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Samantha Cassidy April 13, 2021

Disentangling the Association Between Personality Traits and Cannabis Use and Disorder in Cannabis Users of European Ancestry

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Abstract

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Cannabis use (CU) and use disorder (CUD) are associated with poor health and behavioral outcomes. Past research has reported that lifetime CU and CUD are becoming increasingly prevalent and are associated with poor behavioral outcomes. Individuals with low levels of conscientiousness and openness to experience, and high levels of agreeableness are at increased risk for CU and CUD. However, it is unclear whether the association between personality and CU and CUD is due to shared genetic or environmental factors. Twin studies have found that CU and CUD are heritable with estimates of 61% and 78% respectively. Genome-wide association studies (GWASs) have also found some single-nucleotide polymorphisms (SNPs) to be associated with CU and CUD. Likewise, personality traits have heritability estimates ranging from 41 to 61%, and a GWAS has found that one single nucleotide polymorphism (SNP) is associated with conscientiousness. Based on these observations, the current study examined whether personality traits, which are evident early in life, mediate some of the genetic effects on CU and CUD independent of known polygenic risk for these behaviors. Analyses used data from Wave IV of the National Longitudinal Study of Adolescent to Adult Health (Add Health). Lifetime repeated CU was operationalized by asking if participants had used cannabis five or more times within their lifetime. Add Health used the DSM-IV and assessed CUD through cannabis abuse and dependence. CUD severity was operationalized as a sum score of symptoms endorsed. Personality was measured using the Mini-International Personality Item Pool. Genetic effects were evaluated using polygenic risk scores (PGSs) that were created using summary statistics provided by GWASs for personality, CU, and CUD. We found that low levels of conscientiousness were associated with CUD severity; none of the PRSs predicted their respective phenotype and there was limited evidence for indirect effects of personality PGSs on the cannabis outcomes. These findings contradict our hypotheses and suggest that personality may be more related to initiation of use (not investigated here) rather than severity of use and problems. Future studies should examine cannabis initiation as an outcome variable and consider genome-wide approaches for deriving a PGS.

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Disentangling the Association Between Personality Traits and Cannabis Use and Disorder in Cannabis Users of European Ancestry

Cannabis is the most widely used illicit drug in the United States, and the third most prevalent drug used overall in the United States, falling just behind alcohol and tobacco (Substance Abuse and Mental Health Services Administration, 2019). Cannabis has numerous adverse health effects, particularly on cognitive abilities (Fontes et al., 2011; Meier et al., 2012). Additionally, cannabis use (CU) is associated with worse academic and job performance compared to non-using peers (Palamer et al., 2014). Chronic cannabis users also commonly experience a decreased sense of motivation, perhaps because of their lowered standard levels of dopamine in their striatum after chronic use (Albrechet et al., 2013; Volkow et al., 2010). The effect cannabis has on dopamine is largely because of tetrahydrocannabinol (THC), one of the two main components of cannabis (Cooper & Haney, 2008). THC acts on the cannabinoid type 1 receptors, especially in the nucleus accumbens and ventral tegmental areas of the brain (Cooper & Haney, 2008). By activating the cannabinoid type 1 receptors, a rush of dopamine is released, which leads to euphoria (Iversen, 2008). This surge of dopamine is linked to the long-term negative health outcomes associated with CU, with an increase of THC in cannabis having been linked to an increase of negative effects (Volkow et al., 2014). In contrast, the other main ingredient in cannabis, cannabidiol (CBD), is known to counteract the negative effects of THC. CBD is known to be able to treat psychosis, epilepsy, and inflammation (Schrot & Hubbard, 2016); it can also treat anxiety and sleep disorders (Gloss & Vickrey, 2014). Unlike THC, CBD does not act upon cannabinoid type 1 or type 2 receptors, so it does not result in an excessive dopamine release (Bridgeman & Abazia, 2017). Medical marijuana has higher components of CBD compared to recreational marijuana (Watson et al., 2000). Recreational marijuana has

higher levels of THC than medical marijuana, which is why the negative health outcomes are generally associated with chronic recreational marijuana use (Lafaye et al., 2017). Therefore, recreational marijuana use is the focus of this study.

Individual differences in personality traits have been associated with both CU and CUD (Abadi et al., 2018; Berg et al., 2011; Dash et al., 2019; Terraciano et al., 2008), specifically the traits identified in the Big Five model of personality (John & Srivastava, 1999). Openness to experience refers to the acceptance of novel situations, as well as creativity (John & Srivastava, 1999). Conscientiousness is defined by self-restraint and diligence (John & Srivastava, 1999). Agreeableness is the tendency to be cooperative and trustful of others (John Srivastava, 1999). Terraciano et al. (2008) found that high levels of openness to experience, low levels of conscientiousness, and low levels of agreeableness were associated with increased CU within the past year in adults, with personality having been measured through the Revised NEO Personality Inventory and CU through first asking if they had ever used cannabis and then if they were currently using. Berg et al. (2011) corroborated these results using a sample of college students and measuring repeated CU by asking how often participants used cannabis within the past 30-days and assessed personality through the Ten-Item Personality Inventory. High levels of openness to experience, low levels of conscientiousness, and low levels of agreeableness were also found to be related to increased CUD severity (Abadi et al., 2018; Dash et al., 2019). Dash et al. (2019) measured CUD by combining cannabis abuse and cannabis dependence diagnoses of the sample and personality through the Revised NEO Personality Inventory; they also did find high levels of neuroticism to be associated with increased CUD severity. Abadi et al. (2018) measured just cannabis abuse through the structured clinical interview of the diagnostic and statistical manual of mental disorders (SCID), and personality through the NEO Personality

Inventory. Since openness to experience, conscientiousness, and agreeableness have been consistently found to be associated with CU and CUD, but neuroticism and extraversion were not found to be consistently associated with both cannabis outcomes, this study focused on those three of the Big Five personality dimensions.

Genetic variation also plays a role in the incidence of CU and the severity of CUD (Demontis et al., 2019; Hines et al., 2018; Hodgson et al., 2016; Stringer et al., 2016). The common way to understand genetic influences is through twin studies - twin studies compare phenotypic similarity between pairs of identical twins and fraternal twins to infer the effects of the following three components: additive genetic (i.e., heritability), shared environment, and non-shared environment/measurement error (Compton, 2016). When the desired trait commonly occurs in both identical twins but not in both pairs of fraternal twins, then the trait is considered to be under strong genetic influence (Compton, 2016). However, heritability estimates do not tell researchers which points of variation in our DNA are associated with the desired trait. In order to examine which genetic variants are associated with the desired trait, a genome-wide association study (GWAS) must be conducted. It should be noted that each genetic variant identified in a GWAS is expected to contribute to the heritability estimate of a trait, but has an overall low impact on it, considering that most traits are polygenic (i.e., influenced by many genetic loci across the genome each with a small effect) (Compton, 2016).

CU, CUD, and personality traits all have genetic components. It was found that CU has a heritability estimate of 61% (Hodgson et al., 2016). Moreover, Stringer et al. (2016) conducted a meta-analytic GWAS for CU, operationalizing CU through cannabis initiation. While they found that no SNPs met the normal significance threshold for GWASs ($5x10^{-8}$), they did identify 10 SNPs that met the standard threshold of significance (0.05) (Stringer et al., 2016). CUD has a

reported heritability estimate of 78%, which is greater than the heritability estimate of CU (Hines et al., 2018). Demontis et al. (2019) conducted a GWAS for CUD. They found 26 SNPs associated with CUD that were below the GWAS threshold of significance (Demontis et al., 2019).

Similarly, personality traits are heritable (Jang et al., 1996; Lo et al., 2016). The heritability estimate of agreeableness is 41%, conscientiousness 44%, and openness to experience is 61% (Jang et al., 1996). Lo et al. (2016) performed a GWAS on the personality dimensions. One SNP was found to be significant for conscientiousness; other SNPs did come close to meeting the threshold of significance of 0.05, but ultimately did not meet the threshold (Lo et al., 2016).

While GWASs report SNPs associated with the desired trait, they do not examine the multi-faceted risks associated with the desired trait. In order to examine the genetic effects of the desired variables, we created PGSs for each respective one. The present study subsequently examined both the direct and indirect effects of personality on lifetime repeated CU and CUD severity. We also tested the direct association between the lifetime repeated CU PGS and the phenotype of lifetime repeated CU and the direct association between the CUD severity PGS and the CUD severity phenotype. Moreover, we tested the direct associations between each personality dimension (agreeableness, conscientiousness, and openness to experience) PGS and the cannabis outcomes. Additionally, personality phenotypes were included in the structural equation models as a potential mediator between the PGS of each personality dimension and each cannabis outcome. This allowed us to examine the potential indirect effects of the genetics of personality factors on the cannabis outcomes. See Figure 1 for a visualization of the model. As such, our hypotheses were: 1) if a person has a high PGS for lifetime cannabis use, then they will

be more likely to have repeatedly used cannabis, 2) if a person has a high PGS for CUD, then they will be more likely to have a severe form of CUD, 3) if a person has a low PGS for conscientiousness, then they will be more likely to have repeatedly used cannabis, 4) if a person has a low PGS for conscientiousness, then they will be more likely to have a severe form of CUD, 5) if a person has a low PGS for agreeableness, then they will be more likely to have repeatedly used cannabis, 6) if a person has a low PGS for agreeableness, then they will be more likely to have a severe form of CUD, 7) if a person has a high PGS for openness to experience, then they will be more likely to have repeatedly used cannabis, 8) if a person has a high PGS for openness to experience, then they will be more likely to have a severe form of CUD, 9) the conscientiousness phenotype will mediate the relationship between the conscientiousness PGS and lifetime repeated cannabis use, 10) the conscientiousness phenotype will mediate the relationship between the conscientiousness PGS and CUD severity, 11) the agreeableness phenotype will mediate the relationship between the agreeableness PGS and lifetime repeated cannabis use, 12) the agreeableness phenotype will mediate the relationship between the agreeableness PGS and CUD severity, 13) the openness to experience phenotype will mediate the relationship between the openness to experience PGS and lifetime repeated cannabis use, and 14) the openness to experience phenotype will mediate the relationship between the openness to experience PGS and CUD severity.

Methods

Participants

There was a total of 15,701 participants in Wave IV of the National Longitudinal Study of Adolescent to Adult Health (Add Health) (Harris, 2009). However, there were only 4,953 people of European ancestry who provided genetic data who were also not related to each other. Of those participants, 2,844 had initiated cannabis and provided data on lifetime repeated CU and CUD. The participants were between the ages of 25 and 34 years old (mean age = 28.720; SD = 1.794). The sample was 53.3% biologically male and 46.7% biologically female. This study is covered through Emory University IRB approval IRB00096137 for genetics projects associated with the Behavioral Genetics of Addiction laboratory.

Measures

Demographic characteristics (covariate variables). Participants' age at the time of assessment was measured by inquiring about the month and year of their birth and their age was subsequently calculated by the researchers. Biological sex was operationalized as a dichotomous variable by asking if the participant was biologically male (coded as a 0) or female (coded as a 1). Household income was measured by asking participants to consider the combined income in their household (their own and the other members' of their house before taxes and deductions). After doing so, they had to pick one of the following options that applied to them: less than $5,000, between $5,000 and $9,999, between $10,000 and $14,999, between $15,000 and $19,999, between $20,000 and $24,999, between $25,000 and $29,999, between $30,000 and $39,999, between $40,000 and $49,999, between $50,000 and $74,999, between $75,000 and $99,999, between $100,000 and $149,999, or over $150,000. These responses were coded 0

through 11. Participants could also prefer not to answer or state that they did not know – such responses were considered as NAs.

Personality. The Big Five personality traits were assessed using the 20-question Mini-International Personality Item Pool (Donnellan et al., 2006; Luchetti et al., 2014; see Appendix A). The three personality domains this study examined were agreeableness, conscientiousness, and openness to experience. Analyses focused on composite scores from each of these domains. Participants answered questions that used a 5-point Likert scale (i.e., 1 corresponded with "strongly agree" and 5 corresponded with "strongly disagree"). Responses were averaged for each of the three personality factors. Agreeableness was measured through the following questions: "I sympathize with others' feelings", "I am not interested in other people's problems", "I feel others' emotions", and "I am not really interested in others" (Baldasaro et al., 2012; Donnellan et al., 2006). "I sympathize with others' feelings" and "I feel others' emotions" were reverse-coded. The higher the score was, the more agreeable the participant was thought to be. The agreeableness dimension had a Cronbach's alpha of 0.69, which shows a reasonable internal consistency (Taber, 2017). Conscientiousness was measured through the following questions: "I get chores done right away", "I often forget to put things back in their proper place", "I like order", and "I make a mess of things" (Baldasaro et al., 2012; Donnellan et al., 2006). "I get chores done right away" and "I like order" were reverse-coded. The higher the score was, the more conscientious the participant was thought to be. The conscientiousness dimension had a Cronbach's alpha of 0.69, which shows a reasonable internal consistency (Taber, 2017). Openness to experience was measured through the following questions: "I have a vivid imagination", "I am not interested in abstract ideas", "I have difficulty understanding abstract ideas", and "I do not have a good imagination (Baldasaro et al., 2012; Donnellan et al., 2006). "I

have a vivid imagination" was reverse coded. The higher the score was, the more open to experience the participant was thought to be. The openness dimension had a Cronbach's alpha of 0.73, which shows a reasonable internal consistency (Taber, 2017). These Cronbach's alphas were consistent with past literature on the reliability of the Mini-IPIP. Cooper et al. (2010) found that the Cronbach's alpha for agreeableness was 0.70, 0.68 for conscientiousness, and 0.70 for openness to experience.

Lifetime Repeated Cannabis Use (CU). Lifetime repeated CU was operationalized through the question "Have you used marijuana more than 5 times?". This question was selected from the items Add Health asked since it demonstrated repeated use throughout the participant's entire life, rather than just within the past year, which other items inquired about. It also assessed repeated CU within the participant's lifetime, which is information cannabis initiation does not provide. Participants could either answer yes, which was coded as 1, or no, which was coded as 0; participants who did not report any use were coded as missing and excluded from analyses.

Cannabis Use Disorder (CUD) Severity. CUD severity was assessed through several questions based on the DSM-IV symptoms of abuse and dependence (American Psychiatric Association, 2000); we excluded the item that assessed substance-related legal problems, which was dropped for DSM-V (American Psychiatric Association, 2013). Add Health did not inquire about the symptom of craving that was included in the DSM-V (American Psychiatric Association, 2013). Questions relating to marijuana abuse from the DSM-IV were: "How often has your marijuana use interfered with your responsibilities at work or school?", "How often have you been under the influence of marijuana when you could have gotten yourself or others

hurt, or put yourself or others at risk, including unprotected sex?", "How often have you had legal problems because of your marijuana use, like being arrested for disturbing the peace or anything else?", "How often have you had problems with your family, friends, or people at work or school because of your marijuana use?", and "Did you continue to use marijuana after you realized using it was causing you problems with family, friends, or people at work or school?" (American Psychiatric Association, 2000). Cannabis dependence was measured through the following questions: "Have you ever found that you had to use more marijuana than you used in order to ger the effect you wanted?", "Has there ever been a period when you spent a lot of time using marijuana, getting it, or getting over its effects?", "Have you often used more marijuana or used marijuana longer than you intended?", "Has there ever been a period of time when you wanted to quit or cut down on your use of marijuana?", "When you decided to cut down or quit using marijuana, were you able to do so for at least one month?", "During the first few hours of not using marijuana, do you experience withdrawal symptoms such as craving marijuana, feeling depressed, anxious, restless, or irritable, having trouble concentrating, feeling tired or weak, having trouble sleeping, or change in appetite?", "Have you ever continued to use marijuana after you realized using marijuana was causing you any emotional problems (such as feeling depressed or empty, feeling irritable or aggressive, feeling paranoid or confused, feeling anxious or tense, being jumpy or easily startled) or causing you any health problems (such as persistent cough, sore throat or sinus problems, heart pounding, headaches or dizziness, or sexual difficulties)?", and "Have you ever given up or cut down on important activities that would interfere with your marijuana use like getting together with friends or relatives, going to work or school, participating in sports, or anything else?" (American Psychiatric Association, 2000). For most of the symptoms, participants could either answer yes, which was coded as 1, no, which

was coded as 0, or refuse to answer, which was coded as missing. For a few of the symptoms, participants were asked how often they displayed the symptom and could answer never, 1 time, more than 1 time, or refuse to answer. In order to sum the items, the responses of 1 time or more than 1 time were re-coded as 1 and never was coded as 0. The CUD severity variable was then constructed by summing the number of abuse and dependence criteria observed over the person's lifetime. The subsequent composite scores were then coded to meet DSM-5 criteria of no disorder (0 or 1 symptoms), mild disorder (2 or 3 symptoms), moderate disorder (4 or 5 symptoms), severe disorder (6 or more symptoms) (American Psychiatric Association, 2013). Due to the fact that the variable was left-skewed, it was subsequently log-transformed to be used in analyses.

Genotyping, quality control, and genetic imputation

A total of 15,701 Add Health participants provided saliva samples for Wave IV. Approximately 609,130 single-nucleotide polymorphisms (SNPs) were identified after initial quality control was done by using the programs Illumina Human Omni 1-Quad and Illumina Human Omni-2.5 Quad BeadChip to genotype samples found to be common across 9,974 participants (Highland et al., 2018). The following was then conducted by Brick et al. (2020) and the data was provided for this study. Our analyses focused on participants of European Ancestry to maximize the effectiveness of the model by using the most homogenous group (Brick et al., 2020). Brick et al. (2020) determined ancestry for the six major population groups via a principal components analysis anchored by the 1000 Genomes Project (1KG) Phase III (Version 5) reference panel (The 1000 Genomes Project Consortium, 2015). This identified a homogenous group of 5,437 participants of European Ancestry (Brick et al., 2020). The HRC r1.1 2016

reference panel and Eagle v2.4 phasing with Minimac4 via the Michigan Imputation Server were then used by Brick et al. (2020) to prep the data (Das et al., 2016). Next, 9,735,354 SNPs were selected after cleaning the data to fit GWAS standards (Brick et al., 2020). This was done by eliminating SNPs with the minimal genotyping rate (r^2<0.30), small minor allele frequency (<1%), satisfies Hardy-Weinberg Equilibrium (p p>0.0001), as well as eliminating participants with an overall minimal genotyping rate, had >90% missing data; related participants were also removed (Brick et al., 2020). Ultimately, 4,953 participants of European ancestry, who were also not related to each other, met the genetic requirements in this study.

Analytic Strategy

Summary Statistics. Study hypotheses were tested by first acquiring summary statistics from recent meta-genome-wide association studies (GWASs) of CU and personality. Analyses primarily focused on genome-wide association studies that examined behaviors that were closely related or identical to the aforementioned variables measured in the Add Health sample.

Lifetime Cannabis Use (CU): Stringer et al. (2016) conducted a GWAS for lifetime CU using data from a meta-analysis that examined 32,320 individuals with European Ancestry from 13 discovery samples from the United States, Europe, and Australia. Lifetime CU was measured through cannabis initiation since participants were asked if they had ever used cannabis during their life.

Cannabis Use Disorder: Demontis et al. (2019) performed a GWAS for CUD with data from the Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH). For the study, 79,492 Dutch individuals were genotyped and 2,387 of those participants had CUD. It was

determined that participants met the criteria for CUD using the criteria listed in the ISD-10 (Demontis et al., 2019).

Personality: Summary statistics on personality were obtained from a GWAS done by Lo et al. (2016) that conducted a meta-analysis using 76,600 participants with European Ancestry from the 23andMe and Genetics of Personality Consortium (GPC) samples. 23andMe measured personality through the Big Five Inventory and the GPC through the NEO-Five Factor Inventory (Lo et al., 2016). Analyses focused on summary data for conscientiousness, agreeableness, and openness to experience.

Polygenic Risk Scores (PGSs). Polygenic risk scores were created using the software PLINK (version 1.9) (Purcell et al., 2007) and the Summary-Based Best Linear Unbiased Prediction method implemented in genome-wide complex trait analyses (Yang et al., 2011). Summary statistics were selected from the aforementioned personality GWAS for agreeableness, conscientiousness, and openness to experience (Lo et al., 2016). In the Add Health genetic data, to confirm the work conducted by Brick et al, (2020), Risner et al. (2019) first looked for absent genotype rates per variant, absent genotype rates per individual, and minor allele frequencies. In addition, common SNPs (i.e., minor allele frequency > 1%) that were not in Hardy-Weinberg Equilibrium, or were poorly genotyped or imputed, were excluded from the analysis (Risner et al., 2019). Common SNPs were identified by Risner et al. (2019) between the Add Health genetic data and the summary statistics. Due to limited access to all of the GWAS summary statistics from the aforementioned GWAS, the polygenic risk scores were calculated using SNPs that had at least a nominal level of association (i.e., p-value <0.05). Thus, these analyses are preliminary as newer PGS methods suggest the use of genome-wide SNPs to minimize prediction error across studies.

We then ensured that the Add Health genetic data and the summary statistics had the same reference allele and then SNPs in LD with the nominally significant SNP were removed using LD pruning in PLINK (version 1.9) (Purcell et al., 2017). A new file was then created by PLINK (version 1.9) where the SNPs were matched between the summary statistics and Add Health genetic data (Purcell et al., 2017). Lastly, the score was created by using the variant ID (SNP), reference allele, and effect size in PLINK (version 1.9) via the –score function (Purcell et al., 2007).

Ancestral Principal Components (PCs). In this study, PCs 1 through 10 were included as covariates in the structural equation models to control for allele frequency variation. PCs were derived from genome-wide SNP data across all participants. PCs were each multiplied by a constant of 10,000 due to their small values.

Determination of Direct and Indirect Effects of PGSs on Lifetime Repeated Cannabis Use and Cannabis Use Disorder Severity. We used structural equation modeling in Mplus (version 8) to analyze the potential direct and indirect effects of personality factors on the cannabis outcomes. First, we conducted descriptive statistics that describe the zero-order correlations between personality traits and lifetime repeated CU and CUD severity. Second, we used a series of regression models to examine the association between each PGS and lifetime repeated CU and CUD severity. We also examined the association between each personality PGS and its respective personality outcome. These descriptive regressions were done while controlling for the covariates age, biological sex, household income, and the first ten ancestral principal components. For our main research question, we created two structural equation

models: one with lifetime repeated CU as the dependent variable and the other with CUD severity as the dependent variable. The model was repeated after substituting the personality trait. As such, each model examined the direct and indirect effect of personality PGS while controlling for genetic effects of the lifetime repeated CU or CUD PGS (as appropriate) and other covariates that were regressed on the dependent variable (see Figure 1). We also calculated the Cronbach's alpha for each personality dimension. These analyses used a total of 2,707 participants with complete information due to missingness in the household income variable.

Model fit for each structural equation model was assessed using several goodness of fit indices. These statistics were the Root Mean Square Error of Approximation (RMSEA) (Kenny, 2020), the Standardized Root Mean Square Residual (SRMR) (Kenny, 2020), and Weighted Root Mean Square Residual (WRMR) (DiStefano et al., 2017). The RMSEA represents how well the variables are able to explain the variance of the dependent variable(s) relative to the baseline model (Kenny, 2020). The baseline model is composed of solely the covariates and the dependent variable in question. A RMSEA of below 0.01 indicates excellent fit, between 0.01 and 0.05 good fit, and between 0.05 and 0.08 mediocre fit (MacCullum et al., 1996). Furthermore, the SRMR denotes the change between the actual correlation and the predicted correlation (Kenny, 2020). The model has a good fit if the SRMR value is below 0.08 (Hu & Bentler, 1999). Finally, the WRMR is provided for models that have variables that are calculated using more than one question and represents the weighted mean differences between variances of the sample and values predicted by the model (DiStefano et al., 2017). Models have a good fit when the WRMR value is less than 1.0 (DiStefano et al., 2017).

Results

Descriptive Statistics

Table 1 provides the descriptive statistics for the independent and dependent variables (openness to experience phenotype, agreeableness phenotype, conscientiousness phenotype, CUD severity untransformed and log-transformed, openness to experience PGS, agreeableness PGS, conscientiousness PGS, household income, and age). A total of 137 people had missing data for the household income variable, which indicated a minimal amount of missingness (4.8%). Approximately 79.4% of participants had used cannabis more than five times within their lifetime. Household income was slightly left-skewed with 1.8% of the sample having a household income of less than $5,000, 1.8% between $5,000 and $9,999, 2.4% between $10,000 and $14,999, 3.4% between $15,000 and $19,999, 4.8% between $20,000 and $24,999, 4.5% between $25,000 and $29,999, 10.4% between $30,000 and $39,999, 11.6% between $40,000 and $49,999, 24.4% between $50,000 and $74,999, 14.8% between $75,000 and $99,999, 10.8% between $100,000 and $149,999, and 4.5% over $150,000.

Of the sample, 66.2% reported no CUD, 15.9% reported mild disorder, 8.5% reported moderate disorder, 9.4% reported severe disorder. All personality dimensions and PGSs were relatively normally distributed. Household income was slightly left-skewed; age was bimodal. CUD severity was left-skewed and was log-transformed to approximate a normal distribution.

Zero-Order Correlations

Tables 2 through 7 depicts the results of the zero-order correlations between the independent and dependent variables and covariates. As shown, the agreeableness PGS and the conscientiousness PGS were negatively correlated ($r = -0.325$, $p < 0.001$; Table 2); the agreeableness PGS and the lifetime repeated CU PGS were also negatively associated ($r = -0.054$, $p = 0.032$; Table 2). The agreeableness phenotype was negatively correlated with both the

lifetime repeated CU phenotype (r = -0.099; p = 0.011; Table 3) and the CUD severity phenotype (r = -0.082, p = 0.001; Table 3). Moreover, the conscientiousness phenotype was negatively associated with the CUD severity phenotype (r = -0.097, p < 0.001; Table 3). The personality and cannabis PGSs were not correlated with their respective phenotypes, as seen in Tables 3 and 5. The agreeableness phenotype was positively correlated with both the conscientiousness phenotype (r = 0.153; p < 0.001; Table 7) and the openness to experience phenotype (r = 0.213; p < 0.001; Table 7).

Direct and Indirect Associations Between Personality PGS, Personality, and Cannabis Outcomes

Table 8 shows the model fit statistics. Compared to the model that included only the covariates as predictors of lifetime repeated CU or CUD severity, all other models provided a worse fit to the data, according to their Root Mean Square Error of Approximation (RMSEA) (MacCullum et al., 1996). Both models that have conscientiousness as a predictor variable have a good fit; similarly, models that have openness to experience as a predictor also provided a good fit to the data (MacCullum et al., 1996). This is also confirmed by the Standardized Root Mean Square Residual (SRMR) values (Hu & Bentler, 1999). That said, the Weighted Root Mean Square Residual (WRMR) for the lifetime repeated CU models do not indicate a good fit (DiStefano et al., 2017).

The R-squared values were significantly different from zero for the models predicting CUD severity. Comparison with the r-squared values for the covariate-lifetime repeated CU/CUD models revealed a modest change in variance explained. In the models where CUD severity was the dependent variable, the average change in R-squared was observed to be 0.001.

This indicates that adding the personality traits, and the personality and CU/CUD PGSs to the model did not explain any additional variance in CUD severity contrary to our hypotheses.

Direct Polygenic Effect on Cannabis Outcomes

Figures 2 through 8 depict the results of the path models of our main research question. Neither of the cannabis PGSs were found to be significant predictors of their respective phenotypes.

The models also showed that none of the personality dimensions were phenotypically associated with lifetime repeated CU. On the contrary, conscientiousness was negatively associated with CUD severity ($\beta = -0.071$, $p = 0.001$; Figure 4). None of the personality PGSs were found to be significant predictors of either cannabis phenotype or their respective personality phenotype. There was no evidence of indirect effects of the personality PGSs on CUD severity via their corresponding personality trait. Associations between the covariates and the outcomes of each model are presented in Appendix A.

Discussion

This research was the first to examine both the potential direct and indirect effects of the genetics of personality traits on lifetime repeated CU and CUD severity. The indirect effects were assessed by examining the personality phenotypes as possible mediators. Additionally, we examined the direct effects of the genetics of lifetime CU and CUD severity on their respective phenotypes. We found that conscientiousness was negatively associated with CUD severity. However, we did not find that any of the personality PGSs were significant predictors of lifetime repeated CU or CUD severity. Furthermore, neither agreeableness nor openness to experience

were significant predictors of either cannabis outcome. As such, no indirect relationships were found between personality PGSs and the cannabis outcomes. Contrary to findings from the GWASs the cannabis PGSs were based on, the cannabis PGSs were not associated with their respective outcomes in the current Young Adult population. Similarly, the PGSs for personality traits were not associated with individual differences in personality.

Phenotypically, it has been consistently shown that high levels of openness to experience, low levels of conscientiousness, and low levels of agreeableness were associated with both lifetime repeated CU and CUD (Abdai et al., 2018; Berg et al., 2011; Dash et al., 2019; Terraciano et al., 2008). However, the current study only replicated the conscientiousness association with CUD severity. Despite past evidence for genetic influences on personality traits (Jang et al., 1996; Lo et al., 2016), we did not find any relationship between the personality PGSs and their respective phenotype; though it should be noted that only a single SNP comprised the conscientiousness PGS and the discovery GWAS was underpowered with only 2,000 cases.

These differing results could be because of a variety of factors. First off, we restricted our study to only people who had reported that they had tried cannabis in the first place, which reduced our sample size, but allowed us to not conflate initiation with use. The past literature that had examined the relationship between the Big Five personality dimensions and cannabis use disorder, or just cannabis abuse in the case of Abadi et al. (2018), also looked at the other substances within their research (Abadi et al., 2018; Dash et al., 2019). Therefore, people who had never tried cannabis at all were included in the analyses and could have subsequently inflated the effect sizes they found (Abadi et al., 2018; Dash et al., 2019).

Secondly, a consensus has not been reached on how to measure each variable included in this study. Terraciano et al. (2008) assessed lifetime CU through if participants had ever used

cannabis at all and if they were currently using cannabis, which conflates initiation with repeated use. Berg et al. (2019) measured lifetime CU by asking how often participants had used cannabis in the past 30-days. Stringer et al. (2016) assessed lifetime CU through cannabis initiation for their GWAS and Hodgson et al. (2016) in their twin study measured lifetime CU by asking participants if they had used cannabis more than once within their life. This study, on the other hand, assessed lifetime CU through if participants used cannabis five or more times within their life, but only amongst those who had tried cannabis one or more times in their life. Similarly, this study used CUD severity rather than disorder diagnosis (i.e., case versus control), which would have been more consistent with how Demontis et al. (2019) and Hines et al. (2018) assessed CUD. Thus, the cannabis outcomes did not exactly match in their phenotypic variance. Moreover, Abadi et al. (2018), Jang et al. (1996), and Terraciano et al. (2008), measured personality through the Revised NEO Personality Inventory and Berg et al. (2011) with the Ten-Item Personality Inventory. Lo et al. (2016) used data from 23andMe, which assessed personality through the Big Five Inventory, and the Genetics of Personality Consortium used the Neo-Five Factor Inventory. Dash et al. (2019) operationalized personality through the Big Five Inventory. In contrast, this study measured personality through the Mini-International Personality Item Pool. Additionally, Abadi et al. (2018) only looked at cannabis abuse, whereas this study looked at both cannabis abuse and dependence (the two aspects of CUD) and only looked at cannabis, not other substances like Abadi et al. (2018) and Dash et al. (2019) did.

Thirdly, while relatively high heritability estimates have been reported for the personality dimensions, lifetime CU, and CUD, these heritability estimates do not mean that those traits are caused by that percentage of genes (Jang et al., 1996; Hodgson et al., 2016; Hines et al., 2018). Due to the fact that the GWASs found relatively few to no SNPs associated with the variables,

the PGSs may subsequently not have been powerful enough to be able to detect a possible relationship (Demontis et al., 2019; Lo et al., 2016; Stringer at al., 2016;) and so future larger GWASs may be needed before we are able to operationalize PGSs for these behaviors and traits.

Limitations

There were several limitations to this study that must be considered. This study utilized several predictor variables and subsequently had a relatively small sample size, considering it was limited to participants who had provided genetic data, had tried cannabis before, and provided complete information for all other variables as well. We also only used SNPs from all GWASs that had already been found to meet the significance threshold of 0.05 rather than all SNPs in the genome – this was done because of limited access to the summary statistic files, but it may not have been the optimal threshold for making a prediction. We chose to take a conservative approach and only used a single threshold for nominal significance in the discovery GWASs. Another limitation was that we measured lifetime repeated CU only through one question. This question does not necessarily provide an accurate picture by itself due to the fact that it relies on people's memory of their CU throughout their lifetime. Finally, this study only looked at participants of European descent. This was because most genetic research has been conducted on people of European descent and the allele frequencies differ greatly from race to race. Therefore, in order to have accurate results, we limited our sample to participants of European descent. Consequently, our PGS findings do not generalize to other populations.

Implications

These findings emphasize the importance of generalizability across samples. Polygenic risk scores unfortunately can be limited in how much they are able to predict, especially in a small sample size when the demographic information is even slightly different. For example,

even though Stringer et al. (2016), Demontis et al. (2019), and Lo et al. (2016) all looked at participants of European ancestry, their studies did not exclusively take place in the United States, as Add Health did nor were they well powered. Indeed, it has been shown that for most common diseases, the number of genome-wide significant hits that are discovered increases as the sample size for cases reaches about 10,000 to 100,000 (Sullivan et al., 2018). Stringer et al. (2016) and Lo et al. (2016) included samples from the US as well as Europe and Australia, and Demontis et al. (2019) used iPsych data, which exclusively has Danish participants.

Conclusions & Future Directions

This study examined if personality PGSs were able to predict cannabis outcomes, which had not yet been studied; past literature had solely focused on the relationship between the personality phenotypes and cannabis outcomes (Abdai et al., 2018; Berg et al., 2011; Dash et al., 2019; Terraciano et al., 2008). It was found that the personality PGSs were not able to predict individual differences in lifetime repeated CU and CUD severity. However, this study did replicate prior negative associations between conscientiousness and CUD (Abadi et al., 2018; Dash et al., 2018).

Future studies should examine this research question in a larger sample to determine if there was not enough power to detect an effect that was there or if there truly is no relationship between most of the variables. Additionally, they should use the entire genome to make the PGSs, which would increase the power of the studies. Moreover, another future direction is to examine if personality PGSs are able to predict cannabis initiation, rather than repeated cannabis use, which would have a larger sample size. Finally, future studies should also conduct more GWASs in minority communities and those studies can subsequently be used in other research to

examine the direct and indirect relationships between personality PGSs and cannabis outcomes within those communities.

In summary, while tentative and in need of replication, these approaches are important because they can be used to develop effective interventions for CUD. According to the results of this study, people who have low levels of conscientiousness are at increased risk for developing CUD. Therefore, interventions can be created to target people who have low levels of conscientiousness to try to manage their cannabis use before it becomes CUD.

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List of Tables and Figures

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Figure 1: Overall model of the study. This figure summarizes how the analyses were set-up for this study.

Figure 2: Model depicting association between agreeableness and lifetime repeated CU. The agreeableness PGS, agreeableness phenotype, and lifetime CU PGS were not associated with lifetime repeated CU.

Figure 3: Model depicting association between agreeableness and CUD severity. The agreeableness PGS, agreeableness phenotype, and CUD PGS were not associated with CUD severity.

Figure 4: Model depicting association between conscientiousness and lifetime repeated CU. The conscientiousness PGS, conscientiousness phenotype, and lifetime CU PGS were not associated with lifetime repeated CU.

Figure 5: Model depicting association between conscientiousness and CUD severity. Conscientiousness was a predictor of CUD severity. The conscientiousness PGS and CUD PGS were not associated with CUD severity.

Figure 6: Model depicting association between openness and lifetime repeated CU. The openness PGS, openness phenotype, and lifetime CU PGS were not associated with lifetime repeated CU.

Figure 7: Model depicting association between openness and CUD severity. The openness PGS, openness phenotype, and CUD PGS were not associated with CUD severity.

Table 1. Descriptive Statistics

Variable	Mean	St. Dev	Median	Min	Max	Skew	Kurtosis
Agreeableness Phenotype	2.835	0.619	3.000	0.000	4.000	-0.766	1.130
Conscientiousness Phenotype	2.564	0.701	2.750	0.000	4.000	-0.0369	0.056
Openness Phenotype	2.698	0.62	2.750	0.250	4.000	-0.232	0.191
CUD Untransformed Phenotype	0.626	0.985	0.000	0.000	3.000	1.384	0.577
CUD Log-transformed Phenotype	0.344	0.499	0.000	0.000	1.386	0.999	-0.583
Agreeableness PGS	-0.032	1.000	-0.059	-2.879	4.960	0.515	1.437
Conscientiousness PGS	-0.001	0.978	-0.014	-3.064	3.958	0.078	-0.014
Openness PGS	-0.009	0.997	0.036	-3.434	3.829	-0.173	0.431
CUD PGS	0.028	0.991	0.015	-3.846	3.321	0.045	-0.008
Repeated CU PGS	-0.012	1.004	0.000	-3.429	3.273	0.011	0.030
Income	7.224	2.510	8.000	0.000	11.000	-0.939	0.515
Age	28.698	1.787	28.833	25.083	34.083	0.148	-0.986

Note. Table shows the descriptive statistics of the study variables and covariates. St. Dev is Standard Deviation, Min is Minimum, and Max is Maximum.

Table 2. Zero-Order Correlations Between PGSs

Variable	Agreeableness PGS	Conscientiousness PGS	Openness PGS	CUD PGS	Lifetime CU PGS
Agreeableness PGS	1.000				
Conscientiousness PGS	-0.325***	1.000			
Openness PGS	-0.003	-0.010	1.000		
CUD PGS	0.004	0.000	-0.016	1.000	
Lifetime CU PGS	-0.054*	0.026	-0.007	-0.008	1.000

Note. Table displays correlation coefficients between polygenic risk score variables; * is $p < 0.05$ and *** is $p < 0.001$.

Table 3. Zero-Order Correlations Between Main Study Variables and Cannabis Outcomes		
Variable	Lifetime Repeated CU Phenotype	CUD Severity Phenotype
Agreeableness PGS	-0.030	-0.023
Conscientiousness PGS	0.010	0.025
Openness PGS	0.020	0.018
CUD PGS	N/A	-0.042
Lifetime CU PGS	0.002	N/A
Agreeableness Phenotype	-0.099**	-0.082**
Conscientiousness Phenotype	-0.035	-0.097***
Openness Phenotype	0.064	0.024

Note. Table displays correlation coefficients between main study variables and cannabis outcomes; * is $p < 0.05$, ** is $p < 0.01$, and *** is $p < 0.001$.

Table 4. Zero-Order Correlations Between Covariates and Cannabis Outcomes		
Variable	Lifetime Repeated CU Phenotype	CUD Severity Phenotype
Age	-0.096*	-0.047
Sex	-0.135**	-0.176***
Household Income	-0.080*	-0.102***
PC1	-0.013	-0.001
PC2	0.038	0.020
PC3	0.069	0.021
PC4	-0.050	0.009
PC5	0.010	0..011
PC6	-0.023	-0.016
PC7	-0.052	-0.012
PC8	0.112**	0.015
PC9	0.050*	0.013
PC10	-0.062*	0.003

Note. Table displays correlation coefficients between covariates and cannabis outcomes; * is $p < 0.05$, ** is $p < 0.01$, and *** is $p < 0.001$.

Table 5. Zero-Order Correlations Between Personality PGSs and Respective Phenotypes

Variable	Agreeableness Phenotype	Conscientiousness Phenotype	Openness Phenotype
Agreeableness PGS	0.001	N/A	N/A
Conscientiousness PGS	N/A	-0.021	N/A
Openness PGS	N/A	N/A	0.019

Note. Table displays correlation coefficients between personality polygenic risk scores and respective phenotypes.

Table 6. Zero-Order Correlations Between Covariates and Personality Outcomes			
Variable	Agreeableness Phenotype	Conscientiousness Phenotype	Openness Phenotype
Age	0.009	0.014	-0.091***
Sex	0.412	0.137***	-0.158***
Income	0.045	0.100***	0.045*
PC1	-0.013	-0.047*	-0.026
PC2	-0.004	0.021**	0.037***
PC3	-0.006	0.006	0.007
PC4	0.011	-0.009	-0.005
PC5	-0.046***	-0.024**	0.014
PC6	-0.057**	0.010	-0.039
PC7	-0.053	0.012	-0.027
PC8	0.013	0.007	-0.007
PC9	-0.010	0.010	-0.005
PC10	0.008	-0.033	0.069**

Note. Table displays correlation coefficients between covariates and personality outcomes; ** is $p < 0.01$, and *** is $p < 0.001$.

Table 7. Zero-Order Correlations Between Personality Phenotypes

Variable	Agreeableness	Conscientiousness	Openness
Agreeableness	1.000		
Conscientiousness	0.153***	1.000	
Openness	0.213***	-0.018	1.000

Note. Table displays correlation coefficients between personality phenotypes; *** is $p < 0.001$.

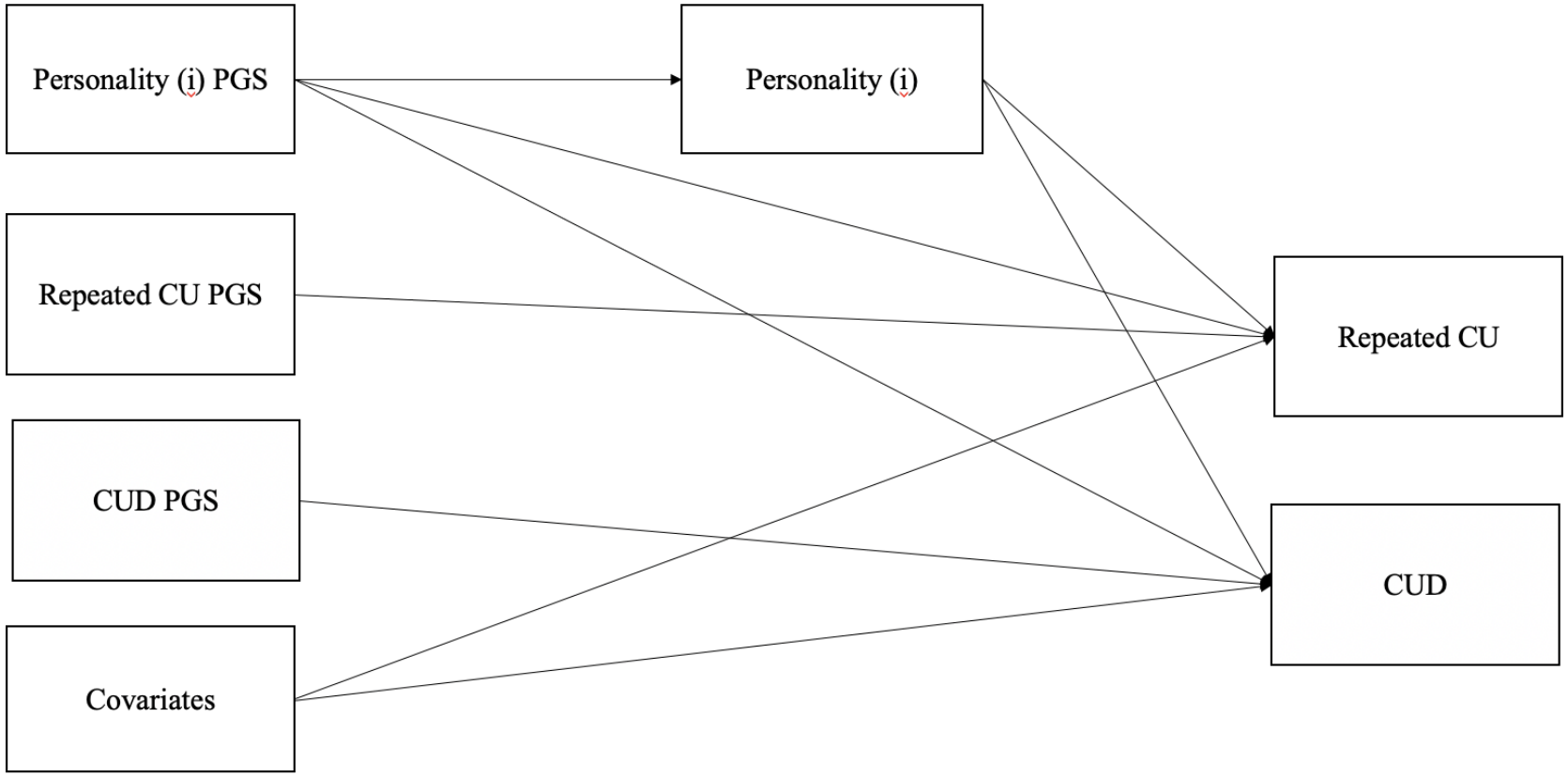
Table 8. Model Fit Statistics

	Overall model fit			Variance explained by predictors	
Model	RMSEA	WRMR	SRMR	R-Squared Cannabis DV	R-Squared Personality DV
Covariates-Lifetime Repeated CU	0.000	0.000	N/A	0.064	N/A
Agreeableness-Lifetime Repeated CU	0.061	2.361	N/A	0.068	0.000
Conscientiousness-Lifetime Repeated CU	0.031	1.335	N/A	0.064	0.000
Openness-Lifetime Repeated CU	0.035	1.473	N/A	0.066	0.001
Covariates-CUD Severity	0.000	N/A	0.000	0.037	N/A
Agreeableness-CUD Severity	0.077	N/A	0.026	0.036***	0.000
Conscientiousness-CUD Severity	0.043	N/A	0.014	0.039***	0.001
Openness-CUD Severity	0.043	N/A	0.014	0.038***	0.001

Note. Table displays model fit statistics; *** is $p < 0.001$. RMSEA is Root Mean Square Error of Approximation, WRMR is Weighted Root Mean Square Residual, and SRMR is Standardized Root Mean Square Residual.

Figure 1

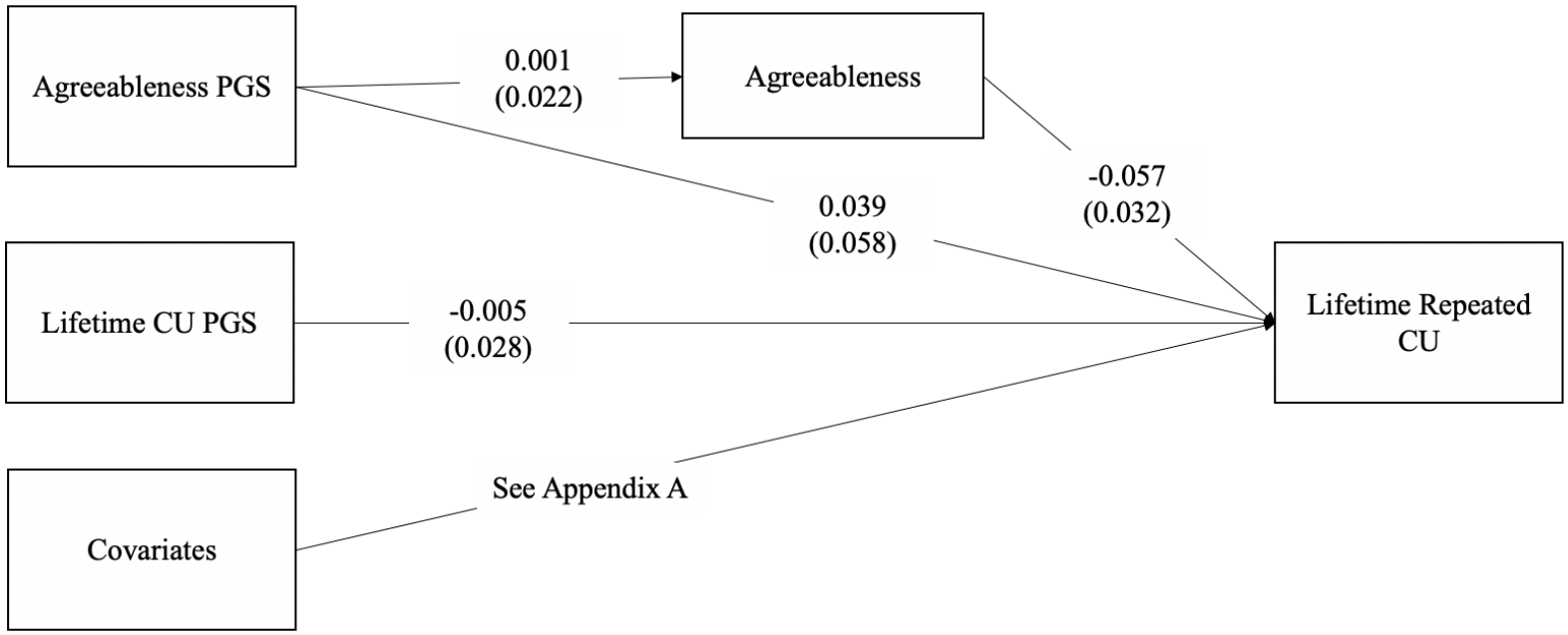
Overall model of the study



Note. Figure depicts how analyses were set-up for the study.

Figure 2

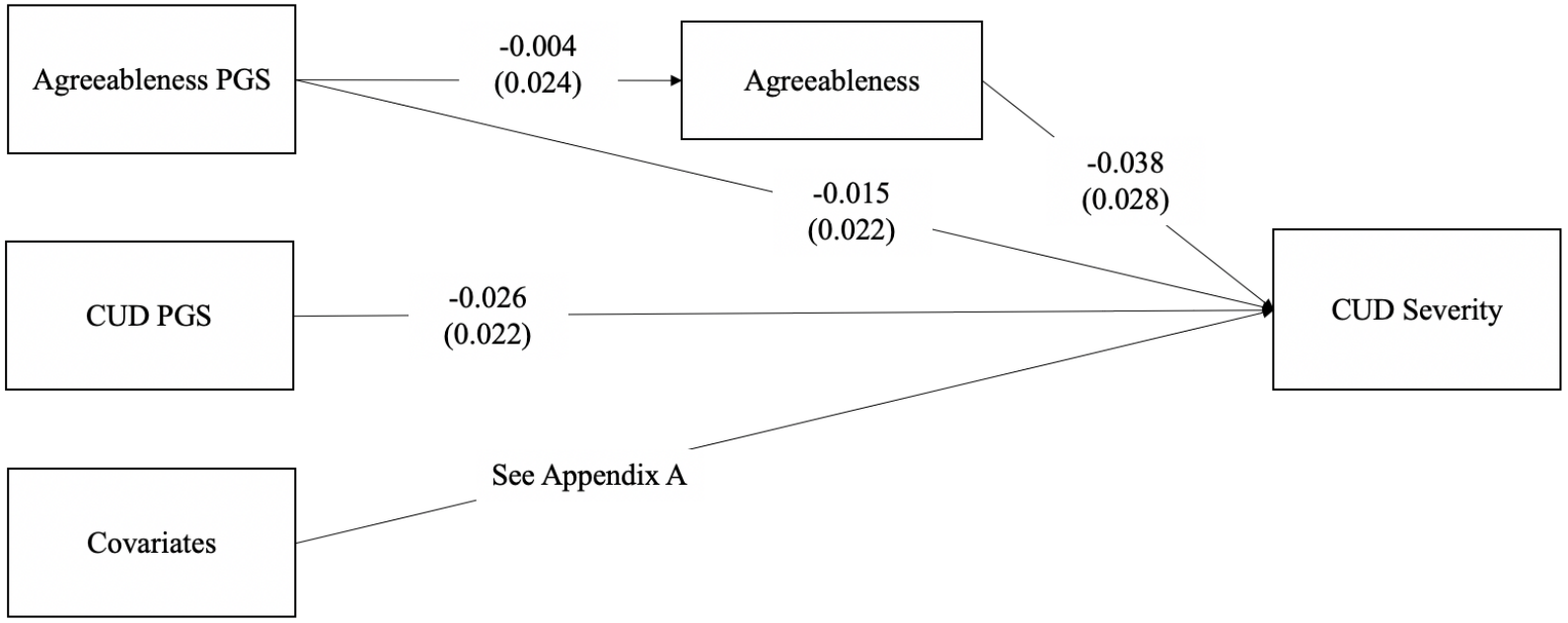
Model depicting association between agreeableness and lifetime repeated CU



Note. Figure demonstrates how analysis examined direct and indirect associations between agreeableness PGS and lifetime repeated CU. The number outside the parentheses is the beta value and the number inside the parentheses is the standard error value.

Figure 3

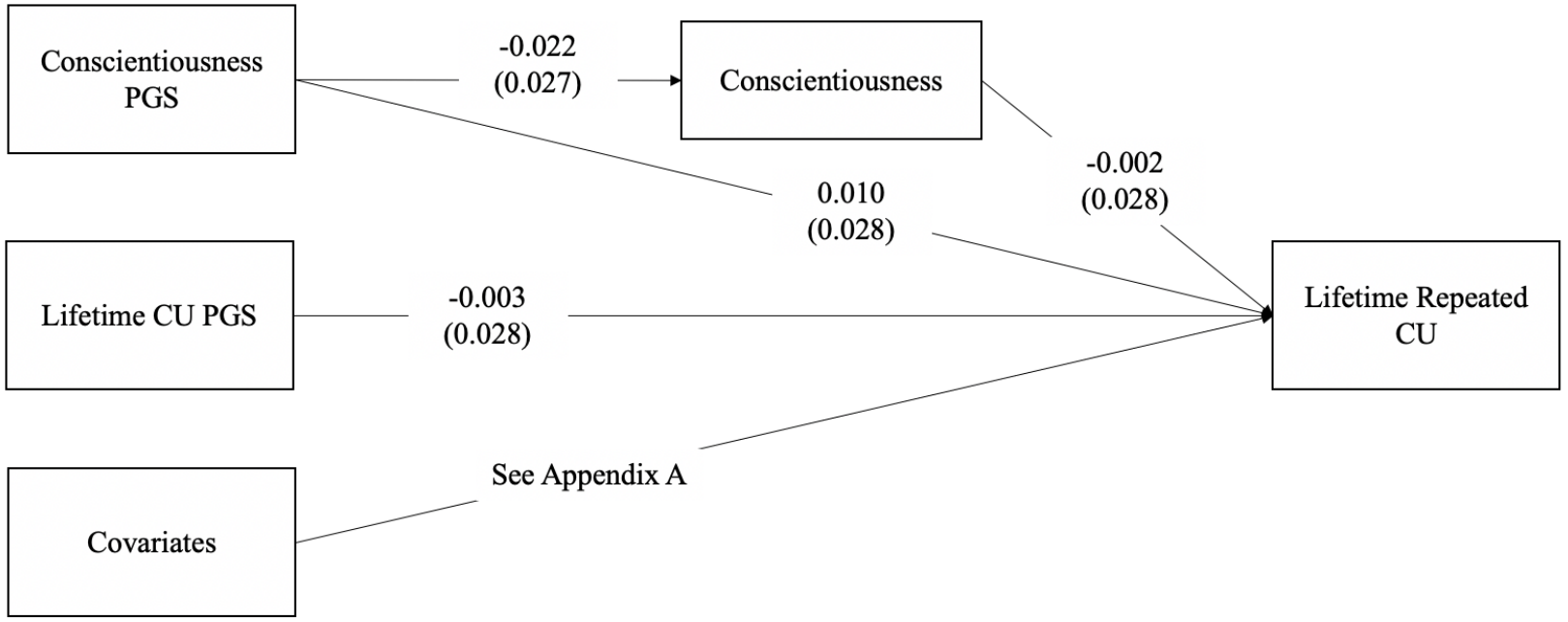
Model depicting association between agreeableness and CUD severity



Note. Figure demonstrates how analysis examined direct and indirect associations between agreeableness PGS and CUD severity. The number outside the parentheses is the beta value and the number inside the parentheses is the standard error value.

Figure 4

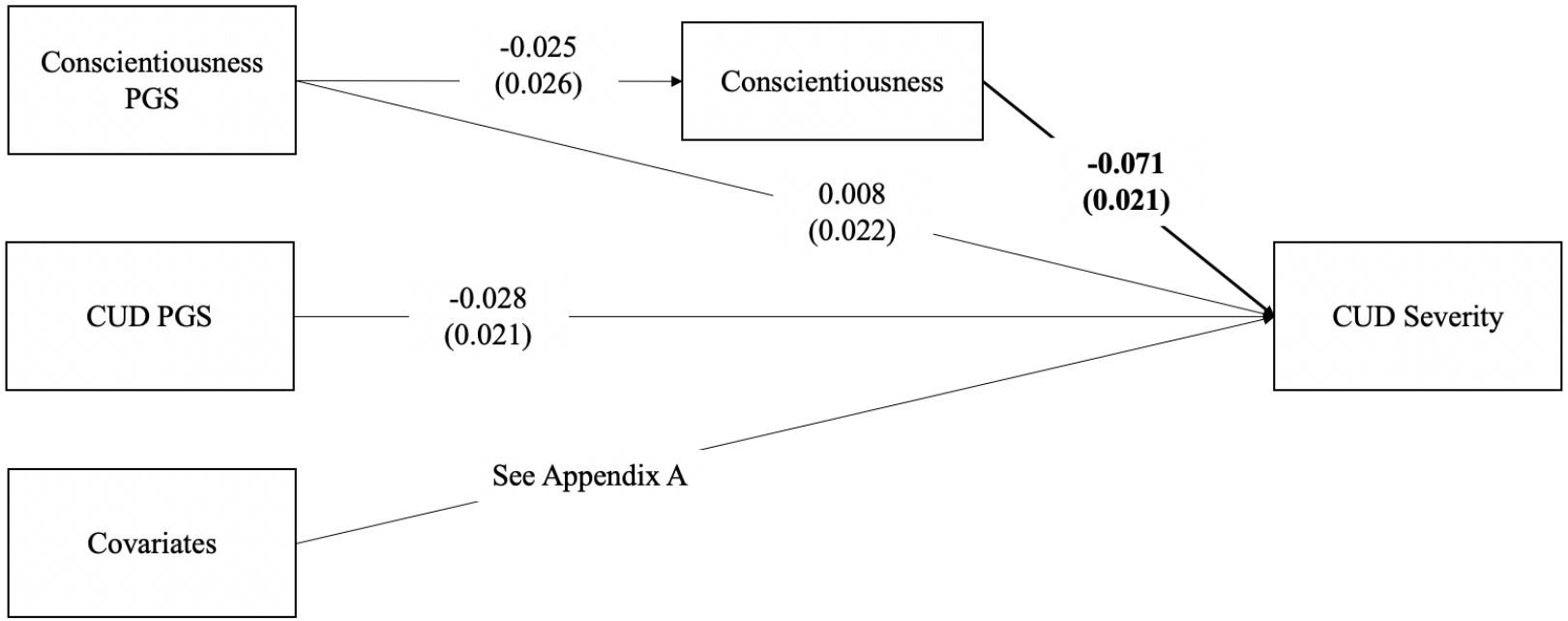
Model depicting association between conscientiousness and lifetime repeated CU



Note. Figure demonstrates how analysis examined direct and indirect associations between conscientiousness PGS and lifetime repeated CU. The number outside the parentheses is the beta value and the number inside the parentheses is the standard error value.

Figure 5

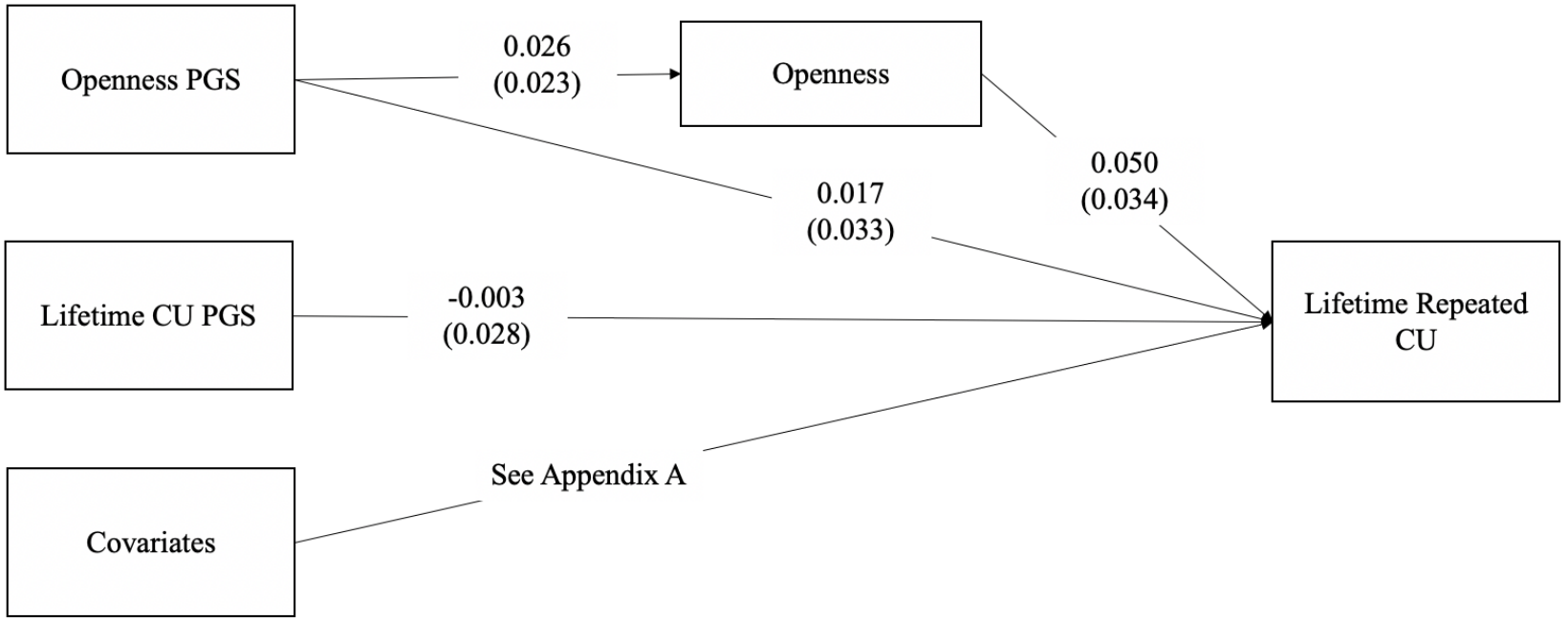
Model depicting association between conscientiousness and CUD severity



Note. Figure demonstrates how analysis examined direct and indirect associations between conscientiousness PGS and CUD severity. The number outside the parentheses is the beta value and the number inside the parentheses is the standard error value.

Figure 6

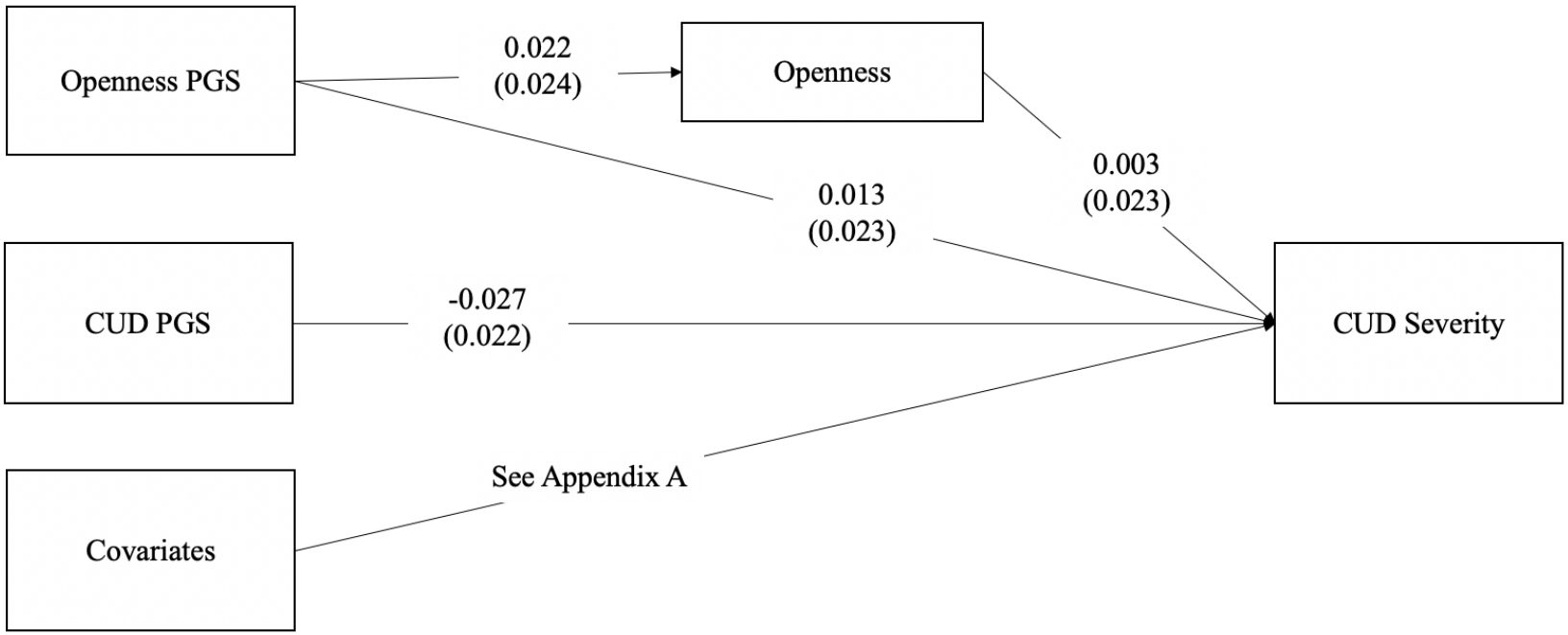
Model depicting association between openness and lifetime repeated CU



Note. Figure demonstrates how analysis examined direct and indirect associations between openness PGS and lifetime repeated CU. The number outside the parentheses is the beta value and the number inside the parentheses is the standard error value.

Figure 7

Model depicting association between openness and CUD severity



Note. Figure demonstrates how analysis examined direct and indirect associations between openness PGS and CUD severity. The number outside the parentheses is the beta value and the number inside the parentheses is the standard error value.

Appendix A

Mini-International Personality Item Pool

How much do you agree with each statement as you generally are now, not as you wish to be in the future?

1. I am the life of the party
2. I sympathize with others' feelings
3. I get chores down right away
4. I have frequent mood swings
5. I have a vivid imagination
6. I worry about things
7. I'm always optimistic about my future
8. I get angry easily
9. I don't talk a lot
10. I am not interested in other people's problems
11. I often forget to put things in their proper place
12. I am relaxed most of the time
13. I am not interested in abstract ideas
14. I am not easily bothered by things
15. I hardly ever expect things to go my way
16. I rarely get irritated
17. I talk to a lot of different people at parties
18. I feel others' emotions

19. I like order

20. I ger upset easily

Appendix B. Regression Coefficients of Covariates in all Models		
Predictors per model	β	SE
Covariates-Lifetime Repeated CU		
Income*	-0.031	0.013
Age*	-0.055	0.023
Sex**	-0.244	0.073
PC1	0.000	0.000
PC2	0.000	0.001
PC3	0.000	0.001
PC4	0.000	0.001
PC5	0.000	0.001
PC6	0.000	0.001
PC7	0.000	0.001
PC8	0.000	0.001
PC9	0.000	0.000
PC10*	0.000	0.000
Covariates-CUD Severity		
Income***	-0.103	0.025
Age	-0.042	0.025
Sex***	-0.153	0.020
PC1	0.001	0.027
PC2	0.007	0.020
PC3	0.053	0.036
PC4	0.041	0.033
PC5	0.002	0.028
PC6	-0.036	0.036
PC7	0.018	0.035
PC8	0.012	0.015
PC9	-0.008	0.025
PC10	0.006	0.022
Agreeableness-Lifetime Repeated CU		
Income*	-0.076	0.032
Age*	-0.095	0.039
Sex**	-0.119	0.036
PC1	0.016	0.046
PC2	0.077	0.110

PC3	0.043	0.061
PC4	-0.031	0.048
PC5	0.054	0.043
PC6	-0.007	0.072
PC7	-0.074	0.128
PC8	0.082	0.063
PC9	-0.012	0.049
PC10*	-0.070	0.031
Agreeableness-CUD Severity		
Income***	-0.100	0.025
Age	-0.040	0.024
Sex***	-0.141	0.022
PC1	0.002	0.027
PC2	0.008	0.020
PC3	0.053	0.036
PC4	0.042	0.033
PC5	-0.001	0.027
PC6	-0.038	0.037
PC7	0.018	0.035
PC8	0.012	0.015
PC9	-0.008	0.025
PC10	0.006	0.021
Conscientiousness- Lifetime Repeated CU		
Income*	-0.076	0.032
Age*	-0.096	0.039
Sex**	-0.118	0.036
PC1	0.014	0.046
PC2	0.076	0.109
PC3	0.043	0.061
PC4	-0.032	0.048
PC5	0.054	0.043
PC6	-0.008	0.072
PC7	-0.076	0.129
PC8	0.084	0.064
PC9	-0.012	0.049
PC10*	-0.069	0.031
Conscientiousness-CUD Severity		

Income***	-0.094	0.025
Age	-0.040	0.025
Sex***	-0.144	0.020
PC1	-0.002	0.027
PC2	0.012	0.020
PC3	0.049	0.035
PC4	0.039	0.033
PC5	-0.003	0.027
PC6	0.037	0.037
PC7	0.022	0.036
PC8	0.013	0.015
PC9	-0.004	0.025
PC10	0.004	0.022
Openness-Lifetime Repeated CU		
Income*	-0.076	0.031
Age*	-0.096	0.039
Sex*	-0.118	0.036
PC1	0.014	0.046
PC2	0.076	0.109
PC3	0.041	0.063
PC4	-0.033	0.050
PC5	0.053	0.043
PC6	-0.009	0.073
PC7	-0.071	0.127
PC8	0.084	0.063
PC9	-0.012	0.049
PC10	-0.070	0.031
Openness-CUD Severity		
Income***	-0.101	0.025
Age	-0.041	0.024
Sex***	-0.153	0.021
PC1	0.003	0.027
PC2	0.009	0.019
PC3	0.052	0.036
PC4	0.041	0.033
PC5	0.000	0.027
PC6	-0.037	0.036
PC7	0.020	0.035

PC8	0.012	0.015
PC9	-0.007	0.025
PC10	-0.006	0.021

Note. Table displays regression coefficients of covariates for all models