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Identifying subtypes of cannabis users based on simultaneous polysubstance use

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ABSTRACT

Background: Cannabis use patterns vary considerably, with many users reporting simultaneous and non-simultaneous use (co-use) of other substances. Despite this, little research has examined the extent to which subtypes of cannabis users may be identified based on their simultaneous and co-use behaviors.

Methods: The sample consisted of adult Australian twins and siblings who reported lifetime cannabis use ($n = 2590$). A latent class analysis was conducted to determine subtypes of cannabis users based on five indicators of substance co-use and simultaneous use. Adolescent correlates (age of substance initiation and conduct disorder) and adult correlates (substance use/disorder and depression) of class membership were assessed. Twin similarity for class membership was also examined.

Results: Four subtypes of users were identified: 1) alcohol co-users, 2) simultaneous alcohol users, 3) simultaneous tobacco users, and 4) simultaneous alcohol, tobacco, and drug users. Compared to co-users of alcohol, simultaneous alcohol users were at increased risk for alcohol problems. Patterns of use that involved simultaneous tobacco and cannabis use (i.e., simultaneous tobacco users and simultaneous alcohol, tobacco, and drug users) were associated with the most problematic outcomes, including substance use and disorder. There was evidence for genetic influences (12–58%) on cannabis use patterns, with higher concordance for latent class membership among monozygotic compared to dizygotic twins ($\chi^2(1) = 7.19, p = 0.007$).

Conclusions: The current study identified four classes of cannabis users at varying degrees of risk. Results suggest that simultaneous tobacco and cannabis use may be especially associated with deleterious outcomes.

1. Introduction

Approximately 4% of the world's population reports past year cannabis use (United Nations Office on Drugs and Crime, 2016), with higher rates in some countries, including the United States (16.3%) and Australia (10.2%; UNODC, 2016). Among cannabis users, there is considerable variability in patterns of use and outcomes. However, efforts to identify subtypes of cannabis users have largely been confined to adolescent and college populations (Chung et al., 2006; Pearson et al., 2017; Reboussin et al., 2007), limiting the understanding of adult cannabis users, for whom rates of use have been increasing rapidly (Hasin et al., 2015).

Two recent studies extended findings on subtypes of cannabis users to adults (Krauss et al., 2017; Manning et al., 2019). In the largest of

these studies ($n = 2444$), four user subtypes were identified based on past month use of three types of cannabis (plant-based, edible, and concentrate), cannabis use patterns, and driving after use (Krauss et al., 2017). Membership in heavy and poly-cannabis use classes (i.e., using multiple forms of cannabis) was associated with living in a legal cannabis state, being a medical patient, male, and nonwhite, and lower educational attainment (Krauss et al., 2017). Another study of adult cannabis users identified five subtypes of users based on quantity and frequency of cannabis use and cannabis-related problems (Manning et al., 2019). Predictors of high-risk use included emotion dysregulation, alcohol use severity, and anxiety sensitivity (Manning et al., 2019). Probing the differences among adult cannabis users can aid in identifying individuals at high risk.

Previous studies, however, have not examined the extent to which

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co-use (using multiple substances, but on different occasions) and simultaneous polysubstance use (SPU; using multiple substances at the same time), may distinguish subtypes of cannabis users. SPU may be more likely to result in synergistic, additive, or interactive drug effects that increase risk of negative outcomes compared to co-use (Abel, 1985; Pennings et al., 2002). Despite potential negative consequences, SPU occurs at high rates among cannabis users, with one study suggesting that up to 80% of cannabis use occasions include alcohol consumption (Pape et al., 2009). Consuming these drugs together may increase risk for alcohol-related blackouts, which are periods of impaired memory formation during a drinking episode (Schuckit et al., 2016). Cannabis and tobacco are also often used simultaneously, partially due to tobacco products (e.g., cigars/cigarillos and e-cigarettes) serving as an effective delivery system for cannabis (Strong et al., 2018). Use of cannabis and tobacco may increase the likelihood of developing cannabis abuse (Agrawal et al., 2009) and may also be associated with greater risk for health problems (Strong et al., 2018). Due to high rates of SPU among cannabis users, simultaneous use of other substances should be considered when developing typologies. In order to determine whether negative effects of SPU are due to the simultaneous nature of use or are merely due to using multiple substances, co-use should also be considered.

The current study evaluated the extent to which patterns of co-use and simultaneous use indicate subtypes of cannabis users among a sample of Australian adults. The extent to which latent classes differed on age of substance initiation, conduct disorder (CD) symptoms, substance use/disorder, and major depression was assessed. These analyses provided external validation, revealing whether classes were qualitatively distinct. We hypothesized that latent classes characterized by simultaneous use, rather than co-use, would be at higher risk for substance use problems and other negative outcomes. Another form of external validation of the latent classes came from the evaluation of twin similarity, which is informative about potential familial contributions to cannabis use patterns, and can provide insights into the underpinnings of individual typologies.

2. Method

2.1. Participants

Participants were members of a cohort of adult twins (born 1972–1979) and their siblings from the Australian Twin Registry who reported lifetime cannabis use. Data were collected via computer-assisted telephone interviews between 2005 and 2009. The current sample consisted of 2590 individuals, including 2268 twins (605 monozygotic females, 355 monozygotic males, 472 dizygotic females, 286 dizygotic males, and 550 dizygotic opposite sex) and 322 siblings. Participants were 22 to 45 years old, with a mean age of 32.08 ($SD = 2.92$). 60.4% were female. For additional details regarding study recruitment and sample characteristics, see Lynskey et al. (2012).

2.2. Variables used to determine latent class membership

2.2.1. Co-use of alcohol and tobacco

Participants who reported drinking at least once a month for six or more months in their lifetime were classified as co-users of alcohol, with 96.6% endorsing this. Participants who reported smoking 100 or more cigarettes in their lifetime were classified as co-users of tobacco (55.9% of the sample).

2.2.2. Simultaneous polysubstance use

Participants reported whether they typically used cannabis with alcohol, tobacco, and/or other drugs; 55.1% of the sample reported typically using cannabis with alcohol, 34.3% typically used with tobacco, and 4.1% typically used with other drugs.

2.3. Correlates of latent class membership

2.3.1. Cannabis use

Participants reported the age they first used cannabis and the number of times using cannabis in their lifetime. The extent of lifetime cannabis use was transformed into a five-level variable to minimize skewness, with individuals who reported using cannabis once coded '1', those who reported using twice coded '2', those who used 3–10 times coded '3', those who used 11–29 times coded '4', and those who used 30 or more times coded '5'. DSM-IV criteria for cannabis abuse and dependence were also assessed (APA, 2000). Symptoms were summed across abuse and dependence criteria in order to obtain a lifetime cannabis use disorder (CUD) symptom count for each participant. 24% of the sample met criteria for CUD based on endorsing at least two lifetime symptoms.

Additional information on cannabis use experiences was assessed, including time spent high and initial liking of cannabis. To assess time spent high, participants reported whether they had ever been high for a whole day or more from using cannabis. 49% of the sample endorsed this. Participants were also asked how much they enjoyed using cannabis the first time they tried it. Participants who reported they had enjoyed using cannabis 'not at all' were coded '0', those who reported enjoying it 'a little' were coded '1', 'some', coded '2', and 'a lot' coded '3'. Fifty-eight percent of the sample reported initially liking cannabis.

2.3.2. Other substance use

The Australian version of the Semi-Structured Assessment of the Genetics of Alcoholism (Bucholz et al., 2015) was used to assess DSM-IV alcohol abuse and dependence (APA, 2000). Symptoms were summed to obtain lifetime and past year alcohol use disorder (AUD) symptom counts, ranging from 0 to 11. Additionally, participants' age of first drink and number of alcohol-induced blackouts were assessed. Individuals who did not report a blackout were coded '0', while those who reported one blackout were coded '1', 2–5 coded '2', and 6 or more coded '3'.

Other substance use behaviors assessed included age of first smoking, the number of DSM-IV lifetime and past year nicotine dependence (ND) symptoms (0–7; APA, 2000), and the number of illicit drug types used in the lifetime and past year (0–9). The illicit drug types assessed in the interview were stimulants, cannabis, cocaine, opiates, sedatives, hallucinogens, dissociatives, solvents, and inhalants.

2.3.3. Conduct disorder

The interview assessed the 15 DSM-IV criteria for CD (APA, 2000). Participants were asked to consider behaviors that occurred before age 18. Criteria for CD include symptoms within four domains: 1) aggression towards people and animals, 2) destruction of property, 3) deceitfulness/theft, and 4) serious rule violations. Criteria were summed across domains, resulting in a total symptom count for each participant.

2.3.4. Major depression

The interview assessed DSM-IV criteria for a lifetime major depressive episode (APA, 2000). Participants who reported five or more symptoms of depression (including depressed mood and/or loss of interest) occurring together for a period of at least two weeks with impairment in functioning were classified as experiencing a lifetime major depressive episode. Depression related to bereavement was excluded.

2.4. Data analysis

Latent class analysis assumes that there exists a small number of mutually exclusive classes within a sample, with each class having distinct response patterns (Hagenaars and McCutcheon, 2002). Models are typically fit for a range of class structures (i.e., 2–8 classes), and maximum likelihood estimation is used to determine the probability that a case falls into a particular latent class. Fit indices are used to

determine which class structure best fits the data while also retaining theoretically meaningful classes.

LCA was used to determine subtypes of cannabis users based on co-use of alcohol and tobacco and simultaneous polysubstance use. Models ranging from a 2- to an 8-class solution were fit within Mplus (v8; Muthén and Muthén, 2017). To account for familial clustering, standard errors were adjusted using the maximum likelihood ratio (MLR) sandwich estimator, which is robust to non-independence of observations. MLR uses random starting values to optimize parameter estimates. For the current study, 500 random sets of starting values were used with a maximum of 50 iterations. The Bayesian Information Criterion (BIC) was used to evaluate model fit. Once a preferred class solution was identified, invariance of the latent class structure across men and women was evaluated.

To investigate the best fitting solution further, we evaluated correlates of class membership, including cannabis use, other substance use/abuse, CD symptoms, and depression using the modified BCH method, named after its developers, Bolck et al. (2004) within Mplus (Asparouhov and Muthén, 2018; Bakk and Vermunt, 2016). This method outperforms others for evaluating correlates and outcomes of latent class membership and performs well even when the variance of the correlate differs substantially across latent classes. Additionally, this model takes into account measurement error by using weights based on classification probabilities. The automatic BCH approach was used to estimate means across classes, and mean differences were tested using Wald chi-square tests. To account for multiple testing, a Bonferroni-adjusted p-value was used to assess significance. A total of 108 pairwise comparisons (6 pairwise comparisons across 18 variables) were conducted, resulting in an adjusted significance level of $p = 0.00046$.

Twin concordance for most likely class membership was evaluated using kappa coefficients within SAS (SAS Institute, 2013). To examine whether concordance for class membership differed for monozygotic (MZ) and dizygotic (DZ) twins, a test of equal kappas was conducted using same-sex twin pairs. Significant differences in concordance would suggest that genetic influences contribute to cannabis use patterns. These omnibus tests were followed by calculating intraclass correlation coefficients (ICCs) within SPSS (IBM Corp, 2017). ICCs use probabilities of class membership for each twin, taking into account classification error. If familial influences contribute to similarity, same-class correlations should be higher than cross-class correlations. Furthermore, if genetic influences contribute to similarity, correlations should be higher for MZ compared to DZ twins. ICCs also provide rough estimates of heritability for each latent class, calculated using the formula $2(r_{MZ} - r_{DZ})^1$, where r_{MZ} and r_{DZ} are the ICCs for MZ and DZ twins, respectively.

3. Results

Table 1 presents model-fitting results. The 4-class solution was identified as the preferred solution. There was no evidence for differential item response probabilities within class for men and women ($\Delta\chi^2(20) = 25.33, p = 0.19$), suggesting that the nature of the class structure did not differ by sex. However, class probabilities could not be constrained to be equal for men and women ($\Delta\chi^2(23) = 49.35, p = 0.001$), meaning that men and women were not equally likely to be assigned to a given latent class. In order to account for these sex differences in the likelihood of class membership, sex was included as a covariate in analyses. Symptom endorsement probabilities for the 4-class solution are shown in Fig. 1.

One co-user class was identified: alcohol co-users ($n = 284; 10.97\%$). Women were almost four times as likely to be in this group compared to the reference group (simultaneous tobacco users;

¹ This formula assumes there are no non-additive genetic effects on cannabis use patterns, which is well-supported by the literature (Agrawal and Lynskey, 2006).

Table 1

Model-fitting results of the latent class analysis.

Model	LMR LRT χ^2	χ^2 p-value	AIC	BIC	Entropy
2-Class	743.72	< 0.0001	10,312.14	10,382.45	0.88
3-Class	145.56	< 0.0001	10,180.57	10,291.90	0.78
4-Class	65.42	0.002	10,129.15	10,281.50	0.71
5-Class	26.12	0.004	10,117.04	10,310.40	0.73
6-Class	11.69	0.55	10,119.35	10,353.72	0.72
7-Class	13.40	0.06	10,121.87	10,397.26	0.77
8-Class	4.93	0.33	10,132.16	10,448.57	0.62

Note: Bold indicates the selected, preferred solution. LMR LRT = Lo-Mendell-Rubin Likelihood Ratio Test.

OR = 3.70 [1.34–8.68]). Individuals in this group reported co-use of alcohol (89.5%), but did not endorse co-use of tobacco (0%). These individuals also had low to moderate rates of SPU: 44% reported typically using alcohol with cannabis, 6.4% reported typically using with tobacco, and 2.5% reported typically using with other drugs. Just 13.4% of alcohol co-users reported past year cannabis use.

The other three classes that were identified were simultaneous user classes. The first was a simultaneous alcohol user class ($n = 1105; 42.66\%$). All individuals in this class reported co-use of alcohol, and under a third (32.8%) reported co-use of tobacco. These users were likely to report typically using alcohol with cannabis (70.2%), but were unlikely to report other forms of SPU (2.1% used with tobacco and 1.2% used with other drugs). 17.1% of simultaneous alcohol users reported past year cannabis use. A class of simultaneous tobacco users was also identified ($n = 745; 28.76\%$). These users reported co-use of both alcohol (92.5%) and tobacco (98.9%). They also reported typically using cannabis with tobacco (53.1%), but were unlikely to use with alcohol (0%) or other drugs (1.7%). Users in this group were more likely to report past year cannabis use (29.7%). Finally, there was a class of simultaneous alcohol, tobacco, and drug (ATD) users ($n = 456; 17.61\%$). These users reported co-use of alcohol (100%) and tobacco (98%). Additionally, they reported typically using cannabis with a variety of substances, including alcohol (100%), tobacco (93.1%), and other drugs (13.6%). 28.3% of simultaneous ATD users had used cannabis in the past year.

3.1. Adolescent correlates of latent class membership

3.1.1. Substance initiation

The latent classes did not differ on their age of first drink ($\chi^2(3) = 9.80, p = 0.02$), with all classes initiating alcohol use around age 15 (see Table 2). However, classes did differ on age of first cigarette smoking and age of first cannabis use. Simultaneous ATD users and simultaneous tobacco users had significantly earlier ages of smoking initiation ($M = 13.19$ and 13.36 , respectively) compared to simultaneous alcohol users and alcohol co-users ($M = 14.38$ and 15.06 , respectively). Simultaneous tobacco users and simultaneous ATD users also reported earlier initiation of cannabis use compared to alcohol co-users and simultaneous alcohol users, who had the latest age of initiation of cannabis use ($M = 19.16, SD = 0.18$). Both simultaneous ATD users and simultaneous tobacco users were around 16 years old when they first used cannabis ($M = 16.88$ and 16.49 , respectively).

3.1.2. Conduct disorder

Alcohol co-users and simultaneous alcohol users reported having on average less than one CD symptom during childhood and did not significantly differ from one another ($\chi^2(1) = 2.05, p = 0.15$). Simultaneous tobacco users and simultaneous ATD users, on the other hand, reported significantly more childhood CD symptoms ($M = 1.53$ and 1.58 , respectively).

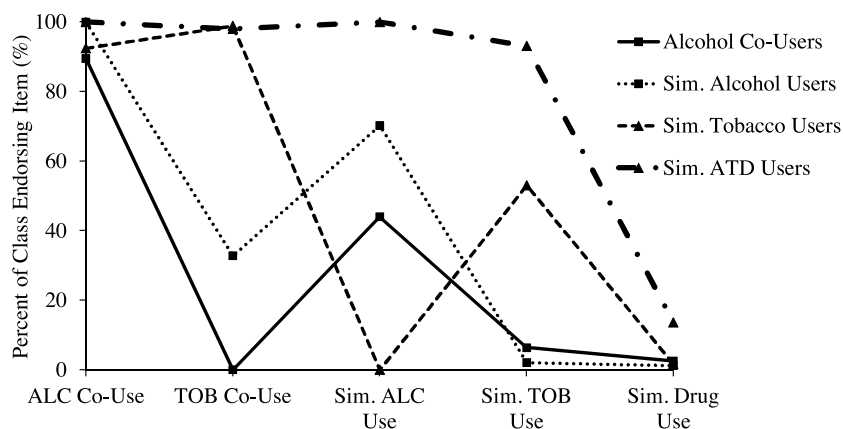


Fig. 1. Symptom endorsement profiles by latent class membership. Note: Sim. = simultaneous, ALC = alcohol, TOB = tobacco, ATD = alcohol, tobacco, and drugs. Dashed lines indicate simultaneous user classes, while the solid line indicates the co-user class. Square markers indicate classes where alcohol is the primary substance used, and triangle markers indicate classes involving simultaneous tobacco use.

Table 2
Demographic characteristics and mean levels of predictor and outcome variables across latent classes.

	Alcohol Co-Users N = 284	Sim. Alcohol (A) Users N = 1105	Sim. Tobacco (T) Users N = 745	Sim. ATD Users N = 456	
Age	Mean (SD) 31.69 (2.92)	Mean (SD) 32.06 (2.90)	Mean (SD) 32.06 (3.07)	Mean (SD) 32.41 (2.75)	ns
Sex (% Female)	98.2%	49.5%	67.1%	52.2%	Co-Use > T > ATD & A
Adolescent Correlates of Latent Class Membership					
	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	
Age of First Drink	15.54 (0.20)	15.34 (0.10)	15.36 (0.09)	15.05 (0.10)	ns
Age of First Smoking	15.06 (0.39)	14.38 (0.18)	13.36 (0.14)	13.19 (0.16)	Co-Use & A > T & ATD
Age of First Cannabis	18.01 (0.38)	19.16 (0.18)	16.49 (0.14)	16.88 (0.13)	A > ATD & T Co-Use > T
Conduct Disorder Symptoms	0.55 (0.09)	0.74 (0.06)	1.53 (0.08)	1.58 (0.09)	T & ATD > Co-Use & A
Adult Correlates of Latent Class Membership					
	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	
Extent of Cannabis Use	3.23 (0.12)	2.88 (0.07)	4.01 (0.07)	3.97 (0.06)	T & ATD > Co-Use & A
Lifetime CUD Symptoms	0.27 (0.13)	0.54 (0.08)	2.45 (0.14)	1.87 (0.14)	T & ATD > Co-Use & A
Initial Liking of Cannabis	1.08 (0.14)	1.28 (0.07)	1.48 (0.07)	1.51 (0.07)	ns
High Full Day (%)	26.3%	37.6%	60.2%	50.6%	T > Co-Use
Lifetime AUD Symptoms	0.67 (0.16)	2.18 (0.10)	2.01 (0.10)	2.92 (0.13)	ATD > A & T > Co-Use
Past Year AUD Symptoms	0.16 (0.10)	0.76 (0.06)	0.67 (0.06)	1.21 (0.09)	ATD > A & T > Co-Use
Experiences of Blackout	1.08 (0.14)	1.48 (0.06)	1.20 (0.06)	1.53 (0.06)	ATD > T
Lifetime ND Symptoms	0.05 (0.06)	0.76 (0.06)	4.17 (0.08)	3.85 (0.07)	T & ATD > A > Co-Use
Past Year ND Symptoms	0.02 (0.02)	0.24 (0.03)	1.50 (0.07)	1.41 (0.08)	T & ATD > A > Co-Use
Lifetime # Illicit Drugs Used	1.98 (0.14)	2.03 (0.07)	2.97 (0.09)	3.03 (0.10)	T & ATD > Co-Use & A
Past Year # Illicit Drugs Used	0.35 (0.08)	0.43 (0.04)	0.70 (0.05)	0.79 (0.06)	T & ATD > Co-Use & A
Lifetime Major Depression (%)	32.7%	17.5%	35.4%	30.9%	Co-Use, T, ATD > A

Note: Sim. = simultaneous, ATD = alcohol, tobacco, and drug, AUD = alcohol use disorder, ND = nicotine dependence, SE = standard error, SD = standard deviation, ns = not significant. Initial Liking of Cannabis is coded such that '0' refers to liking cannabis not at all, '1' refers to a little, '2' to some, and '3' to a lot. Experiences of Blackout is coded such that '0' refers to no lifetime blackouts, '1' to 1 blackout, '2' to 2-5 blackouts, and '3' to 6 or more.

3.2. Adult correlates of latent class membership

3.2.1. Cannabis use

Latent classes differed in their extent of cannabis use, as measured by the number of times smoking cannabis ($\chi^2(3) = 285.67, p < 0.0001$). Alcohol co-users and simultaneous alcohol users both reported relatively low levels of cannabis use (around 3–10 times). Simultaneous tobacco users and simultaneous ATD users, however, reported a greater extent of use and did not differ from one another ($\chi^2(1) = 0.23, p = 0.63$). No pairwise comparisons were significant for initial liking of cannabis ($ps = 0.006 - 0.74$), with all classes initially liking cannabis 'a little' or 'some' on average. Simultaneous tobacco users were significantly more likely to report having been high for a full day or more (60.2%) compared to alcohol co-users (26.3%). Regarding cannabis problems, alcohol co-users and simultaneous alcohol users both reported less than one lifetime CUD symptom, while simultaneous tobacco users and simultaneous ATD users reported more symptoms ($M = 2.45$ and 1.87 , respectively; see Fig. 2).

3.2.2. Other substance use

While simultaneous tobacco users and simultaneous ATD users were similar on other outcomes, the two groups differed in their alcohol-related problems. Simultaneous ATD users had significantly more lifetime and past year AUD symptoms compared to all other groups, reporting around three lifetime symptoms ($M = 2.92$; consistent with a mild AUD diagnosis) and about one past year symptom. Simultaneous alcohol users and simultaneous tobacco users had the second highest levels of AUD symptomatology, with these groups reporting around two lifetime symptoms (consistent with a mild AUD diagnosis) and less than one past year symptom. Alcohol co-users had the fewest AUD symptoms, with less than one symptom both over the lifetime and in the past year. Simultaneous ATD users also had significantly more experiences of alcohol-induced blackouts compared to simultaneous tobacco users ($\chi^2(1) = 14.09, p = 0.0002$). Other classes did not differ in their experiences of blackout.

Simultaneous tobacco users and simultaneous ATD users endorsed the most lifetime ND symptoms and did not significantly differ from one another using the Bonferroni-adjusted significance level ($\chi^2(1) = 8.13$,

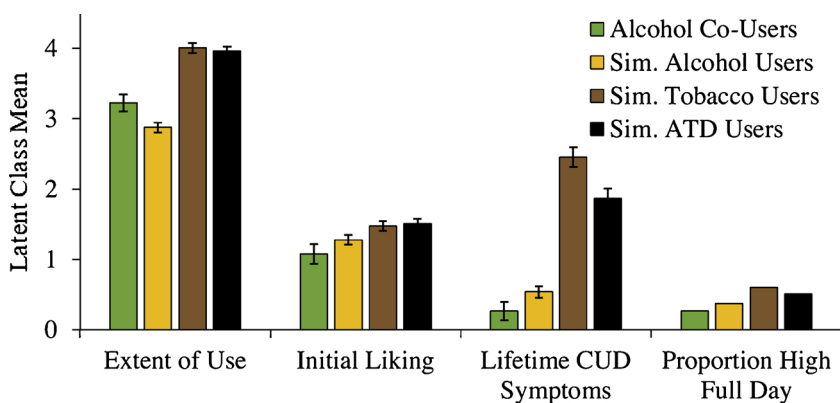


Fig. 2. Cannabis use outcomes across latent classes. Note: Error bars indicate standard errors. Sim. = simultaneous, ATD = alcohol, tobacco, and drugs, CUD = cannabis use disorder. Extent of use was coded such that 1 indicates using marijuana once, 2 indicates using twice, 3 indicates using 3–10 times, 4 indicates using 11–29 times, and 5 indicates using 30 or more times. Initial liking was coded such that 0 indicates initially liking cannabis ‘not at all’, 1 indicates liking ‘a little’, 2 indicates liking ‘some,’ and 3 indicates liking ‘a lot’. Color figure available online.

$p = 0.004$). Similarly, the two groups reported the most past-year ND symptoms ($\chi^2(1) = 0.78, p = 0.38$). Alcohol co-users, who reported low levels of tobacco use, had the fewest ND symptoms over their lifetime and in the past year compared to all other groups.

Finally, regarding illicit drug use, a familiar pattern emerged. Simultaneous tobacco users and simultaneous ATD users both had similar levels of illicit drug use, reporting use of about three illicit drug classes in their lifetime ($M = 2.97$ and 3.03 , respectively). This suggests that the simultaneous tobacco users in the current sample were also drug co-users, using illicit substances when not using cannabis, while simultaneous ATD users reported more simultaneous use of illicit drugs. Alcohol co-users and simultaneous alcohol users on average used two illicit drug classes in their lifetime ($M = 1.98$ and 2.03 , respectively). A similar pattern of results was found for past year illicit drug use.

3.2.3. Major depression

Simultaneous alcohol users had the lowest rates of lifetime major depression (17.5%), significantly differing from all other classes. Other classes did not differ. About one third of alcohol co-users, simultaneous tobacco users, and simultaneous ATD users met criteria for a lifetime major depressive episode.

3.3. Twin similarity of latent class membership

Same-sex twin pairs were significantly concordant for most likely class membership (MZ females $\kappa = 0.30 [0.21 - 0.39], p < .0001$; MZ males $\kappa = 0.25 [0.10 - 0.41], p = .0002$; DZ females $\kappa = 0.12 [0.01 - 0.22], p = .0001$), with the exception of DZ males ($\kappa = 0.13 [-0.04 - 0.31], p = .10$). This pattern of findings generally supports familial influences on cannabis use patterns. Opposite-sex twin pairs were not significantly concordant ($\kappa = 0.02 [-0.03 - 0.07], p = 0.38$), providing potential evidence for sex differences in the contributions to cannabis use patterns. Finally, there was higher concordance for class membership among same sex MZ compared to DZ twins ($\chi^2(1) = 7.19, p = 0.007$), providing support for genetic influences contributing to class membership.

These results were probed further by calculating intraclass correlations within and between latent classes and estimating the heritability of membership in each latent class (see Table 3). Results were largely consistent with the omnibus results presented above: within-class correlations were typically higher than between-class correlations and within-class correlations were higher among MZ compared to DZ twins for all latent classes among both men and women. The four latent classes had heritability estimates ranging from 12 to 58%.

4. Discussion

Patterns of simultaneous substance use and co-use were examined within a large sample of adult Australian lifetime cannabis users. Findings revealed four subtypes, or latent classes, of cannabis users who

Table 3
Intraclass correlations and latent class heritability for monozygotic and dizygotic twins.

		Class Twin 2			
		Alcohol Co-Use	Sim. Alcohol Use	Sim. Tobacco Use	Sim. ATD Use
Class Twin 1					
Monozygotic Female Twins (208 pairs)					
1	0.54	0.33	-0.39	-0.20	
2	0.21	0.23	-0.14	-0.17	
3	-0.26	-0.21	0.32	0.01	
4	-0.26	-0.17	0.09	0.26	
Dizygotic Female Twins (148 pairs)					
1	0.20	0.09	-0.09	-0.12	
2	0.21	0.21	-0.18	-0.10	
3	-0.06	-0.08	0.12	-0.02	
4	-0.26	-0.15	0.11	0.21	
Monozygotic Male Twins (98 pairs)					
1	0.42	0.06	0.00	-0.09	
2	0.09	0.26	-0.06	-0.28	
3	-0.05	-0.27	0.22	0.13	
4	-0.07	-0.05	-0.13	0.21	
Dizygotic Male Twins (75 pairs)					
1	0.09	0.08	-0.04	-0.05	
2	0.03	0.15	-0.10	-0.08	
3	-0.05	-0.13	0.15	0.03	
4	-0.01	-0.08	0.01	0.08	
Dizygotic Opposite Sex Twins (130 pairs)					
Class Female Twin		Class Male Twin			
1	0.04	0.19	-0.08	-0.15	
2	0.02	0.08	-0.02	-0.07	
3	-0.02	-0.06	0.01	0.06	
4	-0.01	-0.15	0.06	0.10	
Estimated Heritability of Latent Class Membership					
	Alcohol Co-Use	Sim. Alcohol Use	Sim. Tobacco Use	Sim. ATD Use	
Females	68%	4%	40%	10%	
Males	66%	22%	14%	26%	
Full Sample	58%	12%	30%	14%	

differed qualitatively from one another in their patterns of substance use. Cannabis use patterns were partially influenced by genetic and shared environmental factors, with twins being more likely to be assigned to the same rather than different latent classes.

As hypothesized, the co-user class, who reported primarily using alcohol and cannabis independently rather than simultaneously, was at lowest risk for problems. Simultaneous alcohol users, who reported typically using alcohol and cannabis together, endorsed significantly more AUD symptoms over their lifetime and during the past year compared to co-users. This is in line with previous research finding that simultaneous alcohol and cannabis users are at greater risk of alcohol-related harms compared to individuals who report using the substances non-simultaneously (Subbaraman and Kerr, 2015). Among the current

sample at least, this heightened risk was not driven by differences in age of initiation of alcohol or cannabis use. Some studies have suggested that heightened risk for alcohol problems among simultaneous users may be due to increased frequency and quantity of alcohol use (Linden-Carmichael et al., 2019; Subbaraman and Kerr, 2015). Post-hoc analyses provided evidence to support this: individuals in the simultaneous alcohol user class were more likely to report high-intensity drinking (drinking beyond the binge threshold of 4+/5+ drinks) ($\chi^2(1) = 58.21, p < 0.00001$) and getting drunk more frequently ($\chi^2(1) = 20.60, p = 0.000006$) compared to those in the co-user group. Simultaneous alcohol and cannabis users may benefit from interventions targeting reductions in alcohol use.

Simultaneous tobacco users and simultaneous ATD users were at highest risk for negative outcomes. Given that both of these groups engaged in simultaneous cannabis and tobacco use, this pattern of use may be especially detrimental. A number of previous studies have demonstrated similar findings, showing that cannabis users who smoke blunts, which are hollowed out cigars or cigarillos that are stuffed with cannabis, have more severe cannabis problems (Fairman, 2015; Ream et al., 2008; Timberlake, 2009). In one animal study, chronic administration of nicotine and THC, the psychoactive ingredient in cannabis, decreased the development of tolerance and increased physical dependence to cannabis (Valjent et al., 2002). These effects of simultaneous cannabis and tobacco use may put individuals at especially high risk of developing abuse and dependence.

4.1. Limitations

The current study was limited by the use of cross-sectional, retrospective assessment. There was some evidence for retrospective bias in reporting ages of onset, particularly initiation of cannabis use, which was correlated with participants' current ages ($r_s = 0.18, p < 0.0001$). Additionally, the replicability of these classes has not yet been established. However, the four latent classes appeared to "breed true" in MZ twin pairs, bolstering confidence in their repeatability.

Changing policies regarding cannabis use may have implications for the study's generalizability. Cannabis use is likely to increase as nations consider non-criminalization and legalization of cannabis. Both at the time of data collection and currently, recreational cannabis use is illegal in Australia (Kwai, 2019). However, since data collection, medicinal use of cannabis has been legalized federally in Australia; additionally, the Australian Capital Territory recently voted to legalize cannabis for recreational use (Kwai, 2019). As the status of cannabis evolves, predictors of patterns of cannabis use and its outcomes may change as well.

Patterns of tobacco use have also changed substantially in recent years. The current study's evaluation of tobacco use was limited in that it assessed only cigarette smoking. Rapid increases in the use of e-cigarettes may have implications for cannabis use, particularly given that devices can be used for vaping tobacco or cannabis products (Budney et al., 2015). Vaping devices are also generally perceived as being safer and more discreet than traditional smoking (Lee et al., 2016; Malouff et al., 2014). Increased perceptions of safety, normativeness, and greater discretion may make these devices especially appealing. Given that tobacco user groups in the current study were at greatest risk for experiencing cannabis problems, research should continue to investigate how emerging trends in tobacco use may affect cannabis use patterns.

Contributors

All authors have reviewed and approved the final manuscript. Davis developed the study concept, conducted the data analyses, and drafted the manuscript. Slutske provided methodological support and assisted in writing and editing all drafts of the manuscript. Lynskey and Agrawal developed the study measures. Lynskey, Agrawal, and Martin conducted the data collection.

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Author note

The original data collection was approved by the Institutional Review Boards at Washington University and Berghofer QIMR, and secondary analysis of these data was determined to be exempt by the University of Missouri Institutional Review Board (project # 1209709; Secondary Data Analyses of Australian Twin Registry Cohorts II and III).

Declaration of Competing Interest

No conflict declared.

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