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

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with a review and contributions from Carsten Hjorthoj, Ph.D., Associate Professor, Copenhagen Research Center for Mental Health, University of Copenhagen;

(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. 2001 Summer;13(3):318-25. doi: 10.1176/jnp.13.3.318. PMID: 11514637. https://pubmed.ncbi.nlm.nih.gov/11514637/

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.
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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, 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. 2015;2(3):233-8 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. 2016;42(5):1262-9. 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. 2015 Sep;29(3):552-63. doi: 10.1037/adb0000103. Epub 2015 Aug 3. Erratum in: Psychol Addict Behav. 2015 Dec;29(4):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. 2016;42(5):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. Lancet. 2007 Jul 28;370(9584):319-28. doi: 10.1016/S0140-6736(07)61162-3. PMID: 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. 2002 Dec;36(6):800-6. doi: 10.1046/j.1440-1614.2002.01089.x. PMID: 12406123. https://pubmed.ncbi.nlm.nih.gov/12406123/

ii. **In addition to research results included in the 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); 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).

Alliende 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.* 2019;45(Suppl 2):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

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. doi: 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. Lancet Psychiatry. 2019]https://www.thelancet.com/action/showPdf?pii=S2215-0366%2819%2930048-3

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. 2017 Jul;47(9):1668-1677. doi: 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 premorbid period is associated with increased risk of onset of schizophrenia and related psychotic disorders. Schizophr Res. 2016 Mar;171(1-3):62-7. doi: 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. 2016 Aug 3;7:136. doi: 10.3389/fpsyt.2016.00136. PMID: 27536254; PMCID: PMC4971430. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4971430/pdf/fpsyt-07-00136.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. 2018 Apr;194:13-17. doi: 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. 2020 Jun;40(5-6):176-183. doi: 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. 2018 Apr;212(4):227-233. doi: 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-Pynttari 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, 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. 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. 2018;175(4):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 (PAF) to heavy use of higher potency cannabis use exceeds the PAF for family history of psychosis.

The PAF for 1st degree family history in schizophrenia cases is reported to be 5.5%, and the PAF for a 1st or 2nd 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 3rd 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 all, 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. 2004 Feb;184:110-7. doi: 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. 2007;93(1-3):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. Lancet Psychiatry. 2015;2(3):233-8
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. 1999 Feb 25;340(8):603-8. doi: 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.

2010;67(3):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. 2018;175(4):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

4. Temporality (the effect has to 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, 2002;325(7374):1212-3. 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. 2005;330:11–15. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC539839/pdf/bmj33000011.pdf

Griffith-Lendering 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. 2013 Apr;108(4):733-40. doi: 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.

2011 Mar 1;342: d738
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3047001/pdf/bmj.d738.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. 2018;212(4):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 Dorsselaer 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. 2021 Apr 29;47(3):594-603. doi: 10.1093/schbul/sbab019. PMID: 33693921; PMCID: PMC8084443.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8084443/pdf/sbab019.pdf

5. Biologic Gradient (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. (1987). Cannabis and schizophrenia. A longitudinal study of Swedish conscripts. The Lancet, 330(8574), 1483-1486.
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, 2002;325(7374):1212-3.
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. 2013;151(1-3):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. 2009,195(6):488-91.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2801827/?report=printable

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. Lancet Psychiatry. 2015;2(3):233-8
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. 2016;42(5):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. Lancet. 2007 Jul 28;370(9584):319-28. doi: 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. 2002;156(4):319-27.
https://www.ncbi.nlm.nih.gov/pubmed/12181101

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

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. 2016 Nov 17;539(7629):369-377. doi: 10.1038/nature20153. PMID: 27853201; PMCID: PMC5123717.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5123717/

Bossong MG, Mehta MA, van Berckel BN, Howes OD, Kahn RS, Stokes PR. Further human evidence for striatal dopamine release induced by administration of Δ9-tetrahydrocannabinol (THC): selectivity to limbic striatum. Psychopharmacology (Berl). 2015 Aug;232(15):2723-9. doi: 10.1007/s00213-015-3915-0. Epub 2015 Mar 25. PMID: 25801289; PMCID: PMC4816196. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4816196/pdf/emss-66024.pdf

Miller CL. On the mechanism of action of antipsychotic drugs: a chemical reaction not receptor blockade. Curr Drug Discov Technol. 2013;10(3):195-208. https://pubmed.ncbi.nlm.nih.gov/23363232/

Seeman P. Schizophrenia and dopamine receptors. Eur Neuropsychopharmacol. 2013 Sep;23(9):999-1009. doi: 10.1016/j.euroneuro.2013.06.005. Epub 2013 Jul 13. PMID: 23860356. https://pubmed.ncbi.nlm.nih.gov/23860356/

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 Chiapelli 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. 2018 Jul;43(8):1675-1680. doi: 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. Delta9-tetrahydrocannabinol and cannabidiol modulate mitogen-induced tryptophan degradation and neopterin formation in peripheral blood mononuclear cells in vitro. J Neuroimmunol. 2009 Feb 15;207(1-2):75-82. doi: 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. 2006 Feb 16;1073-1074:25-37. doi: 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. 1972; 21(24):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. 2012 Jul;13(7):465-77. doi: 10.1038/nrn3257. PMID: 22678511; PMCID: PMC3681811.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3681811/pdf/nihms468169.pdf

Schwarcz, R., Rassoulpour, A., Wu, H.Q., Medoff, D., Tamminga, C.A., Roberts, R.C., 2001. Increased cortical kynurenate content in schizophrenia. Biol. Psychiatry 50 (7), 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. 2018 Oct 15;180(Pt B):632-645. doi: 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. 2020 May;59(5):642-649. doi: 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 AKTI "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 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. Pasman et al., 2018). This could be interpreted to signify that the association between the two disorders may not be causal but instead results from the coincidence of the two disorders having the same genes of risk rather than deriving from a gene-environment interaction. However, the Pasman 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 Pasman 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 Hjorthoj 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 1st or 2nd 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. 2012 Nov 15;72(10):811-6. doi: 10.1016/j.biopsych.2012.06.020. Epub 2012 Jul 24. PMID: 22831980.
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Hjorthøj C, Uddin MJ, Wimberley T, Dalsgaard S, Hougaard DM, Børglum A, Werge T, Nordentoft M. No evidence of associations between genetic liability for schizophrenia and development of cannabis use disorder. Psychol Med. 2021 Feb;51(3):479-484. doi: 10.1017/S0033291719003362. Epub 2019 Dec 9. PMID: 31813396.
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Johnson EC, Demontis D, Thorgeirsson TE, Walters RK, Polimanti R, Hatoum AS, Psychiatric Genomics Consortium Substance Use Disorders Workgroup, et al. A large-scale genome-wide association study meta-analysis of cannabis use disorder. Lancet Psychiatry. 2020

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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. 2004 Aug;29(8):1558-72.
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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 Δ9-tetrahydrocannabinol (THC) to identify key cognitive mechanisms leading to paranoia. Schizophr Bull. 2015;41(2):391-9.
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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 fig. 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 Δ9-tetrahydrocannabinol reflects modulation of prefrontal and striatal function during attentional salience processing. Arch Gen Psychiatry. 2012;69(1):27-36.
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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.
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-Pyntarri 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. Lancet Psychiatry. 2016 Aug;3(8):760-773. doi: 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-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.
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Starzer MSK, Nordentoft M, Hjorthøj C. Rates and Predictors of Conversion to Schizophrenia or Bipolar Disorder Following Substance-Induced Psychosis. Am J Psychiatry. 2018;175(4):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

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.

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