RELATIONSHIP BETWEEN CANNABINOIDS AND PSYCHOSIS

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THESIS: THC can cause psychosis in a small percent of the population with psychotic predisposition, while CBD can reverse drug induced psychosis linked to THC and other classes of pro-psychotic drugs.

Table 1. Meta-analysis of Substance Use and Age at Onset of Psychosis Grouped by Substance, Sex, and Severity of Substance Use

Group	Samples, No.	Effect Size, y: Point Estimate	SE	Variance	95% CI	Between-Sample Heterogeneity	Between-Group Heterogeneity
All studies defined by substance use type							
Alcohol use	22	−0.28	−0.038	0.081	0.007	−0.196 to 0.120	
Cannabis use[a]	41[a]	−2.70	−0.414	0.058	0.003	−0.526 to −0.301	Q=495; df (Q)=130; P (Q)≤.001; I²=78.1
Substance use[b]	68[b]	−2.00	−0.315	0.046	0.002	−0.405 to −0.225	Q=14.52; df (Q)=2; P (Q)=.001
Overall	131	−1.73	−0.264	0.096	0.009	−0.453 to −0.075	
Studies reporting groups by sex							
Females	13	−3.40	−0.365	0.131	0.017	−0.622 to −0.108	Q=276; df (Q)=36; P (Q)≤.001; I²=86.9
Males	24	−1.87	−0.325	0.096	0.009	−0.513 to −0.138	Q=0.1; df (Q)=1; P (Q)=.81
Studies reporting groups of heavy or continued users vs lighter or discontinuing users							
Lighter or discontinued use	10	−2.07	−0.301	0.113	0.013	−0.522 to −0.080	Q=33.7; df (Q)=19; P (Q)=.02; I²=43.7
Heavy or continued use	10	−2.72	−0.428	0.110	0.012	−0.644 to −0.211	Q=0.6; df (Q)=1; P (Q)=.42

Table 2. Meta-regression and Multiple Meta-regression of Factors Associated With Heterogeneity in the Effect Size of Substance Use on the Age at Onset of Psychosis

Factor	Samples, No.[a]	Point Estimate of Slope	SE of Slope	95% CI of Slope	Z Value	P Value	τ²
Meta-regression of sample characteristics							
Proportion using cannabis in substance-using group	114	−0.004	0.001	−0.006 to −0.002	−3.34	<.001	0.088
Ratio of proportion of males in substance-using and control groups	102	−0.240	0.117	−0.469 to −0.011	−2.05	.04	0.089
Proportion of all subjects with schizophrenia	119	0.002	0.002	−0.002 to 0.005	0.83	.41	0.113
Meta-regression of methodological and quality characteristics							
Upper limit of age ≥45 y at presentation	26/131	−0.242	0.082	−0.402 to −0.081	−2.96	.003	0.102
Some substance users in control group	55/131	0.020	0.071	−0.118 to 0.158	−0.28	.77	0.111
Conducted at time of first episode of psychosis	61/131	−0.067	0.068	−0.202 to 0.068	−0.97	.33	0.107
Defined onset as time of initial treatment	44/131	−0.023	0.075	−0.170 to 0.125	−0.30	.76	0.111
Systematic measure for diagnosis and substance use	87/131	0.038	0.074	−0.106 to 0.182	0.52	.60	0.111
Year of publication of studies	131	0.003	0.005	−0.007 to 0.014	0.66	.51	0.111
Multiple meta-regression of factors found to be associated with between-study heterogeneity by meta-regression							
Ratio of proportion of males in substance-using and control groups		−0.253	0.142	−0.532 to 0.025	−1.78	.08	0.078
Proportion of cannabis users	87[b]	−0.004	0.001	−0.006 to −0.001	−2.83	.006	
Age ≥45 y at presentation		−0.216	0.089	−0.390 to −0.025	−2.44	.02	
Constant		0.422	0.210	0.010 to 0.834	2.01	.04	

Large's 2011 study performed a meta-data analysis on many studies and found a definite correlation between adolescent use of cannabis and a decrease in the age at onset of psychosis related disorders (mainly schizophrenia). The authors indicate that much of the raw scientific data derived from various studies did not indicate whether cannabis use predated the onset of psychosis, making the link a correlative rather than causal one. This means the authors cannot be sure if the psychosis increases the likelihood of cannabis use, or if the cannabis increases the likelihood of psychosis, an important distinction.

Large M, Sharma S, Compton MT, Slade T, Nielssen 0 (June 2011). "Cannabis use and earlier onset of psychosis: a systematic meta-analysis". Arch. Gen. Psychiatry 68 (6): 555-61. doi:10.1001/-archgenpsychiatry2011.5. PMID 21300939

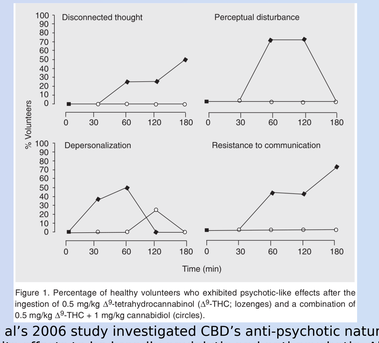

Figure 1. Percentage of healthy volunteers who exhibited psychotic-like effects after the ingestion of 0.5 mg/kg Δ^9-tetrahydrocannabinol (Δ^9-THC; lozenges) and a combination of 0.5 mg/kg Δ^9-THC + 1 mg/kg cannabidiol (circles).

Zuardi et al's 2006 study investigated CBD's anti-psychotic nature, and revealed its effects to be broadly anxiolytic and anti-psychotic. Although THC's ability to induce psychotic-like symptoms seems to suggest CBD's antagonist properties at the cannabinoid are solely responsible for its anti-psychotic properties, CBD's ability to reverse anxiety in cannabinoid-naive subjects suggested otherwise. Amphetamine and ketamine induced psychosis in mice, which effect the dopaminergic neurons (D2) and glutaminergic neurons (NMDA) respectively, were both reversed by CBD administration. This indicates that CBD's anti-psychotic effect may have a broader pharmacological basis than Cbl, D2, or NMDA antagonism alone. This is consistent with Campos et al's 2012 theory that the TRVPl receptor (of which CBD is an agonist) is responsible for contributing to CBD's anti-psychotic effects. Additionally, Zuardi's team found that CBD was both a safe and efficacious alternative treatment for schizophrenia which was well tolerated.

Zuardi AW, Crippa JA, HallakJE, Moreira FA, Guimaraes FS (April 2006)."Cannabidiol, a Cannabis sativa constituent, as an antipsychotic drug". Braz. J. Med. Biol. Res. (Review) 39 (4): 421-9. doi:10.1590/SOI00-879X2006000400001.PMID 16612464

Table I Epidemiological studies on cannabis use and schizophrenia

Study	Study design (c) Year of enrollment	Gender	Number of participants	Follow-up (years)	Age of cannabis users (years)	Outcome n (%)	Diagnostic criteria/ instrument	Definition of cannabis use	Risk of schizophrenia-related outcome associated with cannabis use OR (95% CI)	Adjusted risk (OR, 95% CI)	Confounding variables controlled for	Dose–response relationship	Specificity of risk factor	Specificity of outcome
Swedish conscript cohort Andréasson et al., 1988	Conscript cohort (~50 000) 1969–1970	Male	45 570	15	18	In-patient admission for schizophrenia, 244 (0.5)	ICD–8	Used cannabis > 50 times at age 18 years	4.0 (4.0–4.9)	3.3 (1.8–5.3)	Psychiatric diagnosis at conscription Parents divorced	Yes	No	NA
Zammit et al., 2002	Conscript cohort (~50 000), 1969–1970	Male	50 053	27	18	Hospital admission for schizophrenia, 362 (0.7)	ICD–8/9	Used cannabis > 50 times at 18 years	6.7 (4.5–10.0)	3.1 (1.7–5.5)	Diagnosis at conscription Sex Social recognition Disturbed behaviour and cigarette smoking Place of upbringing	Yes	Yes	NA
NEMESIS van Os et al., 2002	Population-based (70%) 1996	Male and female	4104	3	18–64	(a) Any level of psychotic symptoms, 22 (0.9) (b) Pathology level of psychotic symptoms, 10 (0.5) (c) Need for care, 7 (0.2)	BPRS	Cannabis use at baseline (age 18–17 years)	3.25 (1.5–7.2) 28.54 (7.3–110.9) 16.15 (3.6–72.5)	2.76 (1.3–4.5) 34.17 (5.44–107.5) 12.01 (2.4–44.3)	Age Gender Ethnic group Single-marital status Education Urban dwelling Discrimination	Yes	Yes	NA
Christchurch study Fergusson et al., 2003	Birth cohort (1265) 1977	Male and female	1011	–	21	Psychotic symptoms, NA	SCL–90	DSM–IV cannabis dependent at age 21 years	3.3 (2.0–5.5)	1.8 (1.3–2.4)	Time-varying covariates (e.g. nicotine, alcohol, other drug dependence) Fixed covariates (e.g. gender IQ, parental criminality)	NA	Yes	NA
Dunedin Study Arseneault et al., 2002	Birth cohort (1037) 1972–1973	Male and female	759	11	15–18	Schizophreniform disorder: (a) Symptoms (b) Diagnosis, 25 (3.3)	DSM–IV	Users by the age of 15 years and continued at 18 years	3–6.91 (5.1–8.7) 4.00 (1.1–18.2)	3–6.54 (4.9–8.34) 3.32 (0.7–13.3)	Gender Social class Psychotic symptoms prior to cannabis use	NA	Yes	Yes
Overall risk[1]										2.34 (1.69–3.19)				

BPRS, Brief Psychiatric Rating Scale; NEMESIS, Netherlands Mental Health Survey and Incidence Study; SCL–90, 90–item Symptom Check List.
1. Beta of multiple linear regression.
2. The adjusted odds ratios included in the calculation of the overall risk for psychosis are in bold type. Results across studies were homogeneous (test for heterogeneity: Q–2839 on four degrees of freedom; P–0.580).

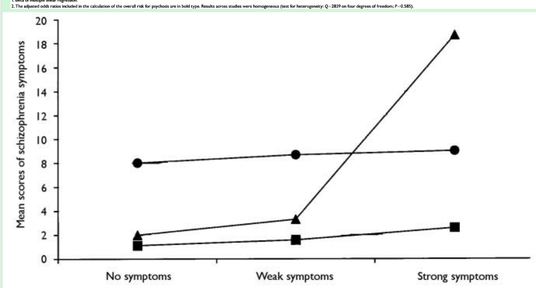

Fig. 1 Interaction between cannabis use at age 18 years and psychotic symptoms at age 11 years in predicting adult schizophrenia symptoms. –■– controls; –●– users by age 15; –▲– users by age 18.

According to Arseneault's 2004 study, although cannabis use is correlated with earlier onset of psychosis in adolescents, they strongly indicate this phenomenon is only believed to occur in at-risk groups, such as family history of psychosis, or symptoms of psychosis predating cannabis use. This is difficult to prove because the mechanism of psychosis development in the brain is not well understood, and the role of cannabinoid receptors in this process is even less well known. An overall acceptance of the fact that cannabis use can exacerbate at- risk (of psychosis) youths pervades the literature on the subject. The author's language best describes the exact nature of the relationship: "Cannabis use appears to be neither a sufficient nor a necessary cause for psychosis. It is a component cause, part of a complex constellation of factors leading to psychosis.

Arseneault L, Cannon M, Witton J, Murray RM (2004). "Causal association between cannabis and psychosis: examination of the evidence". The British Journal of Psychiatry 184(2): 110-117. doi:-10.1192/bjp.184.2.110. PMID 14754822

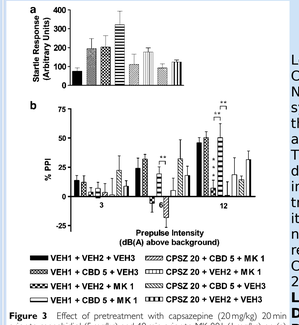

Figure 3 Effect of pretreatment with capsazepine (20 mg/kg) 20 min prior to cannabidiol (5 mg/kg) and 40 min prior to MK-801 (1 mg/kg) on (a) acoustic startle response and (b) prepulse inhibition (PPI) of the startle response in mice. Results are expressed as mean ± SEM. $n = 5$–8. $^{**}P < 0.01$ between treatment groups as indicated, $^{***}P < 0.001$ vs vehicle treatment group (individual planned comparisons, $\alpha = 0.01$) 25). CPSZ = capsazepine, CBD = cannabidiol, MK = MK-801, VEH1 = 1 : 1 : 98 Tween^{80} : EtOH : saline, VEH2 = 1 : 1 : 18 Cremophor^{RK} EL : EtOH : saline, VEH3 = 0.1% ascorbic acid in distilled water.

Long et al's 2005 study investigated CBD's ability to reverse MK—801 (an NMDA antagonist) induced psychotic symptoms in mice. CBD did reverse the effects of MK—801, but when co-administered with capsazepine, a TRVPl antagonist, CBD's effects disappeared. This evidence strongly indicates TRVPl's role in CBD treatable psychosis, and potentially its interrelation to several other neural systems (such as the NMDA receptor seen here, or the D2 and C81 neural systems cited in Zuardi 2006 and Campos 2012).

Long, L. E.; Malone, D. T.; Taylor, D. A. (2005). "Cannabidiol Reverses MK-801-Induced Disruption of Prepulse Inhibition in Mice". Neuropsychopharmacology 31 (4): 795-803.doi:10.1038/sj.npp.-1300838. PMID 16052245

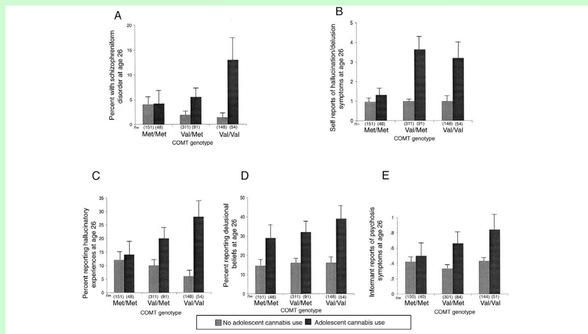

Figure 1. The influence of adolescent-onset cannabis use on adult psychosis is moderated by variations in the COMT gene. **(A)** The percentage of individuals meeting diagnostic criteria for schizophreniform disorder at age 26. **(B)** Means (and standard errors) on age-26 self-reports of symptoms of psychosis (hallucinations and delusions). **(C)** The percentage of individuals reporting at least one hallucination experience at age 26. **(D)** The percentage of individuals reporting at least one delusional belief at age 26. **(E)** Means (and standard errors) on age-26 informant reports of symptoms of psychosis.

Table 3. Comparisons of the Three (Genotype) by Two (Adolescent-Onset Cannabis Use) Groups on Covariates and Outcomes

Covariates[a]	Non-Cannabis-Using Adolescents: Met/Met (n = 151)	Val/Met (n = 311)	Val/Val (n = 148)	Early-Onset Adolescent Cannabis Users: Met/Met (n = 48)	Val/Met (n = 91)	Val/Val (n = 54)
Adult cannabis use (%)[b]	21.8	25.2	25.7	70.2	69.6	71.7
Adolescent use of drugs other than cannabis (%)[c]	1.3	1.0	2.0	41.7	40.0	42.6
Adult use of amphetamines and hallucinogens (%)[d]	15.2	16.7	16.2	52.1	50.6	50.0
Childhood psychotic symptoms (%)[e]	15.4	10.0	13.6	21.6	18.3	14.3
Childhood IQ (M, SD)	110 (13)	107 (13)	108 (14)	107 (13)	107 (13)	107 (12)
Adolescent conduct disorder (%)[f]	10.5	11.5	16.9	52.1	42.4	46.3
Outcomes						
Diagnosis of schizophreniform disorder (%)	4.0	2.3	1.4	4.2	5.5	13.0
Self-reports of psychotic symptoms (M, SD)	.96 (2.8)	.99 (2.8)	.98 (3.1)	1.3 (2.4)	3.6 (6.7)	3.2 (7.1)
Evidence of hallucinatory experiences (%)	12.6	9.7	6.8	14.6	22.0	27.8
Evidence of delusional beliefs (%)	14.6	16.4	15.5	29.2	31.9	38.9
Informant reports of psychotic symptoms (M, SD)	.42 (.71)	.33 (.54)	.44 (.67)	.50 (.87)	.66 (1.1)	.84 (1.1)

[a]The covariates offer alternative explanations of the obtained G × E results. There was no significant association between genotype and any of the covariates (all p values exceed .35). There was a significant association between adolescent-onset cannabis use and adult cannabis use ($p < .001$), use of other drugs in adolescence ($p < .001$), use of amphetamines and hallucinogens in adulthood ($p < .001$), and adolescent conduct disorder ($p < .001$), but not between adolescent-onset cannabis use and childhood psychotic symptoms ($p = .06$) and childhood IQ ($p = .27$). Moreover, the observed G × E interaction could not be accounted for by the pattern of associations in the six exposure cells; that is, when stratified by adolescent-onset cannabis use, the three genotype groups did not differ from each other on any of the covariates.
[b]Percent study members reporting using cannabis, on average, on a monthly basis at age 21 years, 26 years, or both.
[c]Percent study members reporting trying other drugs at age 15 years, 18 years, or both.
[d]Percent study members reporting using amphetamines, hallucinogens, or both at age 21 years, 26 years, or both.
[e]Percent study members reporting "strong" or "weak" psychotic symptoms at age 11 years.
[f]Percent study members meeting diagnostic criteria for conduct disorder between ages 11 and 18 years.

Caspi et al's 2005 study correlated an earlier onset of psychosis in cannabis users with a specific polymorphism in the catecholamine o-methyltransferase gene, specifically the Valine-158 allele was the most likely to be correlated with psychotic symptoms. This indicates that those at risk may potentially be informed through genetic testing. The paper goes so far as to state that cannabis users with a homozygous Methionine-158 genotype will have no such adverse effects from cannabis consumption. Alternatively a study conducted by Zammit et al in 2007 concluded that cannabis use had no modulatory effects on psychotic symptoms or on either valine or methionine allele catecholamine o- methyltransferase.

Caspi A, Moffitt TE, Cannon M, McClayJ, Murray R, Harrington H, Taylor A, Arseneault L, Williams B, Braithwaite A, Poulton R, Craig IW (2005). "Moderation of the Effect of Adolescent-Onset Cannabis Use on Adult Psychosis by a Functional Polymorphism in the Catechol-O-Methyltransferase Gene: Longitudinal Evidence of a Gene X Environment Interaction". Biological Psychiatry 57 (10): 1117-27. doi:10.1016/-j.biopsych.2005.01.026.PMID 15866551

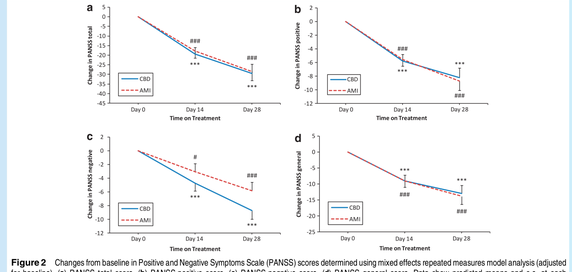

Figure 2 Changes from baseline in Positive and Negative Symptoms Scale (PANSS) scores determined using mixed effects repeated measures model analysis (adjusted for baseline). (**a**) PANSS total score. (**b**) PANSS-positive score. (**c**) PANSS-negative score. (**d**) PANSS general score. Data show predicted means and s.e. at each weak. Statistical significance is calculated between groups ($^{\dagger}P \leq 0.05$, $^{\dagger\dagger}P \leq 0.01$ and $^{\dagger\dagger\dagger}P \leq 0.001$) and vs baseline (that is, 0; *CBD, $^{\#}$AMI; $^{***\#\#\#}P \leq 0.05$, $^{**\#\#}P \leq 0.01$, $^{*\#}P \leq 0.001$).

Table 1 Patterns of cannabis use at baseline and psychotic symptoms at follow up. Figures are numbers (percentages) of participants

Cannabis use at baseline	Any psychotic symptom at follow up: Yes (n=424)	No (n=2013)	At least two psychotic symptoms at follow up: Yes (n=174)	No (n=2263)
Any use (≥5 times)	82 (19.3)	238 (11.8)	44 (25.3)	276 (12.2)
Cumulative frequency*:				
None	342 (80.7)	1775 (88.2)	130 (74.7)	1987 (87.8)
<1 times/month	13 (3.1)	69 (3.4)	5 (2.9)	77 (3.4)
3–4 times/month	18 (4.2)	62 (3.1)	10 (5.7)	70 (3.1)
1-2 times/week	17 (4.0)	40 (2.0)	7 (4.0)	50 (2.2)
3–4 times/week	12 (2.8)	21 (1.0)	8 (4.6)	25 (1.1)
Almost daily	22 (5.2)	46 (2.3)	14 (8.0)	54 (2.4)

*Some percentages do not total 100 because of rounding.

Table 4 Interactions between any cannabis use and predisposition for psychosis

Cannabis use at baseline	No with psychosis outcome*	No without psychosis outcome*	Risk of psychotic symptoms at follow up	Difference in risk: Unadjusted	Adjusted† (95% CI)
No predisposition for psychosis at baseline					
None	294	1642	15%	6%	5.6% (0.4 to 10.8) P=0.033
Any (≥5 times)	59	216	21%		
Predisposition for psychosis at baseline‡					
None	47	133	26%	25%	23.8% (7.9 to 39.7) P=0.003
Any (≥5 times)	23	22	51%		

*Numbers total 2436 because of one missing value on predisposition for psychosis at baseline.
†Age, sex, socioeconomic status, urbanicity, childhood trauma, and predisposition for psychosis at follow up. Test for additive interaction 18.2% adjusted difference in risk (95% confidence interval 1.6 to 34.8), P=0.032 (tests whether risk difference in "predisposition" group is significantly greater than risk difference in "no predisposition" group).

What is already known on this topic

It is generally accepted that cannabis use is strongly associated with psychosis

We do not know whether the association is causal or whether those with a predisposition for psychosis are particularly at risk

What this study adds

Cannabis use in young people moderately increased the risk of developing psychotic symptoms

The risk for the onset of symptoms was much higher in young people with a predisposition for psychosis

Predisposition psychosis at baseline did not predict cannabis use at follow up, thus refuting the self medication hypothesis

The debate over cannabis' causal connection to schizophrenic onset in adolescents has been ongoing in the scientific community for some time, and fortunately has produced a wealth of literature, and more importantly, empirical evidence on the subject. For example, Henquet's 2005 study concludes, "Cannabis use moderately increases the risk of psychotic symptoms in young people but has a much stronger effect in those with evidence of predisposition for psychosis."

Henquet C, Krabbendam L, Spauwen J, Kaplan C, Lieb R, Wittchen HU, van OsJ (2005)."Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people". BMJ 330 (7481): 11-0. doi:-10.1136/ bmj.38267.664086.63.PMC 539839. PMID 15574485

Leweke et al's 2012 study performed a clinical trial with schizophrenic patients comparing the efficacy of CBD versus amisulpride. The study cited previous work's by Lewek where the elevated levels of synpatic anandamide (a endocannabinoid ligand for Cbl receptors in the brain) correlated with CBD plasma levels, indicating CBD's ability to inhibit enzymatic degradation of anandamide (through Fatty Acid Amide Hydrolase or FAAH). The study found that CBD was equally effective as amisulpride (a drug that antagonizes D2 and D3 dopamine receptors) at treating psychotic symptoms of schizophrenia, but with a much reduced profile of side-effects. These findings indicate that proper use or drug-assisted optimization of the transmission of endocannabinoids can preclude harsher dopamine antogonist drug therapy.

Leweke, FM; Piomelli D, Pahlisch F, Muhl D, Gerth CW, Hoyer C, KlosterkotterJ, Hellmich M and Koethe D. (2012). "Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia". Translational Psychiatry 2 (3): e94-.doi:10.1038ltp.-2012.15. PMC 3316151. PMID 22832859

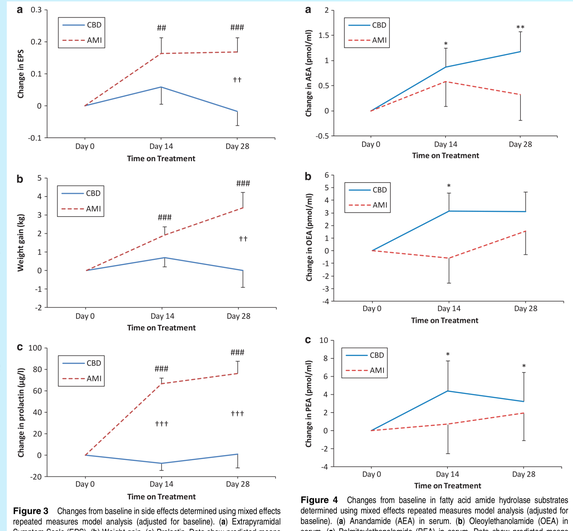

Figure 3 Changes from baseline in side effects determined using mixed effects repeated measures model analysis (adjusted for baseline). (**a**) Extrapyramidal Symptom Scale (EPS). (**b**) Weight gain. (**c**) Prolactin. Data show predicted means and s.e. at each weak. Statistical significance is calculated between groups ($^{\dagger}P \leq 0.05$, $^{\dagger\dagger}P \leq 0.01$ and $^{\dagger\dagger\dagger}P \leq 0.001$) and vs baseline (that is, 0; *CBD, $^{\#}$AMI; $^{***\#\#\#}P \leq 0.05$, $^{**\#\#}P \leq 0.01$, $^{*\#}P \leq 0.001$).

	Attempt to limit reverse causation	Attempt to limit intoxication effects	Approximate change from crude to adjusted OR (%)*
CHDS[31,34,‡]	Adjusted for psychotic symptoms at previous assessment and used SEM to address direction of causation	Used SCL-90to measure outcome. This does not allow identification of symptoms caused by drug intoxication	65% ↓
Dunedin[32,‡]	Adjusted for psychotic symptoms at age 11 years (cannabis measures at age 15 and 18 years)	Used DIS to measure outcome. Excluded symptoms caused solely by drug use	10% ↓
ECA[30]	Excluded people with psychotic diagnosis at baseline	Used DIS to measure outcome. Excluded symptoms caused solely by drug use	30% ↓
EDSP[33]	Adjusted for predisposition to psychosis measured at baseline	Used M-CIDI to measure outcome. Stated that no symptoms were due to acute effects of drug use	15% ↓
NEMESIS[35]	Excluded people with psychotic symptoms at baseline	Used CIDI to measure outcome. Excluded symptoms caused by drug use	50% ↓
NPMS[37]	Excluded people with psychotic symptoms at baseline	Used PSQ to measure outcome. This does not allow identification of symptoms caused by drug intoxication	80% ↓
Swedish conscripts[36,‡]	Excluded people with psychotic diagnosis at baseline	Used ICD clinical diagnosis of schizophrenia as outcome, suggesting intoxication effects unlikely	60% ↓

OR=odds ratio. SEM=structural equation modelling. SCL-90=symptom checklist 90. DIS=diagnostic interview schedule. M-CIDI=Munich version of CIDI. CIDI=composite international diagnostic interview. PSQ=psychosis screening questionnaire. ICD=International classification of diseases. ↓=decrease. *Change between crude OR and that after adjustment for confounding factors was calculated as (crude OR–adjusted OR)/(crude OR–1). †Additional data, to allow estimation of change between crude and adjusted estimates, kindly provided by the researchers.

Table 1: Information on possible alternative causes for associations reported between cannabis use and psychosis outcomes in seven cohorts

Conversely, Moore's 2007 longitudinal study concluded with a very different tone: "The evidence is consistent wit the view that cannabis increases risk of psychotic outcomes independently of confounding and transient intoxication effects, although evidence for affective outcomes is less strong. The uncertainty about whether cannabis causes psychosis is unlikely to be resolved by further longitudinal studies such as those reviewed here. However, we conclude that there is now sufficient evidence to warn young people that using cannabis could increase their risk of developing psychotic illness later in life"

Moore TH, Zammit S, Lingford-Hughes A, Barnes TR, Jones PB, Burke M, Lewis G (2007). "Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review". The Lancet 370 (9584): 319-28. doi:-10.1016ISOI40-6736 (07)61162-3. PMID 17662880

Figure 4 Changes from baseline in fatty acid amide hydrolase substrates determined using mixed effects repeated measures model analysis (adjusted for baseline). (**a**) Anandamide (AEA) in serum. (**b**) Oleoylethanolamide (OEA) in serum. (**c**) Palmitoylethanolamide (PEA) in serum. Data show predicted means and s.e. at each weak. Statistical significance is calculated between groups ($^{\dagger}P \leq 0.05$, $^{\dagger\dagger}P \leq 0.01$ and $^{\dagger\dagger\dagger}P \leq 0.001$) and vs baseline (that is, 0; *CBD, $^{\#}$AMI; $^{***\#\#\#}P \leq 0.05$, $^{**\#\#}P \leq 0.01$, $^{*\#}P \leq 0.001$).