




Adult Psychiatric, Substance, and Functional Outcomes of Different Definitions of Early Cannabis Use

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Objective: Research on associations of early cannabis use with adult functioning reports mixed findings. This may be due, in part, to wide variations in the definitions of early cannabis use. This study aims to compare associations of 4 commonly used definitions of early cannabis use—related to timing, dose, duration, and associated symptoms—with adult outcomes.

Method: Analyses were based on a 20⁺-year longitudinal, community-representative study of 1,420 participants. Between ages 9 and 21 years (8,806 observations), participants were assessed for cannabis use and *DSM-5* cannabis use disorder. In early adulthood (ages 24–26 and 30; 2,424 observations of 1,266 subjects), participants were also assessed for psychiatric, substance use, and functional outcomes.

Results: All definitions of early use were associated with multiple adult outcomes in models that adjusted for sex and race/ethnicity. In models that also adjusted for childhood psychiatric problems and family adversities, only daily use and a persistent developmental subtype (defined as daily/problematic use that began in adolescence and continued into early adulthood) were associated with later substance use/disorders, poorer functional outcomes, and derailments in the transition to adulthood.

Conclusion: Daily, continued-over-time cannabis use beginning on adolescence was most problematic for a range of adult outcomes. Cessation of early use did not fully eliminate later risks; but was associated with fewer negative outcomes, with weaker effect sizes.

Key words: adolescence, cannabis, longitudinal, psychopathology, epidemiology

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The onset of cannabis use during adolescence (or “early use”) is relatively common.¹ Understanding the adverse effects of such early use is a research priority of the National Institute of Drug Abuse and public policy makers. A number of adverse adult outcomes of early use have been identified, with low confidence (eg, for lung cancer) to high confidence (eg, for addiction to cannabis and other substances).² This research is of particular importance, given ongoing brain and psychosocial developments during adolescence, and also movements toward legalization and decriminalization of cannabis in many US states.

A large number of longitudinal studies have examined patterns of early cannabis use and associations with later adverse effects.³ Across these studies, definitions of early use have varied widely, with studies focusing on the following: any use,⁴ frequency of use,^{5–12} *DSM*-based cannabis dependence or cannabis use disorder (CUD),^{13–15} age of onset of use,¹⁶ polysubstance use,¹⁷ and still others focusing on different individual trajectories of use.^{18–26} These approaches index the timing, dose, and duration of use, as well as associated problems. Investigating different aspects of

early cannabis use has scientific value, but differences in definitions of early cannabis use can lead to mixed findings in which one definition of early use is associated with a later outcome but another similar definition is not. Such mixed findings challenge clinicians who seek to provide prognostic information to patients and policy makers looking to make evidence-based decisions about early cannabis access. This is no small concern, as early cannabis use is the subject of significant controversy in the public at large. One apparent solution to the heterogeneity issue is to compare the results of different studies with different definitions of early cannabis use. Such comparisons come with difficulties, however, as studies differ in their sampling approaches, sample characteristics, and assessments. Comparing different definitions of early cannabis use in the same study overcomes such difficulties.

The current study leverages a longitudinal, community-representative study that followed participants prospectively throughout adolescence and then into adulthood (up to age 30 years), and that collected information about onset, frequency of use, and cannabis-related *DSM* symptoms. We propose to compare 4 dimensions of early cannabis use: (1)

very early use, defined as any daily use or *DSM* cannabis use disorder prior to age 16 years; (2) *DSM-5* cannabis use disorder (CUD), defined as the cumulative times that the participant met criteria by age 21 years; (3) daily use, defined as the cumulative times the participant reported daily use by age 21; and (4) individual-developmental subtypes of early use previously identified and validated in this sample.²⁷ It is possible that all 4 definitions of early cannabis use will be associated with adult outcomes similarly. More likely, particular features of early cannabis use will be more strongly associated with adult problems than others.

A number of studies have looked at individual profiles of early cannabis use. The most commonly identified developmental profiles of early cannabis use in the literature include the following: (1) no/minimal use across adolescence and early adulthood; (2) adolescence-limited problematic use (which may extend into the early 20s); and (3) persistent cannabis use that begins in adolescence and continues into early adulthood.^{18-26,28,29} Recently, some studies have also included a group whose use begins in adulthood after the typical peak of cannabis use in the late teens/early 20s.^{11,30,31} We previously studied and validated these developmental groups with respect to childhood and adolescent risk factors.²⁷ All cannabis groups displayed elevated levels of early conduct problems and exposure to other substances in adolescence. However, each group was also associated with distinct risk factors: persistent users were most likely to have had anxiety or depressive disorders in childhood; adolescence-limited users displayed the highest levels of familial risk factors; and adult-onset users were most likely to have been victimized as children. The current study builds off this work by studying these 4 developmental groups—which have been well characterized in terms of childhood risks—with respect to outcomes in adulthood.

Studies of adult outcomes of early cannabis use have examined different adult outcomes, with some focusing on mental health outcomes like depression and anxiety,³² others on substance use outcomes,¹⁷ and stills others focusing on outcomes in important areas of functioning like educational attainment¹⁶ and criminality.⁸ Here, we attempt to index many such aspects of adult functioning in one study by looking at milestones indicative of a successful transition to adulthood, and indicators of mental health disorders, substance use disorders, crime, financial challenges, and social problems during young adulthood. Finally, we examine whether observed associations differ systematically by sex or race/ethnicity, given previously reported differences in the prevalence of cannabis in this sample.^{1,27}

METHOD

Participants

The Great Smoky Mountains Study is a longitudinal, representative study of children in 11 predominantly rural counties in North Carolina.³³ Three cohorts of children, aged 9, 11, and 13 years at intake, were recruited from a pool of some 12,000 children in the 11-county area using a household equal probability, accelerated cohort design. The accelerated cohort design means that each cohort reaches a given age in a different year, controlling for cohort effects. First, potential participants were randomly selected from the population using a household equal probability design. Next, participants were screened for risk of psychopathology; participants screening high were oversampled in addition to a random sample of the rest. About 8% of area residents and sample are African American, and fewer than 1% are Hispanic. American Indians make up 3% of the population of the study area, but were oversampled to constitute 25% of the sample. This design (Figure S1, available online) resulted in $N = 1,420$ participants (49% female). Sampling weights are applied to adjust for differential probability of selection. Thus, the statistical estimates presented here are representative of the population from which the sample was drawn.

Annual assessments were completed until age 16 years and then again at ages 19, 21, 25, and 30 years (11,230 observations of 1,420 participants; 1993–2015). Interviews were completed by a parent figure and the participant to age 16 years, and by the participant only thereafter. Before any interviews, the parent and child signed informed consent/assent forms. The study protocol and consent forms were approved by the Duke University Medical Center Institutional Review Board. Each respondent received an honorarium for participation.

Assessment

All variables were assessed using the a structured interview, the Child and Adolescent Psychiatric Assessment (CAPA) until age 16 years, and its upward extension, the Young Adult Psychiatric Assessment (YAPA) thereafter.^{34,35}

Early Cannabis Use. The structure of the CAPA/YAPA substance use section consists of a preliminary screening section covering the frequency of use of specific substances, followed by a detailed section on symptoms and impairment, asked only if use is reported. The section on frequency of use includes information about age of onset as well as weekly and daily use both in the last 3 months and during the participant's lifetime. The module assesses symptoms of *DSM-IV* abuse and dependence, *DSM-5* cannabis use disorder (CUD), and associated nondiagnostic

features of problematic use. Although *DSM-5* CUD symptoms of craving and withdrawal were not part of *DSM-IV* abuse or dependence diagnostic criteria, these data were collected since the start of the study in 1993. The time frame for determining the presence of diagnostic items was the 3 months immediately prior to the interview to minimize recall biases. Scoring programs written in SAS combined information about the date of onset, duration, and intensity of each symptom from raw variables to derive symptom scores and diagnostic variables, as has been described elsewhere.^{34,36} In a 2-week test–retest study to determine the reliability of participant reporting, the intraclass correlation coefficient (ICC) for the number of substance abuse/dependence symptoms was 0.98.³⁷

The 4 dimensions of early cannabis use are defined as follows: (1) very early use as a dichotomous variable for any daily use or *DSM-5* cannabis use disorder before age 16 years; (2) *DSM-5* SUD as a count variable for the number of assessments up to age 21 years at which the participant met criteria for *DSM-5* cannabis use disorder (range winsorized at 0 to 3+); (3) daily use as a count variable for the number of assessments at which participants reported daily cannabis use up to age 21 (range winsorized at 0 to 3+); and (4) developmental subtypes based on onset and persistence of daily use/*DSM-5* CUD, as defined in a previous paper with this sample.^{1,27} These subtypes include the following: (1) a large no-use group; an adolescence-limited group that reported daily use and/or CUD up to age 21 years but not thereafter; 2) a persistent group that reported daily use and/or CUD up to age 21 and then again in adulthood (age 25 or 30); and finally, (3) an adult-onset group that reported daily use or CUD in adulthood only (age 25 or 30), but not earlier. Together, the different definitions of early cannabis use in this paper highlight frequency and persistence of use, evidence of addiction, precocious use, and specific developmental profiles.

Childhood Covariates. A number of childhood experiences may confound association of early cannabis use with adult outcomes. For example, an apparent association between early cannabis use and adult depression may be accounted for by childhood depression, which is associated with both. This study adjusts for such potential confounding by childhood psychiatric disorders and adverse experiences. Covariate childhood disorders include depressive, anxiety, behavioral (conduct, oppositional defiant, and attention-deficit hyperactivity disorder), and noncannabis substance disorders (eg, tobacco, alcohol, illicit drugs). Covariate childhood adverse experiences include low socioeconomic status, familial instability, family dysfunction, maltreatment, and peer victimization. A full description of how the

psychiatric disorders and adversities were derived is available in the childhood covariates description in the supplemental materials (Supplement 1, available online).

Adult Outcomes. Most outcomes were assessed using the Young Adult Psychiatric Assessment (YAPA),³⁵ an upward extension of the CAPA interview, administered to the participants at ages 25 and 30 years. The assessment of adult psychiatric disorders resembled that of childhood disorders, but used only self-reports as opposed to both self- and parent-report. Adult disorders included any *DSM* anxiety or depressive disorder. Psychosis and bipolar disorder were not included in analyses because of very low prevalence (<1%) in the community. Adult substance use/disorders included daily nicotine use, alcohol use disorder, and any illicit drug use (eg, heroin, cocaine, amphetamines, other opiates).

Standardized scales were derived to provide a broad profile of adult functioning across 4 domains: health, risky/illegal behaviors, wealth (financial/educational), and social function. These scales were created from dichotomous indicators in each domain (eg, college completion for wealth, smoking status for health). In some cases, the indicators were positive if reported at any point in adulthood (eg, smoking status); in other cases, the last observation was used to determine status (eg, educational attainment). Finally, a limited number of deleterious functional outcomes were summed into a “derailments” scale (eg, dropping out of high school, felony charge, social isolation, severe health problems). This scale is indicative of failure to successfully transition to adulthood in terms of work, legal, social, or health milestones. Additional detail on functional outcomes and derailments is provided in Supplement 1 and Table S1, available online.

Analytic Strategy

Sampling weights were applied in all analyses to ensure that results represent unbiased estimates for the original population. All percentages provided in the results are weighted, and sample sizes (Ns) are unweighted. Weighted logistic (for binary outcomes such as psychiatric status), Poisson (for count variables such as number of derailments), and linear (for continuous variables such as the *z* scores for the adult function scales) regression models tested differences in adult outcomes for the different definitions of early cannabis use. All models used SAS PROC GENMOD with robust variance (sandwich-type) estimates derived from generalized estimating equations to adjust the standard errors for the stratified design. Analyses first tested effects of different early cannabis use definitions on adult variables adjusted for sex, race/ethnicity, and cohort. Fully adjusted analyses also adjusted for childhood psychiatric disorders (mood, anxiety, behavioral, and noncannabis substance disorders) and other

childhood adversities (low socioeconomic status, familial instability, family dysfunction, maltreatment, and peer victimization). Given the focus on 11 different adult outcomes, a Bonferroni-based α level of 0.0045 (0.05/11) was used for statistical significance.

Missing Data

Across all waves, 81.8% of all possible interviews were completed, ranging from 74% to 94%. Of the participants, 100% completed at least 1 assessment by age 21 years (ie, the period during which early cannabis use was assessed), and 94.3% had ≥ 3 assessments (median = 7). Of the living participants, 92.4% had an adult outcomes assessment (age 25 or 30). Each of the 4 early use definitions was associated with a slightly increased number of total observations. Any such differences were attenuated when analyzing participants with 3+ observations only (ie, low levels of missingness). There was no evidence of differential attrition related to any of the early cannabis use variables that were used in the primary analysis (all $p = .32-.78$).

RESULTS

Descriptive Information

Table 1 presents the overall prevalence for each of the 4 early cannabis use definitions, for the overall sample and

also by sex and race/ethnicity. About 1 in 4 participants had used cannabis as determined by either daily use or the developmental subtypes. About 15% of participants met criteria for *DSM-5* CUD at some point by age 21 years; only about 5% of the sample met criteria for very early use by age 16 years. For all definitions, except very early use, levels of cannabis use were higher for male than for female participants. There were few differences by race/ethnicity, with some evidence that American Indians were more likely to engage in daily use or adolescence-limited use. African-American participants were more likely to report adult-onset cannabis use (see also Hill et al.²⁷). All cannabis use definitions were strongly associated with childhood covariates of psychiatric functioning and adversities (Table S2, available online).

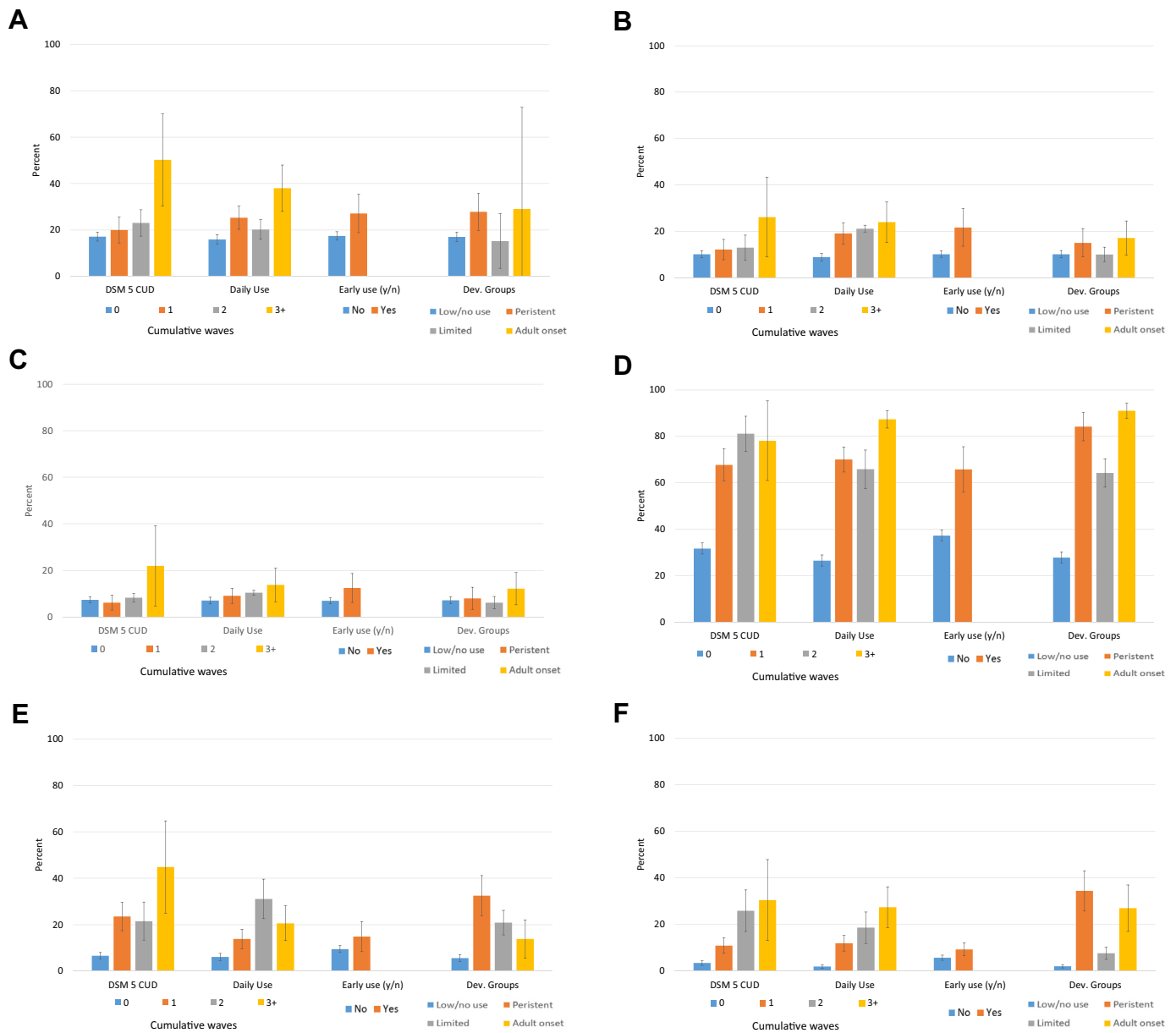
Each definition provides an index of an important aspect of early cannabis use that has been hypothesized to predict later functioning. By design, the developmental subtypes overlapped with the other early use definitions; however, importantly, they each also captured unique information about the patterns of use across developmental periods (Table S3, available online). Very early use was reported by only a subset of individuals who reported daily use. Daily use and *DSM-5* CUD status commonly overlapped.

TABLE 1 Prevalence and Comparisons of Early Cannabis Use Definitions by Sex and Race/Ethnicity

	Total	Female participants	Male participants	p	White	AI	Black	p ^a ; p ^b
	% (n)	% (n)	% (n)		% (n)	% (n)	% (n)	
Total	100 (1,420)	48.9 (630)	51.0 (790)		89.4 (983)	3.7 (349)	6.9 (88)	
Daily use								
0	74.6 (996)	82.5 (498)	67.1 (498)	—	75.7 (709)	66.2 (56)	65.0 (231)	—
1	15.0 (244)	11.2 (78)	18.6 (166)	—	14.7 (165)	18.1 (16)	17.4 (63)	—
2	6.5 (102)	3.4 (34)	9.5 (68)	—	6.0 (59)	9.2 (11)	11.8 (32)	—
3+	3.9 (78)	3.0 (20)	4.8 (58)	.001	3.6 (50)	6.6 (5)	5.8 (23)	.007; .12
DSM-5 dx.								
0	84.2 (1,176)	90.1 (561)	78.5 (615)	—	84.7 (831)	80.5 (64)	78.8 (281)	—
1	9.7 (155)	5.3 (40)	13.9 (115)	—	9.6 (98)	12.0 (15)	10.0 (42)	—
2	4.7 (70)	4.3 (25)	5.0 (45)	—	4.5 (45)	5.4 (6)	6.3 (19)	—
3+	1.5 (19)	0.2 (4)	2.7 (15)	.003	1.2 (9)	2.0 (3)	5.0 (7)	.33; .21
Very early use (<16 y)								
No	95.3 (1,329)	96.4 (594)	94.3 (735)	—	95.3 (925)	92.3 (82)	97.3 (322)	—
Yes	4.7 (91)	3.6 (36)	5.7 (55)	.28	4.7 (58)	7.7 (6)	2.7 (27)	.17; .23
Dev. profiles								
Low/no use	76.4 (884)	84.3 (498)	68.6 (498)	—	77.5 (624)	68.5 (47)	66.5 (213)	—
Adult onset	3.7 (61)	2.1 (18)	5.3 (43)	.02	3.0 (37)	5.1 (8)	11.8 (16)	.07; .02
Adolescence limited	13.3 (200)	10.3 (34)	16.2 (68)	.02	12.9 (122)	20.6 (14)	14.3 (64)	.004; .61
Persistent	6.7 (84)	3.4 (20)	10.0 (58)	.003	6.7 (59)	5.8 (7)	7.4 (18)	.98; .71

Note: Percentages represent row frequencies. Sample sizes are unweighted and percentages are weighted. AI = American Indian; dx. = diagnosis.
^ap is the difference between the White and American Indian participants.
^bp is the difference between the White and Black participants.

FIGURE 1 Associations of Early Cannabis Use Variables With Adult Outcomes



Note: (A) any adult psychiatric disorder; (B) any adult anxiety disorders; (C) any adult depressive disorder; (D) daily nicotine use; (E) DSM alcohol use disorder; (F) illicit drug use (including heroin, cocaine, methamphetamine); (G) health functioning; (H) risky/illegal behavior; (I) financial/educational functioning; (J) social functioning; (K) multiple derailments. Please note color figures are available online.

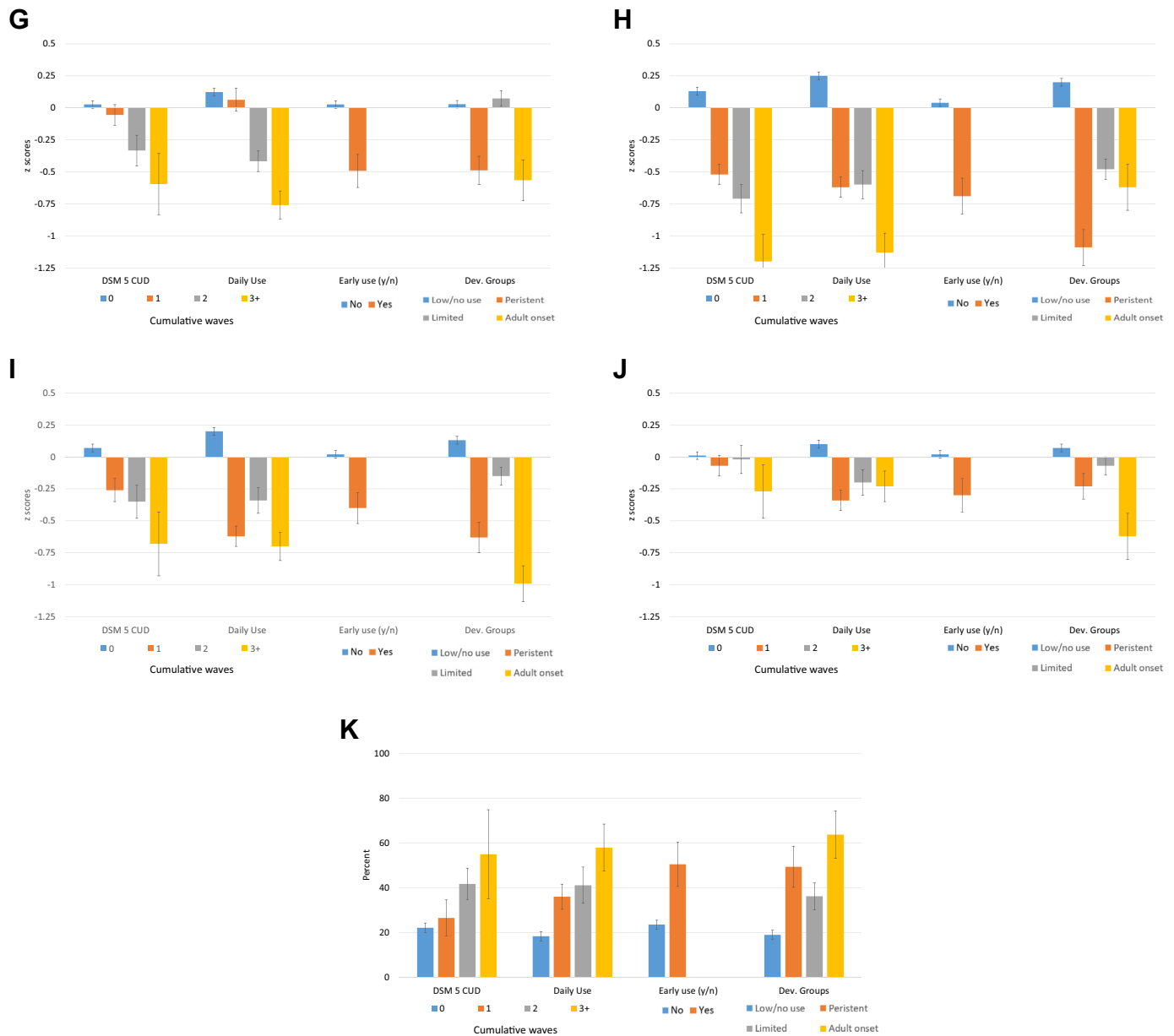
Associations Among Cannabis Use Definitions and Adult Outcomes

Figure 1a to 1k shows the prevalence of each adult psychiatric, substance, and functional outcome for each of the early cannabis use definitions. Table 2 shows the associations of early cannabis use variables with adult outcomes adjusted for sex, race/ethnicity, and cohort only. Each of the definitions of early cannabis use was strongly associated with adult substance disorders, functional outcomes, and

derailments. With respect to psychiatric status, none of the associations met the Bonferroni-adjusted *p* value as statistically significant.

Table 3 shows associations of early cannabis use with adult outcomes adjusted for sex, race/ethnicity, as well as childhood psychiatric disorders and adversities prior to cannabis use. A number of findings are noteworthy. First, the sizes of almost all associations were modestly attenuated after accounting for childhood psychiatric functioning and

FIGURE 1 Continued



adversities, although a number of the associations were moderate to large. Second, none of the associations of cannabis use variables and adult psychiatric disorders met the statistical significance threshold, even in the unadjusted models. Third, a number of cannabis use definitions (cumulative daily use, cumulative *DSM-5* CUD, and the “persistent” group) were associated with elevated risk for substance problems in adulthood, including illicit drug use. Fourth, cumulative daily use and the persistent group were associated with multiple functional outcomes. Indeed, cumulative daily use was associated with every single nonpsychiatric outcome in the adjusted models, with the

exception of social outcomes. Finally, very early cannabis use by age 16 years was associated with few adult outcomes.

Moderation and Sensitivity analyses

Interaction terms between each of the cannabis use variables and sex and race/ethnicity were tested to examine whether associations were sex or race/ethnicity specific (Table S4, available online). Despite differences in the prevalence of the cannabis use variables, there was little evidence of sex- or race/ethnicity-specific associations of early cannabis use and adult outcomes. Follow-up analyses looked at associations of cumulative daily use or persistent group (ie, the 2

TABLE 2 Associations of Early Cannabis Use Definitions With Adult Outcome Scales Adjusted for Sex and Race/Ethnicity

	Cumulative DSM-5 dx.			Cumulative daily use			Very early use			Developmental profiles									
	OR	95% CI	P	OR	95% CI	p	OR	95% CI	p	Persistent vs none			Adolescence only vs none			Adult vs none			
										OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	
Psychiatric dx.																			
Any disorder	1.4	1.0–2.1	.05	1.4	1.1–1.9	.01	2.0	0.8–4.9	.12	2.6	1.1–6.5	.04	1.1	0.5–2.1	.90	2.8	1.1–6.9	.03	
Depression	1.2	0.6–2.3	.55	1.2	0.8–1.8	.44	2.3	0.7–7.5	.16	1.6	0.4–6.3	.54	1.0	0.4–2.7	.99	2.1	0.5–9.0	.31	
Anxiety	1.5	1.0–2.3	.07	1.5	1.1–2.0	.01	2.9	1.0–8.1	.04	2.2	0.8–6.4	.13	1.2	0.5–2.8	.68	2.6	0.9–7.6	.09	
Substance dx.																			
Daily nicotine	1.9	1.4–2.7	.001	2.1	1.7–2.7	<.001	2.4	1.1–5.2	.03	7.1	3.3–15.5	<.001	2.5	1.3–4.7	.005	15.5	5.8–41.2	<.001	
Alcohol dx.	2.1	1.4–3.2	<.001	1.8	1.4–2.5	<.001	1.5	0.5–4.2	.48	6.3	2.3–17.2	<.001	3.9	1.8–8.7	<.001	2.3	0.4–12.4	.32	
Illicit drug use	3.1	2.0–4.8	<.001	3.1	2.2–4.4	<.001	7.4	2.6–21.2	<.001	16.3	5.2–51.6	<.001	3.9	1.3–11.6	.01	2.0	0.6–7.0	.30	
Functional																			
Health	1.2	1.1–1.4	.01	1.3	1.2–1.5	<.001	1.8	1.1–2.8	.02	2.0	1.3–2.9	<.001	1.0	0.9–1.3	.71	2.0	1.2–3.4	.006	
Criminal behavior	1.5	1.3–1.8	<.001	1.6	1.3–1.8	<.001	2.0	1.3–3.0	<.001	3.2	2.1–4.9	<.001	1.9	1.4–2.5	<.001	1.9	0.9–3.9	.08	
Financial	1.3	1.1–1.5	<.001	1.4	1.3–1.6	<.001	1.6	1.1–2.4	.03	2.2	1.5–3.1	<.001	1.3	1.0–1.7	<.001	2.8	1.8–4.5	<.001	
Social	1.1	0.9–1.2	.40	1.2	1.1–1.3	.002	1.4	0.9–2.2	.12	1.4	1.0–1.9	.03	1.2	0.9–1.5	.29	1.9	0.9–4.1	.11	
Derailments	1.2	1.1–1.4	.002	1.4	1.3–1.5	<.001	1.8	1.3–2.5	<.001	2.1	1.6–2.9	<.001	1.5	1.2–1.9	.003	2.0	1.4–2.9	<.001	

Note: Boldface type indicates significance at the Bonferroni-corrected α level of 0.0045. dx. = Diagnosis; OR = odds ratio.

TABLE 3 Associations of Early Cannabis Use Definitions With Adult Outcome Scales Adjusted for Sex, Race/Ethnicity, Childhood Disorders, and Adversities

	Cumulative DSM-5 dx.			Cumulative daily use			Very early use			Developmental profiles								
	OR	95% CI	P	OR	95% CI	p	OR	95% CI	p	Persistent vs none			Adolescence only vs none			Adult vs none		
										OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Psychiatric dx.																		
Any disorder	1.1	0.7–1.7	.69	1.1	0.8–1.6	.40	0.3	0.1–1.0	.06	1.5	0.5–4.1	.44	0.6	0.3–1.4	.22	2.0	0.6–6.4	.23
Depression	0.9	0.5–1.8	.84	1.0	0.6–1.5	.94	0.6	0.1–3.7	.59	0.9	0.2–3.4	.87	0.6	0.3–1.5	.27	1.5	0.4–6.5	.59
Anxiety	1.2	0.7–1.9	.52	1.2	0.9–1.7	.28	0.6	0.2–2.4	.50	1.2	0.4–3.8	.76	0.6	0.2–1.8	.40	1.6	0.4–6.4	.53
Substance use/dx.																		
Daily nicotine	1.7	1.1–2.5	.009	1.9	1.4–2.6	<.001	0.7	0.2–2.1	.46	5.4	2.1–13.8	<.001	2.0	0.9–4.0	.07	12.7	5.0–32.1	<.001
Alcohol dx.	2.6	1.5–4.6	<.001	2.1	1.4–3.1	<.001	0.7	0.2–2.4	.54	8.4	2.5–28.7	<.001	5.4	2.2–13.6	<.001	3.2	0.5–19.9	.21
Illicit drug use	3.1	1.9–4.9	<.001	3.0	2.1–4.1	<.001	2.6	0.5–13.3	.24	13.3	4.6–38.3	<.001	2.8	0.8–9.6	.10	1.5	0.4–5.6	.59
Functional																		
Health	1.2	1.0–1.3	.09	1.2	1.1–1.4	<.001	1.4	0.9–2.1	.14	1.6	1.1–2.3	.009	0.9	0.8–1.1	.71	1.8	1.1–3.0	.03
Criminal behavior	1.4	1.2–1.7	<.001	1.5	1.3–1.7	<.001	1.5	1.0–2.2	.05	2.7	1.8–4.3	<.001	1.6	1.2–2.2	.001	1.7	0.8–3.6	.14
Financial	1.2	1.1–1.4	.009	1.4	1.2–1.5	<.001	1.2	0.8–1.7	.47	2.0	1.4–2.9	<.001	1.2	0.9–1.5	.18	2.4	1.5–3.8	<.001
Social	1.0	0.9–1.2	.96	1.1	1.1–1.3	.03	1.0	0.7–1.4	.87	1.3	0.9–1.8	.10	1.0	0.8–1.3	.86	1.6	0.7–3.7	.25
Derailments	1.1	1.0–1.3	.09	1.3	1.2–1.4	<.001	1.0	0.7–1.4	.97	1.7	1.3–2.3	<.001	1.2	0.9–1.6	.19	1.5	0.9–2.4	.12

Note: All models are adjusted for sex and race/ethnicity, childhood psychiatric disorders (mood, anxiety, behavioral and noncannabis substance disorders) and other childhood adversities (low socioeconomic status, familial instability, family dysfunction, maltreatment, and peer victimization). Boldface type indicates that associations are significant at the Bonferroni-corrected α level of 0.0045. dx. = Diagnosis; OR = odds ratio.

definitions with significant associations with adult derailments in Table 3) with specific derailments, and found the strongest associations with troubles with the law, severe psychopathology, and multiple derailments (Table S5, available online). Alternative versions of the very early use variable were also tested, including a variable indicating weekly use by age 16 years or any cannabis use by age 16 (Table S6, available online). The “any cannabis use” variable was associated with increased rates of illicit drug use, criminal behaviors, and financial troubles in adulthood, although none of these associations met the Bonferroni-corrected p value. Finally, all adjusted analyses were rerun looking at outcomes at age 30 years only (rather than combining ages 25 and 30; see Table S7, available online). Early cannabis use, particularly cumulative daily use and the persistent subtype, were still associated with substance problems and functional outcomes, although a number of significant associations had weakened.

DISCUSSION

What becomes of children and adolescents who use cannabis is the subject of constant public interest and large-scale research efforts. The current analysis leveraged a 20+-year prospective study of a sample with high rates of cannabis use and careful assessment of associated psychiatric problems and adversities to look at the effects of 4 distinct, longitudinal, developmentally informed definitions of early cannabis use across the first 3 decades of life. The different definitions highlighted frequency and persistence of use, evidence of addiction, precocious use, and specific developmental profiles. All definitions were associated with poor adult outcomes, but some definitions were associated with poorer later functioning more consistently and more strongly than others. In particular, cumulative daily use and the “persistent” developmental subtype were associated with adult substance use/disorders and functional outcomes even after accounting for childhood psychiatric problems and adversities and stringent Bonferroni correction for multiple tests. Together, these findings suggest that the highest levels of chronic cannabis use (which occurs in ~4%–8% of the population) is associated with a broad range of poor outcomes that may derail a successful transition to adulthood, with potential long-term consequences for decades to come.

Prospective studies have reported that early cannabis use is associated with later crime, lower educational achievement, with selected milestones of an unsuccessful transition to adulthood, such as failure to form a stable partnership/family, and also with selected psychiatric disorders.^{5,6,8,9,12-14,16,23,38,39} These studies often began assessments in mid-adolescence only, measuring limited aspects of cannabis use. Accordingly,

questions have remained about which aspects of use are most damaging, especially when childhood covariates of both early cannabis use and adult outcomes were adjusted. The current prospective, longitudinal, long-term study added to the existing literature by (1) assessing the majority of participants prior to their initial cannabis exposure, (2) looking at a broad range of adult outcomes (eg, health, criminal, financial functioning), and (3) disentangling which aspects of early cannabis use are linked with long-term outcomes.

The central aim of this analysis was to examine different definitions of early cannabis use—in one study—in the effort to distill which aspects are most problematic for later well-being. Results revealed that daily use that continued over several years, as captured by cumulative daily use and the “persistent” subtype, was most problematic. Both of these definitions were associated with all adult substance outcomes, including illicit drug use, multiple functional outcome scale scores, and total number of derailments. The effect sizes of these associations were generally large, even after accounting for childhood psychiatric problems and adversities. The associations with adult psychiatric health, in contrast, were all attenuated to non-significance after adjustment for childhood covariates.

In contrast, definitions that relied upon either *DSM* cannabis use disorder only, very early cannabis use, or highly frequent use for a limited period of time were not associated with the same breadth of adult outcomes. Our findings support a simple hypothesis that cannabis outcomes are strongly associated with lifetime cannabis dose, and provides less support for hypotheses that the effects of cannabis are developmentally sensitive or due to a particular pattern of addictive symptomatology. Our differences in findings for different early use definitions (and between adjusted and unadjusted models) also provide a potential explanation for the heterogeneity in findings of studies on early cannabis use.

Notably, some definitions showed modest associations with adult outcomes (as opposed to the large associations for persistent users) included individuals who used cannabis frequently (ie, daily in the early use only, adolescence-limited, and adult-onset groups), even if only for a limited amount of time. Thus, cessation of daily use improves the overall future outlook, but any period of daily use is associated with some elevated risks in adulthood.¹³ Indeed, even adult-onset daily use was associated with several problematic outcomes, including poor health and financial problems. Thus, simply delaying frequent cannabis use until adulthood does not shield individuals from all deleterious effects.

This study does have several limitations. The Great Smoky Mountains study is not representative of the US population. Some adverse physical health outcomes of early cannabis use may not be evident until later in life. Also, inferences about causal effects cannot be made, as

unmeasured factors (eg, genetic variants) may account for observed associations.^{40,41} Cannabis use was illegal in North Carolina for the duration of this study, and thus results may or may not generalize to areas in which use is legal. Even in states where use is legal, use is still prohibited under the age of 21 years. Finally, the study applied a strict Bonferroni correction based on the number of outcomes, but some individual results could be due to chance.

Our study adds to a growing consensus that gives pause to arguments that early cannabis use is benign or trivial. The most robust signal for adverse functioning and impairment for years to come was from daily, persistent cannabis use, rather than a *DSM* diagnosis, any early frequent use, or time-limited frequent use. The challenge for policy makers is that it is still not possible *a priori* to predict, with the necessary precision, which cannabis-naïve children or adolescents with low levels of use will transition to such problematic, persistent use.

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