].

Some studies have shown that the changes in sleep across adolescence may partially reflect the underlying changes in brain structure [25–27]. Buchmann et al. [25] showed that the age-related declines in delta power and gray matter during adolescence are highly correlated. Similarly, in NCANDA participants, the relationship between age and delta power was partially mediated by the brain structure of several, mainly frontal and parietal regions (Goldstone et al. [26]). Psychosocial, behavioral, and environmental factors may interfere with these dynamic maturational processes during this vulnerable period of adolescent brain development. Adolescence is a time of risk-taking and initiation of behaviors, such as alcohol drinking. Rates of alcohol use dramatically increase during adolescence and alcohol is by far the most widely used intoxicant among teenagers, with 25% of 8th graders reporting that they tried alcohol, 10% even reaching the point of intoxication and ~8% reporting recent (past 30 days) alcohol use in 2019 [28]. Several studies including NCANDA suggest that heavy drinking affects brain developmental trajectories, with accelerated gray matter loss and attenuated white matter growth, including white matter microstructural integrity [29–32].

Given these apparent effects of alcohol initiation and use on brain structure as well as the known effects of alcohol use on the homeostatic balance of neurotransmitter systems [33, 34] involved in wake–sleep regulation [35], alcohol could also impact sleep in adolescents. A substantial body of literature has shown profound effects of acute or chronic alcohol use on sleep architecture in adults [36], but few studies have focused on adolescence. Based on survey data, adolescents who use alcohol are more likely to report sleep problems than those who abstain, after adjusting for internalizing and externalizing problems [37]. However, a growing body of research from NCANDA and other studies has shown that at least some sleep problems may precede alcohol use, being a risk factor for subsequent alcohol use [38–42]. Beyond the relationship between alcohol use and sleep behavior, few studies have examined relationships between alcohol use and sleep architecture and EEG measures in adolescents. One laboratory study that examined the acute effects of alcohol use on sleep architecture in older adolescents (18–21 years old) showed effects similar to those found in adults; namely, evening alcohol consumption increased N3 (slow wave sleep) and decreased REM sleep, particularly in the first half of the night, and disrupted sleep in the second half compared with a placebo condition [43]. Family history of alcohol use may be important when investigating adolescents: Tarokh and colleagues [44] examined whether family history of alcohol use was associated with sleep architecture and EEG in alcohol-naïve children (ages 9–10 years) and adolescents (ages 15–16 years). They found no differences in sleep architecture but some differences in sleep EEG power in NREM sleep between family history positive and negative children, with family history positive children showing a trend for lower amounts of SWS. To our knowledge, no studies have longitudinally tracked associations between alcohol initiation and use and sleep architecture in adolescents.

The present study used a longitudinal design with four annual timepoints in youth ranging in age from 12 to 21 years old at baseline, to investigate: (1) the developmental changes across adolescence in sleep architecture and EEG measures, focusing on the slower EEG frequency bands (delta and theta), considering possible sex differences and topographic differences across the scalp; and (2) the prospective relationship between alcohol use and sleep architecture and EEG. We hypothesized that the initiation of moderate/high alcohol use in adolescents would be associated with an altered developmental trajectory in sleep architecture and EEG controlling for confounders (e.g. cannabis use).

We examined these longitudinal associations in a naturalistic study, as many adolescents initiated alcohol use, making our study the first such longitudinal examination to include early, middle, and late adolescence, covering the period of many brain maturation processes.

Methods

Participants

This longitudinal analysis included participants in the polysomnographic (PSG) sub-study of the NCANDA study conducted at SRI International and the University of Pittsburgh. All participants included in this analysis (n = 94) were no/low drinkers at baseline and completed three additional annual follow-up visits. For a full description of sample characteristics, recruitment, procedures, and measures of the complete NCANDA study see [45] and for a description of the PSG sub-study, see [4]. Briefly, participants were recruited through distribution of school and community fliers (SRI International) or random digit dialing (Pittsburgh). The study followed an accelerated longitudinal design, recruiting participants who were 12.0–21.9 years at baseline. All participants had a phone interview and in-person screening session including the Semi-Structured Assessment for the Genetics of Alcoholism [46]. Participants were healthy at baseline; none had severe medical conditions or current/past severe psychiatric disorders, and none was using medications known to affect sleep or the central nervous system. None of the participants showed evidence of sleep-disordered breathing, periodic limb movement disorder, or narcolepsy, as assessed from an overnight clinical sleep evaluation. Data describing the characteristics of the sample were obtained from data release version: NCANDA_RELEASE_BASE_REDCAP_MEASUREMENTS_V07.

The institutional review boards of SRI International and University of Pittsburgh approved this study. Adult participants consented to participate, and minors provided written assent in addition to consent from a parent/legal guardian. Participants and parents were compensated for participation according to

site-specific procedures that were approved by the local IRB. Characteristics of the sample at the baseline visit are presented in Table 1. Fourteen participants transitioned to the moderate-heavy drinking category in Year 1, 12 transitioned in Year 2, and 11 transitioned in Year 3. Of the participants transitioning to moderate-heavy drinking at any time point, 5 transitioned back to the no-to-low category at a subsequent time point, with one of them transitioning again to the moderate-heavy drinking category later.

Measures

Alcohol and other substance use

Participants completed the Customary Drinking and Drug use Record (CDDR) [47] at each visit to characterize past and current alcohol and other substance use, including past year drinking frequency (number of days) and quantity (average and maximum number of drinks). Participants were coded at each follow-up visit as no/low drinkers or moderate/heavy drinkers, using the NCANDA modified Cahalan et al. classification [29, 32, 48]. No/low drinkers reported no or low quantity and frequency consumption (e.g. <2 drinks on average, and <4 drinks maximum, and less than once/month). Moderate/heavy drinkers combined those who were moderate drinkers according to Cahalan criteria (low frequency [e.g. <1 time/month]) with moderate quantity consumption [e.g. 2–3 drinks on average, 4–5 drinks maximum], or moderate frequency [e.g. 1 time/week] with low quantity consumption [e.g. 2 drinks on average, <4 drinks maximum] and those who were heavy drinkers according to Cahalan criteria (moderate frequency [e.g. 2 times/month]) with high quantity consumption [e.g. with 3–4 drinks on average, > 4 drinks maximum] to higher frequency [e.g. 1 time/week or more] with moderate quantity consumption [e.g. with 2–3 drinks on average and >4 drinks maximum]. Cannabis was the most common other substance used in the NCANDA sample, and we therefore also considered it in the current analysis using a single question from the CDDR that asked about frequency of cannabis use in the past year (number of days). The CDDR was shown to be internally consistent and reliable over time and across interviewers for the domains assessed of level of substance involvement, withdrawal characteristics, psychological/behavioral dependence symptoms, and negative consequences [47].

Family history of alcohol/drug use

Family history of alcohol/drug problems was assessed with the Family History Assessment Module [45]. To be considered family history positive, participants had at least one or more biological parents with significant problems related to alcohol/drug use, two or more biological grandparents with significant problems related to alcohol/drug use, or one or more biological grandparent and 2 or more other biological second-degree relatives with significant problems related to alcohol/drug use.

Procedure

To familiarize participants with the sleep lab environment and procedures and reduce the first night effect, participants had a non-consecutive PSG overnight session before the sleep architecture PSG recording for the baseline annual visit but not for annual follow-ups. PSG assessments were performed at SRI International (n = 77) or the University of Pittsburgh (n = 17) NCANDA sites in sound-attenuated, temperature-controlled bedrooms. Participants were instructed to maintain a regular sleep–wake schedule for at least five nights before recordings. Each night, a breath alcohol test (S75 Pro, BACtrack Breathalyzers, San Francisco, CA, USA) and urine drug test (10 Panel iCup drug test kit, Instant Technologies, Inc.) confirmed the absence of recent alcohol or drug use. Girls who were post-menarche were studied irrespective of menstrual cycle phase. All participants went to bed in the laboratory at their self-reported typical bedtimes. At SRI, participants woke up at their typical weekday times but at the University of Pittsburgh, participants were allowed to wake up when they chose for that particular night.

Standard, clinical-grade PSG was performed at both sites using the Compumedics Grael HD-PSG system (Compumedics,

Table 1. Characteristics of 94 adolescents, distributed according to sex, who participated in the NCANDA sleep study and are included in the current analysis

Baseline characteristics	Male 57.4% (n = 54)	Female 42. 6 % (n = 40)
Age (y)	15.09 (2.21)	15.10 (2.38)
Body mass index percentile[a]	60.84 (26.23)	51.48 (27.86)
Ethnicity (n)		
White	40	30
Asian	9	9
Black	3	1
Other/undeclared	2	0
Pubertal development score[b]	2.70 (0.69)	3.10 (0.74)
Drinking behaviour across baseline and follow-up visits (n)[c]		
Baseline year	0 moderate/high	0 moderate/high
Year 1 visit	6 moderate/high	8 moderate/high
Year 2 visit	13 moderate/high	11 moderate/high
Year 3 visit	19 moderate/high	14 moderate/high

Data shown as mean (standard deviation) where relevant.
[a]Missing for two participants.
[b]Self-reported pubertal development scores ranged between 1.2 and 4 [100].
[c]Drinking behavior was based on Cahalan categories (no/low vs. moderate/high), as defined in the text.

Abbotsford, Victoria, Australia-4K High-Definition dual platform PSG/EEG amplifier—https://www.compumedics.com.au/products/grael-4k-psg-eeg/). The EEG (F3, F4, C3, C4, P3, P4, O1, O2 referenced to the contralateral mastoids), submental electromyogram, and bipolar electrooculogram were recorded according to American Academy of Sleep Medicine (AASM) guidelines [49] with a sampling rate of 256 Hz. Sleep was visually scored according to AASM criteria. Brief arousals (< 30 s) were scored using AASM criteria.

PSG measures and EEG preprocessing

Time spent in bed (TIB, min) was calculated as the time from lights-out to lights-on, total sleep time (TST, min) as TIB minus time spent to fall asleep and wakefulness after sleep onset (WASO), sleep efficiency (SE; %) as TST/TIB * 100, and sleep onset latency (SOL, min) as the time from lights-out to the first minute of N2 sleep. Time spent in each sleep stage was calculated as a percentage of TST.

EEG data within NREM sleep (N2 and N3 combined) and REM sleep were analyzed for selected electrodes (F3, C3, P3, and O1) using the EEGLAB [50] toolbox for MATLAB (MathWorks, Natick, MA, USA). We analyzed data recorded on the left derivation, however in cases of poor signal quality (maximum of 4 cases for any electrode-frequency range pair), it was replaced by the contralateral derivation.

EEG was re-referenced to the average mastoid and filtered at 0.3–36 Hz with half-amplitude cutoffs at 0.15 and 36.15 Hz. Power spectral analysis was performed with a Fast Fourier transform on each 30-s epoch using 8-s Hanning tapers (*newtimef* function: padratio = 2, timesout = 200) to calculate power density values with 0.125 Hz resolution. Power density (μV^2/Hz) values were then averaged across the delta (0.3 to <4 Hz) and theta (4 to <8 Hz) frequency bands. Epochs containing arousals were removed from analysis. In addition, an automated process was applied to reject outlier epochs from N2 and N3 sleep separately, in both the time and frequency domains. In the time domain, if the EEG was flat for greater than 5-s during the 30-s epoch, or if the maximum value exceeded the median by 10 times the median absolute deviation, that epoch was removed. In the frequency domain, if the power of any band exceeded the median by 15 times the median absolute deviation, that epoch was also removed.

Statistical analysis

To reveal the developmental changes in sleep over time and potentially emerging effects of alcohol use on sleep, both sleep macrostructure and spectral EEG data (EEG power within NREM and REM sleep for delta, theta bands) were analyzed. We performed analyses on the sleep measures of interest using linear mixed effects models (LMMs, R package "lme4") [51]. The models included age (baseline age of the participant measured at the first visit), year of the visit (corresponds to the within-participant change in age), sex (male/female), alcohol use at each visit (low/no, moderate/heavy), family history of alcohol use (yes/no), cannabis use (log transformed), and the relevant two-way interaction terms: sex by age, sex by alcohol use, age by annual visit, age by alcohol use and annual visit by alcohol use, controlling for potential confounding effects of data collection site (factor with two levels), race (Caucasian/White, African American/Black, Asian, Other), ethnicity (Hispanic/Non-Hispanic), socio economic status represented by the maximum number of years of parental education, and body mass index (percentile). Participant ID was included as a random term. Continuous predictors were standardized. Percentage N1, SOL, and WASO, and all power spectra variables were log-transformed to normalize residual distributions. The scalp location of the electrodes (F3, P3, C3, O1) was included as a predictor in the models for EEG spectral analysis. The effects of explanatory variables in the final model were analyzed by likelihood ratio tests: we provide $\chi 2$ and p values of likelihood ratio tests of models with and without the explanatory variable.

Results

Sleep structure

Developmental effects.

Table 2 shows the predictors included in each model for SE, WASO, SOL, TST, and each sleep stage. The LMM for TST showed no effect of age although there was an effect of annual visit reflecting a shortening of TST across annual assessments within participants [$\chi^2(1) = 33.69$, $p < .001$] (Supplementary Figure S1). The main effect of annual visit was not significant for SE, SOL, WASO, %N2, and %N3. The %N1 sleep [$\chi^2(1) = 13.28$, $p < .001$, Figure 1] decreased across the four annual assessments within participants, however, a significant age effect for %N1 [$\chi^2(1) = 6.55$, $p = .010$] showed that older participants had more %N1 sleep overall than younger participants. There was also an effect of age for %N2 sleep [$\chi^2(1) = 16.34$, $p < .001$] and %N3 sleep [$\chi^2(1) = 31.77$, $p < .001$], with older adolescents having more %N2 sleep (Figure 2) and less %N3 sleep (Figure 3). The age effect was significant for SE [$\chi^2(1) = 4.84$, $p = .027$] (Figure 4) with lower SE in older participants. Finally, there was an effect of annual visit for %REM sleep, which increased across annual assessments in the cohort [$\chi^2(1) = 4.98$, $p = .025$] (Supplementary Figure S2). Given that the TST shortened on the within-participant level with every annual visit, which may impact the overall sleep architecture causing disproportionate changes in sleep stages, we ran additional analysis to examine how the absolute durations of the sleep stages were affected. The results showed significant decreases in minutes of N1, N2, and N3 sleep across each annual assessment ($p < .001$), but no change in the duration of REM sleep (Table 2). Considering that we have a wide age-range, and that the year by age interaction is an important indicator for differential age effects, which was marginally significant ($p = .09$) in the case of N1%, we also ran an additional subgroup analysis to investigate the importance/strength of the within-subject effect in different stages of adolescence. We considered three groups based on the age assessed at the baseline year, defining early (12 to 14-year-olds), mid (15 to 17-year-olds), and late (18+-year-old participants) adolescent groups, and rerunning the model for each group separately. This analysis confirmed that all adolescent groups showed a within-subject level decrease in N1%. Also, the between-subject age effect is not pronounced in these restricted adolescent group intervals, and only becomes significant when the complete age-range is considered (in the main analysis).

Alcohol effects.

There were no main effects of drinking behavior on any sleep measures, however, there were significant interaction effects. Being in the moderate/heavy drinking Cahalan category was significantly related to shorter TST in older participants [$\chi^2_{age \times drinking}(1) = 4.76$, $p = .029$] (Figure 5). The drinking category also had an interaction effect with age [$\chi^2_{age \times drinking}(1) = 4.25$, $p = .039$] for SOL. As shown in Figure 6, moderate/heavy drinking was associated with a longer SOL in older participants. In addition, there was an interaction effect between drinking behavior and annual visit for

Table 2. Model outputs for the sleep macrostructure analysis in the NCANDA sleep project (n = 94)

	Log N1 %	Log N1 min	Log SE	Log SOL	Log WASO	N2 %	N2 min	N3 %	N3 min	REM %	REM min	TST
Sleep macrostructure												
Sex	0.30	0.06	0.25	2.67	1.56	1.30	2.81	3.49	1.93	1.57	3.26	2.01
Age	**6.55**	**5.20**	**4.84**	3.54	2.12	**16.34**	**6.92**	**31.77**	**39.43**	1.22	0.17	0.90
Drinking behaviour	0.23	0.13	1.22	1.04	0.21	0.06	0.15	0.06	0.03	0.001	1.98E-05	0.02
Year of the visit	**13.28**	**24.68**	0.91	3.17	3.68	2.47	**22.79**	2.06	**4.67**	**4.98**	0.76	**33.69**
Family history of alcohol use	0.00	0.50	1.08	2.50	0.82	0.00	1.47	0.03	1.56	0.002	1.08	**5.88**
Cannabis consumption	1.30	1.00	0.24	0.66	0.01	0.37	0.03	0.24	0.04	**4.15**	2.36	0.08
Sex by age	0.81	0.86	0.13	0.23	0.30	0.11	0.01	0.03	0.04	0.15	0.16	0.17
Sex by drinking behaviour	0.06	0.04	0.15	0.26	1.39	0.83	0.93	0.02	0.01	2.76	0.84	0.12
Age by drinking behaviour	0.06	0.11	2.92	**4.25**	0.02	0.06	1.66	0.09	1.44	0.23	0.46	**4.76**
Age by year of visit	2.82	1.56	0.14	0.00	0.03	0.71	1.12	0.32	2.59	0.59	0.03	1.45
Drinking behaviour by year of visit	1.26	0.25	1.74	1.09	2.77	0.23	0.66	0.31	0.00	**4.74**	**6.01**	2.72
Conditional R^2	0.37	0.36	0.29	0.38	0.31	0.34	0.27	0.45	0.50	0.27	0.23	0.26

Family history of alcohol use, sex, and drinking behaviour were included as factors. Age (at the baseline visit), cannabis consumption (log transformed), were standardized (z-scored). The random-effects structure included a random intercept for study site and participant ID. Significant results are highlighted with bold. Results of the likelihood ratio test: Chi-square values.

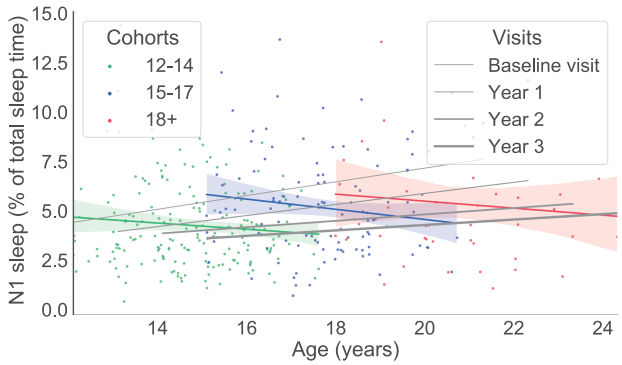


Figure 1. Within-participant trends across baseline and three follow-up annual visits and between-participant level differences at each visit for N1 sleep percentage (n = 94). For the purpose of visualization, participants are grouped into three age cohorts, although age was included in the model as a continues measure. Within-participant trajectories showing decreases across annual assessments (green, blue, red) are fitted using linear regression based on age cohorts defined by age at the baseline visit. Between-participant differences are shown by regression lines fitted for each annual visit (gray lines).

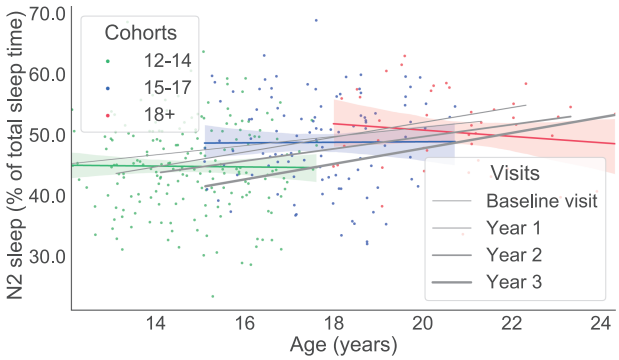


Figure 2. Within-participant trends across baseline and three follow-up annual visits and between-participant level differences at each visit for N2 sleep percentage. For the purpose of visualization, participants are grouped into three age cohorts, although age was included in the model as a continuous measure. Within-participant trajectories showing trends across annual assessments (green, blue, red) are fitted using linear regression based on age cohorts defined by the age in the baseline visit. Between-participant differences are indicated by regression lines fitted for each annual visit (gray lines), showing that the older participants had a higher percentage of N2 sleep.

%REM sleep [$\chi^2_{\text{year} \times \text{drinking}}(1) = 4.74$, $p = .029$] (Figure 7). In those that emerged as moderate/heavy drinkers, %REM sleep declined across follow-up Year 1 to Year 3, an effect not seen in those that remained as no/low drinkers. Note that there was no significant difference in %REM sleep in the baseline year between participants who later emerged into moderate/heavy drinkers and participants who stayed as no/low drinkers across assessments. There were no significant drinking behavior effects on SE, WASO, %N1, %N2, and %N3 sleep.

The effect of Cannabis use was significant on %REM [$\chi^2(1) = 4.15$, $p = .041$] with higher cannabis use being associated with increased %REM (see Supplementary Figure S3). There were no other significant effects of Cannabis use on any of the sleep variables (SE, TST, SOL, WASO, %N1, %N2, and %N3 sleep). Finally, having family history of substance use was significantly associated with shorter TST [$\chi^2(1) = 5.88$, $p = .015$] (see Supplementary Figure S4) in the model but not with any other sleep variables.

To further investigate the identified drinking effects, we ran an additional analysis considering the within-subject level changes after drinking onset in the drinking group. This analysis predicted the TST, SOL, and REM% including the drinking onset (before/after), the age of the participants, sex, and the age by drinking onset interaction. We found a significant interaction between the drinking onset and age both for TST ($p = .04$) and SOL ($p =$

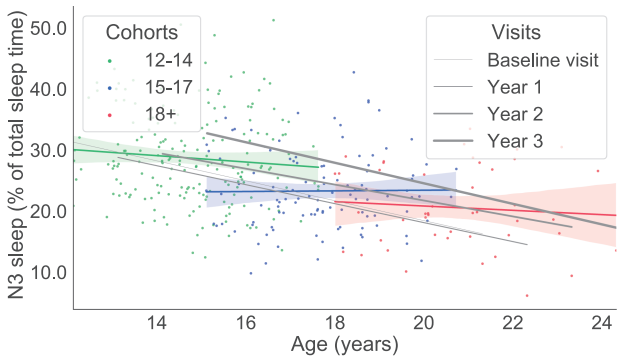


Figure 3. Within-participant trends across baseline and three follow-up annual visits and between-participant level differences at each visit for N3 sleep percentage. For the purpose of visualization, participants are grouped into three age cohorts, although age was included in the model as a continuous measure. Within-participant trajectories showing trends across annual assessments (green, blue, red) are fitted using linear regression based on age cohorts defined by the age in the baseline visit. Between-participant ifferences are indicated by regression lines fitted for each annual visit (gray lines), showing that the older participants had a lower percentage of N3 sleep.

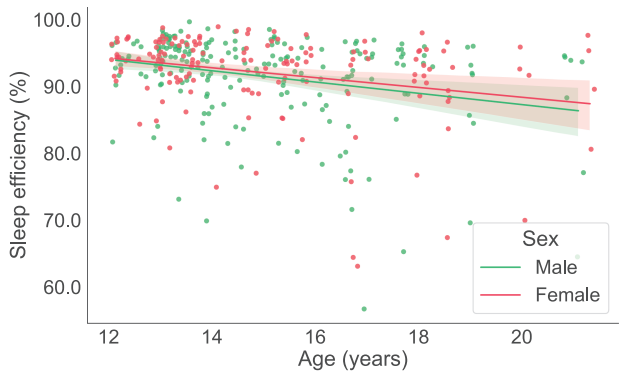


Figure 4. The association between age and sleep efficiency (SE; %), calculated as TST/TIB * 100 for participants (n = 94). Trendlines are fitted using linear regression.

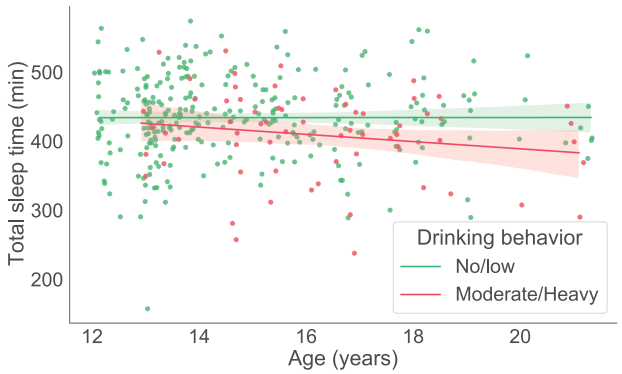


Figure 5. The association between alcohol drinking behavior, classified according to Cahalan categories across follow-up assessments (no/low vs. moderate/heavy drinking) and total sleep time (TST) in NCANDA sleep project participants (n = 94). Being in the moderate/heavy drinking group was associated with shorter TST in older participants. Trendlines are fitted using linear regression. All participants were no/low drinkers at baseline.

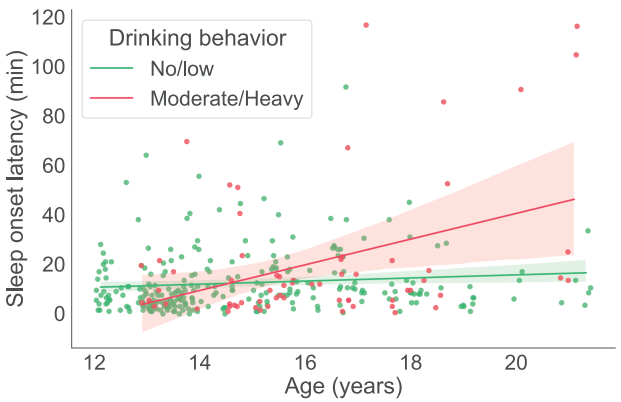


Figure 6. The association between alcohol drinking behavior, classified according to Cahalan categories across follow-up assessments (no/low vs. moderate/heavy drinking) and sleep onset latency (SOL) in NCANDA sleep project participants (n = 94). Moderate/heavy drinking was associated with a longer SOL in older participants. We provide trendlines fitted using linear regression.

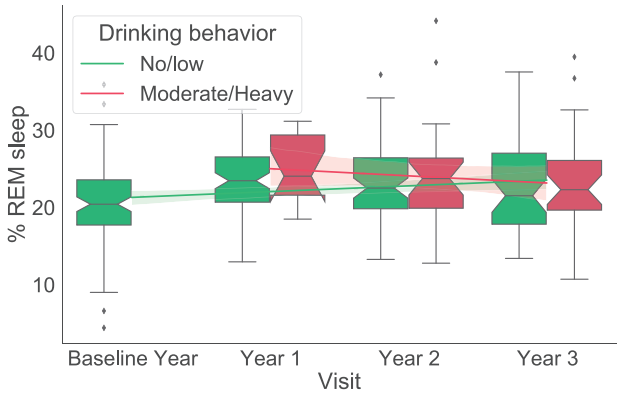


Figure 7. Relationship between the annual visit and %REM sleep (medians ± IQT and outliers) in NCANDA sleep project participants (n = 94). The interaction between alcohol drinking and the year of the visit was significant, showing differential %REM patterns based on the drinking category in the follow-up years.

.01), confirming that the effect of alcohol use was strongest in the older adolescents, who had shorter TST and longer SOL after drinking onset.

NREM sleep spectral EEG power

Developmental effects.

See Table 3 for statistical models for NREM sleep EEG delta and theta power bands. Electrode location was significantly associated with EEG activity for both frequency bands (Table 3). Delta power was highest at frontal sites and lowest at the occipital site. Age [$\chi^2(1) = 52.10$, $p < .001$] and the within-participant level annual change [$\chi^2_{\text{year of visit}}(1) = 187.34$, $p < .001$] were significant predictors of delta power. There was also a significant interaction effect between age and year of visit [$\chi^2_{\text{age} \times \text{year of visit}}(1) = 39.52$, $p < .001$]. This interaction effect is displayed in Figure 8, showing with a slower decline over time at the occipital electrode in the older participants.

Relationships for theta power were similar to those found for delta power. Age was negatively associated with theta power activity [$\chi^2(1) = 55.02$, $p < .001$] and the main effect of the annual visit was also significant [$\chi^2(1) = 299.24$, $p < .001$], however the age

Table 3. Model outputs for the NREM and REM sleep EEG spectral analysis for delta and theta bands in the NCANDA sleep project (n = 94)

	REM		NREM	
	Delta	**Theta**	**Delta**	**Theta**
Sex	1.61	2.39	1.15	0.00
Age	**58.30**	**44.10**	**52.10**	**55.02**
Drinking behaviour	0.19	0.09	**4.86**	0.03
Year of the visit	**149.84**	**220.10**	**187.34**	**299.24**
Electrode location	**1009.14**	**1072.93**	**2637.29**	**1624.24**
Family history of alcohol use	0.01	0.02	1.96	0.03
Cannabis consumption	**3.90**	**5.91**	1.63	0.20
Sex by age	0.07	0.06	0.18	0.15
Sex by drinking behaviour	0.23	1.94	**7.61**	**4.35**
Age by drinking behaviour	1.39	3.66	1.47	2.95
Age by year of visit	**58.63**	**104.84**	**39.52**	**88.73**
Drinking behaviour by Year of visit	3.27	**5.21**	3.55	**3.94**
Conditional R^2	**0.77**	**0.79**	**0.85**	**0.83**

Family history of alcohol use, sex, and drinking behavior were included as factors. Age (at the baseline visit), cannabis consumption (log transformed), were standardized (z-scored). The random-effects structure included a random intercept for study site and participant ID. Significant results are highlighted with bold. Results of the likelihood ratio test: Chi-square values.

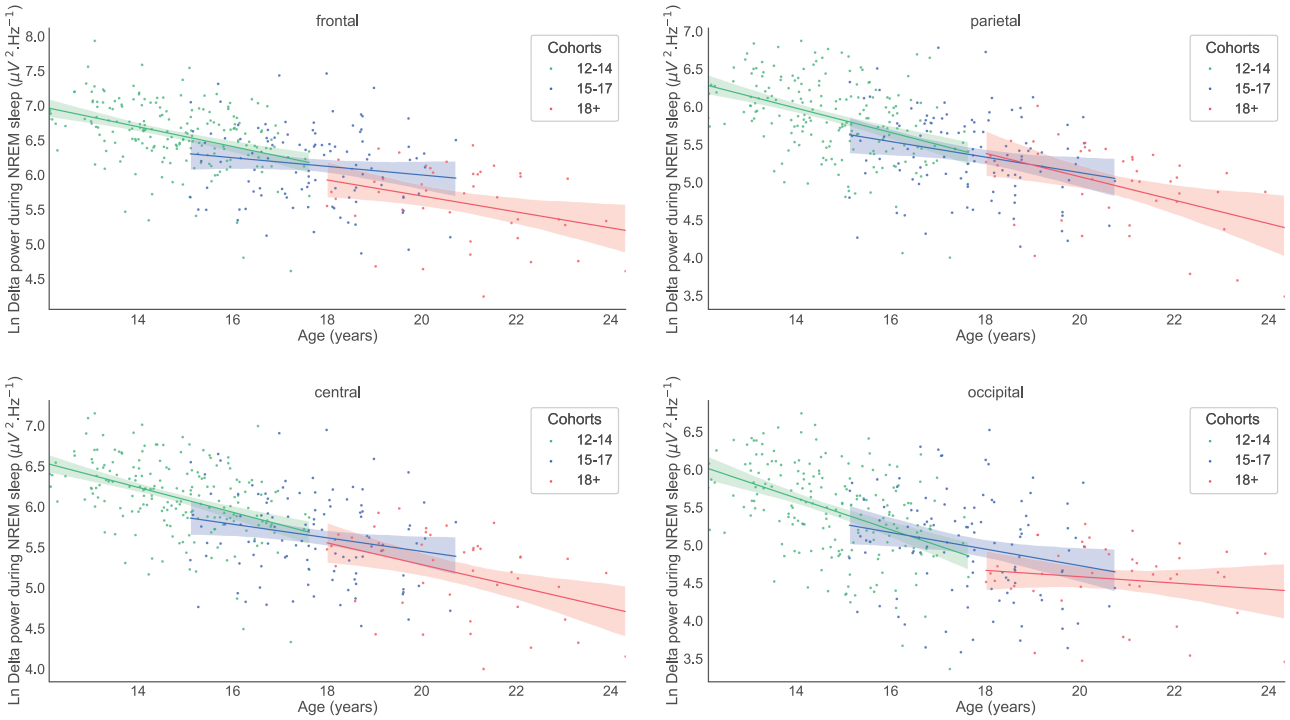


Figure 8. Within-participant changes across baseline and three follow-up annual visits and between subject level differences at each visit for NREM delta power (n = 94). For visualization participants are grouped into three age cohorts although age was included in the model as a continues measure. Within subject trajectories showing changes across annual assessments (green, blue, red) are fitted using linear regression based on age cohorts defined by age at the baseline visit.

× annual visit interaction shows that the older participants had a smaller change in their trajectories than the younger participants [$\chi^2(1) = 88.73$, $p < .001$].

Alcohol effects.

Drinking behavior was significantly associated with delta power in NREM sleep [$\chi^2_{\text{alcohol use}}$ (1) = 4.86, p = .027]. Being in the moderate/heavy drinking Cahalan category was significantly related to lower delta power, especially in male participants, indicated by the significant interaction effect between sex and alcohol use [$\chi^2_{\text{sex × alcohol use}}$ (1) = 7.61, p = .005] (Figure 9). The year of visit by alcohol use interaction effect on the NREM delta power was also marginally significant [$\chi^2(1) = 3.55$, p = .059] pointing towards the need for further examination of the impact of alcohol on the developing brain.

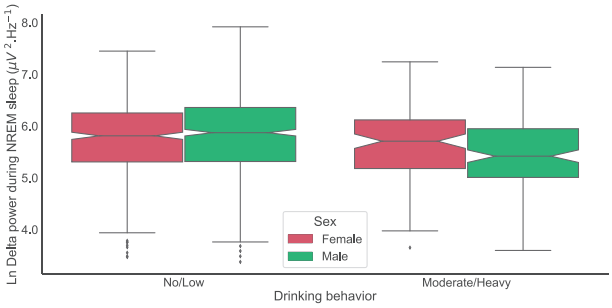


Figure 9. The interaction between alcohol drinking behavior and sex was significant for NREM delta power (medians ± IQT and outliers) in the NCANDA sleep project participants (n = 94), with male participants in the moderate/heavy drinking category having less NREM delta power than those male participants who stayed in the no/low drinking category.

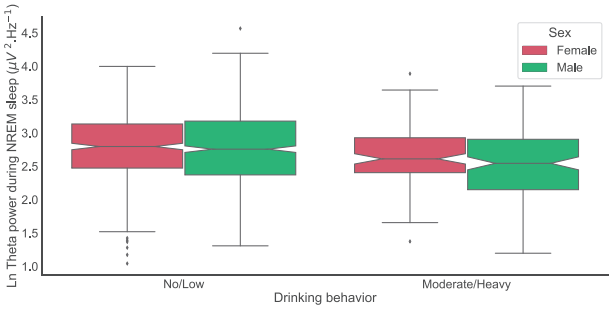


Figure 10. The interaction between alcohol drinking and sex was significant for NREM theta power (medians ± IQT and outliers) in the NCANDA sleep project (n = 94), with male participants in the moderate/heavy drinking category having less NREM theta power than those male participants who stayed in the no/low drinking category.

For theta power in NREM sleep, the alcohol use by year of the visit interaction [$\chi^2_{\text{year of visit} \times \text{alcohol use}}$ [2] (1) = 3.94, p = .047] indicated that participants in the moderate/heavy drinking group had lower theta power at all follow-up assessments compared with those who stayed in the no/low drinking group. In addition, being in the moderate/heavy drinking Cahalan category was significantly related to lower theta power, especially in male participants, as reflected by the significant interaction effect between sex and alcohol use [$\chi^2_{\text{sex} \times \text{alcohol use}}$ (1) = 4.35, p = .036] (Figure 10). We found no interaction between the drinking category and year of the visit for any of the outcome measures.

REM sleep spectral EEG power

Developmental effects.

Similarly to findings for NREM sleep, the electrode location and the year of visit had significant main effects on both delta and theta EEG frequency bands in REM sleep (see Table 3). In addition, there were significant age effects and interaction effects between the year of visit and age (Table 3). Older adolescents had lower delta [$\chi^2(1) = 58.30$, $p < .001$] and theta [$\chi^2(1) = 44.10$, $p < .001$] power than younger adolescents. However, an age-related decline was observed at the within subject level in both frequency ranges, indicated by the main effect of the year of visit.

Alcohol effects.

There were no effects of alcohol on delta EEG activity in REM sleep. However, there was an interaction between year of visit and drinking behavior [$\chi^2(1) = 5.21$, p = .022] on REM sleep EEG activity in the theta frequency band: being in the moderate/heavy drinking Cahalan category was related to lower theta power at Year 1 and Year 2. Finally, cannabis consumption was associated with REM sleep EEG power in both delta and theta frequency bands, indicating that higher levels of cannabis consumption were associated with higher REM delta [$\chi^2(1) = 3.90$, p = .048] and theta [$\chi^2(1) = 5.91$, p = .015] power (see Table 3).

Discussion

The present findings advance the understanding about developmental changes in sleep architecture and EEG, and the associations between emerging alcohol use and sleep, by using a longitudinal design that tracked sleep and drinking behavior in adolescents across 4 years. Our main findings show: (1) an age-related decline in %N3 sleep associated with declines in both delta and theta EEG activity in NREM sleep, effects also evident in REM sleep EEG, with specific patterns according to scalp topography, (2) a decline in TST and a lengthening of SOL after the onset of medium/heavy alcohol use in older adolescents, and (3) changes in REM sleep over time and NREM and REM sleep EEG delta and theta power as a function of drinking behavior. Together, findings indicate developmental changes in sleep and the sleep EEG as adolescents age, and for the first time, the sensitivity of these changes to emerging alcohol use. The functional consequences of these alcohol effects remain to be determined.

Taking advantage of the accelerated longitudinal design of the NCANDA study, with a wide age-range (12–21 years old at baseline) and annual follow-up visits, we confirmed the well-known age-related reduction in SWS sleep and delta (slow wave) EEG power within sleep [3, 20, 21, 44, 52] that likely reflects the synaptic pruning that occurs in the healthy adolescent brain during this developmental stage [21]. Cortical gray matter volume decreases between the ages of 9–25 years in a "back-to-front" (parieto-temporal) manner, as part of the normative reorganization in the adolescent brain [32, 53–56]. Our group and others have linked the age-related decline in delta power with that of gray matter volume in adolescents [25, 26]. Cortical maturation is characterized as increasing in gray matter volume through childhood, peaking in adolescence (frontal lobes: 9.5 years in girls and 10.5 years in boys; temporal lobes: 10.0 years in girls and 11.0 years in boys; parietal lobes: 7.5 years in girls and 9 years in boys) [57], followed by a continuous decline thereafter [53, 58, 59]. Consistent with previous reports [6], our results show topographic differences in how delta power changes over time, with a slower decline over time at the occipital site in older adolescents. These topographic differences are thought to reflect regional differences in the rates of synaptic pruning and neuronal plasticity [20] with earlier maturation of the posterior cortical regions [56, 60] such that there is less change in sleep EEG over the occipital region in older participants. We found similar developmental trends for male and female adolescents in the sleep measures examined. Others reported a sex difference in the timing of the delta decline, with female adolescents starting the period of most rapid delta power decline at 12.53 years, which was 1.2 years earlier than male adolescents [61]. Considering that the age-range examined in our sample did not extend younger than 12 years, we likely missed the start of the most rapid decline in delta power for girls.

The reduction in N3 sleep (N3%) over time was mostly offset by an increase in N2 sleep (N2%), although there was also a substantial reduction in TST as participants got older, with 67% getting less than 7 h of sleep in their 4th laboratory visit. NCANDA annual sleep assessments were scheduled at the convenience

of participants, on either weekdays or weekends, and reflect a snapshot of their sleep. Results are consistent with the literature, showing mostly with self-report or actigraphy, a reduction in sleep duration across adolescence [5, 62]. A meta-analysis of actigraphy studies reported a pooled mean sleep duration of 7.4 h on school nights in adolescents aged 15–18 years [63]. This amount is far below the 8.50–9.25 h of sleep per night needed for teenagers [64], and recommended (8–10 h) by the National Sleep Foundation [65]. Of concern, several studies have concluded that short sleep duration or sleep insufficiency increases risk for subsequent depression [65, 66], suicide attempts, and self-injury [67], substance use [68], and poor academic performance [69] in adolescents.

Alcohol use is known to interfere with the extensive morphometric and functional brain maturation processes during adolescence, resulting in accelerated gray matter loss and attenuated white matter growth [29, 30, 70]. Our data suggest that moderate-heavy alcohol use also interferes with sleep processes, being associated with delayed sleep onset and shortened sleep duration over time in older participants, as well as altered REM sleep and both REM and NREM sleep EEG power in delta and theta bands. The maturation of neural systems, in particular myelination and synaptic pruning are thought to be reflected in sleep [6], and the effects of alcohol use over time on these brain maturation processes, therefore, could directly affect sleep. Studies investigating the association between drinking behavior and sleep architecture have mostly been done in adults [71], particularly in individuals with chronic alcohol use who meet criteria for alcohol use disorder (AUD). Studies in adolescents have either examined acute effects of alcohol administration on sleep architecture only in older adolescents [72], or have examined associations between alcohol use and sleep behavior. Studies about sleep behavior consistently reported that higher alcohol use is associated with more sleep difficulties [37, 73, 74], however, longitudinal studies, including NCANDA, have shown that at least some sleep problems actually precede heavy alcohol use [38–42]. One daily survey study examined associations between binge drinking and sleep the following night, and found that on days when students binge drank, they reported lower sleep quantity and quality that night, and greater next-day tiredness, compared to days they did not binge drink [75]. There is likely a complex and interactional relationship between sleep behavior and alcohol use such that some sleep problems precede initiation of heavy alcohol use in adolescence and others are exacerbated and/or are a consequence of alcohol use. Importantly, our findings with longitudinal data show for the first time how the initiation of moderate-heavy drinking is associated with changes in sleep architecture and EEG measures over time. At baseline, there were no significant differences in sleep architecture and EEG measures in those who went on to drink versus those who stayed as low/no drinkers. With these data, therefore, we are able to show that it was the initiation of moderate-heavy alcohol use that was associated with changes or differences in sleep architecture and not due to pre-existing disruption in the PSG. Consistent with our findings of longer SOL and shorter TST as well as lower delta power in NREM sleep in those who drank moderate-heavy amounts, others have shown in animal models that alcohol exposure during adolescence may result in long-lasting sleep disruptions [76] and reduced SWS [77, 78]. Examining the nationally representative sample of the Monitoring the Future study, Terry-McElrath [79] found that ~6% of US high school seniors reported using alcohol as a sleep aid. Ironically, while adults tend to fall asleep faster after ingesting small amounts of alcohol prior to bedtime [80, 81], both preclinical and human studies in adolescents suggest that alcohol is less sedating during adolescence (and relatively more stimulating) [82–84]. Laboratory-based alcohol administration studies indicate that acute alcohol consumption does not reduce SOL in adolescents and emerging adults, particularly when alcohol is consumed in the evening [43, 85]. Nonetheless, alcohol may still be perceived as a viable sleep aid, especially in adolescents attempting to counter their tendency towards later circadian phase. Indeed, recently published studies leveraging the NCANDA data, reported that greater eveningness, later bedtime, and shorter sleep duration predicted more severe alcohol binge drinking the following year in adolescents [42, 86]. Taken together, our findings in the NCANDA sample show that self-reported sleep problems predict alcohol use and that moderate-heavy alcohol use in turn, is associated with disrupted PSG measures of sleep, including measures of SOL.

The sample of adolescents in NCANDA drank at moderate-heavy levels, however, none of them met criteria for an AUD. Our findings therefore point to the sensitivity of sleep processes to the initiation of alcohol use in adolescence and are concerning given the literature in adolescents and adults showing the chronic effects on sleep architecture of heavy alcohol use [36]. Adolescents who used alcohol or binge drank have significantly shorter sleep duration (<8 h) than those who do not (>8 h) [87], with students getting <5 h of sleep being 68% more likely to use alcohol, and 149% more likely to binge drink [88]. Adults with AUD have shorter TST, poorer SE, less SWS, as well as abnormalities in REM sleep duration and latency compared to age-matched healthy controls [71, 89–91], that persist long into abstinence, and are a significant predictor of relapse [92, 93]. Our results, showing multiple associations with drinking and REM sleep both in the microstructure and in macrostructure analysis, suggest that REM sleep is highly sensitive to the effects of alcohol use, which could reflect effects of alcohol on REM-on/off systems in the brain [36] or could involve interactions between alcohol and neurodevelopment affecting REM regulation. In fact, alterations in %REM sleep and REM sleep EEG were also associated with cannabis use. While very little data exist on adolescent cannabis use in relation to sleep, especially in combination with alcohol use, the data of Cohen-Zion and colleagues published as a conference abstract suggest that both SWS and REM sleep may be impacted in heavy adolescent cannabis users, with greater cannabis intake predicting lower N3 sleep, and past month alcohol use predicting increased %REM sleep in cannabis user teens during a 28-day monitored abstinence period [94]. Earlier studies showed that cannabis use was associated with REM sleep reduction, as well as N3 (SWS) suppression in adults [95, 96]. Nevertheless, findings are inconsistent. The present data show effects of cannabis use were specific to REM sleep. However, these findings should be interpreted cautiously since we did not control for baseline cannabis use (9.7% reported some level of cannabis use at baseline), or the amount, type or the regularity of cannabis use in our cohort. Our results point to the need for further investigation on this topic.

The literature is inconclusive, but given that some studies documented higher sleep EEG alpha spectral power in people with family history of alcohol use [97, 98], we also considered effects of family history of substance use on PSG measures and found only that TST was shorter in those who reported a positive family history. Our findings therefore point towards an effect of alcohol use itself on sleep architecture and EEG that is not driven by family history.

This study has several strengths. NCANDA is a cohort study of a large sample of adolescents, across a wide age-range, and includes both male and female adolescents, with 4-waves of

data collection used in the analysis. Further, alcohol use was carefully tracked over time and sleep was measured objectively with PSG. The study also has some limitations. First, all substance use data were self-reported, which may be biased. Second, although the sample size was relatively large, the older ages were slightly under-represented, which might lead to biased estimates of the associations between sleep and alcohol use in older participants. Also, those who were moderate and heavy drinkers were combined and further studies are needed to determine if there are differences in effects on sleep in relation to severity of alcohol use. Third, although demographic variables were statistically controlled, other factors which may be associated with participant's sleep and substance use, such as circadian preference, were not included. Further study of the NCANDA sample as they progress through young adulthood as well as other longitudinal studies are warranted. In addition, the current sample is ethnically diverse, but not representative of the US population, which limits generalizability. Further studies in more diverse populations of individuals at differing risk for heavy alcohol use need to be conducted to confirm these observations.

In conclusion, our cohort study of American adolescents with four waves of data collection illustrates the major changes in sleep structure and the associations with alcohol use as they progress through adolescence. Further studies are needed to examine the neurobiological mechanisms and functional implications underlying these changes. Both the dynamic maturation of the brain, and the simultaneously occurring sleep changes are highly sensitive to the effects of alcohol, highlighting the need for greater attention to the effects of alcohol use on sleep in youth. Research and clinical data have provided considerable evidence that sleep problems during this vulnerable life stage can increase the probability of developing substance use and other psychiatric disorders later in life [86, 99]. Our findings provide additional evidence of the sensitivity of functional sleep measures to the effects of alcohol in this vulnerable age group, which could set them up for future sleep problems in adulthood.

Supplementary material

Supplementary material is available at *SLEEP* online.

Conflict of Interest

The authors have declared that no competing interests exist.

Disclosure Statement

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Author contributions

OK (Conceptualization, Methodology, Formal analysis, Visualization, Writing - original draft), MdZ (Methodology, Funding acquisition, Writing - review & editing), AG (Methodology, Formal analysis, Writing - review & editing), BH, ST, PF, SB, MB, BN, KN, IC, DY (Investigation, Writing - review & editing), DC, FB (Conceptualization, Investigation, Funding acquisition, Writing - review & editing)

Data Availabilty Statement

The data that support the findings of this study are available upon completion of a data use agreement with the National Institute for National Institute of Alcohol Abuse and Alcoholism, which can be found at https://www.niaaa.nih.gov/national-consortium-alcohol-and-neurodevelopment-adolescence-ncanda.

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