Cannabis and depression: An integrative data analysis of four Australasian cohorts

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ABSTRACT

Background: This study presents an integrative data analysis of the association between frequency of cannabis use and severity of depressive symptoms using data from four Australasian cohort studies. The integrated data comprised observations on over 6900 individuals studied on up to seven occasions between adolescence and mature adulthood.

Methods: Repeated measures data on frequency of cannabis use (not used/< monthly/≥ monthly/≥ weekly) and concurrently assessed depression scores were pooled over the four cohorts. Regression models were fitted to estimate the strength of association between cannabis use and depression. Fixed effects regression methods were used to control for confounding by non-observed fixed factors.

Results: Increasing frequency of cannabis use was associated with increasing depressive symptoms ($p<0.001$). In the pooled data weekly users of cannabis had depression scores that were 0.32 (95%CI 0.27-0.37) SD higher than non-users. The association was reduced but remained significant ($p<0.001$) upon adjustment for confounding. After adjustment depression scores for weekly users were 0.24 (95%CI 0.18-0.30) SD higher than non-users. The adjusted associations were similar across cohorts. There was a weak age x cannabis use interaction ($p<0.05$) suggesting that the association was strongest in adolescence. Attempts to further test the direction of causality using SEM methods proved equivocal.

Conclusions: More frequent cannabis use was associated with modest increases in rates of depressive symptoms. This association was stronger in adolescence and declined thereafter. However, it was not possible from the available data to draw a definitive conclusion as to the likely direction of causality between cannabis use and depression.

Keywords: Cannabis; Depression; Longitudinal study; Integrative data analysis

1. Introduction

In recent years there has been growing interest in the association between the use of cannabis and mental health. An increasing number of studies have shown that that the use of cannabis, and particularly the heavy use of cannabis, is associated with increased risks of: major depression (Arseneault et al., 2002; Bovasso, 2001; Chen et al., 2002; Cheung et al., 2010; Degenhardt et al., 2003a; Fergusson et al., 2002; Hayatbakhsh et al., 2007; Lynskey et al., 2004; Marmorstein and Iacono, 2011; McGee et al., 2000; Patton et al., 2002; Rey et al., 2002; van Laar et al., 2007); psychosis/psychotic symptoms (Andreasson et al., 1987; Arseneault et al., 2002; Fergusson et al., 2005; Henquet et al., 2005; Jablensky et al., 2000; Kuepper et al., 2011; Large et al., 2011; van Os et al., 2002; Zammit et al., 2002); anxiety disorders (Han et al., 2010; Hayatbakhsh et al., 2007; Patton et al., 2002; Rey et al., 2002; Zvolensky et al., 2010); and suicidal behaviours (Beautrais et al., 1999; Borges et al., 2000; Fergusson and Horwood, 1997; Lynskey et al., 2004; Pedersen, 2008). These findings clearly raise the possibility that, by various routes, cannabis may act to increase susceptibility to mental health problems.

However, the view that cannabis use may play a causative role in depression and other mental health problems has been questioned (Degenhardt et al., 2003b; Harder et al., 2008; Macleod et al., 2004; Pedersen, 2008). Several studies have not supported a causal association linking cannabis use problems with depression (Harder et al., 2008; Pedersen, 2008). Specifically, it has been suggested that the observed associations between cannabis use and depression may be due to uncontrolled sources of residual confounding (Macleod et al., 2004). Moreover, the possibility that common individual, social and contextual factors increase the risks of both heavy cannabis use and depression cannot be ruled out (Degenhardt et al., 2003a). For example, there is evidence that a substantial component of the association between cannabis dependence and depression is attributable to shared genetic vulnerabilities (Lynskey et al., 2004).

A further complication concerns the direction of any causal relationship. In particular, it can be argued that any association between cannabis and depression may arise by two quite different sets of causal processes. First, cannabis use may by various mechanisms act to provoke or precipitate the onset of mental health problems. It is biologically plausible that cannabis use may lead to depression as neuropsychological studies in animals (Hill et al., 2006; Tsou et al., 1999) and humans (Dean et al., 2001; Leroy et al., 2001) suggest that cannabis has multiple effects on brain chemistry. Animal studies have demonstrated that serotonin (5HT)-2A receptors are up-regulated and 5HT-1A receptors are down-regulated following long term administration of cannabinoids (Hill et al., 2006). These findings provide a potential neurochemical explanation for the association between cannabis dependence and depression as changes in serotonin regulation have been linked with depression and suicidal behaviour in humans (Bhagwager et al., 2004; Drevets et al., 1999; Sargent et al., 2000). Heavy cannabis use may also contribute to depression indirectly by impairing psychosocial adjustment, from which mental health problems could arise (Degenhardt et al., 2003a). The adverse psychosocial consequences of cannabis use disorders, such as educational under-achievement, unemployment and criminal offending, have been shown to partly explain the observed association between heavy cannabis use and later depression (Marmorstein and Iacono, 2011). Cannabis use may also give rise to depression and other mental health problems through cognitive impairment which persists beyond acute cannabis intoxication (Solowij and Battisti, 2008).

Second, the development of mental health disorders may increase the likelihood that the individual will use cannabis heavily or regularly. This hypothesis proposes that people with depression may use cannabis to relieve their symptoms (Klien and Riso, 1994). Although the self-reported effects of cannabis use support its use for symptomatic relief (Green et al., 2003), the evidence from empirical studies generally does not support a self-medication hypothesis (Arendt et al., 2007; Fergusson et al., 2005; Hayatbakhsh et al., 2007; Patton et al., 2002).

A final issue concerns the effects of age on the relationship between cannabis use and mental health problems. There is growing evidence to suggest that any adverse effects of cannabis use are greatest during adolescence and tend to decline with increasing age (Arseneault et al., 2002; Fergusson et al., 2008; Fergusson et al., 2002; Stefanis et al., 2004). This effect of age on the relationship between cannabis and mental health has been attributed to the possible adverse effects of cannabis on brain structure and functioning during adolescence (Eggan et al., 2010; Malone et al., 2010; Schneider, 2008).

In this paper we address some of these issues by reporting a multiple cohort study of the relationships between the use of cannabis and the development of symptoms of depression in four Australasian cohorts that have gathered data on cannabis use and symptoms of depression over the period from adolescence to young adulthood. These studies include: the Victorian Adolescent Health Cohort Study (Patton et al., 2007); the Personality and Total Health (PATH) Study (Anstey et al., 2011); the Australian Temperament Project (ATP) (Prior et al., 2000); and the Christchurch Health and Development Study (CHDS) (Fergusson and Horwood, 2001; Fergusson et al., 1989). The availability of four data sets gathered by independent investigators in different centres offers the advantages of testing for robust and general associations between the use of cannabis and the development of depressive symptoms.

The paper aims to address three questions regarding the linkages between cannabis and depression using data from these cohorts.

1. Association: To what extent are there consistent dose/response relationships between the extent of cannabis use and the development of depressive symptoms? This stage of the analysis will use random effects regression methods and integrative data analysis to estimate the linkages between cannabis use and depressive symptoms for each study and pooled across studies.

2. Confounding: To what extent can any association between cannabis use and the development of depressive symptoms be explained by third or confounding factors? This stage of the analysis will use fixed effects regression models to control for non-observed fixed sources of confounding. Estimates from the four studies will be combined using integrative data analysis models.

3. Age: To what extent does any association between the use of cannabis and rates of depressive symptoms vary with age? This question will be addressed by extending the statistical models described in 2 to test for age x cannabis use interactions.

2. Method

2.1 Description of studies

2.1.1 The Victorian Adolescent Health Cohort Study (VAHCS). The VAHCS is a longitudinal study of a representative sample of mid-secondary school adolescents resident in Victoria, Australia (Patton et al., 2007). In 1992, participants were recruited at the end of Year 9 (wave 1) or the start of Year 10 (wave 2), and were reviewed on four occasions during adolescence (waves 3-6), with a further three follow-ups in young adulthood (waves 7-9). The present analysis is based on data collected during the first seven waves of the study. Of the sample of 2032 students, 1926 (94.8%) were assessed at least once on measures of cannabis use and depression during the first seven waves.

2.1.2 The Personality and Total Health (PATH) Study. The PATH study is a longitudinal study of the health and well-being of people aged 20-24 (2404 respondents), 40-44 (2530 respondents) and 60-64 (2551 respondents) years who live in the Australian Capital Territory and the neighbouring town of Queanbeyan (Anstey et al., 2011). Interviews commenced in 1999 and each cohort is to be followed up every 4 years over a total of 20 years. The present analysis is based on data collected during the first 3 waves of data collection for the youngest (age 20-24) cohort. A total of 2400

participants (98.8% of the initial cohort) provided data on cannabis use and depression for at least one of these assessments.

2.1.3 The Australian Temperament Project (ATP). The ATP is a longitudinal study of the psychosocial development of a community sample from infancy to adulthood (Prior et al., 2000; Sanson et al., 1985). A representative sample of 2,443 infants was collected through selected Maternal and Child Health Centres across rural and urban areas of the state of Victoria during a specified 2 week period in 1983. Using mail survey methodology, fifteen waves of data have been collected over the past 27 years, from parents, teachers, maternal and child health nurses, and from the age of 11 years onwards, the young people themselves. The present analysis is based on data collected over the four assessments from age 15-16 to age 23-34. A total of 1511 participants (62.1% of the initial cohort) provided data on cannabis use and depression for at least one of these assessments.

2.1.4 The Christchurch Health and Development Study (CHDS). The CHDS is a longitudinal study of a birth cohort of 1265 children born in the Christchurch (New Zealand) urban region in 1977 (Fergusson and Horwood, 2001; Fergusson et al., 1989). These children included 97% of all live births occurring during the recruitment period (15 Apr - 5 Aug 1977). The cohort has now been studied on a total of 22 occasions from birth to age 30 years. The present analysis is based on data collected during assessments at ages 15, 16, 18, 21, 25 and 30: A total of 1065 participants (84.2% of the initial cohort) provided data on cannabis and depression for at least one of these assessments.

Table 1 provides an overview of the characteristics of the four studies, and the measures available to be used in the present analysis. The combined data set from the four studies comprised repeated observations on over 6900 individuals assessed on between 3-7 occasions; at ages spanning the range from adolescence (age 13-15) through to mature adulthood (age 30+); and gathered using a variety of assessment methodologies that spanned self-completed questionnaires,

computer assisted interviews, telephone and face to face interviews. All studies have ethical approval from their respective ethics committees for their involvement in the present study.

INSERT TABLE 1 ABOUT HERE

2.2 Measures

2.2.1 Frequency of cannabis use. All studies included some measure of reported frequency of cannabis use at each assessment. For the CHDS this was based on the past 12 months; for VAHCS on the past 6 months (Waves 1-6) and past 12 months (Wave 7); and for PATH, ATP on current use/use in the past month. Using these data a 4-level measure of the frequency of cannabis use was created for each study: 0 = not used; 1 = used less than monthly; 2 = used at least monthly; 3 = used at least weekly. Since the ATP did not directly assess the category "used less than monthly", for this sample the category was defined based on a criterion of "ever used but not in past month". Three of the four studies (VAHCS, ATP, CHDS) had the potential to add a fifth level of cannabis use – daily use. Restricting the data to three studies and adding a "daily use" category did not alter the study findings (see supplementary analysis).

2.2.2 Depressive symptoms. The four studies all used different measures for the assessment of depressive symptoms. For VAHCS assessment of depressive symptoms was based on selected depression items of the Clinical Interview Schedule (Lewis et al., 1988). For PATH assessment was based on the Goldberg Depression Scale (Goldberg et al., 1988). The ATP used two different scales at different ages: the depression sub-scale from the Short Mood and Feelings Questionnaire (Angold et al., 1995) in adolescence and the depression sub-scale from the short form Depression Anxiety Stress Scale (Lovibond and Lovibond, 1995) in young adulthood. In the CHDS assessment of depressive symptoms was conducted using the Diagnostic Interview Schedule for Children (Costello et al., 1982) in adolescence and the Composite International Diagnostic Interview (World Health Organization, 1993) in adulthood. For three studies (VAHCS, PATH, CHDS) the depression scores

available for analysis were symptom count measures that broadly corresponded to DSM-III-R or DSM-IV symptom criteria for major depression. The ATP depression scores were scale scores rather than symptom counts. The assessment interval for depressive symptoms also varied across studies. For the CHDS symptom scores were based on the past 12 months, the other studies used current/past month as the reference period.

2.3 Statistical methods

The analysis adopted an integrative data analysis framework in which the repeated measures data from the four studies were pooled into a single data set for analysis.

2.3.1 Establishing a common scale of measurement for depressive symptoms. To enable comparison and pooling of effect sizes across studies it was statistically useful to assess the outcome measure depression on a common scale. The approach used in the present analysis was to rescale all depression scores to a common mean of 100 and standard deviation of 10 within waves for each study. The effect of this rescaling was two-fold. First, the rescaling effectively removed any across time or across age variation in mean depression scores both within and between studies. Thus the present analysis was unable to examine between study differences in absolute levels of depression or changes in mean symptom levels over time. However, at the same time, scaling all assessments on a common metric enhanced the potential of the study to make across study comparisons of the strength of the association between frequency of cannabis use and depressive symptoms. Further, since the strength of the cannabis depression association was still free to vary across assessments, it was also possible to examine age related changes in the strength of this association.

2.3.2 Testing the association between frequency of cannabis use and depressive symptoms. The study specific effects of cannabis use on depression scores were estimated by fitting a random effects model (Baltagi, 2005) to the integrated data set from the four cohorts of the form

$$Y_{ijt} = B0 + B1_j X_{ijt} + \nu_i + \varepsilon_{ijt} \quad \text{(EQ1)}$$

where Y_{ijt} was the depression score for the i-th participant from the j-th cohort at the t-th time of observation; X_{ijt} was the corresponding measure of frequency of cannabis use; ν_i was an individual specific random intercept term that was uncorrelated with X_{ijt}; and ε_{ijt} was the residual. EQ1 provides an estimate of the association between depression (Y_{ijt}) and frequency of cannabis use (X_{ijt}) within each cohort taking into account between individual variability in the underlying level of depressive symptoms (ν_i). The coefficients $B1_j$ represent cohort specific effects of cannabis use on depressive scores for the j-th cohort (j = 1, 2, 3, 4). For the integrated dataset the pooled effect of cannabis was estimated from a model that constrained the coefficients $B1_j$ to be equal across cohorts, and a Wald chi square test of homogeneity of parameter estimates across cohorts was derived based on a comparison of the log likelihood statistics for the model in EQ1 compared to the constrained model.

2.3.3 Adjustment for confounding. To control for the confounding effects of non-observed fixed factors the data were reanalysed using fixed effects regression methods (Baltagi, 2005; Greene, 2003). Two sets of models were fitted, corresponding to: a) a cannabis main effects model (EQ2) and b) a main effects model extended to include an age x cannabis use interaction (EQ3):

$$Y_{ijt} = B0 + B1_j X_{ijt} + \alpha_i + \varepsilon_{ijt} \quad \text{(EQ2)}$$

$$Y_{ijt} = B0 + B1_j X_{ijt} + B2_j AGE_{ijt} \times X_{ijt} + \alpha_i + \varepsilon_{ijt} \quad \text{(EQ3)}$$

where α_i was an individual specific intercept term summarising the effects of all non-observed fixed factors influencing depression scores Y_{ijt} that were also correlated with frequency of cannabis use X_{ijt}. EQ2 estimates the association between depression (Y_{ijt}) and frequency of cannabis use (X_{ijt}) within each cohort net of fixed non-observed confounders (α_i). EQ3 expands on this model by permitting the association between depression scores and cannabis use to vary with the age of assessment. Tests of across study homogeneity of main effect and interaction parameter estimates were obtained from F-tests of the null hypothesis that the parameters B1j, B2j respectively could be

constrained equal across studies. All regression models were fitted with Stata10 (StataCorp, 2007) and using robust estimates of standard errors to allow for the effects of clustering within studies.

3. Results

3.1 Associations between frequency of cannabis use and mean depression scores

Table 2 shows the associations between frequency of cannabis use and mean depression scores for each wave in each study. The table also reports estimates of the pooled mean data for each study. The pooled data represent the mean depression scores averaged over all data waves for all levels of cannabis use. Depression scores have been scaled to a mean of 100 and standard deviation of 10 to ensure comparability across studies. For each cohort a test of the significance of the association between frequency of cannabis use and pooled mean depression scores was obtained from a random effects regression model fitted to the integrated data set in which the individual depression scores at each wave in each cohort have been modelled as a linear function of frequency of cannabis use at the same wave (see statistical methods EQ1).

Examination of the table shows evidence of clear, consistent and highly significant ($p<0.001$) trends across all cohorts for increasing frequency of cannabis use to be associated with higher mean depression scores. The pooled data for each cohort suggest an effect size in the small to moderate range, with weekly users of cannabis having pooled mean depression scores that were 3-5 points (.3-.5 SD) higher than those not using cannabis.

INSERT TABLE 2 ABOUT HERE

Table 3 shows the fitted random effects model parameters for the main effect of cannabis use on depression scores for each cohort separately and for a combined model fitted to the integrated data set in which the effect of cannabis use has been constrained to be equal across cohorts. In all cases a linear model was adequate to describe the variations in the observed data. The table also reports a test of homogeneity of effect sizes derived from a Wald chi test of equality of the

regression coefficients across the four cohorts (see statistical methods). Consistent with the findings for the individual cohorts the regression coefficient from the integrated data set suggests a moderate effect size of approximately a 3.2 point (0.32 SD; 95%CI 0.27-0.37 SD) difference in depression scores between weekly users and non-users of cannabis. However, there was evidence of significant (p=.01) between study heterogeneity, that appeared to reflect the fact that the regression coefficient for PATH was somewhat larger than for the other cohorts.

INSERT TABLE 3 ABOUT HERE

3.2 Control for confounding

To examine whether the associations observed in Tables 2 and 3 were due to the effects of confounding by fixed factors correlated with cannabis use or depression, the repeated measures data were re-analysed using fixed effect regression methods. With repeated measures data, fixed effects models provide a mechanism to control for all non-observed sources of confounding by fixed factors correlated with cannabis use that might exert a fixed influence on depression scores over time. Two models were fitted for each data set: a) a simple main effects model for cannabis use (see Statistical Methods EQ2) and b) a model incorporating both a cannabis use main effect and an age x cannabis use interaction term (see Statistical Methods EQ3). Table 4 shows the parameters of the fitted models for each cohort and for the combined integrated data set. In fitting the age interaction models, age was assessed in whole years at the time of assessment centered around age 15. Thus the main effect parameters for model b) give the estimated main effect of cannabis use for each sample at age 15, and the age x cannabis use parameters show the amount by which the age 15 main effect changed for each one year increase in age. Again tests of homogeneity of parameter estimates across studies are also reported.

Comparison with Table 3 shows that for the main effects model (Model a) the effects of cannabis use were reduced in size after adjustment for confounding, but remained statistically

significant ($p<0.05$). After adjustment, the fitted parameter for the integrated data set suggested that weekly users of cannabis had depression scores that were 0.24 (95%CI 0.18-0.30) SD higher than non-users. For the interaction model (Model b) in all cases the estimated age x cannabis use interaction term was negative, suggesting a decreased strength of association with increasing age. The age interaction was not statistically significant for three of the four cohorts (the one exception being VAHCS), but was significant for the integrated data set (B = -0.038; SE = .018; $p<0.05$). In all cases tests of parameter homogeneity suggested that after adjustment for confounding there was no evidence of significant between study variability in model parameters.

INSERT TABLE 4 ABOUT HERE

To illustrate the effects of cannabis use on depression scores after adjustment for confounding, the parameters of the fixed effects Model b) for the integrated data set incorporating the age x cannabis use interaction were used to estimate the fitted adjusted dose response associations for a series of ages from age 15 to age 30. These associations are given in Figure 1. The fitted lines show that at age 15 the adjusted difference between mean depression scores for weekly users and non-users of cannabis equated to an effect size of 0.31 (95%CI 0.21-0.40) SD, which reduced to an effect size of only 0.13 (95%CI 0.02-0.25) SD by age 30.

INSERT FIGURE 1 ABOUT HERE

3.3 Supplementary analysis

3.3.1 Extending the regression models. As a further test of the adjusted effects reported above the fixed effects models were extended to incorporate additional control for time dynamic measures of prior depression and prior cannabis use. These additional covariates did not materially influence the adjusted effect size estimates. In addition, for three of the four cohorts (VAHCS, ATP, CHDS) data were available on daily cannabis use. Analysis using these three cohorts with the measure of

frequency of cannabis use extended to incorporate daily use produced findings that were consistent with the results reported in Tables 2-4 above.

3.3.2 Testing the direction of causality. The preceding results clearly suggest a relationship between depression and cannabis use net of confounding. These findings are consistent with the view that these variables may be causally related. However, it is possible to suggest that any causal relationship may be due to: a) the effects of cannabis use on depression; b) the effects of depression on cannabis use; or c) both a and b. The advantage of longitudinal data is that it is possible to fit structural equation models (SEMs) that permit reciprocal causal pathways (Boden et al., 2010; Fergusson et al., 2009). To examine this possibility, structural equation models were fitted to each study and to the integrated data set to explore the direction of causation implied by the evidence. The method of modelling is described in detail in the online Supplementary Material to this paper. Briefly the modelling approach used linear simultaneous modelling methods to estimate two parameters of interest: a) the parameter B1 reflecting the causal effect of cannabis use on depression; b) the parameter B2 reflecting the causal effect of depression on cannabis use. Table 5 summarises the findings of this analysis and reports for each study and the pooled data set, estimates of the parameters B1, B2 and indices of model fit including: the model chi squared test statistic; the comparative fit index (CFI); the root mean squared error of approximation (RMSEA); and the standardised root mean squared residual correlation (SRMR). The Table shows:

For two of the four studies (PATH, CHDS) there was evidence of a significant path from cannabis use to depression (PATH, B1 = 1.48, SE = .58, $p<0.01$; CHDS, B1 = 0.92, SE = 0.23, $p < 0.001$).

For the remaining two studies (VAHCS, ATP) there was no evidence of a significant path from cannabis use to depression (VAHCS, B1= -0.16, SE = 0.34, $p > 0.60$; ATP, B1 = 0.10, SE = 0.35, $p > 0.70$).

For only one study (VAHCS) was there a significant path from depression to cannabis use (VAHCS, B2 = 0.004, SE = 0.002, $p < 0.05$), with another study (ATP) showing a marginally significant path (ATP, B2 = 0.004, SE = 0.003, $p = 0.08$).

It is clear from this summary that the individual studies gave a somewhat inconsistent account the direction of causation with two studies favouring a path from cannabis use to depression and two studies favouring a path from depression to cannabis use. However, the analysis based on the integrated data set clearly favoured a model in which cannabis use led to depression (B1 = 0.79, SE = 0.20. $p < 0.001$) whereas depression did not lead to cannabis use (B2 = 0.001, SE = 0.002, $p > 0.30$).

In summary findings from the SEM analyses about the direction of causation tended to be inconsistent. These difficulties in identifying the direction of causality using simultaneous linear models are likely to reflect the fact that the after correction for confounding the correlations between cannabis use and depression were relatively weak ($r = 0.06$ - 0.10 approx). Attempting to decompose these weak correlations into component parts reflecting the effects of cannabis use on depression and the effects of depression on cannabis use is likely to have been beyond the analytic precision of the data sets examined.

INSERT TABLE 5 ABOUT HERE

4. Discussion

This study has used an integrative data analysis framework to examine the associations between frequency of cannabis use and depressive symptoms in four large Australasian cohorts. The combined data comprised a total of more than 6,900 participants assessed repeatedly on measures of cannabis use and depression over the period from mid-adolescence to mature adulthood.

4.1 The association between cannabis use and depression

The analysis led to three clear conclusions about the associations between cannabis use and depressive symptoms.

First, there was evidence of a significant linear association between frequency of cannabis use and severity of depression. In this association increasing frequency of cannabis use was related to increasing rates of depressive symptoms. The overall strength of association was in the small to moderate range with changes in cannabis use being associated with a 0.32 (95%CI 0.27-0.37) SD change in depression scores.

Second, the strength of association was reduced but remained statistically significant upon adjustment for confounding by non-observed fixed factors correlated with cannabis use and depression. After adjustment, changes in cannabis use were associated with a 0.24 (95%CI 0.18-0.30) SD change in depression scores. Further, after adjustment for confounding, tests of between study homogeneity were statistically non-significant, suggesting that the associations between cannabis use and depression were similar across cohorts.

Third, there was some evidence from the integrated data set to suggest that the strength of the adjusted association between cannabis use and depression varied with age, such that the associations were strongest in mid-adolescence, reducing to generally weak and negligible effects in mature adulthood.

These results extend the findings of previous research suggesting a linkage between cannabis use and depression (Bovasso, 2001; Cheung et al., 2010; Fergusson et al., 2002; Hayatbakhsh et al., 2007; Patton et al., 2002; Rey et al., 2002; van Laar et al., 2007) by demonstrating the existence of a modest but robust association between frequency of cannabis use and depressive symptoms that is consistent across four large population based studies conducted in different geographic locations, and using different approaches to study design, measurement and timing of assessments. The observation of a decline in the strength of association with increasing age

is also consistent with the wider literature on the harms of cannabis use which suggests that regular or chronic use of cannabis in adolescence may have greater adverse consequences for individual mental health than similar use in adulthood (Arseneault et al., 2002; Fergusson et al., 2008; Fergusson et al., 2002; Stefanis et al., 2004).

4.2 The direction of causation

The study findings clearly raise the possibility of a causal relationship between the use of cannabis and the development of depression. It is clear that such an association could arise by a number of causal routes. First, the use of cannabis may increase risks of depression as a result of the effects of cannabis on the individual's biology, life style or adjustment (Bhagwager et al., 2004; Degenhardt et al., 2003a; Drevets et al., 1999; Marmorstein and Iacono, 2011; Sargent et al., 2000), which in turn increase risks of depression. Second, depression may lead to increased risks of cannabis use as a result of self-medication to relieve depressive symptoms (Klien and Riso, 1994). Finally, it is possible that there is a reciprocal relationship in which cannabis use influences risks of depression and depression influences risks of cannabis use. One of the strengths of longitudinal data sets is that they provide the potential to identify bi-directional relationships through the use of simultaneous linear modelling methods.

In this instance, application of these methods did not lead to a clear answer about the likely direction of causation. In particular, the findings from two studies (PATH, CHDS) favoured a model in which cannabis use led to increased risks of depression whereas the other two studies (VAHCS, ATP) produced the opposite conclusion. Finally, the model fitted to the integrated data set suggested that the predominant direction of any causal influence was likely to be from cannabis use to depression. Given the somewhat confused picture that emerged from this analysis it is apparent that no clear conclusions can be drawn about the likely direction of any causal associations between depression and cannabis use.

4.3 Limitations

This analysis was limited to examination of depression scores derived using different measures in each study. In order to establish commensurability it was necessary to rescale these to a common metric. If item level data for depression scores had been available for all studies it is possible that a more sophisticated form of commensurability could have been established using latent trait or latent variable methods. However, it seems unlikely that such methods would have produced findings that were very different from those reported here. In addition, all studies will have been affected to varying degrees by selection bias arising from the normal processes of sample attrition and missing data that occur in the context of longitudinal research. If these processes were correlated with cannabis use or depression then this may have led to biased estimates of the associations of interest. However, given the consistency of findings across the four studies it seems unlikely that selection bias will have markedly impacted on study findings. Further, the type of cannabis use was not assessed. Higher-potency cannabis (such as sinsemilla) increases the risk of first episode psychosis (Di Forti et al., 2009): thus it may also increase the risk of depression or have greater adverse impacts on the adolescent brain.

These limitations notwithstanding, the present study suggests the presence of a small but consistent association between the use of cannabis and rates of depressive symptoms, with the size of this association declining with age.

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Table 1
Summary of study characteristics.

Study 1: The Victorian Adolescent Health Cohort Study (VAHCS)	
General Description	The VAHCS is a longitudinal study of a representative sample of 2032 mid-secondary adolescents recruited in Victoria, Australia, and studied on a total of 9 occasions from adolescence to adulthood (Patton et al., 2007). The present analysis uses data from the first 7 waves of data collection.
Ages at Assessment (No. Assessed)	Wave 1: 13-16 years (N = 762); Wave 2: 14-18 years (N = 1673); Wave 3: 14-18 years (N = 1659); Wave 4: 14-17 years (N = 1597); Wave 5: 15-18 years (N = 1539); Wave 6: 15-18 years (N = 1506); Wave 7: 19-22 years (N = 1590)
Assessment Method	Waves 1-6: Self-completed computer assisted interview Wave 7: Computer assisted telephone interview
Cannabis Use	Measures: Waves 1-6: Self-reported frequency of cannabis use in past 6 months coded on a 6-point ordinal scale (1 = never; 2 = not in past 6 months; 3 = a few times a year; 4 = monthly; 5 = weekly; 6 = daily) Wave 7: Self-reported ever use (Yes/No), use >5 times in past year (Yes/No) and highest frequency of use in past 12 months coded on a 5-point scale (1 = almost every day; 2 = 3 or 4 days/week; 3 = 1 or 2 days/week; 4 = 1 to 3 days/month; 5 = less than once a month).
Depression	Assessment tool: Clinical Interview Schedule (CIS) (Lewis et al., 1988) Measure: Number of symptoms of depression including depressed mood; loss of interest; decreased energy; feeling inferior; excessive guilt; suicidal thoughts; forgetfulness, poor concentration; sleep problems; loss of appetite leading to weight loss; changed motor activity Reporting period: Past month
Study 2: The Personality and Total Health Study (PATH)	
General Description	The PATH study is a longitudinal study of the health and well-being of three community samples of people aged 20-

	24 (N = 2404), 40-44 (N = 2530) and 60-64 (N = 2551) years who live in the Australian Capital Territory and the neighbouring town of Queanbeyan (Anstey et al., 2011). Interviews commenced in 1999 and each cohort is to be followed up every 4 years over a total of 20 years. The present analysis is based on data collected during the first 3 waves of data collection for the youngest (age 20-24) cohort.
Ages at Assessment (No. Assessed)	Wave 1: 20-25 years (N = 2382); Wave 2: 24-29 years (N = 2123); Wave 3: 28-34 years (N = 1970)
Assessment Method	Self-completed questionnaire (via palm-top PC) with interviewer assistance if required
Cannabis Use	Measures: Self-reported ever use (Yes/No), any use in the past 12 months (Yes/No) and for those who had used in the past 12 months, current frequency of use coded on a 5-point ordinal scale (1 = once a week or more; 2 = once a month; 3 = every 1-4 months; 4 = once or twice a year; 5 = no longer use)
Depression	Assessment tool: Goldberg Depression Scale (Goldberg et al., 1988) Measure: Number of symptoms of depression Reporting period: Past month

Study 3: The Australian Temperament Project (ATP)

General Description	The ATP is a longitudinal study of a representative community sample of 2443 infants recruited through selected Maternal and Child Health Centres across rural and urban areas of Victoria, Australia (Sanson et al., 1985), and studied on a total of 15 occasions from infancy to adulthood. The present analysis is based on data collected over the four assessments from mid-adolescence to young adulthood.
Ages at Assessment (No. Assessed)	Wave 1: 15-16 years (N = 1279); Wave 2: 17-18 years (N = 1208); Wave 3: 19-20 years (N = 1089); Wave 4: 23-24 years (N = 987)
Assessment Method	Self-completed postal questionnaire
Cannabis Use	Measures: Self report ever use (Yes/No) and frequency of use reported as number of days marijuana use in past month
Depression	Assessment tools: Short Mood and Feelings Questionnaire (SMFQ; Waves 1, 2) (Angold et al., 1995); Short Form Depression Anxiety Stress Scale (DASS; Waves 3, 4) (Lovibond and Lovibond, 1995)

	Measure: Scale scores based on sum of depression sub-scale items with each item scored on an ordinal scale of symptom severity. SMFQ items were scored on a 3-point scale (rarely/never; sometimes; very often). DASS items were scored on a 4-point scale (did not apply; applied somewhat/some of the time; applied considerably/much of the time; applied very much/most of the time) Reporting period: Past month
Study 4: The Christchurch Health and Development Study (CHDS)	
General Description	The CHDS is a longitudinal study of a birth cohort of 1265 children born in Christchurch, New Zealand, in 1977 and studied on a total of 22 occasions from birth to age 30 (Fergusson and Horwood, 2001; Fergusson et al., 1989). The present analysis is based on data collected during the 6 assessments conducted between age 15 and age 30
Ages at Assessment (No. Assessed)	Wave 1: 15 years (N = 965); Wave 2: 16 years (N = 953); Wave 3: 18 years (N = 1025); Wave 4: 21 years (N = 1011); Wave 5: 25 years (N = 1003); Wave 6: 30 years (N = 987);
Assessment Method	Face to face interview for NZ residents, telephone interview for participants resident overseas
Cannabis Use	Measures: Waves 1-4: Frequency of cannabis use in past 12 months reported as total number of use occasions in past 12 months Waves 5-6: Frequency of cannabis in past 12 months reported on an 8-point ordinal scale (0=never used; 1=once or twice only; 2 = <monthly; 3 = at least monthly; 4 = at least weekly; 5 = several times a week; 6 = daily; 7 = several times a day)
Depression	Assessment tools: Diagnostic Interview Schedule for Children (DISC; Waves 1, 2) (Costello et al., 1982); Composite International Diagnostic Interview (CIDI; Waves 3-6) (World Health Organization, 1993) Measure: Number of DSM-III-R (Waves 1, 2) or DSM-IV (Waves 3-6) symptoms of Major Depression Reporting period: past 12 months

Table 2
Mean depression scores by frequency of cannabis use and wave/age at assessment for four studies (VAHCS, PATH, ATP, CHDS). (Numbers in brackets are the number of observations on which each mean is calculated.)

(a) VAHCS

		Frequency of Cannabis Use				
Wave	Mean Age at Assessment (yrs)	Never	< Monthly	≥Monthly	≥ Weekly	p
1	14.9	99.3 (675)	103.3 (49)	104.7 (22)	112.1 (16)	
2	15.4	99.2 (1389)	101.7 (144)	105.5 (74)	105.8 (66)	
3	15.9	99.2 (1380)	103.1 (142)	103.4 (60)	102.8 (77)	
4	16.3	99.5 (1291)	102.6 (135)	100.8 (68)	102.8 (103)	
5	16.8	99.5 (1207)	101.3 (165)	101.7 (75)	102.8 (92)	
6	17.4	99.6 (1195)	100.1 (160)	102.0 (62)	102.4 (89)	
7	20.7	99.2 (658)	100.7 (662)	97.6 (55)	101.1 (215)	
Pooled (all waves)		99.4 (7795)	101.3 (1457)	102.1 (416)	102.7 (658)	<0.001

(b) PATH

		Frequency of Cannabis Use				
Wave	Mean Age at Assessment (yrs)	Never	< Monthly	≥Monthly	≥ Weekly	p
1	22.6	99.9 (1578)	101.1 (483)	102.2 (95)	104.6 (226)	
2	26.7	99.4 (1562)	100.2 (358)	102.4 (66)	105.4 (137)	
3	30.7	99.8 (1650)	99.7 (205)	103.6 (32)	103.7 (83)	
Pooled (all waves)		99.4 (4790)	100.5 (1046)	102.5 (193)	104.7 (446)	<0.001

(c) ATP

Wave	Age at Assessment (yrs)	Frequency of Cannabis Use				p
		Never	< Monthly	≥Monthly	≥ Weekly	
1	15-16	99.4 (961)	100.1 (144)	102.8 (126)	102.4 (48)	
2	17-18	99.4 (693)	99.6 (279)	101.9 (151)	101.9 (85)	
3	19-20	99.8 (485)	99.0 (365)	101.5 (131)	103.3 (108)	
4	23-24	99.1 (372)	100.1 (480)	101.7 (77)	102.7 (58)	
Pooled (all waves)		99.5 (2511)	99.7 (1268)	102.0 (485)	102.6 (299)	<0.001

(d) CHDS

Wave	Age at Assessment (yrs)	Frequency of Cannabis Use				p
		Never	< Monthly	≥Monthly	≥ Weekly	
1	15	99.6 (881)	101.6 (65)	115.1 (12)	115.5 (7)	
2	16	99.3 (769)	101.2 (139)	111.0 (27)	103.6 (18)	
3	18	98.9 (598)	101.2 (242)	101.2 (82)	102.4 (103)	
4	21	98.8 (538)	99.6 (215)	102.0 (100)	103.3 (158)	
5	25	99.0 (559)	101.3 (232)	100.3 (76)	101.9 (136)	
6	30	99.4 (657)	101.5 (172)	97.6 (49)	102.5 (109)	
Pooled (all waves)		99.2 (4002)	101.0 (1065)	102.0 (1346)	102.8 (531)	<0.001

Table 3
Fitted random effects parameters for the effect of cannabis use on depression for each cohort separately and the combined integrated data set.

Data Set	B (SE)	p
VAHCS		
Cannabis use	0.87 (0.14)	<0.001
PATH		
Cannabis use	1.49 (0.16)	<0.001
ATP		
Cannabis use	0.87 (0.16)	<0.001
CHDS		
Cannabis use	1.08 (0.16)	<0.001
Integrated data set		
Cannabis use	1.06 (0.08)	<0.001
Test of parameter homogeneity	$\chi^2(3)=11.24$; p=0.01	

Table 4
Fitted fixed effects models for the effect of cannabis use on depression after adjustment for confounding (a) main effects model only (b) model including age x cannabis use interaction.

	Model (a)		Model (b)	
Data Set	B (SE)	p	B (SE)	p
VAHCS				
Cannabis use	0.48 (0.19)	<0.05	1.05 (0.31)	<0.001
Age x cannabis use interaction			-0.197 (0.062)	<0.001
PATH				
Cannabis use	1.17 (0.26)	<0.001	1.44 (0.43)	<0.001
Age x cannabis use interaction			-0.030 (0.036)	0.41
ATP				
Cannabis use	0.71 (0.23)	<0.005	0.97 (0.29)	<0.001
Age x cannabis use interaction			-0.064 (0.050)	0.20
CHDS				
Cannabis use	0.99 (0.20)	<0.001	1.43 (0.34)	<0.001
Age x cannabis use interaction			-0.055 (0.033)	0.09
Integrated data set				
Cannabis use	0.80 (0.11)	<0.001	1.02 (0.17)	<0.001
Age x cannabis use interaction			-0.038 (0.019)	<0.05
Test of parameter homogeneity				
Cannabis use	F(3,6901)=1.9; p=0.13		F(3,6490)=0.54; p=0.65	
Age x cannabis use interaction			F(3,6490)=1.87; p=0.13	

Table 5
Fitted model parameters for the effect of cannabis use on depression (B1) and depression on cannabis use (B2) and goodness of fit indices from SEM analyses.

	Effect of Cannabis Use on Depression		Effect of Depression on Cannabis Use		Model Goodness of Fit Indices			
Data Set	B1 (SE)	p	B2 (SE)	p	$\chi 2$(df)	CFI	RMSEA	SRMR
VAHCS	-0.16 (0.34)	0.64	0.004 (0.002)	<0.05	244.1 (50)	0.977	0.045	0.077
PATH	1.48 (0.58)	<0.01	-0.002 (0.002)	0.38	5.02 (5)	1.000	0.001	0.011
ATP	0.10 (0.35)	0.77	0.004 (0.003)	0.08	37.3 (16)	0.993	0.030	0.032
CHDS	0.92 (0.23)	<0.001	0.001 (0.002)	0.42	154.5 (50)	0.963	0.044	0.049
Integrated data set	0.79 (0.20)	<0.001	0.001 (0.002)	0.35	196.1 (31)	0.980	0.029	0.034

Figure 1

Estimated associations between frequency of cannabis use and mean depression scores at selected ages (15, 20, 25, 30 years) after adjustment for fixed sources of confounding.