

The Bradford Hill Analysis of Causation Applied to Cannabis Use and the Development of Chronic Psychotic Disorders

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(Intent of the Bradford Hill elements as set forth by van Reekum et al., 2001 for neuropsychiatric applications)

van Reekum R, Streiner DL, Conn DK. "Applying Bradford Hill's criteria for causation to neuropsychiatry: challenges and opportunities." *J Neuropsychiatry Clin Neurosci* 13, no. 3 (Summer 2001): 318-25. <https://doi.org/10.1176/jnp.13.3.318>. PMID: 11514637. <https://pubmed.ncbi.nlm.nih.gov/11514637/>.

A draft of this Bradford Hill analysis first appeared on IASIC1.org in June 2021.

Epidemiologist Austin Bradford Hill recognized that no one type of study could fully address the causal relationship between an agent and an outcome in human populations. The analysis he developed to categorize the different types of research necessary to substantiate causation has withstood the test of time.

Although not all key elements he defined can be applied to all types of outcomes, in the case of cannabis causing psychosis, their full application is possible. You will find below what we will term "elements of causation" and the studies that satisfy them. This is intended to be a living document, with edits from leading researchers incorporated as more relevant and up-to-date literature is made available. The sequential versions of the document will be archived for the record.

Updated June 4, 2021

Updated March 4, 2024

1. **Strength of the association** (The stronger the association, the more likely that it is causal.)

Daily use of marijuana with a low to moderate potency of Δ^9 -tetrahydrocannabinol (THC) increases the risk of psychotic outcome by 4 to 5-fold, respectively (Marconi et al., 2016; Di Forti et al., 2015), a very strong association. Moderate potency includes what is known as "skunk" in the UK, which, at ~10% to 15% THC, was considered high potency in the UK but moderate potency by US standards.

Di Forti M, Marconi A, Carra E, Fraitetta 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." *The Lancet Psychiatry* 2, no. 3 (2015): 233-8.

[https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366\(14\)00117-5/fulltext](https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366(14)00117-5/fulltext).

Marconi A, Di Forti M, Lewis CM, Murray RM, Vassos E. "Meta-analysis of the Association Between the Level of Cannabis Use and Risk of Psychosis." *Schizophr Bull* 42, no.5 (2016): 1262-9.

[https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4988731/.](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4988731/)

2. **Consistency of the evidence** (Consistent findings observed by different researchers in different places with different types of subjects strengthens the likelihood of an effect.)
 - i. **Two large meta-analyses of studies into the association between cannabis use and psychosis have been published, one in 2007 (Moore et al.) and one in 2016 (Marconi et al.), in total covering research from the USA, Germany, the Netherlands, the UK, Sweden, New Zealand, Australia, and Finland.** The types of data ranged from cross-sectional case-control comparisons in catchment areas or registries, to prospective studies and birth cohorts. The subjects varied in age range as well as in occupation, from the general population to military conscripts. The two meta-analyses covered a range of potencies and use frequencies and overlapped in six studies but did not overlap for five. Both reported a significant association between marijuana use and psychosis and/or schizophrenia. Although a few studies have found no significant association, most have either been too small in size to detect, at a minimum, the 1.8-fold increase in risk reported by Moore et al.; e.g., Bechtold et al., 2015) did not obtain adequate data on use frequency ("ever use" versus more frequent use) and/or analyzed the prior use of marijuana/ followed the subjects over too short a period of time, e.g., Phillips et al., 2002).

Bechtold J, Simpson T, White HR, Pardini D. "Chronic Adolescent Marijuana Use as a Risk Factor for Physical and Mental Health Problems in Young Adult Men." *Psychol Addict Behav.* 29, no. 3 (Sep 2015) :552-63. <https://doi.org/10.1037/adb0000103>. Epub 2015 Aug 3. Erratum in: *Psychol Addict Behav.* 29, no. 4 (Dec 2015): ix-x. PMID: 26237286; PMCID: PMC4586320. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4586320/pdf/nihms-700940.pdf>.

Marconi A, Di Forti M, Lewis CM, Murray RM, Vassos E. "Meta-analysis of the Association Between the Level of Cannabis Use and Risk of Psychosis." *Schizophr Bull.* 42, no. 5 (2016): 1262-9. [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4988731/.](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4988731/)

Moore TH, Zammit S, Lingford-Hughes A, Barnes TR, Jones PB, Burke M, Lewis G. "Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review." *The Lancet* 370, no. 9584 (Jul 2007): 319-28. [https://doi.org/10.1016/S0140-6736\(07\)61162-3](https://doi.org/10.1016/S0140-6736(07)61162-3). PMID: 17662880. [https://pubmed.ncbi.nlm.nih.gov/17662880/.](https://pubmed.ncbi.nlm.nih.gov/17662880/)

Phillips LJ, Curry C, Yung AR, Yuen HP, Adlard S, McGorry PD. "Cannabis Use Is Not Associated with the Development of Psychosis in an 'Ultra' High-Risk Group." *Aust N Z J Psychiatry* 36, no. 6 (Dec 2002): 800-6. <https://doi.org/10.1046/j.1440-1614.2002.01089.x>. PMID: 12406123. [https://pubmed.ncbi.nlm.nih.gov/12406123/.](https://pubmed.ncbi.nlm.nih.gov/12406123/)

- ii. **In addition to research results included in the preceding meta-analyses, many relevant publications have occurred since that time. Both small and large research projects worldwide have continued to find a significant association between cannabis use and psychosis/schizophrenia, including but not limited to the following reports:** in 11 different cities in Europe (Di Forti et al., 2019); in a countrywide registry-based study in Denmark (Nielsen et al., 2017), and a Danish population-level study illustrating that as cannabis use disorder (CUD) rates increased, the incidence of schizophrenia increased (Hjorthøj et al., 2021) as well as a more recent countrywide registry-based study by the same first author (Hjorthøj et al., 2023) finding that the population-attributable fraction for CUD in those with schizophrenia peaked at 30% in males aged 21–25; **in a case-control study of first episode psychosis patients, finding that cannabis use significantly increased the risk of psychotic disorder independent of the genes associated with familial risk of schizophrenia included in polygenic risk score (PRS) analyses (Austin-Zimmerman et al., 2024);** in a prospective study from Finland (Mustonen et al., 2018); in a population-based case-control study from a hospital in Africa (Lasebikan and Aremu, 2018); in a large case-control study from the USA that assessed use frequency (Davis et al., 2013); in a retrospective temporal study of a first-episode psychosis population in the USA (Kelley et al., 2016); in a population-based study from Canada (Maloney-Hall et al., 2020); and in case-control reports from South America (Allende Serra et al., 2019; Libuy et al., 2018).

Allende Serra LM, Castañeda Agüero CP, Iruretagoyena B, Undurraga J, González A, Crossley N. "T67. Case-control Study of Cannabis Use in First-episode Psychosis in Chile." *Schizophr Bull.* 45, suppl. 2 (2019): S230. https://www.researchgate.net/profile/Juan-Undurraga/publication/332313855_T67_Case_control_study_of_cannabis_use_in_first_episode_psychosis_in_Cjille/links/5d5b680e92851c37636bd344/T67-case-control-study-of-cannabis-use-in-first-episode-psychosis-in-Chile.pdf.

Austin-Zimmerman I, Spinazzola E, Quattrone D, Wu-Choi B, Trotta G, Li Z, Johnson E, Richards AL, Freeman TP, Tripoli G, Gayer-Anderson C. The impact of schizophrenia genetic load and heavy cannabis use on the risk of psychotic disorder in the EU-GEI case-control and UK Biobank studies. *Psychological medicine.* 2024 Nov;54(15):4160-72.
<https://www.cambridge.org/core/services/aop-cambridge-core/content/view/274AF7839E20F0EED1F805FD2CD2FC57/S0033291724002058a.pdf/the-impact-of-schizophrenia-genetic-load-and-heavy-cannabis-use-on-the-risk-of-psychotic-disorder-in-the-eu-gei-case-control-and-uk-biobank-studies.pdf>

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.* 151, no. 1–3 (Dec 2013): 197-202. <https://doi.org/10.1016/j.schres.2013.10.018>. Epub 2013 Nov 5. PMID: 24200416; PMCID: PMC3877688. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3877688/pdf/nihms534094.pdf>.

Di Forti M, Quattrone D, Freeman TP, Tripoli G, Gayer-Anderson C, Quigley H, et al., EU-GEI WP2 Group. "The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study." *The Lancet Psychiatry* 6 (March 19, 2019): 427-36. <https://www.thelancet.com/action/showPdf?pii=S2215-0366%2819%2930048-3>.

Hjorthøj C, Posselt CM, Nordentoft M. "Development Over Time of the Population-Attributable Risk Fraction for Cannabis Use Disorder in Schizophrenia in Denmark." *JAMA Psychiatry* 78, no. 9 (Sep 2021): 1013-19. <https://doi.org/10.1001/jamapsychiatry.2021.1471>.
<https://jamanetwork.com/journals/jamapsychiatry/article-abstract/2782160>.

Hjorthøj C, Compton W, Starzer M, Nordholm D, Einstein E, Erlangsen A, Nordentoft M, Volkow ND, Han B. "Association between cannabis use disorder and schizophrenia stronger in young males than in females." *Psychological Medicine* 4 (May 2023): 1-7.
<https://www.cambridge.org/core/services/aop-cambridge-core/content/view/E1F8F0E09C6541CB8529A326C3641A68/S0033291723000880a.pdf/association-between-cannabis-use-disorder-and-schizophrenia-stronger-in-young-males-than-in-females.pdf>.

Nielsen SM, Toftdahl NG, Nordentoft M, Hjorthøj C. "Association between alcohol, cannabis, and other illicit substance abuse and risk of developing schizophrenia: a nationwide population based register study." *Psychol Med.* 47, no. 9 (Jul 2017): 1668-1677.
<https://doi.org/10.1017/S0033291717000162>. Epub 2017 Feb 7. PMID: 28166863.
<https://pubmed.ncbi.nlm.nih.gov/28166863/>.

Kelley ME, Wan CR, Broussard B, Crisafio A, Cristofaro S, Johnson S, Reed TA, Amar P, Kaslow NJ, Walker EF, Compton MT. "Marijuana use in the immediate 5-year premonitory period is associated with increased risk of onset of schizophrenia and related psychotic disorders." *Schizophr Res.* 171, no. 1-3 (Mar 2016): 62-7. <https://doi.org/10.1016/j.schres.2016.01.015>. Epub 2016 Jan 17. PMID: 26785806; PMCID: PMC4929616.
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4929616/pdf/nihms752585.pdf>.

Lasebikan V, Aremu OO. "Cannabis Use and Associated Harms among Schizophrenia Patients in a Nigerian Clinical Setting: A Case-Control Study." *Front Psychiatry* 7 (Aug 2016): 136.
<https://doi.org/10.3389/fpsy.2016.00136>. PMID: 27536254; PMCID: PMC4971430.
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4971430/pdf/fpsy.2016.00136.pdf>.

Libuy N, de Angel V, Ibáñez C, Murray RM, Mundt AP. "The relative prevalence of schizophrenia among cannabis and cocaine users attending addiction services." *Schizophr Res.* 194 (Apr 2018): 13-17. <https://doi.org/10.1016/j.schres.2017.04.010>. Epub 2017 Apr 18. PMID: 28427930.
<http://repositorio.uchile.cl/bitstream/handle/2250/149979/The-relative-prevalence-of-schizophrenia.pdf?sequence=1>.

Maloney-Hall B, Wallingford SC, Konefal S, Young MM. "Psychotic disorder and cannabis use: Canadian hospitalization trends, 2006–2015." *Health Promot Chronic Dis Prev Can.* 40, no. 5–6 (Jun 2020): 176-183. <https://doi.org/10.24095/hpcdp.40.5/6.06>. PMID: 32529977; PMCID: PMC7367424. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7367424/pdf/40_5-6_6.pdf.

Mustonen A, Niemelä S, Nordström T, Murray GK, Mäki P, Jääskeläinen E, Miettunen J. "Adolescent cannabis use, baseline prodromal symptoms and the risk of psychosis." *Br J Psychiatry* 212, no. 4 (Apr 2018): 227-233. <https://doi.org/10.1192/bjp.2017.52>. PMID: 29557758.
<https://pubmed.ncbi.nlm.nih.gov/29557758/>.

3. **Specificity** (This element of causation dates to a time when one agent was considered causative of one outcome, before science had advanced to an understanding of the complexity of outcomes from one agent, and the number of agents that can cause a similar outcome, as described by van Reekum et al., 2001. Although the Specificity element of causation is limited in its application, it can be considered in the cannabis–psychosis connection in two respects: 1) the effect size of cannabis relative to other drugs of abuse and 2) with respect to the population-attributable fraction size for cannabis as compared to that of family history risk.)

- i. **How marijuana compares to other recreational drugs in the progression from temporary psychosis to schizophrenia: the effect size of cannabis surpasses all other drugs—i.e., as compared to other hallucinogens, cocaine, amphetamines, opioids, or alcohol** (Niemi-Pynttäri et al., 2013; Starzer et al., 2018). Nearly 50% of cases of cannabis-induced psychosis transition to a chronic psychotic disorder, and the other drugs do so at a lower rate.

Niemi-Pynttäri JA, Sund R, Putkonen H, Vormaa H, Wahlbeck K, Pirkola SP. “Substance-Induced Psychoses Converting Into Schizophrenia: A Register-Based Study of 18,478 Finnish Inpatient Cases.” *J Clin Psychiatry* 74, no. 1 (2013): e94.

<https://www.psychiatrist.com/jcp/article/Pages/2013/v74n01/v74n0115.aspx>.

Starzer MSK, Nordentoft M, Hjorthøj C. “Rates and Predictors of Conversion to Schizophrenia or Bipolar Disorder Following Substance-Induced Psychosis.” *Am J Psychiatry* 175, no. 4 (2018): 343-350.

https://ajp.psychiatryonline.org/doi/abs/10.1176/appi.ajp.2017.17020223?rfr_dat=cr_pub%3Dpubmed&url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&journalCode=ajp

- ii. **The fraction of schizophrenia cases attributable (Population Attributable Fraction PAF) to heavy use of higher potency cannabis use exceeds the PAF for family history of psychosis.**

The PAF for first-degree family history in schizophrenia cases is reported to be 5.5%, and the PAF for a first- or second-degree family history in schizophrenia cases is reported to be between 12% (Boydell et al., 2007) and 26% (Ruhrmann et al., 2010). Reaching out to third-degree relatives reduces the effect size such that it is not meaningfully different than the family history of the non-affected population.

The PAF for cannabis use in schizophrenia cases depends on the potency and use rates, ranging from 8% for low potency cannabis (Arseneault et al., 2004) up to 50% for heavy use of higher potency cannabis by a significant proportion of the population (Di Forti et al., 2019).

Arseneault L, Cannon M, Witton J, Murray RM. “Causal association between cannabis and psychosis: examination of the evidence.” *Br J Psychiatry* 184 (Feb 2004): 110-17.

<https://doi.org/10.1192/bjp.184.2.110>. PMID: 14754822.

<https://pubmed.ncbi.nlm.nih.gov/14754822/>.

Boydell J, Dean K, Dutta R, Giouroukou E, Fearon P, Murray R. “A comparison of symptoms and family history in schizophrenia with and without prior cannabis use: implications for the concept of cannabis psychosis.” *Schizophr Res* 93, no. 1–3 (2007): 203-10.

<https://www.sciencedirect.com/science/article/pii/S0920996407001508?via%3Dihub>.

Di Forti 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." *The Lancet Psychiatry* 2, no. 3 (2015): 233-8.

[https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366\(14\)00117-5/fulltext](https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366(14)00117-5/fulltext).

Mortensen PB, Pedersen CB, Westergaard T, Wohlfahrt J, Ewald H, Mors O, Andersen PK, Melbye M. "Effects of Family History and Place and Season of Birth on the Risk of Schizophrenia." *N Engl J Med* 340, no. 8 (Feb 25, 1999): 603-8. <https://doi.org/10.1056/NEJM199902253400803>. PMID: 10029644. <https://www.nejm.org/doi/pdf/10.1056/NEJM199902253400803?articleTools=true>.

Ruhrmann S, Schultze-Lutter F, Salokangas RK, Heinimaa M, Linszen D, Dingemans P, Birchwood M, Patterson P, Juckel G, Heinz A, Morrison A, Lewis S, von Reventlow HG, Klosterkötter J. "Prediction of Psychosis in Adolescents and Young Adults at High Risk: Results from the Prospective European Prediction of Psychosis Study." *Arch Gen Psychiatry* 67, no. 3 (2010): 241-51. <https://jamanetwork.com/journals/jamapsychiatry/fullarticle/210635>.

Starzer MSK, Nordentoft M, Hjorthøj C. "Rates and Predictors of Conversion to Schizophrenia or Bipolar Disorder Following Substance-Induced Psychosis." *Am J Psychiatry* 175, no. 4 (2018): 343-350.

https://ajp.psychiatryonline.org/doi/abs/10.1176/appi.ajp.2017.17020223?rfr_dat=cr_pub%3Dpu_bmed&url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&journalCode=ajp.

4. **Temporality** (The effect must occur after the cause, and in this case, the concept is important to rule out self-medication as a driver of the association.)

In prospective studies, cannabis use has been found to significantly predict developing psychosis (Arseneault et al., 2002; Henquet et al., 2005; Kuepper et al., 2011; Mustonen et al., 2018; van Os et al., 2020), whereas psychotic symptoms at study onset, including those that are prodromal in nature, have generally not been predictive of commencing cannabis use.

However, evidence for some degree of bi-directionality exists (psychosis leading to cannabis use) in almost all the prospective studies, and it reached significance in the work of Griffith-Lendering et al., (2013). Incipient, "prodromal" symptoms of psychosis appeared to have significantly increased the propensity to commence cannabis use, as well as vice versa. Yet critics of the Griffith-Lendering study have pointed to the use of questionnaires to collect the prodromal data rather than clinical interviews common in the other research reports, which from our perspective, may have resulted in overly inclusive responses to poorly phrased questions relevant to prodromal symptoms. For example, the question pertaining to "seeing things that other people do not see" could be misinterpreted to mean having insight into things that other people fail to perceive, a misunderstanding that a clinical interview could correct.

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* 325, no. 7374 (2002): 1212-13. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC135493/pdf/1212.pdf>.

Henquet C, Krabbendam L, Spauwen J, et al. "Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people." *BMJ* 330 (2005): 11–15. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC539839/pdf/bmj3300011.pdf>.

Griffith-Lending MF, Wigman JT, Prince van Leeuwen A, Huijbregts SC, Huizink AC, Ormel J, Verhulst FC, van Os J, Swaab H, Vollebergh WA. "Cannabis use and vulnerability for psychosis in early adolescence—a TRAILS study." *Addiction* 108, no. 4 (Apr 2013): 733-40. <https://doi.org/10.1111/add.12050>. Epub 2013 Jan 3. PMID: 23216690. <https://pubmed.ncbi.nlm.nih.gov/23216690/>.

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* 1, no. 342 (Mar 2011): d738. <https://doi.org/10.1136/bmj.d738>. <https://pubmed.ncbi.nlm.nih.gov/21363868/>.

Mustonen A, Niemelä S, Nordström T, Murray GK, Mäki P, Jääskeläinen E, Miettunen J. "Adolescent cannabis use, baseline prodromal symptoms and the risk of psychosis." *Br J Psychiatry* 212, no. 4 (2018): 227-233. https://www.cambridge.org/core/services/aop-cambridge-core/content/view/D5CAA12A5F424146DABB9C6A6AB4CB56/S0007125017000526a.pdf/adolescent_cannabis_use_baseline_prodromal_symptoms_and_the_risk_of_psychosis.pdf.

van Os J, Pries LK, Ten Have M, de Graaf R, van Dorselaer S, Bak M, Wittchen HU, Rutten BPF, Guloksuz S. "Schizophrenia and the Environment: Within-Person Analyses May be Required to Yield Evidence of Unconfounded and Causal Association—The Example of Cannabis and Psychosis." *Schizophr Bull* 47, no. 3 (Apr 29, 2021): 594-603. <https://doi.org/10.1093/schbul/sbab019>. PMID: 33693921; PMCID: PMC8084443. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8084443/pdf/sbab019.pdf>.

5. **Biologic Gradient** (Has a dose-response relationship, which in pharmacology is considered to be one important element for illustrating that a drug causes a certain outcome.)

Dose-response correlations demonstrate that the heavier the use of cannabis and the more potent the THC content, the more likely a psychotic outcome.

Andréasson S, Engström A, Allebeck P, Rydberg U. "Cannabis and schizophrenia. A Longitudinal Study of Swedish Conscripts." *The Lancet* 330, no. 8574 (Dec 1987): 1483-1486. [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(87\)92620-1/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(87)92620-1/fulltext).

Arseneault L, Cannon M, Poulton R, Murray R, Caspi A, Moffitt TE. "Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study." *BMJ* 325, no. 7374 (2002): 1212-13. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC135493/pdf/1212.pdf>.

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* 151, no. 1–3 (2013): 197-202. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3877688/pdf/nihms534094.pdf>.

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* 195, no. 6 (2009): 488-91.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2801827/?report=printable>.

Di Forti M, Marconi A, Carra E, Fraitetta 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." *The Lancet Psychiatry* 2, no. 3 (2015): 233-8

[https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366\(14\)00117-5/fulltext](https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366(14)00117-5/fulltext).

Marconi A, Di Forti M, Lewis CM, Murray RM, Vassos E. "Meta-analysis of the Association Between the Level of Cannabis Use and Risk of Psychosis." *Schizophr Bull.* 42, no. 5 (2016): 1262-9. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4988731/>.

Moore TH, Zammit S, Lingford-Hughes A, Barnes TR, Jones PB, Burke M, Lewis G. "Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review." *The Lancet* 370, no. 9584 (Jul 28, 2007): 319-28. [https://doi.org/10.1016/S0140-6736\(07\)61162-3](https://doi.org/10.1016/S0140-6736(07)61162-3). PMID: 17662880. <https://pubmed.ncbi.nlm.nih.gov/17662880/>.

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* 156, no. 4 (2002): 319-27.

<https://www.ncbi.nlm.nih.gov/pubmed/12181101>.

Zammit S, Allebeck P, Andréasson S, Lundberg I, Lewis G. "Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study." *BMJ* 325, no. 7374 (Nov 23, 2002): 1199. <http://www.bmj.com/content/325/7374/1199.full.pdf>.

6. Plausibility (a plausible biological mechanism) and **7. Coherence** (the coherence between a plausible biological mechanism and what is already known about the disease—see van Reekum et al., 2001, above). These two elements of causation are best discussed together, and it must be noted that the plausible mechanisms are not mutually exclusive, nor do they preclude other more important mechanisms being added to an understanding of the phenomenon as they are uncovered.

i. **A plausible mechanism concerning dopamine and coherence with what is already known about a chronic psychotic disorder like schizophrenia:** Similar to other drugs of abuse, THC has been shown to increase dopamine synthesis and release in the brain in the majority of animal models (reviewed by Bloomfield et al., 2016) and in human studies (Bossong et al., 2015). Much work has been done illustrating over-activity of the catecholamine dopamine in psychotic disorders like schizophrenia, and most antipsychotic drugs block one or more of the dopamine receptors (reviewed by Seeman et al., 2013), though other interactions of the antipsychotic drugs with catecholamine or indoleamine function may also contribute to their mechanism of action (Miller, 2013).

Bloomfield MA, Ashok AH, Volkow ND, Howes OD. "The effects of Δ^9 -tetrahydrocannabinol on the dopamine system." *Nature* 539, no. 7629 (Nov 17, 2016): 369-377.

<https://doi.org/10.1038/nature20153>. PMID: 27853201; PMCID: PMC5123717.
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5123717/>.

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- ii. **A plausible mechanism concerning the kynurenine pathway and coherence with what is already known about schizophrenia and bipolar disorder with psychosis:** THC has been shown to activate the kynurenine pathway in immune cells, in the concentration range known to be intoxicating, from 10 ng/ml up to several hundred ng/ml (Jenny et al., 2009). Although the immune cells themselves should not cross the blood brain barrier, two of the pathway intermediates can (kynurenine and 3-hydroxykynurenine; Schwarcz et al., 2012). In addition, the older literature on animal models demonstrated that THC increased the activity of one of the initiating enzymes of the pathway (tryptophan 2,3-dioxygenase) in the liver (Poddar and Gosh, 1972). This is coherent with what is known about schizophrenia because many studies have shown an upregulation in kynurenine pathway enzymes and metabolites in psychotic disorders, including schizophrenia (Schwarcz et al., 2001; Miller et al., 2006; reviewed more recently by Chiappelli et al., 2018).

Chiappelli J, Notarangelo FM, Pocivavsek A, Thomas MAR, Rowland LM, Schwarcz R, Hong LE. "Influence of plasma cytokines on kynurenine and kynurenic acid in schizophrenia." *Neuropsychopharmacology* 43, no. 8 (Jul 2018): 1675-1680. <http://doi.org/10.1038/s41386-018-0038-4>. Epub 2018 Feb 27. PMID: 29520060; PMCID: PMC6006321. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6006321/pdf/41386_2018_Article_38.pdf.

Jenny M, Santer E, Pirich E, Schennach H, Fuchs D. " Δ 9-Tetrahydrocannabinol and cannabidiol modulate mitogen-induced tryptophan degradation and neopterin formation in peripheral blood mononuclear cells in vitro." *J Neuroimmunol* 207, no. 1-2 (Feb 15, 2009): 75-82. <https://doi.org/10.1016/j.jneuroim.2008.12.004>. Epub 2009 Jan 22. PMID: 19167098. <https://pubmed.ncbi.nlm.nih.gov/19167098/>.

Miller CL, Llenos IC, Dulay JR, Weis S. "Upregulation of the initiating step of the kynurenine pathway in postmortem anterior cingulate cortex from individuals with schizophrenia and bipolar disorder." *Brain Res.* 1073-1074 (Feb 16, 2006): 25-37. <https://doi.org/10.1016/j.brainres.2005.12.056>. Epub 2006 Jan 30. PMID: 16448631. <https://pubmed.ncbi.nlm.nih.gov/16448631/>.

Poddar MK, Ghosh JJ. "Effect of cannabis extract, Δ^9 -tetrahydrocannabinol and lysergic acid diethylamide on rat liver enzymes. *Biochem Pharmacol.* 21, no. 24 (1972): 3301-3. <https://pubmed.ncbi.nlm.nih.gov/4405370/>.

Schwarcz R, Bruno JP, Muchowski PJ, Wu HQ. "Kynurenines in the mammalian brain: when physiology meets pathology." *Nat Rev Neurosci.* 13, no. 7 (Jul 2012): 465-77. <https://doi.org/10.1038/nrn3257>. PMID: 22678511; PMCID: PMC3681811. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3681811/pdf/nihms468169.pdf>.

Schwarcz R, Rassoulpour A, Wu HQ, Medoff D, Tamminga CA, Roberts RC. "Increased cortical kynurenate content in schizophrenia." *Biol Psychiatry* 50, no. 7 (2001): 521–530. <https://pubmed.ncbi.nlm.nih.gov/11600105/>.

iii. **A plausible mechanism concerning structural changes to the brain and coherence with what is already known about schizophrenia:** The strongest studies of brain structure are those that are longitudinal in nature; i.e., that follow the same individuals over time. In one such study employing MRI scans, Yu et al. (2020) found developmental differences in the right parahippocampal gyrus (a lowered expansion of the uncus) in cannabis users with psychotic experiences. Coherent with this finding, in a cross-sectional study of early schizophrenia patients, Du et al., (2018) found a reduced functional connectivity between the right parahippocampal gyrus and the temporal pole. Such findings merely mark the beginning of MRI studies that will help discern anatomic corollaries of psychotic-like experiences in cannabis users, as schizophrenia involves many brain regions.

Du Y, Fryer SL, Fu Z, Lin D, Sui J, Chen J, Damaraju E, Mennigen E, Stuart B, Loewy RL, Mathalon DH, Calhoun VD. "Dynamic functional connectivity impairments in early schizophrenia and clinical high-risk for psychosis." *Neuroimage* 180, part B (Oct 15, 2018): 632-645. <https://doi.org/10.1016/j.neuroimage.2017.10.022>. Epub 2017 Oct 14. PMID: 29038030; PMCID: PMC5899692. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5899692/pdf/nihms917676.pdf>.

Yu T, Jia T, Zhu L, Desrivières S, Macare C, Bi Y, et al. IMAGEN Consortium. "Cannabis- Associated Psychotic-like Experiences Are Mediated by Developmental Changes in the Parahippocampal Gyrus." *J Am Acad Child Adolesc Psychiatry* 59, no. 5 (May 2020): 642-649. <https://doi.org/10.1016/j.jaac.2019.05.034>. Epub 2019 Jul 18. PMID: 31326579. <https://www.sciencedirect.com/science/article/abs/pii/S0890856719304691>.

iv. **A plausible mechanism involving gene-environment interactions and coherence with what is known about genetic risk for psychosis.** That there is a genetic component to schizophrenia is well established from studies showing how risk level is proportional to degree of relatedness to the affected individual (Gottesman and Shields, 1967). The potential for interactions between whatever those genes are and environmental factors is incontrovertible from well-accepted biological principles. Here, the environmental factor in question is cannabis, and there are reports that specific genes or combinations of genes may interact with cannabis use to augment risk for psychosis, even though they may not have led to psychosis in most carriers who were not cannabis users. For example, a "C" allele of AKT1 was determined by Di Forti et al. (2012) to be significantly more prevalent in first- episode psychosis patients who were cannabis users as compared to psychosis patients who were not users. Unfortunately, the ethnic matching between cases and controls was poor, and the adjustment for the differing

ethnic frequencies in the genetic marker of interest does not solve the problem (for a discussion of this Issue, see Oetjens et al., 2016). A subsequent AKT1 study in subjects with no family history of psychosis (Morgan et al., 2016) also found a significant association between the AKT1 "C" allele and risk for developing psychotic symptoms after cannabis administration under controlled conditions in the clinic, including a strong trend for an effect of ethnicity on the occurrence of the symptoms. Confirmation of the study results would be helpful, in particular because the sign of the standardized regression " β " coefficient for AKT1 does not match that of the raw regression coefficient in Table 2A, an inexplicable result for which no erratum was issued.

A different approach involving multiple genes contributing to what is known as a "polygenic risk score" (PRS) appears promising when applied to a large, ethnically uniform group of subjects. Wainberg et al. (2021) found that frequent cannabis use interacted with the PRS for schizophrenia to significantly augment specific psychotic features (most notably delusions of reference) as compared to PRS gene carriers who did not frequently use cannabis.

In addition to AKT1 and PRS genes, candidate genes predicted to interact with THC from work in animal models have the potential to explain a portion of the gene-environment interactions. For example: 1) genes for receptors that bind THC and have been shown to mediate THC's effect on dopaminergic tone in an animal model; 2) genes for enzymes involved in metabolizing THC and responding to its metabolites; or 3) genes involved in the effect of THC on kynurenine pathway metabolites (see Element 6, parts i and ii above), some of which could theoretically pose risk solely through interaction with cannabis use.

Genetic studies have also been interpreted to undermine cannabis use as being a significant independent risk factor for the general population. A recent study by Kendler et al. (2019) demonstrated that the family history of psychosis was statistically equivalent between cannabis-related schizophrenia cases and typical schizophrenia cases from the general population.

What this and some prior studies of family history failed to do, however, was to determine whether the psychosis cases in the family trees had any association with cannabis or other drug use, which would obviously confound the magnitude of the genetic contribution to psychosis in the group under study.

Yet other genetic association publications point to an overlap between the polygenic risk markers for schizophrenia and polygenic risk markers for lifetime cannabis use (e.g., Pasmán et al., 2018). This could be interpreted to signify that the association between the two disorders may not be causal but instead result from the coincidence of the two disorders having the same genes of risk rather than deriving from a gene-environment interaction.

However, the Pasmán et al. study was heavily criticized for not actually ascertaining a diagnosis in the subjects labeled as having schizophrenia (Erratum in Nature Neuroscience) and, regardless, the PRS for schizophrenia generally explains only a small percentage of "all cause" schizophrenia patients (Laursen et al., 2017), particularly so for the genes covered by Pasmán et al. (3.4 %). Furthermore, other research groups have reported that the schizophrenia-PRS genetic signal in cannabis-using controls was not significantly different than in controls who were non-users (unpublished data in a reply to author, Di Forti et al., 2015), a finding confirmed by the work of Hjorthøj et al. (2021), who found no significant evidence for an association between a high

schizophrenia-PRS signal and the development of a cannabis use disorder in otherwise normal controls. And a recent genome-wide meta-analysis of markers for cannabis use disorder identified only a modest correlation between individual genetic markers of risk for cannabis use disorder and schizophrenia (Figure 2, Johnson et al., 2021). In addition, schizophrenia was not one of the 12 mental disorders found to be significantly associated with the PRS genes for cannabis use disorder.

For these reasons, and because only a minority of individuals who develop schizophrenia have a first- or second-degree family history of psychosis (see Element 3 ii above), gene-environment interactions will continue to have merit as a mechanism worthy of exploration. But the genes identified as having the strongest interaction may not have been manifest in a family history of psychosis absent cannabis use, and will likely not be genes that predispose to cannabis use.

Di Forti M, Iyegbe C, Sallis H, Kolliakou A, Falcone MA, Paparelli A, Sirianni M, La Cascia C, Stilo SA, Marques TR, Handley R, Mondelli V, Dazzan P, Pariante C, David AS, Morgan C, Powell J, Murray RM. "Confirmation that the AKT1 (rs2494732) genotype influences the risk of psychosis in cannabis users." *Biol Psychiatry* 72, no. 10 (Nov 15, 2012): 811-16. <https://doi.org/10.1016/j.biopsych.2012.06.020>. Epub 2012 Jul 24. PMID: 22831980. <https://pubmed.ncbi.nlm.nih.gov/22831980/>.

Di Forti M, Vassos E, Lynskey M, Craig M, Murray RM. "Cannabis and psychosis – Authors' reply." *The Lancet Psychiatry* 2, no. 5 (May 2015): 382. [https://doi.org/10.1016/S2215-0366\(15\)00177-7](https://doi.org/10.1016/S2215-0366(15)00177-7). Epub 2015 Apr 28. PMID: 26360275. <https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366%2815%2900177-7/fulltext>.

Gottesman II, Shields J. "A polygenic theory of schizophrenia." *Proc Natl Acad Sci U S A* 58, no. 1 (Jul 1967): 199-205. <https://doi.org/10.1073/pnas.58.1.199>. PMID: 5231600; PMCID: PMC335617. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC335617/pdf/pnas00677-0218.pdf>.

Hjorthøj C, Uddin MJ, Wimberley T, Dalsgaard S, Hougaard DM, Børghlum A, Werge T, Nordentoft M. "No evidence of associations between genetic liability for schizophrenia and development of cannabis use disorder." *Psychol Med*. 51, no. 3 (Feb 2021): 479-484. <https://doi.org/10.1017/S0033291719003362>. Epub 2019 Dec 9. PMID: 31813396. <https://pubmed.ncbi.nlm.nih.gov/31813396/>.

Johnson EC, Demontis D, Thorgeirsson TE, Walters RK, Polimanti R, Hatoum AS. "A large-scale genome-wide association study meta-analysis of cannabis use disorder." *The Lancet Psychiatry* 7, no. 12 (Dec 2020): 1032-1045. [https://doi.org/10.1016/S2215-0366\(20\)30339-4](https://doi.org/10.1016/S2215-0366(20)30339-4). Epub 2020 Oct 20. PMID: 33096046; PMCID: PMC7674631. <https://www.thelancet.com/action/showPdf?pii=S2215-0366%2820%2930339-4>.

Kendler KS, Ohlsson H, Sundquist J, Sundquist K. "Prediction of Onset of Substance-Induced Psychotic Disorder and Its Progression to Schizophrenia in a Swedish National Sample." *Am J Psychiatry* 176, no. 9 (Sep 1, 2019): 711-719. <https://doi.org/10.1176/appi.ajp.2019.18101217>. Epub 2019 May 6. PMID: 31055966; PMCID: PMC6718312. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6718312/pdf/nihms-1525260.pdf>.

Laursen TM, Trabjerg BB, Mors O, Børghlum AD, Hougaard DM, Mattheisen M, Meier SM, Byrne

EM, Mortensen PB, Munk-Olsen T, Agerbo E. "Association of the polygenic risk score for schizophrenia with mortality and suicidal behavior – A Danish population-based study." *Schizophr Res*. 184 (Jun 2017): 122-127. <https://doi.org/10.1016/j.schres.2016.12.001>. Epub 2016 Dec 6. PMID: 27939829. <https://pubmed.ncbi.nlm.nih.gov/27939829/>.

Morgan CJ, Freeman TP, Powell J, Curran HV. "AKT1 genotype moderates the acute psychotomimetic effects of naturalistically smoked cannabis in young cannabis smokers." *Transl Psychiatry* 6, no. 2 (Feb 2016): e738. <https://doi.org/10.1038/tp.2015.219>. PMID: 26882038; PMCID: PMC4872423. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4872423/pdf/tp2015219a.pdf>.

Oetjens MT, Brown-Gentry K, Goodloe R, Dilks HH, Crawford DC. "Population Stratification in the Context of Diverse Epidemiologic Surveys Sans Genome-Wide Data." *Front. Genet.* 7, no. 76 (May 6, 2016). <https://doi.org/10.3389/fgene.2016.00076>. PMID: 27200085; PMCID: PMC4858524. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4858524/pdf/fgene-07-00076.pdf>.

Pasman JA, Verweij KJH, Gerring Z, Stringer S, Sanchez-Roige S, Treur JL, et al. "GWAS of lifetime cannabis use reveals new risk loci, genetic overlap with psychiatric traits, and a causal influence of schizophrenia." *Nat Neurosci.* 21, no. 9 (Sep 2018): 1161-1170. <https://doi.org/10.1038/s41593-018-0206-1>. Epub 2018 Aug 27. Erratum in: *Nat Neurosci.* 22, no. 7 (Jul 2019): 1196. PMID: 30150663; PMCID: PMC6386176. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6386176/pdf/nihms-1003328.pdf>.

Wainberg M, Jacobs GR, Di Forti M, Tripathy SJ. "Cannabis, schizophrenia genetic risk, and psychotic experiences: a cross-sectional study of 109,308 participants from the UK Biobank." *Transl Psychiatry* 11, no. 1 (Apr 9, 2021): 211. <https://doi.org/10.1038/s41398-021-01330-w>. PMID: 33837184; PMCID: PMC8035271. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8035271/pdf/41398_2021_Article_1330.pdf.

8. Experimental evidence (obtained under controlled conditions where cause and effect are more easily discerned).

i. When studied in controlled clinical settings, a moderate dose of the active ingredient in cannabis (THC) elicits transient psychotic symptoms in normal cohort-controlled subjects with no family history of psychosis, and an increase in the average PANSS, a well-accepted clinical assessment tool to measure positive and negative symptoms of psychosis.

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* 29, no. 8 (Aug 2004): 1558-72. <https://www.nature.com/articles/1300496.pdf>.

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 Δ^9 -Tetrahydrocannabinol (THC) to Identify Key Cognitive Mechanisms Leading to Paranoia."

Schizophr Bull. 41, no. 2 (2015): 391-9.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4332941/pdf/sbu098.pdf>.

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 Theta Coherence by Δ^9 -Tetrahydrocannabinol Is Associated with Positive Psychotic Symptoms."

Neuropsychopharmacology 36, no. 4 (2011): 827-36.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3055738/pdf/npp2010222a.pdf>.

- ii. **Two studies reported the percentage of subjects that experienced psychotic symptoms, specifically 40% of subjects (Morrison et al., 2011, and see figure 2 of Bhattacharyya et al., 2012).**

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 Δ^9 -Tetrahydrocannabinol Reflects Modulation of Prefrontal and Striatal Function During Attentional Salience Processing." *Arch Gen Psychiatry* 69, no. 1 (2012): 27-36.

<https://jamanetwork.com/journals/jamapsychiatry/fullarticle/1107444>.

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 Theta Coherence by Δ^9 -Tetrahydrocannabinol Is Associated with Positive Psychotic Symptoms."

Neuropsychopharmacology 36, no. 4 (2011): 827-36.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3055738/pdf/npp2010222a.pdf>.

9. Analogous evidence (If something similar to A causes something similar to B, then A likely causes B).

This condition is satisfied by the observation that other drugs of abuse that increase dopamine release in the brain (Koob and Volkow, 2016) are capable of resulting in a chronic psychotic disorder similar to that caused by cannabis (Niemi-Pynttari et al., 2013; Starzer et al., 2017). The experimental findings in section 8 are also relevant, because in the clinic, THC elicits a precursor to chronic psychotic disorders (psychotic symptoms); therefore, THC should also cause chronic psychotic disorders.

Koob GF, Volkow ND. "Neurobiology of addiction: a neurocircuitry analysis." *The Lancet Psychiatry* 3, no. 8 (Aug 2016): 760-773. [https://doi.org/10.1016/S2215-0366\(16\)00104-8](https://doi.org/10.1016/S2215-0366(16)00104-8). PMID: 27475769; PMCID: PMC6135092.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6135092/pdf/nihms-985499.pdf>.

Niemi-Pynttari JA, Sund R, Putkonen H, Vormaa H, Wahlbeck K, Pirkola SP. "Substance-Induced Psychoses Converting into Schizophrenia: A Register-Based Study of 18,478 Finnish Inpatient Cases." *J Clin Psychiatry* 74, no. 1 (2013): e94-9.

<https://www.psychiatrist.com/jcp/article/Pages/2013/v74n01/v74n0115.aspx>.

Starzer MSK, Nordentoft M, Hjorthøj C. "Rates and Predictors of Conversion to Schizophrenia or Bipolar Disorder Following Substance-Induced Psychosis." *Am J Psychiatry* 175, no. 4 (2018): 343-50.

https://ajp.psychiatryonline.org/doi/abs/10.1176/appi.ajp.2017.17020223?rfr_dat=cr_pub%3Dp

[u bmed&url ver=Z39.88-2003&rfr id=ori%3Arid%3Acrossref.org&journalCode=ajp.](https://pubmed.ncbi.nlm.nih.gov/339882003/)

Conclusion

The currently available research on cannabis causing chronic psychotic disorders satisfies the Bradford Hill elements of causation. This means that some people who develop a chronic psychotic disorder after using cannabis would not have developed the disorder had they not used cannabis. Even if a certain amount of residual confounding remains, for example unquantified variations in other environmental risks or in genetic background, it is not enough to undermine the effect of cannabis as an independent risk factor.