

Cannabis and Psychosis: Is There a Causal Link?

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INTRODUCTION

Psychosis refers to severe mental illness characterised by the presence of delusions, hallucinations and other associated cognitive and behavioural impairments that grossly interfere with the ability to meet the ordinary demands. The most well known psychosis is schizophrenia

INTRODUCTION (Cont)

Interest in the linkages between cannabis use and the development of psychosis or psychotic symptoms can be traced back to the Indian Hemp Commission of 1894. However, modern interest in this topic can be traced to a study conducted in 1987 by Andreasson and colleagues who looked at the relationship between cannabis use at 18 and later psychosis in a large sample of Swedish conscripts. This study found elevated rates of psychosis amongst those reporting cannabis use.

OTHER RESEARCH

Since Andreasson's original study there have been a series of prospective studies that have examined the link between the use of cannabis and the development of psychosis or psychotic symptoms. These studies include:

Arseneault et al, 2002; Fergusson et al 2003; Van os et al, 2002; Henguet et al 2005; Caspi et al 2005; Zammit et al 2002; Stefanis et al 2004.

In all studies, the use of cannabis has been found to be associated with increased rates of psychosis or psychotic symptoms.

SUMMARY OF PROSPECTIVE STUDIES OF CANNABIS USE AND PSYCHOTIC SYMPTOMS

Study	Sample	Assessment	Outcome measure	Adjusted association between cannabis and psychosis (95% CI)
Andreasson et al	45,570 male Swedish military conscripts aged 18-21	At 15 year follow-up	Clinical diagnosis of schizophrenia	Highest level of use: Relative risk 2.3 (1.0 to 5.3)
Arsenault et al	759 members of New Zealand birth cohort	At age 26	DSM-IV criteria for schizophreniform disorder	Cannabis users by age 15: Odds ratio 1.95 (0.76 to 5.01)
Caspi et al	803 members of New Zealand birth cohort	At age 26	DSM-IV criteria for schizophreniform disorder	Participants with Val/Val variant of COMT gene: Odds ratio 10.9 (2.2 to 54.1)
Fergusson et al	1,055 members of New Zealand birth cohort	At age 25	No of psychotic symptoms in past month	Daily cannabis users: Incident rate ratio = 1.77 (1.28 to 2.44)
Henquet et al	2,437 German participants aged 14 to 24	At baseline and four year follow up	At least one "broad" or two "narrow" psychosis outcomes	Daily cannabis users: Odds ratio 2.23 (1.30 to 3.84)
Van Os et al	4,104 participants in Dutch general population study	Assessed three times over four years	≥1 positive rating on psychotic symptom items	Highest level of use: Odds ratio 6.81 (1.79 to 25.92)

KEY ISSUES

Whilst longitudinal studies have clearly established a correlation between the use of cannabis and later psychosis, there have been ongoing debates about the extent to which this association reflects a causal relationship. Two major threats to validity have been raised.

1. **Confounding.** It has been proposed that the association arises because of third or confounding factors that are correlated with cannabis use and are also related to the development of psychosis. While existing research has controlled a large number of potential confounders, it may be proposed that the association reflects non observed uncontrolled confounding (McCleod et al 2004).

KEY ISSUES (Cont)

2. Reverse Causality: A second explanation is that the association may arise from self medication in which those with psychosis are more prone to use cannabis than other individuals.

AIMS

In this presentation I will describe the findings of a study in which we aimed to control non observed confounders and reverse causality.

CHRISTCHURCH HEALTH AND DEVELOPMENT STUDY AN OVERVIEW

- Initial Study Group (cohort): All children born in the Christchurch urban region during April to August 1977.
- Number studied: 1,265.
- Ages studied: Birth, 4 months, 1 year, annual intervals to 16 and again at ages 18, 21 and 25.

CHRISTCHURCH HEALTH AND DEVELOPMENT STUDY AN OVERVIEW (Cont)

- **Source of Information: Parents, School Teachers, Children, Official Records.**
- **In general terms, the study has aimed to provide a running record of the social background, health and development of a large group of Christchurch born children as they move from infancy into adulthood.**

SAMPLE RETENTION

At age 25, a total of 1,003 participants was studied. This sample represented 79% of the original cohort and 90% of the cohort resident in New Zealand.

MAIN MEASURES

1. **Self reported use of cannabis at: 17-18, 20-21 and 24-25 years.**
2. **Rates of psychotic symptoms assessed using the SCL90 at 18, 21, 25 years.**

ASSOCIATIONS BETWEEN CANNABIS USE AND PSYCHOTIC SYMPTOMS (18, 21, 25)

Frequency of Cannabis Use (Past 12 Months)

Age	Never	Less Than Monthly	At Least Monthly	At Least Weekly	Daily	p
18 Years	0.64 (598)	0.95 (242)	1.07 (82)	1.93 (70)	1.64 (33)	<.0001
21 Years	0.69 (538)	1.00 (215)	1.14 (100)	1.48 (94)	1.61 (64)	<.0001
25 Years	0.60 (559)	0.89 (232)	0.93 (76)	1.15 (81)	1.95 (55)	<.0001

COVARIATE ADJUSTMENT

To take account of confounding factors we used three methods of statistical adjustment.

1. Adjustment for observed covariates: Two methods (population averaged and random effects) adjusted the association for a range of fixed and time dynamic covariate factors. These include: socio-demographic factors; family functioning in childhood; exposure to child abuse; personality factors; mental health prior to cannabis use; peer affiliations; use of other illicit drugs.

COVARIATE ADJUSTMENT (Cont)

2. Adjustment for non observed covariates: In the second analysis we used a technique known as fixed effects regression to adjust for non observed fixed sources of confounding.

A BRIEF INTRODUCTION TO FIXED EFFECTS REGRESSION

To show how fixed effects regression works, assume that we have observed measures of psychosis (Y) and cannabis use (X) of two times. We could write the following model:

$$Y_1 = B_0 + B_1 X_1 + U + E_1 \quad \text{EQ1}$$

$$Y_2 = B_0 + B_1 X_2 + U + E_2 \quad \text{EQ2}$$

Where U denotes non observed fixed factors that influence Y.

A BRIEF INTRODUCTION TO FIXED EFFECTS REGRESSION (Cont)

If we subtract EQ2 from EQ1 we find:

$$(Y1 - Y2) = B1 (X1 - X2) + (E1 - E2)$$

By solving this equation we can estimate B1 net of the non observed factors U.

The fixed effects model is a generalisation of these principles.

ASSOCIATIONS BETWEEN CANNABIS USE AND PSYCHOTIC SYMPTOMS ADJUSTED FOR COVARIATES

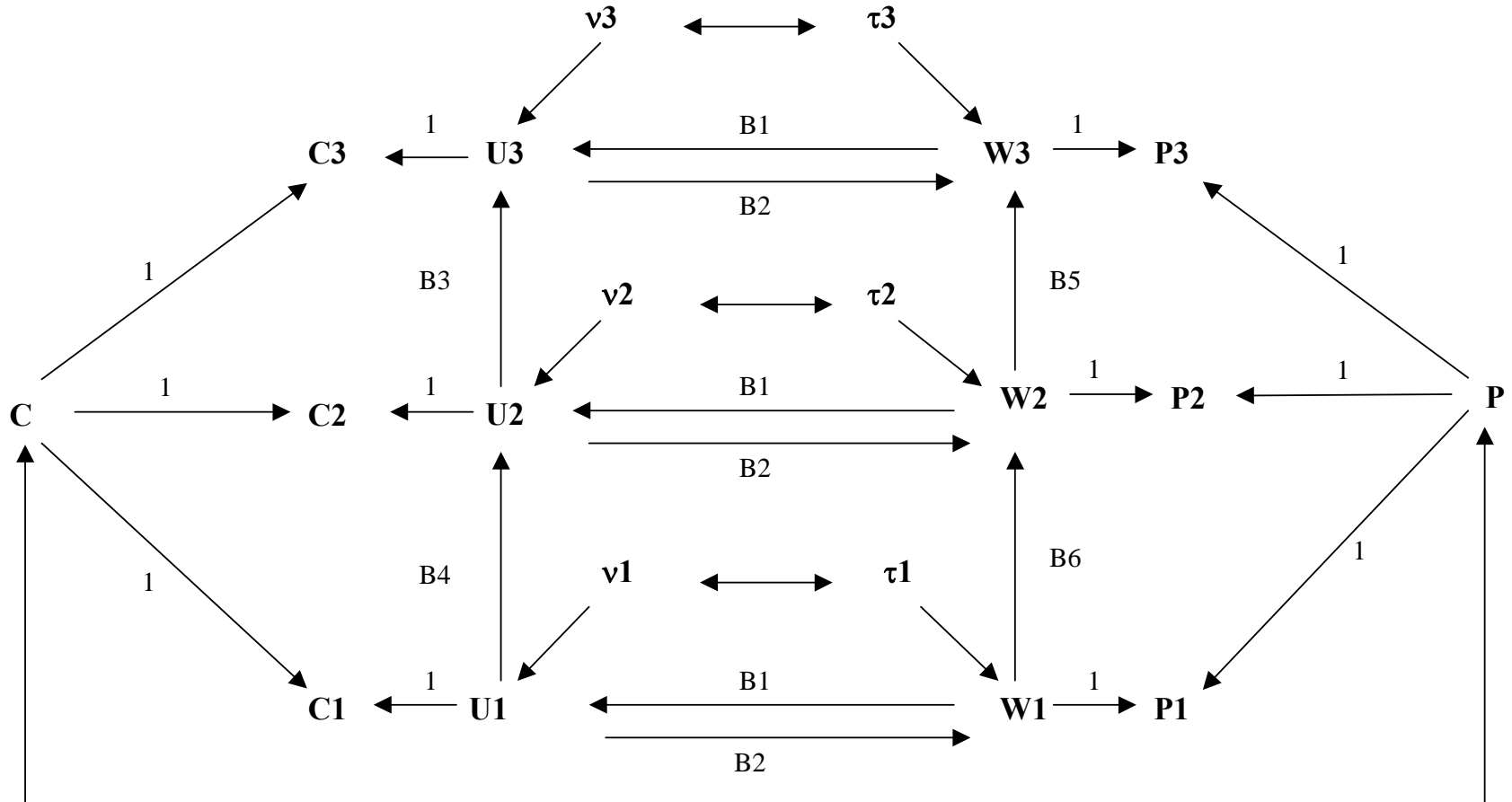
Frequency of Cannabis Use (Past 12 Months)

Covariate Adjustment Model	Never	Less Than Monthly	At Least Monthly	At Least Weekly	Daily	p
Model 1: Population averaged	1	1.12 (1.05-1.20)	1.25 (1.09-1.43)	1.40 (1.14-1.71)	1.56 (1.20-2.04)	<.001
Model 2: Random effects	1	1.12 (1.05-1.19)	1.24 (1.10-1.41)	1.39 (1.15-1.68)	1.55 (1.21-1.99)	<.001
Model 3: Fixed effects	1	1.15 (1.06-1.25)	1.33 (1.13-1.56)	1.53 (1.20-1.95)	1.77 (1.28-2.44)	<.001

ASSOCIATIONS BETWEEN CANNABIS USE AND PSYCHOTIC SYMPTOMS ADJUSTED FOR COVARIATES (Cont)

All models show that after adjustment for confounders daily users had rates of symptoms that were between 1.6-1.8 times higher than non users.

ADDRESSING REVERSE CAUSALITY



Key:

C_t = Cannabis use at time t.
 C = Fixed effects component of C_t.
 U_t = Time dynamic component of C_t.
 v_t = Disturbance term for U_t.

P_t = Psychotic symptoms at time t.
 P = Fixed effects component of P_t.
 W_t = Time dynamic component of P_t.
 τ_t = Disturbance term for W_t.

To examine reverse causality we extended the analysis to fit the multivariate model.

MODEL INTERPRETATION

While the model structure is complex, there are only two parameters of interest:

- 1. B1 which describes the effects of psychosis on cannabis use.**
- 2. B2 which describes the effects of cannabis use on psychosis.**

RECIPROCAL CAUSES MODEL

The results of the structural equation model (below) showed:

- i) The use of cannabis was associated with significant increases in rates of psychotic symptoms.**
- ii) Psychotic symptoms did not lead to an increase in cannabis use.**

RECIPROCAL CAUSES MODEL (Cont)

	Effect of Cannabis Use on Psychotic Symptoms		Effect of Psychotic Symptoms on Cannabis Use	
	B (se)	p	B (se)	p
Autoregressive model incorporating non-observed fixed effects	.352 (.087)	<.001	-.045 (.043)	>.25

Goodness of Fit Indices: LR χ^2 (5) = 4.00, p>.50; RMSEA = .00, p>.98; SRMR = .017; CFI = 1.00.

EVIDENCE IN FAVOUR OF A CAUSAL LINK

- 1. Association: All studies of general population samples have found increased rates of psychosis/psychotic symptoms amongst cannabis users.**
- 2. Dose/Response: Increasing use is associated with increasing risk.**

EVIDENCE IN FAVOUR OF A CAUSAL LINK (Cont)

- 3. Resilience to Confounding:** In all studies associations between cannabis and psychosis/ psychotic symptoms have persisted following control for confounding.
- 4. Control for Reverse Causality:** All studies to date have found that the association cannot be explained by reverse causation in which psychosis leads to the use of cannabis.

EVIDENCE IN FAVOUR OF A CAUSAL LINK (Cont)

- 5. Measurement: Associations have been found using both diagnoses of psychosis and scale score measures of psychotic symptoms.**

SIZE OF EFFECT

While all studies suggest a possible causal link between cannabis and psychosis, the size of the association is relatively small. Estimates suggest that elimination of all cannabis use could reduce overall rates of psychosis by 10%. One reason for the small effect size may be that only minority of the population are susceptible to the effects of cannabis.

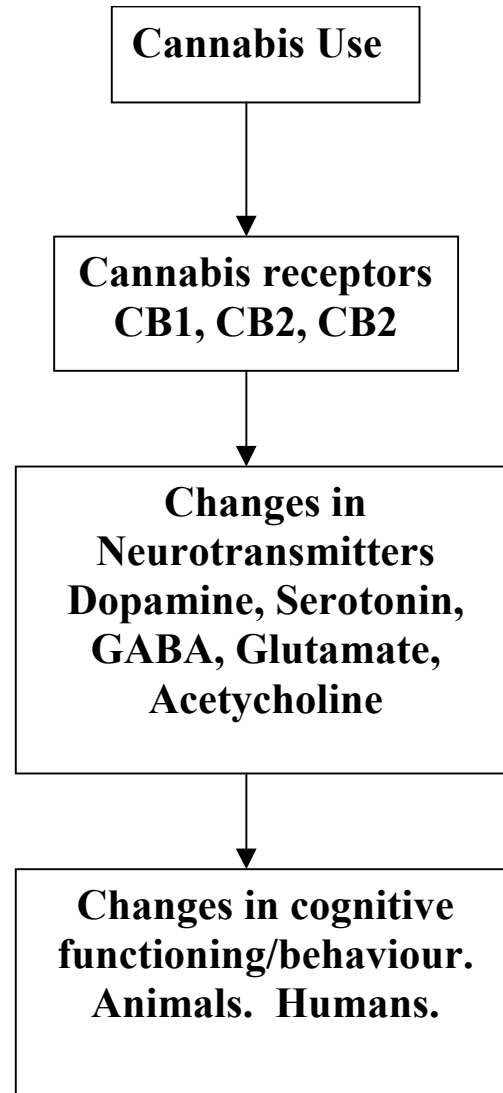
RECENT FINDINGS ON SUSCEPTIBILITY

There is growing research to suggest that the associations between cannabis and psychosis arise because of the effects on cannabis on individuals who are predisposed to psychosis. Recent studies have found that an association between cannabis and psychosis/psychotic symptoms exists for those with a family history or other related factors.

RECENT FINDINGS ON SUSCEPTIBILITY (Cont)

These issues have been highlighted in a recent genetic study reported by Caspi et al which showed that an association between cannabis and psychosis only existed for individuals having a particular variant (Val/Val) of the COMT gene. COMT is a gene which regulates a neurotransmitter known as dopamine. Approximately 25% of the population have the Val/Val variant of COMT. Dopamine has been implicated in the development of schizophrenia.

PATHWAYS LINKING CANNABIS TO PSYCHOSIS



IMPLICATIONS FOR PROHIBITION/LEGALISATION OF CANNABIS

Findings on the link between cannabis and psychosis have been used to argue against attempts to liberalise cannabis laws. As with all issues in the cannabis debate, matters are not straightforward.

ARGUMENT AGAINST LIBERALISATION

It could be suggested that since the use of cannabis may lead to psychosis in susceptible individuals, there are grounds for opposing the liberalisation of the cannabis laws.

ARGUMENT FOR LIBERALISATION

It could also be suggested that since the effects of cannabis on psychosis are small, this link does not provide grounds for opposing liberalisation. The majority of recreational cannabis users do not appear to suffer harmful effects and at current levels of use, cannabis is less harmful than alcohol or tobacco.

WEIGHING THE EVIDENCE

As in all aspects of the cannabis debate, the arguments for and against cannabis legalisation involve weighing the rights of the majority for whom cannabis use is not harmful against the risk of the minority who experience adverse consequences.