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PROTOCOL

Adolescent cannabis use and the later onset of bipolar disorder: protocol for a systematic review and meta-analysis of prospective cohort studies

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Abstract

Background: Cannabis is used by adolescents worldwide. Adolescents are more susceptible to the psychological effects of cannabis because their brains are still developing. Cannabis use in adolescents has been reportedly associated with later onset of bipolar disorder.

Aims: The purpose of this study is to systematically review and analyze longitudinal prospective cohort studies of cannabis use during adolescence and evaluate the risk of developing bipolar disorder.

Methods: We defined the participants, exposures, comparisons, and outcomes (PECO) as follows: (P) adolescents in the 10–19-year age group at the baseline survey; (E) cannabis use at least once during lifetime; (C) never-used cannabis over lifetime; and (O) the onset of bipolar disorder. A systematic search for published prospective cohort studies will be conducted by using the following electronic databases: PubMed, EMBASE, PsycINFO, and Japan Medical Abstracts Society. The quality assessment will be performed by using Risk Of Bias In Non-randomized Studies – of Interventions. Meta-analysis will be done if the included studies that exist are more than three. Heterogeneity will be assessed using Cochran's Q test and I^2. Funnel plots and Egger's test will be done to assess publication bias.

Discussion: This study will clarify the association between adolescent cannabis use and the subsequent development of bipolar disorder, which could be useful for future research directions and policy making.

KEYWORDS
adolescents, bipolar disorders, cannabis use

Trial registration number UMIN000048364.

1 | BACKGROUND

Cannabis is used among adolescents worldwide. The prevalence of cannabis use in US adolescents in the past month was 20.9%.[1] Additionally, about 7% of US high school students use cannabis on a daily basis.[2] In Canada, for adolescents aged 15–19 years, the prevalence of cannabis use in 2015 was 20.6%.[3] In England, 4% of adolescents aged 11–15 years used cannabis in the last month.[4] Similarly, in Australia, 4% of adolescents aged 14–19 years use cannabis weekly.[5] Thus, cannabis use among adolescents has been widely observed, particularly in developed countries.

The regular use of cannabis during adolescence is of great concern because it is associated with an increased likelihood of harmful consequences in this age group.[6] For example, poor academic performance, school abandonment, liability to substance use disorders,[7] earlier onset of psychosis,[8] and neuropsychological decline.[9] Moreover, a previous meta-analysis reported that adolescent cannabis use was associated with subsequent depression and suicidal behavior.[10] These findings suggested that cannabis use in adolescents could have a profoundly negative impact on later life. Accordingly, it would be useful to have further studies that focus on the subsequent effects of cannabis use in adolescents.

Cannabis use in adolescents has also been associated with later onset of bipolar disorder. There was a significant positive association between adolescent cannabis use and later onset of bipolar disorder in all four prospective longitudinal studies focusing on this topic.[11–14] Neurobiological mechanisms by which adolescent cannabis use can lead to the onset of bipolar disorder are not clearly understood, but adolescents are generally considered more vulnerable to the effects of cannabis than adults.[15] Recent studies have provided the following evidence. First, adolescent cannabis use might modulate reward system sensitivity[16] and interfere with mechanisms related to the establishment of axonal connections during development. Second, a recent systematic review demonstrated a state of dopaminergic hyperactivity in mania.[17] Cannabis use during adolescence might cause signaling changes in the mesolimbic system, resulting in dopaminergic hyperactivity.[18] In general, dopaminergic signaling increases during adolescence as part of normal brain maturation.[19] Cannabis use might compound this and increase the tendency to experience hypomanic symptoms.[13] Therefore, cannabis use during adolescence might be associated with the subsequent risk of developing bipolar disorder.

To date and to the best of our knowledge, there has been no systematic review or meta-analysis focusing on the association of cannabis use during adolescence and the risk of future bipolar disorder. A meta-analysis published in 2015 examined the association between cannabis use and bipolar disorders, but this study included both adolescents and adults and therefore did not estimate the specific risk of use during adolescence.[20]

2 | OBJECTIVES

The purpose of this study is to systematically review and analyze longitudinal prospective cohort studies that measured cannabis use during adolescence and evaluate the future risk of bipolar disorder.

3 | METHODS

3.1 | Study design

This systematic protocol was registered in the the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (https://www.umin.ac.jp/ctr/index-j.htm) (Registration No. UMIN000048364). We prepared the protocol in accordance with the 2015 statement of Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P).[21] The PRISMA statement will be used to report the systematic review.[22]

3.2 | Participants, exposures, comparisons, and outcomes, and eligibility criteria of this study

We defined the following participants, exposures, comparisons, and outcomes (PECO) of this systematic review and meta-analysis: (P) adolescents based on the definition of the World Health Organization as individuals in the 10-19-year age group at the baseline survey[23]; (E) cannabis use at least once during lifetime; (C) never-used cannabis over lifetime; and (O) the onset of bipolar disorder.

Inclusion criteria are as follows:

1. Studies that included participants who were in general population, including those with risk factors such as a family history of bipolar disorders.
2. Studies that assessed cannabis use in adolescents (at least 1 assessment point) and then again assessed them for bipolar disorders later.
3. Studies that used a prospective cohort design.
4. Studies published in English or Japanese.
5. Studies published in peer-reviewed journals.

Exclusion criteria are as follows:

1. Studies with participants primarily diagnosed with bipolar disorders, or psychotic disorders such as schizophrenia and schizoaffective disorder.
2. Studies including reviews, letters, commentaries, and conference abstracts will be excluded.

3.3 | Information sources and search strategy

We will conduct a systematic search by using the following electronic bibliographic databases: PubMed, PsycINFO, Embase, and the Japan Medical Abstracts Society databases. Our search terms were based on previous systematic reviews and were also developed by two investigators (NY and AT).[20] The search terms were used in

three groups, cannabis (group 1), bipolar disorder (group 2), and cohort study (group 3). We attached the search terms of each database in Appendix A.

3.4 | Study records

3.4.1 | Data management

A Microsoft Excel (Washington, USA) file will be used to manage the study record, which will be made by KW, MI, and NY. NY will exclude duplicate studies before the screening.

3.4.2 | Selection process

Two investigators (NY and AT) in pairs will eliminate non-relevant studies by examining titles and abstracts. Subsequently, they will independently evaluate full-text eligibility. When they disagree on eligibility during the full-text review, disagreements will be settled by KI. The reasons for excluding studies will be recorded during the full-text review phase.

3.4.3 | Data collection

Data will be extracted independently from the included studies by two investigators (NY and AT) by using a standardized data extraction form. The following relevant information will be extracted from the included studies: author, year of publication, country, number of participants, the methods to define cannabis use (in terms of frequency of use and age at use, if provided), and the methods to define bipolar disorders, as well as control variables for adjustment, duration of follow-up, and follow-up rates and sufficient data for calculating the odds ratio (ORs), relative risks (RRs), or hazard ratio (HRs) with SEs or 95% confidence intervals (Cis) for the association between adolescents cannabis use and the later onset of bipolar disorder. Disagreements will be settled by KI.

3.5 | Data synthesis

Statistical analyses will be performed using STATA software V.16.0 (STATA Corporation). The included studies will be statistically synthesized in a meta-analysis to estimate pooled coefficients and 95% CIs, stratified by types of measures of association OR, RR, and HR. If the included studies report ORs, RRs, or HRs, we will calculate log transformed ORs, RRs, or HRs and determine SEs based on 95% CIs. These parameters will be used in the meta-analysis and for examining publication bias by means of funnel plots and Egger's tests.

3.6 | Risk of bias in individual studies and assessment of publication bias

Two investigators (NY and AT) in pairs will independently conduct the quality assessment of each included study and outcome by using Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I).[24] The ROBINS-I assesses non-randomized studies of interventions (or specific exposures) currently available for cohort studies and case–control studies. The risk of bias is assessed within specified bias domains: confounding, selection of participants for the study, classification of interventions (or specific exposures), deviations from intended interventions (or specific exposures), missing data, measurement of outcomes, and selection of the reported result. The overall risk of bias is classified as low, moderate, severe, critical, and no information. Any discrepancies in the quality assessment will be resolved among NY, AT, and KI. We will assess publication bias by using funnel plots and Egger's test.

3.7 | Statistical methods

3.7.1 | Primary analyses

For the main analysis, we will synthesize adolescent cannabis use and the later onset of bipolar disorder assessed as dichotomous variables. Meta-analysis will be conducted when at least three eligible studies can be collected. If a meta-analysis is not possible, the results will be shown in a narrative review. A fixed-effect model will be used if heterogeneity is not observed, otherwise a random-effects model will be used.[25] Heterogeneity will be assessed using Cochran's Q test and I^2.[26]

3.7.2 | Secondary analyses

Subgroup analyses will be conducted by: (a) studies that assessed the outcome variable (bipolar disorders) was controlled for at baseline and (b) studies whose outcome was assessed by a structured interview.

4 | DISCUSSION

This study is important from the perspectives of directions for future research and public mental health policy-making. To the best of our knowledge, this is the first systematic review and meta-analysis to clarify the association between adolescent cannabis use and later onset of bipolar disorder. Although a previous systematic review and meta-analysis had shown an association between cannabis use and bipolar disorder,[20] this review evaluated the specific risk of adolescent cannabis use and later onset of bipolar disorder. From the perspective of public mental health policy-making, if the findings in

this review demonstrate the negative effects of adolescent cannabis use on subsequent risk of bipolar disorder, there would be a more urgent need to implement cannabis use prevention programs targeting adolescents.

This systematic review and the meta-analysis have some limitations. First, we might not show a strong causal association between adolescent cannabis use and later bipolar disorder. Even if only longitudinal studies adjusted for bipolar disorder at baseline are included, a majority of studies might have overlooked premorbid bipolar disorder, since diagnosis of bipolar disorder in adolescents is quite difficult.[27] Additionally, potential confounders biased the results of the included studies. Not all studies included in the review may have adjusted for other substance use or family history of bipolar disorder. Moreover, the diagnosis of bipolar disorder using different methods may cause heterogeneity across studies.

AUTHOR CONTRIBUTIONS

The study concept was developed by NY and AT. NY wrote the first manuscript of the protocol, and the manuscript was critically revised by the other authors. The search strategy was developed by NY and AT. The study record will be made by KW, MI, and NY. Study selection, data extraction, and quality assessment will be performed by NY and AT, with KI as a third party in case of disagreements. Analyses will be conducted by NY, AT, and KW. All authors have approved the final version of the manuscript.

CONFLICT OF INTEREST

We have no conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ETHICS STATEMENT

Approval of an ethics committee is not required because patient data will not be collected. Our plan is to publish findings in a peer-reviewed journal to provide broad dissemination to researchers and policymakers who are interested in this topic.

REGISTRY AND THE REGISTRATION NO. OF THE STUDY/TRIAL

The study protocol was registered in the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN-CTR ID, UMIN000048364).

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APPENDIX A

SEARCH TERMS USED FOR THE ELECTRONIC DATABASES

Database	Search terms
PubMed	("cannabis"[MeSH Terms] OR "cannabi*"[All Fields] OR ("cannabis"[MeSH Terms] OR "cannabis"[All Fields] OR "marihuana"[All Fields]) OR ("cannabis"[MeSH Terms] OR "cannabis"[All Fields] OR "marijuana"[All Fields] OR "marijuana s"[All Fields]) OR "delta-9-tetrahydrocannabinal"[All Fields] OR ("dronabinol"[MeSH Terms] OR "dronabinol"[All Fields] OR "thc"[All Fields]) OR "tetrahydrocannabivarin"[All Fields] OR "hemp*"[All Fields] OR "hashish*"[All Fields] OR "bhang*"[All Fields] OR "ganja*"[All Fields] OR ("pol orthop traumatol"[Journal] OR "pot"[All Fields]) OR "weed"[All Fields]) AND ("bipolar disorder"[MeSH Terms] OR "bipolar*"[All Fields] OR "manic*"[All Fields] OR "mania*"[All Fields] OR ("mania"[MeSH Terms] OR "mania"[All Fields] OR "hypomania"[All Fields] OR "hypomanias"[All Fields]) OR "affective*"[All Fields] OR "psychos*"[All Fields] OR "mood*"[All Fields] OR "depress*"[All Fields]) AND ("cohort studies"[MeSH Terms] OR "longitudinal studies"[MeSH Terms] OR ("longitudinal studies"[MeSH Terms] OR ("longitudinal"[All Fields] AND "studies"[All Fields]) OR "longitudinal studies"[All Fields] OR ("longitudinal"[All Fields] AND "study"[All Fields]) OR "longitudinal study"[All Fields]) OR (("longitudinal studies"[MeSH Terms] OR ("longitudinal"[All Fields] AND "studies"[All Fields]) OR "longitudinal studies"[All Fields] OR "prospective"[All Fields] OR "prospectively"[All Fields]) AND ("cohort studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields]) OR "cohort studies"[All Fields] OR ("cohort"[All Fields] AND "study"[All Fields]) OR "cohort study"[All Fields])) OR ("prospective studies"[MeSH Terms] OR ("prospective"[All Fields] AND "studies"[All Fields]) OR "prospective studies"[All Fields]) OR ("follow up studies"[MeSH Terms] OR ("follow up"[All Fields] AND "studies"[All Fields]) OR "follow up studies"[All Fields] OR ("follow"[All Fields] AND "up"[All Fields] AND "studies"[All Fields]) OR "follow up studies"[All Fields]) OR ("observational"[All Fields] AND "stud*"[All Fields]))
EMBASE, PsycINFO	(cannabi* OR marihuana OR marijuana OR delta-9-tetrahydrocannabinal OR tetrahydrocannabivarin OR hemp* OR hashish* OR bhang* OR ganja* OR pot OR weed) AND (bipolar* OR manic* OR mania* OR hypomania OR affective* OR psychos* OR mood* OR depress*) AND ((longitudinal study) OR (prospective cohort study) OR (prospective studies) OR (follow-up studies) OR (observational stud*))
Japan Medical Abstracts Society	(大麻 OR マリファナ OR テトラヒドロカンナビノール OR カンナビノイド OR ヘンプ OR ハシシ OR ハシッシュ OR ハシシュ OR ハッシッシ OR ハシ–シ OR バング OR ガンジャ OR チャラス OR ポット OR ウィード) AND (双極性感情障害 OR 双極性障害 OR 躁うつ病 OR 気分障害 OR 躁 OR 軽躁 OR 精神病 OR 抑うつ OR うつ) AND (縦断研究 OR 前向きコホート研究 OR 前向き研究 OR 追跡研究 OR フォローアップ研究 OR 観察研究)