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Adolescent cannabis use and onset of bipolar disorder: gaining causal clarity by viewing the evidence through the Bradford Hill lens

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Perspective

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Abstract

In recent times, several longitudinal studies aimed at clarifying whether cannabis use during adolescence might play a causal role in the subsequent risk of developing bipolar disorder have been published. Although their methodological heterogeneity precludes any meta-analytic approaches, evidence from these studies can be systematically evaluated using the Bradford Hill criteria. A biological gradient is supported by evidence on the dose–response relationship between exposure severity and outcome. As such, the effect of cannabis use on bipolar disorder onset is likely to be strong, coherent, plausible, and based on a clear temporality. In addition, some analogies can be hypothesized between studies testing the possible causal role of cannabis in the development of bipolar disorder and those is schizophrenia. Cannabis may represent a precipitating agent inducing bipolar disorder in a multicausal model of individual vulnerability. However, this relationship seems to be only partially consistent and nonspecific, and the experimental evidence is strongly suggestive but, as yet, inconclusive. Nevertheless, in summary, it seems there is sufficient support for the hypothesis that cannabis use during adolescence may play a causal role in bipolar disorder, although further studies are needed to consolidate the evidence.

Introduction

Bipolar disorder is characterized by manic episodes with or without depressive recurrences, resulting in heterogeneous presentations and an unpredictable course.[1,2] It is associated with poor psychosocial functioning and reduced life expectancy.[3] While several genetic and environmental risk factors for bipolar disorder have been suggested,[4] the etiopathogenetic mechanisms of this disorder remain unknown. Prodromal conditions, such as anxiety disorders, attention deficit hyperactivity disorder, and behavioral disorders, often precede the development of bipolar disorder—potentially allowing anticipation of the illness, though with questionable sensitivity and specificity.[5] However, the focus of research has been redirected to substance use,[6] as comorbidity with bipolar disorders is high in both hospital- and community-based samples.[7] For instance, in a recent study that examined the Norwegian Patient Registry, data revealed that the cumulative transition rate from substance-induced psychosis to bipolar disorder was 4.5% (95% confidence interval [95%CI]: 3.6%–5.5%).[8]

In recent years, a significant proportion of evidence aimed at clarifying the association between cannabis use and bipolar disorder has been published.[9,10] Meta-analytic data have shown that the use of cannabis is frequent in people with bipolar disorder, involving up to a quarter of patients.[10] Cannabis use has been associated with a younger age, male gender, an earlier onset of affective symptoms, psychotic features, and suicide attempts.[10,11] Moreover, recent population-based data have shown that cannabis use disorder in both men and women might be associated with either psychotic or nonpsychotic bipolar disorders.[12] Nonetheless, the efforts of epidemiological research have mainly focused on the investigation of early cannabis use as a risk factor for the subsequent onset of bipolar disorder. Specifically, four longitudinal studies have examined whether cannabis use during adolescence might predict the onset of bipolar disorder or manic/hypomanic symptoms: the Early Developmental Stages of Psychopathology (EDSP) study,[13] the Avon Longitudinal Study of Parents and Children (ALSPAC),[14] the Northern Finland Birth Cohort (NFBC) study[15], and, more recently, the Pelotas Birth Cohort (PBC) study.[16] The main study characteristics of these investigations are reported in Table 1.

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Table 1. Longitudinal Studies Exploring the Association between Cannabis Use during Adolescence on the Onset of Bipolar Disorder

Study	Country	Sample size	Baseline age	Follow-up length	Effect of cannabis use on bipolar disorder	
					Unadjusted	Adjusted[a]
Denissoff et al., 2022 – NFBC study[15]	Finland	6,325	15–16 years	18 years	HR = 3.46 (95%CI: 1.81–6.61)	HR = 1.70 (95%CI: 0.73–3.98)
Jorge et al., 2024 – PBC study[16]	Brazil	3,712	18 years	4 years	OR = 1.82 (95%CI: 1.10–2.93)	OR = 1.79 (95%CI: 0.95–3.19)
Marwaha et al., 2018 – ALSPAC study[14]	United Kingdom	3,370	17 years	5–6 years	OR = 1.64 (95%CI: 1.37–1.96)	OR = 1.42 (95%CI: 1.14–1.77)
Tijssen et al., 2010 – EDSP study[13]	Germany	543[b]	14–17 years	8 years	–	OR = 4.26 (95%CI: 1.42–12.76)

Abbreviations: 95%CI: 95% confidence interval; ALSPAC, Avon Longitudinal Study of Parents and Children; EDSP, Early Developmental Stages of Psychopathology; HR, hazard ratio; NFBC, Northern Finland Birth Cohort; OR, odds ratio; PBC, Pelotas Birth Cohort.
[a]If more than one model was shown, the most comprehensive one was reported.
[b]Subset of subjects without manic symptoms at baseline.

Although their methodological heterogeneity precludes any formal meta-analytic attempt, some useful insights can be drawn by considering the evidence collectively and comparing the outcomes to the requirements of the 9 *Bradford Hill criteria*.[17] Upon interrogating these data to understand better whether early cannabis use is a risk factor for bipolar disorder, we surmise that the following inferences can perhaps be drawn (Table 2).

Adolescent cannabis use and bipolar disorder onset: evaluating the evidence with the Bradford Hill criteria

In terms of *strength of the association*, large effects were found in 2 studies: the NFBC study[15] showed that adolescents who used cannabis had a hazard ratio (HR) for bipolar disorder of 3.46 (95%CI: 1.81–6.61), while the EDSP study[13] estimated a large effect for the onset of manic symptoms (odds ratio [OR] = 4.26; 95%CI: 1.42–12.76) among people who used cannabis at ages 14–17 years. Nonetheless, other studies showed more precise associations albeit they are weaker. The ALSPAC study[14] found that people who used cannabis at 17 years had an OR of 1.64 (95%CI: 1.37–1.96) for hypomania symptoms at 22–23 years. Similarly, the PBC study[16] showed a small association between cannabis use at 18 years and a diagnosis of bipolar disorder at 22 years (OR = 1.82; 95%CI: 1.10–2.93). Methodological differences in study design, the selected at-risk population, and potentially biased post hoc analyses, likely contribute to variations in the strength of the association. This

Table 2. Application of Bradford Hill Criteria to Evidence on Cannabis Use during Adolescence and Onset of Bipolar Disorder

Criterion	Description	Application
Strength of the association	A strong association is more likely to suggest causality. However, a weaker association does not rule out causality.	Strong association found in NFBC and EDSP studies, indicating robust effects. Weaker association in ALSPAC and PBC studies (still supporting a relationship).
Temporality	The exposure must precede the outcome for causality to be established.	Temporality confirmed by longitudinal study designs where cannabis use precedes the onset of bipolar disorder or manic symptoms.
Consistency	The association is consistently observed across different studies, populations, and circumstances. Repetition strengthens the case for causality.	Consistent findings across all reviewed studies showing an association between cannabis use and bipolar symptoms onset. PBC and NFBC studies showing reduced effects after adjusting for confounders.
Coherence	The observed association should not conflict with the natural history or biology of the disease, and it should be consistent with the existing knowledge.	Findings from studies investigating cannabis use during adolescence coherent with those from large cohorts independent of age.
Biological gradient	A greater exposure to the risk factor should result in a greater incidence of the outcome ("dose–response relationship").	Dose–response relationship found in the NFBC and ALSPAC studies, showing higher cannabis use frequency increases the risk of bipolar disorder.
Biological plausibility	A biological mechanism must make sense, based on current scientific knowledge, although it may evolve over time. Lack of knowledge does not exclude causality.	Plausibility supported by emerging neurobiological evidence, especially on the role of the endocannabinoid system.
Specificity	The association is more likely to be causal if it is specific to a particular population, disease, or location.	Specificity not met, as cannabis use has also been linked to psychosis, depression, and other psychiatric disorders.
Analogy	If a similar factor is known to cause a similar outcome, this analogy can provide additional support for a causal relationship.	Analogies can be drawn between cannabis use and its established role in schizophrenia, suggesting a similar precipitating effect on bipolar disorder.
Experimental evidence	Experimental evidence, such as interventions that modify the exposure and observe subsequent changes in outcomes, can provide strong support for causality.	Inconclusive and potentially contradictory findings from experimental design studies.

Abbreviations: ALSPAC, Avon Longitudinal Study of Parents and Children[14]; EDSP, Early Developmental Stages of Psychopathology[13]; NFBC, Northern Finland Birth Cohort[15]; PBC, Pelotas Birth Cohort.[16]

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holds true, especially considering that studies with longer follow-up duration possibly capture a broader range of developmental trajectories and transitions with varying time-dependent effects.

Second, *temporality*—probably the most essential criterion for causal inference[18]—seems highly likely by the longitudinal design of the studies considered, as well as by the explicit exclusion of adolescents who may just be suffering from bipolar disorder at baseline. In particular, the EDSP study included only a subset of adolescents without manic symptoms,[13] while the PBC and NFBC studies explicitly excluded people with either bipolar disorder[16] or even any mental disorder[15] at baseline. Thus, the approaches used in these studies allowed the investigation of a relationship in which cannabis use clearly predated the onset of bipolar disorder/manic symptoms.

Third, the *consistency* criterion is supported by the evidence emerging from all these studies[13-16] that cannabis use during adolescence was associated with the subsequent onset of manic symptoms. However, there were some variations in findings across studies when confounders were accounted for. While these factors did not influence the findings of the ALSPAC[14] and EDSP studies,[13] the PBC study[16] did not show any statistically significant effect of cannabis use on the incidence of bipolar disorder after adjusting for available variables, including lifetime cocaine use (OR = 1.79; 95%CI: 0.95–3.19). In addition, the most comprehensive model from the NFBC study,[15] similarly accounting for other illicit substance use, along with sex, family structure, parental mental disorders, and other clinical variables, did not support the association between baseline cannabis use and subsequent bipolar disorder (HR = 1.70; 95%CI: 0.73–3.98). These findings suggest that the effect of cannabis on bipolar disorder might be impacted by the use of other illicit substances, although the mechanisms of this remain obscure.

In addition, the *coherence* criterion can be considered sufficiently satisfied, as current knowledge in the field does not provide any elements to hypothesize that the causative role of early cannabis use might seriously "conflict with the generally known facts on the natural history and biology"[17] of bipolar disorder. Indeed, findings from studies investigating cannabis use during adolescence consistently converge with those from large cohorts, testing the effects of cannabis use on the risk of bipolar disorder in the general population, independent of age. For instance, recent data from the Danish nationwide registers, accounting for a total of 6,651,765 individuals and 119,526,786 person-years, found that cannabis use disorder was associated with bipolar disorder in both men and women.[12] Moreover, previous studies, based on the Netherlands Mental Health Survey and Incidence Study, showed that baseline cannabis use predicted both bipolar disorder and manic symptoms at follow-up, regardless of relevant confounders.[19,20] Moreover, coherence is supported by the theoretical framework of developmental models for bipolar disorder.[21] Cannabis exposure during adolescence may induce long-lasting changes to the structure and function of brain areas, such as the prefrontal cortex, amygdala, and hippocampus,[22] which may be involved in the pathophysiology of bipolar disorder.[21]

Another important criterion involves the *biological gradient.* Both the ALSPAC study[14] and the NFBC study[15] investigated the dose–response relationship between cannabis use and bipolar disorder. The ALSPAC study[14] found that the risk of hypomania symptoms was significantly higher in adolescents who used cannabis 2–3 times weekly, compared with those with less frequent or no cannabis use (OR = 2.80; 95%CI: 2.02–3.88). In addition, and more specifically, the NFBC study[15] found a dose–response relationship between the frequency of cannabis use and the onset of bipolar disorder, with an increasing risk from an HR of 3.03 (95%CI: 1.44–6.36) among adolescents using cannabis 1–4 times to an HR of 5.55 (95%CI: 1.74–17.73) in those who had used it 5 times or more in their lifetime.

On top of this, there appears to be sufficient *biological plausibility* to support the association between cannabis use and bipolar disorder, given that "what is biologically plausible depends upon the biological knowledge of the day."[17] Indeed, although the relevant neurobiological mechanisms are not entirely understood, it has been recently shown that several potential mechanisms—involving, among others, brain development, mitochondrial activity, inflammatory-related pathways, and the endocannabinoid system—may underlie this relationship.[23] Among them, the putative role of the endocannabinoid system in bipolar disorder has been recently explored. Indeed, this system and its signaling pathways have emerged to be crucial in the regulation of mood and emotions.[24] In particular, it has been suggested that the cannabinoid receptors (CB1 and CB2) might play a key role in the mood dysregulations associated with bipolar disorder.[24]

However, the *specificity* criterion for the relationship between early cannabis use and bipolar disorder is not satisfied, as cannabis use is well known to induce or exacerbate psychotic disorders, with a dose–response relationship.[25] In addition, it may correlate with depression, according to findings from both large population studies[26] and meta-analysis of longitudinal studies.[27] Moreover, community-based data showed that not only cannabis but also tobacco, cocaine/crack, and other illicit substances may play a role in the incidence of bipolar disorder.[6] Nonetheless, the specificity criterion generally has poor validity and is more useful for supporting causation, rather than ruling it out.[28]

Although it is often ignored or wrongly equated to biological plausibility or coherence,[29] *analogy* represents an additional criterion to test causation. The analogy criterion supports the concept that the likelihood of a causal relationship may be strengthened if comparable associations are observed between a similar outcome and a similar exposure.[30] For instance, even if bipolar disorder and schizophrenia are different and separate clinical entities, these disorders may share some environmental risk factors[31] in a complex multicausal model of vulnerability.[32] Considering older, paradigmatic cohort studies investigating cannabis use as a risk factor for schizophrenia,[33-35] we can perhaps speculate that something *analogous* might occur regarding the interplay between cannabis use (as a precipitating/facilitating agent) and the development of bipolar disorder.

Finally, the *experimental evidence* criterion is hard to meet, as it is unavailable in most epidemiologic circumstances.[36] Further, studies on human brain dysfunctions are complex, and those in nonhuman species may be misleading, making it a useful but not necessarily mandatory criterion in the mental health field.[28] Neuroimaging studies on adolescents with bipolar disorder revealed possible effects of cannabis use in frontal and parietal regions,[37] as well as in brain regions involved in emotional processing.[38] However, these findings are inconclusive to date, considering that other studies showed limited brain structural changes associated with cannabis use in people with severe mental illness, including bipolar disorder.[39] Moreover, when testing the possible bidirectional relationship between bipolar disorder and cannabis use, data from experimental studies seem to contradict findings from large epidemiological data. For instance, a 2-sample bidirectional Mendelian randomization study supported a causal effect of bipolar disorder on the risk of using cannabis at least once, but

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no causal effect per se regarding the liability of cannabis use to cause bipolar disorder.[40]

Conclusion

Although the Bradford Hill criteria are not intended as a rigid checklist for testing causation, but rather as a flexible guideline that may favor the interpretation of evidence,[18] it seems there are sufficient, appropriate elements to support the hypothesis that cannabis use during adolescence may play a causal role on the subsequent risk of developing bipolar disorder. Following this approach, given that detailed, time-varying information is incorporated, the causal relationship between early cannabis use and bipolar disorder is likely to be strong, coherent, plausible, and based on a clear temporality. However, it seems to be only partially consistent and nonspecific. This may be due to residual confounding, particularly related to polysubstance use, family history, or sociodemographic factors. Although the reviewed studies accounted for several relevant covariates, the influence of unmeasured confounders cannot be ruled out and may explain some of the inconsistencies. While the experimental evidence is far from being conclusive, the biological gradient is supported by the dose–response relationship between the exposure severity and outcome. In addition, some analogies with the more robust body of evidence on schizophrenia suggest a role for cannabis also in the onset of bipolar disorder, likely to be based on a multicausal theory of the disease.[41]

Additional, adequately powered, longitudinal evidence is needed to explicitly model the causes (early cannabis use) of change (later onset of bipolar disorder) over time.[42] Finally, research in this field may take advantage of "natural experiments" resulting from changes in cannabis policies, by comparing pre- and post-legalization cannabis use patterns and related outcomes in the general population.[43] In particular, our understanding could benefit from investigating the potential impact of medical or recreational cannabis legalization on bipolar disorder rates,[44,45] as is the case for schizophrenia and other psychotic disorders.[46]

Data availability statement. This article does not include any original data. All data referenced in this article are available in the cited published sources.

Author contribution. Conceptualization: all authors; Data curation: F.B., D.C., C.B., M.B., C.C.; Investigation: F.B., D.C., C.B., M.B.; Methodology: all authors; Project administration: F.B., G.S.M., G.C.; Supervision: G.S.M., G.C.; Writing—original draft: F.B., D.C.; Writing—review and editing: C.B., M.B., C.C., G.S.M., G.C.

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