Causal link between classic psychedelic use and mental health

096260 Causal Inference 2020

Final project

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1. Abstract

Classic psychedelics, which include dimethyltryptamine (DMT), lysergic acid diethylamide (LSD), mescaline, and psilocybin, have been studied clinically, anthropologically, and sociologically since the 1960's [1] [2]. Classic psychedelics appear to be both generally safe and potentially therapeutic in the treatment of anxiety disorders, mood disorders, and substance use disorders [3] [4] [5] [6] [7]. One of the intriguing works regarding the association of classical psychedelics and mental health was carried out by Hendricks, they utilized a large population-level analyses to demonstrate that lifetime classic psychedelic use is associated with a reduced likelihood of past month psychological distress and past year suicidality [8], figure 1 is taken form the paper, and classic psychedelic use is shown to have a statistically significant less than 1 odds ratio on mental health. This association is the focus of our work in this project. Where the original work looked only on association, we have looked at the casual effect and not just the association, this was achieved by using a casual graph that was build with the help of a clinical psychiatrist[1], which was followed by applying various causal inference algorithms (S/T learners and Matching).

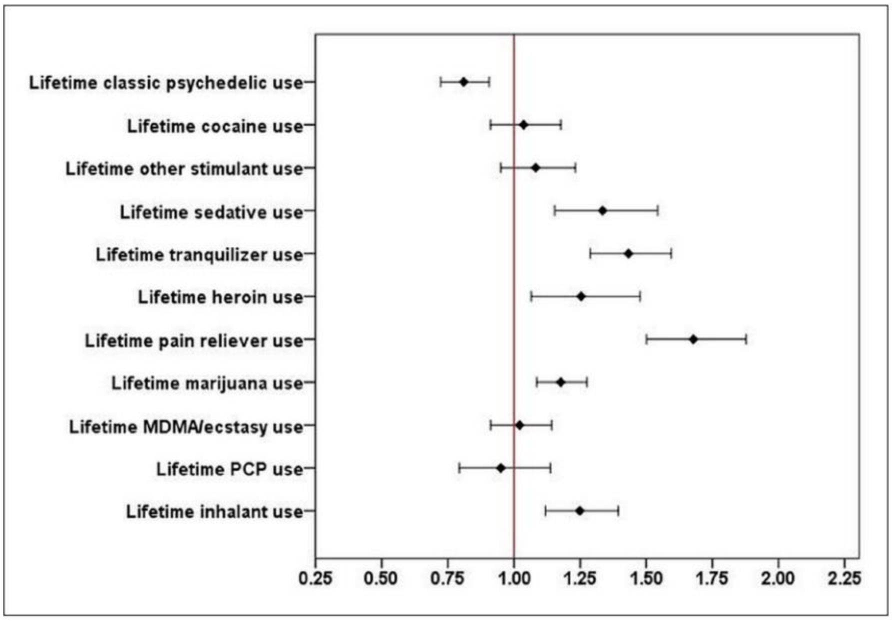


Figure 1. Result of multivariate logistic regression model predicting past month psychological distress. Diamonds are weighted odds ratio point estimates and error bars are 95% confidence intervals. Associations of demographic variables and self-reported engagement in risky behavior with psychological distress are not presented. *n*=191,369 due to missing data on the dependent variable. MDMA: 3, 4-methylenedioxymethamphetamine; PCP: phencyclidine.

Figure 1 - Odds ratio plots from Hendricks et el paper

[1] We would like to thank Dr. Nadav Shalit for his generous help and crucial remarks regarding the various casual assumptions, culminating in our casual graph.

2. Data

Data were obtained from the publicly available NSDUH, a survey of the general, non-institutionalized United States population aged 12 and older administered by the Substance Abuse and Mental Health Services Administration of the US Department of Health and Human Services. The survey uses a multistage probability sampling design where individuals are randomly selected within a roster that accounts for state population size and housing inventory. NSDUH interviewers met with respondents in their homes, who listened to pre-recorded interview guides on headphones and responded via computer prompt. We combined the data from 2008–2019 to maximize sample size while maintaining standardized assessment procedures introduced in 2008. The comprehensive NSDUH sampling and questionnaire methodology can be found on their website https://nsduhweb.rti.org/respweb/about_nsduh.html.

3. Problem Definition

In this project, we used causal inference methods to understand if lifelong use of classical psychedelics affects the current mental state. The treatment group is patients who used classical psychedelics in the past excluding those who started last year, and the mental state was analyzed using the following four outcomes:

Y1 – Past month serious psychological distress

Y2 – Past year serious consideration of suicide

Y3 – Past year suicidal planning

Y4 – Past year suicidal attempt

Features:

The table depicting the features was built with the help of a clinical psychiatrist, each feature was classified as either being a confounder, post-treatment, treatment, or outcome.

Covariate	**Code**	**Casual assumption**
AGE	AGE2	Confounder
OVERALL HEALTH	HEALTH2	Confounder
SEXUAL IDENTITY	SEXIDENT	Confounder
Gender	IRSEX	Confounder
Marital status	IRMARIT	Confounder
Categorical AGE	CATAG1-7	Confounder

EDUCATION	IREDUHIGHST2	Confounder
RELIGIOUS BELIEFS VERY IMPORTANT IN LIFE	RLGIMPT	Confounder
LIKE TO TEST YOURSELF BY DOING RISKY THINGS	RSKYFQTES	Confounder
RC-RACE/HISPANICITY RECODE (7 LEVELS)	NEWRACE2	Confounder
PAST 12 MOS, HOW MANY EMPLOYERS	WRKNUMJOB2	Confounder
IMPUTATION-REVISED # KIDS AGED<18 IN HH	IRK117_2	Confounder
COVERED BY PRIVATE INSURANCE	PRVHLTIN	Confounder
RC-TOTAL FAMILY INCOME RECODE	INCOME	Confounder
COUNTY METRO/NONMETRO STATUS (2013 3-LEVEL)	COUTYP4	Confounder
RC-EVER USED PSILOCYBIN (MUSHROOMS)	PSILCY2	Confounder
RC-EVER USED MESCALINE	MESC2	Confounder
RC-EVER USED PEYOTE	PEYOTE2	Confounder
SPENT MON/MORE GETTING/USING HALLUC PST 12 MOS	HALULOTTM	Confounder
RC-LSD - EVER USED	LSDFLAG	Confounder
RC-LSD - PAST YEAR USE	LSDYR	Confounder
RC-DMT/AMT/FOXY - EVER USED	DAMTFXFLAG	Confounder
RC-DMT/AMT/FOXY - PAST YEAR USE	DAMTFXYR	Confounder
RC-PAST MONTH SERIOUS PSYCH DISTRESS INDICATOR	SPDMON	Outcome
SERIOUSLY THOUGHT ABOUT KILLING SELF IN PAST YEAR	MHSUITHK	Outcome
ATTEMPTED TO KILL SELF IN PAST YEAR	MHSUITRY	Outcome
MADE PLANS TO KILL SELF IN PAST YEAR	MHSUIPLN	Outcome
COCAINE - EVER USED	COCFLAG	Confounder
RC-"CRACK" - EVER USED	CRKFLAG	Confounder
HEROIN - EVER USED	HERFLAG	Confounder
CIGARETTES - EVER USED	CIGFLAG	Confounder
CIGARS - EVER USED	CGRFLAG	Confounder
PIPES - EVER USED	PIPFLAG	Confounder
SMOKELESS TOBACCO - EVER USED	SMKLSSFLAG	Confounder
RC-ANY TOBACCO - EVER USED	TOBFLAG	Confounder
ALCOHOL - EVER USED	ALCFLAG	Confounder
MARIJUANA - EVER USED	MRJFLAG	Post-treatment
HALLUCINOGENS - EVER USED	HALLUCFLAG	Treatment
PCP - EVER USED	PCPFLAG	Confounder
ECSTASY - EVER USED	ECSTMOFLAG	Post-treatment

KETAMINE - EVER USED	KETMINFLAG	Post-treatment
RC-SALVIA - EVER USED	SALVIAFLAG	Post-treatment
RC-INHALANTS - EVER USED	INHALFLAG	Confounder
METHAMPHETAMINE - EVER USED	METHAMFLAG	Confounder
ANY PAIN RELIEVER - EVER USED	PNRANYFLAG	Confounder
ANY TRANQUILIZERS - EVER USED	TRQANYFLAG	Post-treatment
ANY STIMULANTS - EVER USED	STMANYFLAG	Confounder
ANY SEDATIVES - EVER USED	SEDANYFLAG	Post-treatment
ANY PSYCHOTHERAPEUTICS - EVER USED	PSYANYFLAG	Post-treatment

Figure 2 - Features table

4. Methods

As we wish to increase our understanding of the effect of psychedelics on the outcomes for those individuals who were exposed to them, we focus our analysis on the effect on the Treated. Since we ultimately dealing with a binary outcome, it is more informative to predict the class probability rather than the label. Thus, we fitted the data with either a logistic regressor (sklearn.LogisticRegression) or its cross-validated version (sklearn.LogisticRegressionCV) which is stratified to K folds to reduce variance. We used the regressors to predict the class probabilities and we set the maximum convergence iterations to 10,000.

Generally, Our Model is: $Y_i = \beta^T X_i + \gamma T$, for an outcome Y_i, feature vector X_i and learned coefficients vector and scalar β, γ.

To strengthen our results, each of the following steps was made separately for each year of the NSDUH data between 2017-2019, we also wished to run it over all the data but we couldn't solve the computational issues which occurred.

Casual Graph

Each of the features in table 2 can be represented in the following casual graph, using the backdoor adjustment there is the only path that goes through the confounders, as we leave the post-treatment covariates out of the analysis.

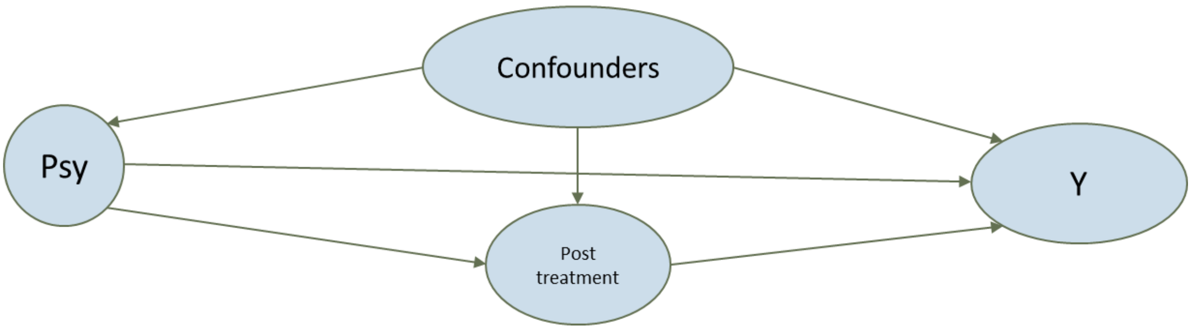


Figure 3 - Casual graph

1. *Odds ratio on the treated approach*

Following Hendricks et al. footsteps, we first tried to estimate the causal effect over the odds ratio, i.e:

$$\frac{\hat{P}(Y_i=1|\ T=1)}{\hat{P}(Y_i=0|\ T=1)} \Big/ \frac{\hat{P}(Y_i=1|\ T=0)}{\hat{P}(Y_i=0|\ T=0)}$$

which corresponds to the question is there a higher/lower probability for risk of the outcome Y_i when treated.

Covariate adjustment

After propensity score analysis using the same type of regressor, we trimmed samples with more than .95 (or < .05) propensity score, and it had a mild effect on our results variance compared to not trimming.

S-learner

After fitting a regressor to our entire data set, we predicted the outcome probabilities for the treated only and its counterfactual by setting manually T=0 and then calculated the odds ratio as written above.

T-learner

Here we fitted two separate regressors for the treated and the untreated and used the first to predict the outcome probabilities for the treated the latter for its counterfactual by setting manually T=0 and then calculated the odds ratio as written above.

Matching

The NSDUH data set is completely categorical where most are practically binary. This allowed us to encode each variable with more than 2 categories to several binary variables making different distance functions such as Euclidean, Manhattan, and Hamming to yield the same results. For computational efficiency reasons, we used Hamming distance which can be defined by the average number of disagreements between two vectors.
After fitting the regressor to the entire data set, we used two types of Matching:
1-1 matching, where for each subject of the treated group we matched the “closest” from the untreated and, calculated the odds ratio for each couple.
1-20 matching, where for each subject of the treated group we matched the “closest” 20 subjects from the untreated and averaged their predicted outcome probability and then calculated the odds ratio.

Balancing effect

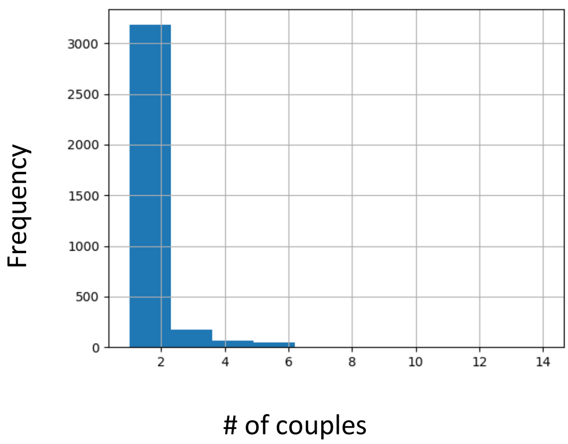
To show our matching effectiveness we present the balance table of the matched vs the entire data set. Recall that we encoded each of our covariates into binary variables, therefore we have in total 67 covariates, we will present here a representative result for the 2017 NSDUH data set and attach the rest to the project files.
Each cell $= \boldsymbol{P(Covariate = 1|T = t)}$

Covariate	Matched		General	
	T=0	T=1	T=0	T=1
Alcohol	0.993539	0.995558	0.877016	0.995558
any tobacco	0.957803	0.96386	0.636692	0.96386
CATAG6_2	0.304058	0.284878	0.354821	0.284878
CATAG6_3	0.239249	0.232183	0.225195	0.232183
CATAG6_4	0.322835	0.333333	0.277776	0.333333
CATAG6_5	0.118312	0.127599	0.106675	0.127599
CATAG6_6	0.015546	0.022007	0.035534	0.022007
Cigarettes	0.92126	0.930951	0.559758	0.930951
Cigars	0.677367	0.696749	0.334194	0.696749
Cocaine	0.320614	0.663436	0.076639	0.663436
COUTYP4_1	0.428225	0.428023	0.451164	0.428023
COUTYP4_2	0.382596	0.383404	0.347662	0.383404
COUTYP4_3	0.189178	0.188573	0.201173	0.188573
Crack	0.057945	0.170604	0.010922	0.170604
HEALTH2_1.0	0.191803	0.189784	0.255747	0.189784
HEALTH2_2.0	0.443166	0.415708	0.410649	0.415708
HEALTH2_3.0	0.301635	0.303654	0.260728	0.303654
HEALTH2_4.0	0.063396	0.090652	0.072654	0.090652
Heroin	0.031698	0.111851	0.005978	0.111851
INCOME_1	0.12558	0.150616	0.154939	0.150616
INCOME_2	0.30103	0.296588	0.300284	0.296588
INCOME_3	0.160105	0.172421	0.166599	0.172421
INCOME_4	0.413285	0.380376	0.378178	0.380376
IRSEX_1	0.619423	0.628104	0.468654	0.628104
IRSEX_2	0.380577	0.371896	0.531346	0.371896
METHAMPHETAMINE	0.093277	0.270139	0.022361	0.270139
pain reliever	0.824349	0.822936	0.609387	0.822936
PCP	0.008076	0.097517	0.003321	0.097517
Pipe	0.200081	0.28407	0.078964	0.28407
RC-INHALANTS - EVER USED	0.202907	0.395922	0.062839	0.395922
SEXIDENT_1	0.918635	0.896628	0.933582	0.896628
SEXIDENT_2	0.025237	0.033313	0.022176	0.033313
SEXIDENT_3	0.056128	0.070059	0.044242	0.070059
smokeless tobacco	0.425399	0.459721	0.175049	0.459721
Stimulants	0.281446	0.410256	0.122394	0.410256

It can be seen from the table that matching is indeed balanced the distribution between the treatment and control group.

Couples Distribution

The following histogram shows that almost every couple is a 1-1 match, only some have more than one which strengthens the validity of our matching technique.



Results of Odd ration

Here we present our results for the 2019 causal Odds ratio, similarly for the other years, it is noticeable that first, we get a different direction of the odds ratio, i.e for the most part, for each outcome and each method, the risk for any of the outcome is greater than 1. T1/T0 is the number of subjects for each treatment.

			2019			
Estimator	**O**	**Predictor**	**Mean**	**STD**	**T1**	**T0**
s_Learner	y1	Logistic	0.98386367	2.7618E-16	4341	11448
t_Learner	y1	Logistic	1.004403737	0.446692413	4341	11448
Matching 1-20	**y1**	**Logistic**	**1.404248456**	**0.756617083**	**4985**	**26896**
s_Learner	y1	LogisticCV	0.987370053	3.06193E-16	4330	11427
t_Learner	y1	LogisticCV	2.363307076	2.488755112	4330	11427
Matching 1-20	**y1**	**LogisticCV**	**1.404638128**	**0.742761639**	**4985**	**26896**
Matching 1-1	y1	LogisticCV	1.588204359	1.420953649	4985	26896
s_Learner	y2	Logistic	1.202845015	2.55285E-16	4341	11448
t_Learner	y2	Logistic	1.299526435	0.730844208	4341	11448
Matching 1-20	**y2**	**Logistic**	**1.634269003**	**0.688691197**	**4985**	**26896**
s_Learner	y2	LogisticCV	1.173842764	3.46414E-16	4330	11427
t_Learner	**y2**	**LogisticCV**	**1.33571314**	**0.526261684**	**4330**	**11427**
Matching 1-20	**y2**	**LogisticCV**	**1.63304853**	**0.677484027**	**4985**	**26896**
Matching 1-1	**y2**	**LogisticCV**	**1.764000684**	**1.203369796**	**4985**	**26896**
s_Learner	y3	Logistic	0.813142886	2.55857E-16	4341	11448
t_Learner	y3	Logistic	1.070003517	0.990601845	4341	11448
Matching 1-20	y3	Logistic	1.213225464	0.715278892	4985	26896
s_Learner	y3	LogisticCV	1.000677996	4.59786E-16	4330	11427

t_Learner	y3	LogisticCV	1.196601913	0.006411381	4330	11427
Matching 1-20	y3	LogisticCV	1.010075476	0.005494473	4985	26896
Matching 1-1	y3	LogisticCV	1.007644702	0.008031909	4985	26896
s_Learner	y4	Logistic	0.828722471	3.0031E-16	4341	11448
t_Learner	y4	Logistic	1.360330521	1.689717775	4341	11448
Matching 1-20	y4	Logistic	1.244373536	0.620360757	4985	26896
s_Learner	y4	LogisticCV	1.002000755	1.82748E-16	4330	11427
t_Learner	y4	LogisticCV	1.257593132	0.015801022	4330	11427
Matching 1-20	y4	LogisticCV	1.310637343	0.505283116	4985	26896
Matching 1-1	y4	LogisticCV	1.407001513	0.936018496	4985	26896

Second, our STD, for the most part, is very large compared to what was presented on the paper we follow. S learner consistently showed a small STD (~1E-16), due to the large STD we can conclude that none of the results are statistically significant.

Analysis of the odds ratio showed that a reason for the high STD could be the fact that the outcomes themselves are 1 for a very small percentage of the population, y1 - 9.4%, y2 - 7.4%, y3 – 0.9%, y4-2.2%.

We conclude that the odds ratio could "jump" easily when dealing with small probabilities (as it's the result of dividing two ratios), hence we decided to repeat the experiment only this time, calculating the ATT instead of the odds ratio for the same setup.

2. *ATE on the treated approach (ATT):*

Everything is identical to the methodology elaborated in the odds ratio part, except instead of calculating the odds ratio we calculate

ATT = $\hat{P}(Y_i = 1 \,|T = 1) - \hat{P}(Y_i = 1 \,|T = 0)$

i.e. the difference in the chance for an outcome Y_i when treated to when untreated.

Results

Here we present our results for the 2019 causal ATT, for y3 and y4 we have a strong indication that the ATT is near 0, while for y1 and y2 our results vary.

			2019			
Estimator	**O**	**Predictor**	**Mean**	**STD**	**T1**	**T0**
s_Learner	y1	Logistic	-0.12%	0.09%	4330	11427
t_Learner	y1	Logistic	-0.28%	12.83%	4330	11427
Matching 1-20	**y1**	**Logistic**	**3.88%**	**7.01%**	**4985**	**26896**
s_Learner	y1	LogisticCV	-0.12%	0.09%	4330	11427
t_Learner	**y1**	**LogisticCV**	**-0.28%**	**12.83%**	**4330**	**11427**
Matching 1-20	**y1**	**LogisticCV**	**3.88%**	**7.01%**	**4985**	**26896**
Matching 1-1	**y1**	**LogisticCV**	**2.71%**	**8.13%**	**4985**	**26896**

s_Learner	y2	Logistic	1.46%	0.87%	4330	11427
t_Learner	**y2**	**Logistic**	**1.05%**	**4.50%**	**4330**	**11427**
Matching 1-20	**y2**	**Logistic**	**4.57%**	**6.23%**	**4985**	**26896**
s_Learner	y2	LogisticCV	1.46%	0.87%	4330	11427
t_Learner	**y2**	**LogisticCV**	**1.05%**	**4.50%**	**4330**	**11427**
Matching 1-20	**y2**	**LogisticCV**	**4.57%**	**6.23%**	**4985**	**26896**
Matching 1-1	**y2**	**LogisticCV**	**3.61%**	**6.82%**	**4985**	**26896**
s_Learner	y3	Logistic	0.00%	0.00%	4330	11427
t_Learner	y3	Logistic	0.22%	0.01%	4330	11427
Matching 1-20	y3	Logistic	0.01%	0.01%	4985	26896
s_Learner	y3	LogisticCV	0.00%	0.00%	4330	11427
t_Learner	y3	LogisticCV	0.22%	0.01%	4330	11427
Matching 1-20	y3	LogisticCV	0.01%	0.01%	4985	26896
Matching 1-1	y3	LogisticCV	0.01%	0.01%	4985	26896
s_Learner	y4	Logistic	0.01%	0.00%	4330	11427
t_Learner	y4	Logistic	0.65%	0.03%	4330	11427
Matching 1-20	y4	Logistic	1.08%	2.56%	4985	26896
s_Learner	y4	LogisticCV	0.01%	0.00%	4330	11427
t_Learner	y4	LogisticCV	0.65%	0.03%	4330	11427
Matching 1-20	y4	LogisticCV	1.08%	2.56%	4985	26896
Matching 1-1	y4	LogisticCV	0.66%	2.88%	4985	26896

Moreover, we get somewhat consistent results for 2018 and 2017 for y4 and y3 but inconsistencies for y1 and y2:

			2018				2017			
Estimator	**O**	**Predictor**	**Mean**	**STD**	**T1**	**T0**	**Mean**	**STD**	**T1**	**T0**
s_Learner	y1	LogisticCV	0.89%	0.73%	4458	12132	-0.944%	0.71%	4351	11450
t_Learner	y1	LogisticCV	-0.51%	6.53%	4458	12132	-1.497%	4.80%	4351	11450
Matching 1-20	y1	LogisticCV	4.00%	7.23%	5069	27119	2.826%	6.34%	4953	27101
Matching 1-1	y1	LogisticCV	3.00%	7.74%	5069	27119	1.688%	7.63%	4953	27101
s_Learner	y2	LogisticCV	1.29%	0.98%	4458	12132	0.067%	0.00%	4351	11450
t_Learner	y2	LogisticCV	1.37%	4.74%	4458	12132	3.034%	0.07%	4351	11450
Matching 1-20	y2	LogisticCV	4.46%	6.82%	5069	27119	0.324%	0.17%	4953	27101
Matching 1-1	y2	LogisticCV	3.53%	6.96%	5069	27119	0.252%	0.23%	4953	27101
s_Learner	y3	LogisticCV	0.00%	0.00%	4458	12132	0.001%	0.00%	4351	11450
t_Learner	y3	LogisticCV	0.58%	3.11%	4458	12132	0.414%	0.00%	4351	11450
Matching 1-20	y3	LogisticCV	0.01%	0.01%	5069	27119	0.008%	0.00%	4953	27101
Matching 1-1	y3	LogisticCV	0.01%	0.01%	5069	27119	0.007%	0.01%	4953	27101
s_Learner	y4	LogisticCV	0.24%	0.30%	4458	12132	0.006%	0.00%	4351	11450
t_Learner	y4	LogisticCV	1.25%	4.78%	4458	12132	0.839%	0.01%	4351	11450
Matching 1-20	y4	LogisticCV	0.05%	0.02%	5069	27119	0.038%	0.02%	4953	27101
Matching 1-1	y4	LogisticCV	0.04%	0.03%	5069	27119	0.029%	0.03%	4953	27101

5. Weaknesses in the analysis

Predicting probabilities

To estimate our outcomes, we trained variants of logistic regression predictors, mostly following Hendricks et al. Doing so, we fitted our predictors to the data to correctly guess the outcome label, but we were not interested in the label but in its probability. Therefore, we can easily think of a scenario where our estimator can label the classes correctly but the actual probabilities not so much. We believe this might be an inherently problematic way to estimate a causal effect.

High/low variance

In many cases, as can be seen above, we got a very high or surprisingly low variance, in both cases, we are unable to explain the reasons for it. In some cases, we get the opposite effect on different years, although the data set is very large and balanced.

6. Discussion

The problem in the original work by Hendricks

The original conclusion was that there is an association between the lifetime use of classical psychedelics and recent mental state. (which could also be one-time use at some point in a person's life and his recent mental state). To us, this sounded like a strong conclusion most notably due to the work done by Johansen et al on the same database that showed **no link** at all between classical psychedelics and mental state [9]. After a careful reading we suspected that the analysis that was carried out by Hendricks is lacking, most notably:

1. There was no adjustment of covariates at all between the treatment and control group.
2. Many of the covariates used are post-treatment.
3. No causal inference methods were used.

Our causal conclusion

From our analysis, we can conclude that the is no causal effect between classical psychedelics and outcomes Y3 and Y4, both in the odds ratio and the ATT analysis.
We have seen some signals regarding outcomes Y1 and Y2, but due to the high variance, none of the results were statistically significant. We must bear in mind that our casual graph assumed no hidden confounder, which of course could be still present. We do believe that the results of the paper by Hendricks are due to flawed analysis and our results reinforce the results achieved by Johansen.
We do believe that classical psychedelic use can affect positively the mental state of the user, but as research has shown, set and setting are quite important [10], and as far as we can tell the users in the NSDUH database most probably had counterproductive set and setting when they have used classical psychedelics, thus negating the effect assuming it is indeed present.

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