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Bachelor Thesis Economics & Business Economics

Psychedelics and anxiety: a Dutch population study

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Abstract

This paper aimed to estimate the effect of classic psychedelics use on anxiety level in the Dutch population, making use of Augmented Inverse Probability Weights estimation with adjustment for definite and potential confounders and one-way variables. Data was drawn from waves 1-7 and 9-14 of the Longitudinal Internet Studies for the Social sciences. Anxiety level, measured on a scale of 1 till 6, on average increases with 0.466 ($p=0.023$) when an individual shifts from not using psychedelics to using them. Results were robust to replacing the outcome variable with the highly-correlated covariate depression. The chance someone is using anxiety medication tends to decrease when an individual shifts from not using psychedelics to using them, the average effect ranging from -3.3% to -4.5% ($p<0.05$) depending on the set of covariates adjusted for. Findings contradict to conclusions from previous research, which found significant reductions in anxiety after psychedelics use.

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1. Introduction

Psychedelics are living up to their name: as uncapturable the definition of the word is, so uncapturable are the effects of the substances that fall within the definition. A certain dose of a given substance may produce different effects in the same individual upon different occasions of usage (Naranjo, 1973). The fifth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5) classifies psychedelics as a group of substances that alter perception, mood and cognition in users in a similar way, while chemical structures are differing (American Psychiatric Association, 2013). This research focuses on classic psychedelics, which include lysergic acid diethylamide (LSD), N,N-dimethyltryptamine (DMT), mescaline and psilocybin.

Earlier research on the effect of psychedelics use on anxiety was mostly performed on individuals diagnosed with anxiety as a consequence of a life-threatening disease (Griffiths et al., 2016; Ross et al., 2016; Grob et al., 2011; Gasser, Kirchner & Passie, 2015; Palhano-Fontes et al., 2019). Research in healthy individuals, however, was mostly performed in a clinical setting (Santos, Landeira-Fernandez, Strassman, Motta & Cruz, 2007; Griffiths, Richards, McCann & Jesse, 2006; Studerus, Kometer, Hasler & Vollenweider, 2011). Ultimately, research on the effect of non-clinical use of psychedelics only investigated the effects of lifetime use on receiving or needing mental health treatment (Krebs & Johansen, 2013), having suicidal plans and thoughts (Johansen & Krebs, 2015) and past month psychological distress (Hendricks, Thorne, Clark, Coombs & Johnson, 2015), instead of anxiety specifically. In contrast to above mentioned publications, this paper investigates the effect of using psychedelics in a non-clinical setting on anxiety specifically and on population-level, by answering the following question.

"*What is the effect of non-clinical psychedelics use on anxiety level in the Dutch population?*"

This research focuses specifically on the Netherlands because of the Dutch policy of toleration regarding drugs. In principle, the possession, cultivation, production, trade, import and export of all substances listed on Schedule I and II of the Opium Act are violations of the Dutch criminal law (art. 2 & 3 Opiumwet, 2021). Schedule I contains all drugs that are defined as narcotics with an unacceptable risk to public health (hard drugs), which includes the isolated active

substances from all classic psychedelics. Schedule II contains all other drugs (soft drugs) and includes both dried and fresh psycho-active mushrooms (Ministerie van Justitie en Veiligheid, 2020). However, multiple organisms containing psycho-active substances are not listed on any of both Schedules. These organisms include sclerotia (which contain psilocybin), mescaline-cacti and DMT-containing plants such as *psychotria viridis*. Because possession, cultivation, production, trade, import and export are not prosecuted, these organisms are legally sold in so called *smartshops*.

Additionally, drug use itself and the possession of user amounts of substances listed on Schedule I or II are not specified as crimes. A user amount of hard drugs is defined as an amount below the maximum of 0.5 gram. Tolerated user amounts for dried and fresh mushrooms are 0.5g and 5g, respectively (art. 2 Aanwijzing Opiumwet, 2015). This rule is implemented with the intention to primarily focus on delicts that cause a higher risk for public health (Ministerie van Justitie en Veiligheid, 2020). As a consequence of the toleration policy, I expect any social desirability bias to be lower in the Netherlands compared to other countries, because of less pressure to give socially acceptable answers in surveys.

According to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), the Netherlands was one of the countries[1] reporting higher rates than average of adolescents between the ages of 18 and 20 that ever used LSD in 1997 (EMCDDA, 1997a). From 2005 onwards, magic mushrooms were the most used psychedelics in the Netherlands. Since the inclusion of these mushrooms in Schedule II of the Dutch Opium Act in 2009, sclerotia, which contain the same active substance as mushrooms, are replacing magic mushrooms in smartshops and online sales (EMCDDA, 2009). Figure 1 (Trimbos-instituut, 2022) shows that the percentage of individuals aged 15-64 that

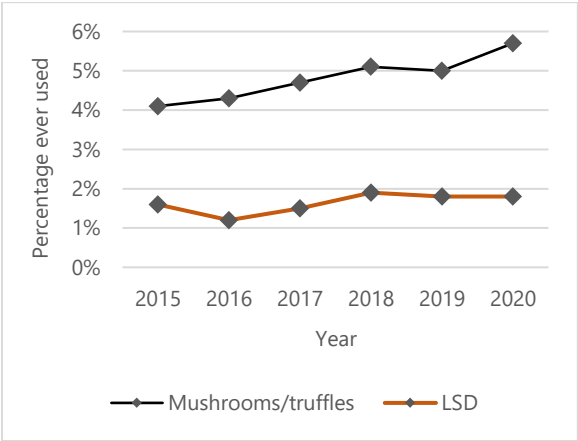

Figure 1: Percentage of individuals aged 15-64 that has ever used magic mushrooms/sclerotia and LSD.

[1] Together with Belgium, the United Kingdom and Spain.

ever used magic mushrooms or sclerotia has been increasing between 2015 and 2020. Furthermore, online-survey data suggests that psychedelics use in Europe increased during the Covid-19 pandemic (EMCDDA, 2021). The EMCDDA mentions that this might be because these substances are preferred over party drugs for at-home use. This increasing trend in psychedelics usage makes it more important to investigate the possible effects of psychedelics on society.

From an economic point of view it is important to investigate the effect of psychedelics use on anxiety, because anxiety and stress disorders should be considered among the most costly of all mental disorders, according to Kessler and Greenberg (2002). Annual cost of anxiety disorders in the US has been estimated to be between $42 billion and $47 billion, excluding long-term opportunity costs and costs associated with comorbidity. As a comparison, the annual cost of depression, which is generally considered the most costly of all physical and mental disorders, has been estimated to be between $44 billion and $53 billion.

Besides the direct monetary cost, anxiety causes an indirect societal cost: the human capital potential of individuals suffering from anxiety is adversely affected by their condition (Kessler & Greenberg, 2002). Specifically, anxiety is associated with elevated risk of early death, subsequent unemployment, and an increased chance of working at low-paying jobs due to reduced ability to cope with the stresses of higher paying jobs. Furthermore, anxiety being diagnosed at a young age raises one's odds of school failure, teenage childbearing and marital instability, which are the core elements of welfare dependency. This cost of public assistance is paid by all taxpayers and thus influences society as a whole.

The Dutch government could take the effect of non-clinical psychedelics use on anxiety level into account when implementing new policies. In case psychedelics use is found to increase anxiety level, the government could for example consider adding sclerotia to Opium Act Schedule I or II to prohibit the possession, cultivation, production, trade, import and export of so called magic truffles. In case an opposite effect is found, they could consider choosing a different approach to address the drug situation. They could, for example, inform individuals through education, which was also the main advise of the Coordination Centre for Assessment and Monitoring of new drugs (CAM; CAM, 2007). However, based on this research no

recommendation can be made implying loosening of the legalisation of psycho-active substances that currently are on Opium Schedule I or II, because the effects of psychedelics use on important factors such as physical health and criminality are not taken into account.

This paper makes use of the LISS Core Study, a longitudinal dataset containing annual information of 14,615 individuals from 2007 till 2021. Augmented Inverse Probability Weights (AIPW) estimation is applied, adjusting for four different sets of covariates. Anxiety level, measured on a scale of 1 till 6, on average increases with 0.466 ($p=0.023$) when an individual shifts from no treatment to treatment. However, three out of four models did not find a significant effect. Results were robust to replacing the outcome variable with the highly-correlated covariate depression (ATE varying from 0,340 to 0,365, $p<0.05$). The chance someone is using anxiety medication tends to decrease when an individual shifts from not using psychedelics to using them, the average effect ranging from -3.3% to -4.5% depending on the set of covariates adjusted for.

The remainder of the paper is structured as follows. Section 2 describes the effect of psychedelics on the human brain and gives an overview of earlier conducted research. After that, Section 3 describes the data used. Section 4 explains AIPW estimation and describes the used models. Results for each model are shown in Section 5. Thereafter, Section 6 summarizes the results, describes the drawbacks of this research and provides the reader with policy implications and recommendations for future research. Section 7 concludes.

2. Theoretical framework

2.1 Effect of usage on the human brain

Classic psychedelics include LSD, DMT, mescaline and psilocybin. These substances have in common that they biochemically are serotonin 2A receptor (5-HT_{2A}R) agonists (Johnson, Hendricks, Barrett & Griffiths, 2019). 5-HT_{2A}R agonists activate the 5-HT_{2A} receptors which are found in multiple areas of the brain, but especially in the brain region essential for learning and cognition, the prefrontal cortex (Hanks & González-Maeso, 2016a). These receptors appear to be responsible for the hallucinogenic effects of psychedelics (Hanks & González-Maeso, 2016b). Notably, psychiatric disorders such as depression and anxiety are related to abnormal

5-HT_{2A} receptor activity in the brain (Jacobsen, Medvedev & Caron, 2012; Celada, Puig, Amargós-Bosch, Adell & Artigas, 2004; Zhang & Stackman Jr, 2015).

CAM (2007) reports that magic mushrooms do not cause physical or mental dependence in users, and comparably, EMCDDA (2006) reports that acute or chronic health problems only rarely occur as a consequence of psychedelic mushroom use.

2.2 Literature review

2.2.1 Trials in clinical setting: individuals suffering from certain medical conditions

Griffiths et al. (2016) found that a single high psilocybin dose significantly and substantially reduced depression and anxiety measures five weeks and six months after treatment. Similarly, Ross et al. (2016) found that anxiety and depression symptoms were significantly and substantially lower at six months after administration for cancer-patients who met criteria for a DSM-5 anxiety-related disorder. In that same target group, Grob et al. (2011) found that psilocybin relative to placebo showed a trend toward decreasing depression severity and anxiety severity two weeks after administration. This effect remained significant up to the last follow-up at six months after treatment. Based on these three studies, Goldberg, Pace, Nicholas, Raison and Hutson (2020) suggest that psilocybin in combination with behavioural support may provide a safe and effective treatment option for reducing symptoms of anxiety and depression in patients with life-threatening cancer.

Comparably, Gasser et al. (2014) found a significant reduction in state anxiety as experienced on a daily basis, and a strong trend towards reduction of trait anxiety in individuals diagnosed with a life-threatening disease, after LSD-assisted psychotherapy. DMT evokes comparable results: Palhano-Fontes et al. (2019) found that ayahuasca-assisted psychotherapy in individuals with treatment-resistant depression significantly improved depression severity. Although the placebo effect was high in this study, improvements in the psychiatric scales in the treatment group were significantly higher than those of the placebo group at all time points after dosing. Even though study designs, psycho-active substances and doses were different between the studies described in Section 2.2.1, transient adverse reactions were similar across studies and resolved within hours of administration of psilocybin. No serious or persistent adverse events were reported in any of the studies. It is noteworthy to mention that treatment

groups were small (n<30) in most of the studies (Ross et al., 2016; Grob et al., 2011; Gasser et al., 2014; Palhano-Fontes et al., 2019).

2.2.2 Trials in clinical setting: healthy individuals

Research in healthy humans is rather limited. Griffiths et al. (2006) studied the psychological effects of a single high dose of psilocybin compared to an inactive placebo. Eight of 36 medically and psychiatrically healthy participants experienced a period of anxiety or unhappiness during the session. However, these effects did not persist beyond the psilocybin administration, and none of the volunteers rated the experience as having decreased their sense of well-being or life satisfaction. Consistently, Studerus et al. (2011) concluded that most participants described the one-time experience of psilocybin as pleasurable, enriching and non-threatening. In contrast, participants in the study of Santos et al. (2007) showed no changes in either trait or state anxiety after consuming ayahuasca. However, the authors emphasize that the participants had at least ten years of experience with ayahuasca and may have begun the study with relatively low levels of anxiety.

2.2.3 Observational studies

Similar to research in healthy individuals, research on the effect of single-time non-clinical use of psychedelics on anxiety is scarce. This is shown by the facts that neither of the following researches zoomed in on anxiety specifically, and that they all investigate the effect of life-time psychedelics use instead of one-time use. Krebs and Johansen (2013) find significant associations of lifetime LSD, psilocybin and mescaline use and lower rates of receiving or needing mental health treatment. They mention that the weak association between psychedelics use and lower rates of mental health problems might reflect beneficial effects of these substances. In a follow-up study, Johansen and Krebs (2015) included data on suicidal thoughts and suicide attempts and find that among individuals with a history of childhood depression, psychedelics use was associated with a lower likelihood of suicidal plans and thoughts. Drawing from a larger number of years of the same sample, Hendricks et al. (2015) found that lifetime classic psychedelic use was associated with a decreased likelihood of past month psychological distress, past year suicidal thinking and planning and past year suicide attempt.

2.3 Hypotheses

All researches mentioned in Sections 2.3.1, 2.3.2 and 2.3.3 are more specific than this research in either setting, target group or treatment. In other words, mentioned researches focus specifically on either clinical setting or non-clinical setting, and specifically on either healthy individuals or individuals suffering from certain medical conditions. Furthermore, they all have in common that the type of psychedelic used is known. Current research includes observational data from the Dutch population, in which setting and doses are unknown. Hence, multiple settings in which psychedelics were used and multiple different substances and doses are possibly included. This is a drawback, because the context in which a drug is taken strongly influence the experience (Hartogsohn, 2017). Furthermore, it is hard to expect a certain effect of psychedelics use on anxiety level based on earlier research. However, considering that besides Santos et al. (2017) all researches found a decrease in the level of the investigated outcome covariate (i.e. anxiety, depression, need of mental health treatment or suicidal thoughts and attempts), I expect a lower level of anxiety for individuals that used psychedelics within the past four years compared to non-users.

Based on the finding of Jacobsen, Medvedev and Caron (2012), Celada et al. (2004) and Zhang and Stackman Jr (2015), that besides anxiety also depression disorders are related to abnormal 5-HT_{2A} receptor activity in the brain, I expect that depression and anxiety level are highly correlated. Therefore, depression level is used as a variable to test the sensitivity for changes in outcome.

To compare the effect of psychedelics on anxiety and depression level with an objective measurement, the effect of psychedelics use on anxiety medication use is estimated. In line with the expectation that anxiety level decreases when psychedelics are used, I expect that the use of anxiety medication drops when psychedelics are used.

3. Data

3.1 Definitions

Cattell and Scheier (1958) define anxiety as "a phenomenon that manifests itself in immediate experience as an unpleasant emotional feeling with a characteristic anticipatory character – the

expectation of impending danger.'' The authors mention that opinions differ on how intense a feeling must be and how long it must last to be described as anxiety. Classic psychedelics are substances that are either naturally occurring or synthesised in laboratories and include LSD, DMT, mescaline and psilocybin[2].

3.2 Dataset

In this paper I make use of data of the LISS (Longitudinal Internet Studies for the Social sciences) panel administered by Centerdata (Tilburg University, The Netherlands). All necessary information from the respondents was collected by use of online questionnaires for which the respondents were paid to complete. I specifically make use of the LISS Core Study, an annual longitudinal study designed to follow changes in the life course and living conditions of the panel members. The dataset contains annual information of 14,615 individuals from 2007 till 2021. No questionnaires were held in 2014. Every year, called a wave, is published as a separate dataset which can be combined by matching an individual's personal identifier.

Wave 8 is considered to be inappropriate for this research because data were collected in July and August, in contrast to all other waves which were collected in winter. This is a problem, because the difference in season affects both anxiety and psychedelics use measurements. In the first place, anxiety in winter is expected to be higher due to seasonal affective disorders (SAD) or winter blues. SAD is a combination of biologic and mood disturbances with a seasonal pattern, most commonly occurring in winter due to the decrease in amount of daylight (Kurlansik & Ibay, 2012). Besides a decreased energy level and a loss of interest or pleasure in most activities, a common symptom of SAD is an increased level of anxiety (Jacobsen, Wehr, Sack, James & Rosenthal, 1987). Prevalence estimates of SAD in general population varied from 0 to 9.7 percent (Magnusson, 2000). Additionally, the prevalence of generalized anxiety disorder in the Netherlands was estimated to be higher in winter than in any other season by De Graaf, Van Dorsselaer, Ten Have, Schoemaker and Vollebergh (2005). In the second place, psychedelics use knows seasonal variation. Lipari (2015) investigated the monthly variation of

[2] Besides LSD, DMT, mescaline and psilocybin, another commonly used substance in psychotherapy is methylenedioxy-methylamphetamine (MDMA). However, MDMA is not a 5-HT_{2A}R agonist and is therefore considered a non-classic psychedelic.

(among others) psychedelics initiation in college students. The results show a peak in the number of first time psychedelic users in October. The biggest difference between two months is a 42% drop in the number of first time users between July and August. Considering that both anxiety level and psychedelics use are influenced by seasonal variation, wave 8 will not be included in this research.

3.3 Assessment of covariates

In the questionnaire, which was conducted in Dutch, the respondents were asked to assess five statements on how they felt during the past month. Possible answers were 1) never, 2) seldom, 3) sometimes, 4) often, 5) mostly or 6) continuously. Responses to the statement 'I felt very anxious' are being used as a variable for anxiety, the outcome of interest. As sensitivity analysis, the assessment of the statement 'I felt depressed and gloomy' is being be used as an outcome variable instead of anxiety. To compare these two subjective outcomes to an objective outcome, the answers to the question 'Are you currently taking medicine at least once a week for anxiety or depression?' is being used. This question was answered with either 'yes' or 'no'. The original survey questions in Dutch are presented in Appendix A.

To assess for psychedelics use, the treatment variable in this research, a question was included in the questionnaire that asked if respondents had used "mind-altering substances (such as LSD, magic mushrooms)" in the past month. The follow-up study of Agin-Liebes et al. (2020) suggests that a single high-dose of psilocybin continues to be associated with reductions in anxiety and depression up to 4.5 years after administration, and therefore respondents remain in the treatment group until four years after the last year they indicated to have used psychedelics.

The question indicating psychedelics use left room for respondent's own interpretation of which substances fall within the category psychedelics, because no overview of included substances was given besides "such as LSD, magic mushrooms". This may cause other substances than LSD, DMT, mescaline and psilocybin to be taken into account when answering the question, which could bias the results when the intention to use of a certain substance

differs from classic psychedelics.[3][4] The user's intention or expectation, the so called *set*, strongly influences the experience and outcome of psychedelics use (Garcia-Romeu & Richards, 2018; Hartogsohn, 2017; Metzner, Litwin & Weil, 1965).

Other variables used in this research are age, gender, educational level, employment status, net monthly income, BMI, whether an individual is diagnosed with cancer, urban character of place of residence, anxiety level in the previous year and whether an individual has trouble with speaking Dutch. Age is defined as age in years at the moment of the interview, captured in integers. Gender is defined as 1) male, 2) female and 3) other. Educational level is defined as level of education in Statistics Netherlands categories: 1) primary school; 2) vmbo (intermediate secondary education, US: junior high school); 3) havo/vwo (higher secondary education/preparatory university education, US: senior high school); 4) mbo (intermediate vocational education, US: junior college); 5) hbo (higher vocational education, US: college) and 6) wo (university). Employment status is captured in a binary variable that equals 1 if a respondent has paid work and 0 otherwise. Net monthly income in euro's is a continuous variable rounded to two decimals. BMI is a continuous variable that is calculated as body weight in kilograms divided by the power of length in centimetres. Whether an individual was diagnosed with cancer equals 1 if a physician told the respondent this last year that (s)he suffer from "cancer or malignant tumor, including leukaemia or lymphoma, but excluding less serious forms of skin cancer" and 0 if not. Urban character of place of residence is defined as the address density per square kilometre surrounding the participant's postal code, categorized as 1) extremely urban (>2500); 2) very urban (1500-2500); 3) Moderately urban (1000-1500); 4) slightly urban (500-1000) and 5) not urban (<500). Anxiety level in the previous year is captured by the responses to the statement 'I felt very anxious' that were entered the year before. Whether an individual has trouble with speaking Dutch is categorized as 1) yes, often have trouble/do not speak Dutch; 2) yes, sometimes and 3) no, never.

[3] Because MDMA usage was captured in a different question in the survey, it can be assumed that respondents did not include their MDMA use when answering the question addressing psychedelics use. This is important because MDMA is, in contrast to psychedelics, associated with social events such as parties (EMCDDA, 2021). Therefore, the intentions of MDMA users may be substantially different from psychedelics use, which are particularly used in specific (religious or cultural) groups. (Van Laar & Van Miltenburg, 2020).

[4] Ketamine, for example, is a dissociative anaesthetic but has psychedelic properties and is therefore used in psychotherapy as well. However, recreational use of ketamine happens mostly in dance cultures and therefore the intention to use differs from classic psychedelics (Jansen, 2000).

3.4 Descriptive statistics

Table 1 shows the demographic characteristics of the treatment group, control group and full sample, respectively, as a percentage of the group. n represent the sum of observations of all 13 waves. In other words, the value include multiple observations of the same individual. As can be seen in columns Treatment group and Control group, the majority of psychedelic users was male (68.5%), in contrast to the group of non-users (46.1%). More than half of the participants fell within age category 26-66 years (68.4%). However, young adults (age 18-25) were overrepresented in the treatment group compared to the control group. For retirees (age 66+) the opposite is true. Furthermore, the majority of participants was employed (56.3%).

Table 1: Demographic sample characteristics of the LISS panel

	Treatment group		**Control group**		**All**	
	%	**St. dev.**	**%**	**St. dev.**	**%**	**St. dev.**
Gender						
Male	68.5	0.465	46.1	0.498	46.2	0.499
Female	31.5	0.465	53.9	0.498	53.8	0.499
Age (years)						
≤11	0.0	0.000	0.0	0.000	0.0	0.000
12-17	2.2	0.145	2.5	0.155	2.5	0.155
18-25	45.2	0.498	8.6	0.280	8.8	0.283
26-66	51.9	0.500	68.5	0.465	68.4	0.465
≥67	0.8	0.090	20.5	0.404	20.4	0.403
Educational level						
Primary school	14.8	0.356	8.8	0.283	8.8	0.283
Vmbo	12.9	0.336	23.4	0.424	23.4	0.423
Havo/vwo	20.8	0.406	10.8	0.311	10.9	0.311
Mbo	22.7	0.420	23.3	0.423	23.3	0.423
Hbo	14.8	0.356	23.7	0.425	23.6	0.425
Wo	13.9	0.346	10.0	0.300	10.0	0.300
Employment status						
Employed	65.6	0.476	56.2	0.496	56.3	0.496
Unemployed	34.4	0.476	43.8	0.496	43.7	0.496
n	422		72,605		73,027	

Note. Values in columns % represent percentages of the group that fall within a certain category; St. dev = standard deviation; n represents the number of observations in each group.

An overview of treatment-related characteristics is shown in Table B.1, and an overview of sample characteristics per wave is provided in Table B.2 of Appendix B. On average, psychedelics users tend to be younger (25.3-32.5 years) than non-users in all waves (45.3-53.8 years). Average net monthly income is higher for non-users in all waves. A possible explanation

could be the difference in age between the groups, with psychedelics users being much younger and therefore probably less earning. Apart from wave 10, average BMI is higher for the control group.

4. Methodology

Controlled randomized experiments are considered the golden standard for causal inference (Imbens & Rubin, 2015; Rosenbaum, 2017) and serve as a benchmark by which the results from other methods are judged (Angrist & Pischke, 2014). However, this research focuses on recreational use of psychedelics, which does not take place in a clinical setting. Users are not screened and educated by professionals before taking drugs, and setting up an experiment with these requirements would be highly unethical. As a consequence, this research relies on observational data and therefore other strategies should be applied to estimate a causal effect.

4.1 Augmented inverse probability weights estimation

Augmented inverse probability weights (AIPW) estimation is used to remove confounding. It does so by creating a pseudo-population based on propensity scores in which the treatment is independent of the observed confounders (i.e. observed variables that are influencing both treatment and outcome). The propensity score is an individual's probability of being assigned to the treatment group, conditioning on a set of pre-treatment characteristics (Weitzen, Lapane, Toledano, Hume & Mor, 2004).

The AIPW estimator fits two models: one modelling treatment assignment (throughout the paper called 'treatment model', or TM), and one modelling the relationship between covariates and the outcome (throughout the paper called 'outcome model', or OM). Treatment assignment is modelled as a binary logistic regression to estimate the propensity score of each individual. Every observation is then weighted by the inverse of its estimated propensity score. In other words, observations in the treatment group receive a weight of $1/P(T = 1|X)$, and observations in the control group receive a weight of $1/(1 - P(T = 1|X))$, where P is the chance of receiving treatment (T) given a set of covariates (X).

After forming weights, two linear regression models are fitted that estimate the outcome under treatment and control conditions, respectively, using the constructed weights. These regressions obtain the treatment-specific predicted outcomes for each observation. In other words, they estimate the outcome if every observation were put in the control group and the outcome if every observation were put in the treatment group. The average treatment effect (ATE) is then estimated by subtracting the weighted mean outcome of the control group from the weighted mean outcome of the treatment group. The average treatment effect of psychedelics use on anxiety and anxiety medication ($\widehat{ATE}_{AIPW}$) is measured by formula (1) (Glynn & Quinn, 2010), which captures the above explanation.

$$\widehat{ATE}_{AIPW} = \frac{1}{n}\sum_{i=1}^{n}\left\{\left[\frac{T_i Y_i}{\hat{\pi}(X_i)} - \frac{(1-T_i)Y_i}{1-\hat{\pi}(X_i)}\right] - \frac{T_i - \hat{\pi}(X_i)}{\hat{\pi}(X_i)\big(1-\hat{\pi}(X_i)\big)}\right. \tag{1}$$
$$\left.\times\left[\big(1-\hat{\pi}(X_i)\big)\hat{\mathbb{E}}(Y_i|T_i=1,X_i) + \hat{\pi}(X_i)\hat{\mathbb{E}}(Y_i|T_i=0,X_i)\right]\right\}$$

where i is a single individual, indexed by i = 1,..., n; T represents treatment, which is binary (T_i ϵ 0 (control), 1 (treatment)); outcome is shown by Y_i and X_i represents a set of observed covariates, which are further discussed in Section 4.2. $\hat{\pi}(X_i)$ is the estimated propensity score of individual i, that is the probability of receiving treatment conditioning on X_i. The first line of equation (1) represents the inverse probability weighting estimator, and the second line shows the augmentation term, which adjusts the IPW estimator by a weighted average of the two regression estimators.

4.2 Covariate selection

4.2.1 Confounders and one-way variables

Besides the treatment and outcome variable, two types of covariates are specified: confounding variables and one-way variables. *Confounding variables* involve all variables that influence both treatment and outcome. In contrast, *one-way variables* only influence either outcome or treatment, but not both. This is visually shown by the Directed Acyclic Graph provided in panel I from Figure 2.

For both confounders and one-way variables reverse causality causes bias, which means that the one-way variable should influence treatment (outcome), but treatment (outcome) is not allowed to affect the one-way variable. The same holds for confounders: the confounding variable should influence both treatment and outcome, but treatment and outcome are not allowed to affect the confounding variable. This is shown by the direction of the arrows in Figure 2. As an example: if the one-way variable urbanity influences the treatment variable psychedelics use, but psychedelics use does not affect urbanity, there is no bias caused by reverse causality. In Section 4.2.3 the causal pathways of all used covariates are described.

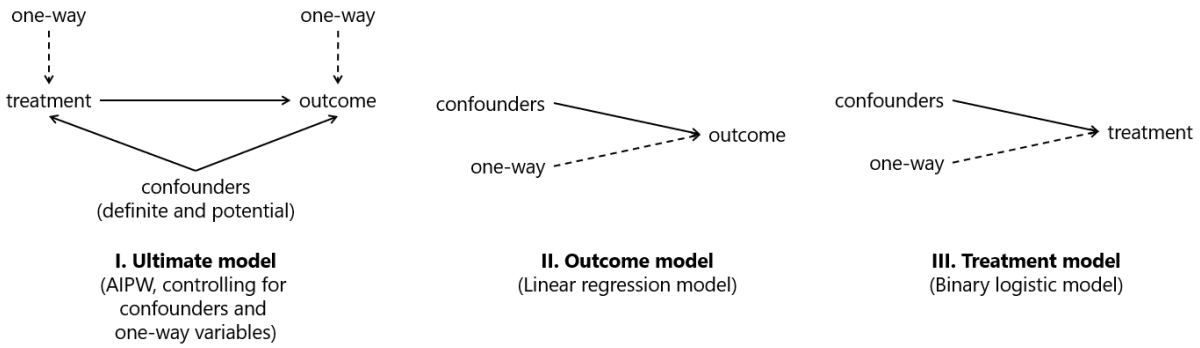

Figure 2: Directed Acyclic Graph representing the causal pathway of the effect of treatment on outcome.

4.2.2 Definite and potential confounders

Apart from categorizing covariates as one-way and confounding variables, all confounding variables are categorized as 'definite' or 'potential'. A confounder is marked as *definite* when without doubt reverse causation is absent. In other words, definite confounders include all observed covariates that influence anxiety and psychedelics use, but these covariates cannot be affected by current anxiety and psychedelics use. These covariates include wave, age, gender, education level, whether an individual is diagnosed with cancer and anxiety level in the previous year.

A confounder is marked as *potential* if there is an existing possibility of reverse causation. These include employment status and net monthly income. Anxiety level and psychedelics use can possibly influence employment status or net monthly income (e.g. when an individual's health status deteriorates because of anxiety of psychedelics use), but this is not given.

4.2.3 Causal pathway covariates

As mentioned in Section 4.2.1, confounding covariates influence anxiety and psychedelics use, but not the other way around. Age, gender, education level, employment status and net monthly income are included because these demographic variables increase the accuracy of the propensity score. Additionally, earlier studies have found relationships between anxiety and gender, age (Krasucki, Howard & Mann, 1998) and socioeconomic status (i.a. Bjelland et al., 2008; Fryers, Melzer & Jenkins, 2003; Lorant et al., 2003). Because women are significantly more likely than men to experience SAD, it is important to add gender to every outcome model (De Graaf et al., 2005; Partonen & Lönnqvist, 1998). The relationship between anxiety level in the previous year and current anxiety level or psychedelics use has not specifically been studied, but because of the absence of reverse causality (i.e. the present cannot influence the past), the variable can be added without potentially increasing bias.

Whether individual is diagnosed with cancer is included in this study, because anxiety can be a serious problem for threatening-ill patients that fail to obtain satisfactory emotional relief from currently available treatment options (Gasser et al., 2014). Cancer-related anxiety affect between 30 and 50% of patients, especially prior to and after chemotherapy (Williams et al., 2021). All in all, cancer patients often develop a chronic syndrome of psychosocial distress having depressed mood, feelings of anxiety and a reduced quality of life (Griffiths et al., 2016).

According to Brookhart et al. (2006), it is important to include one-way variables because these will decrease the variance of an estimated exposure effect without increasing bias. Including variables that are related to the treatment but not to the outcome of interest has the opposite effect. In other words, the propensity score model should include variables that are related to feeling anxious. These include BMI and whether an individual has trouble with speaking Dutch.

Gariepy, Nitka and Schmitz (2010) reviewed papers that used non-clinical population-representative samples when estimating the effect of BMI on anxiety disorders. They show that ten out of thirteen papers find a significant positive effect of BMI on anxiety disorders, and that the others find an insignificant but positive effect as well. Simonsson, Sexton and Hendricks (2021) studied the relationship between BMI and psychedelics use. They find that respondents who reported having ever used a classic psychedelic had significantly lower odds of being

overweight or obese as compared to having a normal weight. However, they state that psychedelics influence physical health not directly, but through improvements of mental health, such as increases in sociality, trait mindfulness and purpose in life. Therefore, in this research is assumed that there is no direct effect of psychedelics on BMI, other than through mental health. Hence, BMI is marked as a one-way variable.

Sevinç and Dewaele (2018) found that majority language anxiety was prevalent in Dutch immigrants' daily life. Majority language anxiety refers to language anxiety experienced by immigrant or minority community members in the language of the majority of the population in a national context. This is captured by the covariate trouble with speaking Dutch. Comparably, Garcia de Blakeley, Ford and Casey (2017) provide support that second language anxiety is present in Spanish adult immigrants in Australia, being the lowest while speaking with friends and the highest when speaking in public.

Based on the reasoning of Brookhart et al. (2006), the binary logistic regression model should include variables that are related to psychedelics use. The urban character of place of residence is included because there are differences in psychedelics use prevalence rates among municipalities of varying address densities in the Netherlands (Abraham, 1999). This may cause residents of more urban areas to initiate in drug use more easily than residents of rural areas.

4.3 Model specification

The AIPW estimator does not require the same set of covariates to be used in both the OM and TM; it only requires that conditional ignorability holds given X_i. Conditional ignorability states that a treated observation with a certain set of covariates X can be compared to a controlled observation with that same set of covariates to estimate the causal effect of treatment for these observations (Huang, Egami, Hartman & Miratrix, 2021). To estimate a true causal effect, confounders should always be included in the model (Glynn & Quinn, 2010; Kurz, 2022), which is shown by the solidness of the arrows in Figure 2. About one-way variables, however, researchers are ambiguous. This dilemma is shown by the dashed lines in panel II and III of Figure 2. Therefore, 4 different models including different sets of covariates are performed to compare the estimates, named A, C.1, C.2 and D.

The sets of covariates are corresponding to specifications A, C and D of the Monte Carlo simulation performed by Glynn and Quinn (2010)[5]. In Specification A both the TM and OM include all observed confounders and their own specific one-way variables. In this research, model A includes definite confounders and one-way variables. In the OM trouble with speaking Dutch and BMI are included, and in the TM the urban character of the place of residence is included.

Specification C includes only confounders. In their simulation, Glynn and Quinn (2010) show that only adding confounding variables to both the OM and TM provides a consistent estimator as long as the sample is large (n>250). Model C.1 includes only definite confounders in both the OM and TM, which are wave, age, gender, education level, whether an individual is diagnosed with cancer and anxiety level in the previous year. Model C.2 includes both definite and potential confounders. This includes the same covariates as Model C.1, but adds net income and employment status.

Specification D includes confounders in both the OM and TM, but only one-way variables in the OM. In model D definite confounders wave, age, gender, education level, whether an individual is diagnosed with cancer and anxiety in the previous year are included in both the OM and TM, and one-way variables trouble with speaking Dutch and BMI are included in the OM.

According to Glynn and Quinn (2010), all specifications are sufficient for consistent estimations of ATEs. However, when not adding one-way variables to the TM (which is the case in Model

[5] A Monte Carlo simulation repeatedly creates random samples to perform a statistical analysis. A detailed explanation of this method is provided by Hanushek and Jackson (2013). The study design of Glynn and Quinn (2010) featured eighteen different scenarios, which implied all possible combinations of three levels of confounding (low, moderate and severe), two mean outcome functions (linear and nonlinear) and three sample sizes (250, 5000 and 1000). Under each scenario thousand datasets were created, resulting in a total of 18,000 Monte Carlo datasets. The LISS panel is based on a true probability sample of household addresses drawn from the population register by Statistics Netherlands, resulting in all members of the target population having an equal probability to be included in the data (Knoef & De Vos, 2009). Therefore I consider the sample of Glynn and Quinn (2010) representative for this research.

C.1, C.2 and D), one achieves better overlap between the treatment and control group, which increases performance. On the other hand, when conditioning on both confounders and one-way variables (which is the case in Model A), more accurate estimates can be obtained. This shows a trade-off between efficiency and accuracy.

4.4 (Un)weighted non-linear squares estimator

Tan (2010) identified that the weighted nonlinear least-squares (WNLS) estimator for parameters of the OM is more robust to model misspecification than the unweighted nonlinear least-squares (NLS) estimator. However, in the models estimating the effect of psychedelics use on anxiety level and depression level, the parameters of the OM are estimated by the less robust NLS estimator, because the WNLS estimator causes convergence issues that cannot be solved by removing a single or few covariates.

4.5 Advantages of AIPW estimation

The first advantage of the AIPW estimator is that it is a doubly robust method, because it requires only either the propensity score model (TM) or outcome model (OM) to be correctly specified, but not both. Detailed proof is provided in Appendix B of Kurz (2022) and Appendix A of Glynn and Quinn (2010).

Besides the doubly robust property, another advantage of the AIPW estimator is that the augmentation term stabilizes the estimator when the propensity score gets close to 0 or 1. In small samples, individuals that receive both treatment and a low propensity score (i.e. is highly unlikely to use psychedelics based on the observed covariates) will provide extreme contributions to the estimation of the ATE. Detailed proof and explanation is provided by Glynn and Quinn (2010). This stabilizing property is especially important for this research, considering the small size of the treatment group (n=422) compared to the control group (n=73,027).

Another advantage is that the AIPW estimator has comparable or lower mean square error than regression estimators, inverse probability weighted (IPW) estimator, and a propensity score matching estimator when both the TM and OM are correctly specified. When one of the models is incorrectly specified, the AIPW estimator is superior (Glynn & Quinn, 2010). AIPW is

also preferred over propensity score matching (PSM), because there is no implementation for PSM for longitudinal data with time-varying treatments (Thoemmes & Ong, 2016).

4.6 Assumptions

Three assumptions should hold to have a causal interpretation of the average treatment effect (Kurz, 2022): the stable unit treatment value assumption (SUTVA), the conditional independence assumption and the positivity assumption. First, the stable unit treatment value assumption (SUTVA) states that the treatment status of a given individual does not affect the potential outcomes of any other individual. An example of a SUTVA violation is the spill-over effect: for example the reduction in risk of infection for unvaccinated individuals when a proportion of a population does get vaccinated. Another violation is the network effect: for example the increase in one's utility when more individuals use a social network. When the SUTVA holds, the ATE represents the difference in average outcomes induced by shifting the entire population from not using to using psychedelics. In this study SUTVA implies that one individual's psychedelics use should not affect one other's anxiety level. Considering that psychedelics use has no spill-over or network effect, it is plausible that this assumption holds.

The conditional independence or ignorability assumption implies that the counterfactual potential outcome (i.e. the unobserved outcome if a treated individual would not be treated and vice versa) for a given individual can be retrieved by using individuals with the same set of observed characteristics (Kurz, 2022). This means that the treatment should be independent of the outcome, which would be the case when individuals are randomly assigned to treatment. However, participants individually decide whether or not they use psychedelics, therefore it is necessary to account for all differences between the treatment and control group to obtain a causal effect. If all differences between these groups are observed and controlled for, the conditional independence assumption holds. As there is no guideline for covariate selection, one cannot test whether this assumption holds. However, based on the reasoning provided in Appendix A, I expect that all confounding variables are included in this research.

Lastly, the positivity assumption states that every individual has a positive nonzero probability of receiving treatment. Individuals with a score lower than 0.00005 are dropped from the estimation to assure this assumption holds.

5. Results

Table 3, 4 and 5 show the results of the estimated models. The noticeably differing number of observations between all models in a certain table is caused by missing values for some variables for some individuals, and by individuals that violate the positivity assumption and are therefore dropped from the estimation.

5.1 Effect of non-clinical psychedelics use on anxiety level

Table 3 shows the marginal potential outcome means (POMs) and average treatment effects (ATEs) on anxiety level for individuals that used psychedelics within the past four years and non-users. As described in Section 4.5, the ATE represents the average change in outcome when an individual would switch from not using psychedelics to using them, estimated by the difference in average outcomes on population level, induced by shifting the entire population from no treatment to treatment

Table 3: Effect of non-clinical psychedelics use on anxiety level.

	Potential outcome means				
Model	**No psychedelics**	**Psychedelics**	**ATE**	**n**	**i**
A	2.105***	2.399***	0.294*	48,741	10,613
	(0.009)	(0.157)	(0.157)		
C.1	2.108***	2.408***	0.300**	49,633	10,895
	(0.009)	(0.151)	(0.151)		
C.2	2.096***	2.490***	0.393**	43,539	9,646
	(0.010)	(0.153)	(0.154)		
D	2.104***	2.380***	0.276*	48,964	10,638
	(0.009)	(0.149)	(0.149)		

Note. ATE = Average Treatment Effect; n = number of observations; i = number of individuals. Parameters of OM estimated by unweighted NLS estimator due to convergence issues. Individually clustered standard errors between brackets. Model A: adjusted for wave, age, gender, education, cancer and anxiety level in the previous year in OM and TM, Dutch and BMI in OM, and urbanity of residence in TM. Model C.1: adjusted for wave, age, gender, education, cancer and anxiety level in the previous year in OM and TM. Model C.2: adjusted for wave, age, gender, education, cancer, anxiety level in the previous year, employment status and net income in OM and TM. Model D: adjusted for wave, age, gender, education, cancer and anxiety level in the previous year in OM and TM, and Dutch and BMI in OM. *p<0.1 **p<0.05 ***p<0.01.

Results indicate that only Model C.1 and C.2, which are only adjusting for confounders, estimate a significant effect of psychedelics use on anxiety at a 5%-significance level. According to these models, anxiety level increases on average with 0.300 (p=0.047) and 0.393 (p=0.010), respectively, when an individual switches from not using to using psychedelics. Model A, which

besides definite confounders adjusts for one-way variables in both OM and TM, does not find a significant effect. A possible cause could be the trade-off between efficiency and accuracy: the one-way variables in the TM increase the accuracy of the propensity score, but as a consequence the overlap between the treatment and control group diminishes.

Similar to Model A, Model D does not find an effect of psychedelics on anxiety level at a 5%-significance level. This result is quite unexpected, because no differences in overlap exist between Model C.1 and D, as the TM is the same for both models. A difference in the number of propensity scores violating the positivity assumption is therefore not a feasible cause. Furthermore, it seems unlikely that the small difference in observations between Model C.1 and D (49,633 and 48,964, respectively) causes the problem, considering that Model C.2, which finds a significant effect, has a much lower number of included observations (i.e. 43,539). That leaves the possibility that either having trouble with speaking Dutch or BMI causes the effect of psychedelics use on anxiety to become insignificant, perhaps due to unnoticed reverse causality.

5.2 Sensitivity analysis

Table 4 shows the marginal POMs and ATEs on depression level for individuals that used psychedelics within the past four years and non-users. As described in Section 2.3, depression level serves as a proxy for anxiety level. Again, the ATE represents the average change in outcome when an individual would switch from not using psychedelics to using them.

The results indicate that psychedelics use increases depression level regardless of which set of covariates is adjusted for. Model A, which obtains the most accurate results, shows that on average depression level is 0.266 (p=0.043) higher for individuals that used psychedelics in the past four years compared to non-users. Only adjusting for definite confounders in Model C.1 results in an average difference in depression level of 0.298 (p=0.045) between psychedelics users and non-users, the latter group showing a lower depression level. Remarkably, the only model that found a significant effect of psychedelics use on anxiety, Model C.2, does not find a significant effect of psychedelics use on depression. Adjustment for one-way variables in the OM in Model D slightly increased the estimate of Model C.1 (ATE=0.340, p=0.028).

Table 4: Effect of non-clinical psychedelics use on depression level.

	Potential outcome means				
Model	**No psychedelics**	**Psychedelics**	**ATE**	**n**	**i**
A	2.020***	2.286***	0.266**	48,741	10,613
	(0.009)	(0.131)	(0.131)		
C.1	2.023***	2.321***	0.298**	49,633	10,895
	(0.009)	(0.149)	(0.149)		
C.2	2.012***	2.321***	0.309*	43,539	9,646
	(0.009)	(0.168)	(0.168)		
D	2.018***	2.358***	0.340**	48,964	10,638
	(0.009)	(0.155)	(0.155)		

Note. ATE = Average Treatment Effect; n = number of observations; i = number of individuals. Parameters of OM estimated by unweighted NLS estimator due to convergence issues. Individually clustered standard errors between brackets. Model A: adjusted for wave, age, gender, education, cancer and anxiety level in the previous year in OM and TM, Dutch and BMI in OM, and urbanity of residence in TM. Model C.1: adjusted for wave, age, gender, education, cancer and anxiety level in the previous year in OM and TM. Model C.2: adjusted for wave, age, gender, education, cancer, anxiety level in the previous year, employment status and net income in OM and TM. Model D: adjusted for wave, age, gender, education, cancer and anxiety level in the previous year in OM and TM, and Dutch and BMI in OM. *p<0.1 **p<0.05 ***p<0.01.

The results in Table 4 are comparable to Table 3. All models show a positive ATE of psychedelics use on anxiety or depression level. The main difference is that the most accurate model, Model A, does not find an effect of psychedelics on anxiety, while it does for depression. The more efficient models, Model C.1, C.2 and D, find similar results for anxiety and depression: the ATE for anxiety is 0.300-0.393 ($p<0.05$), and the ATE for depression is 0.298-0.340 ($p<0.05$). Based on this can be concluded that the results are robust to changes in highly-correlated outcome.

5.3 Comparing subjective to objective

Table 5 shows the marginal POMs and ATEs on anxiety medication use for individuals that used psychedelics within the past four years and non-users. This research serves to compare the subjective anxiety and depression levels to an objective variable. The ATE represents the average change in the chance that an individual is using anxiety medication, when switching from being a non-user to a user of psychedelics.

In contrast to anxiety and depression level, anxiety medication use on average tends to decline when psychedelics are used. According to Model A, which is adjusting for definite confounders and one-way variables in both TM and OM, the chance that an individual is using anxiety medication is decreasing with 4.5% ($p=0.000$) when switching from not using psychedelics to

using them. The more efficient models, C.1 and C.2, which are only adjusting for confounders, show a slightly smaller effect of -3.6% (p=0.000) and -3.3% (p=0.000), respectively. Model D shows a nearly identical effect as Model A: -4.4% (p=0.000).

Table 5: Effect of non-clinical psychedelics use on anxiety medication use.

	Potential outcome means				
Model	**No psychedelics**	**Psychedelics**	**ATE**	**n**	**i**
A	0.045***	0.000	-0.045***	48,695	10,589
	(0.002)	(0.013)	(0.013)		
C.1	0.045***	0.009**	-0.036***	49,606	10,884
	(0.002)	(0.004)	(0.005)		
C.2	0.044***	0.011	-0.033***	43,593	9,637
	(0.002)	(0.008)	(0.009)		
D	0.045***	0.001	-0.044***	48,905	10,617
	(0.002)	(0.011)	(0.012)		

Note. ATE = Average Treatment Effect; n = number of observations; i = number of individuals. Parameters of OM estimated by WNLS estimator. Individually clustered standard errors between brackets. Model A: adjusted for wave, age, gender, education, cancer and anxiety level in the previous year in OM and TM, Dutch and BMI in OM, and urbanity of residence in TM. Model C.1: adjusted for wave, age, gender, education, cancer and anxiety level in the previous year in OM and TM. Model C.2: adjusted for wave, age, gender, education, cancer, anxiety level in the previous year, employment status and net income in OM and TM. Model D: adjusted for wave, age, gender, education, cancer and anxiety level in the previous year in OM and TM, and Dutch and BMI in OM. *p<0.1 **p<0.05 ***p<0.01.

After estimating a positive effect of psychedelics use on anxiety and depression level in Table 3 and 4, the negative effect on anxiety medication use shown in Table 5 is surprising. This result could indicate that individuals use psychedelics as a substitute for anxiety medication. Another explanation could be that in Table 3 and 4 the unweighted non-linear squares estimator was used to estimate the parameters of the OM, while in Table 5 the weighted non-linear squares estimator was used. The latter is more robust to model misspecification than the first (Tan, 2010). Aforementioned would indicate that the OM, the TM or both were misspecified in all four models (A, C.1, C.2 and D) and that the unweighted estimator was not robust to this.

6. Discussion

6.1 Summary

This study represents the first examination of non-clinical psychedelics use on anxiety level and medication use in the Dutch population conducted to date. 110 out of 14,615 participants of the LISS Core Study indicated to have used psychedelics in one or more years between 2007

and 2021. The results suggest that psychedelics use increases anxiety level, independent of which covariates are adjusted for. Measured on a scale of 1 till 6, anxiety level significantly increases between 0.300 and 0.393 when an individual switches from not using psychedelics to using them. The more accurate model including one-way variables did not find a significant result. The most accurate model of the sensitivity analysis shows that depression level significantly increases with 0.266 when an individual changes from not using psychedelics to using them. These results show that the model is robust to changing anxiety level for the highly correlated proxy depression level.

In contrast to the subjective measures anxiety and depression, the chance that someone is using anxiety medication on average tends to decrease when a person switches from being a non-user to a user of psychedelics. According to the most accurate model, the reduction in chance is -4.5%. After estimating positive effects of psychedelics on anxiety and depression, this negative effect on the chance someone is using anxiety medication is surprising. It could indicate that individuals use psychedelics as a substitute for anxiety medication, or that the OM, the TM or both were misspecified in all four models (A, C.1, C.2 and D) and that the unweighted non-linear squares estimator was not robust to this.

In Section 2.3 I hypothesized that anxiety level would be lower among psychedelics users than non-users with similar characteristics. The results do not provide support for this hypothesis. An examination of scores on the statement 'I felt very anxious' and 'I felt depressed and gloomy' of the LISS Core Study indicated that psychedelics users experienced higher levels of anxiety and depression than non-users. However, in contrast to anxiety and depression level estimations, the effect of psychedelics use on anxiety medication use does correspond to the expectations mentioned in Section 2.3. An examination of responses to the question 'Are you currently taking medicine at least once a week for anxiety or depression?' suggested that on average the chance a person is using anxiety medication is lower for individuals that used psychedelics within the past four years compared to non-users.

Besides the estimates of the effect of psychedelics use on anxiety medication use, the findings in this study diverge somewhat from earlier research that has found significant reductions in anxiety level after psychedelic administration (Griffiths et al., 2016; Ross et al., 2016; Grob et al.,

2011; Gasser et al., 2014; Palhano-Fontes et al., 2019; Krebs & Johansen, 2013; Johansen & Krebs, 2015; Hendricks et al., 2015). This inconsistency may be a result of differences in used doses; the used doses (mg/kg body weight) were not registered in the LISS Core Study. A certain dose of a given substance may produce different effects in the same individual upon different occasions of usage (Naranjo, 1973). Psychedelics-induced anxiety during a session has been found to increase with the used dose (Griffiths et al., 2011). Even though these feelings of anxiety do most often not persist beyond administration, it is possible that individuals take this moment of anxiety into account when answering the questions about how they felt in the past month. Not being able to control for dose-differences then causes bias.

Furthermore, there was room for respondent's own interpretation of the definition of psychedelics, because no overview of included substances was given in the questionnaire. As a consequence, substances that fall within multiple categories are not per definition included in the right variable. The user's intention or expectation, the so called *set*, strongly influences the experience and outcome of psychedelics use (Garcia-Romeu & Richards, 2018; Hartogsohn, 2017; Metzner, Litwin & Weil, 1965). Earlier research investigated the effects of specific types of psychedelics instead of psychedelics in general.

6.2 Biases

It is important to mention that a recall bias may have occurred. Aforementioned bias refers to the tendency of individuals without the condition under investigation to underreport the true exposure and vice versa. In other words, this bias occurs if individuals that suffer from anxiety, for example because they are diagnosed with an anxiety disorder, overreport how often they felt anxious in the past month. This causes a problem when the accuracy of recall differs between the treatment and control group (Raphael, 1987). If this is the case, the true effect of psychedelics use could possibly be smaller than reported in this study.

Additionally, the social desirability bias may have influenced the results. This bias refers to the tendency of individuals to respond with what they believe are more socially acceptable answers, rather than choosing answers reflecting their true behaviour. As a consequence, socially desirable responses are over-reported and less desirable responses are under-reported. The bias causes a problem when research involves collecting data on personal or

socially sensitive issues (Grimm, 2010). Psychedelics use can be labelled socially sensitive considering the fact that, besides sclerotia, all psychedelics are included in Schedule I of the Dutch opium law. However, collecting data through a mechanism that allows for privacy, such as an anonymous questionnaire used in current research, decreases social desirability bias.

6.3 Recommendations for future research

Besides performing dose-specific and psychedelic-specific research to resolve the pitfalls mentioned in Section 6.1, another recommendation for future research would be to investigate the influence of *set* and *setting* on the nature of the psychedelic experience. Apart from one's state of mind and expectations when taking the substance (set), also the physical, social, and cultural environment in which the substance is taken (setting) strongly influence one's experience. As an example, data suggest that highly clinical settings are associated with greater anxiety experiences during psilocybin administration than aesthetically furnished laboratory rooms (Studerus, Gamma, Kometer & Vollenweider, 2012). According to Studerus et al. (2012), the small number of earlier research on this topic did not conform to modern methodological standards (i.e. relied on simple correlations).

In addition, in future observational research I would recommend to control for more social context factors, such as whether an individual is in the possession of a substance-selling contact. As described in Section 1, besides sclerotia, mescaline-cacti and DMT-containing plants, the possession, cultivation, production, trade, import and export of all psychedelics is prosecuted. Therefore, whether an individual has connections that illegally sell psychedelics is possibly a strong predictor of whether an individual uses these substances.

Another important social context factor would be peer influence. Multiple studies found that adolescents surrounded by peers with favourable attitudes towards drug use may be more likely to engage in drug use (Grube & Morgan, 1990; Jessor & Jessor, 1977; Bandura, 1969). Besides the influence from peers on initial drug use, Dunsmore and Kaplan (1997) found that individuals with more experienced psychedelic-using peers are significantly less likely to report adverse psychological effects of drug use, because these peers may provide an interpretive framework for understanding the new perceptions and experiences that may appear.

Considering that peer influence can thus be a confounding variable, it is important to control for this in future research.

6.4 Policy implications

The contradicting outcomes provided in this study indicate that the effect of psychedelics use is not straightforward. Based on the result that non-clinical psychedelics use increases anxiety and depression level, the government could consider adding sclerotia to Opium Act Schedule I or II to prohibit the possession, cultivation, production, trade, import and export of magic truffles, in order to prevent the non-clinical, unsupervised use of psychedelics. Moreover, as mentioned in Section 6.1, the inconsistency with earlier findings may be caused by different used doses. This would imply that educating individuals about possible consequences of certain (high) doses would reduce the unfavourable anxiety-increasing effect of psychedelics. Lastly, the significant reduction in anxiety medication use could imply that, among well-informed individuals or in clinical settings, psychedelics could serve as an alternative for regular anxiolytic medicines.

7. Conclusion

Using a doubly-robust estimation method, this study estimated the effect of non-clinical psychedelics use on anxiety, depression and anxiety medication use in the Dutch population. The results suggest that on average psychedelics use increases anxiety and depression level when an individual switches from not using to using psychedelics. In contrast, the chance someone is using anxiety medication tends to be lower among individuals that have used psychedelics within the past four years compared to non-users. The discrepancy between these results shows that the effect of non-clinical psychedelics use is not as clear-cut as possibly is outlined by earlier research in clinical setting. Therefore, the feasibility of psychedelics being an alternative for regular anxiety medication and the impact of set and setting on the anxiolytic effect of psychedelics should be further investigated.

Appendix A: Questionnaire

The full questionnaire was conducted in Dutch. Anxiety level was captured by question ch011, depression level by question ch014, psychedelics use by question ch162 and anxiety medication use by question ch178. Questions that are omitted in the overview below are indicated by the square brackets between two questions (e.g. [ch004-ch005] means that question ch004 and ch005 are omitted). Answer options are shown in italics.

Deze vragenlijst gaat over gezondheid.

[ch004-ch005]

De volgende vragen gaan over hoe u zich voelt en hoe het met u ging in de afgelopen maand. Het is de bedoeling dat u bij elke vraag het antwoord geeft dat het best uw gevoel of gedrag van de afgelopen maand weergeeft. De afgelopen maand…

ch011: …was ik erg zenuwachtig

1. *nooit*
2. *zelden*
3. *soms*
4. *vaak*
5. *meestal*
6. *voortdurend*

[ch012-ch013]

ch014: …voelde ik me neerslachtig en somber

1. *nooit*
2. *zelden*
3. *soms*
4. *vaak*
5. *meestal*
6. *voortdurend*

[ch015-ch158]

Hebt u gedurende de afgelopen maand wel eens één of meer van de volgende middelen gebruikt?

[ch159-ch161]

ch162: Bewustzijnsverruimende middelen (zoals LSD en paddo's)

1. *nooit*
2. *soms*
3. *regelmatig*

[ch163-ch168]

Gebruikt u momenteel minstens eens per week medicijnen voor: (meerdere antwoorden mogelijk)

[ch169-ch177]

ch178: angst of depressie

[ch179-184

Appendix B: Descriptive statistics

Table B.1: Treatment related sample characteristics of the LISS panel

	Treatment group		Control group		All	
	%	St. dev.	%	St. dev.	%	St. dev.
Diagnosed with cancer						
Yes	0.7	0.084	2.2	0.146	2.2	0.145
No	99.3	0.084	97.8	0.146	97.8	0.145
Trouble with speaking Dutch						
Yes, often	2.0	0.139	0.5	0.070	0.5	0.071
Yes, sometimes	17.1	0.377	8.9	0.284	9.3	0.285
No, never	80.9	0.393	90.6	0.291	90.1	0.292
BMI						
Underweight	8.3	0.276	3.3	0.178	3.3	0.179
Healthy	61.1	0.488	50.0	0.500	50.1	0.500
Overweight	24.2	0.429	32.2	0.467	32.2	0.467
Obese	6.1	0.240	13.4	0.340	13.3	0.340
Morbid obese	0.2	0.049	1.1	0.103	1.1	0.103
Urbanity						
Extremely urban	31.6	0.466	14.5	0.352	14.6	0.353
Very urban	11.9	0.324	25.1	0.434	25.0	0.433
Moderately urban	21.4	0.411	21.6	0.411	21.6	0.412
Slightly urban	10.0	0.300	21.2	0.409	21.2	0.409
Not urban	25.1	0.434	17.5	0.380	17.6	0.381
n	422		72,605		73,027	

Note. Values in columns % represent percentages of the group that fall within a certain category; St. dev = standard deviation; n represents the number of observations in each group.

Table B.2: Sample characteristics per wave

	Treatment group					Control group				
wave	obs.	mean age	% employed	mean net income	mean BMI	obs.	mean age	% employed	mean net income	mean BMI
1	9	25.3	44.4	600.89	22.6	6,609	45.3	66.3	1,742.31	25.4
2	19	26.5	52.9	516.22	24.3	5,903	46.4	64.2	1,634.35	25.5
3	22	28.5	50.0	551.09	23.5	6,048	48.2	58.9	1,562.14	25.7
4	31	29.9	55.6	851.85	23.8	5,646	48.9	57.7	1,524.36	25.7
5	31	30.9	56.3	901.88	24.5	5,024	49.9	55.1	1,504.14	25.6
6	30	30.7	62.5	900.53	23.8	5,720	50.1	54.9	1,479.52	25.6
7	26	29.1	75.0	867.53	23.1	5,323	51.0	51.1	1,467.94	25.6
9	21	26.6	85.7	1,320.00	23.0	5,337	51.8	52.8	1,568.55	25.8
10	34	27.9	60.9	1,277.00	30.4	5,872	51.5	53.2	1,649.62	25.9
11	32	28.9	60.0	984.33	23.5	5,405	52.3	52.7	1,736.70	26.0
12	41	29.3	68.6	1,143.26	23.5	5,078	53.1	52.3	1,715.32	26.0
13	56	30.1	77.3	1,261.92	24.6	5,632	52.5	52.3	1,848.30	26.0
14	69	32.5	69.8	1,214.68	24.4	5,008	53.8	52.1	1,865.50	26.0
Total	422					72,605				

Note. Age in years, mean net monthly income in Euro.

Appendix C: Background information psychedelics

Mescaline

Mescaline naturally occurs in wachuma and peyote cacti, which are used for centuries by indigenous Mexicans (Labate & Cavnar, 2016). It was the first psychedelic to become synthesised in a laboratory (Hofmann, 1980; Cassels & Sáez-Briones, 2018). The substance is some 5,000 to 10,000 times less active than LSD and is therefore less interesting for use in psychotherapy (Hofmann, 1980). After the synthesis of mescaline in 1929, it took another decade before psychedelics gained widespread interest. The accidental discovery of the psychological effect of LSD by Albert Hofmann in 1943 meant the beginning of the Psychedelic Age.

LSD: the father of psychedelics in Western society

LSD is the isolated active principle from ergot of rye (Hofmann, 1980). According to Gasser, Kirchner and Passie (2015), the substance enables access to thoughts, associations, feelings and inner processes that are usually excluded from consciousness. Besides being a 5-HT_{2A} agonist, it significantly modulates 5-HT_{1A} receptors. Abnormalities of 5-HT_{1A} receptors are in turn associated with a significant excess of generalized anxiety disorder diagnoses in a case-control design (Molina et al., 2011). Hofmann (1980) states that Werner A. Stoll's ground-breaking studies showed that the nature of LSD's activity could lead to numerous possibilities of medicinal psychiatric uses. As opposed to tranquilizer-type psychopharmaceuticals, LSD makes the patient's problems and conflicts more exposed and more intensely experienced, and therefore more susceptible to psychotherapeutic treatment.

Artists, religious scholars, philosophers and other intellectuals were the first to self-experiment non-medically with LSD. Hofmann (1980) had expected that the use of LSD remained confined to medicine and to experiments within artistic and literary circles, as happened after the scientific publications on mescaline, which evokes psychic effects quite like those of LSD. However, publications of medically supervised LSD experiences were rather reported in daily magazines, which were addressed to the broad public, instead of scientific journals. This lead to LSD becoming very popular in the 1970s, especially in the Netherlands, the United Kingdom and Ireland (EMCDDA, 1997b).

The end of the Psychedelic Age begun after more than ten years of uninterrupted scientific research and medicinal use, with a number of reports of criminal acts, murders, and suicide under the medically unsupervised influence of LSD. In 1968, the United Nations Economic and Social Council called on governments to limit the use of LSD and similar psychedelics to scientific and medical purposes and to impose import and export restrictions to prevent inhabitants from health damage being caused by these substances (United Nations Economic and Social Council, 1968). Most countries implemented strict regulations concerning possession, distribution and use of psychedelics, but LSD-assisted psychotherapy continued in Czechoslovakia, Germany and the Netherlands during the 1970s (Leuner, 1981).

Psilocybin

Psilocybin is a naturally occurring psychedelic substance found in various types of mushrooms. According to Begola and Schillerstrom (2019), its effects are considered to be more strongly visual, more euphoric, and less emotionally intense compared to LSD. Once digested, it is metabolized to psilocin, a 5-$HT_{1A/2A/2C}$ receptor agonist.

DMT

DMT is a normal component of the mammalian brain and is additionally found in a variety of plants (Cameron & Olson, 2018). It is thought to play a role in naturally occurring altered states of consciousness, such as psychosis, dreams, creativity, spiritual phenomena and near-death experiences (Callaway, 1988; Strassman, 2000). DMT alone is not psychoactive after oral administration; it is metabolized by peripheral monoamine oxidase type A (MAO-A) and does not produce psychoactive effects (Riba, McIlhenny, Bouso & Barker, 2015). A common way of ingesting DMT is through ayahuasca, a brew of the Amazonian vine *Banisteriopsis caapi* with admixture plants containing DMT (Kaasik, Souza, Zandonadi, Tófoli & Sussulini, 2021). *Banisteriopsis caapi* contains β-carboline alkaloids that reversibly inhibit peripheral MAO-A, which allows DMT to reach the central nervous system (Dos Santos, Balthazar, Bouso & Hallak 2016).

References

Abraham, M. (1999). Illicit drug use, urbanization, and lifestyle in the Netherlands. *Journal of Drug Issues, 29*(3), 565-585.

Agin-Liebes, G. I., Malone, T., Yalch, M. M., Mennenga, S. E., Ponté, K. L., Guss, J., ... & Ross, S. (2020). Long-term follow-up of psilocybin-assisted psychotherapy for psychiatric and existential distress in patients with life-threatening cancer. *Journal of Psychopharmacology, 34*(2), 155-166.

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders 5th Edition*. Arlington: American Psychiatric Association.

Angrist, J. D., & Pischke, J. S. (2014). *Mastering 'metrics: The path from cause to effect*. Princeton university press.

Bandura, A. (1969). Social-learning theory of identificatory processes. *Handbook of socialization theory and research,* 213, 262.

Begola, M. J., & Schillerstrom, J. E. (2019). Hallucinogens and their therapeutic use: A literature review. *Journal of Psychiatric Practice, 25*(5), 334-346.

Bjelland, I., Krokstad, S., Mykletun, A., Dahl, A. A., Tell, G. S., & Tambs, K. (2008). Does a higher educational level protect against anxiety and depression? The HUNT study. *Social science & medicine, 66*(6), 1334-1345.

Krasucki, C., Howard, R., & Mann, A. (1998). The relationship between anxiety disorders and age. International journal of geriatric psychiatry, 13(2), 79-99.

Brookhart, M. A., Schneeweiss, S., Rothman, K. J., Glynn, R. J., Avorn, J., & Stürmer, T. (2006). Variable selection for propensity score models. *American journal of epidemiology, 163*(12), 1149-1156.

Callaway, J. C. (1988). A proposed mechanism for the visions of dream sleep. *Medical hypotheses, 26*(2), 119-124.

Cameron, L. P., & Olson, D. E. (2018). Dark classics in chemical neuroscience: N, N-Dimethyltryptamine (DMT). *ACS chemical neuroscience, 9*(10), 2344-2357.

Cassels, B. K., & Sáez-Briones, P. (2018). Dark classics in chemical neuroscience: mescaline. *ACS chemical neuroscience, 9*(10), 2448-2458.

Celada, P., Puig, M. V., Amargós-Bosch, M., Adell, A., & Artigas, F. (2004). The therapeutic role of 5-HT_{1A} and 5-HT_{2A} receptors in depression. *Journal of psychiatry and neuroscience, 29*(4), 252-265.

Coördinatiepunt Assessment en Monitoring nieuwe drugs (CAM). (2007, June). *Risicoschatting van psilocine en psilocybine bevattende paddenstoelen (paddo's) 2007*. https://www.rivm.nl/bibliotheek/digitaaldepot/cam_paddo_advies.pdf

De Graaf, R., Van Dorsselaer, S., Ten Have, M., Schoemaker, C., & Vollebergh, W. A. (2005). Seasonal variations in mental disorders in the general population of a country with a maritime climate: findings from the Netherlands mental health survey and incidence study. *American Journal of Epidemiology, 162*(7), 654-661.

Dos Santos, R. G., Balthazar, F. M., Bouso, J. C., & Hallak, J. E. (2016). The current state of research on ayahuasca: A systematic review of human studies assessing psychiatric symptoms, neuropsychological functioning, and neuroimaging. *Journal of Psychopharmacology, 30*(12), 1230-1247.

Dunsmore, M. W., & Kaplan, H. B. (1997). Peer support, perceptions of adverse effects, and the hallucinogenic drug experience. *Applied Behavioral Science Review, 5*(2), 219-230.

EMCDDA. (1997a, November). *Annual Report on the State of the Drugs Problem in the European Union* (Nr. 2).

EMCDDA. (1997b, November). *New Trends in Synthetic Drugs in the European Union* (Nr. 1).

EMCDDA. (1998, November). *Annual Report on the State of the Drugs Problem in the European Union* (Nr. 3).

EMCDDA. (1999, November). *Extended Annual Report on the State of the Drugs Problem in the European Union* (Nr. 5).

EMCDDA. (2000, November). *Jaarverslag over de stand van de drugsproblematiek in de Europese Unie* (Nr. 6).

EMCDDA. (2001, November). *Jaarverslag over de stand van de drugsproblematiek in de Europese Unie* (Nr. 7).

EMCDDA. (2003, November). *Stand van de drugsproblematiek in de Europese Unie en Noorwegen* (Nr. 8).

EMCDDA. (2004, November). *The state of the drugs problem in the European Union and Norway* (Nr. 9).

EMCDDA. (2005, November). *Stand van de drugsproblematiek in Europa* (Nr. 10).

EMCDDA. (2006, November). *Stand van de drugsproblematiek in Europa* (Nr. 11).

EMCDDA. (2007, November). *Annual Report: the State of the Drugs Problem in Europe* (Nr. 12).

EMCDDA. (2008, November). *Annual Report: the State of the Drugs Problem in Europe* (Nr. 13).

EMCDDA. (2009, November). *Annual Report on the State of the Drugs Problem in Europe* (Nr. 14).

EMCDDA. (2010, November). *Annual Report on the State of the Drugs Problem in Europe* (Nr. 15).

Fryers, T., Melzer, D., & Jenkins, R. (2003). Social inequalities and the common mental disorders. *Social psychiatry and psychiatric epidemiology, 38*(5), 229-237.

Garcia de Blakeley, M., Ford, R., & Casey, L. (2017). Second language anxiety among Latino American immigrants in Australia. *International Journal of Bilingual Education and Bilingualism, 20*(7), 759-772.

Garcia-Romeu, A., & Richards, W. A. (2018). Current perspectives on psychedelic therapy: use of serotonergic hallucinogens in clinical interventions. *International Review of Psychiatry, 30*(4), 291-316.

Gariepy, G., Nitka, D., & Schmitz, N. (2010). The association between obesity and anxiety disorders in the population: a systematic review and meta-analysis. *International journal of obesity, 34*(3), 407-419.

Gasser, P., Holstein, D., Michel, Y., Doblin, R., Yazar-Klosinski, B., Passie, T., & Brenneisen, R. (2014). Safety and efficacy of lysergic acid diethylamide-assisted psychotherapy for anxiety associated with life-threatening diseases. *The Journal of nervous and mental disease, 202*(7), 513.

Gasser, P., Kirchner, K., & Passie, T. (2015). LSD-assisted psychotherapy for anxiety associated with a life-threatening disease: a qualitative study of acute and sustained subjective effects. *Journal of Psychopharmacology, 29*(1), 57-68.

Glynn, A. N., & Quinn, K. M. (2010). An introduction to the augmented inverse propensity weighted estimator. *Political analysis, 18*(1), 36-56.

Goldberg, S. B., Pace, B. T., Nicholas, C. R., Raison, C. L., & Hutson, P. R. (2020). The experimental effects of psilocybin on symptoms of anxiety and depression: A meta-analysis. *Psychiatry research, 284,* 112749.

Griffiths, R. R., Johnson, M. W., Carducci, M. A., Umbricht, A., Richards, W. A., Richards, B. D., ... & Klinedinst, M. A. (2016). Psilocybin produces substantial and sustained decreases in

depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. *Journal of psychopharmacology, 30*(12), 1181-1197.

Griffiths, R. R., Johnson, M. W., Richards, W. A., Richards, B. D., McCann, U., & Jesse, R. (2011). Psilocybin occasioned mystical-type experiences: immediate and persisting dose-related effects. *Psychopharmacology, 218*(4), 649-665.

Griffiths, R. R., Richards, W. A., McCann, U., & Jesse, R. (2006). Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. *Psychopharmacology, 187*(3), 268-283.

Grimm, P. (2010). Social desirability bias. *Wiley international encyclopedia of marketing*.

Grob, C. S., Danforth, A. L., Chopra, G. S., Hagerty, M., McKay, C. R., Halberstadt, A. L., & Greer, G. R. (2011). Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. *Archives of general psychiatry, 68*(1), 71-78.

Grube, J. W., & Morgan, M. (1990). Attitude-social support interactions: Contingent consistency effects in the prediction of adolescent smoking, drinking, and drug use. *Social Psychology Quarterly*, 329-339.

Hanks, J. B., & González-Maeso, J. (2016a). Hallucinogens: Circuits, Behavior, and Translational Models. In *Neuropathology of Drug Addictions and Substance Misuse* (pp. 813-820). Academic Press.

Hanks, J. B., & González-Maeso, J. (2016b). Molecular and cellular basis of hallucinogen action. In *Neuropathology of Drug Addictions and Substance Misuse* (pp. 803-812). Academic Press.

Hanushek, E. A., & Jackson, J. E. (2013). *Statistical methods for social scientists*. Academic Press.

Hartogsohn, I. (2017). Constructing drug effects: A history of set and setting. *Drug Science, Policy and Law,* 3.

Hendricks, P. S., Thorne, C. B., Clark, C. B., Coombs, D. W., & Johnson, M. W. (2015). Classic psychedelic use is associated with reduced psychological distress and suicidality in the United States adult population. *Journal of Psychopharmacology, 29*(3), 280-288.

Huang, M., N. Egami, E. Hartman, and L. Miratrix (2021). Leveraging population outcomes to improve the generalization of experimental results.

Hofmann, P. A. (1980). LSD - *My Problem Child* [E-book]. Multidisciplinary Association for Psychedelic Studies.

Imbens, G. W., & Rubin, D. B. (2015). *Causal inference in statistics, social, and biomedical sciences.* Cambridge University Press.

Jacobsen, F. M., Wehr, T. A., Sack, D. A., James, S. P., & Rosenthal, N. E. (1987). Seasonal affective disorder: a review of the syndrome and its public health implications. *American Journal of Public Health, 77*(1), 57-60.

Jacobsen, J. P., Medvedev, I. O., & Caron, M. G. (2012). The 5-HT deficiency theory of depression: perspectives from a naturalistic 5-HT deficiency model, the tryptophan hydroxylase $2^{Arg}439^{His}$ knockin mouse. *Philosophical Transactions of the Royal Society B: Biological Sciences, 367*(1601), 2444-2459.

Jessor, R. & Jessor, S. L. (1977). *Problem Behavior and Psychosocial Development: A Longitudinal Study of Youth.* New York: Academic Press.

Johansen, P. Ø., & Krebs, T. S. (2015). Psychedelics not linked to mental health problems or suicidal behavior: A population study. *Journal of psychopharmacology, 29*(3), 270-279.

Johnson, M. W., Hendricks, P. S., Barrett, F. S., & Griffiths, R. R. (2019). Classic psychedelics: An integrative review of epidemiology, therapeutics, mystical experience, and brain network function. *Pharmacology & therapeutics, 197,* 83-102.

Kaasik, H., Souza, R. C., Zandonadi, F. S., Tófoli, L. F., & Sussulini, A. (2021). Chemical composition of traditional and analog ayahuasca. *Journal of Psychoactive Drugs, 53*(1), 65-75.

Kessler, R. C., & Greenberg, P. E. (2002). The economic burden of anxiety and stress disorders. *Neuropsychopharmacology: The fifth generation of progress, 67*, 982-92.

Knoef, M. & De Vos, K. (2009). *The representativeness of LISS, an online probability panel*. CentERdata, Tilburg.

Krebs, T. S., & Johansen, P. Ø. (2013). Psychedelics and mental health: a population study. *PloS one, 8*(8), e63972.

Kurlansik, S. L., & Ibay, A. D. (2012). Seasonal affective disorder. *American family physician, 86*(11), 1037-1041.

Kurz, C. F. (2022). Augmented inverse probability weighting and the double robustness property. *Medical Decision Making, 42*(2), 156-167.

Labate, B. C., & Cavnar, C. (2016). *Peyote: History, Tradition, Politics, and Conservation.* Santa Barbara, CA: Praeger.

Leuner, H. (1981). *Halluzinogene*. Bern, Switzerland: Hans Huber Verlag.

Lipari, R. N. (2015). Monthly variation in substance use initiation among full-time college students. *The CBHSQ Report*.

Lorant, V., Deliège, D., Eaton, W., Robert, A., Philippot, P., & Ansseau, M. (2003). Socioeconomic inequalities in depression: a meta-analysis. *American journal of epidemiology, 157*(2), 98-112.

Magnusson, A. (2000). An overview of epidemiological studies on seasonal affective disorder. *Acta Psychiatrica Scandinavica, 101*(3), 176-184.

Metzner, R., Litwin, G., & Weil, G. (1965). The relation of expectation and mood to psilocybin reactions: a questionnaire study. *Psychedelic Review, 5,* 3-39.

Ministerie van Justitie en Veiligheid. (2020, June 23). Aanwijzing Opiumwet (2015A003). Openbaar Ministerie. Retrieved 30 May 2022, from https://www.om.nl/onderwerpen/beleidsregels/aanwijzingen/algemeen/aanwijzing-opiumwet-2015a003

Molina, E., Cervilla, J., Rivera, M., Torres, F., Bellón, J. Á., Moreno, B., ... & Gutierrez, B. (2011). Polymorphic variation at the serotonin 1-A receptor gene is associated with comorbid depression and generalized anxiety. *Psychiatric genetics, 21*(4), 195-201.

Naranjo, C. (1973). *The Healing Journey*. New York: Pantheon Books.

Palhano-Fontes, F., Barreto, D., Onias, H., Andrade, K. C., Novaes, M. M., Pessoa, J. A., ... & Araújo, D. B. (2019). Rapid antidepressant effects of the psychedelic ayahuasca in treatment-resistant depression: a randomized placebo-controlled trial. *Psychological medicine, 49*(4), 655-663.

Partonen, T., & Lönnqvist, J. (1998). Seasonal affective disorder: A guide to diagnosis and management. *CNS drugs,* 203-212

Trimbos-instituut. (2022). Bijlagen A3. Drugsgebruik onder 15-64-jarigen - Nationale Drug Monitor. Trimbos-instituut, Utrecht & WODC, Den Haag. Retrieved from https://www.nationaledrugmonitor.nl/bijlagen-drugsgebruik-onder-15-64-jarigen/

Raphael, K. (1987). Recall bias: a proposal for assessment and control. *International journal of epidemiology, 16*(2), 167-170.

Riba, J., McIlhenny, E. H., Bouso, J. C., & Barker, S. A. (2015). Metabolism and urinary disposition of N, N-dimethyltryptamine after oral and smoked administration: a comparative study. *Drug testing and analysis, 7*(5), 401-406.

Rosenbaum, P. R. (2017). *Observation and Experiment: An Introduction to Causal Inference*. Cambridge, MA: Harvard University Press.

Ross, S., Bossis, A., Guss, J., Agin-Liebes, G., Malone, T., Cohen, B., ... & Schmidt, B. L. (2016). Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. *Journal of psychopharmacology, 30*(12), 1165-1180.

Santos, R. D., Landeira-Fernandez, J., Strassman, R. J., Motta, V., & Cruz, A. P. M. (2007). Effects of ayahuasca on psychometric measures of anxiety, panic-like and hopelessness in Santo Daime members. *Journal of ethnopharmacology, 112*(3), 507-513.

Sevinç, Y., & Dewaele, J. M. (2018). Heritage language anxiety and majority language anxiety among Turkish immigrants in the Netherlands. *International Journal of Bilingualism, 22*(2), 159-179.

Simonsson, O., Sexton, J. D., & Hendricks, P. S. (2021). Associations between lifetime classic psychedelic use and markers of physical health. *Journal of Psychopharmacology, 35*(4), 447-452.

Strassman, R. (2000). *DMT: The spirit molecule: A doctor's revolutionary research into the biology of near-death and mystical experiences*. Simon and Schuster.

Studerus, E., Gamma, A., Kometer, M., & Vollenweider, F. X. (2012). Prediction of psilocybin response in healthy volunteers. *PloS one, 7*(2).

Studerus, E., Kometer, M., Hasler, F., & Vollenweider, F. X. (2011). Acute, subacute and long-term subjective effects of psilocybin in healthy humans: a pooled analysis of experimental studies. *Journal of psychopharmacology, 25*(11), 1434-1452.

Thoemmes, F., & Ong, A. D. (2016). A primer on inverse probability of treatment weighting and marginal structural models. *Emerging Adulthood, 4*(1), 40-59.

United Nations Economic and Social Council. (1968, May 23). *Urgent control measures for LSD and similar hallucinogen*. United Nations Office on Drugs and Crime. Retrieved 20 May 2022, from https://www.unodc.org/unodc/en/Resolutions/resolution_1968-05-23_6.html

Van Laar, M. W., & Van Miltenburg, C. J. A. (2020). Epidemiologie van het gebruik van psychedelica in Nederland. *Tijdschrift Voor Psychiatrie, 62*(8), 684-692.

Weitzen, S., Lapane, K. L., Toledano, A. Y., Hume, A. L., & Mor, V. (2004). Principles for modelling propensity scores in medical research: a systematic literature review. *Pharmacoepidemiology and drug safety, 13*(12), 841-853.

Williams, A. M., Khan, C. P., Heckler, C. E., Barton, D. L., Ontko, M., Geer, J., ... & Janelsins, M. C. (2021). Fatigue, anxiety, and quality of life in breast cancer patients compared to non-cancer controls: a nationwide longitudinal analysis. *Breast Cancer Research and Treatment, 187*(1), 275-285.

Zhang, G., & Stackman Jr, R. W. (2015). The role of serotonin 5-HT2A receptors in memory and cognition. *Frontiers in pharmacology, 6,* 225.