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The persistence of the association between adolescent cannabis use and common mental disorders into young adulthood

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ABSTRACT

Aims Debate continues about whether the association between cannabis use in adolescence and common mental disorders is causal. Most reports have focused on associations in adolescence, with few studies extending into adulthood. We examine the association from adolescence until the age of 29 years in a representative prospective cohort of young Australians. **Design** Nine-wave, 15-year representative longitudinal cohort study, with six waves of data collection in adolescence (mean age 14.9–17.4 years) and three in young adulthood (mean age 20.7, 24.1 and 29.1 years). **Participants** Participants were a cohort of 1943 recruited in secondary school and surveyed at each wave when possible from mid-teen age to their late 20s. **Setting** Victoria, Australia. **Measurements** Psychiatric morbidity was assessed with the Revised Clinical Interview Schedule (CIS-R) at each adolescent wave, and as Composite International Diagnostic Interview (CIDI)-defined ICD-10 major depressive episode and anxiety disorder at 29 years. Frequency of cannabis use was measured in the past 6 months in adolescence. Cannabis use frequency in the last year and DSM-IV cannabis dependence were assessed at 29 years. Cross-sectional and prospective associations of these outcomes with cannabis use and dependence were estimated as odds ratios (OR), using multivariable logistic regression models, with the outcomes of interest, major depressive episode (MDE) and anxiety disorder (AD) at 29 years. **Findings** There were no consistent associations between adolescent cannabis use and depression at age 29 years. Daily cannabis use was associated with anxiety disorder at 29 years [adjusted OR 2.5, 95% confidence interval (CI):< 1.2–5.2], as was cannabis dependence (adjusted OR 2.2, 95% CI: 1.1–4.4). Among weekly+ adolescent cannabis users, those who continued to use cannabis use daily at 29 years remained at significantly increased odds of anxiety disorder (adjusted OR 3.2, 95% CI: 1.1–9.2). **Conclusions** Regular (particularly daily) adolescent cannabis use is associated consistently with anxiety, but not depressive disorder, in adolescence and late young adulthood, even among regular users who then cease using the drug. It is possible that early cannabis exposure causes enduring mental health risks in the general cannabis-using adolescent population.

Keywords Anxiety, cannabis, cohort, depression, epidemiology, psychiatry.

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INTRODUCTION

The extent and nature of the association between cannabis use and the more common mental health problems, namely anxiety and depression, has attracted much recent attention [1–7]. An earlier review [8] concluded that there was an association particularly among early-onset regular cannabis users, but that further prospective population-based studies were needed to carefully evaluate the strength of associations; consider potential mechanisms underlying these associations; and extend the age range of follow-up because most studies

measured only adolescent mental health outcomes. Some [3,5,7], but not all, of the recent work [2] has reported positive associations between cannabis use in adolescence and depressive symptoms or episodes in very early adulthood. Very few have extended follow-up to later ages [4]. Some suggest that there may be stronger positive associations between cannabis use and depression in females [3,9] and in early adulthood [5,6].

The links between cannabis use and anxiety disorders are less clear [10]. Cross-sectional studies have often found elevated rates of anxiety disorders among cannabis users, but these associations have not always persisted after controlling for confounding variables [10]. Prospective studies have reported similarly inconsistent findings [11], with some finding an association that persisted after control for confounders [5] and others have not [4,12].

There are good reasons to assess potential consequences of adolescent cannabis use into adulthood. It is possible that adolescent cannabis use may have longer-term effects on brain neurotransmitter systems [13], which may cause psychotic symptoms [14] and perhaps depressive and anxiety symptoms [13,15, 16]. Adolescence is also an important time for the achievement of many developmental milestones: educational, personal, social and occupational. The use of cannabis and other drugs may adversely affect functioning across these domains in ways that impair later mental health.

In this study, we extend an earlier examination of the association between adolescent cannabis use and mental health at the age of 21–22 years [9] in a representative cohort of young Australians until the age of 29 years. We addressed the following questions:

1 Is cannabis use in adolescence associated with depression or anxiety disorders at 29 years?
2 To what extent can any such associations be accounted for by potential confounding variables?
3 What impact does the pattern of cannabis use between adolescence and young adulthood have on the risk of depression and anxiety disorders at 29 years?

METHODS

Sample

Between August 1992 and January 2008 we conducted a nine-wave cohort study of health in adolescents and young adults resident in the state of Victoria, Australia. Data collection protocols were approved by The Royal Children's Hospital's Ethics in Human Research Committee. The cohort was designed to be representative of the Victorian population of mid-secondary-school adolescents in 1992. It was defined by two-stage cluster sampling, with two classes selected at random in each of a state-wide sample of 44 schools, which were selected at random using a state-wide stratified frame of government, Catholic and independent private schools, with probability of selection proportional to the number of students. One class entered the study in the latter part of the ninth school year (wave 1) and the second class 6 months later (wave 2). School retention rates to year 9 in the year of sampling were 98%. Participants were subsequently reviewed at a further four 6-month intervals during the teens (waves–6) with three follow-up waves in young adulthood aged 20–21 years (wave 7), 24–25 years (wave 8) and 28–29 years (wave 9). In waves 1–6, participants self-administered the questionnaire on laptop computers, with telephone follow-up of those absent from school. Waves 7–9 were undertaken using computer-assisted telephone interviews [17].

From a total sample of 2032 students, 1943 (95.6%) participated at least once during the first six (adolescent) waves (Fig. 1). Waves 7–9 were undertaken using computer-assisted telephone interviews [17], with 1756 (53% female) participating in at least one of these waves and known to be alive at the time of the wave 9 survey. Of these, 1282 completed all three young adult waves, 293 completed two and 181 completed one only. Wave 9 interviews were completed by January 2008, at which time 15 cohort members were known to have died, 108 were lost to follow-up and 319 refused to participate. In wave 9, 1501 participants were interviewed between May 2006 and January 2008, 1407 of whom completed the full

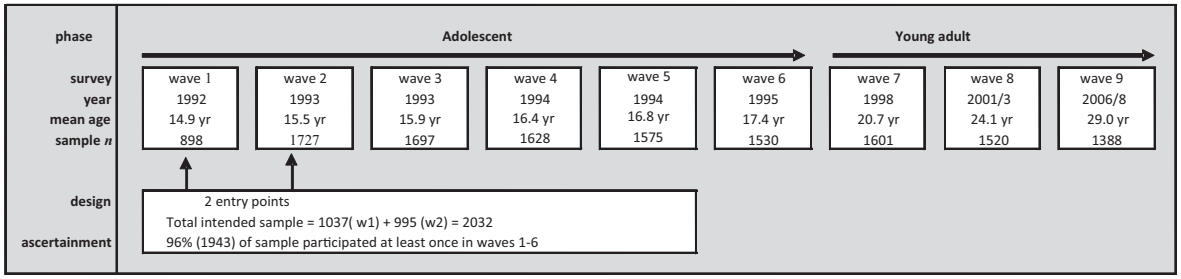

Figure 1 Sampling and ascertainment in the Victorian Adolescent Health Cohort, 1992–2008

(1383) or part (24) interview schedule and 94 completed a reduced hard-copy subset of the questions, without the Composite International Diagnostic Interview (CIDI). The strategy of administering a hard-copy subset of questions was pursued with people who would otherwise not have been surveyed.

Analysis measures

Adolescent symptoms of depression and anxiety were assessed at each adolescent wave using the revised Clinical Interview Schedule (CIS-R). The CIS-R is a branched psychiatric interview designed to assess symptoms of depression and anxiety in non-clinical populations [18,19]. Its 14 subscales delineate the frequency, severity, persistence and intrusiveness of common symptoms and their addition result in a possible total of 55 points. The total scores on the CIS-R were dichotomized so that scores greater than 11 delineated a mixed depression–anxiety state. This was at a lower threshold than syndromes of major depression and anxiety disorder, but at a level where clinical intervention would be considered appropriate [19–21]. Adolescent exposure was assessed by identifying participants who had scored at this level in any adolescent wave (waves 2–6)—this was termed 'clinically significant anxiety/depression'.

Major depressive episode (MDE) was defined according to ICD-10 [22] and was measured at 29 years using the Composite International Diagnostic Interview (CIDI)–Auto.

Anxiety disorder (AD) was defined according to ICD-10 and was measured at 29 years using the CIDI–Short Form [23]. Participants were classified with anxiety disorder if they were diagnosed with any of: generalized anxiety disorder; social phobia disorder; agoraphobia; or panic disorder. Specific phobic disorders were not measured.

Adolescent cannabis use (to wave 6) was assessed using self-reported frequency of use in the previous 6 months, categorized as: never, less than weekly (occasional), weekly and daily. We classified participants according to their maximum frequency of use during the adolescent phase: non-users, occasional users and weekly+ users (weekly or daily).

Young adult cannabis use. Participants in the young adult phase (waves 7–9) were asked to report their maximum cannabis use in the past year. At each wave, we identified participants who were non-users, using cannabis less than weekly (occasional), weekly or more often (daily).

Young adult cannabis dependence

We administered the computerized CIDI (2.1, 12-month version) at all young adult waves to generate the DSM-IV criteria for a diagnosis of cannabis dependence in participants reporting at least weekly cannabis use in the past 12 months. We applied this filter to minimize responder fatigue because we considered that a diagnosis of cannabis dependence required regular cannabis use, given the DSM-IV description of substance dependence as occurring with a 'pattern of repeated (substance) self-administration' [24]. People with three or more criteria were considered to have DSM-IV cannabis dependence.

Cannabis use from adolescence to young adulthood. We constructed a variable to describe the continuity of cannabis use from adolescence to wave 9. Maximum adolescent cannabis use was reduced to the dichotomous variable none/occasional and weekly/daily and then stratified by wave 9 cannabis use measured on three levels: none, occasional/weekly and daily, resulting in a six-level variable.

Background measures included: the participant's sex; neither parent having completed secondary education (yes/no); school location at study inception (non-metropolitan/metropolitan location); and parental divorce/separation by wave 6 (yes/no).

Other substance use. Alcohol consumption in each wave was calculated from a retrospective alcohol diary (beverage- and quantity-specific) in which participants reported alcohol use in the previous week. High-risk alcohol use was defined as 15 or more standard drinks (one standard drink = 10 g alcohol) in the previous week. For each of the young adult waves we identified any illicit drug use as any reported use of ecstasy, cocaine or amphetamines in the past year.

Auxiliary variables

Additional measures believed to be associated with incomplete participation (missing data) were included in an imputation model as auxiliary variables (see Analysis section). These included further background details of the subject's age; level of education (completed secondary education/did not complete); nationality (Australian/non-Australian born); parental smoking status (yes/no); tobacco use (non-smoker, occasional, daily) at each wave and symptoms of depression and anxiety (yes/no) at waves 7, 8 and 9 (CIS-R at wave 7 and the General Health Questionnaire (GHQ-12) [25] at waves 8 and 9). In wave 9 the participant's maximum qualification achieved (secondary education, vocational qualification, degree) and a selection of dichotomous variables with yes/no responses: ever had a baby; currently partnered/married; receiving government welfare; in paid employment.

Analysis

The outcomes of interest in each analysis were MDE and AD measured at wave 9. Cross-sectional and prospective associations of these outcomes with cannabis use and dependence were estimated as odds ratios (OR) [with 95% confidence intervals (CI)], using multivariable logistic regression models. All models were (a) adjusted for background factors, then (b) for these plus alcohol use and, for waves 7–9, other illicit drug use measured concurrently with the cannabis exposure, and finally (c) for all the above plus any adolescent symptoms of anxiety/depression. The increasing levels of cannabis use were entered into the logistic regression models as dummy variables with 'no use' as the baseline category. The Wald test was used to assess the joint null hypothesis of no cannabis effects. Potential modification of cannabis use and dependence effects by sex were also assessed in each model using a Wald test for interaction, with $P < 0.1$ as a threshold for inclusion in the model.

Data collection was undertaken at a developmental point when young people are difficult to trace because of high mobility. There was very low missingness on individual measures, but including individuals who missed waves creates bias in summary measures calculated from these data. To address this, we used the method of multiple imputation [26]. We imputed 20 complete data sets, separately for males and females, under a multivariate normal model in STATA version 11 [27], incorporating all analysis and auxiliary variables. CIS anxiety and depression scores (waves 2–7) and units of alcohol (waves 7–9) were imputed after Box–Cox transformations. Cannabis use, smoking, wave 9 illicit drug use and level of education variables were log-transformed before imputation. Depression and anxiety measures at waves 8 and 9, risky drinking at waves 2–6, illicit drug use at waves 7 and 8, cannabis dependence and dichotomous background measures were imputed as binary variables. Maximum level of parental education and age were imputed as normal variables. After imputation, transformed variables were converted back to their original scale and all were categorized for analysis, with adaptive rounding used for binary measures [28].

Wave 1 was omitted, as it contained observations from only 46% of the cohort, and 182 participants with no adult-phase observations were omitted as they contained too little information. Forty-one participants had responded at one or more adult waves but had only a single adolescent observation in wave 1. When using summarized adolescent measures, we considered it was a reasonable strategy to include these individuals by bringing forward their wave 1 observations to wave 2. Thus the imputation analysis data set was defined by adult phase (waves 7–9) participation ($n = 1761$, 53% female).

Although there was little missingness on individual measures for each survey completed, we used multiple imputation to address potential bias and loss of information arising from respondents' missing waves [26]. Of the 59 outcome, background and auxiliary variables included in the multiple imputation model, four variables were completely observed in the imputation analysis data set, 12 had <10% missing, 32 had 10–<20% missing and 11 had more than 20% missing. No variable was missing for more than 25% of participants. After imputation, a further five participants who had died by wave 9 were excluded from the analysis ($n = 1756$).

All frequencies and odds ratios were obtained by averaging results across 20 imputed data sets with inferences under multiple imputation obtained using Rubin's rules [26]. Data analysis was undertaken using STATA version 11 [27].

RESULTS

The analysis data set consisted of 1756 participants, of whom 931 (53%) were female, 457 (26%) and were attending a school outside the Melbourne metropolitan area at study inception; for 579 (33%) neither parents had completed their education, and 387 (22%) had parents who were divorced or separated by the completions of the participant's schooling, or equivalent age.

At 29 years, there was little association between frequency of concurrent cannabis use and the occurrence of MDE in all adjusted models (Table 1). There was some evidence that cannabis dependence approximately doubled the odds of MDE compared with no cannabis use, after adjusting for background factors and concurrent alcohol use. There was no evidence of effect modification by sex in any of the models (all interactions $P > 0.5$).

Cannabis use and dependence were associated concurrently with an elevated risk of AD. After adjusting for background factors, we found the following pattern of risk associated with cannabis use: daily cannabis users were at 2.3 times the odds (95% CI: 1.1–4.5) of meeting criteria for AD compared to non-users, while weekly users and occasional users were similarly at risk. Those who were cannabis-dependent were at 2.5 times elevated odds (1.3–4.8) compared to those who were not dependent. These effects remained after controlling for other concurrent drug use and adolescent anxiety/depression.

Table 2 shows the levels of cannabis use in adolescence and at waves 7 and 8, as well as the results of analyses examining potential *predictive* associations between cannabis use and dependence during earlier waves and MDE and AD at age 29 years (Table 2). There was little convincing evidence of an association between MDE at age 29 years and earlier cannabis use. In contrast to MDE, there was some evidence of a predictive

Table 1 Cross-sectional association of diagnosis of major depressive episode and anxiety disorder at mean age 29 years with cannabis use in 1756 cohort participants.[a]

Cannabis measure at 29 years			*Major depressive episode at 29 years n = 183*						*Anxiety disorder at 29 years n = 199*					
			Adjusted for background factors		*Further adjusted for concurrent alcohol and other illicit substance use*		*Further adjusted for any adolescent anxiety/ depression (CIS-R > 11)*		*Adjusted for background factors*		*Further adjusted for concurrent alcohol and other illicit substance use*		*Further adjusted for any adolescent anxiety/ depression (CIS-R > 11)*	
		n	*OR*[b]	*(95% CI)*	*OR*[c]	*(95% CI)*	*OR*[d]	*(95% CI)*	*OR*	*(95% CI)*	*OR*	*(95% CI)*	*OR*	*(95% CI)*
Frequency	No use	1270	1		1		1		1		1		1	
	Occasional	294	1.2	(0.72–1.9)	1.2	(0.71–2.0)	1.2	(0.68–2.0)	1.6	(1.0–2.5)	1.8	(1.1–2.9)	1.7	(1.0–2.9)
	Weekly	72	1.2	(0.43–3.3)	1.2	(0.42–3.5)	1.2	(0.40–3.4)	1.7	(0.76–3.8)	1.9	(0.82–4.5)	1.8	(0.78–4.3)
	Daily	119	1.9	(0.80–4.4)	1.9	(0.76–4.7)	1.9	(0.74–4.6)	2.3	(1.1–4.5)	2.5	(1.2–5.1)	2.5	(1.2–5.2)
P-value[e]			0.37		0.45		0.48		0.02		0.02		0.03	
Dependence	No dependence	1684	1		1		1		1		1		1	
	Dependence	72	2.1	(1.0–4.6)	2.1	(0.95–4.5)	1.9	(0.87–4.3)	2.5	(1.3–4.8)	2.4	(1.2–4.8)	2.2	(1.1–4.4)
P-value[e]			0.05		0.07		0.11		0.008		0.01		0.02	

[a]All estimates obtained by averaging across 20 imputed data sets. [b]Odds ratios (OR) from multivariable logistic regression models adjusted for background factors: sex, non-metropolitan school location, low parental education, parental divorce/separation by wave 6. [c]Odds ratios from multivariable logistic regression models adjusted for background factors, high-risk alcohol use in the past week and other illicit substance use: any of amphetamine, cocaine or ecstasy use in the past 12 months. [d]OR from multivariable logistic regression models adjusted for background factors, other concurrent substance use and clinically significant depression/anxiety in adolescence (waves 2–6). [e]Wald *P*-values for joint test of cannabis use or cannabis dependence. CI: confidence interval.

Table 2 Prospective associations of cannabis use at 17, 20 and 24 years with major depressive episode or anxiety disorder identified at mean age 29 years in 1756 cohort participants.[a]

				Major depressive episode at 29 years (wave 9) n = 183						*Anxiety disorder at 29 years (wave 9) n = 199*					
				Adjusted for background factors		*Further adjusted for concurrent alcohol and other illicit substance use*		*Further adjusted for any adolescent anxiety/ depression (CIS-R > 11)*		*Adjusted for background factors*		*Further adjusted for concurrent alcohol and other illicit substance use*		*Further adjusted for any adolescent anxiety/ depression (CIS-R > 11)*	
Wave	*Cannabis use measures*		*n (%)*	*OR*[b]	*(95% CI)*	*OR*[c]	*(95% CI)*	*OR*[d]	*(95% CI)*	*OR*	*(95% CI)*	*OR*	*(95% CI)*	*OR*	*(95% CI)*
Maximum adolescent use (waves 2–6)															
	Frequency	No use	1142 (65.0)	1		1		1		1		1		1	
		Occasional	403 (23.0)	0.87	(0.53–1.4)	0.92	(0.56–1.5)	0.81	(0.49–1.3)	1.2	(0.82–1.8)	1.3	(0.87–1.9)	1.2	(0.77–1.8)
		Weekly+	211 (12.0)	1.2	(0.73–2.0)	1.3	(0.76–2.4)	1.1	(0.60–1.9)	1.5	(0.95–2.5)	1.8	(1.1–3.1)	1.4	(0.84–2.5)
	P-value[e]			0.60		0.50		0.63		0.18		0.07		0.39	
20 years (wave 7)															
	Frequency	No use	730 (41.6)	1		1		1		1		1		1	
		Occasional	775 (44.1)	1.1	(0.74–1.6)	1.1	(0.72–1.6)	0.97	(0.65–1.5)	1.4	(0.92–2.0)	1.3	(0.89–2.0)	1.2	(0.81–1.8)
		Weekly	127 (7.3)	0.91	(0.38–2.2)	0.88	(0.35–2.2)	0.82	(0.32–2.1)	1.1	(0.49–2.4)	0.93	(0.39–2.2)	0.87	(0.36–2.1)
		Daily	124 (7.1)	1.1	(0.53–2.5)	1.1	(0.46–2.7)	0.97	(0.39–2.4)	1.7	(0.87–3.5)	1.4	(0.65–3.1)	1.2	(0.55–2.7)
	P-value[e]			0.95		0.95		0.98		0.29		0.45		0.72	
	Dependence	No dependence	1619 (92.2)	1		1		1		1		1		1	
		Dependence	137 (7.8)	1.0	(0.49–2.2)	1.0	(0.45–2.3)	0.94	(0.41–2.1)	1.4	(0.78–2.7)	1.2	(0.61–2.4)	1.1	(0.55–2.2)
	P-value[e]			0.92		0.95		0.88		0.25		0.59		0.79	
24 years (wave 8)															
	Frequency	No use	1157 (65.9)	1		1		1		1		1		1	
		Occasional	383 (21.8)	1.3	(0.84–1.9)	1.4	(0.93–2.2)	1.5	(0.94–2.3)	1.7	(1.1–2.5)	2.0	(1.3–3.1)	2.0	(1.3–3.1)
		Weekly	114 (6.5)	1.0	(0.44–2.3)	1.3	(0.55–3.1)	1.2	(0.50–2.9)	1.1	(0.48–2.5)	1.5	(0.66–3.6)	1.4	(0.59–3.3)
		Daily	102 (5.8)	1.5	(0.73–3.2)	1.9	(0.85–4.3)	1.6	(0.72–3.7)	2.0	(1.1–3.9)	2.7	(1.3–5.6)	2.3	(1.1–4.9)
	P-value[e]			0.55		0.25		0.35		0.02		0.004		0.008	
	Dependence	No dependence	1642 (93.5)	1		1		1		1		1		1	
		Dependence	114 (6.5)	1.2	(0.56–2.5)	1.3	(0.60–2.9)	1.2	(0.53–2.6)	1.8	(0.97–3.3)	2.1	(1.1–4.0)	1.9	(0.94–3.6)
	P-value[e]			0.68		0.50		0.71		0.06		0.03		0.07	

[a]All estimates obtained by averaging across the imputed data sets. [b]Odds ratios (OR) from multivariable logistic regression models adjusted for background factors: sex, non-metropolitan school location, low parental education, parental divorce/separation by wave 6. [c]OR from multivariable logistic regression models adjusted for background factors and substance use concurrent with cannabis use exposure: high-risk alcohol use in the past week and other illicit substance use [any of amphetamine, cocaine or ecstasy use in the past year (not available for adolescent phase weeks 2–6 exposure)]. [d]OR from multivariable logistic regression models adjusted for background factors, other concurrent substance use and clinically significant depression/anxiety in adolescence (waves 2–6). [e]Wald *P*-values for joint test of cannabis use or cannabis dependence. CI: confidence interval.

association between AD and weekly+ cannabis use during adolescence (which reduced after adjustment for adolescent anxiety/depression). There was an association between daily cannabis use and also cannabis dependence at age 24 (the prior wave), compared with no cannabis use at the same age, and AD at age 29 years. There was no evidence of effect modification by sex in any predictive model for either outcome (all interaction *P*-values >0.17).

Table 3 shows the association between cannabis use patterns across adolescence and young adulthood with MDE and AD at age 29. Compared to the lowest risk category (none or <weekly cannabis use in adolescence and no concurrent use) there was little evidence of increased risk for MDE at 29 years for those who discontinued adolescent use or whose use continued into young adulthood. There was also some weak indication of an elevated risk in both categories that included young adult daily users, which is consistent with the results shown in Table 1.

Similarly, consistent with Table 1, the two groups with concurrent daily cannabis use clearly had a higher risk of AD at 29 years than those in the lowest risk category. Weekly+ adolescent uses who did not report cannabis use at 29 years still had an approximately twofold elevated risk for AD, compared with the lowest risk category. This association was marginally significant after adjustment for psychiatric morbidity during the teens. There was no evidence of effect modification by sex (interaction *P*-value = 0.96 for both models).

DISCUSSION

We have described patterns of cannabis use and their changing associations—both cross-sectional and longitudinal—with mental health problems during almost 15 years of follow-up of this cohort. There was no strong evidence of an association between adolescent cannabis use and MDE at age 29, with or without adjustment for potential confounders. Heavier adolescent cannabis use was associated more consistently with a roughly twofold higher risk of anxiety disorder at 29 years, particularly if cannabis use continued at 29 years. It seemed clearest that early regular cannabis use in adolescence increased risk of anxiety disorder at age 29 years, with slightly higher risks if regular use also occurred at 29 years. A similar level of risk was found at 29 years for people who had not used cannabis regularly (weekly+) in adolescence but who used cannabis at age 29 years. There also appeared to be an increased risk of anxiety disorders at age 29 among adolescent cannabis users, even if they ceased using cannabis in adulthood.

Multiple potential confounders were considered, and the associations for anxiety disorders remained. It is still possible that other confounding variables may explain the observed associations. It is possible, for example, that continued and/or escalating cannabis use is a marker for other life-course features that are also associated with an increased risk of anxiety, such as impaired social role transitions and unemployment [29].

Our findings suggest that the association that has been reported between cannabis use and anxiety in other studies in young adults may arise because the same factors that predispose people to use cannabis also increase their risks for common mental disorders [30–32]. These common factors might include biological, personality, social and environmental factors, or a combination of these factors. This is a plausible hypothesis because social disadvantage is more common among people who are problematic substance users [33] and who meet criteria for common mental disorders [34–36]. There are also higher rates of separation and divorce, and lower rates of being married or in a *de-facto* relationship among people with mental and substance use disorders [34–37]. Other factors that have been associated with both cannabis use disorders and common mental disorders include parental psychiatric illness and family dysfunction [38–41].

It is also possible that the association between cannabis use and anxiety disorders may be causal that was biologically or socially mediated in some way. For example, recent reviews have suggested that there may be specific points during the life-span—in particular, during adolescence (puberty)—when changes in endocannabinoid activity (caused by Δ^9-tetrahydrocannabinol) might have more long-lasting effects on brain functions and behaviour that persist into adulthood [13,14,16]. One possible mechanism could be through changes in hypothalamic–pituitary–adrenal (HPA) axis function: cannabinoid agonists have biphasic effects upon HPA axis activity in animal studies [42]. Furthermore, young people with lower HPA activity (as measured by cortisol levels at waking) were found in one study to have earlier-onset cannabis use, leading the authors to suggest that lower HPA activity may increase sensation seeking to increase stimulation [43]. It could also be that regular cannabis use during adolescence and in young adulthood is one marker of developmental trajectories (including educational and social) that place young people at greater risk of mental health problems. These possibilities would be consistent with the increasing evidence that the associations observed between cannabis use and both anxiety and depression are strongest when cannabis use begins during adolescence.

Limitations

The cross-sectional association between cannabis use and depression/anxiety symptoms in adolescence

Table 3 Associations of continuity between maximum adolescent use and cannabis use at mean age 29 years with major depressive episode and anxiety disorder identified in 1756 cohort participants.[a]

Continuity in cannabis use from adolescence to 29 years			*Major depressive episode at 29 years (wave 9) n = 183*						*Anxiety disorder at 29 years (wave 9) n = 199*					
Maximum adolescent use (waves 2–6)	*Use at 29 years (wave 9)*	*n*	*Adjusted for background factors*		*Further adjusted for concurrent alcohol and other illicit substance use at 29 years*		*Further adjusted for any adolescent anxiety/depression (CIS-R > 11)*		*Adjusted for background factors*		*Further adjusted for concurrent alcohol and other illicit substance use at 29 years*		*Further adjusted for any adolescent anxiety/depression (CIS-R > 11)*	
			OR[b]	*(95% CI)*	*OR*[c]	*(95% CI)*	*OR*[d]	*(95% CI)*	*OR*	*(95% CI)*	*OR*	*(95% CI)*	*OR*	*(95% CI)*
None, <weekly	None	1173	1		1		1		1		1		1	
Weekly+	None	97	1.2	(0.54–2.5)	1.2	(0.56–2.7)	1.0	(0.48–2.3)	2.0	(1.1–3.7)	2.2	(1.1–4.2)	1.8	(0.96–3.5)
None, <weekly	Occasional–weekly	288	1.1	(0.64–1.8)	1.1	(0.64–2.0)	1.1	(0.61–1.9)	1.8	(1.2–2.8)	2.1	(1.3–3.3)	2.0	(1.2–3.3)
Weekly+	Occasional–weekly	79	1.7	(0.77–3.6)	1.7	(0.74–4.0)	1.5	(0.65–3.6)	1.4	(0.60–3.5)	1.7	(0.67–4.2)	1.5	(0.58–3.7)
None, <weekly	Daily	85	2.0	(0.65–5.9)	2.0	(0.63–6.1)	2.0	(0.63–6.3)	2.2	(0.91–5.2)	2.4	(0.98–5.8)	2.5	(1.0–6.1)
Weekly+	Daily	35	1.7	(0.56–5.4)	1.9	(0.57–6.1)	1.6	(0.47–5.2)	3.1	(1.2–8.3)	3.8	(1.3–11)	3.2	(1.1–9.2)

[a]All estimates obtained by averaging across the imputed data sets. [b]Odds ratios (OR) from multivariable logistic regression models adjusted for background factors: sex, non-metropolitan school location, low parental education, parental divorce/separation by wave 6. [c]OR from multivariable logistic regression models adjusted for background factors and, at 29 years, substance use: high-risk alcohol use in the past week and other illicit substance use (any of amphetamine, cocaine or ecstasy use in the past year). [d]OR from multivariable logistic regression models adjusted for background factors, other concurrent substance use and clinically significant depression/anxiety in adolescence (waves 2–6). CI: confidence interval.

weakened during adulthood, with cross-sectional associations observed at some assessment periods and not others. In part, this may have reflected the slightly different assessment approaches used in some waves of assessment, where scales were used that assessed symptoms of both.

Our capacity to see consistent associations with depression may be affected by the limited precision of estimates of the associations, as cannabis prevalence decreased sharply across young adulthood. The overall trend was for cannabis use to decrease over young adulthood, whereas the pattern of use associated most clearly with anxiety disorders was either the maintenance or increasingly frequent use of cannabis in young adulthood. Furthermore, there is the possibility that unmeasured confounders may have explained the associations observed here. Future research needs to consider this possibility in other cohorts across similar ages to examine whether this occurs in other groups. Pooling of cohorts might improve capacity to examine these associations across age periods when cannabis use becomes less prevalent.

CONCLUSIONS

Regular use of cannabis in adolescence was not associated consistently with depressive disorders in late young adulthood (age 29 years) but was associated more consistently with anxiety disorders, even after statistical adjustment for potential confounders. A suggestive trend for higher rates of anxiety disorders later in adulthood in heavier teen users who ceased use in young adulthood raises the possibility that early cannabis use produces an enduring increase in the risks of mental disorders. Further work is required to replicate this finding and clarify whether there is a causal relationship between early heavy cannabis use and anxiety disorders, or whether this association is better explained by residual confounding by social context or temperament.

Declarations of interest

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