

The impact of adolescent cannabis use, mood disorder and lack of education on attempted suicide in young adulthood

Suicide is one of the leading causes of death worldwide among young people. One of the strongest predictors of completed suicide is a previous suicide attempt (1). Suicide attempts are more frequent among young people, and a suicide attempt may be a marker of a lasting trajectory of adverse mental and physical problems into middle adulthood (1,2). There is limited evidence for factors during the adolescent period and the period of transition to young adulthood that increase the risk of attempted suicide. We used a prospective cohort study design incorporating clinical interviews to determine what factors measured at ages 12-15 years are associated with attempted suicide reported at ages 19-24 years.

The methods for the baseline adolescent study have previously been described (3). Using a stratified random sampling technique, 743 students in eight mainstream schools were screened for psychopathology. Adolescents who scored above threshold on the screening instruments or who indicated the presence of significant suicidal ideation (N=140) were invited to attend for interview, along with a group of 174 controls matched for gender, school and school year. 84.3% adolescents from the "at risk" category and 54% of the control group attended for a semi-structured clinical interview, along with a parent or guardian. All 212 young people who were interviewed as young adolescents were invited to take part in a follow-up interview eight years later. Follow-up information was obtained on 168 participants (79% follow-up rate). There were no differences between responders and non-responders in age, gender, parental socio-economic status, "at-risk" status at baseline, or diagnosis of psychiatric disorder at baseline.

We collected exposure information at interview on: family and childhood risk factors (family history of psychiatric illness and experience of childhood trauma, i.e. physical/sexual abuse or witnessing domestic violence); adolescent risk factors (psychopathology, cannabis use and alcohol use); young adult risk factors (psychopathology, cannabis use, self-harm, education level and employment status). The outcome measure was lifetime suicide attempts at 19-24 years old.

Ten percent of participants had made a suicide attempt at some point in their lives up to age 19-24 years. The mean age of those attempting suicide was 20.6 years. Fifty-three percent of those who reported a suicide attempt were female. Hierarchical logistic regression models showed that adolescent mood disorder and adolescent cannabis use, young adult mood and anxiety disorders, and a low level of

education were the most strongly predictive factors for making a suicide attempt when the effects of family psychiatric history, childhood trauma, alcohol use and other psychopathology were taken into account.

Adolescent mood disorder and adolescent cannabis use both independently increased the odds of a suicide attempt 7-fold (OR=7.0, 95% CI: 1.4-34.3; OR=7.5, 95% CI: 1.2-43.8), while young adult mood and anxiety disorders both independently increased the odds of an attempt 11-fold (OR=11.7, 95% CI 1.8-73.9; OR=11.1, 95% CI: 21.0-57.9). Young adults with only secondary-level education had an 8-fold increase in the odds of a suicide attempt compared to those with third-level education (OR=8.0, 95% CI: 1.1-54.4).

There is evidence that substance use disorders in adulthood increase the risk of suicidal behaviours. Here we show that any use of cannabis in the early adolescent period is a strong independent predictor of attempted suicide in young adulthood. We know that significant brain maturation continues to occur during adolescence, particularly in limbic structures such as the hippocampus; and within the prefrontal cortex important processes such as synaptic pruning, myelination and programming of neurotrophic levels are occurring at this time (4). Regular cannabis use can lead to grey matter volume reduction in a range of brain areas, including the medial temporal cortex, the parahippocampal gyrus, the insula and orbitofrontal regions (5). There is evidence of a linear association between the age at onset of cannabis use and both white matter integrity and grey matter volume, suggesting that the earlier the onset of use, the greater the toxic effects on the brain (5,6). Neuroimaging studies of people who have attempted suicide show structural and functional brain changes that are in keeping with those found in cannabis users (7). It is possible that cannabis use in early adolescence, at a vulnerable time for neurodevelopment, leads to or exacerbates ongoing dysfunctional brain changes that prime young people for a maladaptive trajectory towards young adulthood. Those most at risk for attempted suicide may have experienced accumulating risk exposures throughout childhood and adolescence and in young adulthood may lack adequate problem solving skills, as possibly indexed here by low levels of education.

The increasing awareness among the mental health community that we need to focus on early clinical intervention to protect against the worst effects of emotional distress among our young people, both on a personal and

an economic level (8), can only be acted on when we can reliably identify which young people are most at risk. The available evidence suggests that the specialist treatment of psychiatric disorder in adolescence alone is insufficient for the prevention of future suicide attempts (9). We need a more tailored approach to youth mental health and a greater awareness of the different contingencies involved in the pathway to suicidal behaviours such as accumulating risk from adolescent cannabis use, adolescent mood disorders and a lack of education.

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Young adult sequelae of adolescent cannabis use: an integrative analysis

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Summary

Background Debate continues about the consequences of adolescent cannabis use. Existing data are limited in statistical power to examine rarer outcomes and less common, heavier patterns of cannabis use than those already investigated; furthermore, evidence has a piecemeal approach to reporting of young adult sequelae. We aimed to provide a broad picture of the psychosocial sequelae of adolescent cannabis use.

Methods We integrated participant-level data from three large, long-running longitudinal studies from Australia and New Zealand: the Australian Temperament Project, the Christchurch Health and Development Study, and the Victorian Adolescent Health Cohort Study. We investigated the association between the maximum frequency of cannabis use before age 17 years (never, less than monthly, monthly or more, weekly or more, or daily) and seven developmental outcomes assessed up to age 30 years (high-school completion, attainment of university degree, cannabis dependence, use of other illicit drugs, suicide attempt, depression, and welfare dependence). The number of participants varied by outcome (N=2537 to N=3765).

Findings We recorded clear and consistent associations and dose-response relations between the frequency of adolescent cannabis use and all adverse young adult outcomes. After covariate adjustment, compared with individuals who had never used cannabis, those who were daily users before age 17 years had clear reductions in the odds of high-school completion (adjusted odds ratio 0.37, 95% CI 0.20–0.66) and degree attainment (0.38, 0.22–0.66), and substantially increased odds of later cannabis dependence (17.95, 9.44–34.12), use of other illicit drugs (7.80, 4.46–13.63), and suicide attempt (6.83, 2.04–22.90).

Interpretation Adverse sequelae of adolescent cannabis use are wide ranging and extend into young adulthood. Prevention or delay of cannabis use in adolescence is likely to have broad health and social benefits. Efforts to reform cannabis legislation should be carefully assessed to ensure they reduce adolescent cannabis use and prevent potentially adverse developmental effects.

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Introduction

Marked shifts have taken place in attitudes to cannabis use.¹ Moves to decriminalise or legalise cannabis use in several US states and Latin American countries are a sign of such changes in public opinion.² These shifts have happened while debate continues about the long-term health and social sequelae of adolescent cannabis use.^{3,4} Additionally, in some countries adolescents are initiating cannabis use earlier than have those in previous years⁵ and more adolescents are using cannabis heavily.^{6–8} In England, 4% of 11–15 year olds are past-month cannabis users;⁷ about 7% of US high-school seniors are daily or near-daily cannabis users;⁸ and in Australia, less than 1% of 14–19 year olds use daily and 4% use weekly.⁶ This prevalence is particularly concerning because adolescence seems to be a vulnerable developmental period for the consequences of cannabis exposure,⁹ and evidence suggests that early use of cannabis is associated with increased risk of adverse developmental outcomes.^{10–14}

Persisting questions about the long-term effects of adolescent cannabis use have clouded debate.^{12,15,16} The

existing evidence has limitations, including limited statistical power to examine rarer outcomes and less common, more regular patterns of cannabis use than those already assessed; insufficient control for confounding; and a tendency to examine only one outcome or domain. As such, the picture of adolescent cannabis use and its putative health consequences is fractured. We address this issue through the integration of data from three large, long-running longitudinal studies from Australia and New Zealand: the Australian Temperament Project (ATP),¹⁷ the Christchurch Health and Development Study (CHDS),¹⁸ and the Victorian Adolescent Health Cohort Study (VAHCS).¹⁹

In this integrative meta-analysis, we examined the long-term sequelae of adolescent cannabis use on important domains of wellbeing during the transition to adulthood. Specifically, we aimed to develop similar measures of cannabis use and each outcome across all cohorts; examine the association between patterns of use before age 17 years and each outcome in combined data; and adjust the associations reported for a wide

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1: 286–93

See Comment page 249

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range of potential confounding factors drawn from similar domains across studies spanning individual, family, and peer characteristics and behaviours.

Methods

Design and participants

Integrative analyses were developed across the ATP, CHDS, and VAHCS (appendix). The analyses were based on data obtained over relevant assessments (appendix) between ages 13 and 30 years. We chose these cohorts because they had similar measures of cannabis use and outcomes that allowed effective harmonisation. We integrated participant-level data rather than using the more common meta-analytic approach of combining study-level estimates. This approach had at least three advantages: increased sample size and statistical precision,^{20,21} the opportunity to include a wide range of potential confounding factors, and the ability to provide a broad picture of the health and psychosocial consequences of adolescent cannabis use.

Measures and outcomes

Studies varied in measures used to assess cannabis use and outcomes, assessment period (eg, past month, past year), and timings of assessment. However, sufficient commonalities existed to enable integration of data^{22,23} and development of measures that were consistent across studies.^{22,23} We assessed seven outcomes in young people aged between 17 and 30 years, spanning educational attainment, substance use, mental health, and welfare dependence. The number of participants varied by outcome (from 2537 to 3765 participants). We chose the outcomes on the basis of previous research that established a link between a given outcome and cannabis use, and the availability of similar outcome measures across the cohorts. Derivation of the harmonised variables is summarised below, with additional information in the appendix. All dichotomous variables were coded as 0 for no and 1 for yes.

All studies included measures of frequency of cannabis use during mid-adolescence (appendix). We created a five-level measure of the maximum frequency of cannabis use before age 17 years (with 0 as never, 1 as less than monthly, 2 as monthly or more, 3 as weekly or more, and 4 as daily).

All studies obtained data for the completion of high school and university degree attainment. We created a dichotomous measure of high-school completion, and university degree attainment, both by age 25 years.

All studies included a measure of symptoms of cannabis dependence in the past 12 months. The CHDS and VAHCS assessed cannabis dependence with the Composite International Diagnostic Interview. The ATP obtained data for the frequency of five symptoms of cannabis dependence. We created a dichotomous measure of cannabis dependence in the past 12 months between ages 17 and 25 years.

All studies obtained data about use of other illicit drugs in the past month or past year from several categories: inhalants, hallucinogens, ecstasy, amphetamines, methamphetamines, heroin, cocaine, and non-medical use of prescription drugs. We created a dichotomous measure for use of other illicit drugs in the past month to the past year by ages 23–25 years.

The CHDS assessed number of suicide attempts at yearly intervals from ages 17 to 25 years. The VAHCS used the Beck Self-harm Inventory at seven assessment times between ages 16 and 29 years (on average). On the basis of specific items, participants who reported self-harm with a serious intention to end life (eg, suicide attempt) were categorised. We created a dichotomous measure of any suicide attempt made between ages 17 and 25 years for the CHDS and VAHCS. The ATP did not assess suicidal behaviour.

The studies all used different measures to assess depression, and completed assessments at different ages. The CHDS used the Composite International Diagnostic Interview, the VAHCS used the Clinical Interview Schedule, and the ATP used the depression subscale from the short-form Depression Anxiety Stress Scale. We created a dichotomous measure of moderate or severe depression in the past week to the past month between ages 17 and 25 years.

The studies obtained data about present main source of income, including various categories of government support. Because patterns of income are not typically established until the late 20s,²⁴ we used data from the ATP at ages 27–28 years, data from the VAHCS at age 29 years, and data from the CHDS at age 30 years. We created a dichotomous measure of present welfare dependence (excluding education-related government support) at ages 27–30 years.

We noted small between-study variations in the prevalence of adolescent cannabis use and some outcomes (appendix) that might be expected to be present in cohorts obtained from regions of similar cultural and sociodemographic backgrounds.

We selected potential confounding factors from each study on the basis of previous research suggesting that the variables might be correlated with both cannabis use and adverse psychosocial outcomes. These confounding factors spanned individual background and functioning, and parental and peer factors. Factors assessed antecedent to cannabis use were included when available. The appendix provides further information about potential confounding factors.

Statistical analysis

The analysis was based on an integrated dataset that combined participant-level data from the cohorts. The analysis was conducted in four stages. First, we estimated association between extent of adolescent cannabis use and each outcome with data from each study and from the combined dataset. This analysis examined associations

For more on the ATP see <http://www.aifs.gov.au/atp>

See Online for appendix

	Never	Less than monthly	Monthly or more	Weekly or more	Daily	p value*
High-school completion						
ATP	833/897 (93%)	89/100 (89%)	87/102 (85%)	24/35 (69%)	2/2 (100%)	<0.0001
CHDS	307/618 (50%)	106/276 (38%)	18/63 (29%)	11/82 (13%)	0/7	<0.0001
VAHCS	851/977 (87%)	229/282 (81%)	74/90 (82%)	85/108 (79%)	24/39 (62%)	<0.0001
Combined data	1991/2492 (80%)	424/658 (64%)	179/255 (70%)	120/225 (53%)	26/48 (54%)	<0.0001
Degree attainment						
ATP	359/734 (49%)	23/82 (28%)	22/74 (30%)	8/27 (30%)	0/3	<0.0001
CHDS	181/596 (30%)	57/257 (22%)	11/63 (18%)	5/74 (7%)	0/7	<0.0001
VAHCS	415/978 (42%)	89/283 (32%)	23/90 (26%)	13/108 (12%)	6/39 (15%)	<0.0001
Combined data	955/2308 (41%)	169/622 (27%)	56/227 (25%)	26/209 (12%)	6/49 (12%)	<0.0001
Cannabis dependence						
ATP	25/600 (4%)	4/64 (6%)	10/55 (18%)	11/22 (50%)	2/2 (100%)	<0.0001
CHDS	17/619 (3%)	25/276 (9%)	12/64 (19%)	42/82 (51%)	6/7 (86%)	<0.0001
VAHCS	33/912 (4%)	27/259 (10%)	17/83 (21%)	45/99 (46%)	15/33 (46%)	<0.0001
Combined data	75/2131 (4%)	56/599 (9%)	39/202 (19%)	98/203 (48%)	23/42 (55%)	<0.0001
Other illicit drug use						
ATP	88/738 (12%)	18/82 (22%)	17/75 (23%)	12/28 (43%)	1/3 (33%)	<0.0001
CHDS	80/596 (13%)	83/257 (32%)	29/63 (46%)	31/74 (42%)	5/7 (71%)	<0.0001
VAHCS	41/972 (4%)	26/282 (9%)	19/89 (21%)	31/107 (29%)	9/39 (23%)	<0.0001
Combined data	209/2306 (9%)	127/621 (21%)	65/227 (29%)	74/209 (35%)	15/49 (31%)	<0.0001
Suicide attempt†						
CHDS	26/619 (4%)	18/276 (7%)	6/64 (9%)	13/82 (16%)	1/7 (14%)	<0.001
VAHCS	3/972 (<1%)	1/282 (<1%)	4/90 (4%)	5/107 (5%)	1/38 (3%)	<0.001
Combined data	29/1591 (2%)	19/558 (3%)	10/154 (7%)	18/189 (10%)	2/45 (4%)	<0.001
Depression						
ATP	47/898 (5%)	4/98 (4%)	2/102 (2%)	2/34 (6%)	1/3 (33%)	0.661
CHDS	80/619 (13%)	48/276 (17%)	11/64 (17%)	20/82 (24%)	1/7 (14%)	0.006
VAHCS	94/1041 (9%)	25/288 (9%)	13/100 (13%)	10/114 (9%)	5/39 (13%)	0.437
Combined data	221/2558 (9%)	77/662 (12%)	26/266 (10%)	32/230 (14%)	7/49 (14%)	0.032
Welfare dependence‡						
ATP	26/735 (4%)	5/83 (6%)	2/75 (3%)	0/32	0/3	0.491
CHDS	41/581 (7%)	17/258 (7%)	4/61 (7%)	16/72 (22%)	3/7 (43%)	<0.0001
VAHCS	77/895 (9%)	19/259 (7%)	10/90 (11%)	9/93 (10%)	4/40 (10%)	0.578
Combined data	144/2211 (7%)	41/600 (7%)	16/226 (7%)	25/197 (13%)	7/50 (14%)	0.012

Data are n/N (%). ATP=Australian Temperament Project. CHDS=Christchurch Health and Development Study. VAHCS=Victorian Adolescent Health Cohort Study. *p value of the association between adolescent cannabis use and each outcome in each study, and in combined data adjusted for study-specific effects. †The ATP did not assess suicidal behaviour. ‡Assessed at age 28–30 years.

Table 1: Outcomes according to maximum frequency of cannabis use before age 17 years in each study and when data were combined

between the extent of adolescent cannabis use and each outcome with data from each study and from the combined dataset. We tested associations for significance by fitting logistic regression models to the data from each study and from the combined dataset in which the log odds of each outcome were modelled as a linear function of the five-level measure of frequency of cannabis use. The models for the combined data were of the form: $\text{logit}(Y_{ij}) = B_0j + B_1X_{ij}$ where $\text{logit}(Y_{ij})$ was the log odds of the outcome Y for individual i in study j (j=1, 2, 3), and X_{ij} was the corresponding frequency of cannabis use for individual i in study j. The slope parameter for cannabis use (B1) was assumed to be constant across studies. However, the model included study-specific random

intercepts (B_0j) to allow for random sources of between-study heterogeneity that were not otherwise represented in the model. We obtained effect-size estimates (odds ratios [ORs] and 95% CIs) for the combined data pooled over studies.

Second, we adjusted for covariates. To account for confounding factors, we extended the models in the first equation to include these factors. These models were of the form: $\text{logit}(Y_{ij}) = B_0j + B_1X_{ij} + \sum B_{kj}Z_{ikj}$ where Z_{kj} was a series of covariate factors representing the complete set of covariates across all studies j. Overall, we included 53 factors (appendix), but not all these covariates were measured by all studies. To address this inconsistency we developed a null covariate model. In this model if a

covariate was not noted for any study, we set this covariate to a value of zero for that study. The advantage of this approach is that it included all the available data in the analysis. The appendix provides further information about this approach. We obtained estimates of the pooled adjusted ORs and 95% CIs.

The above models assumed a linear effect of cannabis use on the log odds of each outcome, and a common slope parameter (B1) for the effect of cannabis use across studies. To test these assumptions, we extended the above adjusted models in two ways. We first did Wald χ^2 tests to examine the improvement in fit of a categorical representation of cannabis use over and above the linear model for each outcome. In all cases a linear model provided an adequate representation of the effect of cannabis use and no significant departures from linearity were detected. We then extended the models to allow the slope parameter for cannabis use (B1) to vary across studies, and then we did Wald χ^2 tests to test for between-study heterogeneity in the effect of cannabis use. In all cases these tests were non-significant, suggesting that the assumption of a common slope was justified for all outcomes.

For the third stage of the statistical analysis, we did a sensitivity analysis. Although the null covariate model offered the advantage of enabling analysis of all available data, this method could have introduced study-specific biases. To examine the robustness of the null covariate model, we compared results with four alternative estimates of the adjusted ORs, which we derived with a harmonised covariate approach using a reduced set of covariates common to all studies; a covariate score approach in which we used the covariate information in each study to derive an optimum predictor of each outcome, and the single predictor score as a covariate in the combined data; a propensity score approach in which we used the covariate data in each study to derive a prediction model for adolescent cannabis use, and included the estimated propensity score as a covariate for each study; and a standard meta-analytic approach in which covariate-adjusted analyses were done separately for each study, and the study-level result then pooled meta-analytically (appendix). Fourth, we investigated the potential for selection bias. We used multiple imputation to examine the implications of possible selection bias attributable to sample attrition and missing data (appendix).

We did all analyses with STATA SE (version 13).

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Table 1 shows the associations between frequency of cannabis use before age 17 and the outcomes in young adults in each study and in the combined dataset, and the

tests of significance from the fitted regression models for each outcome. At the individual study level, we recorded evidence of significant associations for all outcomes, except depression and welfare dependence in ATP and VAHCS (table 1). For the combined data, all associations were significant, with clear evidence of a dose-response association in which increasing frequency of adolescent cannabis use was associated with declining rates of high-school completion and degree attainment, and increasing risks of cannabis dependence, other illicit drug use, suicide attempt, depression, and welfare dependence. Table 2 and figure 1 show estimates of effect size for each level of cannabis use estimated from the regression model fitted to the combined data for each outcome.

We adjusted the associations in table 1 for confounding by adding the relevant covariates for each study with the null covariate adjustment approach. We included 53 covariate factors from the three studies in the analysis. These covariates spanned individual background and functioning, and measures of parental and peer factors (appendix). Table 2 and figure 2 show the adjusted ORs

	Never	Less than monthly	Monthly or more	Weekly or more	Daily	p value	N
Unadjusted odds ratios							
High-school completion	1	0.67 (0.62-0.73)	0.45 (0.38-0.54)	0.31 (0.24-0.39)	0.21 (0.15-0.29)	<0.0001	3678
Degree attainment	1	0.63 (0.57-0.69)	0.40 (0.33-0.48)	0.25 (0.19-0.33)	0.16 (0.11-0.23)	<0.0001	3415
Cannabis dependence	1	2.75 (2.48-3.06)	7.58 (6.14-9.36)	20.87 (15.20-28.64)	57.45 (37.66-87.64)	<0.0001	3177
Other illicit drug use	1	1.82 (1.66-1.99)	3.31 (2.77-3.94)	6.01 (4.61-7.83)	10.93 (7.68-15.55)	<0.0001	3412
Suicide attempt*	1	1.72 (1.43-2.06)	2.94 (2.04-4.24)	5.05 (2.92-8.74)	8.66 (4.17-18.01)	<0.0001	2537
Depression	1	1.12 (1.01-1.25)	1.26 (1.02-1.56)	1.42 (1.03-1.94)	1.59 (1.04-2.42)	0.032	3765
Welfare dependence†	1	1.17 (1.04-1.32)	1.37 (1.07-1.75)	1.61 (1.11-2.32)	1.88 (1.15-3.07)	0.012	3284
Adjusted odds ratios							
High-school completion	1	0.78 (0.67-0.90)	0.61 (0.45-0.81)	0.47 (0.30-0.73)	0.37 (0.20-0.66)	0.001	3004
Degree attainment	1	0.78 (0.69-0.90)	0.62 (0.47-0.81)	0.49 (0.32-0.73)	0.38 (0.22-0.66)	<0.0001	2834
Cannabis dependence	1	2.06 (1.75-2.42)	4.24 (3.07-5.84)	8.72 (5.39-14.12)	17.95 (9.44-34.12)	<0.0001	2675
Other illicit drug use	1	1.67 (1.45-1.92)	2.79 (2.11-3.69)	4.67 (3.07-7.10)	7.80 (4.46-13.63)	<0.0001	2832
Suicide attempt*	1	1.62 (1.19-2.19)	2.61 (1.43-4.79)	4.23 (1.71-10.47)	6.83 (2.04-22.90)	0.002	2192
Depression	1	1.01 (0.85-1.19)	1.01 (0.72-1.42)	1.02 (0.61-1.69)	1.02 (0.52-2.01)	0.946	2927
Welfare dependence†	1	1.04 (0.84-1.28)	1.08 (0.71-1.63)	1.12 (0.60-2.09)	1.16 (0.50-2.66)	0.727	2664

Data are odds ratios (95% CIs). *Only the Christchurch Health and Development Study and the Victorian Adolescent Health Cohort Study assessed suicidal behaviour. †Assessed at age 28–30 years.

Table 2: Maximum frequency of cannabis use before age 17 years, and each young adult outcome in combined data, before and after adjustment with the null covariate approach

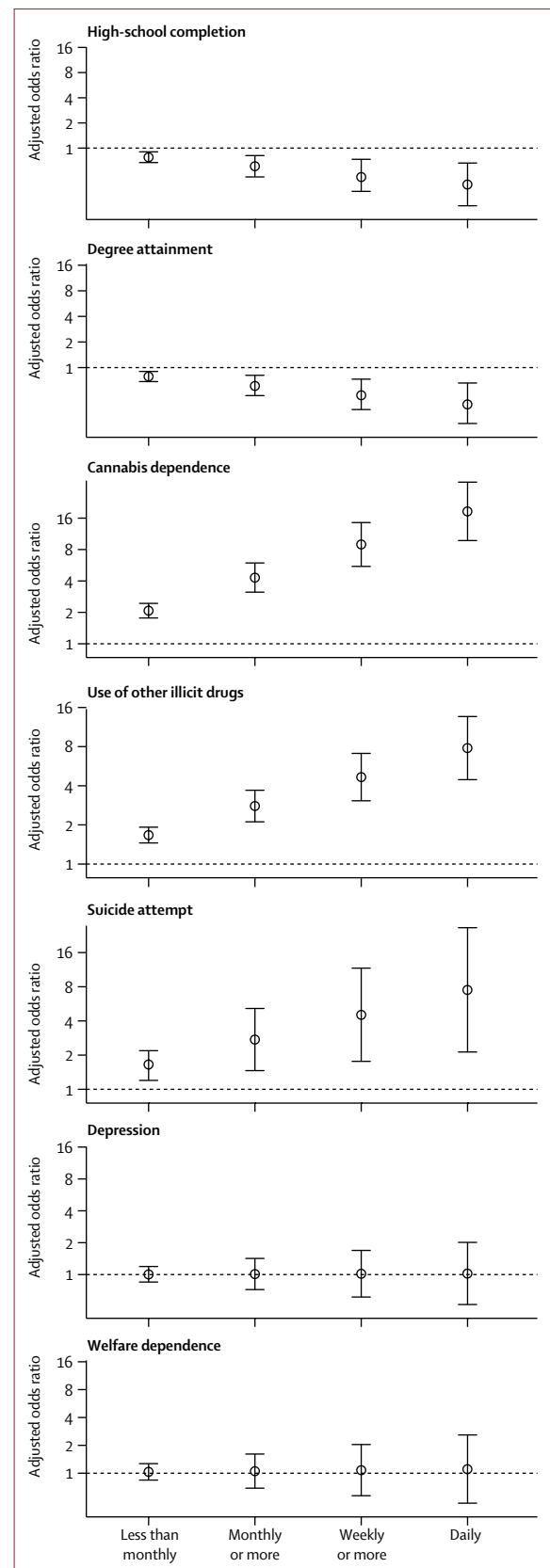
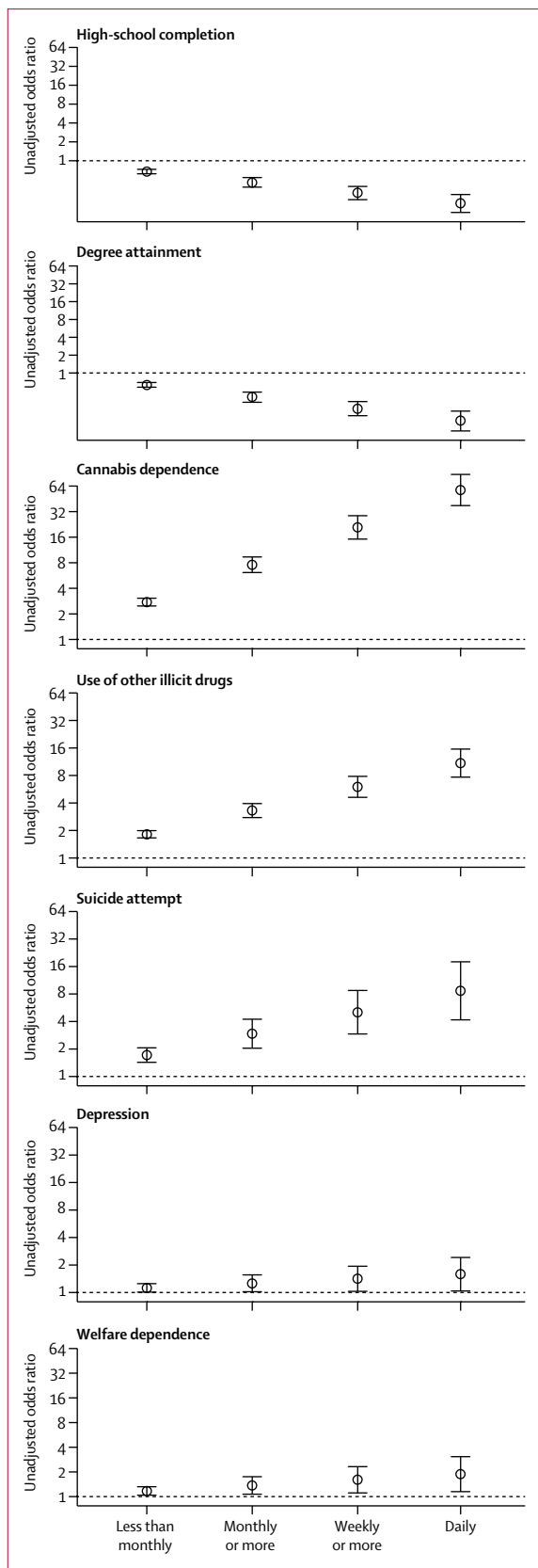


Figure 1: Unadjusted odds ratios (log scale) between maximum frequency of cannabis use before age 17 years and young adult outcomes in combined data, compared with individuals who have never used cannabis. Error bars show 95% CIs.

Figure 2: Adjusted odds ratios (log scale) between maximum frequency of cannabis use before age 17 years and young adult outcomes in combined data, compared with individuals who have never used cannabis. Error bars show 95% CIs.

between the extent of cannabis use and each outcome in the combined data. After adjustment, the associations for depression and welfare dependence were both non-significant and negligible in size (table 2). For all other outcomes the associations remained significant (table 2). The estimates for adjusted ORs suggested that individuals who were daily users before age 17 years had odds of high-school completion and degree attainment that were 63% and 62% lower, respectively, than those who had never used cannabis; furthermore, daily users had odds of later cannabis dependence that were 18 times higher, odds of use of other illicit drugs that were eight times higher, and odds of suicide attempt that were seven times higher (table 2, figure 2).

Results of Wald χ^2 tests of between-study heterogeneity in the effect of cannabis use were non-significant (data not shown), suggesting that the associations were similar across studies for all outcomes.

To examine the sensitivity of the results for adjusted ORs in table 2 to choice of model for adjusting covariates, we repeated the analyses with four alternative approaches to covariate adjustment: harmonised covariate, covariate score, propensity score, and standard meta-analysis (appendix). The findings from table 2 were replicated by these analyses, showing that the results were not dependent on the methodology used to estimate the covariate-adjusted associations. Further analysis using multiple imputation of missing data to control for potential sample selection bias produced findings that were entirely consistent with those of the recorded data (appendix).

Discussion

Our findings show clear and consistent associations between the frequency of adolescent cannabis use and all adverse young adult outcomes. These associations had dose-response characteristics across all seven outcomes, with the strongest effects shown for daily users. For all but two outcomes, associations were resilient to control for the range of potential confounding factors assessed. With control for potential observed confounders, the strength of association substantially reduced, and five of the outcomes remained significant. After adjustment, individuals who had used cannabis daily before age 17 years had odds of high-school completion and degree attainment that were lower than those who had never used cannabis before age 17 years, and higher odds of cannabis dependence, use of other illicit drugs, and suicide attempt. Results were robust to four alternative approaches to covariate adjustment and imputation of missing data.

Several aspects of the study findings support the possibility of a causal relation. First, we recorded strong associations between adolescent cannabis use and all young adult outcomes investigated. Second, the associations had dose-response characteristics with increasing frequency of adolescent use. Third, most

associations were resilient to control for potential confounding factors present before and during adolescence. Studies such as ours are limited in their capacity to explain the mechanisms behind such associations, although some research has suggested that heavy cannabis use in adolescence might affect CNS development;⁹ alternatively, cannabis use in adolescence could be a marker of developmental trajectories that place young people at increased risk of adverse psychosocial outcomes.²⁵ Study findings in relation to high-school completion, university degree attainment, cannabis dependence, and use of other illicit drugs are consistent with previous research investigating the association between early cannabis use and these outcomes.^{10,12,13,23} Although the association between cannabis use and high-school completion probably does not arise from a reverse causal association (school dropout leading to cannabis use),²⁶ this possibility remains plausible.¹⁰ The strong adjusted effects noted for suicide attempt add to a small body of research that supports a more direct relation between cannabis use and suicidal ideation.²⁷ Depression and welfare dependence were not significantly associated with adolescent cannabis use after adjustment. This finding is consistent with previous reviews, which concluded that the effect of cannabis use on these psychosocial outcomes could plausibly be explained by

Panel: Research in context

Systematic review

We did a review of systematic reviews published since the key 2004 paper by Macleod and colleagues.¹⁵ We searched Medline, Global Health, Embase, PsycINFO, and PsycARTICLES with the terms “cannabis or marijuana” and “systematic review” for reports about the effect of cannabis use on psychosocial outcomes (eg, school or university completion, welfare dependence), cannabis dependence, use of other illicit drugs, depression, and suicide. We identified 290 non-duplicate reports, of which nine focused on our key outcomes. Both cross-sectional and longitudinal data link cannabis use with high-school dropout, although reverse causality (dropout leading to cannabis use) remains plausible.¹⁰ Although no review of welfare dependence was identified, existing data from our study cohorts link cannabis use with welfare dependence and unemployment.¹¹ Use of cannabis is associated with development of both cannabis dependence and use of other illicit drugs.^{12,13} Although a causal association with depression is in doubt,^{12,16} heavy use in particular, increases the odds of depression.¹⁴ Initial reports also suggest that prenatal exposure effects subsequent depression.¹⁴ Presently, evidence is insufficient to cite a causal link with suicide.³⁵

Interpretation

Study findings suggest that adolescent cannabis use is linked to difficulties in successfully completing the tasks that mark the transition to adulthood. Prevention or delay of cannabis use in adolescence is likely to have broad health and social benefits. The findings are relevant given the movement in some countries to decriminalise or legalise cannabis raising a possibility that cannabis might become more accessible to young people. In the rapidly changing political and legislative landscape, protection of adolescents from the potential adverse effects of cannabis use is an important facet of legislative reforms for cannabis. Efforts to reform cannabis legislation should be carefully assessed to ensure they reduce adolescent cannabis use and prevent potentially adverse effects on adolescent development.

potential confounding factors that had not been adequately controlled for in studies to date.^{15,16}

This study has some limitations. First, there was some between-study variation in the levels of the outcomes, which could have been shown by variations in estimates of effect size across studies. However, such estimates were very similar, with Wald tests providing no evidence of significant between-study heterogeneity. Second, the criteria for depression in the Australian Temperament Study were weaker than those in other studies. However, irrespective of the way in which depression was measured, the same conclusion holds. Third, although we controlled for many potential confounding factors, the possibility that the recorded associations might show the effects of unmeasured or uncontrolled confounding cannot be completely ruled out.¹⁵ Residual confounding could attenuate the associations. However, analyses that have used fixed-effects regression to control for non-observed confounders suggest that associations between cannabis use and various outcomes persist.^{28,29} Methods of fixed-effects regression³⁰ provide a means to control for non-observed fixed sources of confounding of the associations between an exposure variable and an outcome in repeated measures data. Fourth, measures were obtained by self-report, which might be subject to socially desirable response bias, the extent of which can vary with age.³¹ Presence of such bias could lead to over-reporting or under-reporting of cannabis use. In face-to-face settings (as is generally the case for the cohorts in this study) adolescents might be more likely than adults to under-report risk behaviours,³¹ however, under-reporting would attenuate any observable associations. Fifth, similarities in the cultural and social context and epidemiology of cannabis use between Australia and New Zealand suggest that results can be applied to Australasian populations. Because rates of cannabis use in young people in Australasia are similar to those in other high-income countries (eg, in the USA, Canada, and the UK),^{32,33} generalisability of findings to those settings is supported. Nevertheless, the social and legislative context of cannabis use varies between regions,² and remains an important consideration in the generalisation of these findings.

This study extends previous research of the link between adolescent cannabis use and problems later in life by the integration of data from various sources and the provision of control for a broader range of covariates than possible in traditional meta-analyses. The findings provide evidence of the potential harms of adolescent cannabis use across several domains. The prevention or delay of cannabis use in adolescence might have broad health and social benefits. The findings are particularly relevant as the movement to decriminalise or legalise cannabis gathers momentum in a number of countries (panel).² Research suggests that such changes could lead to an increase in cannabis use mainly through a reduction in price.³⁶ Although the effect of cannabis prices on the intensity and duration of cannabis use is unclear,³⁶ evidence suggests that lower prices might

lead to earlier onset of use.³⁷ This hypothesis is concerning because the adolescent brain is vulnerable to the effects of cannabis⁹ and, as our findings suggest, cannabis use in adolescence is associated with increased risk of adverse developmental outcomes. In the rapidly changing political and legislative landscape, protection of adolescents from the potentially adverse effects of cannabis use is an important facet of cannabis legislative reforms. Despite increased availability of cannabis (for medical use) in some US states, a study³⁸ showed no increase in use among young people in those states. Nonetheless, efforts to reform cannabis legislation should be carefully assessed to ensure they reduce adolescent cannabis use and prevent potentially adverse developmental effects.

Contributors

GCP, LD, DMF, and LJH conceptualised and designed the study. LJH, GCP, CAO, DMF, JWT, CC, and PL acquired the data. ESi, LJH, CAO, ES, and DMH did the data analysis. All investigators, except PL, contributed to data interpretation. ESi, DMF, GCP, LJH, LD, CAO, DMH, and ES drafted sections of the report. All investigators critically revised the paper and approved the final version for publication.

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Declaration of interests

We declare no competing interests.

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Adolescent cannabis use and adverse sequelae in adulthood

Present or previous cannabis use is more common in individuals with low educational attainment than in those with higher levels of educational achievement. Debate surrounds whether this association is attributable to cannabis use being more frequent in socioeconomic groups that are more likely to have poor educational attainment, whether cannabis use is actually a marker of an already established disadvantageous development, or whether the association is a truly causal one.¹

In *The Lancet Psychiatry*, Edmund Silins and colleagues' integrative meta-analysis² assesses the long-term psychosocial sequelae of adolescent cannabis use. The report, which is based on participant-level data from

three studies from Australia and New Zealand, clearly shows a dose-response association between frequency of cannabis use in adolescence and ability to complete specific tasks that mark the transition to adulthood, specifically the ability to achieve high levels of education. After confounder control, individuals who were daily users before age 17 years had reductions in the odds of high-school completion (adjusted odds ratio [OR] 0.37, 95% CI 0.20–0.66) and degree attainment (0.38, 0.22–0.66) compared with those who had never used cannabis. Furthermore, cannabis use was associated with increased risk of suicide attempt (adjusted OR 6.83, 95% CI 2.04–22.90) and, unsurprisingly, later cannabis dependence (17.95, 9.44–34.12) and use of other illicit



See [Articles](#) page 286

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drugs (7-80, 4-46-13-63). The participation rate in the study is impressive, the attrition rates are modest, and the number of confounding factors, assessed across cohorts, is overwhelming and covers a broad range of factors that could affect outcome independently.

Persistent cannabis use has adverse effects, such as low energy and initiative, and impairment of cognitive functions, and these factors are likely to mediate the harmful effect of cannabis on educational attainment. Findings from randomised clinical trials show a negative short-term effect of cannabis intake compared with placebo on cognitive function during, and in the hours following, intoxication. Compared with placebo, dronabinol impaired working memory and verbal fluency in a trial³ involving 22 healthy volunteers. In another trial⁴ with 30 healthy participants, Morrison and colleagues showed that working memory and executive functions were reduced by 10–20% in participants randomised to receive dronabinol.

A randomised clinical trial that exposes some young people to cannabis in various doses for a long term and compares them with other young people given placebo will never be done. Therefore, findings from naturalistic experiments will be relied on to obtain knowledge about whether the harmful effect on cognitive function is temporary. Increasing evidence shows that brain development during adolescence can be harmed by frequent cannabis use, and cognitive functions can be permanently reduced. In the Dunedin birth cohort⁵ cognitive function was examined at age 13 years and again at age 38 years. Continuous cannabis use was associated with neuropsychological decline across all domains of cognitive functioning, and more persistent use was associated more severe decline. Additionally, adolescent-onset cannabis users were more impaired than adult-onset users and neuropsychological functioning in adolescent-onset users was not fully restored after cessation. The investigators concluded that their findings were suggestive of a neurotoxic effect of cannabis on the adolescent brain.

In a review,⁶ Schweinsburg and colleagues concluded that studies of adolescents who were heavy marijuana users showed that there were still persisting deficits at least 6 weeks after discontinuation, particularly in the domains of learning, memory, and working memory.

Moreover, cognitive functions were more severely affected in adolescents than in adults.

Cannabis use in adolescence has also been associated with increased risk of psychosis in adulthood.⁷ Cannabis use is associated with earlier onset of psychosis,⁸ and in patients with cannabis use and psychosis, risk of continuous psychotic symptoms is higher in those who continue to use cannabis than in those who stop.⁹

The convincing results presented by Silins and colleagues² are very valuable and highly appropriate at a time when several American states and countries in Latin America and Europe have decriminalised or legalised cannabis and allow unrestricted marketing of various formulations of the drug. Such changes in legislation will probably be followed by decreased prices and increased use, which will lead to more young people having difficulties with school completion and social and personal maturation, and will increase the risk of psychosis.

Youth is a very vulnerable period in life. Socially, young people need to develop and mature, and to prepare themselves to meet demands in their adult life, such as completing education and finding employment, choosing leisure activities, and finding partners and friends. Cannabis use, especially frequent uses, impairs this development and reduces the likelihood that a young person will be able to establish a satisfactory adult life.

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