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DEVELOPMENTAL TRAJECTORIES IN CANNABIS USE: PREDISPOSITIONS, PEERS, AND ACTIVITY PARTICIPATION

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DEVELOPMENTAL TRAJECTORIES IN CANNABIS USE: PREDISPOSITIONS, PEERS, AND ACTIVITY PARTICIPATION

A thesis proposal submitted in partial fulfillment of the requirements for the degree of Master of Science at Virginia Commonwealth University

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This work is dedicated to my dad, who I think would have been happy to see where I've ended up.

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Abstract

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This study examined the overall and conditional influences of a polygenic score for cannabis initiation, various forms of activity participation, peer deviance, and time on recent cannabis use. Data came from a longitudinal sample of undergraduate college students and was stratified into European American (N_{EA}=3010) and African American ($N_{AA=}$1308) subsamples for genetic analyses. Engagement with church activities predicted lower probability of cannabis use. Peer deviance predicted higher probability of cannabis use Engagement with community activities moderated in the influence of the polygenic risk score in the EA subsample, such that any level of engagement with community activities truncated the influence of the polygenic risk score on probability of recent cannabis use. This effect did not replicate in the AA subset due to low (8%) observed power in this subsample. Results suggests that programs which facilitate engagement with the community may represent a means to reduce the influence of genetic risk loading on cannabis use.

Statement of Purpose

Cannabis use is common and associated with considerable negative consequences to health, cognition, and academic functioning among emerging adult college students. Cannabis use is influenced by both genetic and environmental factors. The role of genetic influences on cannabis use is also moderated by the environment, such that some environments enhance the influence of genetic risk while others limit the influence of genetic risk. The risk-enhancing role of substance-permissive social environments is established in the literature; however, previous studies have not examined the role of extracurricular activity participation as a potential protective factor against the influence of genetic risk for cannabis use. The purpose of the present study is to contribute to the literature on environmental moderators of genetic risk for cannabis use in emerging adult college students. Specifically, this project examines the risk-enhancing role of peer deviance and the protective role of various forms of activity participation on cannabis use in emerging adult college students. This project also tests for variability in these effects over the college years, working from the hypothesis that the influence of genetic risk factors may increase over time. The identification of modifiable environmental factors that moderate the influence of genetic risk on cannabis use represents a critical first step in the development of tailored prevention programming.

Introduction

Cannabis use is common. In the United States, emerging adults endorse elevated rates of cannabis use relative to other age demographics (Schulenberg et al., 2018). Approximately 13.1 million individuals experienced cannabis dependence worldwide in 2010, with individuals between the ages of 20 – 24 from high-income regions accounting for a large proportion of affected individuals (Degenhardt et al., 2013). Current trends in state law towards recreational legalization of cannabis in the United States suggest that rates of use may increase among emerging adults (Hall & Weier, 2015). Cannabis use in emerging adult college students is associated with a wide range of health (Caldeira et al., 2012), neurological (Dager et al., 2018) and academic (Arria, Caldeira, Bugbee, Vincent, & O'Grady, 2015; Arria, Caldeira, et al., 2013; Arria, Garnier-Dykstra, et al., 2013; Caldeira, Arria, O'Grady, Vincent, & Wish, 2008; Caldeira et al., 2012; Suerken et al., 2016) consequences. Conversely, college completion, which cannabis use is negatively associated with (Arria, Caldeira, et al., 2013; Arria, Garnier-Dykstra, et al., 2013), is associated with wide ranging benefits throughout the lifespan (Ma et al., 2016; Perna, 2005), suggesting that the opportunity cost of cannabis use among emerging adult college students is high. Clarification of the etiology of cannabis use in emerging adult college students represents a critical step in limiting the long-term harm associated with the high rates of cannabis use in this group.

Genetic and Familial Predictors of Cannabis Use

Cannabis use is influenced by genetic and familial risk factors. Heritability estimates from twin models suggest that 40-48% of the variance in initiation and 51-59% of the variance in problematic use is attributable to genetic variance (Verweij et al., 2010). Single nucleotide polymorphism (SNP)-based heritability estimates from recent genome-wide association studies (GWAS) suggest that common variants account for 11% of the variance in cannabis initiation

(Pasman et al., 2018). Molecular genetic methods do not currently index the full extent of heritability implied by the twin literature (Manolio et al., 2009). Various explanations have been proposed for this missing heritability problem, such as failure to detect many common variants of small effect, exclusion of rare variants of larger effect from genotyping arrays because of their low population frequency, poor coverage of structural variants in genotyping arrays, a lack of power to detect gene-gene interactions, and overestimation of heritability in twin studies (Manolio et al., 2009). Recent discussions of the missing heritability problem suggest that whole-genome-sequence data on large family-based samples may resolve these methodological issues in the future (Young, 2019). Regardless, these two domains of work converge to suggest that genetics play a substantial role in an individual's risk for cannabis use.

Genome-wide association studies (GWAS) have begun to identify variants associated with cannabis use phenotypes. Earlier GWAS of cannabis use initiation and age at onset failed to identify statistically significant effects in both SNP- and gene-based tests because of small sample size (Minică et al., 2015; Verweij et al., 2013). Complex traits, such as cannabis use, are influenced by many SNPs of small effect (Manolio et al., 2009), which require large samples and greater statistical power to detect. As available sample size has increased, GWAS have identified more significant associations between molecular genetic markers and cannabis phenotypes. Gene-based tests of association in Stringer et al. (2016) first identified associations between cannabis initiation and variation at *NCAM1*, *CADM2*, *SCOC*, and *KCNT2*. A more recent update on this analysis, which added an additional ~150,000 subjects to the sample, has since identified 35 genes and 8 SNPs that are significantly associated with cannabis initiation (Pasman et al., 2018). Aligning with the results reported in Stringer et al. (2016), *CADM2* emerges as a gene that is consistently associated with cannabis use, as well as a range of other substance use and risk-taking behaviors (Pasman et al., 2018). GWAS for age of onset have also made considerable advances, with recent analyses identifying significant association between age of onset of cannabis use and *ATP2C2* in gene-based tests, and 5 correlated SNPs on *ATP2C2* in SNP-based tests (Minică et al., 2018). Most recently, GWAS of cannabis use disorder (CUD) identify a SNP on *CHRNA2* that is significantly associated with CUD (Demontis et al., 2019). While larger samples are required for a more comprehensive understanding of the molecular genetic etiology of cannabis use phenotypes, these recent advances mark an important starting point for efforts to understand the molecular mechanisms underlying the heritability estimates that are presented in twin studies.

Polygenic risk scores (PRS) leverage the patterns of association that are identified in GWAS to facilitate the prediction of complex phenotypes with many SNPs at once. SNPs are first clumped into an independent set of markers, weighted by results from GWAS in an independent sample, and then summed to construct a composite score (Dudbridge, 2013). A series of p-value thresholds for SNP inclusion are tested and the threshold which predicts the most variance in the target phenotype is retained for further analysis (International Schizophrenia Consortium et al., 2009). Methodological challenges associated with polygenic prediction of complex traits include potential confounding by indirect genetic effects and population stratification (Young et al., 2019), as well as poor coverage of rare variants in typical GWAS genotyping arrays (Young, 2019). The calculation of PRS is an area of continuing methodological development in the field of behavior genetics (Privé et al., 2019; Selzam et al., 2019) and the findings of studies employing these methods should be interpreted with these limitations in mind.

Most large GWAS of cannabis use phenotypes examine European ancestry subjects, limiting prediction of cannabis use phenotypes in diverse groups of subjects with PRS calculated from these summary statistics (Duncan et al., 2019). When the discovery and target sample for PRS calculation are not matched, the accuracy of phenotype prediction is limited by differences in minor allele frequency and patterns of linkage disequilibrium between the discovery and target ancestry groups (Martin et al., 2017). The direction of the bias introduced by these differences between ancestry groups is unpredictable (Martin et al., 2017) and the magnitude of overall deficits in prediction are not clear (Duncan et al., 2019). The problems presented by these methodological obstacles are compounded by epidemiological differences between groups. Rates of past 30 day cannabis use among African American college students has increased from 11.2% in 2002 to 23.3% in 2016, while rates of past 30 day cannabis use among European American college students have remained relatively stable at 21.4% in 2002 and 22.8% in 2016 (Odani et al., 2019), underscoring the importance of examining cannabis use in diverse groups of students.

Environmental Predictors of Cannabis Use

Cannabis use is influenced by environmental factors as well. Heritability estimates ranging between 40-59% for various cannabis-related phenotypes suggest that roughly half of the variance in cannabis use is attributable to environmental factors. Peer involvement is a critical developmental task during the transition from adolescence to adulthood (Schulenberg et al., 2004), and it follows naturally that social contexts are an important environmental influence on cannabis use in college students. Most cannabis use among college students occurs in social contexts (Phillips et al., 2018) and risk behavior in college students' social network is a strong predictor of cannabis use (Mason et al., 2014). Relatedly, living on campus (O'Brien et al., 2018; Suerken et al., 2014), perceived social norms (Ecker et al., 2014; LaBrie et al., 2011;

Lewis & Clemens, 2008; Napper et al., 2015; Neighbors et al., 2008; Simons et al., 2006), and peer cannabis use (Kandel, 1973; Pinchevsky et al., 2012) emerge as consistent correlates of cannabis use among college students. The developmental salience of peer involvement in college students marks maladaptive peer contexts as a critical risk factor for cannabis use in this population.

Disengagement from the maladaptive peer contexts that increase risk of substance use requires the availability of alternative, prosocial peer contexts. Previous studies demonstrate that activity participation, broadly defined here as engagement with substance-free activities or programming, is correlated with lower rates of substance use (Correia et al., 2005; Meshesha et al., 2015; Wasmuth et al., 2016). Substance use treatment programs that focus on social engagement and leisure activities demonstrate efficacy in decreasing substance use (Wasmuth et al., 2016). The influence of these mechanisms is also noted in observational studies, where availability of various substance-free activities predicts decreased rates of substance use, including exercise and other extracurricular activities (Correia et al., 2005; Meshesha et al., 2015). Social contexts may represent risk factors, in the case of peer substance use, or protective factors, in the case of substance-free activity participation. To accomplish the developmental task of peer involvement without adopting maladaptive substance use habits, college students must draw a distinction between maladaptive and adaptive peer contexts.

Environmental Moderators of Genetic Influences on Cannabis Use

The interaction of genetic and environmental factors for cannabis use further modify risk for cannabis use. Shanahan & Hofer (2005) propose a framework for conceptualizing the mechanisms by which environmental factors moderate the influence of genetic risk on behavioral outcomes. Social control and enhancement mechanisms are viable candidates to explain the role of various social environments in moderating the influence of genetic risk on cannabis use. Social control GxE effects occur when the social environment places restrictions on the range of behaviors that are treated as acceptable, thereby limiting the influence of genotype on behavior. For example, engagement with substance-free activities may place restrictions on an individual's access to cannabis, limiting the influence of genotype on behavior. Conversely, enhancement GxE effects occur when an environment promotes the influence of genotype on behavior. For example, high levels of peer substance use may expand an individual's access to cannabis, offering more opportunity for their behavior to vary as a function of their genotype.

Aligning with this framework, evidence suggests that the influence of genetic risk on cannabis use is moderated by peer substance involvement, such that the heritability of cannabis use increases with greater peer substance involvement (Agrawal et al., 2010). The influence of genetic risk on cannabis use is also moderated by developmental factors; heritability of cannabis use increases as individuals age into emerging adulthood, coinciding with a parallel decrease in the role of the familial environment (Kendler et al., 2008). Previous studies have not examined whether genetic influences on cannabis use vary over the college years using polygenic methods (Pasman et al., 2019). The interplay between development, peers, and genetic risk is likely to contribute to the high rates of cannabis use in college students, who are often exposed to novel peer contexts in a developmental period where genetic risk for cannabis use is particularly salient.

Peer group norm-sharing is one proposed mechanism of the positive effects of activity participation (Mahoney et al., 2005), suggesting that protective effects may be observed with prosocial contexts opposite to those observed with peer deviance. Aligning with Shanahan & Hofer's (2005) theory of social control mechanisms for GxE effects, activity participation decreases the influence of both general externalizing and alcohol-specific genetic risk on alcohol consumption (Kendler et al., 2011); however, no previous studies have examined if activity participation decreases the influence of genetic risk on cannabis use. The college context represents a convergence of developmental and social risk factors for cannabis use, as well as a potential source of modifiable protective factors. Identification of modifiable protective factors that influence the expression of genetic risk for cannabis use may reduce individual and societal consequences associated with emerging adult college student cannabis use. Activity involvement may represent a modifiable protective factor, attenuating the influence of genetic and environmental risk factors for cannabis use.

Additionally, previous studies have not examined conditional influences of genetic risk in the presence of both risk and protective environments; for example, whether activity participation attenuates the risk-enhancing role of peer substance involvement in the relationship between genetic risk and cannabis use. The potential for developmental variability in the salience of these GxE relationships across the college years remains as an open question as well. Testing these potential 3-way interactions may provide a clearer understanding of the roles of genetic risk, protective factors, and risk factors in predicting cannabis use among college students.

Present Study

The present study aims to examine the overall and conditional influences of genetic risk for cannabis use, peer deviance, and activity participation on cannabis use in a sample of emerging adult college students. Subjects are to be drawn from a longitudinal survey of behavioral and emotional health in a sample of undergraduate college students attending an urban university in the mid-Atlantic United States. Hypotheses will be tested in via estimation of a series of repeated binary logistic regression models. In line with recommendations in Peterson et al. (2019), analyses are stratified by ancestry prior to analysis to address differences in population structure between groups. The current study applies the method developed by Márquez-Luna et al. (2017) to augment prediction by PRS in diverse groups by leveraging smaller ancestry-matched discovery samples in combination with the larger European ancestry discovery samples that are available.

Specific aims and hypotheses are described below.

Statement of Hypotheses

Research Aim 1: Characterize the influence of a polygenic risk score (PRS) for cannabis initiation, peer deviance, and various forms of activity participation on recent cannabis use in European-American (EA) and African-American (AA) subsamples, with additional tests for replication using a self-reported measure of familial risk in place of the PRS.

Hypothesis 1a. Genetic/familial risk for cannabis use will increase the likelihood of recent cannabis use.

Hypothesis 1b. Peer Deviance will increase the likelihood of recent cannabis use.

Hypothesis 1c. Various forms of activity participation will decrease the likelihood of recent cannabis use.

Research Aim 2: Examine potential moderation of the influence of genetic/familial risk for cannabis use on recent cannabis use as a function of time, peer deviance, and activity participation in European-American (EA) and African-American (AA) subsamples, with additional tests for replication using a self-reported measure of familial risk in place of the PRS.

Hypothesis 2a. The influence of genetic/familial risk on cannabis use will increase in later years of emerging adulthood.

Hypothesis 2b. The influence of genetic/familial risk on cannabis use will increase with greater peer deviance.

Hypothesis 2c. The influence of genetic/familial risk on cannabis use will decrease with greater activity participation, across a range of activity categories.

Research Aim 3: Examine if activity participation and peer deviance interact in their respective influence on the expression of genetic/familial risk for cannabis use and if interrelationships between activity participation, peer deviance, genetic/familial risk for cannabis use, and recent cannabis use vary as a function of time. Again, these tests are conducted in European-American (EA) and African-American (AA) subsamples, with additional tests for replication using a self-reported measure of familial risk in place of the PRS.

Hypothesis 3a. The increased risk for cannabis use in subjects high in both peer deviance and genetic/familial risk will be truncated by greater activity participation.

Hypothesis 3b. The role of peer deviance in increasing the influence of genetic/familial risk on cannabis use facilitating expression of genetic risk for cannabis use will increase over time.

Hypothesis 3c. The role of various forms of activity participation in truncating the influence of genetic/familial risk for cannabis use will increase over time.

Methods

Sample

Data are from a longitudinal survey of behavioral and emotional health in a sample of undergraduate college students attending an urban university in the mid-Atlantic United States (Dick et al., 2014). The project was launched in 2011 and currently includes five cohorts of undergraduate students. Cohorts of freshman subjects were enrolled each year from 2011 to

2014. An additional cohort was enrolled in 2017. Initial self-report data were collected in the fall semester of freshman year, with follow-up assessments at every subsequent spring semester. All participants were age 18 or older when they enrolled in the study. Details regarding recruitment efforts can be found in Dick et al. (2014). The sample is representative of the university's student population in terms of gender and ethnicity. Details regarding community-engaged strategies for participant recruitment can be found in Dick (2017). Self-report data were collected using an electronic survey programmed in the Research Electronic Data Capture (REDcap) software (Harris et al., 2009). This study was approved by the university's Institutional Review Board. Participants were presented with consent documentation and indicated that they understood the potential risks and benefits of participating.

Genetic data were collected from consenting participants. Details regarding DNA collection and extraction (Dick et al., 2014) and genotyping, quality control, and imputation (Webb et al., 2017) are available elsewhere. In brief, saliva samples were collected from each participant in Oragene collection tubes, and DNA was isolated according to the manufacturer's instructions. Samples with DNA concentrations of at least 20 ng/ul in 1000 ml were retained for analysis. Genotyping was performed at Rutgers University Cell and DNA Repository (RUCDR) using the Affymetrix BioBank array. Pre-imputation quality control removed Off Target Variants identified in SNPolisher, SNPs missing more than 5% of genotypes, samples missing more than 2% of genotypes, and SNPs missing more than 2% of genotypes after sample filtering. Imputation was conducted using the 1000 Genomes phase 3 reference panel (Sudmant et al., 2015; The 1000 Genomes Project Consortium, 2015).

A subset of participants who provided genetic data were selected for analysis. Participants enrolled in the study in 2013 were not assessed on measures of activity participation in year 4 and this wave was excluded from analysis. Participants enrolled in 2014 were not assessed on measures of activity participation in years 2 and 3 and this cohort was excluded. This sample was stratified into European-American (EA) and African-American (AA) subsets to limit the confounding effects of population stratification on estimation of genetic influences. The resulting subsets included 3010 EA subjects and 1308 AA subjects. The EA sample was 57.5% female, with mean ages 19.01, 19.92, and 20.92 at year 1, year 2, and year 3 respectively. The AA sample was 72.6% female, with mean ages 18.91, 19.89, and 20.89 in year 1, year 2, and year 3 respectively. Demographic information for each sample is reported in Table 1 and Table 2.

Measures

Covariates

Ancestry Principal Components

Ancestry Principle Components were calculated using SmartPCA (Eigenstrat) to match each DNA sample to the best fitting 1000 Genomes reference population (1000 Genomes Project Consortium et al., 2015) using Mahalanobis distance. More details regarding the calculation of these measures can be found in Webb et al. (2017).

Sex was assessed in either the fall or spring of subjects' freshman year with a single item, with response option “Male” and “Female”.

Age was assessed as a continuous variable calculated from self-reported date of birth.

Outcome

Cannabis use measurement varied by assessment wave: use since attending college at year 1 spring, and past 12 month use at subsequent spring follow-ups. Earlier cohorts were asked if they had used cannabis over the given time period and, if yes, if they had used cannabis 6 or more times over that time interval. Later cohorts were asked if they had used cannabis over the given time period and, if yes, how many times over that time interval. Free response measurements of quantity of cannabis use were collapsed into categories for correspondence with the earlier, ordinal assessments resulting in an ordinal measure coded indexing no use (0), '1-5 times use' (1), and '6+ times use' (2). A binary indicator for recent use was calculated by collapsing the categories '1-5 times use' and '6+ times use' for use in repeated logistic regression models. The original ordinal coding scheme of this measure was used in polygenic risk score calculation procedures.

Predictors

Time was operationalized as assessment period. Assessment periods include year 1 spring, year 2 spring and year 3 spring. This measure was coded -1, 0, 1 to reduce collinearity between product terms and main effects.

Peer deviance was assessed using 6 items initially compiled for use in (Kendler et al., 2008). Measurement period varies by assessment wave: since attending college at year 1 spring and past 12 month at subsequent spring follow-ups. Subjects were asked how many of their peers smoked cigarettes, got drunk, had problems with alcohol, drunk alcohol, had problems with the law, and smoked marijuana over the corresponding time interval, with response options None, A few, Some, Most, All. For subjects with non-missing data on at least 3 items, the mean of available data was multiplied by 6 to calculate a composite measure of peer deviance with a possible range of 6-30. The resulting measure was standardized prior to analysis. Cronbach's alpha in the EA subset for times 1, 2, and 3 were 0.87, 0.86, and 0.83, respectively. Cronbach's alpha in the AA subset for times 1, 2, and 3 were 0.86, 0.84, and 0.81, respectively.

Activity participation was assessed at spring follow-up assessments using 4 items adapted from previous analyses in Kendler et al. (2011). Subjects were asked how often they participate in organized sports activities such as intramurals or club sports, school activities such as student government or service fraternities, community activities such as volunteer organizations or interest groups, or church-related activities other than worship service, with response options Never, Rarely, Sometimes, and Often. Each of these measures was standardized prior to analysis.

Parenting style was assessed at year 1 fall using a selection of items from the Steinberg Parenting Styles Index (Steinberg et al., 1992) for use in supplemental analyses. Subjects reported their level of agreement with the following statements: "My parents said I should give in on arguments rather than making people angry", "My parents helped me with my schoolwork if there was something I didn't understand", "My parents told me that their ideas were correct and that I should not question them", "My parents knew who my friends were", "My parents acted cold and unfriendly if I did something they didn't agree with", and "My parents spent time just talking with me", with response options 'Strongly agree", "Agree somewhat", "Disagree somewhat", "Strongly disagree". Cronbach's alpha in the EA subset was 0.65. Cronbach's alpha in the AA subset was 0.60.

Term GPA was obtained from the enrollment office of the university site for use in supplemental analyses.

Polygenic Risk Scores (PRS) were calculated using weights from a large genome-wide association study (GWAS) of cannabis initiation in 184,765 European ancestry subjects (Pasman et al., 2018). Summary statistics excluding the 23&Me sample were obtained and meta-analyzed with the 23&Me sample that was originally included in this GWAS using METAL (Willer, Li, & Abecasis, 2010) resulting in a file with 14,819,284 SNPs. There were 2,877,316 SNPs in common between the summary statistics file and the genotyped sample after quality control. The clumping and thresholding method (International Schizophrenia Consortium et al., 2009) was used to identify independent SNPs for optimal phenotype prediction. SNPs were clumped by linkage disequilibrium (LD) using the *clump* procedure in PLINK (Purcell et al., 2007), based on an $R^2 = 0.25$ and 500kb window, resulting in 1,308,830 SNPs for creating polygenic risk scores. PRS were created based on thresholds of GWAS P-values (P<0.0001, P<0.001, P<0.01, P<0.05, P<0.10, P<0.20, P<0.30, P<0.40, P<0.50) as a linear function of the number of effect alleles that an individual possessed, weighted by the product of the sign of the SNP effect and the negative logarithm (base 10) of the associated GWAS *p*-value—that is, -1 or 1*((-1)*LOG(*p*-value)).

Multi-ancestry polygenic risk scores (MultiPRS) (Márquez-Luna, Loh, & Price, 2017) were created for analyses in the AA subset. Ancestry-matched 10-fold PRS were created within the AA subset of S4S by iteratively using 90% of the total sample as a discovery sample for the remaining 10% of the sample, creating weights from GWAS of recent cannabis use within our sample. Subjects' most recent measurement for ordinal cannabis use between years 1 – 4 was then regressed on the ancestry-matched 10-fold PRS, sex, age, and the EA PRS separately for each P-value threshold. Predicted values from each of these regressions were extracted to create MultiPRS at each of the previously described P-value thresholds (P<0.0001, P<0.001, P<0.01, P<0.05, P<0.10, P<0.20, P<0.30, P<0.40, P<0.50).

Data Analysis

Hypotheses and the initial analytic plan were preregistered using the Open Science Framework. The project can be found at the following link (https://osf.io/s5kam/). Departures from the original analytic plan include the use of binary logistic regression rather than ordered logistic regression and the use of multiple imputation rather than listwise deletion. Statistical assumption of the model that was originally specified in the preregistration were not met, and the adjustments in the project as written now were made to ensure valid inference. Hypotheses tested here remain unchanged from the preregistration.

Multiple Imputation

The 'mice' package in R was used to impute missing data for peer deviance and activity participation predictor variables (Buuren & Groothuis-Oudshoorn, 2011). Data at each measurement wave were imputed in wide format and reshaped to long prior to analysis. In addition to the variables included in the analysis model, the following auxiliary variables were included in the imputation model to improve the quality of imputation: term GPA (years 1-4), traumatic events (years 1-4), stressful events (years 1-4), lifetime tobacco use (years 1-4), illicit stimulant use (years 1-4), cocaine use (years 1-4), opioid use (years 1-4), binge drinking (years 1-4), alcohol consumption (years 1-4), antisocial behavior (years 1-4), UPPS lack of perseverance (year 1), UPPS negative urgency (year 1), UPPS positive urgency (year 1), and UPPS sensation seeking (year 1). These variables were selected because of their association with the predictor variables that were being imputed. 100 datasets were imputed with 30 iterations each and estimates from each imputed dataset were pooled using Rubin's Rule (Rubin, 1987).

Marginal Models and Tests of Moderation

Repeated measures logistic regression models were fit by generalized estimating equations (GEE) using the 'geepack' package (Højsgaard, Halekoh, & Yan, 2005) in R (R Core Team, 2014) to predict recent cannabis use. AR1 working correlation structure was specified to account for within-subjects correlation in cannabis use over time. All models with PRS controlled for sex and 10 ancestry principle components. Age was excluded from analyses because of redundancy with the included measure for time. Hypothesized interaction effects were tested in a series of 3 models per subset. Model 1 estimated the main effects of the PRS, categories of activity participation, peer deviance, and time on cannabis use controlling for 10 ancestry principle components and sex. Model 2 included all hypothesized two-way interaction terms: PRS by time, PRS by peer deviance, and PRS by activity participation categories. Model 3 included all hypothesized three-way interaction terms: PRS by peer deviance by each activity participation category, PRS by peer deviance by time, PRS by each activity participation category by time, as well as all possible 2-way interactions between familial risk, peer deviance, and activity participation. This analytic plan was also repeated with a self-reported measure of familial risk in place of the PRS.

In line with recommendations in Keller (2014), significant interactions were then tested in a model which controlled for all 2-way interactions between each variable in the product-term of interest and all covariates. A model with these additional controls in place is reported where significant interactions are detected. If no significant interaction was detected, additional controls were not necessary and results from the uncontrolled model are reported. Bonferroni correction for 4 tests (EA PRS, AA PRS, EA Familial Risk, AA Familial Risk) was applied to p-values for the significant interaction terms from the model with additional controls. Plots were constructed to facilitate interpretation of significant interaction effects using the ggplot2 package (Wickham, 2009) in R. Plots depict predicted values from models that include the additional controls recommended in Keller (2014). Predicted logits and error bars for predictions from pooled coefficient estimates were calculated using the implementation of the delta method included in the “car” package in R (Fox & Weisberg, 2019) with the pooled covariance matrix of the coefficient estimates defined as the elementwise mean of covariance matrices of coefficient estimates from the 100 imputed datasets. Simple slopes analysis for significant interactions was conducted using an online calculator tool (Preacher et al., 2016).

Supplemental Analyses: Gene-Environmental Correlation, Sensitivity Analyses, and Power Analysis

Zero-order correlations between the PRS and environmental predictors were estimated to assess gene-environment correlation (rGE). Confidence intervals for these correlations were constructed using estimated standard errors. Repeated measures logistic regression models estimated by GEE were also estimated with term GPA included as a time-varying covariate as a final check of the robustness of the findings to confounding by academic performance.

Post-hoc power analysis for the main effect of the PRS in the EA and AA subsets was conducted using the method defined in Li & McKeague (2013) for GEE marginal models. Type 1 error rate was set to 0.05 and all parameter settings for the power analysis function were drawn from the main effects models in EA and AA subsets. Parameter settings drawn from these analyses include the model intercept, the coefficient estimate for the effect of the PRS, the estimated within-subjects correlation in cannabis use, the mean of the PRS, the standard deviation of the PRS, and the cluster size. The default value of iterations for Monte Carlo integration (10000000) was maintained.

Results

PRS Optimization

The most predictive P-value threshold for the EA PRS and the AA MultiPRS were identified for subsequent analyses. Recent cannabis use was regressed on the EA PRS and a set of 10 EA Within-Ancestry Principle Components in the EA subset. The score threshold which accounted for the most variance in recent cannabis use was used for subsequent analyses. This procedure was repeated in the AA subset with the AA MultiPRS and 10 AA Within-Ancestry Principle Components. Bonferroni corrected p-values for 9 tests were used to assess the statistical significance of the PRS. The $P<0.05$ score performed best in the EA subset and the $P<0.001$ MultiPRS performed best in the AA subset. Figure 1 and Figure 2 present the change in R^2 when adding each PRS to a model with 10 PCs predicting subjects' most recent measurement for ordinal cannabis use between years 1 – 4.

Descriptive Statistics

European American Sample Descriptive Statistics

The overall prevalence of cannabis use in the EA sample was relatively stable over time, with 49.33% endorsing use at year 1, 52.17% endorsing use at year 2, and 49.67% endorsing use at year 3. Overall rates of activity participation were generally stable across time as well, with the exception of a notable increase in engagement with school activities from year 1 to year 2; 50.74% of subjects report any engagement with school activities in year 1, increasing to 61.37% in year 2. Community activities were the most commonly endorsed activity, followed by school activities, recreational sports, and church activities. Descriptive statistics for unstandardized measures of interest in the EA sample are presented in tables 3 and 4.

African American Sample Descriptive Statistics

The overall prevalence of cannabis use in the AA sample was somewhat lower than the EA sample with 39.81% endorsing use at year 1, 47.83% endorsing use at year 2, and 41.94% endorsing use at year 3. Overall rates of activity participation were generally stable across time as well, with the exception of a notable increase in engagement with both school activities and community activities from year 1 to year 2; 50.74% of subjects report any engagement with school activities in year 1, increasing to 61.37% in year 2 and 65.79% of subjects report any engagement with community activities in year 1 increasing to 76.22% in year 2. Community activities were the most commonly endorsed activity, followed by school activities, church activities, and recreational sports. Descriptive statistics for unstandardized measures of interest in the AA sample are presented in tables 5 and 6.

Gene-Environment Correlation: Zero-order correlations

European American Sample Zero-Order Correlations

Zero-order correlations between the PRS and environments of interest were estimated to examine the potential for rGE. The PRS was modestly correlated with Peer Deviance at year 1 (r=0.07, 95% CI [0.03,0.11]) and year 3 (r=0.07, 95% CI [0.01, 0.13). The PRS was also modestly correlated with Community Activities at year 1 (r=-0.06, 95% CI [-0.10, -0.01]). Correlations between the PRS and other environmental predictors were not significant (Table 27). Notably, the PRS was significantly correlated with cannabis use in year 1 (r=0.09, 95% CI [0.03, 0.14]) and year 3 (r=0.11, 95% CI [0.03, 0.18]).

African American Sample Zero-Order Correlations

The analysis testing rGE in the EA subset was repeated in the AA subset. Zero-order correlations between the PRS and environments of interest were estimated to examine the potential for rGE. The PRS was not significantly correlated with any environmental predictors (Table 28). The PRS was also not significantly correlated with cannabis use at any time point.

Cannabis Use as a Function of Genetic and Environmental Factors in European Americans

Main Effects in the European American Sample

The within-subjects correlation in cannabis use was estimated to be 0.59. Peer deviance (OR=2.33, P<0.001) predicted greater odds of cannabis use. Cannabis use was also more likely in later years (OR=1.15, P=0.001). Community activities (OR=0.87, P=0.002) and church activities (OR=0.83, P<0.001) predicted lower odds of cannabis use. The PRS (OR=1.05, P=0.486), organized sports (OR=1.015, P=0.748), and school activities (OR=0.92, P=0.054) did not predict recent cannabis use (Table 7 and Figure 3).

Two-way Interactions in the European American Sample

The within-subjects correlation in cannabis use was estimated to be 0.59. Product terms testing the interaction of PRS by time (OR=1.008, P=0.848), PRS by peer deviance (OR=1.12, P=0.059), PRS by school activities (OR=1.07, P=0.125), and PRS by church activities (OR=0.97, P=0.571) were not statistically significant. The product term testing the interaction of PRS by community activities (OR=0.87, P=0.002) was statistically significant (Table 8 and Figure 4). A model including all 2-way interactions of the PRS by each covariate and community activities by each covariate was estimated to assess potential confounding of this interaction effect. The statistical significance of the product term was robust to these additions to the model (OR=0.86, P<0.001) (Table 9). A plot of predicted logits by PRS at varying levels of engagement with community activities (Figure 5) suggests that the influence of PRS is lower when engagement with community activities is higher. Simple slopes analysis indicates that subjects who report "Never" engaging with community activities have higher odds of recent cannabis use as a function of their PRS (OR=1.25, P=0.026), while PRS does not influence recent cannabis use in subjects who report engaging with community activities "Rarely" (OR=1.08, P=0.35), "Sometimes" (OR=0.94, P=0.47), or "Often" (OR=0.81, P=0.056) (Table 10). The p-value for this interaction term was still statistically significant after Bonferroni correction for 4 tests (corrected P= 0.0016).

Additionally, the product term testing the interaction of the PRS by organized sports (OR=1.11, P=0.026) was statistically significant (Table 8 and Figure 4). Again, a model including all 2-way interactions of the PRS by each covariate and organized sports by each covariate was estimated to assess potential confounding of this interaction effect. The statistical significance of the product term was robust to these additions to the model (OR=1.13, P=0.012) (Table 11). A plot of predicted logits by PRS at varying levels of engagement with organized sports suggests that the influence of PRS is higher when engagement with organized sports is higher (Figure 6). Simple slopes analysis indicates that subjects who report “Often” engaging with organized sports have higher odds of recent cannabis use as a function of their PRS (OR=1.29, P=0.040), while PRS does not influence recent cannabis use in subjects who report engaging with recreational sports “Never” (OR=0.94, P=0.504), “Rarely” (OR=1.04, P=0.614), or “Sometimes” (OR=1.16, P=0.121) (Table 13). The p-value for this interaction term was no longer statistically significant after Bonferroni correction for 4 tests (corrected P= 0.076) and these results should be interpreted with caution.

Three-way Interactions in the European American Sample

The within-subjects correlation in cannabis use was estimated to be 0.60. The product terms testing the interaction of PRS by school activities by peer deviance (OR=0.90, P=0.022) and PRS by church activities by peer deviance (OR=0.91, P=0.043) were statistically significant (Table 13 and Figure 7). Two additional models were estimated which controlled for all 2-way interactions between each variable in the product-term of interest and all covariates. The product terms for the interaction of PRS by school activities by peer deviance (OR=0.98, P=0.469) (Table 14) and PRS by church activities by peer deviance (OR=0.99, P=0.703) (Table 15) were not statistically significant in these models, suggesting that these 3-way interactions are not robust to the addition of proper statistical controls. All other 3-way interaction terms were not statistically significant (Table 13 and Figure 7).

Cannabis Use as a Function of Genetic and Environmental Factors in African Americans

Main Effects in the African American Sample

The within-subjects correlation in cannabis use was estimated to be 0.40. Peer deviance (OR=2.69, P<0.001) predicted greater odds of cannabis use. Church activities (OR=0.82, P=0.004) predicted lower odds of cannabis use. The PRS (OR=1.08, P=0.377), organized sports (OR=1.01, P=0.868), school activities (OR=1.00, P=0.981), community activities (OR=0.87, P=0.066), and time (OR =1.14, P=0.058) did not predict recent cannabis use (Table 16 and Figure 8).

Two-way and Three-way Interactions in the African American Sample

The within-subjects correlation in cannabis use was estimated to be 0.40 in the model testing 2-way interactions. No 2-way interaction terms were statistically significant (Table 17 and Figure 9). Within-subjects correlation in cannabis use was estimated to be 0.42 in the model testing 3-way interactions. No 3-way interaction terms were statistically significant (Table 18 and Figure 10).

Supplemental Analyses

Cannabis Use as a Function of Familial/Environmental Factors in European Americans

Main Effects in the European American Sample

The within-subjects correlation in cannabis use was estimated to be 0.61. Self-reported familial risk predicted higher odds of cannabis use (OR=1.33, P<0.001). Peer deviance (OR=2.22, P<0.001), and time (OR=1.15, P=0.001) also predicted greater odds of cannabis use. Church activities (OR=0.84, P=0.001) and community activities (OR=0.86, P=0.001) predicted lower odds of cannabis use. School activities (OR=1.00, P=0.981) and organized sports (OR =1.02, P=0.689) did not predict recent cannabis use (Table 19 and Figure 11).

Two-way Interactions in the European American Sample

Within-subjects correlation in cannabis use was estimated to be 0.61. The significant interactions in the EA PRS two-way interaction model did not replicate; familial risk by organized sports (OR=1.08, P=0.674) and familial risk by community activities (OR=0.96, P=0.372) were not statistically significant. Additionally, product terms testing the interaction of familial risk by time (OR=1.037, P=0.41), familial risk by peer deviance (OR=0.98, P=0.059), and familial risk by church activities (OR=1.00, P=0.974) and were not statistically significant. Further diverging from the results of the EA PRS model, the product term testing the interaction of PRS by school activities (OR=0.91, P=0.019) was statistically significant (Table 20 and Figure 12). A model including all 2-way interactions of the familial risk by each covariate and school activities by each covariate was estimated to assess potential confounding of this interaction effect. The statistical significance of the product term was robust to these additions to the model (OR=0.92, P=0.039) (Table 21). A plot of predicted logits by PRS at varying levels of engagement with community activities (Figure 13) suggests that the influence of PRS is lower when engagement with community activities is higher. Simple slopes analysis indicates that subjects who report engaging with community activities "Never" (OR=1.44, P<0.001), "Rarely" (OR=1.34, P<0.001), and "Sometimes" (OR=1.24, P=0.012) have higher odds of recent cannabis use as a function of familial risk, while familial risk does not influence recent cannabis use in subjects who report engaging with community activities "Often" (OR=1.14, P=0.197) (Table 22). The p-value for this interaction term was no longer statistically significant after Bonferroni correction for 4 tests (corrected P= 0.156) and these results should be interpreted with caution.

Three-way Interactions in the European American Sample

Within-subjects correlation in cannabis use was estimated to be 0.61. Similar to the analyses conducted with the EA PRS, no 3-way interaction terms were statistically significant in the EA familial risk model (Table 23 and Figure 14).

Cannabis Use as a Function of Familial/Environmental Factors in African Americans

Main Effects in the African American Sample

Within-subjects correlation in cannabis use was estimated to be 0.44. In contrast to the AA PRS Main Effects model, self-reported familial risk predicted higher odds of cannabis use (OR=1.23, P=0.025). Peer deviance also predicted greater odds of cannabis use (OR=2.50, P<0.001). Church activities (OR=0.81, P=0.705) predicted lower odds of cannabis use. Time (OR=1.14, P=0.055), school activities (OR=1.00, P=0.998) and organized sports (OR =1.00, P=0.954) did not predict recent cannabis use (Table 19 and Figure 11).

Two-way and Three-way Interactions in the African American Sample

Results in the AA familial risk interaction models were similar to the results of the AA PRS interaction models. Within-subjects correlation in cannabis use was estimated to be 0.44 in the model testing two-way interactions. No two-way interaction terms were statistically significant (Table 25 and Figure 16). Within-subjects correlation in cannabis use was estimated to be 0.45 in the model testing 3-way interactions. No 3-way interaction terms were statistically significant (Table 26 and Figure 17).

Sensitivity Analyses Covarying for GPA

As a final test for the stability of these effects, all GEE models were estimated controlling for term GPA as a time-varying covariate. All results in both the EA and AA subsets were robust to this addition. These results can be found in figures 18 - 220for the EA subset and 21-23 in the AA subset.

Power Analysis

Observed power for the main effect of the PRS in the EA sample was estimated to be approximately 83%. Observed power for the main effect of the PRS in the AA sample was estimated to be approximately 8%. Power curves for the observed effect size for the main effect of the PRS in EA and AA subsets are presented in figure 24. To further explore these estimates of observed power, additional curves were plotted with effect size for the PRS increased by 2-fold, 3-fold, 5-fold, and 10-fold for the EA (figure 25) and AA subset (figure 26). Under a 2-fold increase, power to detect the main effect for the EA PRS with the sample size of the current analyses (n=3010) approaches 100%. Under a 5-fold increase, power to detect the main effect for the AA PRS with the sample size of the current analyses (n=1308) is approximately 82% and under a 10-fold increase power approaches 100%. This gradient of power estimates suggests that the small effect size of the AA PRS is the primary contributor to the low observed power in the AA subset.

Discussion

This work examined 3 research aims: 1. Characterize the influence of a polygenic risk score (PRS) for cannabis initiation, peer deviance, and various forms of activity participation on recent cannabis use, 2. Examine potential moderation of the influence of genetic/familial risk for cannabis use on recent cannabis use as a function of time, peer deviance, and activity participation, and 3. Examine whether activity participation and peer deviance moderate genetic/familial risk for cannabis use and if interrelationships between activity participation, peer deviance, genetic/familial risk for cannabis use, and recent cannabis use vary as a function of time. These aims align with models that test for main effects (Aim 1), two-way interactions (Aim 2), and three-way interactions (Aim 3). Each research aim is discussed in turn below.

Research Aim 1: Main Effects of Genetic Predispositions, Peers, and Activity Participation

Research Aim 1 was comprised of 3 specific hypotheses: (1a) Genetic/familial risk for cannabis use will increase the likelihood of recent cannabis use, (1b) Peer Deviance will increase the likelihood of recent cannabis use, and (1c) Various forms of activity participation will decrease the likelihood of recent cannabis use.

With regards to the PRS, hypotheses 1a, genetic/familial risk for cannabis use will increase the likelihood of recent cannabis use, was not supported in repeated binary logistic regression models estimated by GEE in the EA or AA sample. Power to detect the main effect of the PRS in the AA sample was estimated to be low in this analysis (8%), suggesting that future analyses with larger, ancestry-matched discovery samples for PRS construction may arrive at a different conclusion. On the other hand, power to detect the main effect of the PRS in the EA sample was estimated to be reasonably high (83%). This null finding, juxtaposed with the significant interactions of the PRS and activity participation environment variables in the EA sample points towards the conditional nature of genotypic effects on cannabis use phenotypes, at least in this young adult sample; genetic effects on cannabis use are observed under specific environmental conditions, but not when these small effects are averaged across all environments.

Contrasting these results with the PRS, hypothesis 1a was supported in both the EA and AA sample when analyses were conducted with a self-reported measure of familial risk. There are two plausible interpretations of this discrepancy. Familial risk represents a more powerful proxy for heritable influences on cannabis use and may circumvent methodological problems involved in the construction of PRS. This is particularly relevant in the AA sample, where the

PRS was calculated in part from an EA discovery sample. Deficits in the cross-ancestry portability of PRS are well documented (Martin et al., 2017; Duncan et al., 2019). If the null findings for the AA PRS are the result of low observed power, significant results for heritable familial risk in the AA sample may suggest that a main effect may be detected with a more powerful PRS. This interpretation is somewhat less likely in the EA sample, where no main effect was detected for the PRS despite reasonably high observed power. Notably, self-reported familial risk is confounded with the familial environment and represents a noisy measure of heritable influences on cannabis use. Discrepancy between the effect of the PRS and the effect of self-reported familial risk may arise as a result of this confounding, regardless of power.

Hypotheses 1b, peer deviance will increase the likelihood of recent cannabis use, and 1c, various forms of activity participation will decrease the likelihood of recent cannabis use, were largely supported in both the EA and AA samples. Aligning with a substantial body of work (Kandel, 1973; Mason et al., 2014; Phillips et al., 2018; Pinchevsky et al., 2012), peer deviance was shown to be a strong environmental predictor of cannabis use in both samples. In regards to hypothesis 1c, church activities emerged as a consistent protective factor between the EA and AA samples. This aligns with previous work to suggest that the availability of substance-free activities to engage with is associated with lower rates of substance use (Correia et al., 2005; Meshesha et al., 2015; Wasmuth et al., 2016). No interaction effects were detected involving church activities, indicating that this protective effect is not conditional on PRS. A protective effect for community activities is also detected in the EA sample; however, detection of a two-way interaction between community activities and PRS suggests that this protective effect is better understood with respect to its interaction with genotypic influences on cannabis use, such that engagement with community activities is protective against the risk-enhancing effects of the

PRS. This protective effect is not replicated in the AA sample, although the proximity of the estimated p-value to the 0.05 cut off (P=0.066) may suggest that this discrepancy reflects differences in power between the two samples. Previous studies suggest that perceived social norms influence substance use phenotypes (Ecker et al., 2014; LaBrie et al., 2011; Lewis & Clemens, 2008; Napper et al., 2015; Neighbors et al., 2008; Simons et al., 2006). Thus, permissive social norms in peer groups that engage in substance use and restrictive social norms in church-engaged peer groups represent one possible mechanism of the main effects of peer deviance and church activities. Future work should consider the potential interrelationships between peer deviance, activity participation, and social norms related to substance use.

Research Aim 2: Two-way Interactions of Genetic Predispositions, Peers, and Activity Participation

Research Aim 2 was comprised of 3 specific hypotheses: (2a) The influence of genetic/familial risk on cannabis use will increase in later years of emerging adulthood, (2b) The influence of genetic/familial risk on cannabis use will increase with greater peer deviance, and (2c) The influence of genetic/familial risk on cannabis use will decrease with greater activity participation, across a range of activity categories.

Diverging from previous work (Agrawal et al., 2010; Kendler et al., 2008), hypotheses 2a, the influence of genetic/familial risk on cannabis use will increase in later years of emerging adulthood, and 2b, the influence of genetic/familial risk on cannabis use will increase with greater peer deviance, were not supported in either the EA or AA samples. The current analyses examine 3 years of data within emerging adulthood and it may be that this time range is not long enough to detect the moderating effects of time that have been documented in previous analyses. Null findings for the interaction of peer deviance by PRS are unexpected, but point towards the apparent consistency of the association between peer deviance and cannabis use, regardless of level of genetic risk loading.

Hypothesis 2c, the influence of genetic/familial risk on cannabis use will decrease with greater activity participation, across a range of activity categories, was partially supported. Initially, three of the two-way interactions by forms of activity participation were significant in the EA analyses: PRS by community activities, PRS by recreational sports, and familial risk by school activities. All three interaction terms were still statistically significant after controlling for all 2-way interactions between each variable in the product-term of interest and all covariates; however, only the interaction of PRS by community activities survived correction for multiple testing. Thus, the risk enhancing effect of recreational sports and the protective effect of school activities warrant replication in future work and should be interpreted with caution here. The interaction of PRS by community activities proved to be robust to the inclusion of additional controls and correction for multiple testing and is treated as the primary focus of the current analyses. No two-way interactions were statistically significant in the AA sample.

Simple slopes analysis suggested that the effect of the PRS on recent cannabis use was only statistically significant among subjects who endorse “Never” engaging with community activities. Thus, even subjects who endorsed “Rarely” engaging with community activities were not at greater risk of recent cannabis use as a function of their PRS. These findings have implications for the design of evidence-based prevention and intervention programming for college students. Level of engagement with community activities represents a modifiable environmental influence that moderates the influence of an otherwise stable risk factor, the PRS. Genetic risk loading for cannabis use itself cannot be directly altered; however, programs that encourage engagement with community activities may limit the influence of genetic risk loading on cannabis use via the interaction effect identified in this work. Shanahan & Hofer's (2005) theory of GxE effects suggests that this moderation effect represents an example of the social control mechanism, where social contexts restrict the range of behaviors that are considered acceptable and overshadow the modest effects of genetic risk loading for cannabis use. This interpretation aligns with previous studies which suggest that peer group norm-sharing is a mechanism of the protective effects of activity participation (Mahoney et al., 2005). The results of the current work suggest that even occasional exposure to the social norms involved in community engagement can robustly limit the influence of genetic risk for cannabis use.

Research Aim 3: Three-way Interactions of Genetic Predispositions, Peers, and Activity Participation

Research Aim 3 was comprised of 3 specific hypotheses: (3a) The increased risk for cannabis use in subjects high in both peer deviance and genetic/familial risk will be truncated by greater activity participation, (3b) The role of peer deviance in increasing the influence of genetic/familial risk on cannabis use facilitating expression of genetic risk for cannabis use will increase over time, and (3c) The role of various forms of activity participation in truncating the influence of genetic/familial risk for cannabis use will increase over time. Hypotheses 3a was not support; no interaction effect was observed such that the influence of the PRS was conditional on varying levels of both peer deviance and activity participation. Additionally, hypotheses 3b and 3c were not supported; any moderating effects of peer deviance or activity participation were not observed to vary over time.

Limitations

These analyses have a number of limitations that should be considered. Foremost, the AA PRS was calculated, in part, from GWAS summary statistics from an external EA discovery sample. Application of the multiPRS method, using ancestry-matched GWAS summary statistics from the target sample in PRS calculation (Márquez-Luna et al., 2017), improves prediction in diverse samples; however, power was still limited in the AA sample. As larger, ancestry-matched discovery samples become available, more powerful analyses in diverse samples will become feasible. Additionally, two of the three two-way interactions reported here did not survive correction for multiple testing. Finally, PRS calculated in samples of unrelated subjects cannot differentiate between direct and indirect genetic effects. Without modelling the genotype of subjects' parents, confounding of subjects' genotypes and parenting environment, via parents' genotypes, remains as an alternate explanation of any PRS effects described here. (Young et al., 2019).

Future Directions

Foremost, future analyses should aim to utilize larger, ancestry-matched discovery samples for PRS calculation as they become available in order to improve power and allow for more informative analyses in diverse groups of students. Application of PRS to target samples of related individuals also offers a means to address confounding by indirect genetic effects. Future analyses should explore the interaction effects described in the current work further. The interaction of recreational sports by PRS and school activities by familial risk did not survive multiple testing correction and may represent viable targets for further assessment in larger samples with more power. The more robust interaction of community activities by PRS might also be explored further. Shanahan & Hofer's (2005) theory suggests that the mechanism of this interaction effect is likely to relate to the social norms that pervade among peer groups that are engaged in community activities. Further assessment of the particular social norms that may account for the protective effects of engagement with community activities may inform the development of programs that aim to implement this finding to reduce risk of cannabis use.

Conclusion

In summary, social contexts and the interaction of social contexts with genetic risk factors are important determinants of recent cannabis use. Peer deviance predicts higher odds of recent cannabis use and church activities predicts lower odds of recent cannabis use, regardless of genetic risk loading. Engagement with community activities is protective against the influence of genetic risk loading for cannabis use, such that even occasional engagement with community activities limits the influence of genetic risk factors. Programs which facilitate engagement with the community may represent a means to reduce the influence of genetic risk loading. The identification of statistically significant interaction effects in this work are limited to the EA sample. As larger, ancestry-matched discovery samples for PRS calculation become available, more informative analyses in diverse groups of subjects will become feasible.

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Tables

Table 1

Demographics for the EA subset

EA Demographics		
Sex	n	Proportion
Male	1250	0.415
Female	1731	0.575
Missing	28	0.010
Age	Mean	SD
Year 1	19.01	0.60
Year 2	19.92	0.42
Year 3	20.92	0.42

Table 2

Demographics for the AA subset

AA Demographics		
Sex	n	Proportion
Male	358	0.274
Female	950	0.726
Age	Mean	SD
Year 1	18.91	0.58
Year 2	19.89	0.47
Year 3	20.89	0.57

Table 3

Frequencies for the EA subset

EA Frequencies N(%)				
Cannabis use	No use	1-5 times use	6+ times use	
Year 1	1068 (50.67%)	411 (19.50%)	629 (29.84%)	
Year 2	651 (47.83%)	179 (13.15%)	531 (39.02%)	
Year 3	533 (50.33%)	179 (16.90%)	347 (32.77%)	
Community Activities	Never	Rarely	Sometimes	Often
Year 1	651 (36.95%)	482 (27.36%)	416 (23.61%)	213 (12.09%)
Year 2	450 (32.07%)	385 (27.44%)	350 (24.95%)	218 (15.54%)
Year 3	323 (29.94%)	298 (27.62%)	302 (27.99%)	156 (14.46%)_
Recreational Sports	Never	Rarely	Sometimes	Often
Year 1	843 (47.68%)	374 (21.15%)	280 (15.84%)	271 (15.33%)
Year 2	680 (48.33%)	308 (21.89%)	224 (15.92%)	195 (13.86%)
Year 3	552 (51.11%)	233 (21.57%)	167 (15.46%)	128 (11.85%)
School Activities	Never	Rarely	Sometimes	Often
Year 1	871 (49.26%)	442 (25.00%)	286 (16.18%)	169 (9.56%)
Year 2	542 (38.63%)	385 (27.44%)	264 (18.82%)	212 (15.11%)
Year 3	393 (36.32%)	268 (24.77%)	250 (23.11%)	171 (15.80%)
Church Activities	Never	Rarely	Sometimes	Often
Year 1	1142 (64.70%)	290 (16.43%)	197 (11.16%)	136 (7.71%)
Year 2	909 (65.54%)	282 (20.33%)	123 (8.870%)	73 (5.26%)
Year 3	718 (67.42%)	208 (19.53%)	83 (7.79%)	56 (5.26%)

Table 4

Descriptive Statistics for the EA subset

EA subset Descriptive Statistics				
	Mean	SD	Minimum	Maximum
PRS	-0.01	0.01	-0.03	0.01
Peer Deviance				
Year 1	16.19	4.85	3	30
Year 2	16.02	6.64	3	29
Year 3	15.70	4.36	4	28

Table 5

Frequencies for the AA subset

AA Frequencies N(%)				
Cannabis use	No use	1-5 times use	6+ times use	
Year 1	617 (61.09%)	207 (20.50%)	186 (18.42%)	
Year 2	404 (57.96%)	132 (18.94%)	161 (23.1%)	
Year 3	317 (58.06%)	84 (15.38%)	145 (26.56%)	
Community Activities	Never	Rarely	Sometimes	Often
Year 1	274 (34.21%)	194 (24.22%)	221 (27.59%)	112 (13.98%)
Year 2	171 (23.78%)	160 (22.25%)	243 (33.80%)	145 (20.17%)
Year 3	133 (23.75%)	111 (19.82%)	169 (30.18%)	147 (26.25%)
Recreational Sports	Never	Rarely	Sometimes	Often
Year 1	362 (45.19%)	180 (22.47%)	161 (20.10%)	98 (12.23%)
Year 2	340 (47.16%)	170 (23.58%)	118 (16.37%)	93 (12.90%)
Year 3	284 (50.62%)	130 (23.10%)	70 (12.48%)	77 (13.73%)
School Activities	Never	Rarely	Sometimes	Often
Year 1	325 (40.57%)	202 (25.22%)	172 (21.47%)	102 (12.73%)
Year 2	202 (28.17%)	189 (26.36%)	194 (27.06%)	132 (18.41%)
Year 3	157 (27.99%)	114 (20.32%)	149 (26.56%)	141 (25.13%)
Church Activities	Never	Rarely	Sometimes	Often
Year 1	315 (39.57%)	180 (22.61%)	158 (19,85%)	143 (17.96%)
Year 2	250 (35.41%)	204 (28.90%)	164 (23.23%)	88 (12.46%)
Year 3	197 (35.62%)	185 (33.45%)	110 (19.89%)	61 (11.03%)

Table 6

Descriptive statistics for the AA subset

AA subset Descriptive Statistics				
	Mean	SD	Minimum	Maximum
PRS	1.70	0.01	1.48	1.89
Peer Deviance				
Year 1	13.80	4.94	4	30
Year 2	13.49	4.65	5	27
Year 3	13.27	4.40	3	28

Table 7

Main effects of PRS and predictors on recent cannabis use using binary repeated logistic regression estimated by GEE in the EA subset

EA Subset PRS Main Effects

	OR	Lower 95% CI	Upper 95% CI	P
ICC Cannabis Initiation P< 0.5	1.047	0.920	1.192	0.486
Time	1.150	1.061	1.247	0.001
Organized Sports	1.015	0.925	1.115	0.748
School Activities	0.922	0.849	1.002	0.054
Community Activities	0.866	0.792	0.946	0.002
Church Activities	0.827	0.744	0.919	0.0004
Peer Deviance	2.331	2.090	2.601	0

Table 8

Two-way interaction effects of PRS and predictors on recent cannabis use using binary repeated logistic regression estimated by GEE in the EA subset

EA Subset PRS Two-way Interaction

	OR	Lower 95% CI	Upper 95% CI	P
PRS	1.030	0.906	1.172	0.652
Time	1.152	1.062	1.249	0.001
Organized Sports	1.013	0.922	1.113	0.788
School Activities	0.919	0.846	0.997	0.043
Community Activities	0.869	0.795	0.949	0.002
Church Activities	0.831	0.748	0.924	0.001
Peer Deviance	2.361	2.118	2.633	<0.001
PRS by Time	1.008	0.932	1.089	0.848
PRS by Peer Deviance	1.108	0.996	1.233	0.059
PRS by Organized Sports	**1.111**	**1.013**	**1.219**	**0.026**
PRS by School Activities	1.066	0.982	1.157	0.125
PRS by Community Activities	**0.876**	**0.805**	**0.953**	**0.002**
PRS by Church Activities	0.970	0.872	1.079	0.571

Table 9

Two-way interaction effect of PRS and community activities on recent cannabis use after controlling for interaction of variables of interest and covariates using binary repeated logistic regression estimated by GEE in the EA subset

EA Subset PRS Controlled 2-way Interaction; Community Activities X PRS

	OR	Lower 95% CI	Upper 95% CI	P
Sex	1.215	0.925	1.596	0.162
PRS	1.046	0.888	1.233	0.588
Time	1.152	1.062	1.251	0.001
Organized Sports	1.022	0.930	1.123	0.653
School Activities	0.921	0.847	1.001	0.052
Community Activities	0.858	0.766	0.962	0.009
Church Activities	0.833	0.749	0.928	0.001
Peer Deviance	2.405	2.155	2.684	0
PRS by Time	1.013	0.934	1.098	0.759
PRS by Peer Deviance	1.125	1.014	1.249	0.026
PRS by Organized Sports	1.127	1.026	1.237	0.012
PRS by School Activities	1.058	0.973	1.150	0.184
PRS by Community Activities	**0.860**	**0.790**	**0.935**	**0.0004**
PRS by Church Activities	0.971	0.871	1.084	0.605
E1 by Community Activities	0.078	0.001	9.560	0.298
E2 by Community Activities	0.183	0.001	49.912	0.553
E3 by Community Activities	4.451	0.061	324.168	0.495
E4 by Community Activities	0.048	0.0004	5.473	0.209
E5 by Community Activities	0.113	0.001	17.902	0.399
E6 by Community Activities	0.113	0.001	15.373	0.385
E7 by Community Activities	3.885	0.029	527.917	0.588
E8 by Community Activities	5.090	0.062	415.464	0.469
E9 by Community Activities	1.104	0.016	77.783	0.964
E10 by Community Activities	0.013	0.0001	1.869	0.087
E1 by PRS	1.081	0.001	1,273.045	0.983
E2 by PRS	3,580.972	0.375	34,236,529.000	0.080
E3 by PRS	19.818	0.018	21,974.170	0.404
E4 by PRS	2.419	0.001	4,900.556	0.820
E5 by PRS	0.163	0.0003	83.843	0.569

E6 by PRS	0.632	0.001	384.573	0.888
E7 by PRS	0.203	0.0002	213.122	0.654
E8 by PRS	0.001	0.00000	2.199	0.078
E9 by PRS	0.346	0.0004	280.691	0.756
E10 by PRS	44.395	0.023	85,942.200	0.326
Sex by PRS	0.928	0.700	1.231	0.605
Sex by Community Activities	1.018	0.851	1.218	0.847
Time by Community Activities	1.055	0.964	1.156	0.244
Community Activities by Peer Deviance	0.977	0.892	1.072	0.626

Table 10

Conditional effects of the PRS on recent cannabis use at different levels of engagement with community activities in the EA subset

Conditional Effects of PRS by Community Activities on Recent Cannabis Use				
Community Activities	OR	Lower 95% CI	Upper 95% CI	P
Never	1.25	1.03	1.52	0.026
Rarely	1.08	0.92	1.28	0.350
Sometimes	0.94	0.79	1.12	0.472
Often	0.81	0.66	1.01	0.056

Table 11

Two-way interaction effect of PRS and organized sports on recent cannabis use after controlling for interaction of variables of interest and covariates using binary repeated logistic regression estimated by GEE in the EA subset

EA Subset Controlled 2-way Interaction; Recreational Sports X PRS

	OR	Lower 95% CI	Upper 95% CI	P
Sex	1.199	0.911	1.578	0.195
PRS	1.036	0.878	1.222	0.676
Time	1.166	1.073	1.267	0.0003
Organized Sports	0.978	0.871	1.097	0.700
School Activities	0.919	0.845	1.001	0.052
Community Activities	0.854	0.780	0.935	0.001
Church Activities	0.836	0.750	0.932	0.001
Peer Deviance	2.425	2.172	2.708	0
PRS by Time	1.022	0.943	1.107	0.595
PRS by Peer Deviance	1.126	1.015	1.248	0.025
PRS by Organized Sports	**1.125**	**1.020**	**1.240**	**0.019**
PRS by School Activities	1.054	0.969	1.147	0.220
PRS by Community Activities	0.874	0.803	0.951	0.002
PRS by Church Activities	0.970	0.869	1.082	0.580
E1 by Organized Sports	0.062	0.0001	59.522	0.428
E2 by Organized Sports	0.133	0.001	15.962	0.409
E3 by Organized Sports	0.044	0.00004	49.487	0.384
E4 by Organized Sports	8.132	0.078	848.623	0.377
E5 by Organized Sports	3.884	0.017	868.870	0.623
E6 by Organized Sports	1.418	0.006	331.335	0.900
E7 by Organized Sports	0.537	0.003	84.266	0.810
E8 by Organized Sports	8.607	0.056	1,316.003	0.402
E9 by Organized Sports	140.150	1.089	18,030.560	0.046
E10 by Organized Sports	5,523.270	36.849	827,870.900	0.001
E1 by PRS	0.761	0.001	869.027	0.939
E2 by PRS	2,912.186	0.198	42,787,465.000	0.103
E3 by PRS	18.055	0.014	23,427.420	0.429
E4 by PRS	1.361	0.001	2,805.930	0.937
E5 by PRS	0.131	0.0003	64.801	0.521

E6 by PRS	0.516	0.001	303.864	0.839
E7 by PRS	0.550	0.0005	628.555	0.868
E8 by PRS	0.001	0.00000	1.300	0.058
E9 by PRS	0.218	0.0003	158.064	0.650
E10 by PRS	30.614	0.016	57,884.530	0.374
Sex by PRS	0.909	0.687	1.203	0.503
Sex by Organized Sports	1.185	0.960	1.462	0.114
Time by Organized Sports	1.037	0.951	1.130	0.414
Organized Sports by Peer Deviance	1.009	0.918	1.108	0.854

Table 12

Conditional effects of the PRS on recent cannabis use at different levels of engagement with organized sports in the EA subset

Conditional Effects of PRS by Recreational Sports on Recent Cannabis Use				
Recreational Sports	OR	Lower 95% CI	Upper 95% CI	P
Never	0.94	0.78	1.13	0.504
Rarely	1.04	0.88	1.23	0.614
Sometimes	1.16	0.96	1.40	0.121
Often	1.29	1.01	1.65	0.040

Table 13

Three-way interaction effects of PRS and predictors on recent cannabis use using binary repeated logistic regression estimated by GEE in the EA subset

EA Subset Three-Way Interaction

	OR	Lower 95% CI	Upper 95% CI	P
PRS	1.041	0.913	1.186	0.551
Time	1.154	1.065	1.250	0.0004
Organized Sports	1.018	0.926	1.118	0.717
School Activities	0.924	0.851	1.003	0.058
Community Activities	0.877	0.803	0.959	0.004
Church Activities	0.839	0.754	0.934	0.001
Peer Deviance	2.392	2.142	2.671	0
PRS by Time	0.998	0.925	1.076	0.958
PRS by Peer Deviance	1.053	0.950	1.166	0.325
PRS by Organized Sports	1.135	1.034	1.246	0.008
PRS by School Activities	1.094	1.009	1.186	0.030
PRS by Community Activities	0.870	0.799	0.947	0.001
PRS by Church Activities	0.971	0.874	1.079	0.588
Organized Sports by Peer Deviance	1.017	0.925	1.118	0.727
School Activities by Peer Deviance	0.911	0.840	0.988	0.025
Community Activities by Peer Deviance	0.980	0.895	1.073	0.660
Church Activities by Peer Deviance	1.086	0.994	1.187	0.067
Time by Peer Deviance	1.082	0.994	1.177	0.068
Organized Sports by Time	1.011	0.926	1.104	0.806
School Activities by Time	1.110	1.009	1.220	0.031
Community Activities by Time	1.018	0.925	1.121	0.714
Church Activities by Time	1.053	0.960	1.156	0.273
PRS by Organized Sports by Peer Deviance	0.928	0.843	1.022	0.130
PRS by School Activities by Peer Deviance	**0.902**	**0.826**	**0.985**	**0.022**
PRS by Community Activities by Peer Deviance	0.996	0.907	1.094	0.933
PRS by Church Activities by Peer Deviance	**0.909**	**0.829**	**0.997**	**0.043**
PRS by Time by Peer Deviance	0.930	0.859	1.007	0.075
PRS by Time by Organized Sports	1.084	1.000	1.176	0.050
PRS by Time by School Activities	0.975	0.893	1.064	0.569
PRS by Time by Community Activities	1.052	0.955	1.159	0.301
PRS by Time by Church Activities	0.982	0.908	1.063	0.661

Table 14

Three-way interaction effect of PRS, school activities, and peer deviance on recent cannabis use after controlling for interaction of variables of interest and covariates using binary repeated logistic regression estimated by GEE in the EA subset

EA Subset Controlled 3-way Interaction; School Activities X PRS X Peer Deviance

	OR	Lower 95% CI	Upper 95% CI	P
Sex	1.372	1.213	1.553	0.00000
PRS	1.080	0.997	1.170	0.061
Time	1.139	1.092	1.188	0
Organized Sports	0.972	0.927	1.020	0.250
School Activities	0.961	0.906	1.019	0.182
Community Activities	0.907	0.866	0.949	0.00003
Church Activities	0.883	0.838	0.930	0.00000
Peer Deviance	2.094	1.957	2.241	0
PRS by Time	1.007	0.965	1.050	0.748
PRS by Peer Deviance	1.020	0.968	1.075	0.463
PRS by Organized Sports	1.029	0.981	1.080	0.238
PRS by School Activities	1.010	0.965	1.057	0.673
PRS by Community Activities	0.971	0.927	1.017	0.209
PRS by Church Activities	0.982	0.933	1.034	0.496
Sex by School Activities	0.977	0.895	1.067	0.606
E1 by School Activities	1.207	0.106	13.722	0.879
E2 by School Activities	0.850	0.069	10.412	0.899
E3 by School Activities	1.323	0.140	12.453	0.807
E4 by School Activities	1.545	0.138	17.245	0.724
E5 by School Activities	0.372	0.035	3.964	0.412
E6 by School Activities	0.740	0.075	7.332	0.797
E7 by School Activities	1.425	0.142	14.336	0.763
E8 by School Activities	1.341	0.135	13.360	0.802
E9 by School Activities	0.410	0.041	4.112	0.448
E10 by School Activities	0.631	0.064	6.213	0.694
Organized Sports by School Activities	0.994	0.955	1.035	0.776
School Activities by Community Activities	0.978	0.939	1.018	0.280
School Activities by Church Activities	1.022	0.981	1.065	0.302
Sex by Peer Deviance	0.997	0.898	1.106	0.954

E1 by Peer Deviance	0.336	0.020	5.768	0.452
E2 by Peer Deviance	0.874	0.051	14.863	0.926
E3 by Peer Deviance	1.063	0.061	18.567	0.967
E4 by Peer Deviance	0.230	0.016	3.374	0.283
E5 by Peer Deviance	4.916	0.304	79.502	0.262
E6 by Peer Deviance	0.967	0.065	14.488	0.981
E7 by Peer Deviance	0.449	0.030	6.722	0.562
E8 by Peer Deviance	2.655	0.152	46.450	0.504
E9 by Peer Deviance	0.200	0.014	2.897	0.238
E10 by Peer Deviance	1.066	0.066	17.159	0.964
Organized Sports by Peer Deviance	1.005	0.959	1.054	0.833
Community Activities by Peer Deviance	0.988	0.942	1.036	0.614
Church Activities by Peer Deviance	1.006	0.960	1.053	0.815
Sex by PRS	0.990	0.873	1.122	0.875
E1 by PRS	0.392	0.014	10.737	0.580
E2 by PRS	1.572	0.032	76.717	0.820
E3 by PRS	4.414	0.203	95.932	0.345
E4 by PRS	0.122	0.003	4.640	0.257
E5 by PRS	3.632	0.140	94.468	0.438
E6 by PRS	0.769	0.025	23.171	0.880
E7 by PRS	0.447	0.016	12.510	0.635
E8 by PRS	0.092	0.003	2.929	0.177
E9 by PRS	0.160	0.005	4.701	0.288
E10 by PRS	10.940	0.405	295.784	0.155
School Activities by Peer Deviance	0.996	0.950	1.044	0.873
Time by Peer Deviance	0.958	0.913	1.006	0.085
Time by Organized Sports	1.016	0.971	1.064	0.486
Time by School Activities	1.046	0.995	1.100	0.075
Time by Community Activities	0.975	0.926	1.026	0.324
Time by Church Activities	1.010	0.965	1.058	0.664
PRS by Organized Sports by Peer Deviance	0.982	0.937	1.028	0.435
PRS by School Activities by Peer Deviance	**0.982**	**0.934**	**1.032**	**0.469**
PRS by Community Activities by Peer Deviance	1.013	0.963	1.065	0.615
PRS by Church Activities by Peer Deviance	0.990	0.944	1.037	0.664
PRS by Time by Peer Deviance	0.985	0.937	1.036	0.560
PRS by Time by Organized Sports	1.022	0.977	1.069	0.341
PRS by Time by School Activities	0.992	0.944	1.043	0.763
PRS by Time by Community Activities	1.011	0.960	1.065	0.670

PRS by Time by Church Activities	1.003	0.960	1.049	0.881

Table 15

Three-way interaction effect of PRS, church activities, and peer deviance on recent cannabis use after controlling for interaction of variables of interest and covariates using binary repeated logistic regression estimated by GEE in the EA subset

EA Subset Controlled 3-way Interaction; Church Activities X PRS X Peer Deviance

	OR	Lower 95% CI	Upper 95% CI	P
Sex	1.370	1.211	1.550	0.00000
PRS	1.080	0.997	1.170	0.060
Time	1.138	1.091	1.187	0
Organized Sports	0.972	0.927	1.020	0.249
School Activities	0.947	0.906	0.991	0.018
Community Activities	0.905	0.864	0.948	0.00002
Church Activities	0.879	0.820	0.941	0.0002
Peer Deviance	2.093	1.956	2.239	0
PRS by Time	1.007	0.965	1.050	0.750
PRS by Peer Deviance	1.020	0.968	1.075	0.462
PRS by Organized Sports	1.030	0.982	1.081	0.229
PRS by School Activities	1.012	0.967	1.058	0.617
PRS by Community Activities	0.969	0.926	1.015	0.188
PRS by Church Activities	0.977	0.927	1.029	0.378
Sex by Church Activities	1.036	0.933	1.150	0.510
E1 by Church Activities	0.049	0.002	1.040	0.053
E2 by Church Activities	0.546	0.027	11.227	0.695
E3 by Church Activities	0.324	0.017	6.103	0.452
E4 by Church Activities	0.617	0.036	10.719	0.741
E5 by Church Activities	3.312	0.199	55.234	0.404
E6 by Church Activities	0.763	0.042	13.748	0.854
E7 by Church Activities	1.057	0.060	18.561	0.970
E8 by Church Activities	4.339	0.278	67.645	0.295
E9 by Church Activities	3.936	0.221	70.006	0.351
E10 by Church Activities	0.263	0.016	4.306	0.349
Organized Sports by Church Activities	0.994	0.952	1.038	0.793
Community Activities by Church Activities	0.967	0.925	1.011	0.134
School Activities by Church Activities	1.027	0.983	1.073	0.232
Sex by Peer Deviance	0.999	0.900	1.109	0.983

E1 by Peer Deviance	0.353	0.021	5.910	0.469
E2 by Peer Deviance	0.932	0.055	15.766	0.961
E3 by Peer Deviance	1.072	0.062	18.603	0.962
E4 by Peer Deviance	0.199	0.013	2.944	0.240
E5 by Peer Deviance	5.588	0.337	92.541	0.230
E6 by Peer Deviance	0.871	0.058	13.107	0.920
E7 by Peer Deviance	0.458	0.030	6.931	0.574
E8 by Peer Deviance	2.692	0.153	47.463	0.499
E9 by Peer Deviance	0.210	0.014	3.061	0.254
E10 by Peer Deviance	1.115	0.069	17.957	0.939
Organized Sports by Peer Deviance	1.006	0.959	1.055	0.812
Community Activities by Peer Deviance	0.986	0.940	1.034	0.559
Church Activities by Peer Deviance	1.007	0.961	1.055	0.767
Sex by PRS	0.991	0.874	1.124	0.890
E1 by PRS	0.287	0.010	7.872	0.460
E2 by PRS	1.526	0.031	74.082	0.831
E3 by PRS	5.511	0.254	119.633	0.277
E4 by PRS	0.115	0.003	4.305	0.242
E5 by PRS	4.453	0.169	117.402	0.371
E6 by PRS	0.679	0.022	20.543	0.824
E7 by PRS	0.514	0.018	14.434	0.696
E8 by PRS	0.102	0.003	3.237	0.195
E9 by PRS	0.157	0.005	4.618	0.283
E10 by PRS	9.977	0.370	268.765	0.171
School Activities by Peer Deviance	0.996	0.950	1.044	0.874
Time by Peer Deviance	0.957	0.912	1.005	0.076
Time by Organized Sports	1.015	0.970	1.062	0.523
Time by School Activities	1.046	0.995	1.099	0.077
Time by Community Activities	0.971	0.923	1.022	0.257
Time by Church Activities	1.012	0.966	1.061	0.614
PRS by Organized Sports by Peer Deviance	0.982	0.937	1.028	0.432
PRS by School Activities by Peer Deviance	0.982	0.934	1.032	0.468
PRS by Community Activities by Peer Deviance	1.013	0.963	1.065	0.618
PRS by Church Activities by Peer Deviance	**0.991**	**0.945**	**1.039**	**0.703**
PRS by Time by Peer Deviance	0.987	0.939	1.037	0.595
PRS by Time by Organized Sports	1.022	0.977	1.069	0.350
PRS by Time by School Activities	0.992	0.944	1.043	0.763
PRS by Time by Community Activities	1.012	0.961	1.065	0.657

PRS by Time by Church Activities	1.004	0.960	1.050	0.849

Table 16

Main effects of MultiPRS and predictors on recent cannabis use using binary repeated logistic regression estimated by GEE in the AA subset.

AA Subset Main Effects

	OR	Lower 95% CI	Upper 95% CI	P
ICC Cannabis Initiation MultiPRS P< 0.001	1.082	0.908	1.290	0.377
Time	1.139	0.996	1.304	0.058
Organized Sports	1.012	0.883	1.159	0.868
School Activities	1.002	0.859	1.168	0.981
Community Activities	0.865	0.741	1.010	0.066
Church Activities	0.822	0.718	0.940	0.004
Peer Deviance	2.685	2.296	3.140	<0.001

Table 17

Two-way interaction effects of MultiPRS and predictors on recent cannabis use using binary repeated logistic regression estimated by GEE in the AA subset

AA Subset 2-way Interaction

	OR	Lower 95% CI	Upper 95% CI	P
MultiPRS	1.078	0.906	1.282	0.396
Time	1.137	0.990	1.306	0.069
Organized Sports	1.014	0.885	1.162	0.841
School Activities	0.998	0.854	1.167	0.981
Community Activities	0.865	0.741	1.010	0.066
Church Activities	0.823	0.717	0.944	0.006
Peer Deviance	2.709	2.312	3.175	<0.001
MultiPRS by Time	0.971	0.847	1.114	0.674
MultiPRS by Peer Deviance	1.104	0.935	1.304	0.241
MultiPRS by Organized Sports	0.968	0.848	1.105	0.631
MultiPRS by School Activities	0.959	0.810	1.136	0.632
MultiPRS by Community Activities	1.161	0.998	1.351	0.053
MultiPRS by Church Activities	1.091	0.951	1.253	0.214

Table 18

Three-way interaction effects of MultiPRS and predictors on recent cannabis use using binary repeated logistic regression estimated by GEE in the AA subset

AA Subset 3-Way Interaction

	OR	Lower 95% CI	Upper 95% CI	P
MultiPRS	1.072	0.900	1.276	0.436
Time	1.123	0.977	1.292	0.103
Organized Sports	1.013	0.876	1.171	0.864
School Activities	0.993	0.848	1.162	0.929
Community Activities	0.881	0.755	1.028	0.108
Church Activities	0.858	0.745	0.988	0.033
Peer Deviance	2.742	2.327	3.232	<0.001
MultiPRS by Time	0.936	0.810	1.082	0.370
MultiPRS by Peer Deviance	1.117	0.956	1.306	0.164
MultiPRS by Organized Sports	0.959	0.834	1.103	0.555
MultiPRS by School Activities	0.959	0.811	1.133	0.621
MultiPRS by Community Activities	1.143	0.984	1.328	0.081
MultiPRS by Church Activities	1.071	0.931	1.233	0.337
Organized Sports by Peer Deviance	1.079	0.923	1.262	0.338
School Activities by Peer Deviance	0.996	0.846	1.173	0.964
Community Activities by Peer Deviance	1.019	0.871	1.191	0.818
Church Activities by Peer Deviance	0.865	0.757	0.988	0.032
Time by Peer Deviance	1.006	0.871	1.161	0.939
Organized Sports by Time	0.901	0.774	1.049	0.180
School Activities by Time	0.980	0.838	1.146	0.801
Community Activities by Time	0.990	0.838	1.169	0.904
Church Activities by Time	1.054	0.898	1.237	0.518
MultiPRS by Organized Sports by Peer Deviance	1.144	0.984	1.330	0.080
MultiPRS by School Activities by Peer Deviance	0.948	0.803	1.118	0.525
MultiPRS by Community Activities by Peer Deviance	1.124	0.971	1.303	0.118
MultiPRS by Church Activities by Peer Deviance	0.982	0.853	1.129	0.795
MultiPRS by Time by Peer Deviance	1.036	0.894	1.200	0.639
MultiPRS by Time by Organized Sports	0.922	0.783	1.087	0.334
MultiPRS by Time by School Activities	0.965	0.806	1.154	0.694

MultiPRS by Time by Community Activities	1.016	0.865	1.193	0.849
MultiPRS by Time by Church Activities	0.896	0.758	1.061	0.203

Table 19

Main effects of familial risk and predictors on recent cannabis use using binary repeated logistic regression estimated by GEE in the EA subset

EA Subset Familial Risk Main Effects

	OR	Lower 95% CI	Upper 95% CI	P
Familial Risk	1.329	1.173	1.506	<0.001
Time	1.151	1.063	1.246	0.001
Organized Sports	1.019	0.931	1.115	0.689
School Activities	0.927	0.854	1.006	0.071
Community Activities	0.863	0.789	0.943	0.001
Church Activities	0.841	0.759	0.933	0.001
Peer Deviance	2.220	1.990	2.476	<0.001

Table 20

Two-way interaction effects of familial risk and predictors on recent cannabis use using binary repeated logistic regression estimated by GEE in the EA subset.

EA Subset Familial Risk 2-way Interaction

	OR	Lower 95% CI	Upper 95% CI	P
Familial Risk	1.345	1.187	1.522	<0.001
Time	1.146	1.058	1.241	0.001
Organized Sports	1.020	0.932	1.117	0.667
School Activities	0.931	0.858	1.010	0.086
Community Activities	0.862	0.789	0.942	0.001
Church Activities	0.840	0.758	0.931	0.001
Peer Deviance	2.233	2.001	2.493	<0.001
FamRisk by Time	1.037	0.951	1.132	0.408
FamRisk by Peer Deviance	0.979	0.887	1.081	0.674
FamRisk by Organized Sports	1.077	0.983	1.179	0.111
FamRisk by School Activities	0.907	0.837	0.984	0.019
FamRisk by Community Activities	0.959	0.874	1.052	0.372
FamRisk by Church Activities	0.998	0.906	1.100	0.974

Table 21

Two-way interaction effect of familial risk and familial risk by school activities on recent cannabis use after controlling for interaction of variables of interest and covariates using binary repeated logistic regression estimated by GEE in the EA subset

EA Subset Familial Risk Controlled 2-way Interaction; School Activities X Familial Risk

	OR	Lower 95% CI	Upper 95% CI	P
Sex	1.260	0.964	1.647	0.090
Familial Risk	1.323	1.133	1.544	<0.001
Time	1.145	1.058	1.240	0.001
Organized Sports	1.026	0.936	1.124	0.586
School Activities	0.925	0.834	1.025	0.135
Community Activities	0.865	0.791	0.945	0.001
Church Activities	0.839	0.757	0.929	0.001
Peer Deviance	2.227	1.996	2.485	<0.001
FamRisk by time	1.029	0.943	1.122	0.524
FamRisk by Peer Deviance	0.981	0.886	1.086	0.710
FamRisk by Organized Sports	1.079	0.984	1.182	0.106
FamRisk by School Activities	0.919	0.848	0.996	0.039
FamRisk by Community Activities	0.962	0.876	1.056	0.416
FamRisk by Church Activities	0.991	0.898	1.094	0.859
Sex by FamRisk	1.061	0.804	1.399	0.677
Sex by School Activities	1.039	0.880	1.226	0.653
School Activities by Peer Deviance	0.945	0.868	1.028	0.189
Time by School Activities	1.106	1.015	1.205	0.022
Organized Sports by School Activities	0.970	0.899	1.046	0.426
School Activities by Community Activities	0.967	0.896	1.043	0.387
School Activities by Church Activities	1.046	0.967	1.131	0.261

Table 22

Conditional effects of the familial risk on recent cannabis use at different levels of engagement with school activities in the EA subset

Conditional Effects of Familial Risk by School Activities on Recent Cannabis Use				
School Activities	OR	Lower 95% CI	Upper 95% CI	P
Never	1.44	0.19	0.54	0.0001
Rarely	1.34	0.13	0.44	0.0003
Sometimes	1.24	0.05	0.38	0.0122
Often	1.14	-0.07	0.34	0.1973

Table 23

Three-way interaction effects of familial risk and predictors on recent cannabis use using binary repeated logistic regression estimated by GEE in the EA subset.

EA Subset Familial Risk 3-Way Interaction				
	OR	Lower 95% CI	Upper 95% CI	P
Familial Risk	1.362	1.197	1.549	0.00000
Time	1.149	1.059	1.246	0.001
Organized Sports	1.021	0.932	1.118	0.662
School Activities	0.931	0.856	1.012	0.095
Community Activities	0.865	0.791	0.946	0.002
Church Activities	0.843	0.759	0.936	0.001
Peer Deviance	2.267	2.029	2.532	0
FamRisk by Time	1.034	0.947	1.129	0.455
FamRisk by Peer Deviance	1.002	0.904	1.111	0.965
FamRisk by Organized Sports	1.083	0.987	1.189	0.093
FamRisk by School Activities	0.919	0.846	0.998	0.045
FamRisk by Community Activities	0.960	0.874	1.054	0.388
FamRisk by Church Activities	0.985	0.891	1.089	0.768
Organized Sports by Peer Deviance	1.040	0.944	1.145	0.431
School Activities by Peer Deviance	0.927	0.853	1.006	0.069
Community Activities by Peer Deviance	0.966	0.882	1.058	0.454
Church Activities by Peer Deviance	1.071	0.983	1.166	0.117
Time by Peer Deviance	1.079	0.991	1.175	0.078
Organized Sports by Time	1.015	0.930	1.108	0.738
School Activities by Time	1.098	1.002	1.203	0.045
Community Activities by Time	1.016	0.924	1.117	0.746
Church Activities by Time	1.039	0.949	1.139	0.406
FamRisk by Organized Sports by Peer Deviance	0.995	0.907	1.090	0.908
FamRisk by School Activities by Peer Deviance	1.050	0.965	1.142	0.259
FamRisk by Community Activities by Peer Deviance	0.996	0.919	1.080	0.927
FamRisk by Church Activities by Peer Deviance	1.017	0.934	1.107	0.694
FamRisk by Time by Peer Deviance	0.996	0.915	1.085	0.935
FamRisk by Time by Organized Sports	1.089	0.994	1.193	0.069
FamRisk by Time by School Activities	0.958	0.871	1.053	0.370

FamRisk by Time by Community Activities	0.979	0.890	1.077	0.662
FamRisk by Time by Church Activities	0.960	0.875	1.054	0.393

Table 24

Main effects of familial risk and predictors on recent cannabis use using binary repeated logistic regression estimated by GEE in the AA subset.

AA Subset Familial Risk Main Effects

	OR	Lower 95% CI	Upper 95% CI	P
Familial Risk	1.227	1.026	1.466	0.025
Time	1.137	0.997	1.296	0.055
Organized Sports	1.004	0.877	1.149	0.954
School Activities	1.000	0.862	1.160	0.998
Community Activities	0.860	0.739	1.002	0.053
Church Activities	0.805	0.705	0.920	0.001
Peer Deviance	2.493	2.135	2.911	<0.001

Table 25

Two-way interaction effects of familial risk and predictors on recent cannabis use using binary repeated logistic regression estimated by GEE in the AA subset

AA Subset Familial Risk 2-way Interaction

	OR	Lower 95% CI	Upper 95% CI	P
Familial Risk	1.252	1.055	1.486	0.010
Time	1.141	0.998	1.304	0.053
Organized Sports	1.000	0.877	1.141	0.998
School Activities	0.998	0.860	1.159	0.982
Community Activities	0.857	0.737	0.997	0.045
Church Activities	0.798	0.697	0.913	0.001
Peer Deviance	2.517	2.150	2.946	<0.001
FamRisk by Time	0.898	0.801	1.005	0.062
FamRisk by Peer Deviance	0.913	0.797	1.045	0.187
FamRisk by Organized Sports	1.026	0.864	1.217	0.771
FamRisk by School Activities	1.004	0.856	1.177	0.961
FamRisk by Community Activities	1.040	0.874	1.237	0.662
FamRisk by Church Activities	0.961	0.819	1.127	0.623

Table 26

Three-way interaction effects of familial risk and predictors on recent cannabis use using binary repeated logistic regression estimated by GEE in the AA subset

AA Subset Familial Risk 3-Way Interaction

	OR	Lower 95% CI	Upper 95% CI	P
Familial Risk	1.222	1.028	1.453	0.023
Time	1.152	1.008	1.315	0.037
Organized Sports	0.975	0.847	1.122	0.720
School Activities	1.003	0.864	1.164	0.969
Community Activities	0.866	0.747	1.003	0.055
Church Activities	0.823	0.717	0.945	0.006
Peer Deviance	2.513	2.148	2.939	<0.001
FamRisk by Time	0.933	0.814	1.069	0.317
FamRisk by Peer Deviance	0.941	0.814	1.088	0.413
FamRisk by Organized Sports	1.000	0.849	1.179	0.999
FamRisk by School Activities	0.982	0.834	1.157	0.831
FamRisk by Community Activities	1.079	0.904	1.288	0.401
FamRisk by Church Activities	0.952	0.807	1.123	0.559
Organized Sports by Peer Deviance	1.067	0.924	1.232	0.377
School Activities by Peer Deviance	0.983	0.843	1.146	0.827
Community Activities by Peer Deviance	1.034	0.897	1.192	0.644
Church Activities by Peer Deviance	0.848	0.739	0.973	0.019
Time by Peer Deviance	1.017	0.885	1.168	0.816
Organized Sports by Time	0.908	0.784	1.051	0.197
School Activities by Time	1.015	0.871	1.184	0.845
Community Activities by Time	0.949	0.812	1.108	0.506
Church Activities by Time	1.056	0.902	1.237	0.496
FamRisk by Organized Sports by Peer Deviance	0.922	0.809	1.051	0.225
FamRisk by School Activities by Peer Deviance	1.163	0.989	1.366	0.067
FamRisk by Community Activities by Peer Deviance	0.891	0.774	1.024	0.105
FamRisk by Church Activities by Peer Deviance	1.086	0.923	1.278	0.320
FamRisk by Time by Peer Deviance	1.012	0.878	1.167	0.865
FamRisk by Time by Organized Sports	0.900	0.779	1.041	0.156
FamRisk by Time by School Activities	0.990	0.827	1.184	0.910

FamRisk by Time by Community Activities	1.237	1.049	1.460	0.012
FamRisk by Time by Church Activities	0.947	0.801	1.119	0.522

Table 27

Zero order correlations of the PRS with various environments in the EA subset

	Zero-Order Correlation with PRS in the EA subset
Y1 Cannabis Use	0.09 [0.03,0.14]
Y2 Cannabis Use	0.05 [-0.02,0.12]
Y3 Cannabis Use	0.11 [0.03,0.18]
Male	0.01 [-0.03,0.04]
Year 1 Recreational Sports	0.00 [-0.05,0.04]
Year 2 Recreational Sports	-0.05 [-0.1,0.0]
Year 3 Recreational Sports	-0.04 [-0.10,0.02]
Year 1 School Activities	0.00 [-0.05,0.04]
Year 2 School Activities	0.01 [-0.04,0.06]
Year 3 School Activities	0.01 [-0.05,0.07]
Y1 Community Activities	-0.06 [-0.10,-0.01]
Y2 Community Activities	-0.02 [-0.07,0.03]
Y3 Community Activities	-0.06 [-0.12,0.00]
Y1 Church Activities	-0.05 [-0.09,0.00]
Y2 Church Activities	-0.04 [-0.1,0.01]
Y3 Church Activities	-0.04 [-0.1,0.02]
Y1 Peer Deviance	0.07 [0.03,0.11]
Y2 Peer Deviance	0.06 [0.00,0.11]
Y3 Peer Deviance	0.07 [0.01,0.13]
Y1 Steinberg 1	0.03 [0.00,0.07]
Y1 Steinberg 2	-0.05 [-0.09,-0.02]
Y1 Steinberg 3	0.02 [-0.01,0.06]
Y1 Steinberg 4	0.03 [0.00,0.07]
Y1 Steinberg 5	0.00 [-0.04,0.03]
Y1 Steinberg 6	-0.04 [-0.07,0.00]

Table 28

Zero order correlations of the PRS with various environments in the AA subset

Zero-Order Correlation with PRS in the AA subset	
Y1 Cannabis Use	0.01 [-0.07,0.09]
Y2 Cannabis Use	0.05 [-0.05,0.14]
Y3 Cannabis Use	0.02 [-0.08,0.13]
Male	-0.02 [-0.07,0.04]
Year 1 Recreational Sports	-0.02 [-0.09,0.05]
Year 2 Recreational Sports	-0.05 [-0.12,0.02]
Year 3 Recreational Sports	-0.01 [-0.10,0.07]
Year 1 School Activities	0.03 [-0.04,0.09]
Year 2 School Activities	0.07 [-0.01,0.14]
Year 3 School Activities	0.02 [-0.06,0.10]
Y1 Community Activities	0.04 [-0.03,0.11]
Y2 Community Activities	0.04 [-0.04,0.11]
Y3 Community Activities	0.03 [-0.06,0.11]
Y1 Church Activities	0.03 [-0.04,0.09]
Y2 Church Activities	0.03 [-0.04,0.11]
Y3 Church Activities	0.02 [-0.06,0.11]
Y1 Peer Deviance	-0.01 [-0.07,0.05]
Y2 Peer Deviance	-0.03 [-0.10,0.04]
Y3 Peer Deviance	-0.02 [-0.11,0.06]
Y1 Steinberg 1	-0.05 [-0.11,0.00]
Y1 Steinberg 2	0.00 [-0.05,0.06]
Y1 Steinberg 3	0.02 [-0.04,0.07]
Y1 Steinberg 4	0.01 [-0.05,0.06]
Y1 Steinberg 5	0.00 [-0.06,0.05]
Y1 Steinberg 6	0.01 [-0.05,0.06]

Figures

Figure 1

Variance in ordinal cannabis use explained by PRS calculated at various P-value thresholds for the EA subset after Bonferroni correction

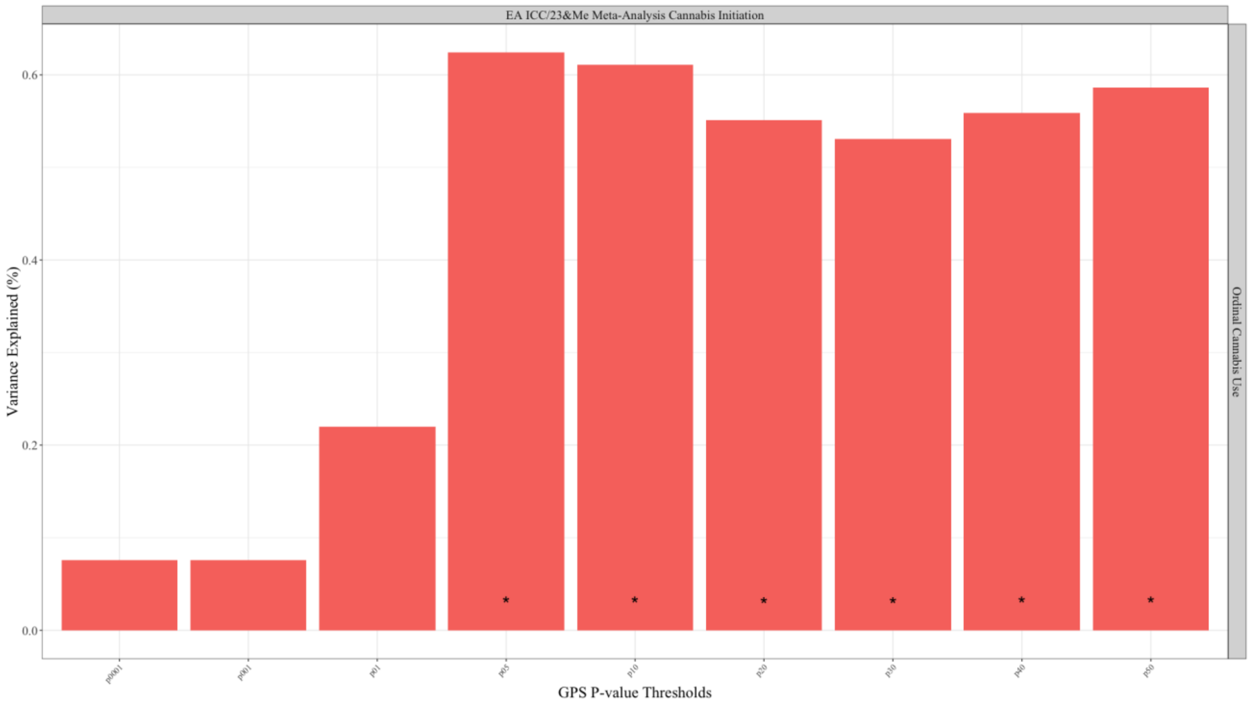


Figure 2

Variance in ordinal cannabis use explained by PRS calculated at various P-value thresholds for the AA subset after Bonferroni correction

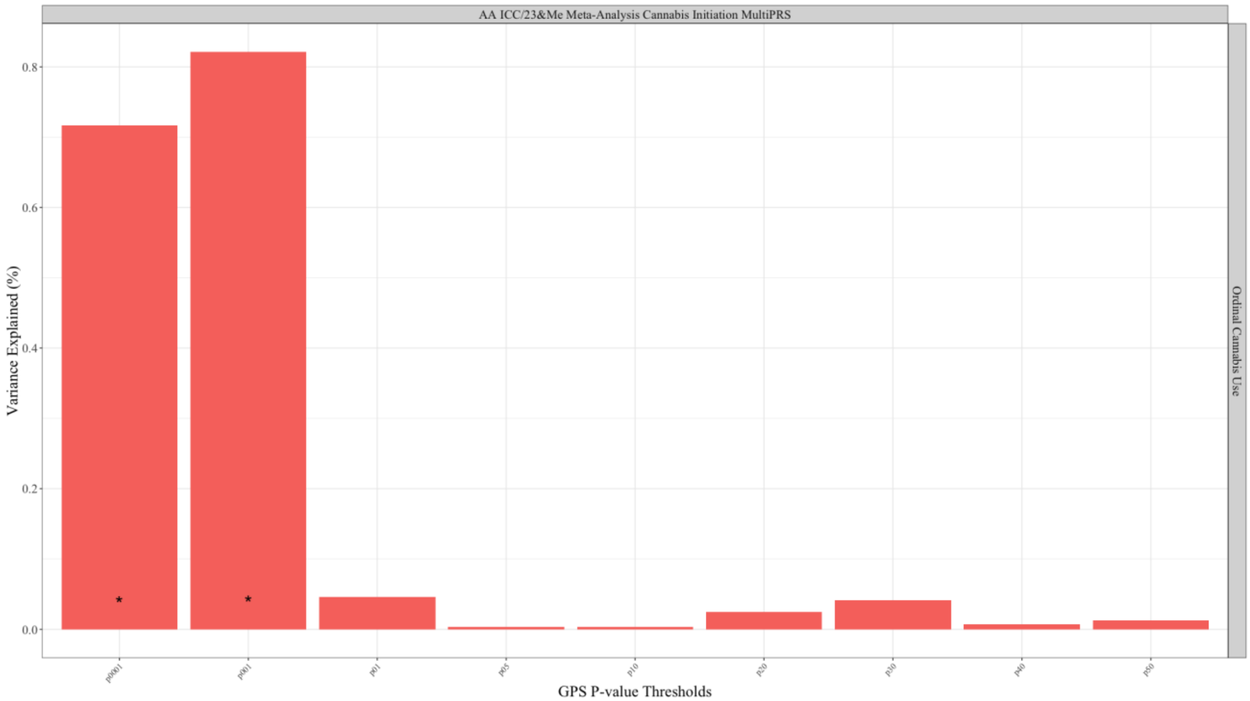


Figure 3

Main effects of PRS and predictors on recent cannabis use using binary repeated logistic regression estimated by GEE in the EA subset

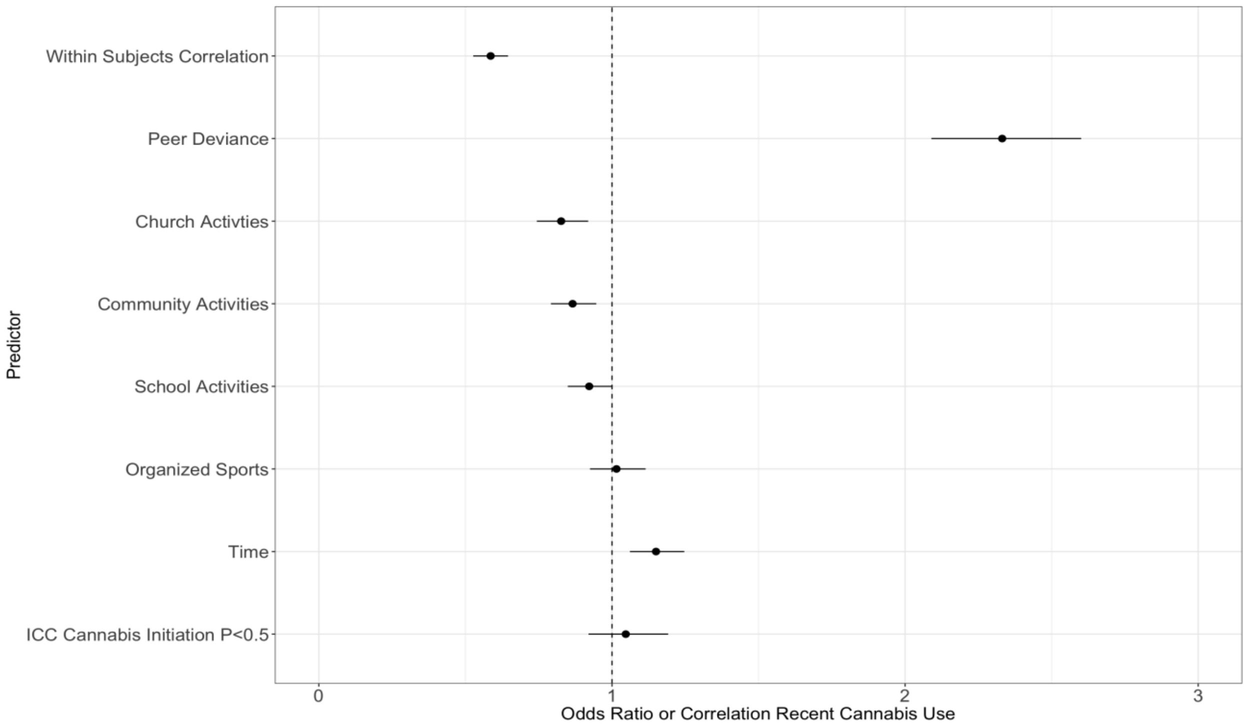


Figure 4

Two-way interaction effects of PRS and predictors on recent cannabis use using binary repeated logistic regression estimated by GEE in the EA subset

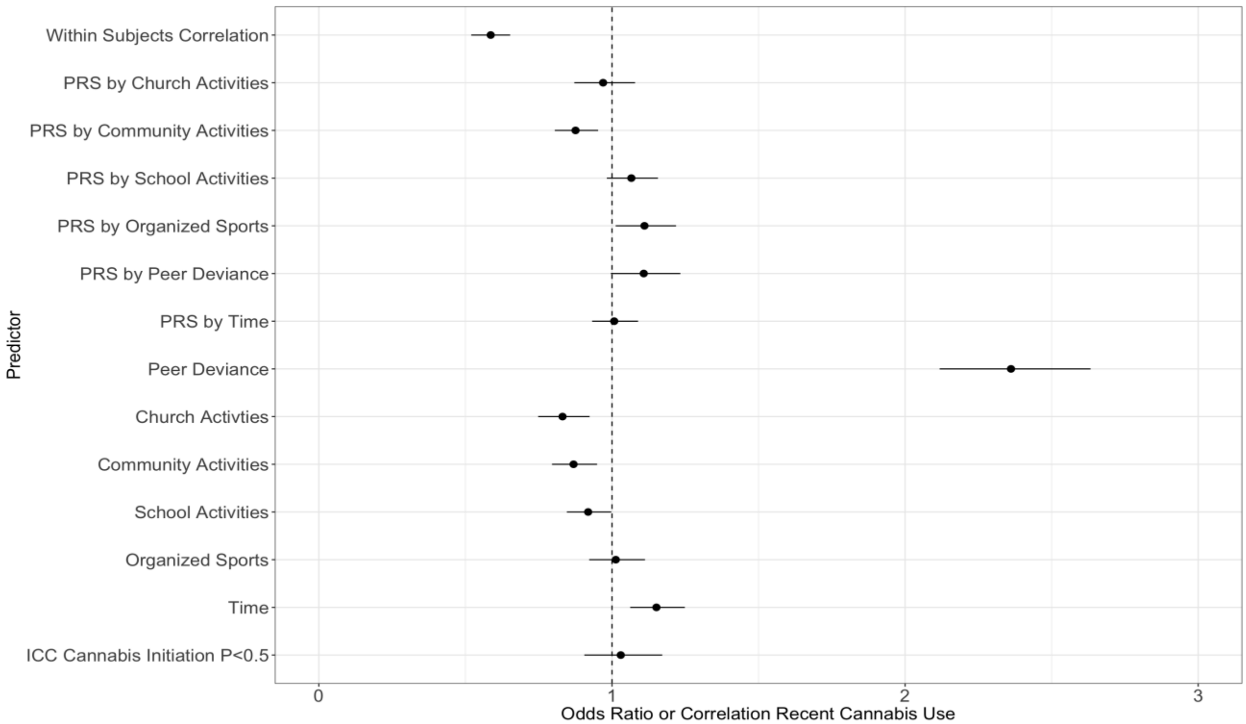


Figure 5

Conditional effects of the PRS on recent cannabis use at different levels of engagement with community activities in the EA subset.

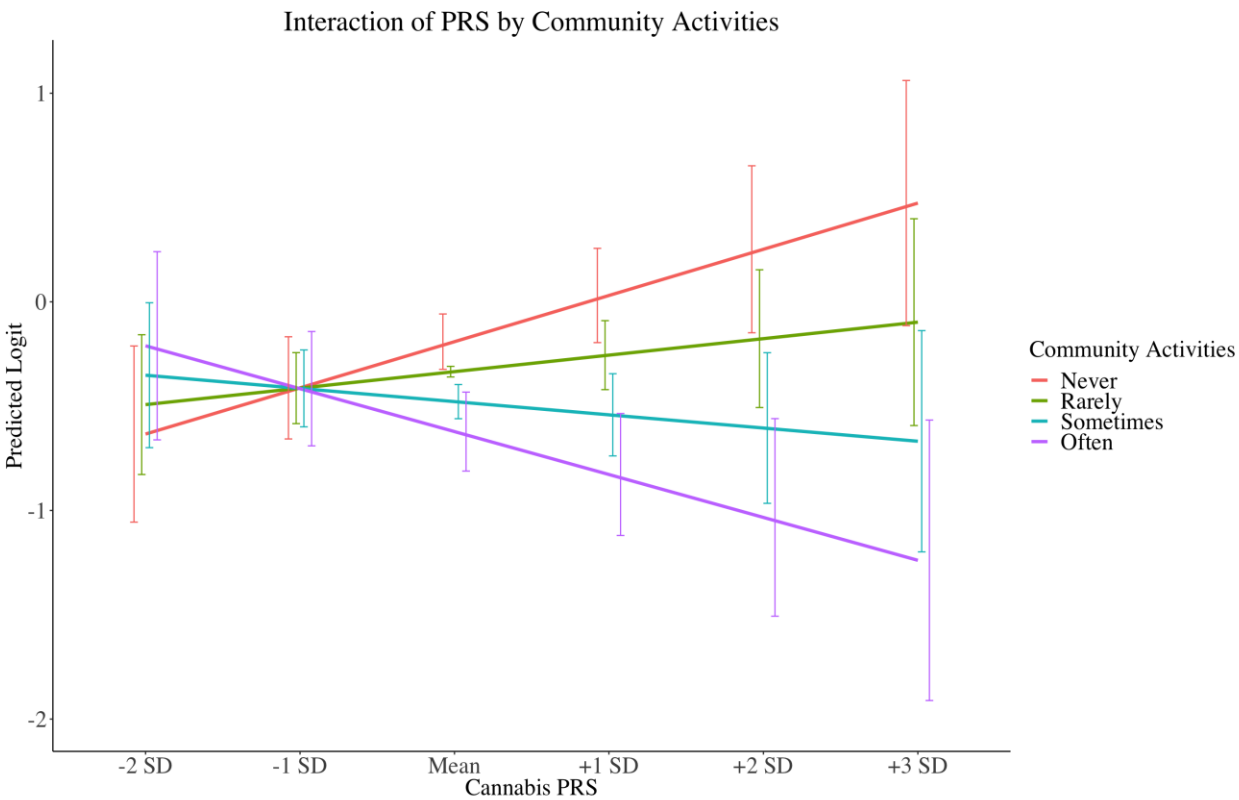


Figure 6

Conditional effects of the PRS on recent cannabis use at different levels of engagement with organized sports in the EA subset

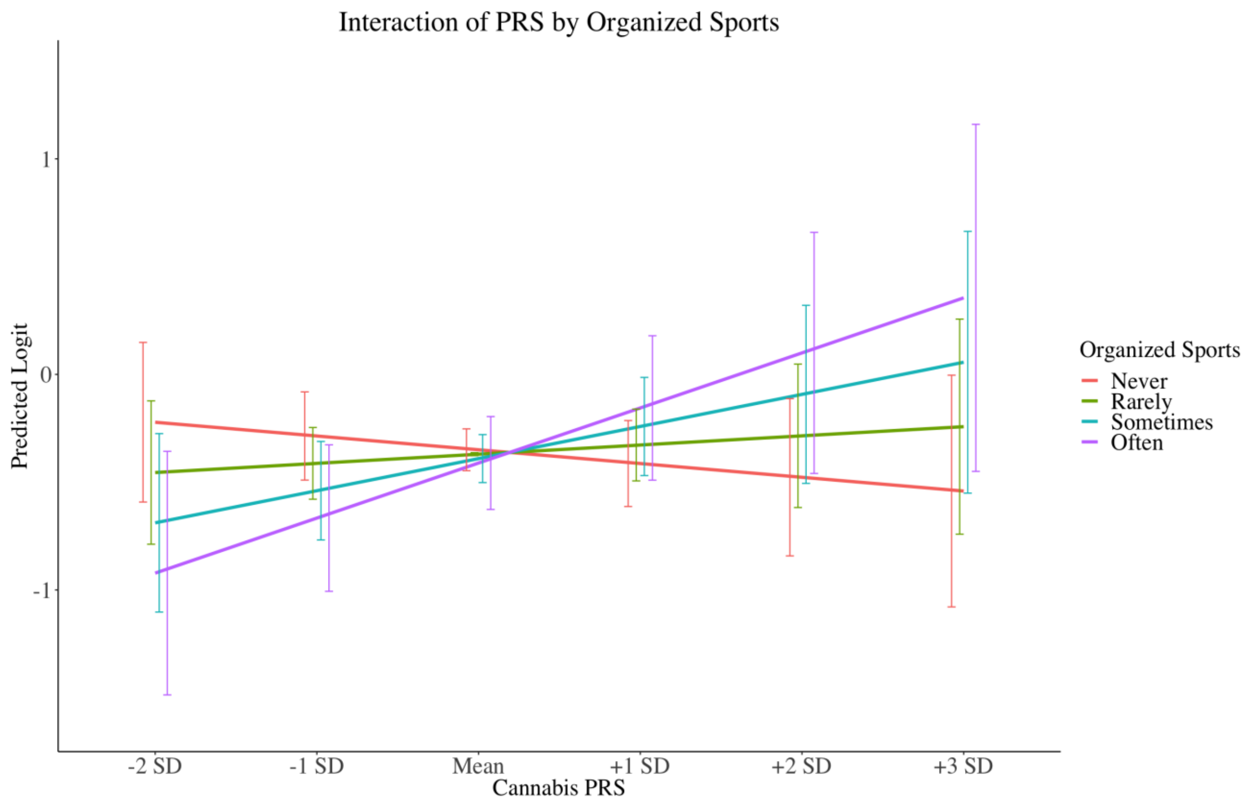


Figure 7

Three-way interaction effects of PRS and predictors on recent cannabis use using binary repeated logistic regression estimated by GEE in the EA subset

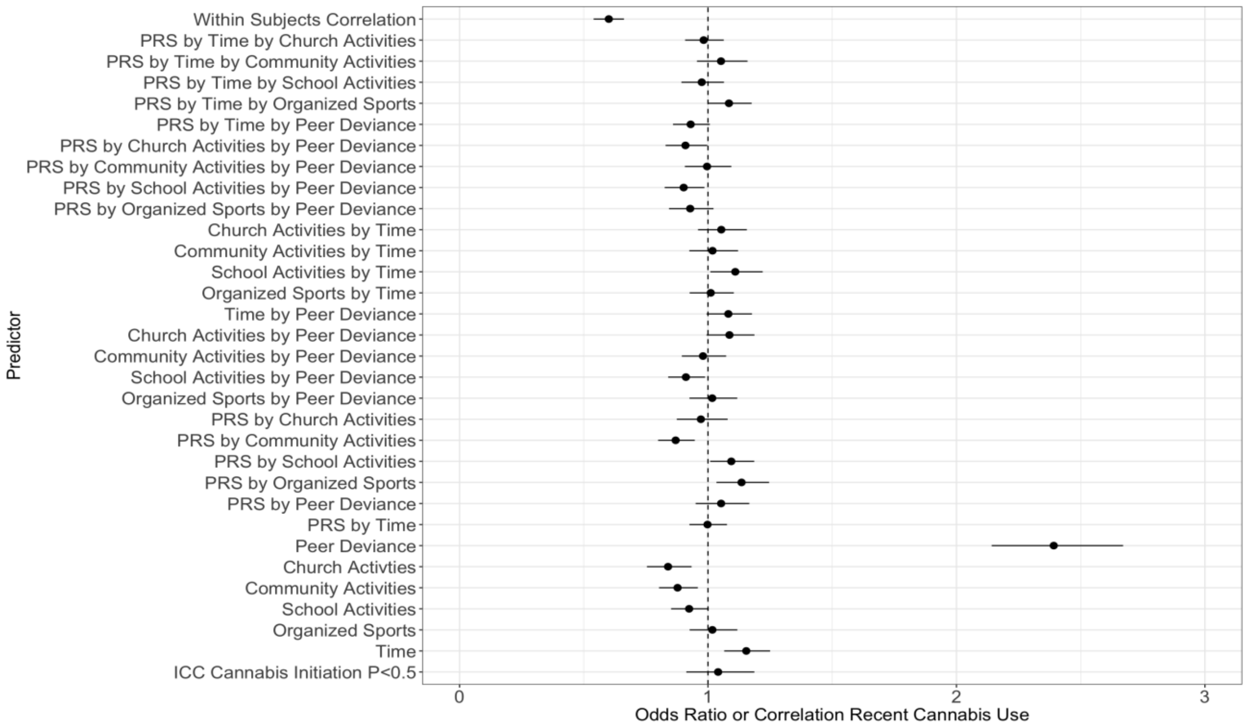


Figure 8

Main effects of MultiPRS and predictors on recent cannabis use using binary repeated logistic regression estimated by GEE in the AA subset

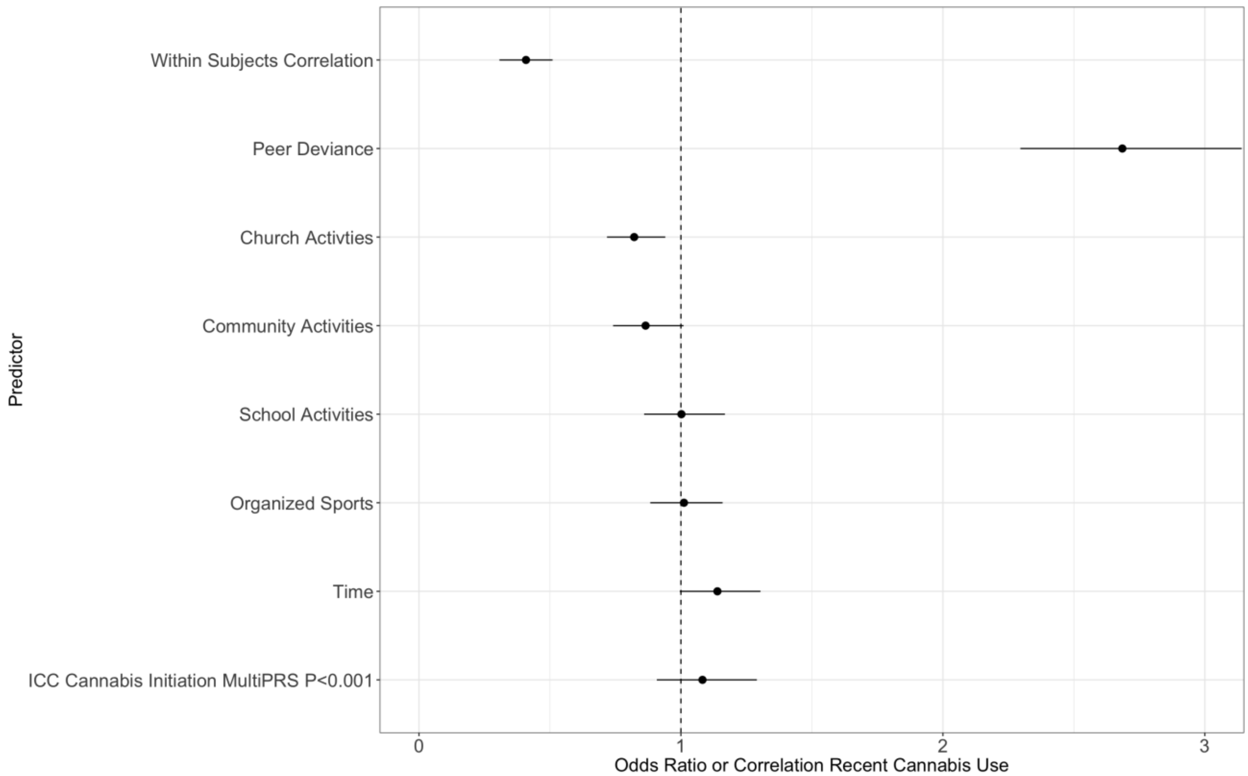


Figure 9

Two-way interaction effects of MultiPRS and predictors on recent cannabis use using binary repeated logistic regression estimated by GEE in the AA subset

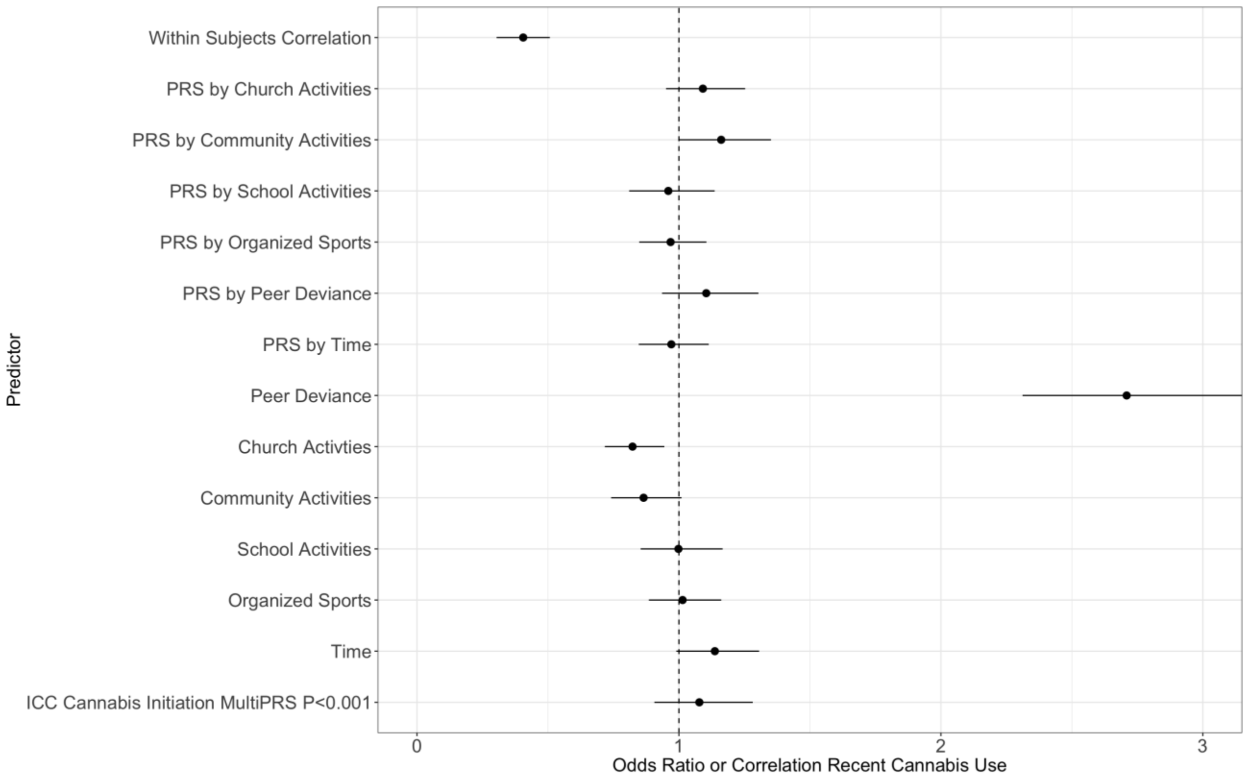


Figure 10

Three-way interaction effects of MultiPRS and predictors on recent cannabis use using binary repeated logistic regression estimated by GEE in the AA subset

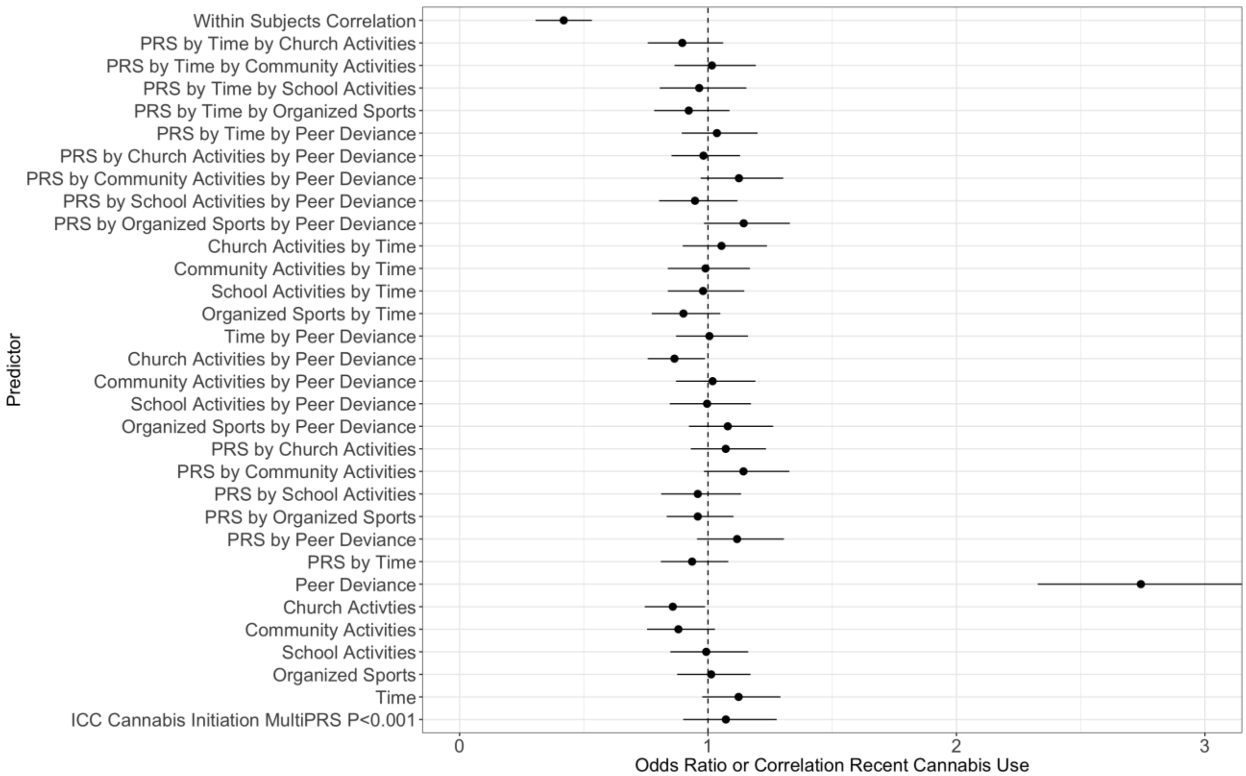


Figure 11

Main effects of familial risk and predictors on recent cannabis use using binary repeated logistic regression estimated by GEE in the EA subset

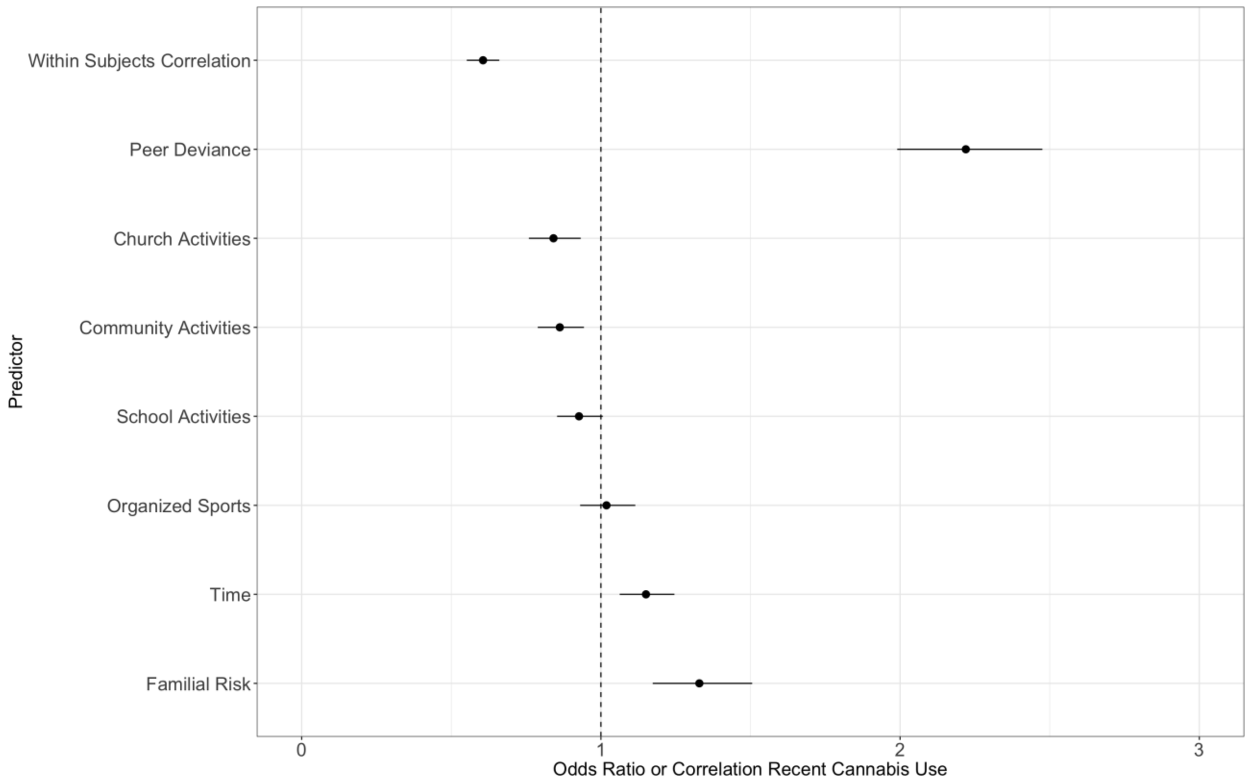


Figure 12

Two-way interaction effects of familial risk and predictors on recent cannabis use using binary repeated logistic regression estimated by GEE in the EA subset

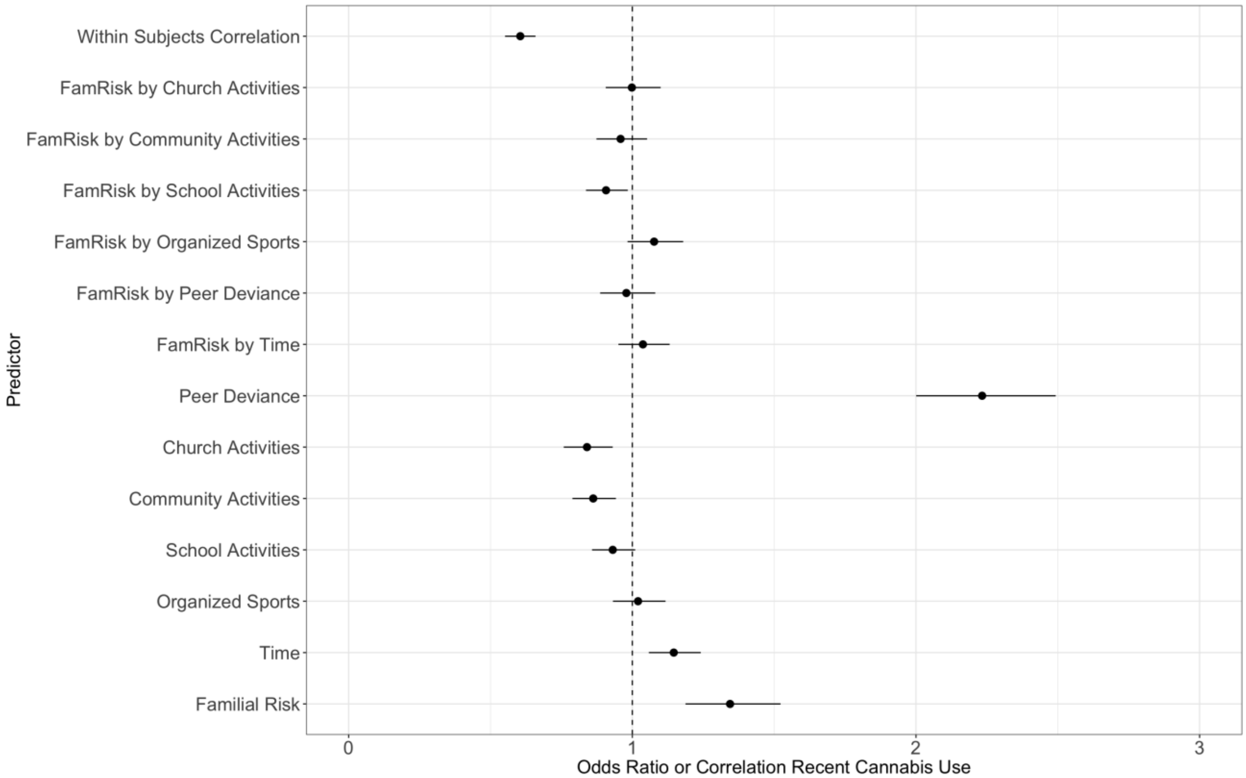


Figure 13

Conditional effects of familial risk on recent cannabis use at different levels of engagement with school activities in the EA subset

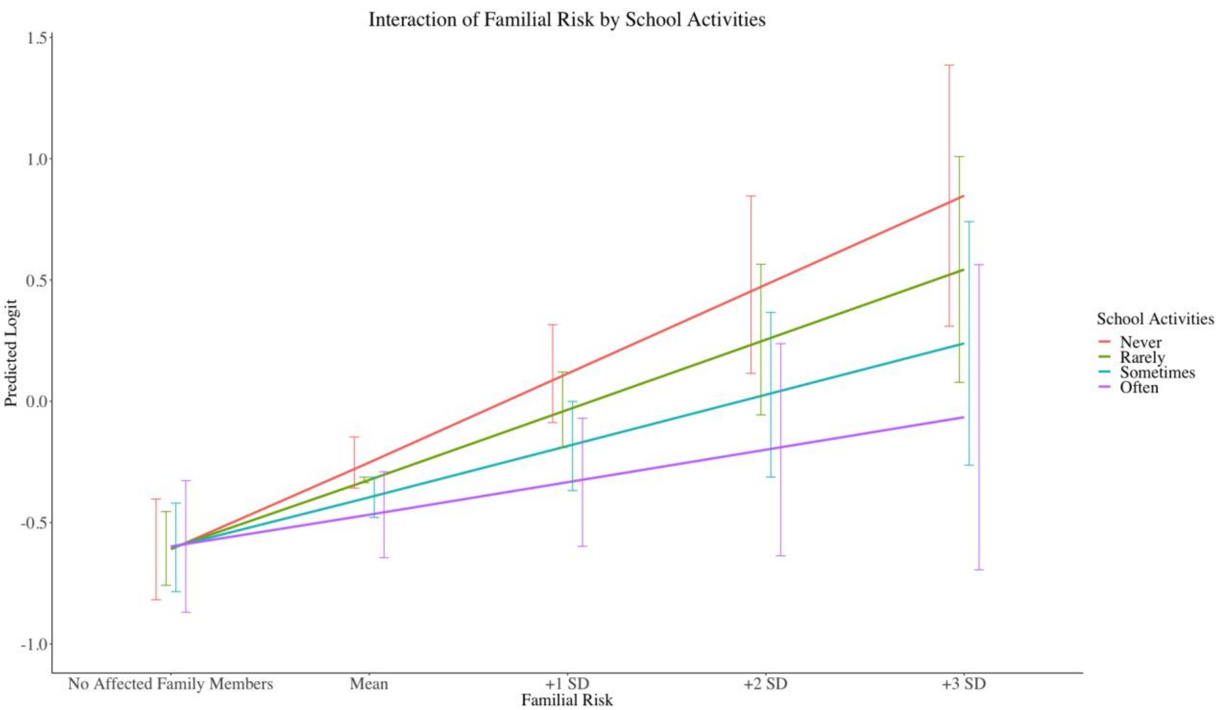


Figure 14

Three-way interaction effects of familial risk and predictors on recent cannabis use using binary repeated logistic regression estimated by GEE in the EA subset

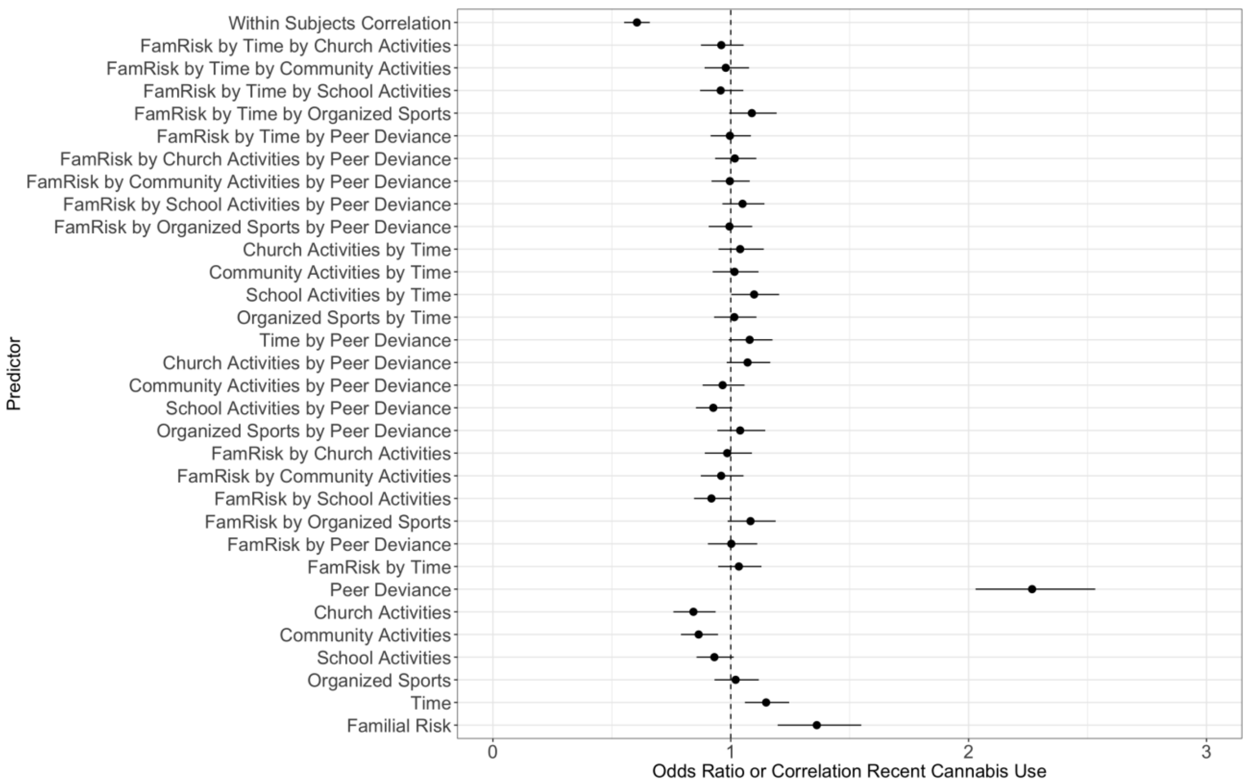


Figure 15

Main effects of familial risk and predictors on recent cannabis use using binary repeated logistic regression estimated by GEE in the AA subset

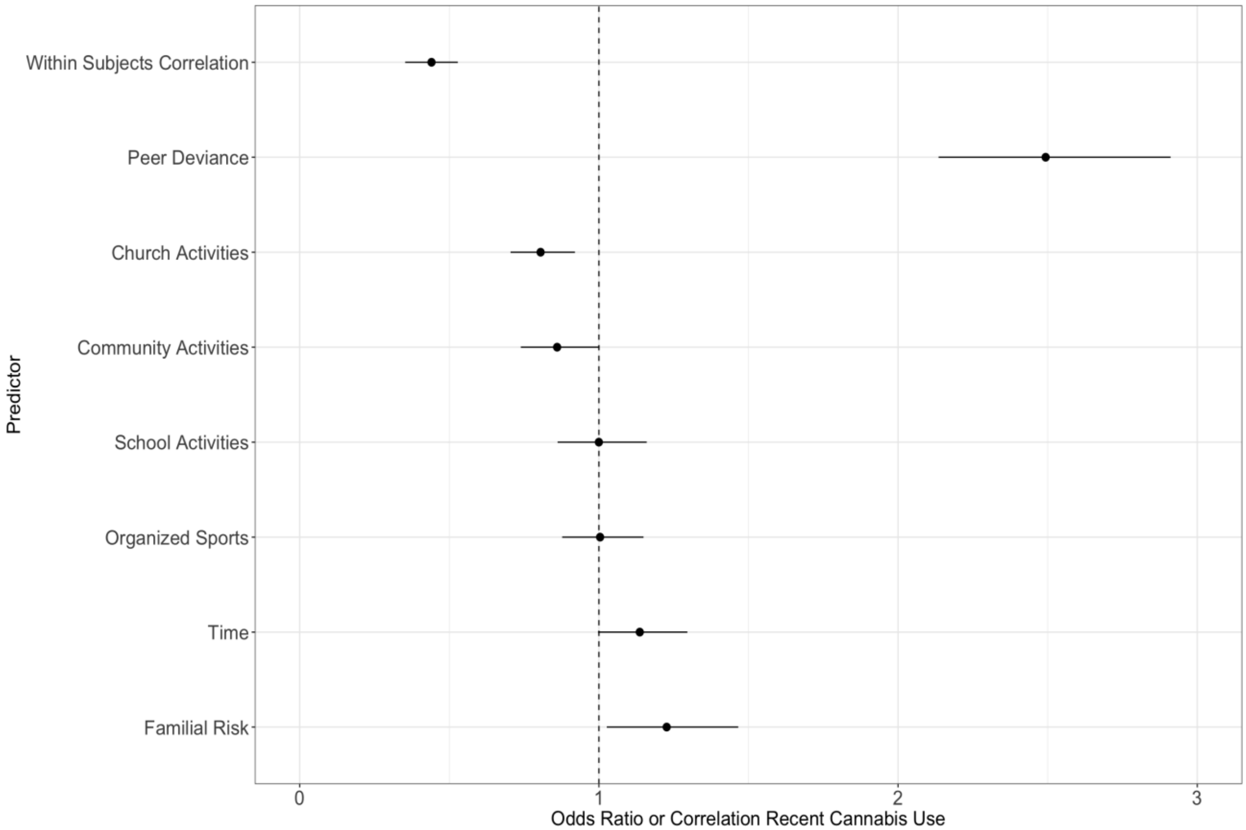


Figure 16

Two-way interaction effects of familial risk and predictors on recent cannabis use using binary repeated logistic regression estimated by GEE in the AA subset

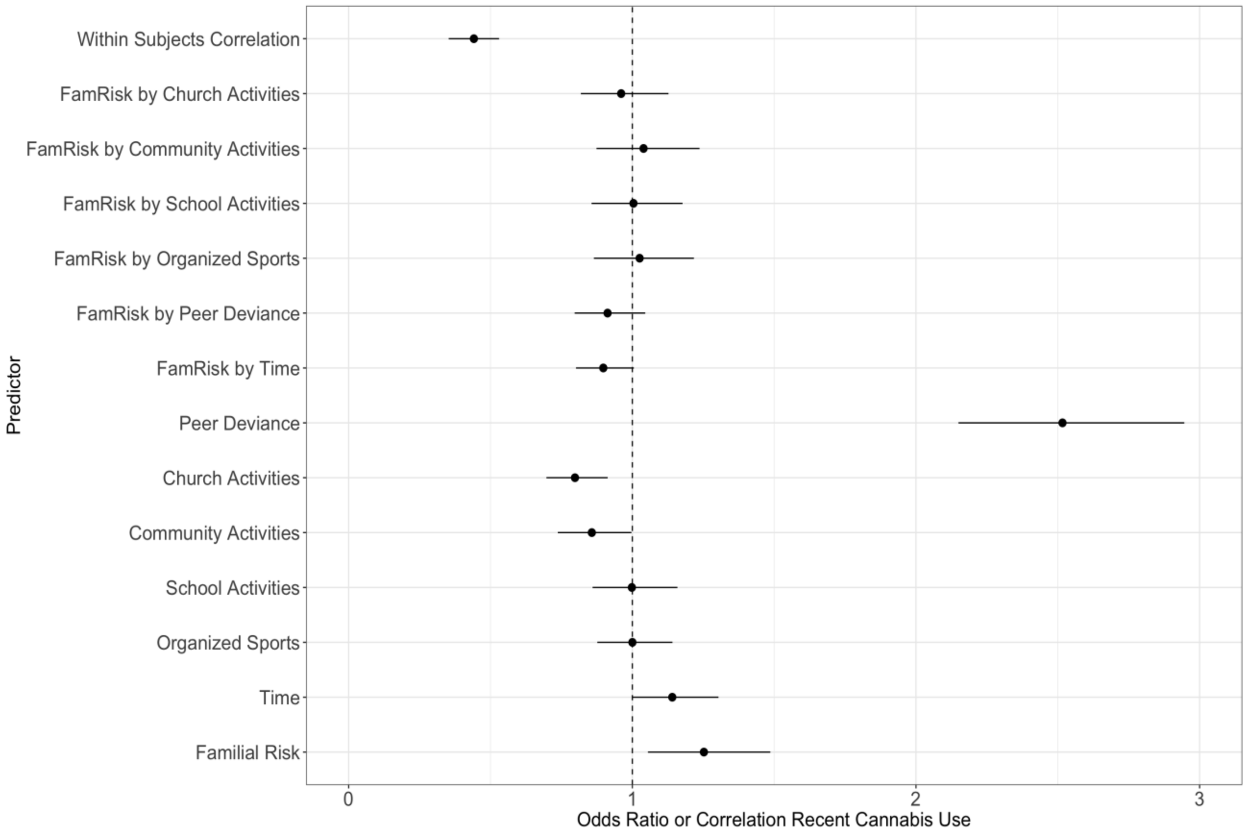


Figure 17

Three-way interaction effects of familial risk and predictors on recent cannabis use using binary repeated logistic regression estimated by GEE in the AA subset

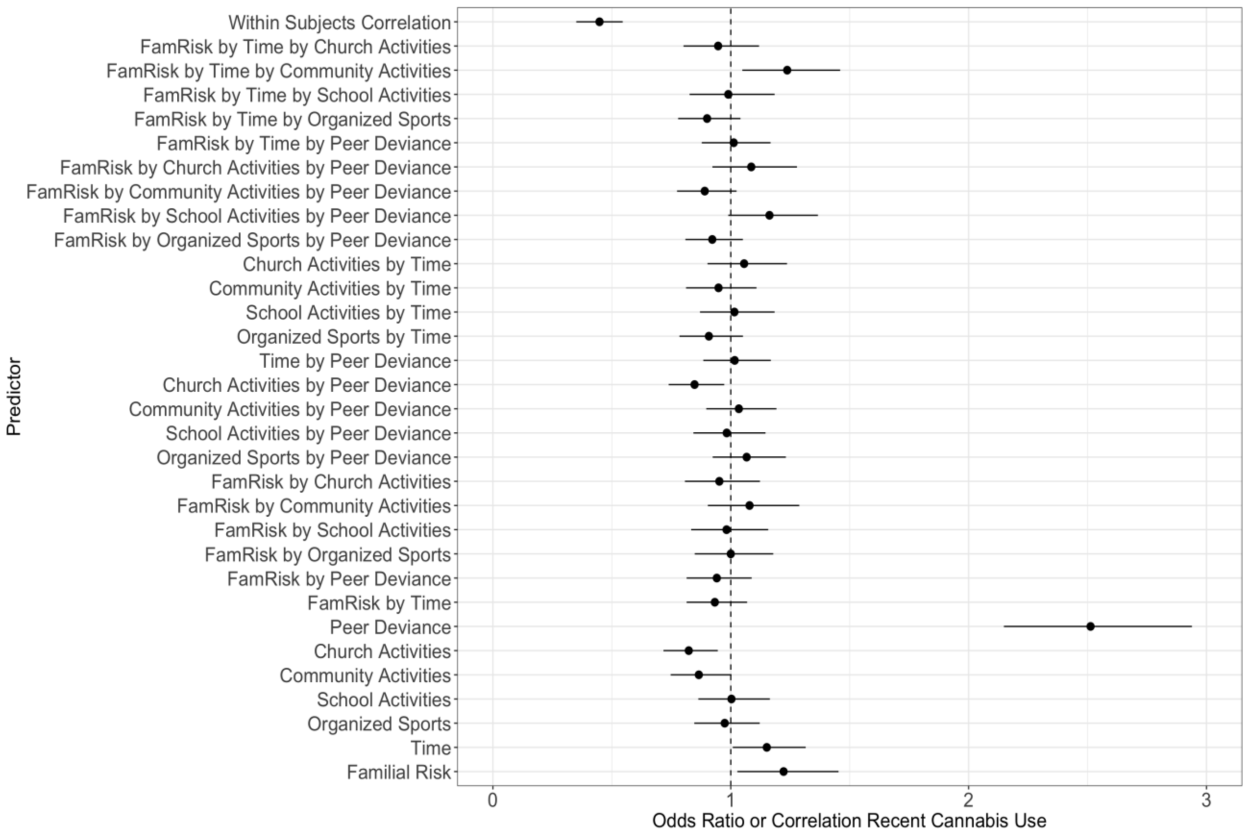


Figure 18

Main effects of the PRS and predictors on recent cannabis use using binary repeated logistic regression estimated by GEE in the EA subset after controlling for term GPA as a time-varying covariate.

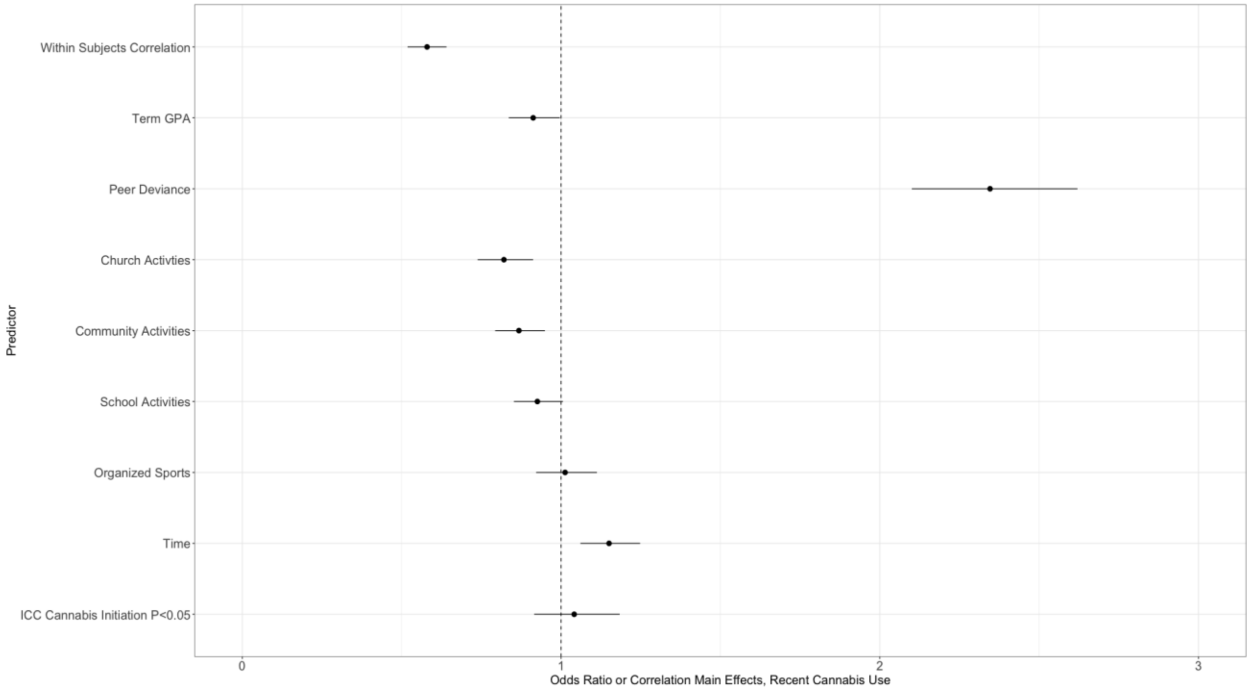


Figure 19

Two-way interaction effects of PRS and predictors on recent cannabis use using binary repeated logistic regression estimated by GEE in the EA subset after controlling for term GPA as a time-varying covariate

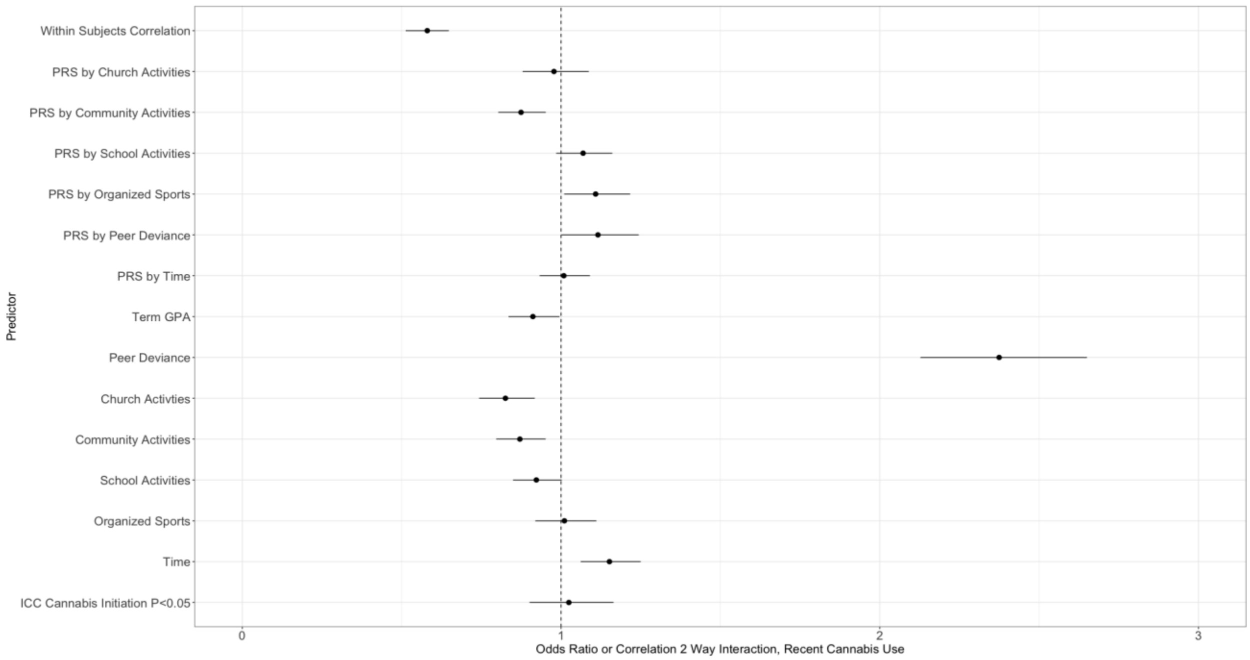


Figure 20

Three-way interaction effects of the PRS and predictors on recent cannabis use using binary repeated logistic regression estimated by GEE in the EA subset after controlling for term GPA as a time-varying covariate

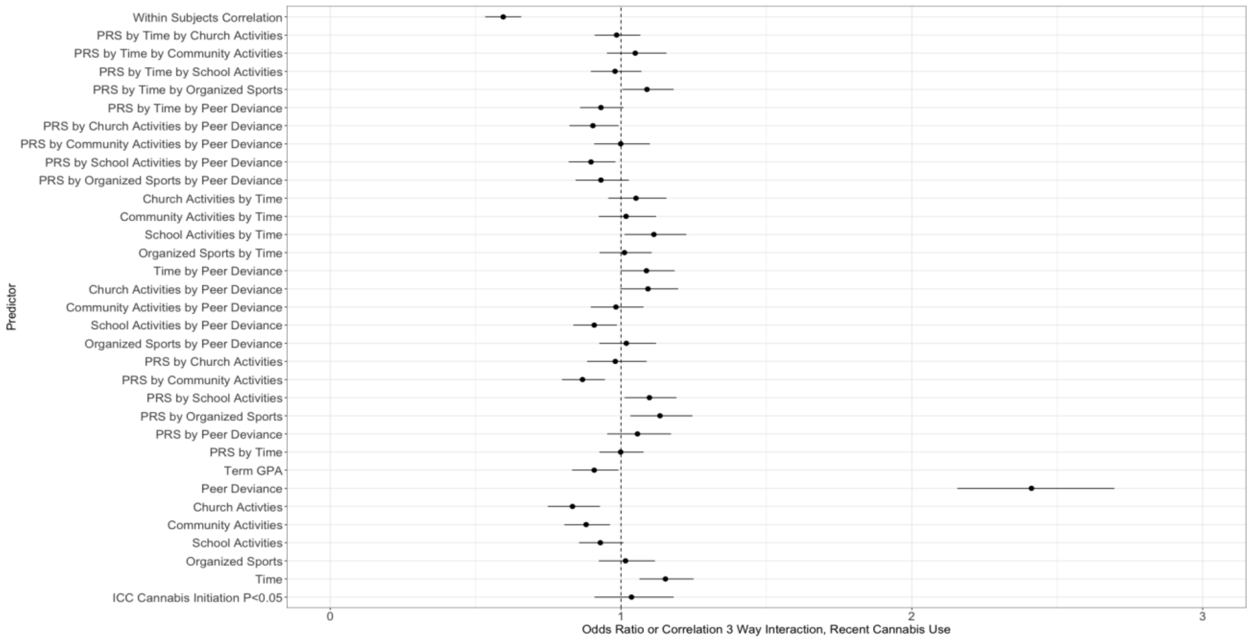


Figure 21

Main effects of the PRS and predictors on recent cannabis use using binary repeated logistic regression estimated by GEE in the AA subset after controlling for term GPA as a time-varying covariate

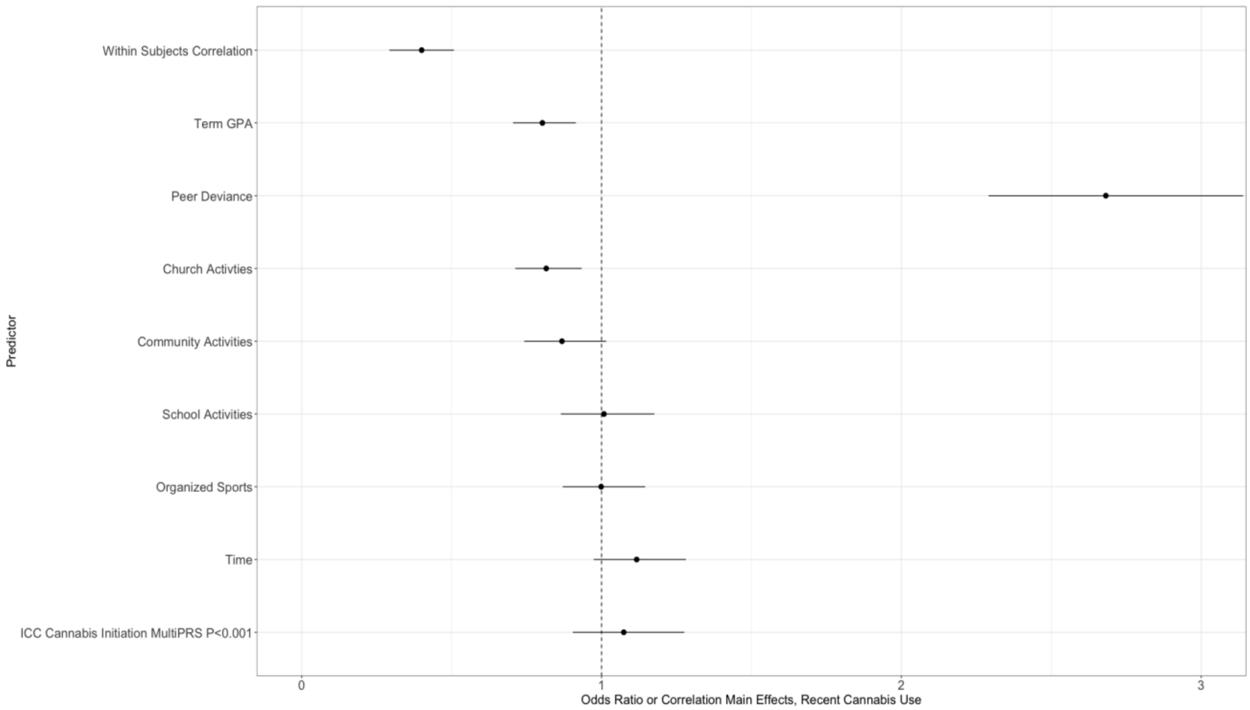


Figure 22

Two-way interaction effects of PRS and predictors on recent cannabis use using binary repeated logistic regression estimated by GEE in the AA subset after controlling for term GPA as a time-varying covariate

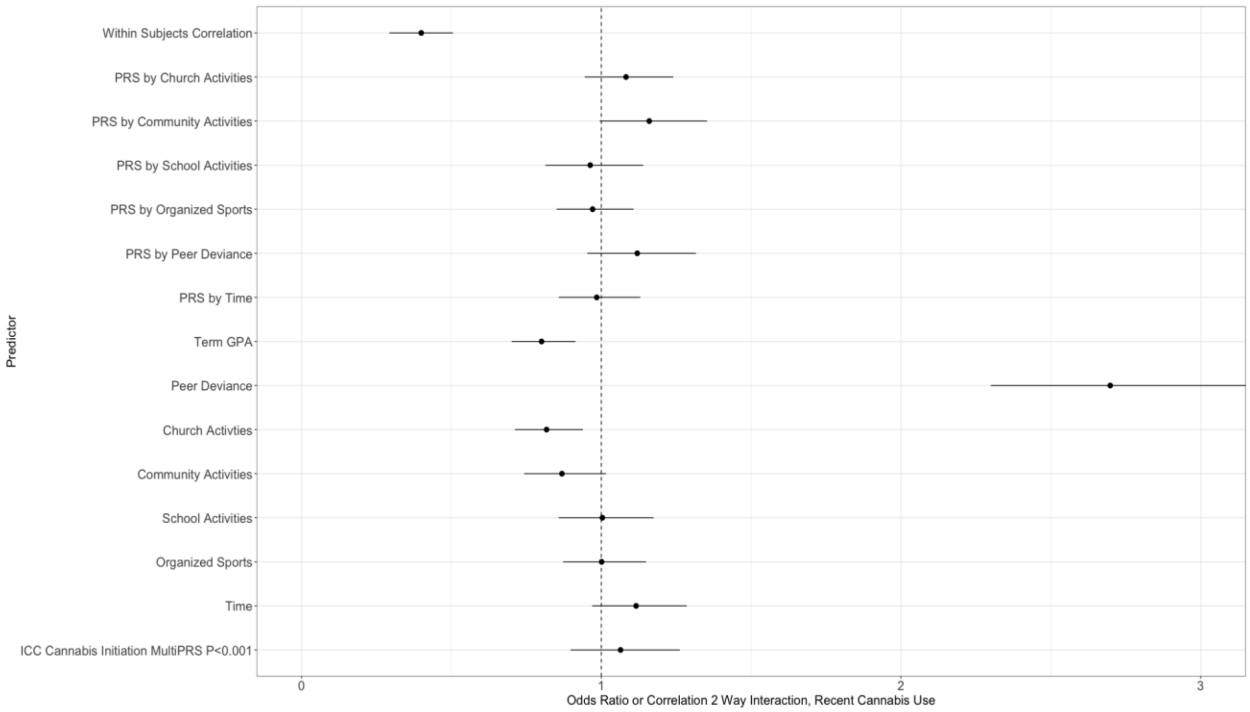


Figure 23

Three-way interaction effects of the PRS and predictors on recent cannabis use using binary repeated logistic regression estimated by GEE in the AA subset after controlling for term GPA as a time-varying covariate

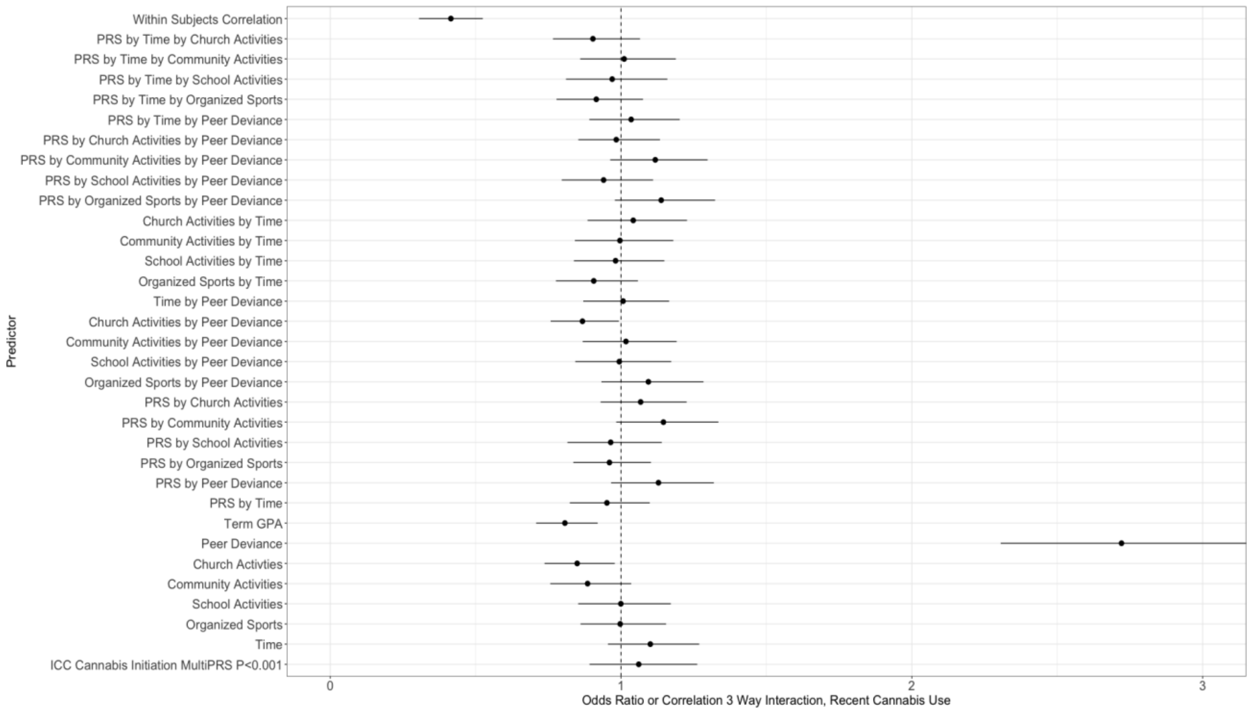


Figure 24

Estimates of observed power for the main effect of the PRS in EA and AA subset GEE Marginal Models

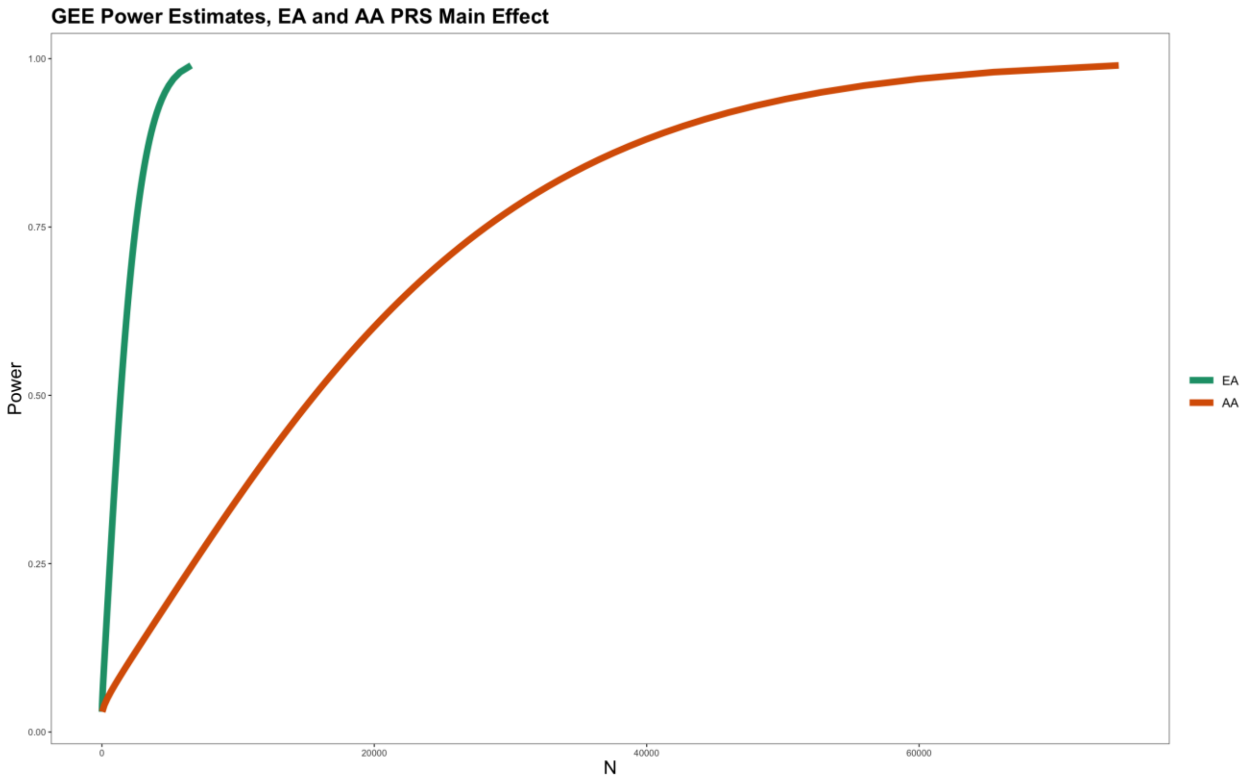


Figure 25

Power to detect the main effect of the PRS in the EA subset under various -fold increases of the effect size

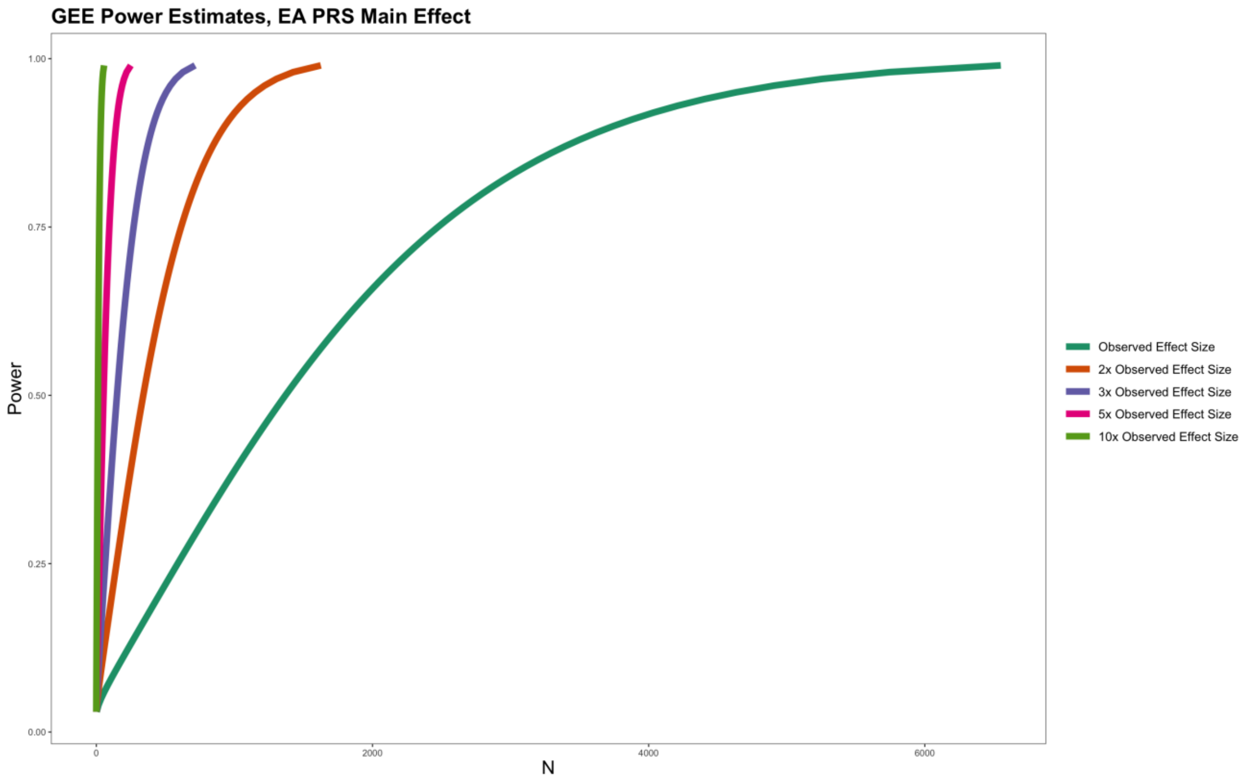
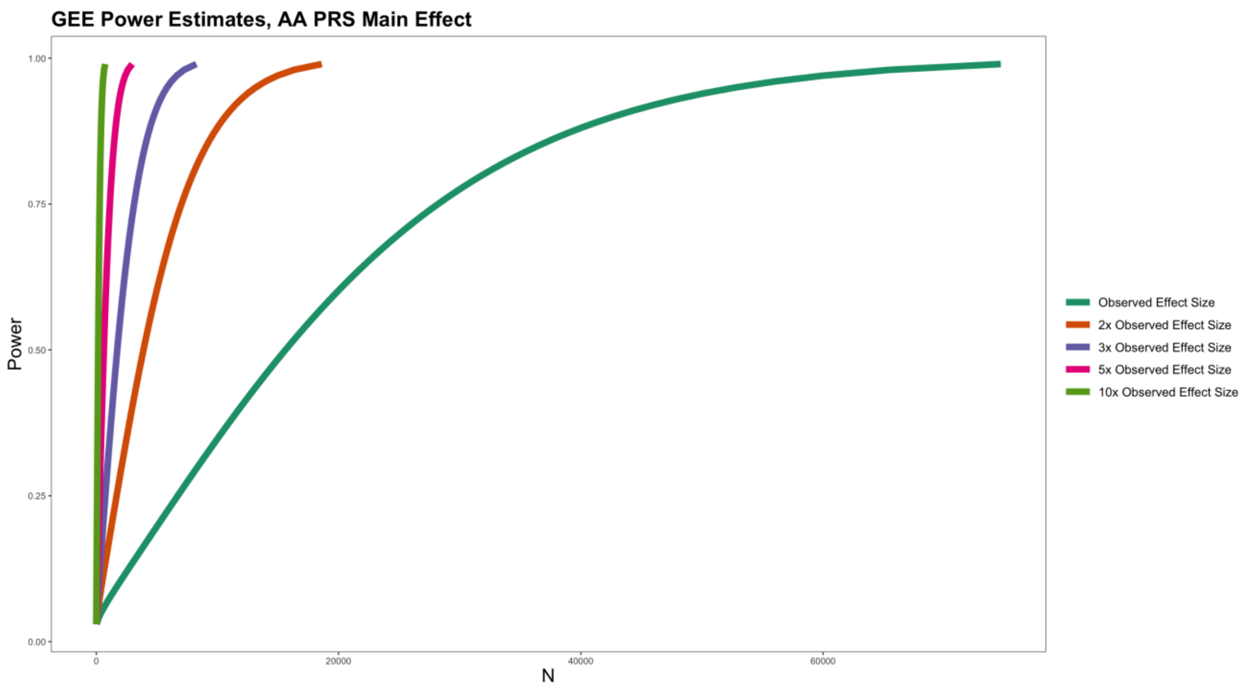


Figure 26

Power to detect the main effect of the PRS in the AA subset under various -fold increases of the effect size



Vita

Nathaniel Stembridge Thomas was born on September 5, 1993 in Maryland. He graduated from Centreville High School in Clifton, Virginia in 2011. He received his Bachelor of Science in Psychology from Virginia Commonwealth University in 2014 and his Master of Science in Addiction Studies in 2015, jointly conferred by Virginia Commonwealth University, King's College London, and The University Adelaide. After graduate school, he worked as a research assistant at the Examining, Development, Genes, and Environment lab at Virginia Commonwealth University. In 2018, Nate enrolled in Virginia Commonwealth University's Developmental Psychology PhD program.