**Risk thresholds for the association between frequency of cannabis use and the development of psychosis: A systematic review and meta-analysis**

**Supplementary Materials**

eTable 1. PRISMA 2020 Checklist

eMethods 1. Database Search Strategies

eMethods 2. Full text exclusions and reasoning

eTable 2. Risk of Bias Assessments

eFigure 1. Additional Heterogeneity Assessment

eFigure 2. Funnel Plot Tests for Publication Bias

eTable 3. Certainty of the Evidence Assessment Using the GRADE Approach

**eTable 1. PRISMA 2020 Checklist**

| **Section and Topic**  | **Item #** | **Checklist item**  | **Location where item is reported**  |
| --- | --- | --- | --- |
| **TITLE**  |  |
| Title  | 1 | Identify the report as a systematic review. | Page 1 |
| **ABSTRACT**  |  |
| Abstract  | 2 | See the PRISMA 2020 for Abstracts checklist. | Page 3 |
| **INTRODUCTION**  |  |
| Rationale  | 3 | Describe the rationale for the review in the context of existing knowledge. | Page 5–7 |
| Objectives  | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. | Page 7 |
| **METHODS**  |  |
| Eligibility criteria  | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | Page 8-9 |
| Information sources  | 6 | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | Page 8 |
| Search strategy | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | Supplementary eMethods 1 |
| Selection process | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | Page 9 |
| Data collection process  | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | Page 9-10 |
| Data items  | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | Page 9-10 |
| 10b | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | Page 9-10 |
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | Page 11 |
| Effect measures  | 12 | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. | Page 10 |
| Synthesis methods | 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). | Page 10 |
| 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | Page 10-11 |
| 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | Table 2 /Figure 2Figure 3 |
| 13d | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. | Page 10-11 |
| 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). | Supplemental eFigure 1 |
| 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | Page 10-11 |
| Reporting bias assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | Page 11 |
| Certainty assessment | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | Page 11 |
| **RESULTS**  |  |
| Study selection  | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. | Page 12Figure 1 |
| 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | SupplementaleMethods 2 |
| Study characteristics  | 17 | Cite each included study and present its characteristics. | Page 12Table 1 |
| Risk of bias in studies  | 18 | Present assessments of risk of bias for each included study. | Supplementary eTable 2 |
| Results of individual studies  | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | Figure 3 |
| Results of syntheses | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | Figure 3 |
| 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | Figure 3 |
| 20c | Present results of all investigations of possible causes of heterogeneity among study results. | Page 13 SupplementaleTable 2 |
| 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. | Page 13 |
| Reporting biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | Page 13Supplemental eFigure 2 |
| Certainty of evidence  | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | Page 14 SupplementaleTable 3 |
| **DISCUSSION**  |  |
| Discussion  | 23a | Provide a general interpretation of the results in the context of other evidence. | Page 14 |
| 23b | Discuss any limitations of the evidence included in the review. | Page 16-17 |
| 23c | Discuss any limitations of the review processes used. | Page 16-17 |
| 23d | Discuss implications of the results for practice, policy, and future research. | Page 15-16 |
| **OTHER INFORMATION** |  |
| Registration and protocol | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | Page 7 |
| 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | Page 7 |
| 24c | Describe and explain any amendments to information provided at registration or in the protocol. | N/A |
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | Page 19 |
| Competing interests | 26 | Declare any competing interests of review authors. | Page 18 |
| Availability of data, code and other materials | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | Page 7 |

*From:*  Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

**eMethods 1. Database Search Strategies**

**Embase search strategy (OVID)**

1. Exp cannabis/
2. Exp cannabis addiction/
3. Exp “cannabis use”/
4. Cannab\*.mp.
5. Hashish.mp.
6. Marijuana.mp.
7. Marihuana.mp.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. Exp psychosis/
10. Psychos\*.mp.
11. Psyhchotic.mp.
12. Psychiatr\*.mp.
13. Psychopathol\*.mp.
14. “Psychotic feature\*.mp.
15. Delusion\*.mp.
16. Hallucinat\*.mp.
17. Schizo\*.mp.
18. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
19. Exp “dose response”.mp.
20. “Dose response”.mp,
21. “Dose-response”.mp.
22. Frequen\*.mp.
23. “Heavy use”.mp.
24. 19 or 20 or 21 or 22 or 23
25. 8 and 18 and 24
26. Limit 25 to (yr=”2010–current”)

**Medline Search Strategy (OVID)**

1. Exp Marijuana Abuse/
2. Exp Cannabis/
3. Cannab\*.mp.
4. Hashish.mp.
5. Marijuana.mp.
6. Marihuana.mp.
7. 1 or 2 or 3 or 4 or 5 or 6
8. Exp Psychotic Disorders/
9. Psychos\*.mp.
10. Psychotic.mp.
11. Psychiatr\*.mp.
12. Psychopathol\*.mp.
13. “Psychotic feature\*”.mp.
14. Delusion\*.mp.
15. Hallucinat\*.mp.
16. Schizo\*.mp.
17. 8 or 9 or 10 or 11 or 12 or 12 or 14 or 15 or 16
18. Exp Dose-Response Relationship, Drug/
19. “Dose response”.mp.
20. “Dose-response”.mp.
21. Frequen\*.mp.
22. “Heavy use”.mp.
23. 18 or 19 or 20 or 21 or 22
24. 7 and 17 and 23
25. Limit 24 to yr=”2010–current”

**PsychINFO Search Strategy (OVID)**

1. Exp Cannais/
2. Exp Marijuana Usage/
3. Exp “Cannabis Use Disorder”/
4. Cannab\*.mp.
5. Hashish.mp.
6. Marijuana.mp.
7. Marihuana.mp.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. Exp Psychosis/
10. Psychotic.mp.
11. Psycho\*.mp.
12. Psychiatr\*.mp.
13. Psychopathol\*.mp.
14. “Psychotic feature\*”.mp.
15. Delisuon\*.mp.
16. Hallucinat\*.mp.
17. Schizo\*.mp.
18. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19. “Dose response”.mp.
20. “Dose-response”.mp.
21. Frequen\*.mp.
22. “Heavy use”.mp.
23. 19 or 20 or 21 or 22
24. 8 and 18 and 23
25. Limit 24 to yr=”2010–current”

**CINAHL Search Strategy (EBSCO)**

S1. (MH “Cannabis+”)

S2. “Cannab\*”

S3. “Marijuana”

S4. “Marihuana”

S5. “Hashish”

S6. S1 OR S2 OR S3 OR S4 OR S5

S7. (MH “Psychotic Disorders+”)

S8. “Psychotic”

S9. Psychiatr\*

S10. “Psychopathol\*”

S11. “Psychotic feature”

S12. “Delusion\*”

S13. “Hallucinat\*”

S14. “Schizo\*”

S15. S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14

S16. (MH “Dose-Response Relationship, Drug”)

S17. (MH “Dose-Response Relationship)

S18. “Dose-response”

S19. “Dose response”

S20. “Frequen\*”

S21. “Heavy use”

S22. S16 OR S17 OR S18 OR S19 OR S20 OR S21

S23. S6 AND S15 AND S22

S24. Limiters – published date: 20100101-20211231

**Web Of Science (Clarivate)**

#1 ALL=(cannab\* OR hashish OR marijuana OR marihuana)

#2 ALL=(psychos\* OR psychiatr\* OR psychopathol\* OR psychotic feature OR delusion\* OR hallucinat\* OR schizo\*)

#3 ALL=(dose response OR dose-response OR frequen\* OR heavy use)

#4 #1 AND #2 AND #3

#5 #1 AND #2 AND #3

Refined by: PUBLICATION YEARS: (2021 OR 2020 OR 2019 OR 2018 OR 2017 OR 2016 OR 2015 OR 2014 OR 2013 OR 2012 OR 2011 OR 2010)

**eMethods 2. Full text exclusions and reasoning**

1. Aas M, Melle I, Bettella F, et al. Psychotic patients who used cannabis frequently before illness onset have higher genetic predisposition to schizophrenia than those who did not. *Psychol Med*. 2018;**48**(1):43–9.

*Reason for exclusion: incorrect outcomes*

1. Addington J, Buchy L, Cadenhead K, et al. Substance use in individuals at clinical high risk of psychosis. *Schizophr Bull*. 2015;**41**(SUPPL. 1):S104.

*Reason for exclusion: conference abstract*

3 Addington J, Piskulic D, Liu L, et al. Comorbid diagnoses for youth at clinical high risk of psychosis. *Schizophr Res.* 2017;**190**(90–5).

*Reason for exclusion: incorrect study population*

4 Ahsan MS, Mullick MS, Begum K, et al. Substance use among the patients with first episode psychosis. *Mymensingh Med J*. 2018;**27**(2):213–20.

*Reason for exclusion: incorrect study design*

5 Albertella L, Le Pelley ME, Yucel M, Copeland J. Age moderates the association between frequent cannabis use and negative schizotypy over time. *Addict Behav*. 2018;**87**(183–89).

*Reason for exclusion: incorrect outcomes*

6 Alibrahim O, Elawad N, Misau YA, Shaikh TM, Allam N. Drug dependence and psychotic symptoms: A retrospective study of adolescents who abuse drugs at Al-Amal hospital in Jeddah, Saudi Arabia. *J Public Health Afr*. 2012;**3**(1):19–21.

*Reason for exclusion: incorrect outcomes*

1. Allegri F. Cannabis use and age of onset in first episode of psychosis: A gender issue? *Schizophr Res.* 2012;**136**(SUPPL. 1):S25.

*Reason for exclusion: conference abstract*

1. Anglin D, Tayler R, Tikhonov A, DeVylder J. The role of aberrant salience in the association between early cannabis use and psychotic-like experiences. *Schizophr Bull*. 2019;**45**(SUPPL. 2):S168.

*Reason for exclusion: conference abstract*

9 Arbabzadeh-Bouchez S, Guillem E, Vorspan F, Bellivier F. Comorbidity in 207 cannabis users in a specific outpatient setting. *Encephale.* 2015;**41**(SUPPL. 1):S22-S7.

*Reason for exclusion: incorrect outcomes*

1. Auther A. Cannabis use and prodromal symptoms of psychosis. *Schizophr Res.* 2010;**117**(2-3):164.

*Reason for exclusion: conference abstract*

11 Barrigón ML, Gurpegui M, Ruiz-Veguilla M, et al. Temporal relationship of first-episode non-affective psychosis with cannabis use: a clinical verification of an epidemiological hypothesis. *J Psychiatr Res*. 2010;**44**(7):413–20.

*Reason for exclusion: incorrect study design*

1. Barrigón ML, Ruiz-Veguilla M, Moreno JM, et al. Drug use and age at onset of psychosis*. Eur Psychiatry.* 2010;**25**(SUPPL. 1).

*Reason for exclusion: conference poster*

13 Barrera A, Rocha MP, Leiderman E. Use of cannabis and incidence of psychotic symptoms: Evidence from Buenos Aires. *Vertex.* 2016;**XXVII**(130):447–51.

*Reason for exclusion: incorrect study design*

14 Barrowclough C, Emsley R, Eisner E, Beardmore R, Wykes T. Does change in cannabis use in established psychosis affect clinical outcome? *Schizophr Bull.* 2013;**39**(2):339–48.

*Reason for exclusion: incorrect study population*

15 Bechtold J, Hipwell A, Lewis DA, Loeber R, Pardini D. Concurrent and sustained cumulative effects of adolescent marijuana use on subclinical psychotic symptoms. *Am J Psychiatry.* 2016;**173**(8):781–9.

*Reason for exclusion: incorrect outcomes*

16 Beck K, Wursch L, Studerus E, et al. Cannabis use and clinical correlates in patients with an at-risk mental state and first episode of psychosis. *Eur Psychiatry*. 2018;**48**(SUPPL. 1):S122.

*Reason for exclusion: conference abstract*

17 Bereza Z. Six-month outcome of patients with bipolar disorder and cannabis abuse following hospitalization for a first manic or mixed episode. Eur *Neuropsychopharmacol*. 2016;**26**(SUPPL. 2):S690–S91.

*Reason for exclusion: conference abstract*

18 Bernardini F, Gobbicchi C, Attademo L, et al. Cannabis use, psychotic-like experiences and aberrant salience in a sample of Belgian students*. J Nerv Ment Dis*. 2018;**206**(7):493–500.

*Reason for exclusion: incorrect outcomes*

19 Bernardini F, Puchalski S, Gobbicchi C, et al. Cannabis use, psychotic-like experiences and aberrant salience in a sample of Belgian students. *Schizophr Bull.* 2018;**44**(Supplement 1):S363–S64.

*Reason for exclusion: conference abstract*

20 Bianconi F, Bonomo M, Marconi A, et al. Differences in cannabis-related experiences between patients with a first episode of psychosis and controls. *Psychol Med*. 2016;**46**(5):995–1003.

*Reason for exclusion: incorrect outcomes*

21 Boks MPM, Van Gastel WA, Schubart CD, et al. Cigarette smoking is equally strongly associated with psychotic-like experiences as cannabis use. *Schizophr Res*. 2014;**153**(SUPPL. 1):S9.

*Reason for exclusion: conference abstract*

22 Bonomo M, Bianconi F, Di Forti M, et al. Differences in cannabis-related experiences between patients with a first episode of psychosis and healthy controls. *Schizophr Res.* 2014;**153**(SUPPL. 1):S287.

*Reason for exclusion: conference poster*

23 Bourque J, O'Leary-Barrett M, Conrod P. The impact of cannabis use and emerging psychotic experiences explained by sleep problems and anxiety symptoms. *J Am Acad Child Adolesc Psychiatry*. 2016;**55**(10 SUPPL. 1):S233.

*Reason for exclusion: conference poster*

24 Brañas A, Barrigón ML, Garrido-Torres N, et al. U-shaped curve of psychosis according to cannabis use: New evidence from a snowball sample. *J Psychopharm.* 2016;**30**(12):1331–38.

*Reason for exclusion: incorrect outcomes*

25 Brennan D, Madigan K, Lawlor E, Turner N, Clarke M, O'Callaghan E. Age at onset of first psychotic sign of those who abuse substances in a first episode psychosis cohort. *Early Interv.* 2012;**6**(SUPPL.1):116.

*Reason for exclusion: conference abstract*

26 Calvo E, Ellman L, Mittal V, Schiffman J. Alcohol and Cannabis Use in Individuals at Clinical High-Risk for Psychosis - Relationship Between Symptom Course and Patterns of Use. *Biol Psychiatry*. 2020;**87**(9 SUPPL):S247.

*Reason for exclusion: conference abstract*

27 Cohen AS, Buckner JD, Najolia GM, Stewart DW. Cannabis and psychometrically-defined schizotypy: Use, problems and treatment considerations*. J Psychiatr Res*. 2011;**45**(4):548–54.

*Reason for exclusion: incorrect outcomes*

28 Colizzi M, Murray R. Cannabis and psychosis: What do we know and what should we do? *Br J Psychiatry.* 2018;**212**(4):195–6.

*Reason for exclusion: editorial*

29 Compton MT, Broussard B, Kelley M, Wan CR. Premorbid cannabis use and earlier age at onset of psychosis: Findings from two studies in the U.S. *Schizophr Res.* 2014;**153**(SUPPL. 1):S169.

*Reason for exclusion: conference poster*

30 Corsi-Zuelli F, Marques L, Da Roza DL, et al. Cannabis consumption increases risk of psychosis in a subgroup of patients with high peripheral blood inflammation. *Schizophr Bul*l. 2020**;46**(SUPPL. 1):S21–S2.

*Reason for exclusion: conference abstract and missed duplicate*

31 Coutinho L, Higuchi C, Cavalcante DA, et al. Cannabis use impacts symptom presentation in antipsychotic naive patients in first episode of psychosis (FEP). *Schizophr Bull.* 2018;**44**(SUPPL. 1):S153.

*Reason for exclusion: conference abstract*

32 Coyne J. Cannabis and psychosis. *The Lancet Psychiatry*. 2015;**2**(5):380–1.

*Reason for exclusion: letter to the editor*

33 Cretu A, Garaz G. Cannabis use and psychosis onset. *Eur Neuropsychopharmacol*. 2012;**22**(SUPPL. 2):S401.

*Reason for exclusion: conference abstract*

34 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.

*Reason for exclusion: incorrect outcomes*

35 Davis GP, Levin FR, Wang S, Blanco C. The relationship between cannabis use and psychosis in a nationally representative sample. *Am J Addict*. 2013**;22**(3):308.

*Reason for exclusion: conference abstract*

36 Degenhardt L, Saha S, Lim CCW, et al. The associations between psychotic experiences and substance use and substance use disorders: findings from the World Health Organization World Mental Health surveys. *Addiction.* 2018;**113**(5):924–34.

*Reason for exclusion: incorrect study design*

37 De Hert M, Wampers M, Jendricko T, et al. Effects of cannabis use on age at onset in schizophrenia and bipolar disorder. *Schizophr Res*. 2011;**126**(1-3):270–6.

*Reason for exclusion: Incorrect study population*

38 Del Cacho N, Nunez C, Ochoa S, et al. Cannabis use and cognitive function in first episode psychosis: Differential effect of heavy use. *Psychopharmacology*. 2016;**233**(5):809–21.

*Reason for exclusion: incorrect study population*

39 Dervaux A, Krebs MO, Laqueille X. Is cannabis responsible for early onset psychotic illnesses? *Neuropsychiatry*. 2011;**1**(3):203–7.

*Reason for exclusion: editorial*

40 Di Forti M, Morgan C, Stilo S, et al. The role of high potency cannabis use and psychosis genetic liability in moderating the risk for onset of psychotic disorders. *Early Interv*. 2010;**4**(SUPPL. 1):34.

*Reason for exclusion: conference abstract*

41 Di Forti M, Murray R, Lewis C, Quattrone D, Morgan C, Lynskey M. Cannabis use across Europe: A ticket to psychosis? *Schizophr Bull*. 2017;**43**(SUPPL. 1):S30.

*Reason for exclusion: conference abstract*

42 Di Forti M, Murray R, Stilo SA, Morgan C. Additive interaction between cannabis use and social adversity on predicting psychosis: Beyond the main effects. *Schizophr Bull*. 2015;**41**(SUPPL. 1):S154.

*Reason for exclusion: conference abstract*

43 Di Forti M, Quattrone D, Tripoli G, et al. Some of the individual differences in risk to develop psychosis among cannabis users can be explained by where they live and by their age at first use. *Schizophr Bull*. 2018;**44**(SUPPL. 1):S110.

*Reason for exclusion: conference abstract*

44 Di Forti M, Murray R. The role of high potency cannabis use and psychosis genetic liability in moderating the risk for onset of psychotic disorders. *Schizophr Bull*. 2011;**37**(SUPPL. 1):50.

*Reason for exclusion: conference abstract*

45 Dragt S, Nieman DH, Wesselius C, et al. Does cannabis use influence the severity of symptoms and impair daily functioning in help-seeking young people with an at-risk mental state for psychosis? *Early Interv*. 2010;**4**(SUPPL. 1):98.

*Reason for exclusion: conference abstract*

46 Eren F, Dilbaz N, Sonmez EO, Turan O, Gündüz N, Turan H. Evaluation of the effect of schizotypy on cannabis use predictors. *Psychiatr Clin Psychopharmacol*. 2017;**27**(4):337–43.

*Reason for exclusion: incorrect outcomes*

47 Eren F, Sonmez EO, Dilbaz N. Evaluation of the effect of schizotypy on cannabis use predictors*. Klinik Psikofarmakoloji Bulteni*. 2015;**25**(SUPPL. 1):S79.

*Reason for exclusion: conference abstract*

48 Evins AE, Green AI, Kane JM, Murray RM. The effect of marijuana use on the risk for schizophrenia. *J Clin Psychiatry*. 2012;**73**(11):1463–8.

*Reason for exclusion: commentary*

49 Falcone A, Murray R, Iyegbe C, Powell J, Di Forti M. Vulnerability to cannabis-related psychosis: Association with frequency and potency of cannabis use, and interaction with genes regulating dopamine signaling. *Lancet*. 2014;**383**(SUPPL. 1):S41.

*Reason for exclusion: conference abstract*

50 Fekih-Romdhane F, Labidi A, Ridha R, Cheour M. Assessment of mental states at risk of psychotic transition in a sample of young male prisoners in Tunisia. *Encephale*. 2020;**46**(5):348–55.

*Reason for exclusion: incorrect study population*

51 Fidalgo TM, Sanchez ZM, Caetano SC, Maia LO, Carlini EA, Martins SS. The association of psychiatric symptomology with patterns of alcohol, tobacco, and marijuana use among Brazilian high school students. *Am J Addict*. 2016;**25**:416–25.

*Reason for exclusion: incorrect study population*

52 Fraser S, Hides L, Philips L, Proctor D, Lubman DI. Differentiating first episode substance induced and primary psychotic disorders with concurrent substance use in young people. *Schizophr Res*. 2012;**136**(1-3):110–15.

*Reason for exclusion: incorrect study population*

53 Gage S, Hickman M, Heron J, Munafo M, Zammit S. Cannabis use and psychotic experiences in UK teenagers - A longitudinal study. *Eur Neuropsychopharmacol*. 2012;**22**(SUPPL. 2):S315.

*Reason for exclusion: conference abstract*

54 Gage SH, Munafo MR, Smith GD, MacLeod J, Hickman M. Cannabis and psychosis. *Lancet Psychiatry*. 2015;**2**(5):380.

*Reason for exclusion: letter to the editor*

55 Galletly C, Clark L, McFarlane A, et al. Childhood lead exposure, childhood trauma, substance use and subclinical psychotic experiences – a longitudinal cohort study. *Psychiatry Res.* 2016;**239**:54–61.

*Reason for exclusion: incorrect outcomes*

56 Germann M, Marschall T, Brederoo S, Sommer I. Drug abuse affects the risk of stressful hallucinations in the general Dutch population. *Schizophr Bull.* 2020;**46**(SUPPL. 1):S72.

*Reason for exclusion: conference abstract*

57 Gicas KM, Cheng A, Panenka WJ, et al. Differential effects of cannabis exposure during early versus later adolescence on the expression of psychosis in homeless and precariously housed adults. *Prog Neuropsychopharmacol Biol Psychiatry.* 2021;**106**:110084.

*Reason for exclusion: incorrect outcomes*

58 Gilman JM, Sobolewski SM, Evins AE. Cannabis use as an independent risk factor for, or component cause of, schizophrenia and related psychotic disorders. In: Compton MT, Manseau MW, editors. The complex connection between cannabis and schizophrenia. San Diego, CA, US: Elsevier Academic Press US; 2018. p. 221–46.

*Reason for exclusion: book chapter*

59 Gonçalves-Pinho M, Bragança M, Freitas A. Psychotic disorders hospitalizations associated with cannabis abuse or dependence: A nationwide big data analysis. *Int J Methods Psychiatr Res*. 2020;**29**(1):e1813.

*Reason for exclusion: incorrect study design*

60 Goyal RG, Bangalore S, Mermon D, Montrose D, Prasad K, Keshavan M. Impact of cannabis on individuals at high risk for psychosis. *Biol Psychiatry*. 2012;**71**(8 SUPPL. 1):96S.

*Reason for exclusion: conference abstract*

61 Hammond CJ. Adolescent marijuana use and vulnerability for neuropsychiatric disorders. *Psychiatr Times.* 2014;**31**(12):1-3.

*Reason for exclusion: commentary*

62 Hides L, Quinn C. Are Cannabis Induced Psychotic-Like Experiences (PLEs) Associated with the Frequency of Cannabis Use? *Early Interv.* 2016;**10**:105.

*Reason for exclusion: conference abstract*

63 Huijbregts SCJ, Griffith-Lendering MFH, Vollebergh WAM, Swaab H. Neurocognitive moderation of associations between cannabis use and psychoneuroticism. *J Clin Exp Neuropsychol*. 2014;**36**(8):794–805.

*Reason for exclusion: incorrect study population*

64 Icick R, Guillaume S, Gard S, et al. Correlates of cannabis use disorders among bipolar outpatients enrolled in the Bipolar Expert Centers French network. *Eur Psychiatry.* 2013;**28**(SUPPL. 1).

Reason for exclusion: conference abstract

65 Iruretagoyena B, Crossley N, Gonzalez-Valderrama A, et al. Clinical factors associated with cannabis use in a Chilean sample of first episode psychosis patients. *Schizophr Bull.* 2018;**44**(SUPPL. 1):S364.

*Reason for exclusion: conference abstract*

66 Jones JD, Calkins ME, Scott JC, Bach EC, Gur R, E. Cannabis use, polysubstance use, and psychosis spectrum symptoms in a community-based sample of U.S. youth. *J Adolesc Health.* 2017;**60**(6):653–59.

*Reason for exclusion: incorrect study population*

67 Joye A, Morgan C, McEvoy S, Curran HV. Dependency, psychosis and frequency of use in high vs. low potency cannabis preference. J *Psychopharm.* 2011;**25**(8):A37.

*Reason for exclusion: conference abstract*

68 Kirli U, Elbi H, Kayahan B, et al. Quitting cannabis decreases but does not eliminate psychosis risk: Evidence from a 7 years large population-based cohort. *Eur Neuropsychopharmacol*. 2016;**26**(SUPPL. 1):S53–S4.

*Reason for exclusion: conference poster*

69 Knopf A. Cannabis use precedes psychosis symptoms in teens: Research. *Alcoholism & Drug Abuse Weekly*. 2018;**30**(31):6–7.

*Reason for exclusion: editorial*

70 Knopf A. Daily, high‐potency cannabis linked to first psychosis. *Alcoholism & Drug Abuse Weekly.* 2019;**31**(14):3–5.

*Reason for exclusion: editorial*

71 Korver N, Nieman DH, Becker HE, et al. Symptomatology and neuropsychological functioning in cannabis using subjects at ultra-high risk for developing psychosis and healthy controls. *Aust N Z J Psychiatry*. 2010;**44**(3):230–36.

*Reason for exclusion: incorrect outcomes*

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*Reason for exclusion: conference abstract*

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**eTable 2. Risk of Bias Assessments**

|  |
| --- |
| **Newcastle Ottawa Scale risk of bias assessments for cohort studies** |
| **Reference** | **Selection** | **Comparability** | **Outcome** | **Total** | **Quality** |
|  | Representativeness of the exposed cohort | Selection of the non exposed cohort | Ascertainment of exposure | Demonstration that outcome of interest was not present at start of study | Comparability of cohorts on the basis of design or analysis | Assessment of outcome | Was follow-up long enough for outcomes to occur | Adequacy of follow-up of cohorts |  |  |
| Bugra, 2013 | \* | \* | \* | \* | \*\* |  |  |  | 6 | Moderate |
| Rössler, 2012 | \* | \* | \* |  | \*\* | \* | \* | \* | 8 | High  |
| Valmaggia, 2014 |  | \* | \* | \* |  |  | \* | \* | 5 | Moderate |
| **Newcastle Ottawa Scale risk of bias assessments for case-control studies** |
| **Reference** | **Selection** | **Comparability** | **Outcome** | **Total** | **Quality** |
|  | Is the case definition adequate? | Representativeness of the cases | Selection of controls | Definition of controls | Comparability of cases and controls on the basis of design or analysis | Ascertainment of exposure | Same method of ascertainment for cases and controls | Non-response rate |  |  |
| Arranz, 2018 | \* | \* | \* | \* | \*\* |  | \* |  | 7 | High |
| Buchy, 2015 | \* | \* |  | \* |  |  | \* |  | 4 | Moderate |
| Castañeda, 2020 | \* | \* | \* | \* | \*\* |  | \* |  | 7 | High |
| Di Forti, 2015 | \* | \* | \* | \* | \*\* |  | \* |  | 7 | High |
| Di Forti, 2019 | \* | \* | \* | \* | \*\* |  | \* |  | 7 | High |
| Núñez, 2016 | \* | \* | \* | \* | \*\* |  | \* |  | 7 | High |
| Sideli, 2018 | \* | \* | \* | \* | \*\* |  | \* |  | 7 | High |

**eFigure 1. Additional Heterogeneity Assessment**



The sampling error variance on level 1 is small, making up only roughly 12.78%. The value of I2 at Level-2 (the amount of heterogeneity variance across estimates within study), is much higher, totaling roughly 86.67%. Between-study heterogeneity makes up I2 Level-3=0.57% of the total variation in our data. Overall, this indicates that there is substantial within-study heterogeneity on the 2nd level. Hence, a large proportion of the total variance, can be explained by differences within studies.

**eFigure 2. Funnel Plot Tests for Publication Bias**



Some evidence of funnel plot asymmetry for overall, however, majority of estimates are clustered around summary effect estimate. The counter enhanced funnel plot did not reveal studies to be missing in areas of low statistical significance. Also need to be interpret with caution as response categories are not equal across studies and such trend was not observed across individual response categories. Another limitation is number of studies, minimum recommended number of studies to test publication bias is 10 or more.

**eTable 3. Certainty of the Evidence Assessment Using the GRADE Approach**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Quality Assessment** | **# of Patients** | **Effect** | **Quality** | **Importance** |
| # of Studies(design) | Risk of Bias | Inconsistency | Indirectness | Imprecision | Publication Bias | Other  | Cannabis | No cannabis | RR (95% CI) |
| Development of Psychosis – Daily/Near daily use |
| 10(7 case-control,3 cohort) | Low | Not serious1 | Not serious | Not serious | Not serious2 | Evidence of dose-response gradient3 | 3415 | 12301 | **OR 1.77**(1.04-3.01) | ⨁⨁⨁◯Moderate | CRITICAL |

1 Significant heterogeneity (Q = 66.27; df = 7; p = 0.00; I2 = 87.2%) identified. A large proportion of the heterogeneity was due to variance within studies (86.67%) with a small amount being due to heterogeneity across studies (I2 = 0.57%). Because a large proportion of the variance was due to heterogeneity within studies, certainty of the evidence was not rated down due to heterogeneity. A possible reason for observed heterogeneity is the small versus large effects observed across studies, as seen in manuscript Figure 3.

2 The counter-enhanced funnel plot did not reveal studies to be missing in areas of low statistical significance.

3 Evidence of a dose-response gradient with increasing risk of psychosis with increasing frequency of cannabis use. Rate up (+1) from low certainty to moderate.