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Bidirectional Causal Relationship between Substance Abuse and Mental Illness: A Systematic Review

Nkporbu AK[1*], Oti IK[2] and Stanley P C[1]

[1]Department of Neuropsychiatry, University of Port Harcourt Teaching Hospital, Nigeria
[2]Department of Physiotherapy, University of Port Harcourt Teaching Hospital, Nigeria

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Abstract

This systematic review explores the bidirectional causal relationship between substance abuse and mental illness, two conditions that frequently co-occur and intensify one another. Substance abuse, involving harmful use of alcohol, drugs, or prescription medications, is strongly associated with mental illnesses such as depression, anxiety disorders, schizophrenia, and bipolar disorder. Both conditions share genetic, psychological, and environmental risk factors, and their co-occurrence contributes to disability, poor quality of life, and increased healthcare and economic costs. Following PRISMA 2021 guidelines, a systematic search of PubMed/MEDLINE, Scopus, Web of Science, and PsycINFO was conducted to identify peer-reviewed studies examining reciprocal effects of substance abuse and mental illness. Eligible studies included empirical research, systematic reviews, and meta-analyses that assessed how substance use influences mental health outcomes and, conversely, how mental illness predisposes individuals to substance misuse. Findings indicate that depressive symptoms predict subsequent cigarette and e-cigarette use, while cannabis and alcohol use predict later depressive symptoms, particularly during the COVID-19 pandemic. These results highlight the role of societal stressors in amplifying the relationship between substance use and mental health. Evidence suggests that the relationship is neither purely unidirectional nor explained by a single factor but emerges from a convergence of neurobiological changes, executive dysfunction, self-medication tendencies, and broader social and cultural influences. The review underscores the importance of integrated treatment approaches that address both substance use and mental illness simultaneously, rather than in isolation. Preventive strategies, early detection, stigma reduction, and community-based interventions are crucial to breaking the cycle of comorbidity. Future research should prioritize longitudinal studies to clarify causality, identify protective factors, and develop evidence-based, culturally sensitive interventions that improve recovery outcomes across diverse populations.

***Corresponding author:** Nkporbu A K, Department of Neuropsychiatry, University of Port Harcourt Teaching Hospital, Nigeria.

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Introduction

Substance abuse is the harmful or hazardous use of psychoactive substances such as alcohol, drugs, or prescription medications in a way that impairs judgment, physical health, or social functioning. It often leads to addiction, tolerance, withdrawal symptoms, and long-term damage to the brain and body [1]. Mental illness is a broad range of mental health conditions that affect a person's mood, thinking, and behaviour, which include depression, anxiety disorders, schizophrenia, and bipolar disorder [2]. Substance abuse and mental illness often occur together (a condition known as dual diagnosis). People with mental illness may use drugs or alcohol to cope with symptoms such as anxiety, depression, or trauma. Substance abuse can trigger or worsen mental health conditions by altering brain chemistry, both conditions share risk factors such as genetic vulnerability, stress, trauma, and environmental influences, each condition tends to worsen the other, making recovery more difficult without integrated treatment (National Institute of Mental Health, 2024).

Each year about 30% of the general population suffers from a mental disorder [3]. Of these, mental illness and substance abuse frequently occur. The impact of these categories of disorders on individual life and on society can be substantial; they are related to functional disability, lost quality of life, and increased economic and health care deficiency [4]. People with lifetime substance abuse (14-20 % of the general population) indeed have increased estimated lifetime prevalence of mental illness ranging 20% to 40% vice versa, among people with lifetime mental illness 15-20% of the general population, the lifetime prevalence of substance abuse has been estimated 18% [5-7]. Sometimes, mental illness and substance abuse even co-occur at the same time, which leads to even more negative consequences than the pure conditions, such as higher levels of disability, more suicidality and poorer treatment outcomes [8]. The temporal order of the association between mental illness and substance abuse is unclear. Establishing this temporal order could help to unravel mechanisms underlying this association and thereby improve treatment interventions [9,10].

Substance abuse is a significant global public health crisis. In the United States alone, the societal cost of Substance abuse has grown to be in excess of 740 billion dollars annually and worldwide Substance abuse exceed all other mental health disorders in regard to premature mortality due to illness [11,12]. Many treatments for Substance abuse focus on the management of withdrawal symptoms and the reduction of craving sequelae that are also heavily emphasized in the preclinical addiction literature. Although treating withdrawal symptoms in abstinent patients is a critical step toward recovery, relapse often occurs long after these symptoms have subsided and therefore there is increasing interest in other mechanisms that outlast these processes. An ever-growing body of clinical research indicates that the deregulations of executive function, a diverse set of cognitive processes responsible for purposeful, goal-directed behaviour plays a fundamental role in the development and maintenance of Substance abuse [13]. The prevalence of cognitive comorbidities across substance classes, their role in the initiation and maintenance of harmful patterns of substance use, and the long-lasting nature of these deficits compared to other consequences of drug use suggests that Substance abuse may be best characterized as a disease of executive dysfunction. Although it is indisputable that cognitive deficits are comorbid with Substance abuse, the relationship between the two is complex. It has long been held that prolonged exposure to substances of abuse, such as alcohol and psychostimulants, promote neuroadaptations that produce cognitive abnormalities. However, substantial evidence suggests that executive dysfunction is also a risk factor for Substance abuse, therefore making it difficult to determine the direction and nature of causality in between these variables in clinical populations. Given this complexity, animal models, where risk factors and exposure can be fully measured and controlled, offer unique advantages for probing the relationship between cognitive function and substance use.

The prevalence of depressive disorders has increased in the US, particularly during COVID-19 [14-17]. One study using national data documented that the proportion of US adults experiencing mild, moderate, and severe depressive symptoms before versus during COVID-19 increased from 16.2% to 24.6%, 5.7% to 14.8%, and 0.7% to 5.1%, respectively [18]. Another study documented that prevalence of depressive disorder quadrupled from 2019 to 2020 [17]. These pandemic-related increases may have resulted from several factors (e.g., loss of employment or income, social isolation, increased childcare responsibilities), [19-21]. Depressive disorders are particularly prevalent among young adults (National Institute of Mental Health, 2022); among young adults (ages 18–34), prevalence increased from 2018 (7.8%) to 2020 (15.2%) [22]. The prevalence of depressive disorders also differs by other sociodemographic characteristics, with higher rates among women, White and multiracial individuals (National Institute of Mental Health, 2022), some foreign-born subgroups, and those of higher socioeconomic status (per education and income) and who are married (National Institute of Mental Health, 2022) [23,24]. Additionally, during COVID-19, parents reported greater increases in depressive symptoms and stress, perhaps due to increased childcare demands [19].

Depression has been shown to be prospectively associated with later substance use behaviours, including cigarette, e-cigarette, cannabis and alcohol use [25,26]. Several sociodemographic sub-groups are particularly impacted by substance use, including younger adults men, and sexual minorities with sociodemographic subgroups disproportionately impacted across substances like Whites for alcohol and tobacco, Blacks for cannabis, some foreign-born immigrants for alcohol and tobacco, higher socioeconomic status for alcohol, and less education for cannabis and cigarettes [27-31].

This study systematically review and critically examine the bidirectional causal relationship between substance abuse and mental illness, by evaluating existing empirical evidence to determine how substance use contributes to the onset or worsening of mental disorders, and conversely, how mental illness increases vulnerability to substance abuse. This review also seeks to identify common risk factors, underlying mechanisms, and implications for prevention, diagnosis, and integrated treatment strategies.

Methodology

Research Framework

This research employs PRISMA (Preferred Reporting Items for Systematic Reviews) for the literature on bidirectional causal relationship between substance abuse and mental illness Publications for 2021 are included in the analysis. The PRISMA framework, as shown in Figure 1, was employed in the study's methodology.

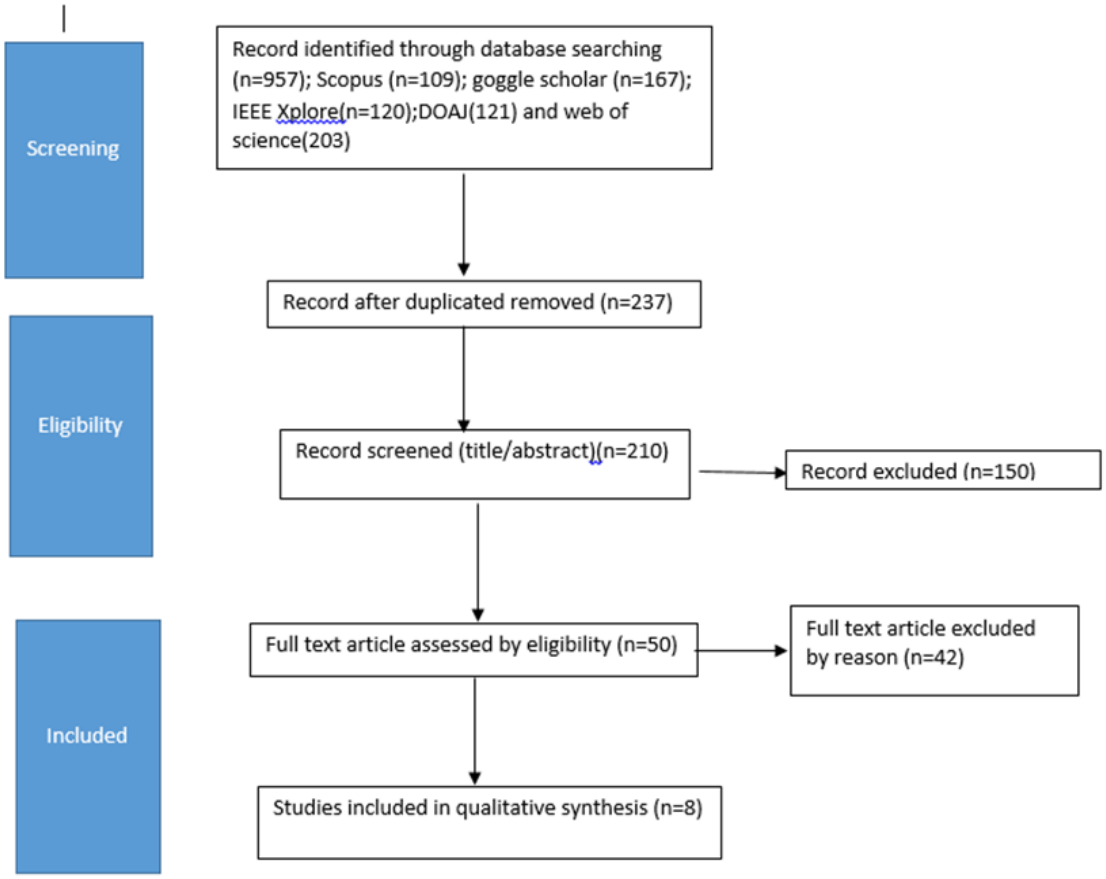

Figure 1: PRISMA framework

Sources and Searching Strategy

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2021 guidelines to enhance methodological rigor, transparency, and replicability. A comprehensive literature search was performed to identify peer-reviewed studies that examined the bidirectional causal relationship between substance abuse and mental illness across various populations, age groups, and contexts.

Four major electronic databases: PubMed/MEDLINE, Scopus, Web of Science, and PsycINFO; were systematically searched due to their broad coverage of biomedical, psychological, and social science research. These databases were selected to ensure the inclusion of studies that address the complex interplay between substance abuse and mental illness from clinical, and psychosocial perspectives [32].

The search strategy utilized a combination of keywords and Boolean operators such as “substance abuse”, “substance use disorder”, “mental illness”, “mental health disorders”, “bidirectional relationship”, “causality”, and “dual diagnosis”. Keywords were refined and expanded through preliminary scoping searches and informed by existing systematic reviews and empirical studies in the field. Filters were applied to restrict results to empirical peer-reviewed articles published in English. No time restrictions were imposed on publication year to allow for the inclusion of both historical and contemporary research evidence.

Eligibility Criteria

A multi-stage filtering method was used to guarantee that the retrieved publications were appropriate for study. The following standards were used:

Category	Inclusion Criteria	Exclusion Criteria
Study type	Peer-reviewed empirical studies (quantitative, qualitative, or mixed-methods), systematic reviews, and meta-analyses.	Editorials, commentaries, opinion pieces, conference abstracts without full papers, unpublished theses, or grey literature
Population	Studies involving individuals diagnosed with substance abuse/substance use disorders (SUDs) and mental illness (e.g., depression, anxiety, schizophrenia, bipolar disorder).	Studies focusing exclusively on either substance abuse or mental illness without examining their interaction.
Exposure/Focus	Research explicitly examining the bidirectional relationship (i.e., how substance abuse influences mental illness and vice versa).	Studies investigating only unidirectional effects (e.g., only substance abuse leading to mental illness or vice versa).
Context/Setting	Studies conducted in any setting (clinical, community, institutional, or general population) across diverse geographical regions.	Studies limited to animal models or laboratory experiments without human subjects.
Language	Articles published in English.	Articles published in languages other than English.
Publication date	No restriction (both historical and recent studies included).	None (date is not an exclusion criterion).

Study Selection

The process for study selection involved:

- Screening titles and abstracts for relevance.
- Assessing full texts against inclusion and exclusion criteria.
- Selecting studies for detailed analysis descriptions.

Quality Assessment

The papers were evaluated for quality and relevance based on their connection with the research subject, journal impact factor, and citation impact. A simplified technical assessment checklist (leakage controls, baselines, reproducibility, dataset provenance, threat model clarity, and validation technique) was employed for peer-reviewed empirical investigations. We used the AACODS (authority, accuracy, coverage, objectivity, date, importance) criteria for grey literature, giving official UK, EU, and US agencies priority [33].

Data Analysis

Our data analysis focused on the descriptive analyses to characterize the sample and bivariate analyses to assess sociodemographics in relation to depressive symptoms and use of each substance, separately. The distributions of depressive symptoms were approximately normal (skewness 0.88-1.0). However, the distributions of substance use were slightly skewed (skewness varying 0.23-3.25), so we conducted log transformation for each substance use variable (skewness varying 0.11-1.61).

To assess changes in depressive symptoms and substance use across the 3 waves, we conducted multilevel linear regression modelling, for depressive symptoms and log transformed substance use variables with a random intercept to account for the clustering of repeated measures within each participant. Time was included as a categorical variable; changes over time (W1-W2, W2-W3, W1-W3) were estimated.

Cross-lagged panel models (CLPM, i.e., a type of longitudinal structural equation modelling) were used to assess bidirectional associations between depressive symptoms and substance use. CLPM assesses cross-lagged relationships between 2 variables (i.e., an antecedent variable predicting a second variable at a later time point), as well as autoregressive relationships (or stability) of a single variable over time, accounting for contemporary correlations between the residuals of 2 variables measured concurrently. Other analytic approaches were considered, specifically random intercept CLPM however, this approach was rejected because it is recommended for data including at least 4 waves of data only captures temporal fluctuations around individual person means – ignoring potential effects of between-person causes, and has limited ability to control for unobserved confounders in estimating cross-lagged effects [34-38].

For each substance, the initial CLPM estimated cross-lagged and autoregressive paths freely without constraints. We then used Wald tests to assess equality of cross-lagged relationships between depressive symptoms and substance use. If Wald tests yielded non-significant results (suggesting associations did not differ over time), paths were constrained to be equal over time. Robust maximum likelihood was used to account for possible skewness. Non-significant Chi-square tests ($p > .05$), Root Mean Square Error of Approximation (RMSEA) ≤ 0.08, Tucker–Lewis index (TLI) > 0.95, and comparative fit index (CFI) > 0.95 were used to indicate good model fit [39]. Models included MSA of residence and sociodemographic covariates, selected based on the literature [40]. (Note: Preliminary analyses indicated no differences in results if covariate selection was restricted, e. g., omitting nativity, and children.) Mplus 8.1 was used for CLPM, missing values were accounted for with full information maximum likelihood, and significance level was set at $p < .05$.

Results

Participant Characteristics

Participants were on average 24.56 years old (SD = 4.71), 56.5% female, 31.6% sexual minority, 71.6% White, 5.3% Black, 12.2% Asian, 10.9% other race, and 11.4% Hispanic (Table 1). Bivariate analyses (Table 1) indicated that greater depressive symptoms correlated with more days of use of each substance and weak-moderate correlations in substance use behaviours (range = 0.06–0.25; p's < 0.001). Significant ($p < .05$) correlates of depressive symptoms included being younger, sexual minority, White or other race, Hispanic, less educated, and unemployed. More days of use of each substance correlated with being a sexual minority (except for alcohol), US-born, and married/living with a partner/other marital status (vs. single). Additional details are provided in Table 1.

Table 1: Sociodemographics, Depressive Symptoms & Substance Use Among Young Adults In 6 Us Metropolitan Statistical Areas, Fall 2018 (Wave 1 [W1]), N = 3,006.

Variables Sociodemographics	Total N (%) or *M (SD)	W1 PHQ-2 M (SD) or *r	^p	W1 Cigarette Use M (SD) or *r	^p
Age *	24.56 (4.71)	−0.10	<0.001	0.16	<0.001
Male #	1,271 (43.5)	1.66 (1.69)	0.567	4.00 (8.69)	0.119
Female	1,648 (56.5)	1.62 (1.65)		3.50 (8.65)	
Sexual minority	950 (31.6)	2.19 (1.80)	<0.001	4.65 (9.64)	<0.001
No	2,056 (68.4)	1.43 (1.57)		3.35 (8.23)	
Race					
White	2,151 (71.6)	1.69 (1.68)	<0.001	3.84 (8.84)	<0.001
Black	159 (5.3)	1.38 (1.57)		5.09 (9.99)	
Asian	367 (12.2)	1.44 (1.57)		1.68 (5.72)	
Other	329 (10.9)	1.95 (1.81)		4.96 (9.60)	
Hispanic	343 (11.4)	1.89 (1.77)	0.011	4.88 (9.12)	0.012
No	2,663 (88.6)	1.64 (1.67)		3.62 (8.66)	
Foreign born	286 (9.5)	1.59 (1.66)	0.408	2.62 (7.39)	0.020
No	2,720 (90.5)	1.68 (1.68)		3.88 (8.84)	

W1 E-cigarette Use		W1 Cannabis Use		W1 Alcohol Use	
M (SD) or *r	^p	M (SD) or *r	^p	M (SD) or *r	^p
−0.05	0.007	0.00	0.875	0.13	<0.001
7.77 (11.83)	<0.001	5.48 (9.94)	0.138	6.10 (6.96)	0.030
5.75 (10.70)		4.94 (9.45)		5.57 (6.17)	
7.51 (11.73)	0.004	7.02 (10.78)	<0.001	5.76 (6.81)	0.938
6.25 (11.02)		4.45 (9.13)		5.78 (6.40)	
7.30 (11.73)	<0.001	5.57 (9.99)	<0.001	6.28 (6.67)	<0.001
3.35 (7.52)		5.04 (9.94)		4.54 (6.19)	
3.58 (8.62)		2.35 (6.31)		3.45 (4.74)	
7.47 (11.48)		6.60 (10.66)		5.68 (6.85)	
7.06 (11.06)	0.472	5.64 (9.93)	0.442	5.63 (6.38)	0.656
6.60 (11.29)		5.21 (9.73)		5.79 (6.55)	
4.49 (9.65)	0.001	2.59 (6.74)	<0.001	4.84 (6.46)	0.011
6.88 (11.40)		5.55 (9.97)		5.87 (6.53)	

Variables Sociodemographics	Total N (%) or *M (SD)	W1 PHQ-2 M (SD) or *r	^p	W1 Cigarette Use M (SD) or *r	^p
Employment					
Student	825 (27.5)	1.63 (1.64)	<0.001	1.86 (6.04)	<0.001
Unemployed	244 (8.1)	2.26 (1.96)		7.60 (12.13)	
Full-time	1,202 (40.0)	1.46 (1.61)		4.22 (9.18)	
Part-time	735 (24.5)	1.87 (1.69)		3.87 (8.63)	
Relationship status					
Single	1,876 (62.4)	1.73 (1.71)	0.052	3.12 (7.92)	<0.001
Married/living with partner	1,089 (36.2)	1.57 (1.63)		4.75 (9.78)	
Other	41 (1.4)	1.63 (1.64)		6.88 (10.93)	
Children in the home	611 (20.3)	1.66 (1.75)	0.851	5.88 (10.65)	<0.001
No	2,395 (79.7)	1.68 (1.66)		3.22 (8.07)	
W1 depressive symptoms *§	1.67 (1.68)	–	–	0.17	<0.001
W1 depressive symptoms ≥ 3	2,290 (76.2)	4.15 (1.13)		6.11 (10.29)	
No	716 (23.8)	0.89 (0.89)	<0.001	3.03 (8.03)	<0.001
W1 number of days used past 30 *					
Cigarettes	3.76 (8.72)	0.17	<0.001	–	–
E-cigarettes	6.65 (11.26)	0.11	<0.001	0.15	<0.001

W1 E-cigarette Use M (SD) or *r	^p	W1 Cannabis Use M (SD) or *r	^p	W1 Alcohol Use M (SD) or *r	^p
5.34 (10.14)	<0.001	3.76 (8.16)	<0.001	4.48 (5.39)	<0.001
7.11 (11.84)		7.00 (11.49)		3.67 (5.42)	
6.68 (11.48)		4.96 (9.59)		7.08 (7.22)	
7.94 (11.76)		6.88 (10.68)		5.79 (6.39)	
5.99 (10.70)	<0.001	4.77 (9.12)	<0.001	5.41 (6.22)	<0.001
7.66 (12.00)		5.96 (10.58)		6.39 (7.00)	
10.12 (13.57)		9.61 (12.49)		5.95 (6.54)	
8.24 (12.17)	<0.001	6.16 (10.74)	0.011	4.35 (6.21)	<0.001
6.25 (10.99)		5.03 (9.47)		6.14 (6.56)	
0.11	<0.001	0.16	<0.001	0.03	0.080
8.26 (11.62)		6.95 (11.03)		5.76 (6.68)	
6.15 (11.10)	<0.001	4.74 (9.26)	<0.001	5.78 (6.49)	0.954
–	–	–	–	–	–

Variables Sociodemographics	Total N (%) or *M (SD)	W1 PHQ-2 M (SD) or *r	^p	W1 Cigarette Use M (SD) or *r	^p
Cannabis	5.26 (9.75)	0.16	<0.001	0.25	<0.001
Alcohol	5.77 (6.53)	0.03	0.080	0.14	<0.001
W1 past 30-day use status					
Cigarettes	808 (26.88)	2.23 (1.83)	<0.001	–	–
No	2,198 (73.12)	1.47 (1.58)		–	–
E-cigarettes	1,133 (37.69)	2.01 (1.73)	<0.001	571 (50.40)	<0.001
No	1,873 (62.31)	1.47 (1.62)		237 (12.65)	
Cannabis	1,178 (39.24)	1.98 (175)	<0.001	497 (42.19)	<0.001
No	1,824 (60.76)	1.47 (1.60)		310 (17.00)	
Alcohol	2,303 (76.61)	1.67 (1.67)	0.921	675 (29.31)	<0.001
No	703 (23.39)	1.67 (1.72)		133 (18.92)	

W1 E-cigarette Use M (SD) or *r	^p	W1 Cannabis Use M (SD) or *r	^p	W1 Alcohol Use M (SD) or *r	^p
0.24	<0.001	–	–	–	–
0.06	0.002	0.12	<0.001	–	–
571 (70.67)	<0.001	497 (61.59)	<0.001	675 (83.54)	<0.001
562 (25.57)		681 (31.03)		1628 (74.07)	
–	–	678 (60.05)	<0.001	925 (81.64)	<0.001
–	–	500 (26.70)		1378 (73.57)	
678 (57.56)	<0.001	–	–	1044 (88.62)	<0.001
451 (24.73)		–	–	1257 (68.91)	
925 (40.17)	<0.001	1044 (45.37)	<0.001	–	–
208 (29.59)		134 (19.12)		–	–

Past 30-day use prevalence was highest at W1 for cigarettes (26.9%) and e-cigarettes (37.7%), and roughly equal across waves for cannabis (39.2–40.0%) and alcohol (71.2–76.9%; Table 2). As presented in Table 3, multilevel modelling indicated significant W1-W2 decreases in depressive symptoms (p =.024), but significant W2-W3 increases (p <.001); decreases in past 30-day cigarette and e-cigarette use across both periods (p's < 0.001); increases in cannabis use in each period (W1-W2: p =.028; W2-W3: p =.004); and W2-W3 decreases in alcohol use (p <.001), but no W1-W2 change. After adjusting for covariates, findings were similar,

except change in depressive symptoms at W1-W2 (non-significant).

Table 2: Average depressive symptoms and days of cigarette, e-cigarette, cannabis & alcohol use (in the past 30-days) among young adults in 6 US metropolitan statistical areas assessed in Fall 2018 (Wave 1 [W1]), 2019 (W2) and 2020 (W3), respectively.

	W1 N = 3,006		W2 N = 2,375
Variable	M (SD)	N (%) with score ≥ 3	M (SD)
Depressive symptoms	1.67 (1.68)	716 (23.8)	1.58 (1.67)
Past 30-day substance use	Days of use among all participants M (SD)	Reported any past 30-day use N (%)	Days of use among all participants M (SD)
Cigarettes	3.76 (8.72)	808 (26.9)	2.79 (7.42)
E-cigarettes	6.65 (11.26)	1,133 (37.7)	4.94 (9.94)
Cannabis	5.26 (9.75)	1,178 (39.2)	4.94 (9.37)
Alcohol	5.77 (6.53)	2303 (76.6)	5.47 (6.16)

	W3 N = 2,476	
N (%) with score ≥ 3	M (SD)	N (%) with score ≥ 3
514 (21.6)	1.80 (1.72)	612 (24.7)
Reported any past 30-day use N (%)	Days of use among all participants M (SD)	Reported any past 30-day use N (%)
572 (24.1)	2.48 (7.10)	483 (19.5)
776 (32.7)	4.41 (9.75)	623 (25.2)
945 (40.0)	5.72 (10.20)	990 (40.0)
1,827 (76.9)	5.57 (6.79)	1,763 (71.2)

Table 3: Change of depressive symptoms, days of cigarette, e-cigarette, cannabis & alcohol use (in the past 30-days) over time, in Fall 2018 (Wave 1 [W1]), 2019 (W2) and 2020 (W3).

	Cigarette			
	Estimated change over time			
Time	b (SE)	p	Adjusted* b (SE)	p
W1	Ref.		Ref.	
Change W1 to W2	−0.07 (0.02)	<0.001	−0.06 (0.02)	<0.001
Change W2 to W3	−0.08 (0.02)	<0.001	−0.07 (0.02)	<0.001
Change W1 to W3	−0.14 (0.02)	<0.001	−0.13 (0.02)	<0.001
	Alcohol			
	Estimated change over time			
Time	b (SE)	p	Adjusted* b (SE)	p
W1	Ref.		Ref.	
Change W1 to W2	−0.02 (0.02)	0.185	−0.03 (0.02)	0.095
Change W2 to W3	−0.07 (0.02)	<0.001	−0.07 (0.02)	<0.001
Change W1 to W3	−0.09 (0.02)	<0.001	−0.10 (0.02)	<0.001

E-cigarette				Depressive symptoms			
Estimated change over time				Est. change over time			
b (SE)	p	Adjusted* b(SE)	p	b (SE)	p	Adjusted* b (SE)	p
Ref.		Ref.		Ref.		Ref.	
−0.10 (0.02)	<0.001	−0.09 (0.02)	<0.001	−0.08 (0.03)	0.024	−0.05 (0.03)	0.14
−0.13 (0.02)	<0.001	−0.13 (0.02)	<0.001	0.22 (0.04)	<0.001	0.21 (0.04)	<0.001
−0.23 (0.02)	<0.001	−0.22 (0.02)	<0.001	0.15 (0.03)	<0.001	0.16 (0.03)	<0.001
Cannabis							
Estimated change over time							
b (SE)	p	Adjusted* b (SE)	p				
Ref.		Ref.					
0.04 (0.02)	0.028	0.04 (0.02)	0.024				
0.05 (0.02)	0.004	0.05 (0.02)	0.005				
0.10 (0.02)	<0.001	0.10 (0.02)	<0.001				

Cross-lagged panel Model (CLPM) on Depressive Symptoms and Substance use

The initial CLPM models (using log transformed use variables) did not fit the data. Thus, based on modification indices, second-order autoregressive paths of W3 on W1 for both depressive symptoms and each substance use variable were included for each model. In each case, the model fit was significantly improved. Then, we assessed equality of cross-lagged paths for antecedent depressive symptoms correlating with later substance use over time and cross-lagged paths for antecedent substance use correlating with depressive symptoms over time. For cigarettes and e-cigarettes, Wald tests suggested non-significant differences in each path over time, so we constrained the cross-lagged paths to be equal over time. For cannabis and alcohol, Wald tests showed significant differences over time for antecedent use in relation to later depressive symptoms, but not the reverse associations; thus, the latter were constrained to be equal over time.

Model fit was excellent for cigarettes (Chi-square = 2.570[df = 4], p =.632, RMSEA = 0.000, CFI = 1.0, TLI = 1.0, SRMR = 0.002), e-cigarettes (Chi-square = 6.698[df = 4], p =.153, RMSEA = 0.015, CFI = 0.999, TLI = 0.987, SRMR = 0.003), cannabis (Chi-square = 6.515[df = 3], p =.089, RMSEA = 0.020, CFI = 0.999, TLI = 0.973, SRMR = 0.003), and alcohol (Chi-square = 4.148[df = 3], p =.246, RMSEA = 0.011, CFI = 1.0, TLI = 0.989, SRMR = 0.002).

Greater antecedent depressive symptoms correlated with more days of subsequent cigarette (standardized path coefficient, $\beta = 0.03$, SE = 0.01, p =.011) and e-cigarette use ($\beta = 0.03$, SE = 0.01, p =.021), but fewer days of alcohol use ($\beta = -0.02$, SE = 0.01, p =.035; see Figure. 1). W2 cannabis use and alcohol use, respectively, were related to W3 depressive symptoms (cannabis: $\beta = 0.09$, SE = 0.02, p <.001; alcohol: $\beta = 0.06$, SE = 0.02, p =.002). No other cross-lagged associations were significant [41].

Discussion

In this diverse sample of US young adults, findings indicated that depressive symptomatology and substance use behaviours were more stable during the year prior to (2018–2019) versus during the pandemic (2019–2020). These findings might suggest the potential role of pandemic-related societal instability and stressors in impacting depressive symptoms and substance use [19-21]. Furthermore, depressive symptoms and cannabis use increased in both periods (particularly during the pandemic), while cigarette and e-cigarette use decreased in both periods, and alcohol use decreased during the pandemic. These findings somewhat align with national data, indicating increases in depressive symptoms and cannabis use and decreases in cigarette and alcohol use from 2018 to 2020 however, our findings differ from national data that indicate increases in e-cigarette use [22,42,43].

Notably, no hypothesized bidirectional associations between depressive symptoms and substance use were found. Instead, earlier depressive symptoms were associated with more days of subsequent cigarette and e-cigarette use before and during the pandemic, while earlier cannabis and alcohol use were associated with later depressive symptoms, but only from Fall 2019 to Fall 2020. Interestingly, depressive symptoms were associated with fewer days of alcohol use during both periods. Current findings must be contextualized with the existing literature regarding each substance and reflecting on the various potential underlying pathways, as posited by several theoretical explanations [44,45].

Regarding cigarettes and e-cigarettes, current findings are consistent with some literature, for example the 2017 systematic review that showed that depressive symptoms consistently predict subsequent cigarette smoking [46]. However, our findings contradict the systematic review's findings regarding bidirectionality, which were undermined by a very small number of studies reporting bidirectionality, particularly for the relationship between depression and smoking level (n = 2) [46]. Current findings align with earlier study results indicating that antecedent depressive symptoms in young adults predicted future e-cigarette use, but not reverse associations, but contradict earlier findings indicating a bidirectional relationship between depressive symptoms and e-cigarette use in adolescents [47,48]. It is worth noting that the first-order stability (autoregressive) coefficients were larger for cigarette and e-cigarette use than depressive symptoms, making it difficult to observe cross-lagged effects for these use variables. Nevertheless, current findings and the available literature suggest that, at least in young

Current results regarding cannabis and alcohol use align with some research indicating that later depressive symptoms are associated with earlier cannabis and alcohol use respectively [52,53]. However, these relationships were only documented during the pandemic period; that is, Fall 2019 cannabis and alcohol use, respectively, were associated with greater increases in depressive symptoms by Fall 2020. Moreover, we found no association between earlier depressive symptoms and increased cannabis or alcohol use, contradicting existing findings that depressive symptoms predicted cannabis use and showing bidirectional correlations between depression and cannabis and alcohol use [25,26,54-60]. In fact, current findings indicated that fewer prior depressive symptoms were associated with more subsequent alcohol use. Collectively, these findings could be interpreted by the literature suggesting that cannabis and alcohol may be used for social or other reasons but may also increase depressive symptoms which may be particularly true during societal stressors or periods of isolation [61-63].

These findings have implications for research and practice. First, findings suggest that use of one substance does not equate to the others in terms of depressive symptoms as an underlying mechanism, and vice versa. In young adults – who represent the age group at highest risk for using cigarettes, e-cigarettes, cannabis, and alcohol the trajectories and reasons for use may be particularly distinct (e.g., social reasons for cannabis and alcohol) [14,43,64-72]. Moreover, how substance use behaviours have been impacted by COVID-19 have also differed. While some studies indicated increases in use of cigarettes, e-cigarettes cannabis and alcohol some indicate decreases in cigarette and e-cigarette use [14,19,73-77]. However, the broader literature (over time) is even more mixed in terms of the associations between these substance use behaviours and depressive symptoms, potentially due to differences across study samples (e.g., age of cohort, sample size), sociodemographic compositions of samples, the measures of depression and substance use employed, the length and number of follow-up periods, and the specific analytic approaches used, among other reasons. Thus, we must advance the literature, with a particular eye toward ensuring rigorous methods. For example, future research assessing substance use and psychological factors across multiple time-points (e.g., intensive, short-term diary studies or experience sampling methods) could use random intercept CLPM to advance our understanding of within- and between-person dynamics and of the strengths and limitations of these different analytic approaches [34,36,38]. In practice, intervening on depression and substance use simultaneously among individuals with co-occurring depression and substance use disorders is the optimal approach and current findings underscore the need to monitor substance use over time among patients reporting only depression, and vice versa [78,79].

Study limitations include limited generalizability to other US young adults. Substance use rates should not be interpreted as prevalence rates, as our sampling design aimed to achieve a sample with roughly a third being current e-cigarette and cigarette users – and thus, they likely have higher other substance use rates. This may also explain the particularly high rates of depressive symptoms in this sample (~21%-24%) across periods relative to the national estimates (~8–15%) [22]. In addition, these analyses did not account for polyuse, as we aimed to assess bidirectional associations between use of each specific substance in relation to depressive symptoms and documented differential associations. Notably, no strong collinearity was found among the substance use variables and depressive symptoms. Nonetheless, future research might use longitudinal latent class analysis to address polyuse. Finally, our measures were limited in scope (i.e., not exhaustive of all potentially important factors) and by their self-reported nature.

Conclusions

This systematic review highlights the complex and bidirectional causal relationship between substance abuse and mental illness. Evidence shows that substance use can precipitate or worsen psychiatric disorders through neurobiological, psychological, and social pathways, while mental illness often increases vulnerability to substance misuse as a form of self-medication or coping mechanism. The interplay between the two conditions contributes to a cycle of relapse, poor treatment adherence, and adverse health and social outcomes.

Addressing this dual relationship requires integrated treatment approaches that simultaneously target both

substance use and mental health disorders rather than treating them in isolation. Preventive strategies, early detection, and coordinated care models are essential for breaking the cycle and improving long-term recovery outcomes. Future research should focus on longitudinal studies to better clarify causality and on developing context-specific interventions tailored to diverse populations.

Earlier depressive symptoms were associated with greater cigarette and e-cigarette use before and during the pandemic, while earlier cannabis and alcohol use were related to later depressive symptoms, but only from fall 2019 to fall 2020. Moreover, depressive symptomatology and substance use behaviours were more stable prior to versus during COVID-19, underscoring the impact of this major societal stressor. These findings should inform intervention efforts to optimize the physical and mental health outcomes among young adults, especially as the population continues to experience the impact of COVID-19 and may face other societal stressors in the future. Furthermore, research should further elucidate explanatory mechanisms of associations between depressive symptoms and use of specific substances, across specific populations, in order to advance this area of research.

Furthermore, the review emphasizes that no single factor fully explains this relationship; rather, it emerges from a convergence of genetic predisposition, environmental stressors, socioeconomic inequalities, and cultural influences. This underscores the need for a multidimensional framework in both research and treatment.

In order to address this bidirectional link, integrated treatment techniques are needed, which treat mental health and substance use disorders concurrently rather than separately. To end the cycle and enhance long-term recovery results, preventive measures, early detection, and integrated care approaches are crucial.

Finally, the findings highlight the importance of stigma reduction, policy reform, and community-based interventions in supporting affected individuals. Future research should prioritize longitudinal studies to clarify causal directions further, investigate protective factors, and develop evidence-based, culturally sensitive interventions that can be applied across diverse populations [80].

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