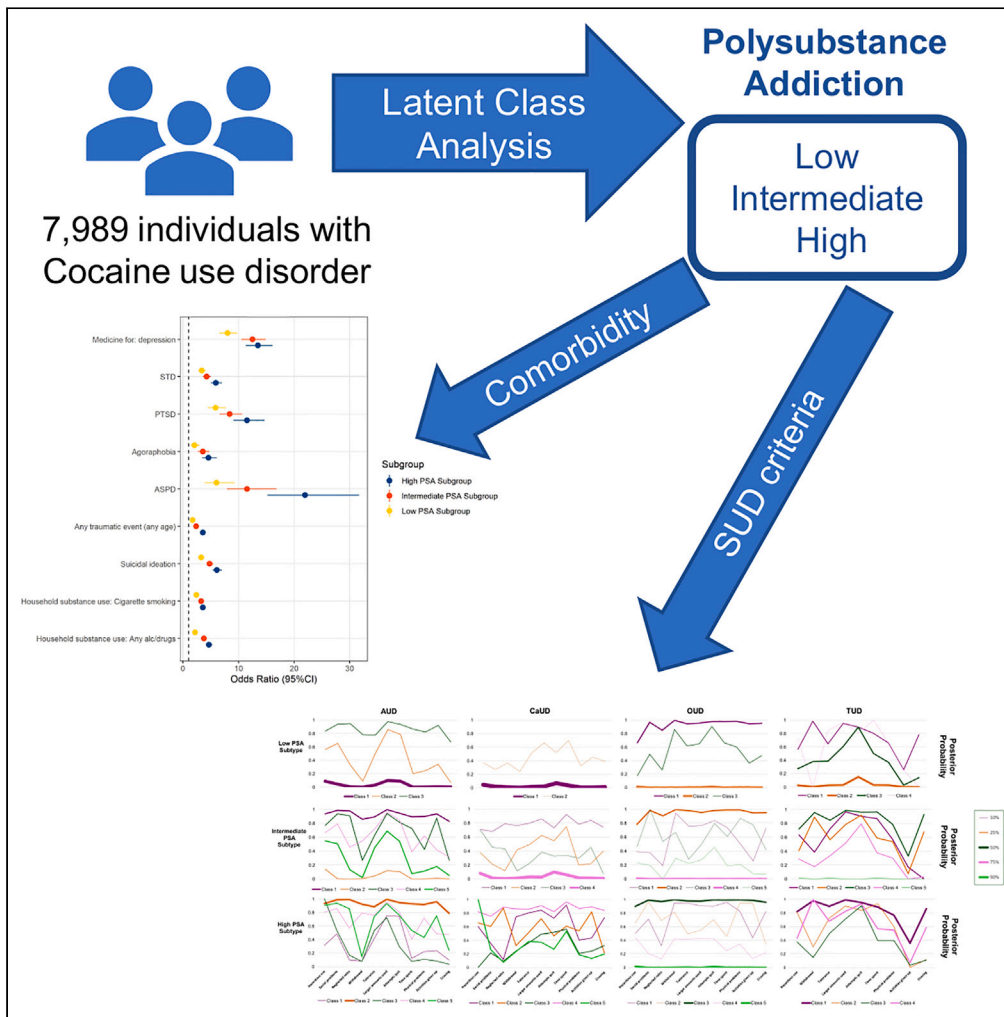


Article

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Highlights

Latent class analysis was conducted in 7,989 people with cocaine use disorder (CoUD)

Three CoUD subgroups were identified with varying levels of polysubstance addiction

These CoUD subgroups were differentially associated with a range of comorbidities

The findings are informative to modeling polysubstance addiction in studies of CoUD

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Article

Polysubstance addiction patterns among 7,989 individuals with cocaine use disorder

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SUMMARY

To characterize polysubstance addiction (PSA) patterns of cocaine use disorder (CoUD), we performed a latent class analysis (LCA) in 7,989 participants with a lifetime DSM-5 diagnosis of CoUD. This analysis identified three PSA subgroups among CoUD participants (i.e., low, 17%; intermediate, 38%; high, 45%). While these subgroups varied by age, sex, and racial-ethnic distribution ($p < 0.001$), there was no difference with respect to education or income ($p > 0.05$). After accounting for sex, age, and race-ethnicity, the CoUD subgroup with high PSA had higher odds of antisocial personality disorder (OR = 21.96 vs. 6.39, difference- $p = 8.08 \times 10^{-6}$), agoraphobia (OR = 4.58 vs. 2.05, difference- $p = 7.04 \times 10^{-4}$), mixed bipolar episode (OR = 10.36 vs. 2.61, difference- $p = 7.04 \times 10^{-4}$), posttraumatic stress disorder (OR = 11.54 vs. 5.86, difference- $p = 2.67 \times 10^{-4}$), antidepressant medication use (OR = 13.49 vs. 8.02, difference- $p = 1.42 \times 10^{-4}$), and sexually transmitted diseases (OR = 5.92 vs. 3.38, difference- $p = 1.81 \times 10^{-5}$) than the low-PSA CoUD subgroup. These findings underscore the importance of modeling PSA severity and comorbidities when examining the clinical, molecular, and neuroimaging correlates of CoUD.

INTRODUCTION

Substance use disorders (SUDs) represent heterogeneous patterns of behavioral, cognitive, and physiological features associated with the chronic use of a substance, despite problems that arise from its use.¹ Among SUDs, cocaine use disorder (CoUD) contributes to significant morbidity, mortality, personal, and healthcare expense, posing a considerable public health problem.² In 2019, nearly 5.5 million people in the United States reported using cocaine in the past year and 1 million met criteria for CoUD.³

Polysubstance use and addiction are defined as the consumption and abuse of more than one substance over a short period of time or concurrently.⁴ These are both common and associated with adverse consequences.⁵ People who use and abuse multiple substances have worse treatment outcomes,^{6,7} higher risk of mortality compared to people that use one substance,⁸ and are statistically more likely to experience an overdose, violence, and accidental injuries than those that use one substance.⁹ With respect to the risk of polysubstance use among cocaine users, 72.7% of cocaine-involved deaths registered in 2017 involved opioids.¹⁰

Modeling patterns of polysubstance addiction (PSA) among substance users can help to define high-risk groups within diagnostic boundaries. Latent class analysis (LCA) is a statistical method that can be used to identify groups of people (referred to as classes) based on similar patterns of manifest response variables.¹¹ This allows one to identify more homogeneous groups within a heterogeneous population.¹² Studies have used LCA within samples of people who use substances or received a SUD diagnosis to evaluate patterns of association with comorbid SUDs and clinically relevant variables.^{13,14} Previous studies examined nationally representative samples^{15,16} and treatment-seeking populations.^{17–19} However, these types of study designs feature limited sample sizes for low-prevalence SUDs such as CoUD.

Latent variable modeling approaches have also been used to identify classes of people with certain patterns of symptoms. The approach has been used in posttraumatic stress disorder (PTSD)^{20,21} and individuals reporting manic episodes.²² These studies revealed that different latent symptom typologies are

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differentially related to meaningful clinical and neurobiological markers. However, in SUDs, these approaches focused mainly on alcohol^{23,24} and cannabis use disorders.^{25–27} Addiction studies employing latent variable modeling approaches to characterize PSA mostly used measures of quantity, frequency, and duration of use for multiple substances;²⁸ several others used SUD diagnoses as indicator variables, as we did in the present study.^{29,30} To our knowledge, no studies assessed PSA patterns in individuals with CoUD. However, previous research has identified latent classes of cocaine dependence based on other approaches.^{31,32}

Using data from the large Yale-Penn cohort, we investigated PSA latent classes in 7,989 participants with lifetime DSM-5 CoUD diagnoses. Within these latent classes of CoUD, we also characterized symptom profiles and tested their associations with clinically meaningful mental and physical health variables. Our results show that clusters of CoUD-affected individuals have different patterns of PSA and of psychiatric and somatic comorbidities. These findings have important implications for modeling CoUD heterogeneity in studies of addiction-ascertained cohorts (e.g., molecular, brain imaging, and treatment investigations).

RESULTS

Sample characteristics

Among 7,989 Yale-Penn participants with a lifetime diagnosis of CoUD, 39% were female, and the average age was 41 years (ranging from 18 to 76 years old, standard deviation = 9.6 years). The sample included mostly African Americans (47%) and European Americans (36%). With respect to comorbid SUDs, 82% met criteria for alcohol use disorder (AUD), 57% for cannabis use disorder (CaUD), 49% for opioid use disorder (OUD), and 86% for tobacco use disorder.³³ Unfortunately, the sample size available for other substances in Yale-Penn cohort was too small to be included in the analyses performed in the present study (Table S1). With regard to household substance use, 51% reported being aware of at least one adult in their household using any drugs or alcohol before the participant was 13 years of age. Participants with CoUD had household members who used cocaine (9%), heroin (5%), abused prescription drugs (4%), or used other illegal drugs (16%), and 47% and 65% were aware of household members who drank alcohol or smoked cigarettes, respectively. Table 1 summarizes the sample characteristics.

Diagnosis-based latent class analysis

Our initial LCA of CoUD-affected individuals was based on diagnoses of AUD, CaUD, OUD, and TUD. With only four dichotomous variables, we could identify only a two-class model.³⁴ Considering a posterior probability ≥ 0.70 , we assigned 1,367 individuals (17%) to Class-1 and 3,616 individuals (45%) to Class-2. No participant had a posterior probability greater than 0.7 for both classes. Conversely, the remaining 38% of the CoUD sample ($n = 3,006$) had a posterior probability < 0.7 with respect to both diagnosis-based latent classes. We assigned these participants to a separate subgroup. Based on these results and the prevalence of other SUDs in these three groups (Table 1), we defined three CoUD subgroups: a low-PSA subgroup (i.e., diagnosis-based Class-1), an intermediate-PSA subgroup (i.e., the group of participants with posterior probabilities < 0.7 for both diagnosis-based classes), and a high-PSA subgroup (i.e., diagnosis-based Class-2). Relative to the overall CoUD sample, the low-PSA subgroup was older (42.5 vs. 40.7 years of age, $p < 0.0001$), had a higher proportion of females (52% vs. 39%, $p < 0.0001$) and non-Hispanic African Americans (56% vs. 47%, $p < 0.0001$), and a smaller proportion of non-Hispanic European Americans (26% vs. 36%, $p < 0.001$). An opposite pattern was present for the high-PSA subgroup, which was slightly younger (39.2 vs. 40.7 years of age, $p < 0.0001$), had a smaller proportion of females (30% vs. 39%, $p < 0.0001$) and non-Hispanic African Americans (41% vs. 47%, $p < 0.0001$), and a larger proportion of non-Hispanic European Americans (42% vs. 36%, $p < 0.0001$) than the overall CoUD sample. The intermediate-PSA subgroup showed characteristics intermediate between the two other subgroups and more similar to the overall CoUD sample. No differences were observed between the CoUD subgroups and the overall CoUD sample on education or income ($p > 0.05$).

The distribution of SUD diagnoses for the low-PSA subgroup had lower prevalence of SUD diagnoses than the overall CoUD sample: 30% vs. 82% for AUD ($p < 0.0001$), 6% vs. 57% for CaUD ($p < 0.0001$), 41% vs. 49% for OUD ($p < 0.0001$), and 50% vs. 80% for TUD ($p < 0.0001$). Conversely, the high-PSA subgroup included higher rates of SUD comorbidity, with 100% of individuals meeting criteria for AUD ($p < 0.0001$), CaUD ($p < 0.0001$), and TUD ($p < 0.0001$). The intermediate-PSA subgroup showed a similar distribution of AUD (84% vs. 82%, $p < 0.05$), OUD (46% vs. 49%, $p < 0.05$), and TUD (87% vs. 86%, $p > 0.05$), but a much lower proportion of CaUD cases (29% vs. 57%, $p < 0.0001$) than the overall CoUD sample. Figure S1 shows

Table 1. Characteristics of the full CoUD sample and diagnosis-based LCA subgroups based on AUD, CaUD, OUD, and TUD diagnoses

	Full CoUD sample (n = 7,989)	Low-PSA (n = 1,367)	Intermediate-PSA (n = 3,006)	High-PSA (n = 3,616)
Age-years, median (IQR)	41 (35–47)	42 (37–48)	42 (36–48)	40 (32–46)
Sex, n (%)				
Male	4879 (61)	652 (48)	1685 (56)	2542 (70)
Female	3110 (39)	715 (52)	1321 (44)	1074 (30)
Race/Ethnicity, n (%)				
African American, not Hispanic	3754 (47)	768 (56)	1488 (50)	1498 (41)
European American, not Hispanic	2905 (36)	360 (26)	1032 (34)	1513 (42)
African American, Hispanic	212 (3)	41 (3)	65 (2)	106 (3)
European American, Hispanic	504 (6)	82 (6)	182 (6)	240 (7)
Native American	60 (1)	18 (1)	18 (1)	24 (1)
Asian	12 (0)	2 (0)	5 (0)	5 (0)
Pacific Islander	7 (0)	0 (0)	5 (0)	2 (0)
Socioeconomic factors, n (%)				
Highest education completed ^a , median (IQR)	5 (4–6)	5 (4–6)	5 (3–6)	5 (4–6)
High school diploma	2183 (27)	401 (29)	814 (27)	968 (27)
General Educational Development (GED)	1508 (19)	179 (13)	518 (17)	811 (22)
Currently in school	528 (7)	95 (7)	176 (6)	257 (7)
Employed past year	4957 (62)	768 (56)	1792 (60)	2397 (66)
Employed currently	2260 (28)	367 (27)	869 (29)	1024 (28)
Working full-time	1151 (14)	182 (13)	438 (15)	531 (15)
Household gross income ^b , median (IQR)	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)
Substance use disorders, n (%)				
AUD	6561 (82)	413 (30)	2532 (84)	3616 (100)
CaUD	4581 (57)	88 (6)	877 (29)	3616 (100)
OUD	3909 (49)	560 (41)	1395 (46)	1954 (54)
TUD	6903 (86)	684 (50)	2603 (87)	3616 (100)
Comorbid substance use disorders, n (%)				
0	116 (1)	116 (8)	0 (0)	0 (0)
1	757 (9)	757 (55)	0 (0)	0 (0)
2	2105 (26)	494 (36)	1611 (54)	0 (0)
3	3057 (38)	0 (0)	1395 (46)	1662 (46)
4	1954 (24)	0 (0)	0 (0)	1954 (54)
Household substance use, n (%)				
Any alcohol/drugs	4109 (51)	522 (38)	1531 (51)	2056 (57)
Alcohol use	3736 (47)	460 (34)	1374 (46)	1902 (53)
Cocaine use	686 (9)	64 (5)	229 (8)	393 (11)
Heroin use	379 (5)	53 (4)	128 (4)	198 (5)
Other illegal drugs	1313 (16)	110 (8)	423 (14)	780 (22)
Prescription drug abuse	325 (4)	29 (2)	102 (3)	194 (5)
Cigarette smoking	5197 (65)	775 (57)	1956 (65)	2466 (68)
Suicidal thoughts and behaviors, n (%)				
Suicidal ideation	3391 (42)	460 (34)	1238 (41)	1693 (47)

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Table 1. Continued

	Full CoUD sample (n = 7,989)	Low-PSA (n = 1,367)	Intermediate-PSA (n = 3,006)	High-PSA (n = 3,616)
Suicide plan	1525 (19)	197 (14)	579 (19)	749 (21)
Suicide attempt	1333 (17)	187 (14)	527 (18)	619 (17)
Childhood trauma, n (%)				
Any traumatic event (any age)	5519 (69)	819 (6)	1994 (66)	2706 (75)
Witnessed violence	1543 (19)	221 (16)	527 (18)	795 (22)
Witnessed violence (2+)	920 (12)	137 (10)	285 (9)	498 (14)
Victim of violence	514 (6)	80 (6)	182 (6)	252 (7)
Abused sexually	1257 (16)	192 (14)	483 (16)	582 (16)
Abused physically	786 (10)	91 (7)	295 (10)	400 (11)
Psychopathology, n (%)				
ADHD	653 (8)	50 (4)	225 (7)	378 (10)
ASPD	1314 (16)	89 (7)	383 (13)	842 (23)
Conduct disorder	260 (3)	31 (2)	85 (3)	144 (4)
Gambling disorder	869 (11)	88 (6)	272 (9)	509 (14)
Agoraphobia, no Panic disorder	251 (3)	29 (2)	89 (3)	133 (4)
Agoraphobia	511 (6)	54 (4)	189 (6)	268 (7)
Bipolar I	393 (5)	34 (2)	134 (4)	225 (6)
MDE 1	944 (12)	155 (11)	362 (12)	427 (12)
MDE 2	612 (8)	75 (5)	230 (8)	307 (8)
MDD	1157 (14)	184 (13)	445 (15)	528 (15)
MDE	1355 (17)	187 (14)	210 (17)	648 (18)
Mixed episode	338 (4)	22 (2)	110 (4)	206 (6)
OCD	250 (3)	28 (2)	89 (3)	133 (4)
Panic disorder	548 (7)	66 (5)	211 (7)	271 (7)
PTSD	1397 (17)	186 (14)	511 (17)	700 (19)
Social phobia	446 (6)	44 (3)	157 (5)	245 (7)
Social phobia generalized	356 (4)	33 (2)	129 (4)	194 (5)
Medical history/Physical health, n (%)				
Rating of physical health ^c , median (IQR)	3 (2–4)	3 (2–4)	3 (2–4)	3 (2–4)
High blood pressure	2228 (28)	387 (28)	892 (30)	949 (26)
Migraine headaches	1272 (16)	215 (16)	483 (16)	574 (16)
Brain injury	1221 (15)	147 (11)	437 (15)	637 (18)
Unconscious >5 min	1370 (17)	182 (13)	490 (16)	698 (19)
Epilepsy	559 (7)	90 (7)	205 (7)	264 (7)
Meningitis/Encephalitis	127 (2)	22 (2)	56 (2)	49 (1)
Stroke	168 (2)	35 (3)	66 (2)	67 (2)
Heart disease	355 (4)	69 (5)	150 (5)	136 (4)
Liver disease	1543 (19)	216 (16)	623 (21)	704 (19)
Thyroid	249 (3)	54 (4)	107 (4)	88 (2)
Asthma	1746 (22)	286 (21)	670 (22)	790 (22)
Diabetes	604 (8)	102 (7)	251 (8)	251 (7)
Cancer	248 (3)	46 (3)	103 (3)	99 (3)
HIV/AIDS	557 (7)	115 (8)	233 (8)	209 (6)

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Table 1. Continued

	Full CoUD sample (n = 7,989)	Low-PSA (n = 1,367)	Intermediate-PSA (n = 3,006)	High-PSA (n = 3,616)
STD	2121 (27)	329 (24)	793 (26)	999 (28)
Medicine for: nervousness	2311 (29)	317 (23)	902 (30)	1092 (30)
Medicine for: sleep	2647 (33)	271 (27)	1020 (34)	1256 (35)
Medicine for: depression	2988 (37)	420 (31)	1166 (39)	1402 (39)
Medicine for: headaches	732 (9)	112 (8)	285 (9)	335 (9)
Medicine for: energy	220 (3)	33 (2)	80 (3)	107 (3)
Medicine containing steroids	982 (12)	160 (12)	389 (13)	433 (12)

CoUD, Cocaine use disorder; PSA, Polysubstance addiction; LCA, Latent class analysis; AUD, Alcohol use disorder; CaUD, Cannabis use disorder; OUD, Opioid use disorder; TUD, Tobacco use disorder; ADHD, Attention-deficit/hyperactivity disorder; ASPD, Antisocial personality disorder; MDE 1, One major depressive episode; MDE 2, Second major depressive episode; MDD, Major depressive disorder; MDE, Major depressive episode; OCD, Obsessive-compulsive disorder; PTSD, Posttraumatic stress disorder; STD, Sexually transmitted disease.

^aHighest education completed: variable ranging from 1 to 8, where 1 = "grade 2–8 completed"; 2 = "grade 9 completed"; 3 = "grade 10 completed"; 4 = "grade 11 completed"; 5 = "grade 12 completed"; 6 = "technical school or 1–3 years of college"; 7 = "BA, BSc"; 8 = "MA, MS, JD, MD, PhD".

^bHousehold income: 1. \$0–\$9,999/year; 2. \$10,000–\$39,999/year; 3. \$40,000–\$150,000 or more/year.

^cRating of physical health: 1. poor; 2. fair; 3. good; 4. very good; 5. excellent.

the counts of comorbid substance use disorders in the three subgroups, while [Table S2](#) reports the SUD distribution in African Americans and European Americans across the overall CoUD sample and three CoUD subgroups.

Criteria-based latent class analysis

To further investigate PSA patterns within each of the CoUD subgroups ([Table 1](#)), we conducted additional LCAs using DSM-5 diagnostic criteria for AUD, CaUD, OUD, and TUD. The number of diagnostic-criteria latent classes in each of the SUDs considered was defined based on Akaike information criterion, Bayesian information criterion, bootstrap likelihood ratio test, and entropy statistics ([Tables S3 to S5](#)). [Figure 1](#) summarizes the number of diagnostic-criteria latent classes, their posterior probabilities, and predicted class membership across the three CoUD subgroups. Considering the number of diagnostic-criteria latent classes, the low-PSA subgroup showed the best fit to the data with two diagnostic-criteria latent classes for CaUD, three for AUD and OUD, and four for TUD. Conversely, four or five diagnostic-criteria latent classes across the SUDs considered were the best fits for the intermediate- and high-PSA subgroups.

Considering the posterior probabilities and the predicted class memberships of the diagnostic-criteria latent classes, we observed unique PSA patterns across the CoUD subgroups. Specifically, most individuals included in the low-PSA subgroup were assigned to latent classes with <20% posterior probability of diagnostic criteria for AUD (predicted class membership = 73%), CaUD (predicted class membership = 95%), and TUD (predicted class membership = 50%). Conversely, the high-PSA subgroup showed 44% predicted class membership for a latent class with >78% posterior probability across AUD diagnostic criteria and 43% predicted class membership for a latent class with >76% posterior probability across TUD diagnostic criteria with the exception of the TUD criterion "Important activities are reduced or given up because of use." With respect to CaUD, the high-PSA subgroup showed diagnostic-criteria latent classes (predicted class membership ranging from 16% to 25%) with different patterns of posterior probabilities. Participants in the intermediate-PSA subgroup were evenly distributed across diagnostic-criteria latent classes with different patterns of posterior probabilities for AUD and TUD. Conversely, 75% of this subgroup was predicted to be assigned to a latent class with <10% posterior probability of CaUD diagnostic criteria. Interestingly, there was a similar finding with respect to OUD diagnostic criteria across the three CoUD subgroups. Specifically, two diagnostic-criteria latent classes were predicted to include >70% of the individuals (split almost evenly) with one having >65% posterior probability for OUD criteria and the other having <5% posterior probability for OUD criteria.

With respect to the individual CoUD diagnostic criteria, the most pronounced difference between low- and high-PSA subgroups was for "Repeated substance use in situations where it is physically hazardous" (40%

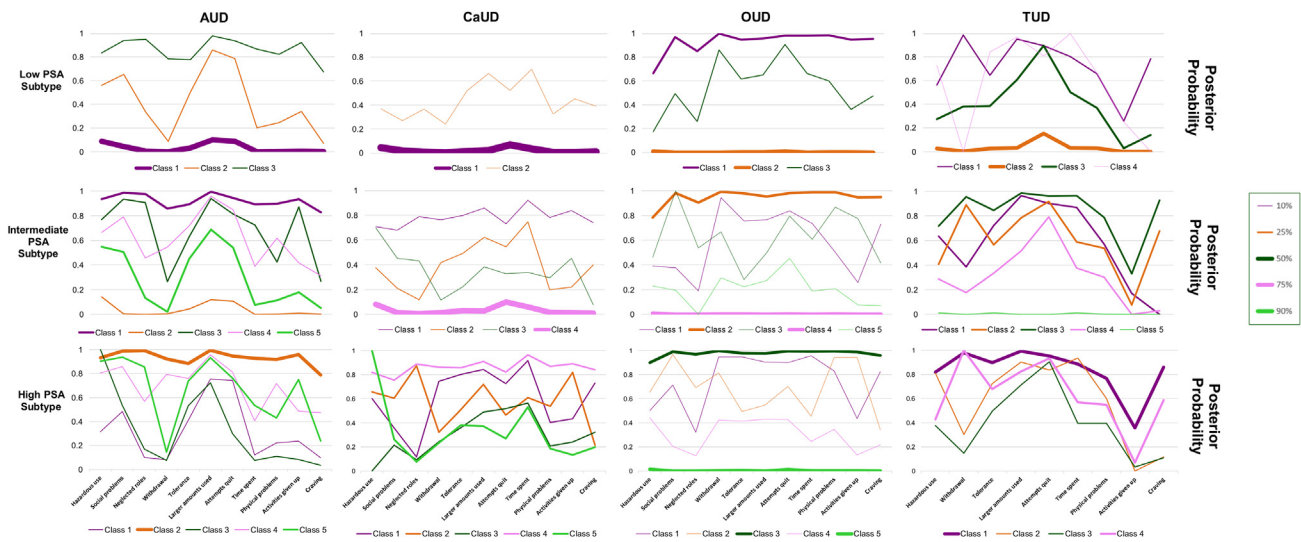


Figure 1. Patterns of the posterior probabilities of the criteria-based latent classes across CoUD subgroups

The posterior probabilities of the best-fit latent class models identified for AUD, CaUD, OUD, and TUD criteria with respect to the three CoUD subgroups. Line thickness corresponds to the proportion of the diagnosis-based subgroup that was stratified to a particular criteria-based class.

vs. 70%) while the least pronounced was for “Persistent desire/unsuccessful efforts to stop using” (93% vs. 94%). The percent difference between these two subgroups ranged from 17% to 9% for the other CoUD diagnostic criteria (Table S6). Considering the overall criterion count, 59% of the individuals in the high-PSA subgroup met ten or more CoUD criteria while this was observed in only 34% of the low-PSA subgroup (Table S7). The frequency distribution of the CoUD diagnostic criteria in the intermediate-PSA subgroup was similar to that observed in the overall sample (Tables S6 and S7).

Psychiatric and somatic associations of CoUD subgroups

The analyses above demonstrated that the diagnosis-based subgroups of Yale-Penn participants with CoUD are linked to different PSA patterns. To understand their associations with psychopathology, suicidality, traumatic experiences, household substance use, medical conditions, and socioeconomic status (SES), we tested the three CoUD subgroups with respect to 2,952 Yale-Penn participants who did not meet criteria for any of the 5 SUDs of interest. After accounting for age, sex, and race-ethnicity and applying Bonferroni-correction for multiple testing (corrected p value threshold $<7.94 \times 10^{-4}$), we observed that many of the CoUD subgroups were associated with more severe adversity and comorbidities than the control group, with significant effects observed within each of the domains tested (Table S8).

When comparing the associated effect sizes between the subgroups, no difference was observed with respect to the SES-related variables (difference- $p > 0.05$), but all other categories included at least one trait with Bonferroni-corrected differences in the effects detected comparing the three CoUD subgroups to controls (Figure 2). The low-PSA subgroup had lower odds to report household use of any substance (OR = 2.18, 95% confidence interval (CI) = 1.87–2.53) compared with either the intermediate-PSA subgroup (OR = 3.76, 95%CI = 3.33–4.23; difference- $p = 2.64 \times 10^{-8}$) or the high-PSA subgroup (OR = 4.66, 95%CI = 4.13–5.25; difference- $p = 1.09 \times 10^{-14}$). A significant difference between the low- and high-PSA subgroups was also present for household cigarette smoking (OR = 2.38 vs. 3.58, difference- $p = 8.2 \times 10^{-5}$). The three CoUD subgroups were associated with increased odds of household use of cocaine when growing up, but there was no difference in the strength of the associations (difference- $p > 0.05$). With respect to psychopathology, the high-PSA subgroup was associated with higher odds of antisocial personality disorder (ASPD, OR = 21.96 vs. 6.03, difference- $p = 8.08 \times 10^{-6}$), agoraphobia (OR = 4.58 vs. 2.05, difference- $p = 7.04 \times 10^{-4}$), and PTSD (OR = 11.54 vs. 5.86, difference- $p = 2.67 \times 10^{-4}$) than the low-PSA subgroup. Significant-corrected differences in effect size were also observed among the three CoUD subgroups in relation to experiencing or witnessing a major traumatic event, where the effect size was largest for the high-PSA subgroup (OR = 11.54, 95%CI = 9.07–14.68), and progressively smaller for the intermediate-PSA subgroup (OR = 8.38, 95%CI = 6.60–10.65) and low-PSA subgroup (OR = 5.86, 95%CI = 4.46–7.71; low-PSA vs. high-PSA

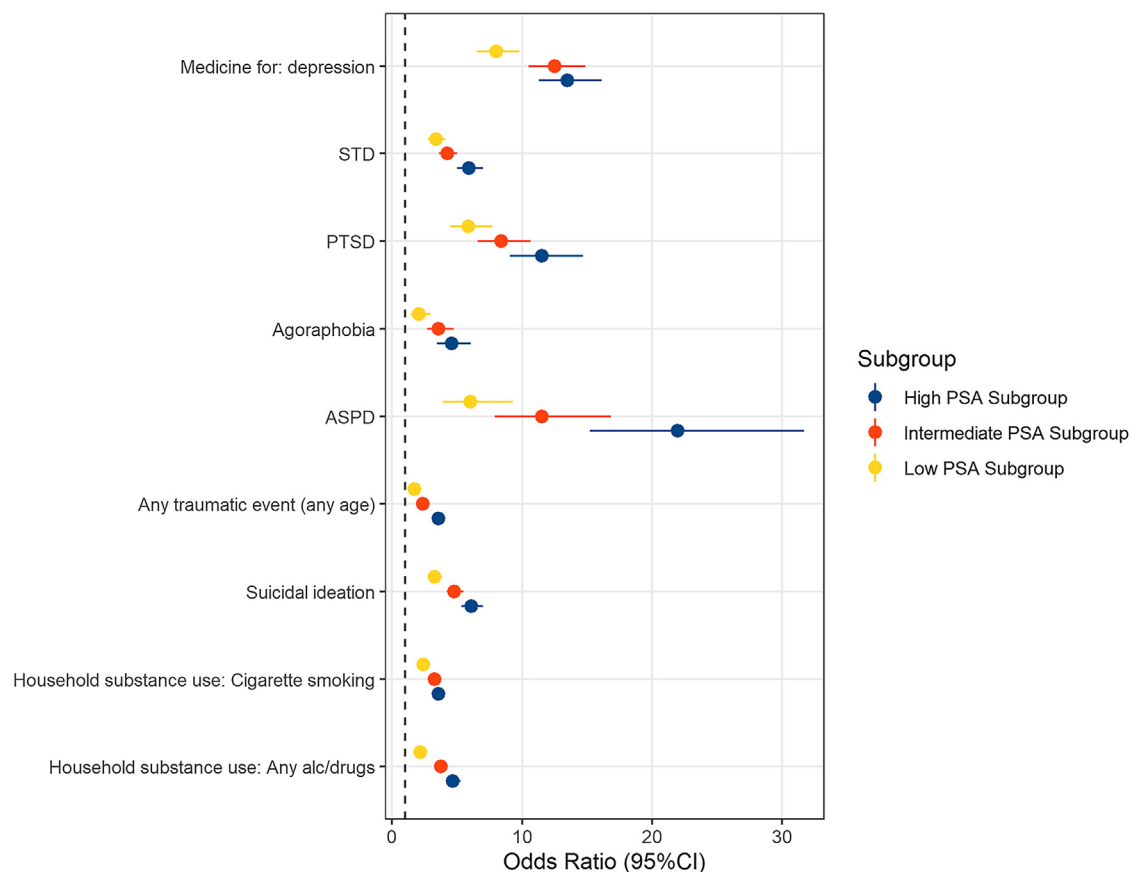


Figure 2. Traits with statistically significant differences across CoUD subgroups in the association strength observed when compared to the control group

Odds ratios and 95% confidence intervals (95%CI) are shown. STD: Sexually transmitted disease, PTSD: posttraumatic stress disorder, ASPD: antisocial personality disorder, PSA: Polysubstance addiction.

difference- $p = 8.5 \times 10^{-16}$; low-PSA vs. intermediate-PSA difference- $p = 3.28 \times 10^{-4}$; high-PSA vs. intermediate-PSA difference- $p = 4.41 \times 10^{-7}$). Differences were also present in the strength of the associations of the three CoUD subgroups with suicide ideation (high-PSA OR = 6.1 vs. low-PSA OR = 3.27, difference- $p = 5.43 \times 10^{-9}$; low-PSA OR = 3.27 vs. intermediate-PSA OR = 4.79, difference- $p = 3.29 \times 10^{-4}$). Considering medical history, when compared to controls, the high-PSA subgroup was associated with increased odds of being diagnosed with sexually transmitted diseases (STD; OR = 5.92 vs. 3.38, difference- $p = 1.81 \times 10^{-5}$) and taking depression medication (OR = 13.49 vs. 8.02, difference- $p = 1.42 \times 10^{-4}$) than the low-PSA subgroup.

DISCUSSION

To date, most molecular and brain imaging studies investigated CoUD-affected individuals as a singular entity, in comparison with control samples or groups of participants affected by other substance use or psychiatric disorders.^{35,36} Due to the low prevalence of CoUD in the general population, few investigations of nationally representative cohorts examined differences among individuals with CoUD.³⁷ Clinically ascertained CoUD cohorts provide a larger proportion of individuals with the disorder and offer opportunities for more in-depth clinical and phenotypic characterization. As mentioned, molecular and brain imaging studies of CoUD have mostly investigated differences between this group and controls or individuals with other psychiatric conditions.^{35,36} Understanding CoUD heterogeneity in the context of PSA and commonly comorbid psychiatric and somatic comorbidities may help inform the development of more precise treatments for this population. We investigated the phenotypic diversity of 7,989 individuals with a lifetime CoUD diagnosis recruited in the Yale-Penn cohort. Leveraging this large, deeply phenotyped sample, we found that CoUD is characterized by latent typologies of individuals with different profiles of psychiatric

and somatic comorbidities. Although the Yale-Penn cohort was ascertained based on the presence of addictive disorders and is not representative of the general population, our results highlight how CoUD heterogeneity could affect molecular, brain imaging, and treatment studies of addiction-ascertained samples.

Our initial LCA based on DSM-5 SUD diagnoses (i.e., AUD, CaUD, OUD, and TUD) distinguished three CoUD subgroups: low PSA (17%), intermediate PSA (38%), and high PSA (45%). In line with sex differences present among individuals with SUDs from epidemiologic studies,³⁸ most of the individuals included in the high-PSA subgroup were males. With respect to race/ethnicity, the low-PSA subgroup had a higher percentage of non-Hispanic European Americans while the high-PSA subgroup included more non-Hispanic African Americans than the overall CoUD sample. This trend parallels those reported by the National Epidemiologic Survey on Alcohol and Related Conditions-III (NESARC-III), which similarly found that non-European Americans were the majority among cocaine-only users and European Americans were the majority among cocaine-cannabis users.³⁹ As shown in a comparison between the 2001–2002 NESARC and 2012–2013 NESARC-III, there are racial-ethnic differences among cocaine users and CoUD-affected individuals.⁴⁰ Although ethnic and racial differences in CoUD are likely affected by disparities in income, education, unemployment, and discrimination,^{40,41} the relationship between cocaine addiction and SES also appears to be affected by temporal trends. Indeed, although in the 1980s cocaine use was more prevalent among highly educated individuals, during the 1990s it became more prevalent among less educated individuals and in the 2000s it increased among higher education subgroups, but not in the lowest.⁴⁰ We found no major differences among CoUD subgroups with respect to income or education. This indicates that in the Yale-Penn cohort, the differences among CoUD subgroups may be influenced by cultural factors related to sex and racial-ethnic differences rather than economic differences and education.

While the general patterns observed in the LCA based on SUD diagnoses were confirmed by the LCA based on SUD diagnostic criteria (i.e., the low-PSA subgroup corresponds to CoUD with low probability of other SUD diagnostic criteria; the intermediate-PSA subgroup corresponds to intermediate probability of other SUD diagnostic criteria; the high-PSA subgroup corresponds to CoUD with high probability of other SUD diagnostic criteria), we also observed some substance-specific patterns in the criterion-based LCA. For example, most participants included in the low- and intermediate-PSA subgroups were characterized by a very low posterior probability (<10%) of CaUD diagnostic criteria. Another notable substance-specific pattern was seen with OUD diagnostic criteria, where in all CoUD subgroups participants were mostly split between a class with high posterior probabilities and a class with low posterior probabilities. Most previous studies investigating PSA in CoUD have focused on the frequency or severity of substance use.^{42,43} These analyses may not have as great resolution as the analyses we performed using SUD diagnostic criteria. In the NESARC cohort, cocaine-opioid users represent about one-third of cocaine users.⁴⁴ This may, at least in part, explain why a consistent number of Yale-Penn participants with low posterior probabilities of OUD diagnostic criteria were included in the CoUD subgroup with high PSA. With respect to CoUD severity, the majority of CoUD individuals with high PSA met ten or more CoUD criteria. This is in line with evidence from NESARC-III analyses where “very high quantity use” and “daily use” of cocaine were associated with polysubstance use.²⁸ Additionally, NESARC-III analyses focused on quantity, frequency, and duration of cocaine use and identified three cocaine use patterns,⁴⁵ which appear to overlap with the CoUD subgroups we observed in the Yale-Penn cohort.

In line with the well-known association of CoUD with mental and physical health,⁴⁶ the three CoUD subgroups identified in our study were all associated with increased suicidal behaviors, traumatic experience, psychopathology, and somatic comorbidities relative to controls (i.e., individuals without any SUDs). However, we additionally observed several traits where the strength of the associations was statistically different among the three CoUD subgroups. With respect to household substance use, individuals in the low-PSA subgroup demonstrated smaller magnitude associations with alcohol and any drug use in the household they grew up in (compared with the intermediate- and high-PSA subgroups), cigarette smoking (compared with the high-PSA subgroup), and other illegal drugs (compared with the high-PSA subgroup). Of note, the strength of the association with household use of cocaine and heroin did not differ across CoUD subgroups. Previous studies showed that a family history of substance use is associated with polysubstance use.^{47–49} Our findings add to this literature and suggest that family use of multiple types of substances may be a risk factor for PSA in CoUD. Another difference among CoUD subgroups was related to suicidal behaviors. While all CoUD subgroups were associated with increased suicidal behaviors (i.e., ideation,

planning, and attempt) relative to controls, suicide ideation showed smaller magnitude associations with the low-PSA subgroup, compared with the other subgroups. The association of suicidal behaviors with cocaine addiction and polysubstance use is well established.^{50–52} However, to our knowledge, the current study is the first to investigate suicidality in the context of PSA among individuals with CoUD. The finding that suicide ideation may be differentially impacted by PSA can be particularly noteworthy with respect to suicide prevention among high-risk individuals, such as those affected by CoUD.

Associations among CoUD, traumatic experiences, and PTSD were previously identified in multiple studies.^{53,54} We found evidence for this association in the Yale-Penn cohort and observed differences in the strength of the associations across CoUD subgroups. Specifically, individuals belonging to the low-PSA subgroup were least strongly associated with having experienced a traumatic event and had the lowest odds of having a PTSD diagnosis. However, there were no differences across CoUD subgroups in their association with different types of traumatic events experiences (e.g., violence, physical abuse, and sexual abuse). With respect to other psychiatric disorders, ASPD showed the strongest associations with the high-PSA subgroup where individuals in this group had a 22-fold increase in the odds of having an ASPD diagnosis in the Yale-Penn cohort. Although low- and intermediate-PSA subgroups were also associated with ASPD, there is a strong difference in ASPD association strength between high- and low-PSA subgroups (ASPD OR = 21.96 vs. 6.03, difference- $p = 8.08 \times 10^{-6}$). This is in line with previous studies in treatment-seeking substance users showing that CoUD and polysubstance use are both associated with ASPD with the latter having a larger effect.^{55,56} Agoraphobia was the other psychiatric comorbidity showing differences across CoUD subgroups. Cocaine use and cocaine dependence have been previously associated with agoraphobia in treatment-seeking individuals and in community surveys.^{57,58} We confirmed this relationship with CoUD in the Yale-Penn cohort, but also observed that CoUD with high PSA is more strongly associated with agoraphobia than CoUD with low PSA. With respect to somatic comorbidities, we observed differences among CoUD subgroups with respect to two health outcomes, STDs and the use of depression medication. There is a vast literature supporting the association of CoUD and PSA with STD risk.^{59–62} In Yale-Penn, the stronger STD association with the high-PSA subgroup than with the low-PSA subgroup is in line with these previous findings. While all CoUD subgroups were associated with traits related to depression (e.g., major depressive disorder and major depressive episodes), there was no statistically significant difference in the strength of the associations. Conversely, depression medication was more strongly associated with the high-PSA subgroup than the low-PSA subgroup. This suggests that more severe CoUD cases such as those affected by high PSA may be more frequently treated with antidepressants, despite available evidence not supporting their efficacy in treating symptoms of CoUD.⁶³ Alternatively, the stronger association between the high-PSA subgroup and antidepressant medication treatment could reflect greater severity or chronicity of major depression or other disorders treated with antidepressants than those in the low- or intermediate-PSA subgroups.

In conclusion, we identified three CoUD subgroups in the Yale-Penn cohort, reflecting different PSA degrees that were associated with different patterns of psychiatric and somatic comorbidities. Although the results may not generalize to general population samples, our findings nevertheless highlight the need for modeling PSA when analyzing CoUD in cohorts ascertained for addiction research such as those investigated in molecular and neuroimaging studies. Further research is needed to assess how these patterns of PSA coincide or differ in a general population. Once validated, patterns of PSA in CoUD could be assessed molecularly and with neuroimaging approaches to develop our understanding of these conditions. The application of LCA approach to PSA may also have clinical implications. Indeed, while PSA can be considered a continuum of behaviors, our study demonstrated that data-driven approaches can be used to assign the probability of a certain individual to be affected by negative outcomes associated with PSA. This approach may be useful to define population groups at high risk of PSA-related negative health outcomes.

Limitations of the study

Although our study contributes to the characterization of CoUD heterogeneity in a large sample, we acknowledge five main limitations. First, Yale-Penn participants were recruited for addiction genetic studies for more than 20 years. Accordingly, the associations observed may not reflect those present in the general population. As discussed previously, they may be also affected by the temporal changes in cocaine use that occurred during this time span. Second, we used the Semi-Structured Assessment for Drug Dependence and Alcoholism (SSADDA), which was designed to obtain DSM-IV diagnoses. To investigate addiction in the context of DSM-5, we derived DSM-5 SUD diagnoses from additional information collected with the SSADDA. While all DSM-5 diagnostic criteria were adequately mapped for most

SUDs, two TUD criteria (i.e., social problems and neglected roles) were not available in the SSADDA. This may have affected our ability to investigate TUD comorbidity in the context of CoUD. Third, although the SSADDA is a previously validated diagnostic instrument,^{64,65} the information collected may have been impacted by self-report bias.⁶⁶ Fourth, the majority of the sample investigated had yearly household incomes below \$40,000. This may have limited our ability to investigate the impact of socioeconomic factors on PSA of individuals affected by CoUD. Fifth, the Yale-Penn cohort did not recruit participants less than 18 years of age. Accordingly, further studies will be needed to investigate PSA patterns in adolescents.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

Supplemental information can be found online at <https://doi.org/10.1016/j.isci.2023.107336>.

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AUTHOR CONTRIBUTIONS

B.S. and R.P. conceived of the study and wrote the paper. B.S. performed the analyses. R.H.P. helped design the analyses. Y.Z.N. and A.K. supported the analyses. R.H.P., D.S.T., Y.Z.N., A.K., H.R.K., and J.G. contributed to paper improvement. R.P. oversaw and supervised the study.

DECLARATION OF INTERESTS

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INCLUSION AND DIVERSITY

We support inclusive, diverse, and equitable conduct of research.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
Phenotype data from the Yale-Penn cohort of substance dependence	dbGaP repository	phs000952.v1.p1
Phenotype data from the Yale-Penn cohort of alcohol dependence	dbGaP repository	phs000425.v1.p1
Software and algorithms		
glca (R package)	Kim & Chung, 2020	https://kim0sun.github.io/glca/
poLCA (R package)	Linzer & Lewis, 2011	https://github.com/dlinzer/poLCA
RStudio	RStudio Team, 2022	https://github.com/rstudio/rstudio , RRID:SCR_000432

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Renato Polimanti (renato.polimanti@yale.edu).

Materials availability

This study did not generate new unique reagents.

Data and code availability

- The data from the Yale-Penn cohort are available in dbGaP (<https://www.ncbi.nlm.nih.gov/gap/>) under accession numbers phs000952.v1.p1 and phs000425.v1.p1.
- Additional information regarding the data and the analyses included in the present study can be requested to the [lead contact](#).

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

Participants in this study are from the Yale-Penn cohort, which was recruited to investigate the genetics of substance use disorders and their comorbid conditions.^{67–72} Participants were recruited from five US sites: Yale School of Medicine (APT Foundation, New Haven, CT, USA), University of Connecticut Health Center (Farmington, CT, USA), University of Pennsylvania Perelman School of Medicine (Philadelphia, PA, USA), Medical University of South Carolina (Charleston, SC, USA), and McLean Hospital (Belmont, MA, USA). The descriptive characteristics of the sample used in this study are reported in the Results section, with further demographic details included in [Table 1](#). The studies were approved by the institutional review boards at each site and written informed consent was obtained from each participant. Individuals younger than 18 years of age were not recruited in Yale-Penn cohort.

METHOD DETAILS

Participants were interviewed by trained personnel using the SSADDA. The SSADDA produces lifetime diagnoses of substance use disorders and other mental illnesses.^{64,65} The SSADDA includes items to diagnose substance dependence and abuse for the major substances of abuse, except for tobacco, for which there is no abuse diagnosis. In the present study, we derived lifetime DSM-5 diagnoses of SUD for alcohol, cannabis, cocaine, opioid, and tobacco. However, for DSM-5 tobacco use disorder, there are only 9 criteria available in the SSADDA. Additionally, we extracted from the SSADDA information regarding several psychiatric and behavioral traits. These included phenotypes relate to suicidality, household substance use, traumatic experiences, and psychopathology. Data related to SES and physical health were also included in the analyses. [Table S9](#) describes the items included and how they were assessed.

QUANTIFICATION AND STATISTICAL ANALYSIS

LCA was first performed including participants with a lifetime CoUD diagnosis ($n = 7,989$) and using lifetime AUD, CaUD, OUD, and TUD as indicator variables. These SUDs were chosen for the analyses due to their prevalence in the Yale-Penn cohort. We assigned participants to the resulting classes if they had posterior probability ≥ 0.7 as previously proposed.^{73,74} Next, within each diagnosis-based latent class, we performed LCAs, in which we analyzed the specific criteria for each SUD separately (alcohol, opioid, cannabis, and tobacco). To determine the best-fitting solution, we fit models beginning with 2 classes and increased the number of classes by one at each step. We selected the best-fitting solution based on model-fit statistics, size of the smallest class, and the interpretability and applicability of the model.⁷⁵ Goodness-of-fit statistics included the BIC and AIC.⁷⁵ For the criteria-based classes, we selected models that produced classes with $\geq 5\%$ of the sample of the diagnosis-based class. This is a common and recommended practice to ensure latent classes are generalizable.⁷⁶ When there was disagreement between these indicators, we selected models with the highest entropy⁷⁷ and most significant BLRT.⁷⁵

Next, we investigated differences between each diagnosis-based latent class and Yale-Penn participants who did not meet criteria for any of the 5 SUDs of interest ($n=2,952$). This analysis was performed using logistic regression models with age, sex, and self-reported race-ethnicity categories as covariates. The dependent variables included traits related to psychopathology, suicidality, traumatic experiences, household substance use, medical conditions, and SES. For variables on which multiple classes differed significantly from controls, we used z-tests to assess differences between the effect size of the associations observed with respect to the classes. All analyses were done in RStudio.^{33,78} The polCA package^{79,80} was used to conduct the LCAs and glca package⁸¹ was used to test for significant differences between LCA models.