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Research paper

Cannabis use, depression and anxiety: A 3-year prospective population-based study

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ABSTRACT

Background: Whether or not cannabis use may increase the risk for depression and/or anxiety is not clear. For one thing, it has not been possible to draw a definitive conclusion regarding the direction of causality, i.e. whether cannabis use increases the risk for depression/anxiety or vice versa. This study aimed at examining possible associations between cannabis use, depression and anxiety, using all three measures as both exposure and outcome.
Methods: Data were obtained from a longitudinal cohort study comprising 8598 Swedish men and women, aged 20–64, with a three-year-follow-up.
Results: Adjusted for sex and age, cannabis use at baseline was associated with an increased relative risk (RR) for depression and anxiety at follow-up, with RR=1.22 [1.06–1.42 CI 95%] for depression and RR=1.38 [1.26–1.50 CI 95%] for anxiety. Adjusted for all confounders (alcohol and illicit drug use, education, family tension, place of upbringing), the associations were no longer statistically significant; RR=0.99 [0.82–1.17 CI 95%] for depression and RR=1.09 [0.98–1.20 CI 95%] for anxiety. Age-adjusted, reporting depression or anxiety at baseline increased the risk of cannabis onset at follow-up three years later; RR=1.62 [1.28–2.03 CI 95%] and RR=1.63 [1.28–2.08 CI 95%] respectively. However, adjusted for other illicit drug use the associations were no longer statistically significant.
Limitations: Lack of information on frequency of cannabis use and of age of initiation of use.
Conclusions: We found no longitudinal associations between cannabis use and incidence of depression/anxiety, or between depression/anxiety and later cannabis use onset.

1. Introduction

Whether cannabis use increases the risk of depression has not been established. It has been suggested that the active ingredient in cannabis, tetrahydrocannabinol (THC), in the long term may affect serotonin and other neurotransmitters in ways that produces depressive symptoms (Martin et al., 2002). There is, however, little research evidence to support this direct effect of cannabis. Other possible suggested pathways are that cannabis use contributes to certain negative life events, for example disengagement from education, with an increased risk of unemployment and subsequent depression as a result (Lev-Ran et al., 2014; Degenhardt et al., 2003; Marmorstein and Iacono, 2011), or that the observed associations are instead results of overlapping risk factors, for example parental psychiatric disorders (Degenhardt et al., 2003) which increase the risk for both cannabis use and depression.

Results based on a Swedish male cohort showed an increased risk of hospitalization from depression in men reporting heavy cannabis use in adolescence, but this association disappeared after adjusting for conduct problems in childhood (Manrique-Garcia et al., 2012). A recent meta-analysis, pooling data from 14 studies, showed that cannabis use at early ages, particularly heavy use, was associated with an increased risk of depression (Lev-Ran et al., 2014). However, there was large heterogeneity in the included studies and, as stressed by the authors, further longitudinal studies are needed.

Another debated issue is whether cannabis use increases the risk of anxiety. About 20–30 percent show anxiety reactions after smoking cannabis as an immediate intoxication effect (Thomas, 1993), but whether cannabis is associated with anxiety also in a long term perspective is not clear. One longitudinal study found that adolescent cannabis use was associated with anxiety in young

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adulthood also after adjusting for a number of related factors, such as other substance use, education and family situation (Degenhardt et al., 2012). Other studies have also reported on this association (Moore et al., 2007; Crippa et al., 2009; Hayatbakhsh et al., 2007; Van Laar et al., 2007; Windle and Weisner, 2004), but the results are inconsistent since in many of these studies the associations have disappeared after covariate adjustments.

Thus, much of the relationship between cannabis use, depression and anxiety remains unclear. For one thing, it has not been possible to draw a definitive conclusion regarding the direction of causality. Many previous cohort studies have failed to control for baseline depression and/or anxiety (Lev-Ran et al., 2014; Crippa et al., 2009). Also, even though sex is known to affect both prevalence of depression and anxiety (Bahrami and Yousefi, 2011) as well as prevalence of cannabis use (Lev-Ran et al., 2014), with the former being higher in women and the latter higher in men; those discrepancies between the sexes have not been examined in more detail. A recent cross-sectional study showed cannabis use to be a better indicator of poor mental health in women than in men (van Gastel et al., 2014) and cannabis use disorder has been associated with major depressive disorders in females but not in males (Durdle et al., 2008). Still, possible longitudinal associations need further examination.

By using a population based cohort with data on cannabis use, depression and anxiety both at baseline and follow-up, we aimed to find out whether there is an association between cannabis use and depression and/or anxiety; the direction of the association and if the associations are different for men and women.

2. Methods

2.1. Study population

The analyses comprised data from the Mental Health, Work and Relations study (PART by Swedish acronym), a longitudinal population-based study on mental illness in Stockholm, Sweden. Five random samples of equal size were drawn from the Stockholm County population register ($N \approx 858.000$) at regular intervals between 1998 and 2000 (T_0) among Swedish citizens age 20–64 residing in Stockholm. In total, 19.742 individuals were sent a questionnaire, to which 10.441 responded (53%). These individuals were contacted again after three years with a postal questionnaire (2001–2003) (T_1), to which 8.613 responded (83%).

Non-participation was high, and has been analysed by comparing information from national registers for participants and non-participants in two previous studies, showing that those with low income, low education, of non-Nordic origin, unmarried and having a psychiatric diagnosis were less likely to participate (Lundberg et al., 2005; Bergman et al., 2010). Because questionnaire respondents who did not answer all questions were contacted by telephone and asked to give supplementary information, the internal missing (respondents' non-response to individual items) is generally low and this is also the case for the questions on drug use. At both waves of data collection (T_o and T_1), double-phase random subsamples were invited for psychiatric interview (Schedules for Clinical Assessment in Neuropsychiatry) in order to validate the psychiatric scales in the questionnaire (Forsell, 2005; Lundin et al., 2015a, 2015b).

The ethical review board at the Karolinska Institutet, Stockholm, approved the study, and informed consent was obtained from all participants.

3. Measures

3.1. Cannabis use

The study exposure was life-time cannabis use (T_0). Those who responded positive to a question on lifetime use of illicit drugs ("*Have you ever used narcotics?*") were asked to indicate which type(s) of drug(s) they had used. Six fixed alternatives were indicated: cannabis (hashish or marijuana), stimulants (e.g. amphetamine), opiates (opium, heroin, morphine, crack etc.), hallucinogens (e.g. LSD), cocaine and ecstasy. A second question asked about recency ("*When did you last use narcotics?*"), with six answer alternatives: today, last week, last month, last 12 months and more than 12 months ago. These two questions were converted into assumed cannabis consumption (a dichotomous variable, indicating ever use of cannabis). When examining possible reverse associations; cannabis use onset ("last 12 months or more often" at T_1) was instead the study outcome.

3.2. Depression and anxiety

Depression was measured using the *Major Depression Inventory* (MDI), both at T_0 and T_1 which asks about presence of DSM-IV and ICD-9 depressive symptoms in the last 14 days. The original version includes10 items and each has five response categories, indicating presence from 'no' (0) to 'all the time' (4). MDI is typically scored either by DSM-IV/ICD-10 algorithm or as a summary index ranging from 0 to 50. Based on a previous validation of the MDI, we chose the summary index over the algorithm scoring method because the index had excellent agreement with depressive disorder (AUC=0.80) (Forsell, 2005). At the cut off of 20 or more points the MDI had high combined sensitivity and specificity for detecting depressive disorders: 0.67 and 0.79 (Forsell, 2005).

Anxiety was at T_0 measured using a revised version of the Sheehan Patient-Rated Anxiety Scale (SPRAS) (Sheehan, 1983; Hällström et al., 2003). Two items, 'sudden unexpected attacks of intense worries or panics' and 'are you afraid that any of these problems will reoccur?', included in DSM-IV, were added, All items in SPRAS refer to amount of distress in the last 30 days with Likert response alternatives ranging from 'not at all' (0) to 'very much' (4), which were dichotomized as present or not, and computed into a summary score (range 0–80). Those with a score of >18 (the 90th percentile) were considered cases.

At T_1, anxiety was measured using the Symptom Checklist (SCL) items for Anxiety (10 items) (Lipman et al., 1979). Questions on 'amount of distress' refer to the last week and were rated on a five-point Likert scale ranging from 'not at all' (0), to 'very much' (4). We computed individual means for the anxiety items. A cut point of 1.75 was used as a diagnostic proxy for any anxiety syndrome (sensitivity and specificity=63.2 and 83.8, AUC=0.80 for detecting any DSM-IV anxiety (Lundin et al., 2015b).

When examining possible reverse associations; depression and anxiety at baseline (T_0) were instead the study exposures.

3.3. Confounders

In this study, we adjusted for potential confounders that have been found to influence the associations between cannabis, depression and anxiety, such as other substance use, education and childhood adverse circumstances (Feingold et al., 2015; Manrique-Garcia et al., 2012; Degenhardt et al., 2012). Furthermore, as previous research indicate that both prevalence of cannabis use and of anxiety and depression may be higher in the Stockholm region as compared to the rest of Sweden (Carlsson et al., 2013; Danielsson and Allebeck, 2015), and that ethnicity may affect the associations examined (Compton et al., 2000), we also accounted for the factors.