



Cannabis and psychosis: the impact of polydrug use

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Cannabis and psychosis: the impact of polydrug use

Abstract

Objectives: While research has consistently identified an association between cannabis use and psychosis, few studies have examined this relationship in a polydrug context (i.e. combining cannabis with other illicit substances).

Methods: The present study sought to examine the association between recreational drug use (cannabis only v. polydrug) and psychotic disorders. Analysis was conducted on a large, representative survey of young Danish people aged 24 (N = 4,718). Participants completed self-report measures of lifetime drug use and this information was linked to the Danish psychiatric registry system.

Results: Multivariate binary logistic regression analysis was used to examine the association between drug use (no drug use, cannabis only, cannabis and other drug) and ICD-10 psychotic disorders, while controlling for gender and parental history of psychosis. Compared with no drug use, the use of cannabis only did not increase the risk of psychosis while the odds ratio for cannabis and other drug were statistically significant.

Conclusions: Psychosis risk may be associated with the cumulative effect of polydrug use.

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Introduction

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An association between cannabis use and psychosis has been well-documented in the epidemiological literature (Gage, Hickman, & Zammit 2016). Indeed, a recent meta-analysis found evidence of a dose-response relationship, in which the heaviest users (in terms of both frequency and strength of substance consumed) were almost four times as likely to experience clinical-level psychotic outcomes compared with non-users (Marconi, Di Forti, Lewis, Murray & Vassos, 2016). Despite such findings, the potential causal role of cannabis use in the development of psychosis continues to be debated. There are a number of methodological challenges that impede the investigation of this association (Ksir & Hart, 2016). In the absence of experimental studies, it is difficult to isolate the unique effect (if any) that cannabis consumption has on psychosis (Ksir & Hart, 2016). With regards to epidemiological evidence, it is worth noting that while an association has consistently been reported, cannabis is the most the most commonly used recreational drug worldwide (Morely et al., 2015; Grant et al., 2015; National Institutes of Health, 2015; Haberstick et al., 2014; Degenhardt et al., 2013), and it is associated with many other well-documented risk factors for psychosis (Ksir & Hart, 2016) such as a pre-existing vulnerability to psychosis (Power et al., 2014). In their review of the extant literature, and paying attention to the Bradford Hill (1965) criteria for inferring causality from epidemiological data, Ksir and Hart (2016, p. 11) concluded that cannabis use in itself was not a definitive causal factor for psychosis, rather that "...early use and heavy use of cannabis are more likely in individuals with a vulnerability to psychosis".

One methodological challenge that has received relatively little interest in the literature is the issue of polydrug use. Cannabis use is the most commonly used drug within a

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2
3 polydrug context; studies of typologies of polydrug use have observed high levels of cannabis
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5 use across a range of groups that differ both qualitatively (in terms of the types of substances
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7 consumed) and quantitatively (in terms of their class counts, and associations with physical
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9 and mental health outcomes) (Stefanis, Dragovic, Power, Jablensky, Castle, & Morgan, 2014;
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11 Smith, Farrell, Bunting, Houston & Shevlin, 2011; Fergusson, Boden & Horwood, 2006;
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13 Lynskey et al., 2006; Carlson, Wang, Falck & Siegal, 2005; Mitchell & Plunkett, 2000).
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15 While there have been many plausible hypotheses to explain the biological mechanisms that
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17 link cannabis use and psychosis (Solowij et al., 2013; Bhattacharyya et al., 2009; Rais et al.,
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19 2008; Szeszko et al., 2007; Linszen & van Amelsvoort, 2007; D'Souza et al., 2000) research
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21 suggests that psychosis is also related to the use of other illicit drugs. For example, stimulants
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23 (Sara, Burgess, Malhi, Whiteford, & Hall, 2014; Medhus et al., 2015) and hallucinogens
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25 (Marona-Lewicka, Nichols, & Nichols, 2011) have also been identified as risk factors for the
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27 development of psychotic disorders/experiences. As cannabis use frequently co-occurs with
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29 the use of other drugs that have been shown to be associated with psychosis risk, and given
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31 that cannabis is the most widely used recreational drug, it is possible that the unique
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33 deleterious effect of cannabis use may have been overstated in previous research.
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41 Despite the fact that cannabis and other illicit substances are frequently used together,
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43 the association between cannabis use and psychosis has rarely been studied in a polydrug
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45 context. While a number of studies have found associations between cannabis use and
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47 psychosis, even after controlling for the presence of other drugs, the findings have been
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49 somewhat inconsistent and there were significant methodological differences between these
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51 studies. Van Os et al. (2002) examined the association between self-reported cannabis use
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53 and any psychotic disorder in general population (n=4,045) and clinical (n=59) samples
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55 followed over a three year period. A strong, effect of cannabis use on later psychotic disorder
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3 was observed, and was not attenuated when other drug use was included in the model.
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5 Henquet and colleagues (2006) examined the relation between cannabis use and psychotic
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7 symptoms in individuals with above average predisposition for psychosis who first used
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9 cannabis during adolescence (n=2,437). The inclusion of other drug use and predisposition to
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11 psychosis led to an attenuated effect, with the adjusted point estimate moderate in strength
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13 (OR = 1.67). Arguably the most comprehensive study which controlled for other drug use
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15 was conducted by Zammit, Allebeck, Andreasson, Lundberg, and Lewis (2002). Using
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17 Swedish conscript data (n=50,087) they examined the association between self-reported
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19 cannabis and other drug use and later psychiatric admissions, assessed using data linkage.
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21 Overall, cannabis use had a dose-response association with psychotic diagnosis, even in those
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23 who reported using only cannabis, however the inclusion of other drugs led to attenuated
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25 effects. Gage et al., (2014) examined the association between cannabis use and subsequent
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27 psychotic experiences (PLEs) in a cohort of adolescents (n= 1,756). They found that, when
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29 the confounding effects of tobacco, alcohol, and other drugs were controlled for, the effect of
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31 cannabis use on PLE dropped to a relatively minor level (OR=1.25).
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39 The majority of studies that have examined the cannabis-psychosis association have
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41 treated other drug use as a covariate. Fewer studies have explicitly examined the impact of
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43 combining cannabis with other substances on the subsequent development of psychosis.
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45 Studies that have taken this approach have found that such a combination resulted in
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47 considerably higher levels of risk compared with cannabis use alone. For example, Van Dam,
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49 Earleywine, and DiGiacomo, (2008) examined schizotypal symptoms in users of both legal
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51 and illicit substances (n= 328). Participants were divided into three groups based on their
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53 drug use patterns; legal drug only, cannabis and legal drug, cannabis polydrug. Those in the
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55 legal drug and cannabis-legal drug groups did not differ significantly on self-reported
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3 schizotypy, whereas those in the polydrug group scored significantly higher. Similarly, in a
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5 community cohort followed over 30 years (n=591), Rössler et al. (2012) found considerably
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7 stronger associations between “multiple-drug use” (i.e. cannabis plus at least one other drug)
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9 and psychotic experiences, compared with the use of cannabis alone. This effect was
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11 particularly strong when the analyses focussed on “schizophrenia nuclear symptoms”
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13 suggesting that polydrug use may be a risk for more severe, clinical levels of psychosis.
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15 Given that these studies have focussed primarily on self-reported psychotic-like experiences,
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17 further research is required exploring the impact of polydrug use on clinical psychosis.
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23 The main aim of this study was to assess the association between patterns of
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25 recreational drug use (no drug use, cannabis only, cannabis and other drug) and psychotic
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27 disorders. Data from a large interview survey based on a stratified random probability
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29 sample of young Danish people aged 24 years was used to assess life-time drug use and this
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31 information was linked to the Danish psychiatric registry for identification of participants
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33 who had a life-time ICD-10 diagnosis of a psychotic disorder and also to control for parental
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35 psychotic disorder. It was predicted that cannabis use and polydrug use would both be
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37 significantly associated with a diagnosis of a psychotic disorder while controlling for parental
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39 psychosis. It was expected that the effect size would be larger for polydrug use compared to
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41 cannabis only.
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Method

Participants and Procedures

Information on drug use was collected as part of a Danish national study conducted by *The Danish National Centre for Social Research* between 2008 and 2009. The aim of this study was to gather mental health related data from young Danish people. A stratified random probability sample (N = 4,718) drawn from the entire birth cohort of Danes born in 1984 (participants aged 24 years) were contacted (participants aged 24 years and 2,980 individuals agreed to be interviewed. The response rate was 63%. Participation in the interview was voluntary and the study was approved by the Danish Data Protection Agency. To increase the number of participants, who had been victims of childhood abuse and neglect, children who had been in child protection, were over-sampled by a ratio of 1:2 of “child protection cases” versus “non-child protection cases.” A child protection case was defined as a case when the local authority (according to the files of local social workers) had provided support for the child and the family or placement with a foster family due to concerns about the well-being and development of the child. A total of 852 interviews were conducted with individuals who had been previously identified by the Danish authorities as child protection cases. To account for the oversampling of child protection cases and to ensure findings were representative of the total Danish population of young people aged 24, the data was analysed using a weight variable with a weighted child protection status of 6.3% of the total sample. A structured interview was conducted by telephone, or by residential visit if telephone contact could not be made (mean duration of interview was 43 minutes). All individuals who volunteered to take part in the interview received written contact prior to the interview informing them of the process of the interview, the nature of the questions to be asked, and the process of confidentiality. All interviewers were formally trained and instructed by *The Danish National*

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3 *Centre for Social Research* and participated in test trials to become familiar with the
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5 questionnaire and the coding procedures.
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10 The survey responses were linked to data from the Danish Civil Registration System
11 and the Danish Psychiatric Central Register. A detailed description of the structure of CRS
12 was provided by Pedersen, Gøtzsche, Møller, and Mortensen (2006), and Thygesen, Daasnes,
13 Thaulow, and Brønnum-Hansen (2011). Access to the CRS was provided by *Denmark*
14 *Statbank* upon completion of a research proposal. The relevant variables requested are
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16 matched to individuals using the person's civil registry number (CPR). The CPR identifies
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18 people at the individual level and allows information to be collated across different registries.
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26 27 Measures

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29 The survey included a section on drug use. Participants were asked "Have you ever tried..."
30 and the following drugs were listed: amphetamine (Speed), cannabis (hashish/pot), cocaine
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32 (coke/crack), LSD (acid), mushrooms with narcotic effect, heroin, solvents (sniffing), other
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34 (ecstasy). Each drug was scored 'Yes' (1) or 'No' (0). The scores were recoded into a
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36 categorical variable that represented (1) no drug use, (2) cannabis only, and (3) cannabis and
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38 any other drug.
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45 The outcome variable was a diagnosis of psychotic disorder recorded between the
46 years 1984 and 2005 (approximating an age range from birth to 21 years). Every time a
47 person has contact with a psychiatric hospital or department in Denmark they receive an ICD-
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49 10 (previously ICD-8/9) diagnosis code that is recorded on the Psychiatric Central Register.
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51 The diagnosis is made by a psychiatrist. For this study we used information from the
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3 psychotic disorder (ICD-10 F20-F29; ICD8/9 295, 298.09, 298.19, 298.29, 298.39, 298.89,
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5 297, 298.99, 299). This data is available as part of the Danish Civil Registration System
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7 (CRS) and the Danish Psychiatric Central Register. Parental data for all was also available
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9 from four years prior to birth (1980) to 2005; parental psychosis was indicated if either parent
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11 had a ICD-10 (F20-F29) diagnosis during this time period.
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14 15 16 Analysis

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18 Chi-square tests were used to examine the bivariate associations between the predictor and
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20 outcome variables. Binary logistic regression analysis was used to examine the association
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22 between drug use category and psychotic disorder. Analyses were conducted using SPSS
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24 version 21 (IBM Corp., 2012)
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29 **Results**

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33 Slightly more than half of the sample were male (52.2%), 14 (0.5%) had received a diagnosis
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35 of a psychotic disorder, and there were 45 (1.5%) cases of parental diagnosis of psychosis.
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37 Almost half of the participants reported no drug use (48.4%), a further 31.6% reported using
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39 cannabis only and 20.0% reported using cannabis and any other drug. The bivariate
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41 associations between the psychosis diagnosis and other variables are reported in Table 1.
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47 Table 1 about here
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51 Table 1 shows that there was no association between psychosis diagnosis and gender or
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53 parental psychosis. There was a significant association between psychosis diagnosis and drug
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55 use with more participants with a diagnosis having reported using cannabis and other drug(s).
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57 The variables were entered into a binary logistic regression with the psychosis diagnosis as
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3 the dependent variable. Gender, parental psychosis and drug use were entered as predictors
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5 with the 'No drug' category used as the reference level. The model was statistically
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7 significant ($\chi^2 = 13.68$, $df = 4$, $p < .05$; Cox & Snell $R^2 = .004$; Nagelkerke $R^2 = .07$). The
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9 results in table 2 show that, compared to the no drug use group, cannabis use only did not
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11 increase the risk of psychosis while the odds ratio for was cannabis and other drug were
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13 statistically significant (OR=5.96).
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20 Table 2 about here
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24 In order to determine which drugs in combination with cannabis were contributing to
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26 this effect a series of chi-square analyses were conducted. The drug use data were recoded
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28 into seven binary variables to represent the use of (1) amphetamine with cannabis, (2)
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30 cocaine with cannabis, (3) LSD with cannabis, (4) mushrooms with cannabis, (5) heroin with
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32 cannabis, (6) solvents with cannabis, and (7) other drug with cannabis. Chi-square tests were
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34 used to test the association between these variables and psychosis diagnosis. The chi-square
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36 tests were significant for amphetamine with cannabis ($\chi^2 = 6.30$, $df = 1$, $p < .05$; OR = 3.71
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38 95% CI 1.24 – 11.14), cocaine with cannabis ($\chi^2 = 12.96$, $df = 1$, $p < .01$; OR = 5.66 95% CI
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40 1.95 – 16.42), mushrooms with cannabis ($\chi^2 = 20.00$, $df = 1$, $p < .01$; OR = 8.26 95% CI 2.74
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42 – 24.89), and solvents with cannabis ($\chi^2 = 10.57$, $df = 1$, $p < .01$; OR = 5.15 95% CI 1.71 –
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44 15.46). Finally, to examine the effect of the number of different drugs used a variable that
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46 was computed that represented the total number of different drugs used, ranging from 0 (no
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48 drug use) to 7 (all drugs). This variable was entered as a predictor in a binary logistic
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50 regression with psychosis as the dependent variable. The model was statistically significant
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52 ($\chi^2 = 7.20$, $df = 1$, $p < .01$) and the odds ratio for the number of different drugs used was 1.38
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3 (95% CI 1.11 – 1.68). This indicates that each additional drug that is used increases the
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5 likelihood of a diagnosis of psychosis.
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8 9 Discussion

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12 The main aim of this study was to assess the association between patterns of recreational drug
13 use (no drug use, cannabis only, cannabis and other drug) and psychotic disorders. It was
14 predicted that cannabis use alone and polydrug use would both be significantly associated
15 with a diagnosis of a psychotic disorder while controlling for parental psychosis. It was also
16 expected that the effect size would be larger for polydrug use compared to cannabis only. The
17 results partially supported the hypotheses. Although there was a significant bivariate
18 association between psychosis diagnosis and drug use, with more participants with a
19 diagnosis having reported using cannabis and other drugs, the logistic regression showed that
20 there was no significant effect for cannabis only. Only polydrug use was significantly related
21 to psychosis, with the odds increasing by almost six times compared to the ‘no drug’ group.
22 Follow-up analyses showed that different combinations of cannabis and other drugs were
23 associated with psychosis; cannabis in combination with amphetamine, cocaine, mushrooms
24 and solvents were all significantly associated with psychosis. There was also a significant
25 dose-response relationship for the number of different drugs used and psychosis.
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46 Although a large number of previous studies have examined the relationship between
47 cannabis use and subsequent psychosis, the use of other drugs has largely been reduced to
48 covariate status (e.g. Gage et al., 2014; Henquet et al., 2006; van Os et al., 2002; Zammit et
49 al., 2002). Studies that have controlled for the presence of other drugs have delivered
50 equivocal results, with some reporting moderate-to-strong associations between cannabis use
51 and subsequent psychosis (van Os et al., 2002; Zammit et al., 2002; Henquet et al., 2006),
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3 while others have reported greatly attenuated effects (Gage et al., 2014). Studies that have
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5 tested specific permutations of polydrug use have suggested that the combination of cannabis
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7 with other substances leads to markedly increased risk for psychosis. Van Dam, Earleywine,
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9 and DiGiacomo (2008), found those who used legal drugs alone and those who combined
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11 legal drugs with cannabis did not differ significantly on a self-report measure of schizotypy,
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13 while those who combined cannabis with other illegal drugs scored significantly higher.
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15 Similarly, Rössler et al. (2012) examined data from a Swedish cohort followed over a thirty
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17 year period and found that polydrug users had a significantly greater risk of developing
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19 psychotic experiences compared with those who used cannabis alone. Both of these studies
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21 used sub-clinical measures of psychosis. The present study adds to the literature by
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23 demonstrating a similar association when a clinical diagnosis of psychotic disorder is used
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25 as the primary outcome measure. This provides indirect evidence for the ‘psychosis
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27 continuum’ (Strauss, 1969, van Os, Hanssen, Bijl, & Ravelli, 2000) as it suggests that risk
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29 factors for psychosis operate in a consistent manner at both clinical and sub-clinical levels
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31 of psychosis.
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39 The findings of the present study indicate that, when patterns of cannabis and
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41 polydrug use are examined in greater detail, the unique effect of cannabis consumption is
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43 greatly attenuated. As such, the effect of cannabis use on the development of psychosis may
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45 have been overstated in previous studies which failed to control for confounding effects of
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47 other drugs. One explanation for the consistent findings of an association between cannabis
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49 and psychosis is that cannabis use is a proxy for other drug use, and it may be that other drugs
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51 represent the true risk factor. Indeed, in the present study the number of different drugs used
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53 was associated with psychosis in a ‘dose-response’ fashion. However, there does not appear
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55 to be specificity as different drugs have been shown to be associated with increased risk of
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3 psychosis or psychotic-like experiences; methamphetamine (McKetin, Hickey,
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5 Devlin, Lawrence, 2010), cocaine (Thirthalli & Benegal, 2006), and psychedelics (Kuzenko
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7 et al., 2011). The present findings highlight the importance of considering cannabis use
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9 within a broader polydrug context when attempting to infer causal links with psychosis.
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11 There are also clinical implications associated with these findings. It would be preemptive to
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13 state that smoking cannabis is a benign activity in relation to mental health, as much more
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15 research is required. In addition, the negative social, cognitive and physical consequences of
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17 cannabis use have been well documented (see review by Hall, 2015).
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23 Although cannabis use may be a proxy indicator for other forms of drug use, it is also
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25 likely to be associated (or interact) with other risk factors for psychosis such as childhood
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27 trauma (Houston, Murphy, Shevlin, & Adamson, 2011), familial risk for psychosis
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29 (Giordano, Ohlsson, Kendler, Sundquist, & Sundquist, 2014), ethnicity and social
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31 disadvantage (Morgan et al., 2009). Therefore, future studies of the effects of cannabis should
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33 place cannabis use within a broader context of correlated risk-factors, such as the social
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35 defeat model (Selten, van der Ven, Rutten, & Cantor-Graae, 2013).
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41 Although it may be difficult to isolate the unique effect of cannabis use on psychosis
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43 using epidemiological methods, alternative methods may be of use. Up until very recently,
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45 experimental studies using human subjects were all but impossible given the legal status of
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47 cannabis. Although animal studies offer some insight, there is no reliable model of psychosis
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49 in animals, making the generalization of findings difficult (Murray & DiForti, 2016).
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51 Following the legalisation of recreational marijuana in various parts of the USA in 2016,
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53 there will be increasing opportunities to test for causal associations between cannabis use and
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55 psychosis. This presents an opportunity to test different aspects of cannabis use that have
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3 been implicated in the “dose-response” relationship, e.g. frequency, type and strength
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5 (Marconi, Di Forti, Lewis, Murray & Vassos, 2016).
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10 The findings of the present study should be considered in light of the following
11 limitations. First, drug use was assessed using retrospective self-reports, which are open to
12 under- or over-reporting. Second, the temporal ordering of drug use and diagnosis of
13 psychosis cannot be established. Third, participant information about the frequency, type or
14 strength of cannabis use was not available, meaning the dose-response nature of the cannabis-
15 psychosis association could not be examined. Fourth, information regarding psychotic
16 diagnosis was only available up until age 21, yet it is relatively common for psychosis to
17 emerge up to the age of 35 years (Kessler, Amminger, Aguilar-Gaxiola, Alonso, Lee, &
18 Ustun, 2007). As such, the lifetime prevalence rate for psychotic disorder was relatively low
19 in the present sample. Further research over a greater age range is recommended. Fifth, the
20 genetic risk for psychosis was only approximated by using data for parental diagnosis of
21 psychosis. Data were limited to a recorded diagnosis anytime from four years prior to the
22 birth of the study child until the child was assessed aged 21, likely leading to an
23 underestimation of parental psychosis. Finally, the cell counts for the psychosis variable are
24 very unbalanced, with a small number of psychosis cases. This can cause problems with the
25 estimation of the logistic model. The effects of ‘rare event’ outcomes have been shown to
26 produce bias in the estimates by underestimating the probability of the outcome variable
27 (King & Zeng, 2001). The non-significant effect for the ‘Cannabis only’ category of the drug
28 use variable should be interpreted in light of the potential of a Type 2 error occurring.
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54 In summary, this study aimed to assess the relationship between patterns of
55 recreational drug use (no drug use, cannabis only, cannabis and other drug) and psychotic
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3 disorders. There was no significant effect for cannabis alone, but cannabis in conjunction
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5 with other drugs was statistically significant. Follow-up analyses indicated that polydrug use
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7 was significantly associated with increased risk of psychosis. Future research should address
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9 the context of cannabis use, both as part of more complex patterns of drug use but also in the
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11 context of a broader set of social, economic, and psychological risk factors.
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Acknowledgements

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18 The authors assert that all procedures contributing to this work comply with the ethical
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20 standards of the relevant national and institutional committee on human experimentation with
21
22 the Helsinki Declaration of 1975, as revised in 2008. The authors assert that ethical approval
23
24 for publication of this audit has been provided by their local REC. This research received no
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Table 1. Cross Tabulation of Psychosis Diagnosis, Gender, Parental Psychosis and Drug Use.

	Psychosis Diagnosis		χ^2 (df)	p
	No Count (%)	Yes Count (%)		
	No (N=2964)	Yes (N=14)		
Gender (Male)	1546 (52.2%)	7 (50.0%)	.03 (1)	.87
Parental Psychosis	45 (1.5%)	0 (0%)	.22 (1)	.64
Drug use				
No drug use	1437 (48.5%)	4 (28.6%)		
Cannabis only	940 (31.7%)	2 (14.3%)		
Cannabis and other drug	586 (19.8%)	8 (57.1%)	12.23 (2)	p < .01

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Table 2. Binary Logistic Regression for Psychosis Diagnosis, Gender, Parental Psychosis and Drug Use.

	B	Sig.	OR	95% C.I.
Gender (Male)	-.56	.32	.57	(0.19 - 1.72)
Parental Psychosis	.64	.68	1.90	(0.09 - 39.81)
No drug use (reference category)				
Cannabis only	-.37	.68	.69	(0.12 - 4.07)
Cannabis and other drug	1.79	.01	5.96	(1.71 - 20.75)

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