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Sleep as a Mediator Between Cannabis Use and Psychosis Vulnerability: A Longitudinal Cohort Study

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***Objectives*: Increasing evidence implicates cannabis consumption as a key risk factor in the development of psychosis, but the mechanisms underpinning this relationship remain understudied. This study proposes to determine whether sleep disruption acts as a mediator of the cannabis-to-psychosis relationship.*Study Design*: This longitudinal study assessed measures of cannabis use frequency, sleep quality (SQ), and psychotic-like experiences (PLEs) were collected using self-reported questionnaires. Data were collected from September 2012 to September 2018. Data were collected from a general population sample of adolescents who entered the seventh grade in 31 schools in the Greater Montreal area. The study uses data collected on an annual basis from 3801 high school students from grades 7 to 11. The aforementioned measures were measured using the Detection of Alcohol and Drug Problems in Adolescents questionnaire, a SQ Likert scale, and measures the Psychotic-Like Experiences Questionnaire for Children.*Study Results*: *Results* show a reciprocal 1-year cross-lagged effect of cannabis use and sleep (β = −0.076, 95% CI = −0.037 to −0.018, *P* = .000), of sleep on cannabis use (β = −.016, 95% CI = −0.025 to −0.006, *P* = .007), of sleep on PLEs (β = −0.077, 95%CI = −0.014 to −0.051, *P* = .000), and of PLEs on sleep (β = −0.027, 95% CI = −0.037 to −0.018, *P* = .000). We additionally found a 2 years indirect lagged-effect of cannabis use on PLEs (β = 0.068, 95% CI = 0.024 to 0.113, *P* = .011) mediated by 1-year sleep (β = 0.006, 95% CI = 0.003 to 0.009, *P* = .001).*Conclusions*: Our results suggest sleep disruptions simultaneously aggravate, and are aggravated by, cannabis addiction and PLEs. The longitudinal sleep-mediated effect of cannabis use on PLEs encourages further research into the role of sleep as a potential therapeutic target in the prevention of cannabis-related psychosis.**

Key words: cannabis/sleep/longitudinal/psychotic-like experiences

Introduction

The legalization of cannabis across a growing number of jurisdictions poses challenges for policy makers and clinicians concerned about the effects of this drug on public health. In adolescents, cannabis consumption is associated with an increased frequency of psychotic-like experiences (PLEs); sub-clinical psychotic symptoms whose frequency is associated with heightened risk of later psychosis.[1] The etiology of psychosis remains poorly understood due to its inherent complexity and a number of methodological challenges.[2] The study of the early developmental stages of psychosis has been limited by the inability to reliably identify at-risk adolescents. PLEs can be defined as transitory and sub-clinical hallucinations, delusions, and perceptual changes. High frequency of such experiences has been identified as a potential indicator of later transition to psychosis.[3] Moreover, some have shown that while the frequency of PLEs typically decreases during adolescence, adolescents who report a gradual increase of such experiences are at greater risk of mental health disorders in general and psychosis in particular.[3]

The association between sleep disorders and psychosis is attracting increasing recognition although the nature of this relationship remains poorly understood.[4] Comorbid sleep disorders are common in psychotic patients, although prevalence reports are highly inconsistent ranging from 21% to 100%.[4] A meta-analysis found evidence of increased sleep latency, decreased overall sleep time, and decreased sleep efficiency in

medication-free psychotic patients.[5] There remains significant disagreements as to which aspects of sleep are most responsible for this association.[5] Psychotic patients with co-morbid sleep disorders report significant deterioration of their quality of life and increase paranoia, hallucinations, and cognitive symptoms.[6] In a randomized controlled study of cognitive behavioral therapy for insomnia (CBTi), sleep improvements mediated a reduction of paranoia and hallucinations among university undergraduates at risk of psychosis.[7] Conversely, in adolescents at ultra-high-risk of psychosis, actigraphic measures indicate increased wake-time after sleep onset and decreased sleep efficiency compared to healthy controls.[8] A recent study also indicated that the relationship of sleep disruption and paranoia is bidirectional, while the effect of sleep disruption on hallucinations appears unidirectional.[9]

Recent studies increasingly suggest that cannabis has a complex effect on sleep, with some positive short-term benefits (eg, decreased sleep latency) and generally negative long-term effects (eg, lower sleep quality [SQ]).[10,11] Different molecular components of cannabis interfere with sleep architecture through their adhesion to the canonical cannabinoid receptors CB1.[12] By disrupting phases of sleep, cannabis likely interferes with the crucial physiological mechanism they support: Rapid eye movement (REM) supports normal brain development, declarative, and implicit memory consolidation and slow wave sleep (SWS) supports growth hormone release, neurotoxic metabolite clearance (eg, β-amyloid), immunity, and declarative memory consolidation.[13,14] Preliminary evidence suggests that Δ-9-*tetrahydrocannabinol* (THC) diminishes sleep latency and increases SWS at low dose and has the reverse effect at higher doses.[12] Cannabis withdrawal is associated with a reduction of SWS, increases in sleep latency, and a sharp increase in REM sleep.[12,15] The sharp increase in REM sleep following withdrawal is thought to be associated with patient reports of vivid of dreams and nightmares, which can persist for months following cannabis discontinuation.[15] This suggests that sleep may serve as a mediator between cannabis use and increased incidence of PLE and subsequent psychotic disorders. Conversely, sleep disruption is associated with future cannabis use. Sleep difficulties in early adolescence are associated with increased future cannabis use.[16] In one survey, 14%–15% of college students reported using cannabis and alcohol as a sleep aid.[17]

Using data from a representative adolescent population (CoVenture), the following study aims to test the hypothesis that sleep mediates the relationship between cannabis use and PLEs.[18] As such, the first objective of the present study is to demonstrate that the long-term effect of cannabis use on PLEs is mediated by a deterioration of sleep parameters. The second objective of the present study is to assess the presence of cross-lagged effects between cannabis use and sleep parameters and between sleep parameters and PLEs, to examine the extent to which these variables form a maladaptive positive feedback loop.

Methods

Participants

The data used in the present study derives from the CoVenture study, a longitudinal population-based cohort study. The participants were 3801 youths recruited from 31 schools in Greater Montreal are making this sample epidemiologically representative of the average size and socioeconomic index of each of the city's school districts. Participants were assessed on a yearly basis from grades 7 to 11 with data collection starting in September 2012 and ending in 2018. All participants were included in the analysis if they had completed baseline assessments.

A detailed description of the measures and procedures of this study is publicly available (ClinicalTrials.gov identifier: NCT01655615).[18] Informed consent was obtained from participants and their parents. Ethical approval was obtained from the ethics review board of the CHU Sainte-Justine Research Center. Of the 3801 CoVenture participants, 719 were invited to take part in personality-targeted alcohol and drug prevention intervention. While the intervention may have limited the consumption of cannabis in our sample, there is no reason to believe it confounded the relationship between cannabis use and either sleep parameters or PLEs.

Measures

Cannabis Consumption..

Cannabis consumption was assessed using the Detection of Alcohol and Drug Problems in Adolescents questionnaire. Participants were called upon to rate their consumption frequency on a 6-point scale (0 = never, 1 = occasionally, 2 = approximately once a month, 3 = Weekends or once or twice during the week, 4 = Three times or more a week but not every day, 5 = Every day).[19]

Sleep Parameters..

Sleep was assessed using a one-month retrospective questionnaire composed of the following items: SQ (4 = very well, 3 = well, 2 = badly, 1 = very badly) and wake after sleep onset frequency (WASOF: 4 = none in the last month, 3 = less than one per week, 2 = 1 to 2 times per week, 1 = 3 times of more per week). A composite sleep score (CSS) was created by a simple averaging of the aforementioned questions' scores. SQ, wake after sleep onset and latency are the most frequently reported sleep complaints in subjective assessments of schizophrenic patients[20] and are more elevated in patients with schizophrenia compared to individuals with other psychopathologies such bipolar disorder.[21] The accuracy of self-report questionnaires (sensitivity 73%–97.7% and specificity 50%–96%) compares favorably to that of objective measures such as actigraphy

and polysomnography while providing complementary clinical information.[22]

Psychotic-Like Experiences..

PLEs such as hallucinations, delusional beliefs, suspiciousness, strange experiences, and feelings of grandiosity in the past 12 months were assessed with the nine items, Psychotic-Like Experiences Questionnaire for Children (PLEQ-C).[23] The PLEQ-C contains the following 9-items assessing the belief (1) that their thoughts are being read, (2) that they can read the thoughts of others, (3) that media are sending them subliminal messages, (4) the they are being spied upon, (5) that they are under the control of a special power, (6) that their body has been changed in some way, (7) that they have special powers as well as the presence of (8) auditory and (9) visual hallucinations. Participants were asked to rate their response on a 3-point scale (0 = not true; 1 = somewhat true; 2 = certainly true). Cronbach's □ ranged from 0.77 to 0.80 between baseline and fifth assessment. Three items presented positive predictive power (ranging from 80% to 100%) for interview-verifiable PLEs.[24] The dimensional measure of PLEs consisted in the sum of all items on the PLEQ-C.

Analytical Approach

A random effect cross-lagged panel model (RE-CLPM)[25] was used to ascertain the temporal association between sleep parameters, cannabis consumption, and PLEs. The RE-CLPM approach takes advantage of longitudinal datasets by accounting for the temporal precedence of variables. Whereas ethical and practical considerations make it impossible to study such questions in humans, this approach makes it possible to determine the directionality of the effects. We performed a cross-lagged panel model examining the bidirectional association between cannabis use and CSS and between CSS and PLEs. In addition, this panel looked at the bidirectional association of cannabis with PLEs (2 years later) and, for significant associations, at ascertained the mediating effect of CSS (1 year later). Auto-regressive effects were used to control for the effect of time and concurrent effects correlations were used to control for between-group effects. The lagged-effects and auto-regressive effects were pooled, but the concurrent effects were allowed to vary over time. Variables were treated as continuous and a maximum likelihood with robust standard errors was used to account for missing data. The aforementioned analysis was performed using Mplus 8.3 software. A 95% CI and standard error were calculated for each analysis.

Results

The sample used in this study consisted of 3801 adolescents (51% female, mean age = 12.8, SD = 0.45 years), studying from grades 7 to 11. A total of 3627 (95.4%) participants met the data quality threshold to be included in the analysis, which required them to have complete data for at least two successive time points. Participants who received the addiction prevention intervention were also included in the analysis. Between the first and fifth year of the study the number of participants reporting using cannabis at least once a month increased from 69 (1.8%) to 417 (16.3%), the number of participants reporting at least one PLE decreased from 1497 (68.9%) to 1237 (48.1%), and the number of participants reporting poor or very poor sleep increased from 418 (19.4%) to 992 (38.8%). The present analysis produces a root mean square error of approximation of 0.045, indicating a good model fit.[26] Cannabis use (95% CI = 0.121 to 0.173), the CSS (95% CI = 0.205 to 0.262), PLEs (95% CI = 0.159 to 0.210) were highly auto-correlated over time. See table 1 (d, e, f) to observe how the concurrent effects cannabis use and sleep parameters (95% CI: year 1: −0.032 to −0.002, year 2 −0.777 to −0.538, year 3: −0.013 to −0.253, year 4: −0.408 to −0.155, year 5: −0.502 to −0.288), sleep parameters and PLEs (95% CI: year 1: −0.763 to −0.558; year 2: −0.100 to 0.072, year 3: −0.353 to −0.152 year 4: −0.293 to −0.076 year 5: −0.328 to −0.071), and cannabis use and PLEs (95% CI: year 1:, −0.763 to −0.558, year 2: −0.100 to 0.072, year 3: −0.353 to −0.152, year 4: −0.293 to −0.076, year 5: −0.328 to −0.071).

We found evidence of 1 year direct cross-lagged relationships of cannabis use on the CSS (95% CI = 0.307 to 0.370) and of the CSS on cannabis use (95% CI = −0.290 to −0.220) as well as the relationship of the CSS on PLEs (95% CI = 0.320 to 0.386) and of PLEs on the CSS (95% CI, −0.364 to −0.320). We also found evidence of a 2-year direct lagged-relationship between cannabis use and PLEs (95% CI = 0.035 to 0.090) but not of PLEs on cannabis use after adjusting for multiple comparisons (95% CI = 0.268 to 0.330). A subsequent mediation analysis revealed that the CSS mediated the aforementioned relationships between cannabis use and PLEs (95% CI, 0.109 to 0.142). The auto-regressive effects are displayed in table 2 and results of the direct and indirect cross-lagged effects are presented in table 1. The values of the results presented in both tables are standardized using the variances of the continuous latent variables and of the background and outcome variables (Table 3) . The combination of statistically significant autoregressive, direct, and indirect effects are displayed in figure 1.

Discussion

This research shows evidence of a reciprocal cross-lagged effect of cannabis use with the aforementioned sleep parameters and of these sleep parameters with PLEs within this adolescent cohort. In addition, there was evidence of a two-year lagged relationship between cannabis use and PLEs; an effect that was partly mediated by a

Table 1. Cross-Lagged Panel Model: Autoregressive Effects and Concurrent Effects

	Lag interval (Years)	Estimate	Estimate/SE	CI	*P*
Autoregressive (a) Cannabis	First to second	0.147	9.188	0.121 to 0.173	<.001
Autoregressive (b) Sleep	First to second	0.233	13.477	0.205 to 0.262	<.001
Autoregressive (c) Psychotic-like experiences	First to second	0.185	12.078	0.159 to 0.210	<.001
	Concurrent (Years)	**Estimate**	**Estimate/SE**	**CI**	***P***
Concurrent (d) Cannabis and sleep	First year	−0.017	−1.913	−0.032 to −0.002	.056
	Second year	−0.657	−9.063	−0.777 to −0.538	<.001
	Third year	0.120	1.488	−0.013 to 0.253	.137
	Fourth year	−0.281	−3.657	−0.408 to −0.155	<.001
	Fifth year	−0.395	−6.080	−0.502 to −0.288	<.001
Concurrent (e) Sleep and psychotic-like experiences	First year	−0.661	−10.594	−0.763 to −0.558	<.001
	Second year	−0.014	−0.268	−0.100 to 0.072	.789
	Third year	−0.252	−4.115	−0.353 to −0.152	<.001
	Fourth year	−0.185	−2.791	−0.293 to −0.076	.005
	Fifth year	−0.199	−2.554	−0.328 to −0.071	.011
Concurrent (f) Cannabis and psychotic-like experiences	First year	0.030	1.131	−0.014 to 0.073	.258
	Second year	−0.665	−5.681	−0.857 to −0.472	<.001
	Third year	−1.202	−12.315	−1.363 to −1.041	<.001
	Fourth year	−0.913	−10.744	−1.053 to −0.773	<.001
	Fifth year	−0.761	−8.064	−0.917 to −0.606	<.001

Table 2. Response Frequency: Cannabis Use, Psychotic-Like Experiences, and Composite Sleep Score

	Year 1	Year 2	Year 3	Year 4	Year 5
Cannabis use					
Never	3586 (95%)	2874 (90%)	2326 (80%)	1959 (71%)	1573 (62%)
Occasionally	104 (3%)	197 (6%)	356 (12%)	494 (18%)	566 (22%)
Approximately once a month	27 (1%)	49 (2%)	67 (2%)	100 (4%)	161 (6%)
Weekend of once or twice during the week	16 (1%>)	37 (1%)	88 (3%)	95 (3%)	133 (5%)
Three times or more a week but not every day	12 (1%>)	15 (1%>)	33 (1%)	47 (2%)	60 (2%)
Every day	14 (1%>)	12 (1%>)	35 (1%)	59 (2%)	63 (2%)
Total	3759	3184	2905	2754	2556
Psychotic-like experiences					
0	675 (31%)	996 (38%)	1123 (41%)	1326 (48%)	1337 (52%)
1 to 2	709 (33%)	855 (32%)	967 (35%)	907 (33%)	804 (31%)
3 to 4	359 (17%)	386 (15%)	359 (13%)	292 (10%)	231 (9%)
5 to 6	178 (8%)	195 (7%)	126 (5%)	104 (4%)	80 (3%)
7 to 8	149 (7%)	142 (5%)	122 (4%)	99 (4%)	80 (3%)
9 to 10	60 (3%)	34 (1%)	36 (1%)	23 (1%)	18 (1%)
11 to 12	25 (1%)	17 (1%)	13 (0%)	16 (1%)	9 (0%)
13 to 14	17 (1%)	11 (0%)	19 (1%)	15 (1%)	15 (1%)
Total	2172	2636	2765	2782	2574
Composite sleep score					
4–3.1	85 (4%)	108 (4%)	145 (5%)	184 (7%)	208 (8%)
3–2.1	333 (15%)	524 (20%)	655 (24%)	720 (26%)	784 (31%)
2–1.1	118 (55%)	1405 (54%)	1470 (54%)	1481 (54%)	1238 (48%)
1–0	551 (25%)	555 (21%)	473 (17%)	366 (13%)	324 (13%)
Total	2154	2592	2743	2751	2554

deterioration of the CSS the following year. The reciprocal relationships uncovered by our analysis suggest that both cannabis use and PLEs form positive feedback loops with sleep parameters.

Our results are in line with recent reports of a long-term lagged effect of cannabis use on sleep disruptions. This suggests that beyond its acute effect on sleep, cannabis use may induce long-term disruption of processes involved in healthy sleep.[27] We are also the first to report a sleep-mediated lagged-relationship between cannabis use and vulnerability to psychosis. Despite the broadness of the sleep parameters use in this study, they remain some

Table 3. Cross-lagged Panel Model

Direct effects: Cannabis and sleep quality	Lag Interval (Years)	Estimate	Estimate/SE	CI	*P*
(a) Cannabis use on sleep quality	First to second	0.338	17.762	0.307 to 0.370	<.001
(b) Sleep quality on cannabis use	First to second	−0.255	−12.062	−0.290 to −0.220	<.001
Direct effects: Sleep quality and psychotic-like experiences					
(a) Sleep quality on psychotic-like experiences	First to second	0.353	17.623	0.320 to 0.386	<.001
b) Psychotic-like experiences on sleep quality	First to second	−0.342	−25.621	−0.364 to −0.320	<.001
Direct effects: Cannabis use and psychotic-like experiences					
(a) Cannabis use on psychotic-like experiences	First to Third	0.063	3.729	0.035 to 0.090	<.001
(b) Psychotic-like experiences on cannabis use	First to Third	0.299	15.780	0.268 to 0.330	<.001
Indirect effect via sleep quality					
(c) Cannabis use on psychotic-like experiences via sleep quality	Pooled 2-year lags	0.125	12.271	0.109 to 0.142	<.001

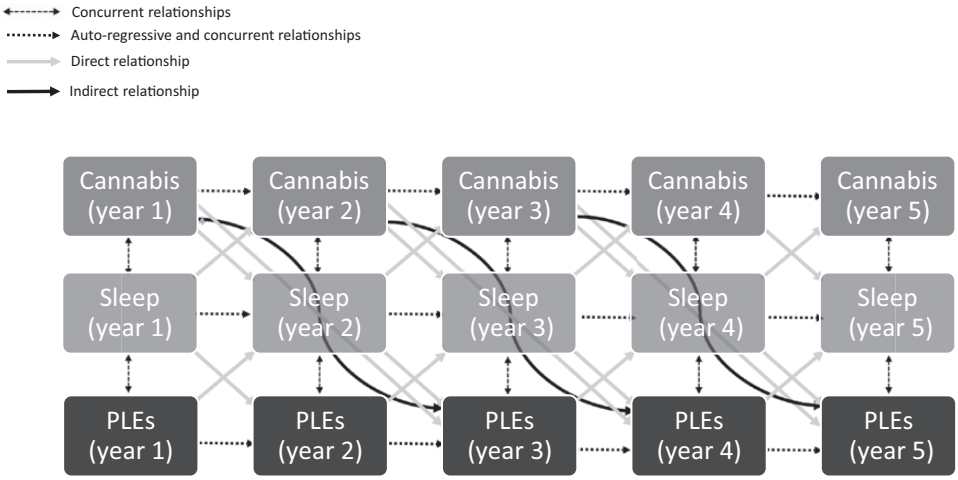

Fig. 1. Represents statistically significant autoregressive, direct, and indirect pathway of the fixed-effect cross-lagged panel model. PLE, psychotic-like experiences.

of the most clinically relevant subjective measures.[22] A deterioration of SQ signals the disruption of one or more underlying subcomponents of sleep; a subcomponent that might in turn be differently affected by specific aspects of cannabis use. For instance, different THC to cannabinadiol (CBD) ratios may yield a different effect on SQ. THC is generally reported to have negative effects on SQ, despite apparent short-term benefits on sleep onset latency while CBD may be salutary for conditions such as REM sleep behavior disorder and excessive daytime sleepiness.[10] The impact of time delays between time of cannabis intake and sleep onset may also play a significant role. An experience sampling study showed shorter delays decreased sleep onset latency without affecting wake after sleep onset.[28] These results should be interpreted with the understanding that the authors did not account for cannabis dose. Furthermore, cannabis discontinuation, even at a low dose, has a clear deleterious effect on sleep parameters.[12] Withdrawal is associated with a decrease in SWS and sleep duration along with an increase in WASOF, sleep onset latency, and REM sleep.[12] This rebound in REM activity may explain vivid and often disturbing dreams reported for up to a month and a half following discontinuation.[15] The long-term cannabis-related deterioration of sleep parameters revealed by our study may also be a consequence of cannabinoid interference with normal human chronobiology. The secretion of endogenous cannabinoid anandamide (a CB1 receptor agonist) drops before sleep onset and spikes to three times its normal concentration at wake time.[29] Consuming THC before bedtime, therefore, activates the CB1-mediated endocannabinoid system at a time when natural chronobiology lowers its activity in preparation for sleep.[29]

Conversely, our results indicate poor sleep increased cannabis use the following year. A possible explanation for this relationship includes an increase in internalizing and externalizing symptoms resulting in sleep deprivation, which may in turn enhance drug-seeking behavior.[30] An alternative explanation is that the popular perception of cannabis as a sleep aid, entices individuals with sleep difficulties to self-medicate with the drug. Such behavior is frequent among college students where one study reports 4% of college-age participants report the use of

cannabis as a sleep-aid.[17] While users report immediate benefits (eg, longer sleep duration and shorter wake-after sleep onset), they also complain of greater daytime fatigue the following day.[17]

To the best of our knowledge, these results are the first to report a negative lagged-effect of PLEs frequency on sleep parameters. However, prior research has shown a bidirectional association of sleep disruption on the paranoid dimension of PLEs, suggesting that anxiety-provoking delusions may interfere with normal sleep.[9] The stress generated by certain PLEs may therefore interfere with sleep by keeping participants in a state of hypervigilance.

The lagged effect of cannabis on PLEs is consistent with previous analyses of the CoVenture dataset which showed a 1-year lagged effect.[1] The 2-year lagged-effect revealed by our analysis further supports the robustness of this association and the temporal persistence of the effects cannabis on PLEs. While this association may be explained by a number of underlying mechanisms, our results are the first to implicate sleep as a viable mediator. While the overall effect is relatively small, it remained statistically significant over a 2-year lagged period, therefore, warranting further investigation. Future studies should rely on comprehensive measures of cannabis use, sleep, and psychotic vulnerability to identify the subcomponents that are most responsible for the overall effect. To assess this mediated effect over a shorter period, experience sampling, actigraphy, and timeline follow-back approaches could be used. Additionally, a neuroimaging study combining all three of these variables as part of a single design would make it possible to study their potential additive effect on brain structures, function, and development.

This line of research also holds promise in the prevention of psychosis. Cognitive behavioral therapies for psychosis (CBTp) are currently being developed and tested. These therapies have shown some success in the delay and prevention of a first episode amongst vulnerable individuals.[31] CBTi has demonstrated its efficacy for prolonging sleep duration and improving psychiatric comorbidities such as anxiety and depression.[32] This suggests that addressing sleep issues as part of CBTp interventions be synergistic. Finally, poor sleep and strange dreams represent a significant obstacle to cannabis cessation making the treatment of sleep-related problems a useful tool in the treatment of cannabis addiction.[33,34]

Strengths and Limitations

Although our study provides significant insights on the relationship between sleep, cannabis use and psychosis, it presents some limitations. First, our questionnaires only provide broad measures of cannabis use and subjective sleep parameters. As a result, our analyses could not account for a number of factors that are likely to play a crucial role in the complex relationships outlined in the present study. The effects of cannabis could be modulated by its chemical composition (eg, THC:CBD ratio), patterns of use (eg, latency between intake and sleep onset), and the experience of frequent withdrawal effects. The effect of sleep could be modulated by specific segments of sleep architecture (eg, REM, sleep spindle frequency, SWS), sleep behavior (eg, sleep onset latency, wake after sleep onset, total sleep time), and specific patterns of circadian rhythm distortions (eg, loss of rhythmicity, loss of regularity, sleep phase shift). Second, CoVenture data collection was made through questionnaires administered on a yearly basis. This makes it impossible to assess lagged-mediation relationships occurring over shorter intervals. This is a fundamental difference between our study and the vast majority of the literature previously cited as long-term degradation should be treated as a different phenomenon insofar as it may be indicative of negative long-term neuroplastic changes. To determine whether the mediation of sleep is of causal nature, future studies will have to include potential covariates and dismiss alternative causal pathways.

Conclusion

To the best of our knowledge, the present study is the first to show the mediating role of sleep in the cannabis-to-psychosis relationship. The findings suggest that sleep could constitute a target for cannabis-related psychosis prevention strategies.

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Conflict of Interest

The Authors have declared that there are no conflicts of interest in relation to the subject of this study.

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