A Synopsis of the Numerous Studies Supporting an Causal Relationship between Marijuana Use and The Chronic Psychotic Disorder Schizophrenia

A meta-analysis of all studies worldwide showing association between marijuana use and schizophrenia:

Moore TH, Zammit S, Lingford-Hughes A, et al. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. Lancet. 2007;370:319–328.
http://dirwww.colorado.edu/alcohol/downloads/Cannabis_and_behavior.pdf

> "There was an increased risk of any psychotic outcome in individuals who had ever used cannabis…with greater risk in people who used cannabis most frequently. There is now sufficient evidence to warn young people that using cannabis could increase their risk of developing a psychotic illness later in life."

The most recent study conducted in the United States (Columbia University, New York), showing a high risk (odds ratio, "OR") for schizophrenia spectrum disorders, particularly in those who become cannabis-dependent:

Davis GP, Compton MT, Wang S, Levin FR, Blanco C. Association between cannabis use, psychosis, and schizotypal personality disorder: findings from the National Epidemiologic Survey on Alcohol and Related Conditions. Schizophr Res. 2013 Dec;151(1-3):197-202.

> "There was a similar dose-response relationship between the extent of cannabis use and schizotypal personality disorder (OR=2.02 for lifetime cannabis use, 95% CI 1.69-2.42; OR=2.83 for lifetime cannabis abuse, 95% CI 2.33-2.43; OR=7.32 for lifetime cannabis dependence, 95% CI 5.51-9.72). Likelihood of individual schizotypal features increased significantly with increased extent of cannabis use in a dose-dependent manner."

Studies that corrected for general genetic background effects and many non-cannabis environmental variables by comparing siblings. The risk ratios are somewhat lower than general population studies, because genetic predisposition is more or less controlled for:

*McGrath J, Welham J, Scott J, Varghese D, Degenhardt L, Hayatbakhsh MR, Alati R, Williams GM, Bor W, Najman JM. Association between cannabis use and psychosis-related outcomes using sibling pair analysis in a cohort of young adults. Arch Gen Psychiatry. 2010; 67(5):440-***7.**

> "Longer duration since first cannabis use was associated with multiple psychosis-related outcomes in young adults... the longer the duration since first cannabis use, the higher the risk of psychosis-related outcomes...
> Compared with those who had never used cannabis, young adults who had 6 or more years since first use of cannabis (i.e., who commenced use when around 15 years or younger) were twice as likely to develop a nonaffective psychosis...
> This study provides further support for the hypothesis that early cannabis use is a risk-modifying factor for psychosis-related outcomes in young adults."

Giordano GN, Ohlsson H, Sundquist K, Sundquist J, Kendler KS. The association between cannabis abuse and subsequent schizophrenia: a Swedish national co-relative control study. Psychol Med. 2014 Jul 3:1-8. [Epub ahead of print]
http://journals.cambridge.org/download.php?file=%2FPSM%2FS0033291714001524a.pdf&code=79f795824a92c8eead870197ef071dd8

> "Allowing 7 years from initial CA registration to later diagnosis, the risk for schizophrenia in discordant full sibling pairs remained almost twofold….The results of this study therefore lend support to the etiologic hypothesis, that CA is one direct cause of later schizophrenia."

Those diagnosed with schizophrenia who also use recreational drugs are much more likely to be violent, including those who use cannabis:

Fazel S, Långström N, Hjern A, Grann M, Lichtenstein P. Schizophrenia, substance abuse, and violent crime. JAMA. 2009 May 20;301(19):2016-23.

> "The risk was mostly confined to patients with substance abuse comorbidity (of whom 27.6% committed an offense), yielding an increased risk of violent crime among such patients (adjusted OR, 4.4; 95% CI,3.9-5.0), whereas the risk increase was small in schizophrenia patients without substance abuse comorbidity (8.5% of whom had at least 1 violent offense; adjusted OR,1.2; 95% CI, 1.1-1.4; P<0.001 for interaction)."

Fazel S, Gulati G, Linsell L, Geddes JR, Grann M. Schizophrenia and violence: systematic review and meta-analysis. PLoS Med. 2009 Aug;6(8):e1000120. doi: 10.1371/journal.pmed.1000120. Epub 2009 Aug 11.

> "The effect of comorbid substance abuse was marked with….. an OR of 8.9" (as compared to the general population)

Arseneault L, Moffitt TE, Caspi A, Taylor PJ, Silva PA. Mental disorders and violence in a total birth cohort: results from the Dunedin Study. Arch Gen Psychiatry. 2000;57(10):979-86.

> "for having more than two of these disorders at once…..the OR (odds ratio for violence) was, …..for marijuana dependence plus schizophrenia spectrum disorder, 18.4"

Harris AW, Large MM, Redoblado-Hodge A, Nielssen O, Anderson J, Brennan J. Clinical and cognitive associations with aggression in the first episode of psychosis. Aust N Z J Psychiatry. 2010 Jan;44(1):85-93.

> 'The use of cannabis with a frequency of more than fourfold in the previous month was the only factor that was found to be associated with serious aggression'

Self-report of psychotic symptoms by otherwise healthy users (12% to 15%):

Thomas H. A community survey of adverse effects of cannabis use. Drug Alcohol Depend. 1996 Nov;42(3):201-7.

> "This survey estimates the frequency of various adverse effects of the use of the drug cannabis. A sample of 1000 New Zealanders aged 18-35 years were asked to complete a self-administered questionnaire on cannabis use and associated problems. The questionnaire was derived from criteria for the identification of cannabis abuse which are analagous to criteria commonly used to diagnose alcoholism. Of those who responded 38% admitted to having used cannabis. The most common physical or mental health problems, experienced by 22% of users were acute anxiety or panic attacks following cannabis use. Fifteen percent reported psychotic symptoms following use."

Smith MJ, Thirthalli J, Abdallah AB, Murray RM, Cottler LB. Prevalence of psychotic symptoms in substance users: a comparison across substances. Compr Psychiatry. 2009 May-Jun;50(3):245-50. doi: 10.1016/j.comppsych.2008.07.009. Epub 2008 Sep 23.

> "Among all users of substances without a diagnosis of abuse or dependence, cannabis users reported the highest prevalence of psychotic symptoms (12.4%)."

Barkus EJ, Stirling J, Hopkins RS, Lewis S.. Cannabis-induced psychosis-like experiences are associated with high schizotypy Psychopathology 2006;39(4):175-8.

> "In the sample who reported ever using cannabis (72%) the means for the subscales from the CEQ were as follows: ……Psychotic-Like Experiences (12.98%)."

Rates of psychotic symptoms in those with cannabis dependence as compared to non-dependent users and nonusers:

Fergusson DM, Horwood LJ, Swain-Campbell NR. Cannabis dependence and psychotic symptoms in young people. Psychol Med. 2003 Jan;33(1):15-21.

> *"Young people meeting DSM-IV criteria for cannabis dependence had elevated rates of psychotic symptoms at ages 18 (rate ratio = 3.7; 95% CI 2.8-5.0; P < 0.0001) and 21 (rate ratio = 2.3; 95% CI 1.7-3.2; P < 0.0001)."*

Smith MJ, Thirthalli J, Abdallah AB, Murray RM, Cottler LB. Prevalence of psychotic symptoms in substance users: a comparison across substances. Compr Psychiatry. 2009 May-Jun;50(3):245-50. doi: 10.1016/j.comppsych.2008.07.009. Epub 2008 Sep 23.

> "more than half of the respondents who were dependent on cocaine (80%), cannabis (63.5%), amphetamines (56.1%), and opiates (53.1%) reported psychotic symptoms. Among all users of substances without a diagnosis of abuse or dependence, cannabis users reported the highest prevalence of psychotic symptoms (12.4%)..... There was also a marked increase in the risk for psychotic symptoms when dependence became moderate or severe for cannabis (OR=25.1, OR=26.8; respectively)."

Studies on the psychotomimetic properties of THC administered to healthy individuals in the clinic:

D'Souza DC, Perry E, MacDougall L, Ammerman Y, Cooper T, Wu YT, Braley G, Gueorguieva R, Krystal JH. The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. Neuropsychopharmacology. 2004 Aug;29(8):1558-72.

> "Δ-9-THC (1) produced schizophrenia-like positive and negative symptoms; (2) altered perception;(3) increased anxiety; (4) produced euphoria; (5) disrupted immediate and delayed word recall, sparing recognition recall; (6) impaired performance on tests of distractibility, verbal fluency, and working memory (7) did not impair orientation; (8) increased plasma cortisol. These data indicate that D-9-THC produces a broad range of transient symptoms, behaviors, and cognitive deficits in healthy individuals that resemble some aspects of endogenous psychoses."

Morrison PD, Nottage J, Stone JM, Bhattacharyya S, Tunstall N, Brenneisen R, Holt D, Wilson D, Sumich A, McGuire P, Murray RM, Kapur S, Ffytche DH. Disruption of frontal θ coherence by Δ9-tetrahydrocannabinol is associated with positive psychotic symptoms. Neuropsychopharmacology. 2011;;36(4):827-36.

> "Compared with placebo, THC evoked positive and negative psychotic symptoms, as measured by the positive and negative syndrome scale (p<0.001)…… The results reveal that the pro-psychotic effects of THC might be related to impaired network dynamics with impaired communication between the right and left frontal lobes.
> "

Bhattacharyya S, Crippa JA, Allen P, Martin-Santos R, Borgwardt S, Fusar-Poli P, Rubia K, Kambeitz J, O'Carroll C, Seal ML, Giampietro V, Brammer M, Zuardi AW, Atakan Z, McGuire PK. Induction of psychosis by Δ9-tetrahydrocannabinol reflects modulation of prefrontal and striatal function during attentional salience processing. Arch Gen Psychiatry. 2012 Jan;69(1):27-36. doi: 10.1001/archgenpsychiatry.2011.161.

> "Pairwise comparisons revealed that □9-THC significantly increased the severity of psychotic symptoms compared with placebo (P<.001) and CBD (P<.001).",

Freeman D, Dunn G, Murray RM, Evans N, Lister R, Antley A, Slater M, Godlewska B, Cornish R, Williams J, Di Simplicio M, Igoumenou A, Brenneisen R, Tunbridge EM, Harrison PJ, Harmer CJ, Cowen P, Morrison PD. How Cannabis Causes Paranoia: Using the Intravenous Administration of ∆9-Tetrahydrocannabinol (THC) to Identify Key Cognitive Mechanisms Leading to Paranoia. Schizophr Bull. 2014 Jul 15. pii: sbu098. [Epub ahead of print]

> "THC significantly increased paranoia, negative affect (anxiety, worry, depression, negative thoughts about the self), and a range of anomalous experiences, and

reduced working memory capacity."

For data on dose-response (a very large study by Zammit et al., and another by van Os et al.) and the greater risk for psychosis posed by high strength marijuana (DiForti et al.):

Zammit S, Allebeck P, Andreasson S, Lundberg I, Lewis G, 2002, Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study. BMJ. 2002 Nov 23;325(7374):1199. http://www.bmj.com/content/325/7374/1199.full.pdf

> "We found a dose dependent relation between frequency of cannabis use and risk of schizophrenia, with an adjusted odds ratio for linear trend across the categories of frequency of cannabis use used in this study of 1.2 (1.1 to 1.4, P < 0.001). The adjusted odds ratio for subjects with a history of heaviest use of cannabis (> 50 occasions) was 3.1 (1.7 to 5.5).....Cannabis use is associated with an increased risk of developing schizophrenia, consistent with a causal relation. This association is not explained by use of other psychoactive drugs or personality traits relating to social integration."

van Os J, Bak M, Hanssen M, Bijl RV, de Graaf R, Verdoux H. Cannabis use and psychosis: a longitudinal population-based study. Am J Epidemiol. 2002 Aug 15;156(4):319-27.

> ".....further evidence supporting the hypothesis of a causal relation is demonstrated by the existence of a dose-response relation.. between cumulative exposure to cannabis use and the psychosis outcome..... About 80 percent of the psychosis outcome associated with exposure to both cannabis and an established vulnerability to psychosis was attributable to the synergistic action of these two factors. This finding indicates that, of the subjects exposed to both a vulnerability to psychosis and cannabis use, approximately 80 percent had the psychosis outcome because of the combined action of the two risk factors and only about 20 percent because of the action of either factor alone."

DiForti M, Morgan C, Dazzan P, Pariante C, Mondelli V, Marques TR, Handley R, Luzi S, Russo M, Paparelli A, Butt A, Stilo SA, Wiffen B, Powell J, Murray RM. High-potency cannabis and the risk of psychosis. Br J Psychiatry. 2009,195(6):488-91.

> "78% (n = 125) of the cases group preferentially used sinsemilla (skunk) compared with only 31% (n = 41) of the control group (unadjusted OR= 8.1, 95% CI 4.6–13.5). This association was only slightly attenuated after controlling for potential confounders (adjusted OR= 6.8, 95% CI 2.6–25.4)..... Our most striking finding is that patients with a first episode of psychosis preferentially used high-potency cannabis preparations of the sinsemilla (skunk) variety..... our results suggest that the potency and frequency of cannabis use may interact in further increasing the risk of psychosis."

DiForti M, Marconi A, Carra E, Fraietta S, Trotta A, Bonomo M, Bianconi F, Gardner-Sood P, O'Connor J, Russo M, Stilo SA, Marques TR, Mondelli V, Dazzan P, Pariante C, David AS, Gaughran F, Atakan Z, Iyegbe C, Powell J, Morgan C, Lynskey M, Murray RM. Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study. Lancet Psychiatry, online February 18, 2015, http://dx.doi.org/10.1016/S2215-0366(14)00117-5.

> "In the present larger sample analysis, we replicated our previous report and showed that the highest probability to suffer a psychotic disorder is in those who are daily users of high potency cannabis. Indeed, skunk use appears to contribute to 24% of cases of first episode psychosis in south London. Our findings show the importance of raising awareness among young people of the risks associated with the use of high-potency cannabis. The need for such public education is emphasised by the worldwide trend of

liberalisation of the legal constraints on cannabis and the fact that high potency varieties are becoming much more widely available."

For data on percent of those with marijuana-induced psychosis who go on to receive a diagnosis of a schizophrenia spectrum disorder:

Arendt M, Mortensen PB, Rosenberg R, Pedersen CB, Waltoft BL. Familial predisposition for psychiatric disorder: comparison of subjects treated for cannabis-induced psychosis and schizophrenia. Arch Gen Psychiatry. 2008;65(11):1269-74. http://archpsyc.ama-assn.org/cgi/reprint/65/11/1269

"Approximately half of the subjects who received treatment of a cannabis induced psychosis developed a schizophrenia spectrum disorder within 9 years after treatment..... The risk of schizophrenia after a cannabis-induced psychosis is independent of familial predisposition..... cannabis-induced psychosis may not be a valid diagnosis but an early marker of schizophrenia..... Psychotic symptoms after cannabis use should be taken extremely seriously."

Niemi-Pynttäri JA, Sund R, Putkonen H, Vorma H, Wahlbeck K, Pirkola SP. Substance-induced psychoses converting into schizophrenia: a register-based study of 18,478 Finnish inpatient cases. J Clin Psychiatry. 2013 74(1):e94-9.

"Eight-year cumulative risk to receive a schizophrenia spectrum diagnosis was 46% for persons with a diagnosis of cannabis-induced psychosis ..... chances for amphetamine-, hallucinogen-, opioid-, sedative- and alcohol-induced (schizophrenia spectrum diagnoses) were 30%, 24%, 21%, and 5% respectively."

For cause and effect (which comes first: psychosis or marijuana use):

Arseneault L, Cannon M, Poulton R, Murray R, Caspi A, Moffitt TE, 2002, Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study.BMJ. 2002 Nov 23;325(7374):1212-3.

"Firstly, cannabis use is associated with an increased risk of experiencing schizophrenia symptoms, even after psychotic symptoms preceding the onset of cannabis use are controlled for, indicating that cannabis use is not secondary to a pre-existing psychosis. Secondly, early cannabis use (by age 15) confers greater risk for schizophrenia outcomes than later cannabis use (by age 18). Thirdly, risk was specific to cannabis use, as opposed to use of other drugs...."

Henquet C, Krabbendam L, Spauwen J, et al. Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. BMJ. 2005;330:11–15. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC539839/pdf/bmj33000011.pdf

"Exposure to cannabis during adolescence and young adulthood increases the risk of psychotic symptoms later in life. Cannabis use at baseline increased the cumulative incidence of psychotic symptoms at follow up four years later...but has a much stronger effect in those with evidence of predisposition for psychosis.....Predisposition for psychosis at baseline did not significantly predict cannabis use four years later.."

and also:

Kuepper R, van Os J, Lieb R, Wittchen HU, Höfler M, Henquet C. Continued cannabis use and risk of incidence and persistence of psychotic symptoms: 10 year follow-up cohort study.BMJ. 2011 Mar 1;342: d738 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3047001/pdf/bmj.d738.pdf

"In individuals who had no reported lifetime psychotic symptoms and no reported lifetime cannabis use at baseline, incident cannabis use over the period from baseline to T2 increased the risk of later incident psychotic symptoms over the period from T2 to T3

(adjusted odds ratio 1.9, 95% confidence interval 1.1 to 3.1; P=0.021).....There was no evidence for self medication effects, as psychotic experiences at T2 did not predict incident cannabis use between T2 and T3 (0.8, 0.6 to 1.2; P=0.3)."

For data on those who quit using when psychotic symptoms develop (further evidence against self-medication):
Fergusson DM, Horwood LJ, Ridder EM. Tests of causal linkages between cannabis use and psychotic symptoms. Addiction. 2005;100(3):354-66.

For degree of risk relative to other drugs:

Niemi-Pynttäri JA, Sund R, Putkonen H, Vorma H, Wahlbeck K, Pirkola SP. Substance-induced psychoses converting into schizophrenia: a register-based study of 18,478 Finnish inpatient cases. J Clin Psychiatry. 2013 74(1):e94-9.

"Eight-year cumulative risk to receive a schizophrenia spectrum diagnosis was 46% for persons with a diagnosis of cannabis-induced psychosis ..... chances for amphetamine-, hallucinogen-, opioid-, sedative- and alcohol-induced (schizophrenia spectrum diagnoses) were 30%, 24%, 21%, and 5% respectively."

Smith MJ, Thirthalli J, Abdallah AB, Murray RM, Cottler LB. Prevalence of psychotic symptoms in substance users: a comparison across substances. Compr Psychiatry. 2009 May-Jun;50(3):245-50. doi: 10.1016/j.comppsych.2008.07.009. Epub 2008 Sep 23.

"more than half of the respondents who were dependent on cocaine (80%), cannabis (63.5%), amphetamines (56.1%), and opiates (53.1%) reported psychotic symptoms. Among all users of substances without a diagnosis of abuse or dependence, cannabis users reported the highest prevalence of psychotic symptoms (12.4%)..... There was also a marked increase in the risk for psychotic symptoms when dependence became moderate or severe for cannabis (OR=25.1, OR=26.8; respectively)."

Another angle on the potential confound of self-medication: genetic predisposition for schizophrenia does not predict cannabis use:

Veling W, Mackenbach JP, van Os J, Hoek HW. Cannabis use and genetic predisposition for schizophrenia: a case-control study. Psychol Med. 2008 Sep;38(9):1251-6. Epub 2008 May 19.

"BACKGROUND: Cannabis use may be a risk factor for schizophrenia. RESULTS: Cannabis use predicted schizophrenia [adjusted odds ratio (OR) cases compared to general hospital controls 7.8, 95% confidence interval (CI) 2.7-22.6; adjusted OR cases compared to siblings 15.9 (95% CI 1.5-167.1)], but genetic predisposition for schizophrenia did not predict cannabis use [adjusted OR intermediate predisposition compared to lowest predisposition 1.2 (95% CI 0.4-3.8)]."

For data on potential benefits of cessation:
González-Pinto A, Alberich S, Barbeito S, Gutierrez M, Vega P, Ibáñez B, Haidar MK, Vieta E, Arango C. Cannabis and first-episode psychosis: different long-term outcomes depending on continued or discontinued use. Schizophr Bull. 2011 May;37(3):631-9. Epub 2009 Nov 13.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3080669/pdf/sbp126.pdf

"OBJECTIVE: To examine the influence of cannabis use on long-term outcome in patients with a first psychotic episode, comparing patients who have never used cannabis with (a) those who used cannabis before the first episode but stopped using it during

follow-up and (b) those who used cannabis both before the first episode and during follow-up..... CONCLUSION: Cannabis has a deleterious effect, but stopping use after the first psychotic episode contributes to a clear improvement in outcome. The positive effects of stopping cannabis use can be seen more clearly in the long term."

Kuepper R, van Os J, Lieb R, Wittchen HU, Höfler M, Henquet C. Continued cannabis use and risk of incidence and persistence of psychotic symptoms: 10 year follow-up cohort study.BMJ. 2011 Mar 1;342: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3047001/pdf/bmj.d738.pdf

"The finding that longer exposure to cannabis was associated with greater risk for persistence of psychotic experiences is in line with an earlier study showing that continued cannabis use over time increases the risk for psychosis in a dose-response fashion. This is also in agreement with the hypothesis that a process of sensitisation might underlie emergence and persistence of psychotic experiences as an indicator of liability to psychotic disorder."

For data on marijuana use resulting in an earlier age of onset of schizophrenia (suggestive of causality), see Dragt et al. and a meta-analysis (see Large et al.,); also: a very extensive (676 schizophrena patients) and therefore more statistically powered analysis (see DeHert paper); two papers showing that the age-of-onset effect may be specific to those without a family history (see Scherr et al. and Leeson et al., papers); two studies that evaluate the age of onset specific to gender (Veen et al. and Compton et al.) which is important because comparing across genders can be confounded by the greater tendency of males to engage in risky behavior (the conclusions are not the same in terms of gender; the gender distribution was slightly better in the Veen et al. study) and finally, two papers of relevance to specificity of age of onset effect to cannabis, a meta-analysis of published studies on age of onset that shows another drug of abuse (tobacco) is not associated with a decreased age of onset (Myles et al.) and a study showing that ecstasy, LSD, stimulants, or sedatives did not have an effect to lower age of onset whereas cannabis use did (Barnes et al.) :

Large M, Sharma S, Compton MT, Slade T, Nielssen O. Cannabis Use and Earlier Onset of Psychosis: A Systematic Meta-analysis. Arch Gen Psychiatry. 2011 68(6):555-61. http://www.ncbi.nlm.nih.gov/pubmed/21300939

"The results of meta-analysis provide evidence for a relationship between cannabis use and earlier onset of psychotic illness, and they support the hypothesis that cannabis use plays a causal role in the development of psychosis in some patients. The results suggest the need for renewed warnings about the potentially harmful effects of cannabis."

Dragt S, Nieman DH, Schultze-Lutter F, van der Meer F, Becker H, de Haan L, Dingemans PM, Birchwood M, Patterson P, Salokangas RK, Heinimaa M, Heinz A, Juckel G, Graf von Reventlow H, French P, Stevens H, Ruhrmann S, Klosterkötter J, Linszen DH; on behalf of the EPOS group.Cannabis use and age at onset of symptoms in subjects at clinical high risk for psychosis. Acta Psychiatr Scand. 2011 Aug 29. doi: 10.1111/j.1600-0447.2011.01763.x. [Epub ahead of print]

"Cannabis use and age at onset of symptoms in subjects at clinical high risk for psychosis. Objective: Numerous studies have found a robust association between cannabis use and the onset of psychosis. Nevertheless, the relationship between cannabis use and the onset of early (or, in retrospect, prodromal) symptoms of psychosis remains unclear. The study focused on investigating the relationship between cannabis use and early and high-risk symptoms in subjects at clinical high risk for psychosis. Results: Younger age at onset of cannabis use or a cannabis use disorder was significantly related to younger age at onset of six symptoms ($0.33 < r(s) < 0.83$, $0.004 < P < 0.001$). Onset of cannabis use preceded symptoms in most participants. Conclusion: Our results provide support that cannabis use plays an important role in the development of psychosis in vulnerable individuals."

De Hert M, Wampers M, Jendricko T, Franic T, Vidovic D, De Vriendt N, Sweers K, Peuskens J, van Winkel R.Effects of cannabis use on age at onset in schizophrenia and bipolar disorder. Schizophr Res. 2011 Mar;126(1-3):270-6.

> "BACKGROUND: Cannabis use may decrease age at onset in both schizophrenia and bipolar disorder, given the evidence for substantial phenotypic and genetic overlap between both disorders....RESULTS:... Both cannabis use and a schizophrenia diagnosis predicted earlier age at onset. There was a significant interaction between cannabis use and diagnosis, cannabis having a greater effect in bipolar patients....DISCUSSION:.... Our results suggest that cannabis use is associated with a reduction in age at onset in both schizophrenic and bipolar patients. This reduction seems more pronounced in the bipolar group than in the schizophrenia group: the use of cannabis reduced age at onset by on average 8.9 years in the bipolar group, as compared to an average predicted reduction of 1.5 years in the schizophrenia group."

Scherr M, Hamann M, Schwerthöffer D, Froböse T, Vukovich R, Pit schel-Walz G, Bäuml J.. Environmental risk factors and their impact on the age of onset of schizophrenia: Comparing familial to non-familial schizophrenia. Nord J Psychiatry. 2011 Aug 31. [Epub ahead of print]

> "Background and aims: Several risk factors for schizophrenia have yet been identified. The aim of our study was to investigate how certain childhood and adolescent risk factors predict the age of onset of psychosis in patients with and without a familial component (i.e. a relative with schizophrenia or schizoaffective disorder). Results: Birth complications and cannabis abuse are predictors for an earlier onset of schizophrenia in patients with non-familial schizophrenia. No environmental risk factors for an earlier age of onset in familial schizophrenia have been identified."

Leeson VC, Harrison I, Ron MA, Barnes TR, Joyce EM. The Effect of Cannabis Use and Cognitive Reserve on Age at Onset and Psychosis Outcomes in First-Episode Schizophrenia. Schizophr Bull. 2011 Mar 9. [Epub ahead of print]
http://schizophreniabulletin.oxfordjournals.org/content/early/2011/03/09/schbul.sbq153.full.pdf+html

> *"Objective: Cannabis use is associated with a younger age at onset of psychosis, an indicator of poor prognosis, but better cognitive function, a positive prognostic indicator. We aimed to clarify the role of age at onset and cognition on outcomes in cannabis users with first-episode schizophrenia as well as the effect of cannabis dose and cessation of use.....Conclusions: Cannabis use brings forward the onset of psychosis in people who otherwise have good prognostic features indicating that an early age at onset can be due to a toxic action of cannabis rather than an intrinsically more severe illness. Many patients abstain over time, but in those who persist, psychosis is more difficult to treat."*

Veen ND, Selten JP, van der Tweel I, Feller WG, Hoek HW, Kahn RS. Cannabis use and age at onset of schizophrenia. Am J Psychiatry. 2004 Mar;161(3):501-6.
http://ajp.psychiatryonline.org/cgi/reprint/161/3/501

> "The results indicate a strong association between use of cannabis and earlier age at first psychotic episode in male schizophrenia patients."

Compton MT, Kelley ME, Ramsay CE, Pringle M, Goulding SM, Esterberg ML, Stewart T, Walker EF. Association of pre-onset cannabis, alcohol, and tobacco use with age at onset of prodrome and age at onset of psychosis in first-episode patients. Am J Psychiatry. 2009 Nov;166(11):1251-7. Epub 2009 Oct 1. http://ajp.psychiatryonlie.org/cgi/reprint/166/11/1251

> "Whereas classifying participants according to maximum frequency of use prior to onset (none, ever, weekly, or daily) revealed no significant effects of cannabis or tobacco use on risk of (editor's note: "timing of") onset, analysis of change in frequency of use prior to onset indicated that progression to daily cannabis and tobacco use was associated with an increased risk of onset of psychotic symptoms. Similar or even stronger effects were

observed when onset of illness or prodromal symptoms was the outcome. A gender-by-daily-cannabis use interaction was observed; progression to daily use resulted in a much larger increased relative risk of onset of psychosis in females than in males."

Myles N, Newall H, Compton MT, Curtis J, Nielssen O, Large M. The age at onset of psychosis and tobacco use: a systematic meta-analysis. Soc Psychiatry Psychiatr Epidemiol. 2011 Sep 8. [Epub ahead of print]

"Unlike cannabis use, tobacco use is not associated with an earlier onset of psychosis."

Barnes TR, Mutsatsa SH, Hutton SB, Watt HC, Joyce EM. Comorbid substance use and age at onset of schizophrenia. Br J Psychiatry. 2006 Mar;188:237-42.
http://bjp.rcpsych.org/content/188/3/237.full.pdf+html

"Alcohol misuse and any substance use (other than cannabis use) were not significant in relation to age at onset..... those patients in the sample who reported that they had used cannabis had an earlier age at onset of psychosis than other patients who did not report cannabis use but who shared the same profile with regard to the other variables (e.g. comparing men who reported alcohol misuse and use of both cannabis and other drugs with men who had the same characteristics apart from the fact that they had not used cannabis)."

Data from other cultures

Sarkar J, Murthy P, Singh SP. Psychiatric morbidity of cannabis abuse. Indian J Psychiatry. 2003 Jul;45(3):182-8.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2952166/pdf/IJPsy-45-182.pdf

"The paper evaluates the hypothesis that cannabis abuse is associated with a broad range of psychiatric disorders in India, an area with relatively high prevalence of cannabis use. Retrospective case-note review of all cases with cannabis related diagnosis over a 11 -year period, for subjects presenting to a tertiary psychiatric hospital in southern India was carried out. Information pertaining to sociodemographic, personal, social, substance-use related, psychiatric and treatment histories, was gathered. Standardized diagnoses were made according to Diagnostic Criteria for Research of the World Health Organization, on the basis of information available.Cannabis abuse is associated with widespread psychiatric morbidity that spans the major categories of mental disorders under the ICD-10 system, although proportion of patients with psychotic disorders far outweighed those with non-psychotic disorders. Whilst paranoid psychoses were more prevalent, a significant number of patients with affective psychoses, particularly mania, was also noted."

Rodrigo C, Welgama S, Gunawardana A, Maithripala C, Jayananda G, Rajapakse S. A retrospective analysis of cannabis use in a cohort of mentally ill patients in Sri Lanka and its implications on policy development. Subst Abuse Treat Prev Policy. 2010 Jul 8;5:16.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2910013/pdf/1747-597X-5-16.pdf

"BACKGROUND: Several epidemiological studies have shown that cannabis; the most widely used illegal drug in the world, is associated with schizophrenia spectrum disorders (SSD)..... CONCLUSIONS: Self reported LTC (editor's note: life time cannabis) use was strongly associated with being diagnosed with SSD (editor's note: schizophrenia spectrum disorders".

Population study showing change in incidence rate in young when drug laws are eased

Ajdacic-Gross V, Lauber C, Warnke I, Haker H, Murray RM, Rössler W. Changing incidence of psychotic disorders among the young in Zurich. Schizophr Res. 2007 Sep;95(1-3):9-18. Epub 2007 Jul 16.

> "There is controversy over whether the incidence rates of schizophrenia and psychotic disorders have changed in recent decades. To detect deviations from trends in incidence, we analysed admission data of patients with an ICD-8/9/10 diagnosis of psychotic disorders in the Canton Zurich / Switzerland, for the period 1977-2005. The data was derived from the central psychiatric register of the Canton Zurich. Ex-post forecasting with ARIMA (Autoregressive Integrated Moving Average) models was used to assess departures from existing trends. In addition, age-period-cohort analysis was applied to determine hidden birth cohort effects. First admission rates of patients with psychotic disorders were constant in men and showed a downward trend in women. However, the rates in the youngest age groups showed a strong increase in the second half of the 1990's. The trend reversal among the youngest age groups coincides with the increased use of cannabis among young Swiss in the 1990's."

Estimates of how many men aged 20-40 would have to avoid regular marijuana use for one year in order to prevent one case of schizophrenia in that same year (but for number relevant to a 20 year avoidance of schizophrenia by avoiding regular marijuana use during 20 years, divide by 20):

Hickman M, Vickerman P, Macleod J, Lewis G, Zammit S, Kirkbride J, Jones P. If cannabis caused schizophrenia--how many cannabis users may need to be prevented in order to prevent one case of schizophrenia? England and Wales calculations. Addiction. 2009;104(11):1856-61.

> "In men the annual mean NNP (number needed to prevent) for heavy cannabis and schizophrenia ranged from 2800 [90% confidence interval (CI) 2018–4530] in those aged 20–24 years to 4700 (90% CI 3114–8416) in those aged 35–39".

<u>Key studies interpreted to diminish the connection between marijuana and schizophrenia:</u>

Proal AC, Fleming J, Galvez-Buccollini JA, Delisi LE. A controlled family study of cannabis users with and without psychosis. Schizophr Res. 2014 Jan;152(1):283-8.

> "The results of the current study, both when analyzed using morbid risk and family frequency calculations, suggest that having an increased familial risk for schizophrenia is the underlying basis for schizophrenia in these samples and not the cannabis use. While cannabismay have an effect on theage of onset of schizophrenia it is unlikely to be the cause of illness."
>
> **Rebuttal:** *Miller CL. Caution urged in interpreting a negative study of cannabis use and schizophrenia. Schizophr Res. 2014 Apr;154(1-3):119-20.*
>
> **"**The morbid risk reported for the relatives of the non-cannabis-using patients (Sample 3) was actually 1.4-fold higher than the cannabis using patients (Sample 4), but the study did not have enough power to statistically confirm or refute a less than 2-fold difference. An increase in sample size would be required to do so, and if the observed difference were to be confirmed, it would explain not only why the Sample 4 data fits poorly with a multigene/small environmental impact model but also would give weight to the premise that cannabis use significantly contributes to the development of this disease.

Power RA, Verweij KJ, Zuhair M, Montgomery GW, Henders AK, Heath AC, Madden PA, Medland SE, Wray NR, Martin NG. Genetic predisposition to schizophrenia associated with increased use of cannabis. Mol Psychiatry. 2014 Jun 24. doi: 10.1038/mp.2014.51. [Epub ahead of print] *http://emilkirkegaard.dk/en/wp-content/uploads/Genetic%20predisposition%20to%20schizophrenia%20associated%20with%20increased%20use%20of%20cannabis.pdf*

> "Our results show that to some extent the association between cannabis and schizophrenia is due to a shared genetic aetiology across common variants. They suggest that individuals with an increased genetic predisposition to schizophrenia are both more likely to use cannabis and to use it in greater quantities."

Rebuttal: Had this paper been titled "The causal genes for schizophrenia have been discovered" it would never have been published. In the absence of a consistent finding of genes of major effect size for schizophrenia, this study of inconsistently associated genes of low effect size is meaningless.

Buchy L, Perkins D, Woods SW, Liu L, Addington J. Impact of substance use on conversion to psychosis in youth at clinical high risk of psychosis. Schizophrenia Res 156 (2-3): 277–280.

"Results revealed that low use of alcohol, but neither cannabis use nor tobacco use at baseline, contributed to the prediction of psychosis in the CHR sample".

Rebuttal: The study was small in size and the age range of their subjects at study onset was large (12 to 31) which included both subjects that had not reached the peak age of risk for schizophrenia even by the end of the study as well as subjects who were well past the peak age of onset of schizophrenia. The fact that the study screened out psychotic individuals was problematic for the latter group, in that those who were most vulnerable to the psychosis inducing effects of cannabis would already have converted to psychosis by that age.

Overview of Key Public Health Issues Regarding the Mental Health Effects of Marijuana

For the monetary cost of schizophrenia to the U.S. annually ($63 billion in 2002 dollars):

Wu EQ, Birnbaum HG, Shi L, Ball DE, Kessler RC, Moulis M, Aggarwal J. The economic burden of schizophrenia in the United States in 2002. J Clin Psychiatry. 2005 Sep;66(9):1122-9.

For the trends in adolescent drug, alcohol and cigarette use, showing an upward tick in marijuana use as medical marijuana has become more prevalent, and that the mind-altering drug legal for adults (alcohol) is still more commonly used by teens than is marijuana:

Johnston, L. D., O'Malley, P. M., Bachman, J. G., & Schulenberg, J. E. (2012). Monitoring the Future national results on adolescent drug use: Overview of key findings, 2011. Ann Arbor, MI: Institute for Social Research, The University of Michigan.

For a summary of Sweden's drug law experience:

Hallam C., 2010, Briefing paper 20, The Beckley Foundation: What Can We Learn from Sweden's Drug Policy Experience?
www.beckleyfoundation.org/pdf/BriefingPaper_20.pdf
"in the case of Sweden, the clear association between a restrictive drug policy and low levels of drug use is striking. In his foreword to the article on Sweden's Successful Drug Policy, Antonio Maria Costa is frank enough to confess that, "It is my firm belief that the generally positive situation of Sweden is a result of the policy that has been applied to address the problem".

For data showing the relationship between drug enforcement policies in Europe and drug use, such that Sweden has a zero tolerance policy on drugs and has one of the lowest rates of "last month use" in Europe (1%), 4-fold lower than the Netherlands and 7-fold lower than Spain and Italy, two countries that have liberalized their enforcement policies so that marijuana possession carries no substantive penal*ty.*

European Monitoring Centre for Drugs and Addiction, 2012 Annual report
http://www.emcdda.europa.eu/attachements.cfm/att_190854_EN_TDAC12001ENC_.pdf