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Cannabis use patterns and different phenotypes in relation to other drugs use: latent class analyses from the Sao Paulo Megacity Mental Health Survey

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Abstract

Cannabis is the most widely used substance in Brazil. This study examined subtypes of individuals who use cannabis based on usage characteristics and correlates with other substance consumption and harms.

Data are from the São Paulo Megacity Mental Health Survey (N = 5,037). Latent class analysis (LCA) was performed considering age of onset, use frequency, tobacco consumption, heavy episodic drinking (HED), alcohol use disorder (AUD) and substance use disorder. Logistic regression assessed class correlates, and further analysis compared socio-demographic, health and behavioral indicators.

A 4-class model was optimal for 496 individuals. The 'Polydrug' class (26.2%) and the 'Former' class (5.9%) showed earlier onset and highest frequency of cannabis use, with strongest harm associations. 'Polydrug' class had higher odds of other drug use (OR=3.0), tobacco use (OR=2.5), HED (OR=1.8), and AUD (OR=1.5), compared to lighter-use groups. About 30% of those who use cannabis are at increased risk for negative outcomes, particularly those with early, frequent, and polydrug use patterns.

Brazil's public health should prioritize targeted prevention on the risks associated with early and frequent cannabis, and polydrug use. Addressing this at-risk group is essential for harm reduction and a health-focused approach.

Keywords: Subtypes of individuals who use cannabis, latent class analysis, population-based study, heavy episodic drinking

1. Introduction

Cannabis is one of the most widely used substance globally (1). There has been an discernible increase in its consumption among adolescents and adults, whether used independently or in combination with alcohol, tobacco and other substances (2–4). In recent years, there has been a notable shift in focus towards the public health implications of cannabis use and associated issues. This is particularly evident in the past decade, which has witnessed a series of changes in cannabis policy, leading to a reduction in the perceived risks associated with its use (1,5).

Cannabis is also the most commonly used substance in Brazil (6–9) with a 12-month use prevalence of 2.5% in the general population (8,9), and nearly half of users consuming it on a daily basis (8). While the 12-month prevalence is lower compared to other countries — such as the USA (17.5%) (10), Canada (25%) (11), and European nations like Germany (7.1%), Spain (11.0%), and France (11.0%) (12) — the high frequency of use among Brazilian consumers highlights a distinct pattern that deserves further attention. Furthermore the consumption has increased during the pandemic, while the perception of risk has decreased by 40%, despite the various health consequences (13).

The available epidemiological evidence on the negative consequences of cannabis use on health worldwide undoubtedly demonstrates various effects, including cognitive and coordination impairment (14,15); fatal and non-fatal motor vehicle accidents under the influence of cannabis (16); respiratory impairments (including chronic bronchitis); and worsening or onset of psychosis in predisposed individuals (17,18). In the meantime, a number of key characteristics have been demonstrated to be consistently predictive of adverse outcomes, including early use (e.g. below the age of 16 years) and frequent use (e.g. on a weekly basis or more frequently) or chronic cannabis use (19–22). . The concurrent use of cannabis with alcohol, tobacco and/or other substances during

adolescence has been associated with higher levels of consumption and a greater prevalence of adverse outcomes. These include an increased risk of developing a substance use disorder later in adulthood (23,24) and also acute consequences, such as blackouts and riskier driving and accidents (3,25). The majority of studies examining cannabis use patterns were conducted in other countries, utilizing samples comprising college and high school students and young adults (26–28). These studies have typically identified four classes of individuals who use cannabis primarily distinguished by differences in the frequency of cannabis use and the extent of associated negative consequences. Notwithstanding the relevance of these works, there remains a paucity of understanding with regard to the heterogeneity of adults who use cannabis' patterns, as well as the combined use of cannabis with other substances, particularly in low- and middle-income countries. Fischer et al. (29) provided a typology of people who use cannabis within a nationally representative Canadian population sample. The lighter class (32%) was predominantly composed of occasional users with a reduced quantity of cannabis consumption compared to the past 12 months. They initiated cannabis use at or below the age of 21 and were more prevalent among females and married individuals. The class with the earliest onset and the highest frequency of cannabis use (22.9%) exhibited a greater prevalence of adverse outcomes, including health issues, other substance use, alcohol dependence, cannabis use and related problems, risky driving under the influence, and a higher proportion of unemployed and low-income individuals. Recently, a study conducted with adults identified five latent classes of people who use cannabis, ranging from light, infrequent users with few problems to heavy, frequent users with more problems (30). The present study is primarily concerned with lifetime use of cannabis within a representative Brazilian population sample. To this end, Latent Class Analysis (LCA), a widely used methodological approach (31-34), is employed to profile distinct subtypes of people who use cannabis and associated phenotypes in relation to other drug use, to establish multidimensional group profiles and, subsequently, to investigate behavioural and health-related outcomes. As with alcohol, public health policy should focus on the specific features or contexts of use that are known to predict individual and population-level risk or harm outcomes. These include underage drinking, heavy episodic drinking, alcohol-related violence, and drinking and driving (35). Similarly, the predictors of negative consequences

related to cannabis use should be identified and better communicated, justifying the present research.

In light of the aforementioned considerations, this paper set out to achieve the following objectives: : (a) document distinct groups of individuals who use cannabis based on defined use features in the Brazilian population such as age of onset (AOO) distribution of cannabis use, frequency of cannabis use, use in the past year, tobacco use, heavy episodic drinking, alcohol use disorders, drug use disorders, other drug use; (b) consider sociodemographic correlates (gender, income, employment status, education, social deprivation, parental SUD Problem) for the subtypes of individuals who use cannabis; (c) examine the conditional prevalence of each class according to the WMH Sheehan Severity scale; and (d) examine the public health implications of cannabis use in order to contribute to the ongoing discourse surrounding cannabis use policy and development of targeted interventions for individuals with problematic cannabis use(36).

2. Methods

2.1. Ethics Committee Approval

The procedures for recruitment, obtaining informed consent, and protection of human subjects involved during field procedures of São Paulo Megacity Health Survey were approved by the Research and Ethics Committee of the University of São Paulo Medical School (Project number 792/03).

2.2. Sample

The São Paulo Megacity Mental Health Survey (SPMHS) is a cross-sectional population-based study, designed to evaluate psychiatric morbidity in a representative sample in the general population, aged 18 years or more, living in the São Paulo Metropolitan Area (SPMA). Respondents were selected through a multistage probabilistic process covering the 39 municipalities of SPMA, without replacement. Respondents were assessed using the World Mental Health Study (World Mental Health Survey) Composite International Diagnostic Interview (WMH-CIDI) of the World Health Organization (37), which was translated and adapted to Brazilian Portuguese (38). Data collection occurred between May 2005 and April 2007, by trained interviewers. The final sample assessed was composed of

5,037 individuals, with a response rate of 81.3%. The current analyses were restricted to 496 subjects who used cannabis at least once in their lifetime.

The WMH-CIDI is composed of clinical and non-clinical sections, arranged in two parts, generating diagnoses according to DSM-IV and ICD-10. All respondents received the assessment modules of mood, anxiety, and impulse control disorders, along with substance abuse and suicidal behavior, considered nuclear disorders, as well as a sociodemographic module. Blind clinical reappraisal using the Structured Clinical Interview for DSM-IV Axis I disorder (SCID-I) for last 12-month DSM-IV Disorders in a probabilistic subsample of WMH respondents found generally good agreement between WMH-CIDI diagnoses and SCID diagnoses (39). Preliminary results of the clinical reappraisal study in the SPMHS with a probability subsample of 775 respondents, not included in the previous validation study, showed good total classification accuracy (range: 76%–99%) and an area under the Receiver Operating Characteristics curve around 0.7 for any disorder (data available from the authors).

2.3. Measures

2.3.1. Latent Class Analysis variables

The 496 people who reported lifetime cannabis use were asked a series of questions embedded in the WMH-CIDI (34). In the present study, we tried to include part of the variables used in the latent class model proposed by Fisher et al. (31) for the Canadian population, using the 2004 Canadian Addiction Survey. We also included substance use variables, aiming the investigation of lifetime trajectories of cannabis use. We selected the following variables for the latent class analysis model:

- Age of onset of cannabis use: divided in four categories - up to 15, 16-17, 18-21, 22-25, more than 25 years;
- Lifetime cannabis use (number of days of use in quartiles) - up to 5, 6-230, 231-900, more than 900;
- Past-year cannabis use – yes or no;
- Smoking status - never, former, current;

- Lifetime alcohol use disorders – including DSM-IV alcohol abuse and DSM-IV alcohol dependence;
- Lifetime drug use– including non-medical use of prescription drugs (amphetamines, opioids, tranquilizers) or cocaine or ecstasy or hallucinogens or opioids;
- Past-year heavy episodic drinking – consumption of 5 or more alcohol units in 2 hours for males, or 4 or more doses for females (40;41).

2.3.2. Latent Class Analysis Correlates

The following sociodemographic correlates were considered: gender (female and male); household income, defined in categories (low = up to 7,050 US dollars/year, and high = more than 7,050) based on the respondent's household income per family member divided by the median income-per-family member in the entire sample; employment status (working/student/homemaker/retired, and unemployed/other¹); education (up to 8 – less than high school, and more than 8 years); and parental substance use disorder (SUD) problem. In addition, an index of neighborhood social deprivation (SD) level was developed to reflect social conditions in the São Paulo Metropolitan Area geographical space using data from the 2000 Census (42), which was also investigated as a correlate in the present study. This index represents a combination of socio-economic deprivation dimension (income, level of education, family size, and percentage of families headed by a woman with low educational level) and the population's age structure. The SD index ranges from 1 (no social deprivation) to 8 (high social deprivation). These levels were summarized in two indicators: no/low/medium (1-5), and high/very high NSD (6-8). Unfortunately, we were not able to include both age and marital status variables in the regression models because of lack of convergence.

¹ Other = Non-regular or informal employment.

2.3.3. Latent Classes Indicators

Three variables were used as indicators for the latent classes. First, a composite measure in the WMH-CIDI, named WMH severity (37) assessed internal impairment (where respondents self-evaluate the impairment caused by a given disorder) using questions which focused on the worst lifetime impairment due to a particular disorder, in conjunction with five questions in each diagnostic section that assessed impairment among 12-month cases (four questions from Sheehan Disability Scales). Severe cases were defined as having at least 3 out of 4 of the Sheehan domains (43). Second, a series of yes/no questions inquired about the presence of the following current clinical conditions: accident/injury/intoxication, cardiovascular, neurological, cancer, diabetes, digestive, respiratory, arthritis, chronic pain disorders (chronic back or neck pain and other chronic pain), and headache. The results were aggregated in a categorical variable named 'clinical disease'. Third, service use was assessed by asking respondents if they ever saw any professional (primary care, psychiatrist, other medical specialist, or other health professional) for any health problem, including mental health and/or substance use problems, in the past year.

2.4. Statistical analysis

All analyses were performed with Mplus version 6 (44), using sampling weights and complex survey design measures. Descriptive statistics were used to describe the sample. Specifically, counts and percentages were used to describe categorical variables. Latent class analysis (LCA) was conducted with Mplus version 6.0, using maximum likelihood ratio estimation. The random option in Mplus was applied to ensure convergence for the most successful LCA models. Specifically, 500 sets of random starting values were used in the initial phase, and 10 optimizations were used in the final stage of convergence. This process ensured that the best log-likelihood value for each model was replicated several times. Several statistical indices were used to assess model fit, including log-likelihood (LL), Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC) and sample-size-adjusted BIC (SSABIC). A value of log-likelihood loud together with smaller amounts in AIC, BIC, and SSABIC may reflect a parsimonious model (45). However, the BIC value has been shown to be more reliable than other information (46). The Vuong-Lo-

Mendell-Rubin (VLMR) adjusted likelihood ratio test was used to assess model fit during the LCA. Entropy was also calculated to assess the precision of class assignment in the LCA. Missing data were handled directly within the latent class analyses using the robust full information maximum likelihood (FIML) estimator in MPlus. This approach allows for the inclusion of all available data points, ensuring that missing values do not bias the results while maximizing the utility of the dataset. FIML assumes that the data are missing at random (MAR), which is a reasonable assumption for our study design.

Once the number of classes was determined, we used polytomous logistic regression models (as in (47)) in Mplus (pseudo-class draw method) to investigate the association between latent classes and the correlates (gender, income, employment, education, social deprivation and parental SUD problem). To address the issue of multiple comparisons inherent in the polytomous logistic regression models, we applied the False Discovery Rate (FDR) correction using the Benjamini-Hochberg procedure. This approach controls the expected proportion of false positives among statistically significant findings, balancing the need to limit Type I error inflation with maintaining statistical power. Adjusted p-values were calculated for all predictors (gender, income, employment, education, social deprivation, and parental SUD) across latent classes to ensure the robustness of the results. This correction was performed post hoc on the original p-values. The Mplus auxiliary option was used to identify the indicators (WMH severity, clinical disease, and service visit) for which the equality of means across latent classes were tested using pseudo-class-based multiple imputations (48).

3. Results

Table 1 presents the prevalence of socio-demographic variables of lifetime cannabis use and the rest of the sample of the São Paulo metropolitan area. There was a remarkably higher prevalence of younger (56.85 %), male (72.38 %), and not married (43.35 %) among those who reported lifetime cannabis use compared to the rest of the SPMHS sample. In contrast, there were higher levels of homemaker/retired (28.41 %), and low-educated individuals (28.28%) in the rest of the sample.

Table 1. Prevalence of socio-demographic variables of lifetime cannabis use and the rest of the sample of the São Paulo metropolitan area, 2005-2007.

	Lifetime Cannabis Use (n = 496)			Rest of the Sample (n = 4,541)				
Variables	n*	%	SE	n*	%	SE	χ^2	p
Age (years)								
18-34	282	56.85	0.52	1559	34.33	0.86	104.29	<0.0001
35-54	186	37.50	0.34	1974	43.47	0.87		
≥ 55	28	5.65	0.59	1008	22.20	0.60		
Gender								
Female	137	27.62	0.29	2713	59.74	0.89	122.34	<0.0001
Male	359	72.38	0.64	2850	40.26	0.62		
Household Income**								
Low	240	48.39	0.40	2327	51.24	0.95	0.02	0.887
High	256	51.61	0.50	2214	48.76	0.54		
Employment Status								
Working/Student	367	73.99	0.70	2719	59.88	0.82	116.56	<0.0001
Homemaker/Retired	40	8.06	0.13	1290	28.41	0.50		
Unemployment/Other	89	17.94	0.28	532	11.72	0.58		
Education (years)								
Low (≤ 4)	60	12.10	0.19	1284	28.28	0.72	36.26	<0.0001
Low-Average (5-8)	134	27.02	0.28	1128	24.84	0.60		
High (≥ 9)	302	60.89	0.60	2129	46.88	0.93		
Marital Status								
Married/Cohabiting	281	56.65	0.50	2969	65.38	0.78	6.83	<0.05
Not married	215	43.35	0.48	1575	34.62	0.88		

* Estimated value of n since after de imputation of weights/clusters/strata it is not possible to calculate the exact value of n.

**Household Income: Low = up to 7,050 dollars/year; High = more than 7,050 dollars/year.

To determine the best number of latent classes, fit statistics of successive LCA models with an increasing number of classes were obtained (Table 2). A four-class model was determined to be the best fit. The BIC decreased from 6094.68 for a three-class model to 5868.67 in a four-class model before increasing in subsequent models (5908.31 for the five-class model). Entropy for the four-class model was acceptable (> 0.8) for all the models except the six-class one. The six-class model had the highest value of log-likelihood and the lowest value of AIC. The five-class model had the lowest value of SSABIC. No model had a significant value of p -Vuong. Considering the discordance among almost all the LCA indexes, the four-class model was chosen as the most parsimonious, based on the BIC as the most reliable index in cases like these.

Table 2. Latent class analysis model comparison and fit indexes in lifetime cannabis use in the São Paulo Metropolitan Area, 2005-2007.							
Model	LL	AIC	BIC	SSABIC	p-Vuong	Entropy	df
Two-class	-2938,14	5934,29	6056,28	5964,23	0,241	0,820	1169
Three-class	-2910,79	5909,59	6094,68	5955,02	0,914	0,867	1155
Four-class	-2763,65	5637,31	5868,67	5694,09	1,000	0,806	903
Five-class	-2740,03	5618,06	5908,31	5689,31	1,000	0,804	889
Six-class	-2724,50	5614,99	5964,15	5700,01	0,7603	0,752	876
Seven-class	-2816,65	5841,31	6278,78	5948,68	0,7732	0,804	1095
Eight-class	-2805,42	5848,84	6349,42	5971,71	0,7861	0,833	1079
Nine-class	-2790,87	5849,75	6413,43	5988,11	0,7676	0,868	1065
Ten-class	-2776,89	5851,51	6478,58	6005,65	0,7602	0,842	1050

The following four classes emerged: LIGHT/NO PROBLEMS; LIGHT/OTHER DRUG POLYDRUG; and FORMER (Table 3 and Figure 1). Table 4 presents the sociodemographic correlates of such latent classes. Table 5 presents the conditional prevalence of WMH

severity, clinical diseases and health service visits per each latent class. No significant differences were found for clinical diseases and health service visits among the classes.

Table 3. *Distribution of lifetime cannabis use within four latent classes in São Paulo Metropolitan Area, 2005-2007.*

Category	Light/No problem(22.4%)		Light/other drug (46.7%)		Polydrug (26.2%)		Former (5.9%)	
	%	SE	%	SE	%	SE	%	SE
Age of Cannabis First Use (in years)								
<i>Up to 15</i>	0.165	0.046	0.138	0.035	0.545	0.072	0.089	0.104
<i>16-17</i>	0.297	0.103	0.209	0.038	0.245	0.050	0.480	0.184
<i>18-21</i>	0.334	0.082	0.380	0.055	0.210	0.058	0.241	0.093
<i>22-25</i>	0.158	0.060	0.170	0.041	0.000	0.000	0.000	0.000
<i>26 or older</i>	0.046	0.051	0.104	0.030	0.001	0.005	0.19	0.153
Lifetime Use (in days)								
<i>Up to 5</i>	0.789	0.074	0.777	0.047	0.000	0.000	0.011	0.084
<i>6-230</i>	0.168	0.075	0.202	0.044	0.298	0.066	0.469	0.190
<i>231-900</i>	0.031	0.034	0.021	0.015	0.127	0.049	0.000	0.000
<i>900 or more</i>	0.013	0.012	0.000	0.000	0.575	0.079	0.52	0.213
Past-year Use	0.096	0.041	0.048	0.022	0.677	0.057	0.000	0.000
Tobacco Use								
<i>Never Smoker</i>	0.400	0.078	0.272	0.049	0.173	0.050	0.000	0.003
<i>Former Smoker</i>	0.442	0.111	0.131	0.037	0.126	0.037	1.000	0.003
<i>Smoker</i>	0.158	0.128	0.597	0.049	0.702	0.051	0.000	0.000
Alcohol Use Disorder	0.000	0.000	0.350	0.059	0.475	0.058	0.618	0.168
Other Drug Use	0.000	0.000	0.414	0.066	0.830	0.038	0.822	0.106
Heavy Episodic Drinking	0.010	0.046	0.366	0.054	0.341	0.055	0.000	0.000

Figure 1. Distribution of the four latent classes of individuals who use cannabis users identified through LCA in the São Paulo Metropolitan Area (2005–2007).

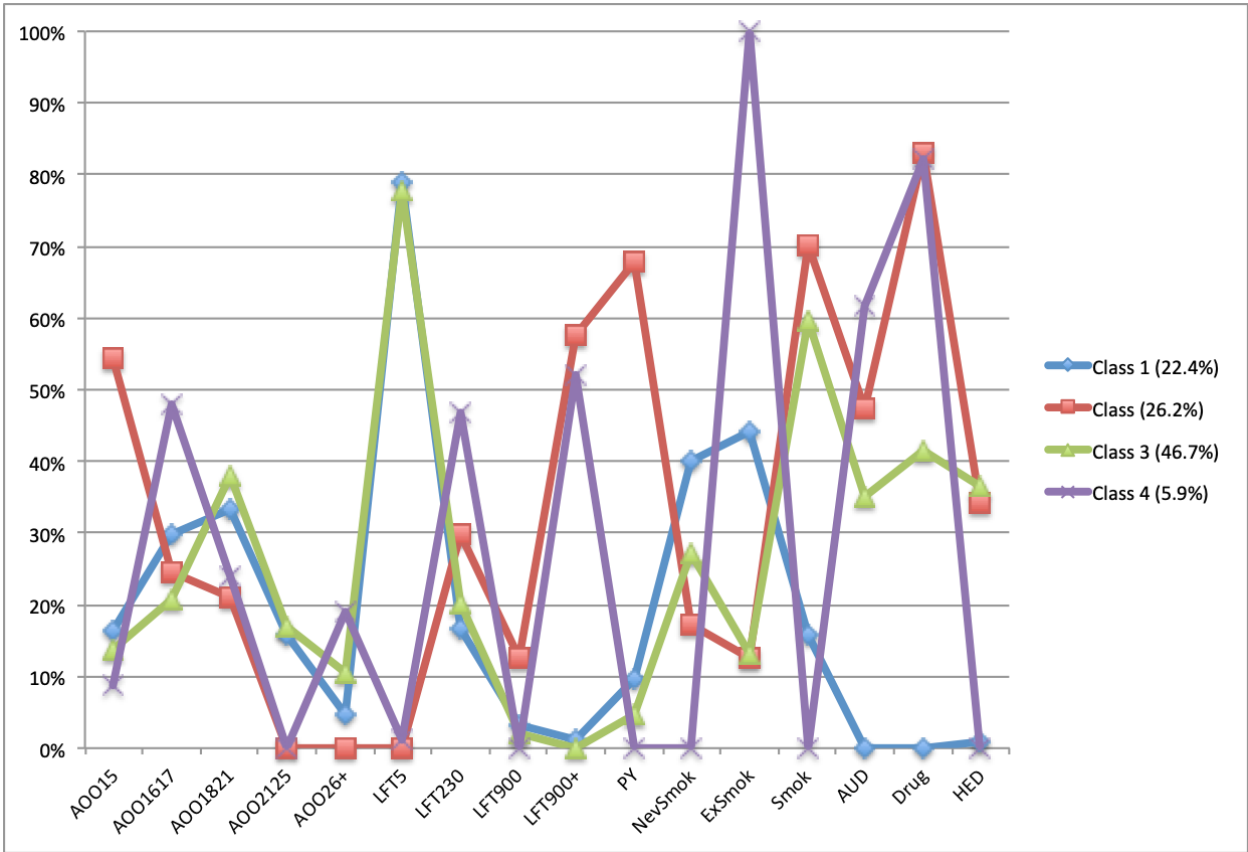


Table 4. Logistic Regression Models with FDR-Adjusted (Benjamini-Hochberg) p-values for Sociodemographic Correlates Within Latent Classes Among Lifetime Cannabis Users in São Paulo Metropolitan Area, 2005-2007.

Variable	Class (Ref: Polydrug)	OR	95% CI		p-value	Corrected p-value
Gender: Female (vs Male)	Light/No Problems	1.12	0.52	2.41	0.756	0.900
Gender: Female (vs Male)	Light/Other Drug	1.42	1.1	1.83	0.015	0.040
Gender: Female (vs Male)	Former Class	2.1	0.49	9.12	0.328	0.450
Income: Low (vs High)	Light/No Problems	0.92	0.17	5.08	0.928	0.980
Income: Low (vs High)	Light/Other Drug	1.01	0.4	2.56	0.980	0.980
Income: Low (vs High)	Former Class	2.77	0.83	9.19	0.106	0.220
Employment: Unemployed (vs Working/Student/Homemaker/Retired)	Light/No Problems	4.26	0.85	21.4	0.080	0.160
Employment: Unemployed (vs Working/Student/Homemaker/Retired)	Light/Other Drug	4.53	1.36	15.2	0.002	0.010
Employment: Unemployed (vs Working/Student/Homemaker/Retired)	Former Class	2.85	0.49	16.4	0.240	0.360
Education: Low (vs High)	Light/No Problems	2.71	0.44	16.6	0.280	0.390
Education: Low (vs High)	Light/Other Drug	1.57	0.43	5.66	0.460	0.600
Education: Low (vs High)	Former Class	3.52	0.53	23.2	0.190	0.320
Social Deprivation: High (vs Not High)	Light/No Problems	0.94	0.32	2.79	0.910	0.980
Social Deprivation: High (vs Not High)	Light/Other Drug	1.63	0.43	6.12	0.460	0.600
Social Deprivation: High (vs Not High)	Former Class	5.17	1.35	19.7	0.003	0.010
Parental SUD: Yes (vs No)	Light/No Problems	4.02	0.79	20.3	0.090	0.160
Parental SUD: Yes (vs No)	Light/Other Drug	2.44	0.65	9.09	0.190	0.320
Parental SUD: Yes (vs No)	Former Class	0.89	0.05	13.9	0.940	0.980

Table 5. Conditional prevalence per four latent classes of lifetime cannabis use in São Paulo Metropolitan Area, 2005-2007.

Latent Class	Light/No Problem	Light/other drug	Polydrug	Former
	%(SE)	%(SE)	%(SE)	%(SE)
WMH Mild Severity (&)	12.1 (0.02)	14.2 (0.03)	14.5 (0.03)	6.0 (0.04)
WMH Moderate Severity (&)	14.2 (0.02)	6.3 (0.02)	7.8 (0.02)	9.0 (0.05)
WMH Severe Severity (+)	56.3 (0.04)	46.3 (0.05)	70.4 (0.04)	65.7 (0.08)
Clinical Disease (&)	63.3 (0.04)	59.4 (0.05)	62.2 (0.04)	75.5 (0.08)
Any Health Service visit in the past year (&)	78.8 (0.03)	84.5 (0.03)	82.6 (0.03)	86.8 (0.06)
<i>SE = Linearized Standard Error</i>				
<i>Results on the Chi-squared tests: (*) Overall test significant plus significant differences between the third class and the other classes;</i>				
<i>(#) Overall test significant plus significant difference between the first two classes; (&) No significant differences found; (+) Overall test significant plus significant difference among the first three classes.</i>				

LIGHT/NO PROBLEM (nearly a quarter of the participants) was composed of lifetime cannabis use without further use and problems, with most individuals reporting using cannabis up to 5 times during their lifetime, first use around 18- to 21-year-old, no cannabis use in the past year, without current tobacco or other drug use, HED and AUD. No sociodemographic correlates were found for this class.

With almost half of the sample, LIGHT/OTHER DRUG consisted of participants with positive use for cannabis without current use, but alcohol related problems. Most participants reported using cannabis up to 5 times, late age of experimentation (first of use at age 18 on and no use in the past year). However, these individuals endorsed elevated frequencies of tobacco use (80% of current smokers), and approximately 40% of other drug use, HED and AUD. Evidence for associations between this latent class and socio-demographic correlates was found. This class was associated with female gender and unemployment/other, when compared to POLYDRUG. The lowest level of WMH severe severity was found in this class (46.3%, SE = 0.05).

FORMER was the small class of the sample (5.9%), which was composed of participants who were former cannabis and tobacco users. Most participants reported somewhat early experimentation with cannabis (around 16-17-year-old), with high lifetime frequency of cannabis use (peaks in the 231-900 and 900+ categories) but denied consumption in the past year. All the individuals were former smokers, and none reported past year HED. However, more than 60% of these individuals reported AUD. Moreover, the vast majority reported other drug use (82.2%). Social deprivation predicted this class in the regression model, compared to those in the POLYDRUG class. No differences with the other classes regarding WMH severity was found.

Approximately a quarter of the sample was included in POLYDRUG (26.2%). This class consisted of cannabis current and frequent users, with participants reporting using 230 times or more during their lifetime, the earliest age of experimentation (first use up to 17 years old). Most of this class members reported using cannabis in the last year. In this class, there were the highest frequencies of current tobacco and other drug use, HED and AUD. The highest WMH severe severity was found in this class (70.4%, SE = 0.04). This was the reference class in the sociodemographic logistic regression models. It was associated with the reference categories of gender (male), employment status (working/student/homemaker/retired), and social deprivation (not high), when compared to LIGHT/OTHER DRUG (gender and employment) and FORMER (social deprivation). The two light cannabis use classes (LIGHT/NO PROBLEM and LIGHT/OTHER DRUGS) comprised approximately 70% of all users. The majority of these users were described as having initiated cannabis use at an advanced age (18 or older) and having used the drug on an occasional basis (up to five times) without current use. A quarter of the participants (22.4%) were classified as belonging to the LIGHT/NO PROBLEM category. This group was characterized by a later age of onset of cannabis use and a history of sporadic cannabis consumption, with no current use of tobacco or other drugs, and no history of heavy drinking or alcohol use disorder. Conversely, the majority of cannabis light users exhibited notable other substance use or hazardous drinking, such as heavy drinking or Alcohol Use Disorder (AUD) (46.7%, classified as LIGHT/OTHER DRUG).

4. Discussion

4.1. Cannabis Use Subtypes and Phenotypes

To the best of our knowledge, this is the inaugural study to assess the typology of individuals who used cannabis and associated phenotypes in relation to other drug use, employing LCA analyses within a representative population sample in Brazil. This study's identification of four distinct subtypes of people who used cannabis—LIGHT/NO PROBLEM, LIGHT/OTHER DRUG, POLYDRUG and FORMER—is similar to other studies (27,28) and offers a nuanced perspective on cannabis use patterns in Brazil. The findings corroborate and extend previous research which has demonstrated the existence of heterogeneity in cannabis use trajectories (20,22,29). In contrast with studies that have demonstrated a discernible progression from minimal to more substantial use, our results indicate less straightforward trajectories, which reflects the complexity of these behaviors across culture, time and population.

The considerable number of individuals in the LIGHT/OTHER DRUG category underscores the importance of examining co-occurring substance use, a crucial aspect that is frequently overlooked in analyses that focus exclusively on cannabis. As has been observed in this study, even occasional cannabis use during adolescence and early adulthood has been demonstrated to be associated with an increased risk of later alcohol and tobacco dependence and other drug use (49). This emphasizes the necessity for interventions to be more comprehensive than solely targeting cannabis use, and to acknowledge the complex interplay of various substances. The POLYDRUG and FORMER classes, which are characterized by early onset, high frequency, and substantial co-morbidity, underscore the potential for severe consequences associated with problematic cannabis use. The small size of the FORMER class warrants further investigation into the factors leading to cessation and long-term outcomes. The two lightest classes were distinguished phenotypically by their use of and problems related to other substances. The LIGHT/OTHER DRUG class exhibited elevated frequencies of tobacco use, other drug use, and alcohol-related problems (HED and AUD). Although many individuals use cannabis infrequently and without problematic consequences the consumption of alcohol in a heavy pattern, tobacco and other drugs potentially expose the users to several chronic conditions, in particular to inflammatory diseases, mental health problems, such as AUD, and all-cause

mortality (50,51). Furthermore, one third of all people who used cannabis were current or former heavy users, respectively concentrated in the POLYDRUG and FORMER classes. These classes were identified by the highest lifetime frequency and the earliest age of onset of cannabis use. Such classes were disproportionately associated with a range of harms, including the use of other drugs, tobacco, harmful drinking, and alcohol use disorders, as well as with a severe level of WMH. These patterns of cannabis heavy users are consistent with the existing literature, which indicates that over one-third of individuals who use cannabis may meet the criteria for a diagnosis of cannabis abuse or dependence according to the DSM-IV criteria over the course of their lifetime (52). Additionally, the association with heavy episodic drinking, AUD, tobacco and other drug use provides further insight into the problematic patterns of cannabis use that have traditionally been associated with high frequency, near-daily or daily, (28,53) or early onset of cannabis use (5,24,29,52). Although the association of polydrug use and harm is well established in the literature (54,55), our study provides insight into a concerning profile of individuals who use cannabis and encourages further research on the trajectories of cannabis use in low- and middle-income countries. Recent studies have demonstrated that individuals who use multiple drugs present a significantly elevated risk for developing a drug use disorder, with a cumulative incidence exceeding 10%, when compared to those who use cannabis exclusively (19). The characterisation of polydrug trajectories will facilitate the identification of specific risk factors associated with patterns of cannabis use and associated health consequences.

In general, among those who consume cannabis heavily, the distinction was made in terms of current use of cannabis and tobacco. A small proportion was likely abstaining from these substances due to the negative consequences associated with their use. It is already established that the early onset of cannabis use is a predictor of subsequent drug-related problems (19). However this study provides evidence of an association with other drug use, HED and AUD. This is a particularly concerning phenomenon in Brazil where almost 40% of the individuals who used cannabis exhibit signs of dependence, which appears to be higher among those with a history of substance use disorders (SUD) (56). The findings also indicate that 13.8% of Brazilian college students are past-year users. When the transitions from the first use of a drug to the first use of another drug were analyzed, it was observed

that cannabis was used prior to the use of several other drugs. Conversely, the opposite pattern was not identified (57,58).

4.2. Sociodemographic Correlates and Contextual Factors

The relationship between sociodemographic factors and different patterns of cannabis use also merits further investigation. The disproportionate representation of women in the LIGHT/OTHER DRUG category (almost half of the sample) and the association between unemployment and other employment status and cannabis use suggests the need for a more comprehensive examination. Potential explanations for this phenomenon include elevated stress levels, limited access to support services, and differential social stigma surrounding substance use. Women who used cannabis frequently reported HED, which is consistent with the last Global Status Report on Alcohol and Health 2018 (35) showing a worldwide decrease in the HED prevalence and an increase in Brazil (15,40,41). The POLYDRUG class was found to be associated with male gender, in line with previous studies (59,60), employment status (working/student/homemaker/retired), and low social deprivation (52). Similarly, the relationship between social deprivation and the FORMER class suggests the potential influence of neighbourhood-level factors on patterns of cannabis use.

It is important to note that those in the FORMER class exhibited area-level neighborhood characteristics that reflected social disadvantage. In particular, residence in more deprived areas was linked to past heavy cannabis use, current other drug use, heavy drinking, and alcohol-related disturbances. Globally, significant social and contextual factors that increase the probability of initiating cannabis use include the early consumption of tobacco and alcohol (22,24,55). While we are unable to infer causality, it is plausible that individuals residing in disadvantaged neighborhoods, characterized by social exclusion and deprivation, may be more susceptible to stress, possess fewer coping resources, and experience various forms of violence and adversity (61). Additionally, the high density of alcohol and other drug outlets (62-66) may contribute to the prevalence of substance use in these communities. Further research could examine the influence of access to substances, social support networks and community-level interventions on the formation of these patterns.

4.3. Clinical outcomes and health implications

As cannabis control regimes are evolving in different countries (36), there is a need for a more nuanced understanding of the Brazilian context with regard to cannabis use and associated risks, with a view to reducing health and other risks from use.

The findings of the study highlight a significant correlation between problematic cannabis use (POLYDRUG and FORMER classes) and an increased risk of mental health and other health issues. The elevated levels of WMH of severe severity within these groups indicate a need for targeted interventions that address both mental health and substance use disorders. This result is consistent with a substantial body of literature indicating a correlation between cannabis consumption, particularly during the early stages and at high levels, and an array of mental health concerns (20,22,29).

The current study identified distinct groups of individuals who used cannabis and established associations between differential risk and harm outcomes. The POLYDRUG class exhibited the highest WMH severity index, which is consistent with the early age of onset and high frequency of cannabis use, in addition to high rates of other substances use and problems. The second highest WMH severity score was observed in the FORMER class, who had been abstinent from both cannabis and tobacco use over the past year, but still reported the use of other drugs. The WMH severity score serves as a supplementary indicator for the more problematic use patterns observed in these groups, as measured by the presence of specific disorders, clinical conditions and the search for mental health or clinical assistance reported by the study subjects. Recent research on patterns of cannabis consumption from 1992 to 2020 (10) indicate a significant increase in the prevalence of daily, monthly, and past-year users. In particular, the number of individuals that used it on a daily basis increased 14 times, monthly users quadrupled, and past-year users tripled. In light of these observations, it is imperative to consider the potential implications of cannabis consumption in Brazil, particularly in relation to the major social and contextual factors that may contribute to the initiation of cannabis use. It is noteworthy that the consumption of alcohol at an early age is a prevalent phenomenon in our country, as evidenced by previous studies (67,68).

It is necessary to provide commentary on the trends of perceived harmfulness of cannabis use. Epidemiological evidence indicates that the perceived harmfulness of cannabis among

young people began to decline as early as 1991, well before the enactment of medical cannabis legislation in other jurisdictions (19). It is not possible to infer such a phenomenon in Brazil. Cannabis use is either perceived as extremely dangerous for individuals and their families, due to the belief that it always leads to dependence and/or other negative consequences (69,70), or it is seen as safe and harmless, particularly among the youngest, who are influenced by information that lacks scientific backing. The outcomes of the present study indicate that early cannabis use is associated with adverse health outcomes and HED and AUD. This aligns with prior research suggesting that individuals who co-use cannabis and alcohol are more likely to experience negative consequences from drinking, which in turn predicts a greater likelihood of experiencing additional consequences (71). It is notable that Brazilian adolescents are embedded in a drinking culture typified by elevated alcohol consumption per occasion. In fact, 10–20% of students have experienced at least one episode of heavy episodic drinking (HED) in the past month (72,73). This underscores the imperative for prevention programs tailored to this population and addressing the combined use of multiple substances, including alcohol, tobacco, and cannabis. The earlier the onset of cannabis use, the greater the risk of developing a substance use disorder. This is because heavy episodic drinking is a significant risk factor for the early onset of cannabis use (74).

The situation is made even more concerning by the addition of further evidence from the literature, which indicates that increases in the frequency of cannabis use by an individual are specifically associated with increases in some of the more severe types of alcohol-related consequences (75). While the literature regarding the concurrent use of alcohol and cannabis presents evidence to support both hypotheses of cannabis acting as a substitute for (a replacement for alcohol effects, leading to a decreased use) or a complement to (an enhancer of alcohol effects, resulting in increased use), the mechanisms for the impact of cannabis use on alcohol-related outcomes remain unclear (76). Nevertheless, discussions about the health consequences related to changes in the legal status of cannabis represent one of the most significant global topics in this field of study (77). In Brazil, this discussion has recently intensified and remains a point of contention. Health professionals express concern about potential increases in cannabis consumption among young people (78), while those in the criminal justice system advocate for decriminalization and the regulation of

social use, citing the country's alarming prison situation, which ranks among the worst in the world, second only to China and the United States (79).

The present study identified distinct user profiles, characterized by differences in a wide range of traits. It is not only those who initiated at an early age or in a high frequency who can be considered problematic users; those who consume other drugs and have negative consequences related to heavy drinking and AUD are also included in this category. Those with greater social deprivation are at an increased risk of developing problematic patterns. It seems unlikely that a single approach to interventions targeting cannabis use would prove sufficient. Even a punitive approach would be inadequate for addressing this important and complex topic. The implementation of punitive policies towards the possession and use of other substances has been observed to have a limited impact on the national rates of illegal drug use. Moreover, an appropriate public health framework for reducing the early and frequent use of cannabis and other drugs could be achieved targeting effective interventions at the 30% of users who experience particularly high levels of risks and harms, as well as the increased health risks associated with the combined use of other drugs (77,80).

In considering the regulation of cannabis in Brazil, it is important to note that the discussion should take into account the recommendations set forth for the control of alcohol (81,82) and tobacco (83). These recommendations include delaying the first use of these substances, prohibiting their use in public spaces, and establishing driving under the influence prohibitions. Additionally, the discussion should address advertising prohibitions, restrictions on the types of products, flavors, or additives used, and the ten target areas proposed by the WHO to reduce the harmful use of alcohol (35). Moreover, it is crucial to consider the diverse range of experiences and models that have been implemented in other global contexts (84). Such examples undoubtedly serve as valuable points of reference, providing a framework for contextualization and potential adaptations to the unique realities present in Brazil.

Notwithstanding, the dearth of conspicuous discrepancies in the prevalence of clinical disorders and healthcare utilization across socioeconomic groups suggests that the impact of cannabis consumption on overall health status may be relatively constrained. A more detailed analysis is required to elucidate the relationship between heavy cannabis use, problematic patterns and utilization of health services. Further research employing

longitudinal study designs is required to elucidate the relationship between cannabis use patterns and subsequent health outcomes.

4.4. Limitations

This study has limitations. One limitation that certainly may have affected this study's estimates is the level of source of underestimation of cannabis and other illegal drug involvement (and perhaps alcohol and tobacco use), but not necessarily a source of bias with respect to estimated associations with other variables (9). Social stigma and legal practices in Brazil might affect self-reported cannabis use. Attempts were made to ensure that truthful, honest answers were provided by participants in these surveys in four major ways. Additionally, the data were collected between 2005 and 2007, which introduces temporal limitations, as patterns of substance use, social norms, and policies may have evolved since then.

Retrospective reporting of age of first drug use may be subject to error, given that respondents are being asked about events that, for older persons, may have occurred decades ago. It is unlikely that response or other biases completely account for the strong trends observed here. In this study, there were contrasting cohort trends across different drug subtypes, suggesting that a pattern of "forgetting" did not apply.

Previous research has found that earlier use and heavy cannabis use in terms of frequency are associated with later problematic drug use/dependence (85), and by studying patterns of cannabis use and phenotype in relation to other drugs use this paper has shown that use of other substances would predispose individuals towards cannabis use problems.

Therefore, a limitation is that age at onset of use and problems for other substances were not considered herein, and a stage-sequential approach to study cannabis use in Brazil in the future may clarify such findings.

We have not found any association between cannabis use classes and substance use and disorders among parents. However, future studies should include other indicators in the latent profile analysis (86,87), such as poor quality of parent-child relationships, parental conflict have been found to increase the risk of alcohol and other drug use during adolescence (49,55). Evidence from genetic epidemiology also corroborates the role of inherited predispositions towards other drugs consumption taking and related dependence

(88) and improves understanding of problematic/heavy polydrug use and mutual characteristics (89).

As with other studies in this field, the major limitations are that it is rather not possible to adequately measure all plausible confounders to fully control for the effects of such variables. Thus, more studies are necessary to better understand aspects like genetic factors, variables that might influence the vulnerability to both cannabis use initiation, problematic use and its trajectories (55,90), environmental influences (family environment, prenatal influences, parental style, and socio-economic status) and also recent trends regarding cannabis use, as the increased D-9-tetrahydro-cannabinol (THC) levels and the increased popularity of water- pipes or bongs which permit the delivery of large bolus doses of THC (5,91,92).

While the absence of a clear progression pattern in terms of age of first use and frequency indicators was observed, this is likely due to the cross-sectional nature of our dataset. Methods such as Latent Growth Analysis (LGA) or Growth Mixture Models (GMM) could provide insights into developmental trajectories. However, these approaches require longitudinal data, which was not available in this study. Future research applying these methods could further refine our understanding of cannabis use patterns over time.

5. Conclusion

This study provides novel epidemiologic data on cannabis use patterns and associated phenotypes in a representative sample from the São Paulo Megacity Mental Health Survey. Key findings reveal distinct latent classes of cannabis users, with the earliest age of first use and highest frequency of use disproportionately linked to harms, including other drug use, tobacco use, HED, and AUD. These results emphasize the need for greater attention to the public health impacts of cannabis use in Brazil, particularly among young adults, and the associated risks of other substance use. A health-centered policy approach—prioritizing prevention, treatment, and public education over punitive measures—offers a more effective path to mitigate the harms of cannabis use and promote the health and dignity of individuals and communities. Future research is essential to monitor trends, assess treatment demands, and refine interventions to address cannabis-related problems in Brazil and other low- and middle-income countries.

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- Figure 1. Distribution of the four latent classes of individuals who use cannabis identified through LCA in the São Paulo Metropolitan Area (2005–2007).