Adolescent Behavioral Disinhibition and its Relationship to Marijuana Use Development

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Abstract

Behavioral disinhibition is a highly heritable risk factor for drug use, yet how it relates to marijuana use development is under-studied. We addressed this using independent twin samples from Colorado (N=2608) and Minnesota (N=3630), assessed from adolescence to early adulthood. We fit a biometric latent growth model of marijuana use using data from up to four waves of assessment between ages 14-24, to examine change in marijuana use and its relationship with a factor model of behavioral disinhibition. The factor structure of behavioral disinhibition, as well as its association with early marijuana use (r~.8) and increase in use (r~.3), was similar in both states. Early use was moderately heritable in both states. Increase in use was highly heritable in Minnesota ($h^2$ =.81) but not Colorado ($h^2$ =.14), and shared environmental effects were larger in Colorado ($c^2$=.53) than Minnesota ($c^2$=0). State differences in variance components could reflect state differences in culture or legal landscape. We found significant genetic correlations between disinhibition and early use in both states, as well as between disinhibition and increase in use in Minnesota ($r_g$=.37). Lastly, exploratory analyses in Minnesota indicate that marijuana use decreases across the late 20s. This decline is strongly heritable ($h^2$=.79) and moderately, negatively correlated with adolescent disinhibition (r=-.54). We conclude that adolescent behavioral disinhibition is positively related to early marijuana use and increase in use and negatively related to decrease in use in adulthood. This study broadens our understanding of adolescent risk and later marijuana use.

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# Chapter 1

## Introduction

The National Epidemiologic Survey on Alcohol and Related Conditions estimated that past-year prevalence of cannabis use disorder in the United States doubled from 2002 to 2013, consistent with comparable increases in marijuana use over that time (Hasin et al., 2015). Prevalence of marijuana use and cannabis use disorder was highest among adults age 18-29, with 21.2% reporting past-year marijuana use and 7.5% meeting criteria for past-year DSM-IV cannabis abuse or dependence. Given the changing cultural and legal landscape around marijuana use and the association between marijuana use and cultural attitudes towards use (see Cerdá et al., 2012, Hasin et al., 2017), studies of marijuana use development and its correlates are particularly timely.

Most individuals who use marijuana begin in mid- to late-adolescence (Richmond-Rakerd, Slutske, & Wood, 2017). Average use increases gradually until the mid-20s and declines thereafter. Many risk factors for marijuana experimentation and regular use have been documented, but few genetically informative studies have evaluated the etiological nature of these relationships during the transition from adolescence to adulthood. This is important, as the initiation of marijuana use, frequency of use, and problematic use are heritable (Verweij et al., 2010; Hines et al., 2018), and so the relationship between risk factors and marijuana use and development may be due to shared genetic influences.

A meta-analysis of 28 twin studies conducted by Verweij et al. (2010) indicated that marijuana use initiation was ~44% heritable, and problematic cannabis use was ~55% heritable. These marijuana use behaviors are genetically correlated at $r_g$~.62 (Gillespie, Neale, & Kendler, 2009), and show substantial genetic correlations with many other forms of substance use and dependence (Grant, et al., 2016; Kendler, Jacobson, Prescott, & Neale, 2003; Kendler, Schmitt, Aggen, & Prescott, 2010; Vrieze, Hicks, Iacono, & McGue, 2012). One explanation for such observed genetic correlation is that various manifestations of substance use, including different measures of use of the same substance (e.g., initiation and regular use) are each influenced by a more general genetic predisposition to what has variously been termed behavioral disinhibition and externalizing psychopathology in general, including substance misuse (Iacono, Malone, & McGue, 2008; Krueger et al., 2002; Young, et al., 2000, Vanyukov et al., 2012).

Highly disinhibited Individuals are characterized by the tendency to act impulsively and seek reward without considering consequences (Vanyukov et al., 2012). Confirmatory factor models support the notion that underlying these behaviors is a highly heritable ($h^2$~80%) latent factor, on which measures of externalizing psychopathology including symptoms of substance dependence, antisocial behavior, and personality measures of low impulse control load strongly (Young et al., 2000; Kendler et al., 2003a; Krueger et al., 2002; Hicks, et al., 2011). A key aspect of this formulation is that the liability to substance use conferred by behavioral disinhibition increases risk for all drugs, rather than for one specific drug over another (Iacono, Malone, & McGue, 2008; Hicks et al., 2004; Kendler et al., 2003b). Thus, this general liability accounts for the observed comorbidity among forms of substance use and comorbidity between substance use/dependence and other externalizing disorders.

Behavioral disinhibition predicts a wide variety of substance use measures, including age of initiation, experimentation, regular use, and dependence (McGue, Irons, and Iacono, 2015; Sousa et al., 2011; Palmer et al., 2013; Iacono et al., 1999; Prisciandaro et al., 2012; King et al., 2004). For example, behavioral disinhibition is associated with both adolescent onset of alcohol use disorder and alcohol use disorder with persistent course. (McGue, Iacono, Legrand, Malone, & Elkins, 2001; Hicks, Iacono, & McGue, 2010). Conduct disorder, another indicator of behavioral disinhibition, predicts alcohol, marijuana, and cigarette initiation and subsequent use (Sibley et al., 2014). Furthermore, rule breaking and aggression were associated with increased probability of marijuana use and increased frequency of use among users (Colder et al., 2018).

While associations between substance initiation, later use, and behavioral disinhibition have been robustly and replicably documented, none have examined the relationship between externalizing or behavioral disinhibition and development and change in frequency of marijuana use during adolescence and young adulthood in genetically informative samples. For example, the relationship of childhood ADHD (a commonly used indicator of behavioral disinhibition) to frequent marijuana use during adolescence, appeared due to shared familial environment and genetic effects, rather than a causal influence of ADHD (Elkins, Saunders, Malone, Keyes, McGue, & Iacono, 2018). Moreover, lifetime cannabis use has been genetically correlated with antisocial behavior at $r_g$~.69 (Tielbeek, Vink, Polderman, Popma, Posthuma, & Verweij, 2018). To the extent that behavioral disinhibition is a highly heritable vulnerability, genetically informed studies are essential to understand the nature of this construct and how it may be related to marijuana use over time.

To evaluate these questions, we leveraged two large twin samples, one from Colorado and one from Minnesota. We were able to replicate findings and evaluate the similarity of results across these independent studies. We evaluated measurement invariance of a behavioral disinhibition factor in adolescence and tested whether it predicted marijuana use frequency spanning adolescence to early adulthood. We evaluated the equivalence of the relationship between behavioral disinhibition and marijuana use development between the two samples. Lastly, we evaluated the decline in marijuana use across early adulthood and examined how behavioral disinhibition may relate to desistance of use.

# Chapter 2

## Method

### *Participants*

Twin participants from both states were initially assessed in adolescence and were followed through early adulthood. Colorado participants were recruited through the Colorado Twin Registry and assessed as part of the Center for Antisocial Drug Dependence (CADD; see Rhea et al., 2006, and Rhea et al., 2013). There were 2608 individuals from 1442 twin pairs: 699 monozygotic (MZ) pairs and 468 same-sex dizygotic (DZ) pairs and 275 opposite-sex dizygotic pairs. To help ensure comparability with Minnesota, which recruited only same-sex dizygotic twins, one twin from each opposite sex pair was randomly selected for inclusion and their co-twin's data were set to missing. Opposite-sex twins therefore contributed information to estimates of means and variances, but not biometric variance decompositions. 84.7 of Colorado twins self-reported as white, 9.5% reported as non-black Hispanic, and the remaining 5.8% as other. DNA was collected from twins seen in-person and zygosity confirmed by DNA testing (Rhea et al., 2006).

Minnesota participants were recruited and assessed through the Minnesota Twin Family Study. There were 3630 participants from 1815 twin pairs: 1163 monozygotic (MZ) pairs and 652 same-sex dizygotic (DZ) pairs. Ethnicity in Minnesota was determined via parent-report or birth-record report. About 8% more twins were reported as white in Minnesota (94.4%) versus Colorado (86.4%). 1.3% of Minnesota twins reported as Hispanic and the remaining 4.3% as other. Serological analyses were conducted in instances where initial estimates of zygosity were not in agreement. Most Minnesota twins were also evaluated with genome-wide genotyping (Miller et al., 2012).

*Wave Structure*

The present study utilizes data from five waves of assessment in Minnesota and 3 in Colorado. In Minnesota, participants were assessed at target ages of 14, 17, 20, 24, and 29, and exact ages of assessment are tightly clustered around the target age. Participation in particular assessments depends on recruitment cohort (see Iacono and McGue, 2002; Keyes et al., 2009, for additional details).  In Colorado, participants were assessed approximately every five years, with age at intake ranging from 11-19 years, for a total of three waves of assessment.

*Measures of Behavioral Disinhibition*

We selected three indicators of behavioral disinhibition. Indicators were chosen to maximize similarity between Colorado and Minnesota in both measure content and age of assessment. We selected alcohol dependence symptoms, conduct disorder, and ADHD. For alcohol dependence and conduct disorder, we chose the assessment closest to age 17, excluding assessments earlier than age 15 and after age 21. This not only helped maximize sample size and ensure that the age distribution between Minnesota and Colorado were as similar as possible, but also avoided age effects in Colorado from the inclusion of individuals who have had different opportunities to use alcohol (participants younger than 15 may have had limited opportunity, participants over 21 have legal access to alcohol). Lastly, this age window ensured that participants were past the reporting period for conduct disorder and minimizes recall bias, as diagnostic criteria in DSM-IIIR and DSM-IV require that symptoms must be present by age 15. For ADHD, we used the youngest available assessment in both Colorado and Minnesota to minimize the effects of recall bias, as diagnostic criteria in DSM-IIIR and DSM-IV require that at least some ADHD symptoms must appear before age 7.

To evaluate alcohol dependence, twins in both Colorado and Minnesota were administered an adapted version of the Composite International Diagnostic Instrument-Substance Abuse Module (CIDI-SAM; Cottler, 2000). Lifetime conduct disorder symptoms were assessed through self-report in Minnesota using a modified section from the Structured Clinical Interview for DSM-III-R Personality Disorders (SCID-II; Spitzer et al., 1987). For conduct disorder in Minnesota, the Enrichment Sample (approximately 26% of the total Minnesota sample) was not assessed comparably (in terms of reporting period) to Colorado and the other Minnesota twins, they were therefore set to missing. In Colorado, conduct disorder was assessed through self-report using the Diagnostic Interview Schedule (DIS; Robins et al., 2000) or Diagnostic Interview Schedule for Children (DISC; Shaffer et al., 2000), depending on participant age. In Minnesota, Attention Deficit Hyperactivity Disorder (ADHD) was assessed using the Diagnostic Interview for Children and Adolescents-Revised (DICA–R, Reich, 2000). In Colorado, ADHD was assessed using the DISC.

The measures used to evaluate disorder symptoms were based on DSM-IIIR in Minnesota, and DSM-IV in Colorado, which are largely but not perfectly similar. Differences between versions of the DSM necessitated phenotype harmonization between the two samples. Prior to any analysis of data, we reviewed the symptoms of each disorder in each diagnostic system, removing symptoms specific to one system or the other. Retained and excluded symptoms are presented in Supplemental Table 1. Retained symptoms were used to calculate symptom counts for analysis (13 symptoms for ADHD, 9 for alcohol dependence, and 12 for conduct disorder).

*Marijuana Frequency Measures*

We utilized marijuana use frequency data from all waves of assessment in each state (e.g. waves 1, 2, and 3 in Colorado, waves 14, 17, 20, 24, and 29 in Minnesota). Marijuana use frequency was assessed in Colorado as the number of days in the last 180 days a participant used marijuana. In Minnesota, use frequency was assessed as average frequency of use in the last 12 months as: never, less than once a year, less than once a month but at least once a year, about once a month, 2 or 3 times a month, 1 or 2 times a week, 3 to 4 times a week, nearly every day, and daily. We combined the categories "never" and "less than once a year" into one category corresponding to "did not use in the last year". Responses were harmonized between cohorts by recoding values in the Colorado data from exact number of days in last 180 to match the ordinal categories used in Minnesota. Colorado participants who had reported no lifetime use or no use in the reporting window received the equivalent of a Minnesota value "did not use in the last year". For those Colorado participants who did report using marijuana in the last 180 days the conversion to Minnesota values are as follows: 1-3 days corresponds to "less than once a month but at least once a year", 4-6 days corresponds to "about once a month", 7-19 days corresponds to "2 or 3 times a month", 20-54 days corresponds to "1 or 2 times a week", 55-99 days corresponds to "3 or 4 times a week", 100-179 days corresponds to "nearly every day", and 180 days corresponds to "daily". The correlation between raw continuous and rescaled ordinal scores in Colorado was .892 (95% CI [.885, .899].

*Descriptives*

Tests of mean differences accounted for the nested structure of the twin data by fitting an ACE decomposition twin model for each group and estimating the mean of each group, then comparing the fit between a model in which the group means were free to vary against a model in which the group means were constrained to be the same. We compared means for all behavioral and drug measures between gender within each state (i.e., Minnesota males to Minnesota females and Colorado males to Colorado females) and within gender between each state (i.e., Minnesota males to Colorado males and Minnesota females to Colorado females). Heritability estimates for alcohol dependence, ADHD, and conduct disorder were estimated with a biometric variance decomposition for each trait in each state (Martin and Eaves, 1977).

*Measurement Invariance of Adolescent Behavioral Disinhibition*

Behavioral disinhibition was modeled in a confirmatory factor model on which symptom counts of alcohol dependence, ADHD, and conduct disorder load. This model is consistent with prior work (e.g., see Krueger et al, 2002, Young et al., 2000) but does not use identical indicators because the present models were selected to maximize content similarity between states. Symptom counts were residualized within each state by age, $age^2$, age × cohort, cohort, and sex. Age and $age^2$ were included as covariates to control for the age ranges we have for our participants. Age × cohort, where cohort refers to two distinct recruitment efforts within the Colorado sample and three within the Minnesota sample, was included as a covariate to control for potential differences due to recruitment cohort (see Iacono and McGue, 2002; Keyes et al., 2009; Rhea et al., 2006; Rhea et al., 2013 for additional details regarding the cohort structure of each study). Models were fit using OpenMx v2.6.9 (Boker et al., 2011; Neale et al., 2016). We used a standard biometric variance decomposition within a common pathway model to estimate the genetic (A), shared environmental (C), and unique environmental (E) variance components of the common and specific factors extracted from alcohol dependence, ADHD, and conduct disorder. To evaluate fit, the common pathway model was compared to a saturated model using likelihood ratio tests, the Akaike/Bayesian Information Criteria (AIC/BIC; Vrieze, 2012), and the root mean square error of approximation (RMSEA; Hu & Bentler, 1999).

We conducted tests of measurement invariance across the two samples (Meredith, 1993) including: invariance of standardized loading patterns (often termed configural invariance), weak factorial invariance to test whether standardized loadings are equivalent, strong factorial invariance of unstandardized loadings, and strict factorial invariance of unstandardized loadings and specific factors. For any invariance test passed, we further restricted the variance decomposition of the common factor to be equivalent across the two samples, something we term here "biometric" invariance.

*Modeling the Development of Marijuana Use Across Adolescence and Early Adulthood*

We used latent growth-curve modeling to examine marijuana use development. The number of available waves of assessment across the two studies allowed for modeling initiation of use and the linear increase in use across adolescence between ages 14 to 24; all assessments between these ages were included in the model. We chose 24 as our maximum age because marijuana use is known to decrease on average during the mid-to-late 20s. Indeed, in these samples, actual use was maximized at age 22, but there are few observations taken at exactly this age. A generalized additive mixed model was fit to the data to evaluate evidence for nonlinear trends (Lin & Zhang, 1999) and this predicted curve indicates decline in use in the mid 20s as well. To maximize the number of observations and waves of assessment yet maintain close proximity to the age of maximum use, we chose to use assessments up to age 24. We estimated a latent intercept, which represents the expected use at initiation, and a latent slope, which represents average increase in use across adolescence. We centered the intercept at 16.5 as that is the mean age of marijuana use initiation in our samples. Participants' exact ages at assessment were used to allow for individually-varying factor loadings from the latent slope to each observed marijuana variable, termed definition variables in OpenMx. Both the latent intercept and slope were regressed on sex; age was accounted for via the individually-varying time metric. The latent intercept and slope were allowed to correlate, via a Cholesky decomposition, with the latent behavioral disinhibition phenotype in order to examine the relationship between premorbid general risk and marijuana initiation and increase in use.

We used a standard biometric variance decomposition within the latent growth model to estimate the genetic (A), shared environmental (C), and unique environmental (E) variance components of the latent intercept and slope as well as the specific factors extracted from the marijuana variables. Global fit indices are not available when evaluating models with individually-varying time metrics (Grimm, Ram, & Estabrook, 2017; Sterba, 2014) therefore, to evaluate relative fit the latent growth model was compared to an intercept-only alternative model using difference in log-likelihood, AIC, and BIC. We conducted tests of equivalence of the mean and variance of the slope and intercept, as well as correlations between all latent factors, across the two samples. Tests of statistical significance were conducted by constraining the parameter of interest to 0 and using a likelihood ratio test to compare the constrained model to a model in which the parameter was freely estimated.

*Decline in Use Across Early Adulthood*

In an exploratory analysis, we modeled decline in marijuana use in the Minnesota sample. We consider this analysis exploratory in the present context only because the Colorado sample did not have sufficient numbers of assessment waves to support non-linear growth. To model decline in use we employed a piecewise model, in which the intercept and ascending slope were modeled from 14-24 as described above, and the decline in use was modeled across ages 25 through early 30s.The descending slope was free to correlate with behavioral disinhibition and the intercept and adolescent slope. We decomposed the variance in all latent factors into genetic, shared environmental, and unique environmental components. We evaluated relative fit by comparing the piecewise latent growth model to alternative intercept-only and linear models using log-likelihood, AIC, and BIC.

Chapter 3

Results

*Descriptive Statistics*

Table 3.1 contains descriptive statistics for the behavioral disinhibition indicators, including average age at assessment, sample size, and mean and standard deviation of all symptom counts. Descriptives are split by measure, state, and sex.

| **Meas.** | Sex | State | N | Mean age at assessment (SD) | MZ | DZ | Mean Symptom Count (SD) [residualized SD] | Test of between state difs. $\chi^2$ (p) | Test of between gender difs. $\chi^2$ (p) |
|---|---|---|---|---|---|---|---|---|---|
| **ADHD** | M | MN | 1730 | 13.6 (2.7) | 1118 | 612 | 1.39 (1.98) [0.67] | 2.3 (.13) | 57.2 (< .001) |
| | | CO | 1167 | 14.9 (2.2) | 594 | 573 | 1.25 (2.38) [0.71] | | 10.7 (.001) |
| | F | MN | 1867 | 13.8 (2.8) | 1185 | 682 | 0.87 (1.59) [0.58] | 0.5 (.48) | |
| | | CO | 1310 | 15.0 (2.2) | 723 | 587 | 0.94 (1.99) [0.63] | | |
| **Alcohol Dep.** | M | MN | 1628 | 17.5 (0.6) | 1042 | 586 | 0.65 (1.44) [0.54] | 6.3 (.01) | 42.6 (< .001) |
| | | CO | 1012 | 18.0 (1.6) | 521 | 491 | 0.83 (1.53) [0.56] | | 10.6 (.001) |
| | F | MN | 1771 | 17.6 (0.7) | 1137 | 634 | 0.31 (1.05) [0.40] | 28.4 (< .001) | |
| | | CO | 1175 | 18.1 (1.7) | 649 | 526 | 0.60 (1.30) [0.52] | | |
| **Con. Dis.** | M | MN | 1165 | 17.5 (0.6) | 776 | 389 | 1.12 (1.58) [0.61] | 1.4 (.24) | 180.4 (< .001) |
| | | CO | 1012 | 18.1 (1.5) | 522 | 490 | 1.21 (1.43) [0.57] | | 74.3 (.001) |
| | F | MN | 1308 | 17.6 (0.7) | 842 | 466 | 0.27 (0.73) [0.36] | 74.7 (< .001) | |
| | | CO | 1177 | 18.3 (1.6) | 650 | 527 | 0.63 (0.96) [0.47] | | |

Table 3.1: Descriptive Statistics. N, MZ, and DZ columns refer to number of individuals, not number of twin pairs. Meas. = Measure; ADHD=Attention Deficit Hyperactivity Disorder; Alcohol Dep. = Alcohol Dependence; Con. Dis. = Conduct Disorder; M=Male, F=Female; MZ=Monozygotic; DZ=Dizygotic; MN=Minnesota; CO=Colorado; SD=Standard Deviation. Residualized SD refers to the standard deviation of the residuals which were analyzed in the behavioral disinhibition factor model, symptom counts were regressed on age, $age^2$, age × cohort, cohort, and sex. Test of between state differences refers to testing equivalence of symptom count means in Colorado and Minnesota within each gender. Test of between gender differences refers to testing equivalence of symptom count means in males and females within each state.

Results of mean comparisons are presented in Table 3.1; we compared model fit as indexed by difference in log likelihood, which under the null hypothesis of equal means is distributed as $\chi^2$. Symptom counts did not differ significantly in Minnesota and Colorado for ADHD in males ($\chi^2$=2.3, df=1, p=.13) and females ($\chi^2$=.5, df=1, p=.48) and for conduct disorder in males ($\chi^2$=1.4, df=1, p=.24). All other comparisons (every measure split by sex) were significantly different between states at $p<.05$. When comparing males to females within each state, males had higher raw scores than females on ADHD, alcohol dependence, and conduct disorder; $p<.05$ for all comparisons.

Table 3.2 presents the cross-twin cross-trait correlation matrix of the residualized symptom counts in Minnesota and Colorado. The diagonal of the table contains cross-twin within-trait correlations. Heritability, computed via a standard ACE biometric model, was .34 (95% confidence interval=[.19, .41]) in Colorado and .35 [.27, .40] in

Minnesota for ADHD, .29 [.13, .48] in Colorado and .56 [.48, .60] in Minnesota for alcohol dependence, .30 [0, .51] in Colorado and .15 [0, .35] in Minnesota for conduct disorder.

| | $ADHD_A$ | $AlcDep_A$ | $ConDis_A$ |
|---|---|---|---|
| | Colorado MZ | | |
| $ADHD_B$ | **.35*** | .14* | .23* |
| $AlcDep_B$ | .18* | **.53*** | .30* |
| $ConDis_B$ | .25* | .24* | **.48*** |
| | Colorado DZ | | |
| $ADHD_B$ | **.14*** | .11* | .17* |
| $AlcDep_B$ | .07 | **.38*** | .21* |
| $ConDis_B$ | .06 | .27* | **.32*** |
| | Minnesota MZ | | |
| $ADHD_B$ | **.35*** | .15* | .18* |
| $AlcDep_B$ | .17* | **.53*** | .28* |
| $ConDis_B$ | .21* | .31* | **.36*** |
| | Minnesota DZ | | |
| $ADHD_B$ | **.12*** | .16* | .19* |
| $AlcDep_B$ | .06 | **.26*** | .15* |
| $ConDis_B$ | .10* | .22* | **.33*** |

Table 3.2: Twin correlation matrices split by state and zygosity. Cross-twin within-trait correlations are bolded on the diagonal. Subscript of A refers to twin A and subscript of B refers to twin B within a twin pair. AlcDep is alcohol dependence, ConDis is conduct disorder, all other abbreviations same as in Table 3.1. * = $p<.05$

*Behavioral Disinhibition Latent Factor Modeling*

Single-latent-factor models were fitted to residualized symptom counts for alcohol dependence, ADHD, and conduct disorder. In Minnesota, among covariates, only sex was a significant predictor for alcohol dependence, ADHD, and conduct disorder. In Colorado, age, $age^{2,}$ and sex were significant predictors of alcohol dependence. Sex, project, and age × cohort were significant predictors of conduct disorder. Sex was the only significant predictor of ADHD. Results of these regressions are presented in Table A.2. Figure 3.1 shows the parameter estimates obtained for the common factor model fitted as a multi-group model to both states (with no parameter constraints between states). Overall, the model fit the data well ($\chi^2$=131.1, df=74, p=4.8×10$^{-5}$; RMSEA=.015; Model AIC=-8,071.8, Saturated Model AIC=-8.054.9; Model BIC=-107,242.3, Saturated Model BIC=-106,774.9). The values of the standardized loadings of the latent phenotype on each measure are remarkably similar between states and the pattern of loadings is the same, with conduct disorder loading the most strongly and ADHD the least.

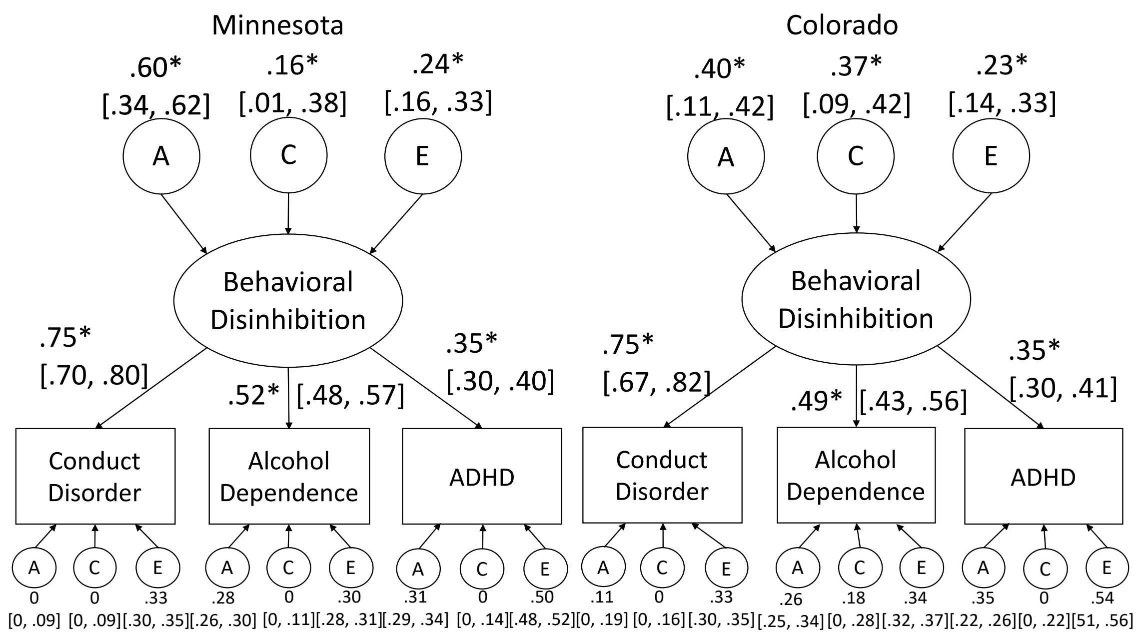


Figure 3.1: Loadings and biometric estimates for the common factor models fit to the Minnesota and Colorado behavioral data. All freely estimated parameters are shown. Those that could be set as invariant are denoted with an asterisk. Numbers in brackets represent 95% confidence intervals around the point estimates.

*Measurement Invariance of Adolescent Behavioral Disinhibition*

Configural measurement invariance holds in the model depicted in Figure 3.1, in that the pattern of standardized factor loadings is the same in each sample. Results of these tests are presented in Table 3.3; all models presented are compared to the unconstrained two-group model. For tests of weak, strong, biometric, and strict invariance, we found no decrement in fit for all models, except strict invariance ($\chi^2$=60.4, df=12, p=1.9×$10^{-8}$), which is evidence of no significant differences between states for the respective parameter estimates. Factor loadings (standardized and unstandardized) are invariant across Minnesota and Colorado (weak and strong invariance). The variance decomposition of the latent factor is also invariant across Minnesota and Colorado (biometric invariance). The only parameters that are not invariant are the residual variances for each indicator (strict invariance) These analyses suggest that strong and biometric measurement invariance holds between the two samples, which is reasonable evidence to support moving forward with behavioral disinhibition, as modeled here, in the analyses of between-state differences in marijuana use development over time.

| Model | -2LL | df | est. par. | AIC | BIC | $\chi^2$ | LRT | diff df | p |
|---|---|---|---|---|---|---|---|---|---|
| Base | 24,504.2 | 16,288 | 36 | -8,071.8 | -107,242.3 | 131.1 | - | - | - |
| Weak | 25,505.1 | 16,291 | 36 | -8,076.9 | -107,265.7 | 132.0 | 0.89 | 3 | .83 |
| Strong | 24,506.3 | 16,291 | 33 | -8,075.7 | -107.264.5 | 133.2 | 2.03 | 3 | .57 |
| Bio. | 24,505.8 | 16,291 | 33 | -8.076.2 | -107,264.9 | 132.8 | 1.61 | 3 | .66 |
| **Bio. and Strong** | **24,507.7** | **16,294** | **30** | **-8080.3** | **-107,287.3** | **134.7** | **3.51** | **6** | **.74** |
| Strict | 24,564.6 | 16,300 | 24 | -8.035.4 | -107,278.9 | 191.6 | 60.40 | 12 | 1.9 × $10^{-8}$ |

Table 3.3: Measurement invariance results for factor model of behavioral disinhibition. The base model is the single factor model. Biometric invariance constrains the factor variance components to be equivalent between states. -2LL = log likelihood; df = degrees of freedom for model; est. par. = Estimated Parameters; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; LRT = Likelihood Ratio Test, diff df= degrees of freedom for LRT. Best fitting model (by AIC and BIC) is bolded.

*Marijuana Use Development and Adolescent Behavioral Disinhibition*

We found that a linear growth model adequately described change in marijuana use frequency from age ~14 to 24 in Minnesota and Colorado as it fit better than the alternative intercept-only model (Linear model AIC=10,267.5, Alternative model AIC=11,744.2; Linear model BIC=-175,050.0, alternative model BIC=-173,262.8; Linear model log-likelihood=71,141.5, alternative model log-likelihood=72,516.2, difference in log-likelihood=1,374.7, difference in estimated parameters=22).

The mean intercept in Minnesota was .634 (95% CI=[.51, .72]) and in Colorado it was .828 [.64, 1.01]; this represents the expected marijuana use at age 16.5, which corresponds approximately to less than one use per month on the ordinal frequency scale. The variance of the intercept was .45 [.40, .50] in Minnesota and .42 [.35, .51] in Colorado. The mean slope was .205 [.17, .24] in Minnesota and .235 [.19, .28] in Colorado and the variance of the slope was .03 [.027, .035] in Minnesota and .02 [.013, .025] in Colorado. Figure 3.2 depicts the raw trajectories in each state as well as the generalized additive mixed model-predicted mean trajectory (with 95% confidence interval bands around the mean) for males and females.

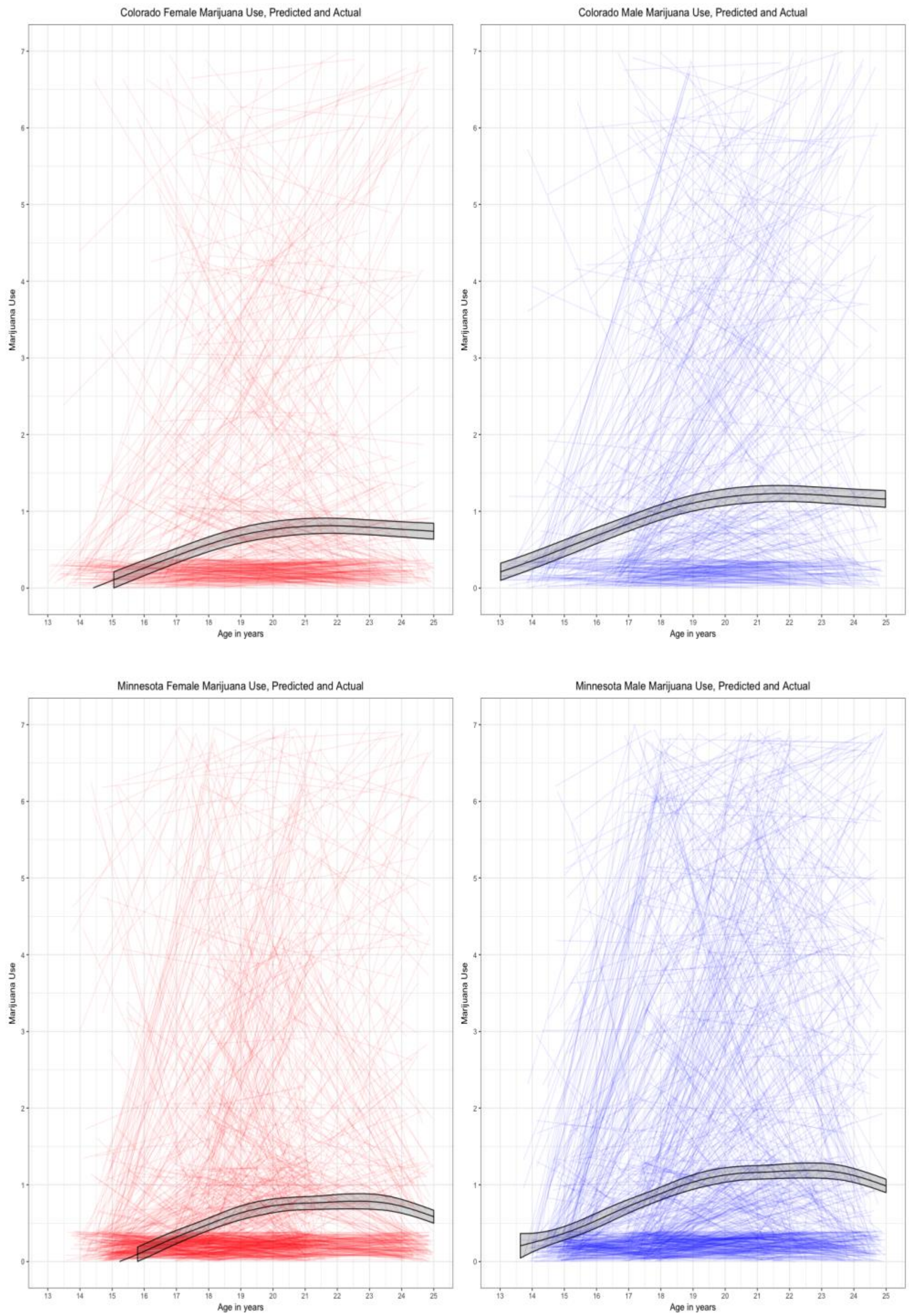

Figure 3.2: Individual level trajectories of marijuana use. Colored lines represent individual change in marijuana use, split by sex (red/left is female and blue/right is male) and by state (top is Colorado, bottom is Minnesota). Black lines are predicted mean marijuana use over time fitted via a generalized additive mixture model in each state. The shaded ribbon represents the 95% confidence interval around the predicted mean trajectory.

The mean of the intercept was not found to be different between states ($\chi^2$=2.96, df=1, p=.09). The variance of the intercept was not significantly different between states ($\chi^2$=.28, df=1, p=.60). The mean of the latent slope was also not significantly different between states ($\chi^2$=1.0, df=1, p=.32). The variance of the latent slope was significantly different between states ($\chi^2$=10.0, df=2, p=.002) with Minnesota having larger variance. Table 3.4 contains the biometric variance decomposition estimates for each latent factor as well as the corresponding significance test evaluating if each estimate is significantly different from 0.

| Parameter | Sample | Proportion of variance | [95% CI] | LRT | p |
|---|---|---|---|---|---|
| Behavioral Disinhibition $A^2$ | MN | .60 | [.40, .77] | 57.6 | $3.2\times10^{-14}$ |
| | CO | .38 | [.13, .71] | 14.9 | $1.2\times10^{-4}$ |
| Behavioral Disinhibition $C^2$ | MN | .17 | [.04, .34] | 9.5 | $2.1\times10^{-3}$ |
| | CO | .39 | [.10, .62] | 9.6 | $1.9\times10^{-3}$ |
| Behavioral Disinhibition $E^2$ | MN | .22 | [.15, .30] | 59.4 | $1.3\times10^{-14}$ |
| | CO | .22 | [.14, .31] | 29.2 | $6.6\times10^{-8}$ |
| Intercept $A^2$ | MN | .54 | [.37, .74] | 88.3 | $5.6\times10^{-21}$ |
| | CO | .41 | [.15, .69] | 16.4 | $5.3\times10^{-5}$ |
| Intercept $C^2$ | MN | .32 | [.13, .48] | 10.8 | $1.0\times10^{-3}$ |
| | CO | .48 | [.21, .73] | 15.6 | $7.7\times10^{-5}$ |
| Intercept $E^2$ | MN | .14 | [.10, .19] | 114.7 | $9.1\times10^{-27}$ |
| | CO | .11 | [.04, .20] | 12.9 | $3.3\times10^{-4}$ |

| | | | | | |
|---|---|---|---|---|---|
| Slope $A^2$ | MN | .81 | [.71, .89] | 95.6 | $3.1\times10^{-23}$ |
| | CO | .14 | [.01, .61] | 3.9 | $4.8\times10^{-2}$ |
| Slope $C^2$ | MN | 0 | [0, .06] | <.1 | $9.0\times10^{-1}$ |
| | CO | .53 | [.17, .84] | 9.8 | $1.8\times10^{-3}$ |
| Slope $E^2$ | MN | .19 | [.12, .27] | 63.1 | $2.0\times10^{-15}$ |
| | CO | .25 | [.08, .47] | 11.9 | $5.7\times10^{-4}$ |

Table 3.4: Biometric decomposition of linear growth model parameters. Parameter significance was obtained by estimating a base model in which all parameters were free to vary, then setting each parameter in turn to 0 and comparing the constrained model to the base model. LRT = Likelihood Ratio Test. All tests were 1 degree of freedom tests. 95% CI refers to the 95% confidence interval around the estimate.

A notable difference between Colorado and Minnesota is the biometric decomposition of the slope. The change in marijuana use is more heritable in Minnesota than in Colorado ($\chi^2$=7.5, df=1, p=.006). The shared environmental component of the change in marijuana use is larger in Colorado than Minnesota ($\chi^2$=8.6, df=1, p=.003).

All three latent factors were free to correlate, and we expected a correlation between behavioral disinhibition and the growth factors since behavioral disinhibition is a risk factor for substance initiation and it is related to young adult substance use. Phenotypic correlations are presented in Table 3.5. We found behavioral disinhibition was strongly correlated with use at age ~16 and moderately correlated with increase in use over time. The phenotypic correlations could be equated across states (behavioral disinhibition-intercept $\chi^2$=3.0, df=1, p=.08; behavioral disinhibition-slope $\chi^2$=.26, df=1, p=.61). Use at age ~16 and increase in use were also strongly correlated and the magnitude of correlation was larger in Colorado than Minnesota ($\chi^2$=5.3, df=1, p=.02).

We also decomposed the phenotypic correlations into genetic, shared environmental, and unique environmental components and these results are presented in Table 3.5. We found significant genetic and shared environmental correlations between adolescent behavioral disinhibition and the intercept in both states. We also found a significant genetic correlation between the intercept and slope in both states.

| | | BD-Intercept (p) | BD- Slope (p) | Intercept-Slope (p) |
|---|---|---|---|---|
| Phenotypic | MN | .854 ($1.0\times10^{-117}$) | .262 ($7.3\times10^{-12}$) | .621 ($1.2\times10^{-30}$) |
| | CO | .781 ($2.9\times10^{-43}$) | .296 ($8.9\times10^{-6}$) | .827 ($1.2\times10^{-15}$) |
| Genetic | MN | .890 ($5.8\times10^{-12}$) | .366 ($2.5\times10^{-5}$) | .751 ($4.6\times10^{-12}$) |
| | CO | .998 ($1.6\times10^{-4}$) | .986 (.12) | .995 ($4.8\times10^{-2}$) |
| Shared Environment | MN | 1 ($2.0\times10^{-3}$) | ---- | ---- |
| | CO | .780 ($2.1\times10^{-3}$) | .250 (.24) | .801 ($2.2\times10^{-3}$) |
| Unique Environment | MN | .645 ($3.9\times10^{-8}$) | .060 (.60) | .802 ($4.5\times10^{-8}$) |
| | CO | .276 (.14) | -.203 (.28) | .885 ($2.1\times10^{-3}$) |

Table 3.5: Phenotypic correlations and their decompositions. BD=Behavioral Disinhibition. In Minnesota, there is no C component of the slope so those correlations are not estimated. Note that genetic and environmental correlations are scaled according to the genetic and environmental variances.

*Tests in Minnesota of adolescent increase and adult decrease in marijuana use.*

A piecewise growth model was fit to the marijuana frequency data in Minnesota. The first piece was equivalent to the previously fit growth model, spanning ages 14-25 with the intercept centered at 16.5 The second piece spanned ages 25-33. The piecewise model fit better than the alternative intercept-only model (Piecewise model AIC=9,647.1, Alternative model AIC=11,980.0; Piecewise model BIC=-115,119.5, alternative model BIC=-112,924.2; Piecewise model log-likelihood=54,985.1, alternative model log-likelihood=57,368.0, difference in log-likelihood=2,382.9, difference in estimated parameters=25). The piecewise model also fit better than the alternative linear model (Piecewise model AIC=9,647.1, Alternative model AIC=10,569.8; Piecewise model BIC=-115,119.5, alternative model BIC=-114,273.9; Piecewise model log-likelihood=54,985.1, alternative model log-likelihood=55,935.8, difference in log-likelihood=-950.7, difference in estimated parameters=14).

The piecewise results regarding the intercept mean and variance, first slope mean and variance, and their relationships with behavioral disinhibition agree with the results from the multigroup linear group model. The mean of the second slope was -.147 [-.19, -.11] with variance .017 [.012, .023]. This indicates that on average, people decrease their marijuana use after age 25 into their late twenties and early thirties. The second slope variance was biometrically decomposed and we found additive genetic effects to account for 79% of the descending slope variance [.53, .95]. The shared environment accounted for 9%, though this point estimate was not significantly different from 0 ($\chi^2$=2.8, df=1, p=.09). The nonshared environment accounted for 12% of the variance in decline in use [.02, .28]. The correlation between behavioral disinhibition and the second slope was -.54 [.67, -.42], indicating that higher behavioral disinhibition is associated with smaller decreases in use in early adulthood. The correlation between the intercept and the second slope was -.77 [-.90, -.63] meaning that greater use at age 16.5 is associated with smaller decreases in use in early adulthood. The correlation between the first and second slopes was -.79 [-.88, -.68] meaning that greater increase in use across adolescence is associated with less decrease in use across young adulthood.

# Chapter 4

## Discussion

The present study evaluated adolescent behavioral disinhibition, and its prospective relationship with marijuana use development across adolescence through young adulthood. These relationships were evaluated in two independent longitudinal twin studies spanning ages 14 to 30, with 3+ waves of assessment. Our results provide evidence that adolescent behavioral disinhibition can be robustly and reliably measured in two large independent studies. Behavioral disinhibition is moderately heritable, in agreement with results of previous studies of these samples (see Young et al., 2000, 2009; Krueger et al., 2002; Hicks et al., 2004), and the magnitude of this heritability is the same in each state. The contributions of the shared and unique environments do not significantly differ across the states. Furthermore, the relationship between behavioral disinhibition and young-adult marijuana use is indistinguishably similar in both states. Establishing biometric invariance of adolescent behavioral disinhibition and its relationship with young adult marijuana use is critical in order to use the model in future analyses, such as the growth model presented here.

We found that there is little difference in the initial level of marijuana use (age ~16.5) and the rate at which individuals in Minnesota or Colorado increase their use from ages 14 to 25. The initial level of marijuana use was moderately heritable in both Minnesota ($h^2$=.54) and Colorado ($h^2$=.41). The shared environment also contributed to the initial level of marijuana use in Minnesota (C=.32) and Colorado (C=.48). This suggests that marijuana use at age 16.5 is moderately influenced by the family environment one grows up in, as well as other shared environmental influences such as neighborhood or peers. Our estimates for the biometric decomposition for the intercept agree with published biometric decomposition estimates of marijuana frequency at age 16-17 (Kendler, Schmitt, Aggen, & Prescott, 2008). While the variance in use at initiation was similar in magnitude and decomposition between states, there were a few notable significant differences in the variance in change in use. There was greater variance in increase in use in Minnesota compared to Colorado, although this may be due partly to the longer recall period for marijuana frequency measurements in Minnesota (12-month recall compared to 6-month recall in Colorado). The increase in marijuana use over time was also heritable in each state, though it was more heritable in Minnesota ($h^2$=.81) compared to Colorado ($h^2$=.14). Furthermore, the shared environment plays little role in the change in use in Minnesota, but plays a moderate role in change in use in Colorado ($c^2$=.53). Between-state differences in slope variance decomposition were statistically significant.

We speculate that the different cultures regarding marijuana use in Minnesota and Colorado could manifest as a shared environmental influence. While all the marijuana data presented here were collected prior to recreational cannabis legalization in 2014 in

Colorado, it is possible that legalization was preceded by longer-term changes in societal attitudes toward marijuana use. It may also be that these societal attitudes were less prominent in the early 2000s, about the time that the Colorado sample was ~16 years old, the age at which our intercept was centered. In the decade following year 2000, when the Colorado sample was aging into older adolescence and young adulthood, these societal attitudes toward marijuana matured, which may have occurred at the family level, where some families were sympathetic toward marijuana legalization while others were not. Medical marijuana legalization in Colorado also may have had an impact prior to 2014. Hasin et al. (2017) suggest that policy changes in 2009-2010 regarding medical marijuana may have influenced illicit marijuana use in the population. Judging by marijuana laws, no such societal attitudes have yet permeated Minnesota families to this extent. In this way, there may be more variation in the family marijuana environment in Colorado versus Minnesota. This would lead to a relatively smaller heritability and larger environmental effects. In the same vein, Legrand et al. (2007) demonstrated that major environmental factors, such as urban vs. rural rearing environment, can attenuate heritability; marijuana social norms and policy could be one such factor with regards to differences in heritability of the change in marijuana use in Colorado ($h^2$=.14) relative to Minnesota ($h^2$=.81).

Regardless of the etiological considerations, the increase in use over time was moderately correlated with behavioral disinhibition both states (Minnesota r=.26, Colorado r=.30). The results also indicate that behavioral disinhibition was strongly associated with initial level of use at age 16.5 (Minnesota r=.85, Colorado r=.78). These associations were not statistically different between the two states, indicating that the relationship between behavioral disinhibition and development of marijuana use is highly consistent across these studies. Decompositions of the phenotypic correlations show that significant genetic etiology is shared between the level of marijuana use at age 16.5 and change in marijuana use, as well as with behavioral disinhibition in adolescence. There was also significant shared influence of the rearing environment on level of marijuana use at ag 16.5 and behavioral disinhibition in adolescence in both states.

In addition, exploratory analyses in the Minnesota sample indicate that marijuana use decreases during the participants' late 20s and this decline is attributable to genetic ($h^2$=.79) and non-shared ($e^2$=.12) environmental influences. The decline is related to adolescent behavioral disinhibition (r=-.54), average marijuana use at age 16.5 (r=-.77), and increases in marijuana use during early adolescence (r=-.79).

Limitations of this study include a lack of racial diversity in both samples. While differences in study design between states could be considered a limitation, it is in many ways a strength. Our results show that our models are robust despite such differences, including mild differences in wave structure, age of assessment, and measures. An additional limitation is the ordinal measure of marijuana use, which may be less interpretable compared to truly quantitative alternatives. Further work could examine alternative conceptualizations of marijuana use, such as transitions between initiation, regular use, and problematic use, as previous research suggests there are shared and distinct genetic influences on initiation and problematic use (Verweij et al., 2010; Gillespie, Neale, & Kendler, 2009).

An additional limitation is the lack of longitudinal representation of behavioral disinhibition. Our indicators were measured once in mid-adolescence, intended to capture behavioral disinhibition in adolescence and the relationship between adolescent behavioral disinhibition and later substance use. Given that ADHD and conduct disorder symptoms must be present by adolescence, they are not well-suited as indicators in adulthood. Investigating adult behavioral disinhibition would necessitate the use of alternate indicators, such as antisocial personality disorder. We are unable to draw causal conclusions regarding this relationship, as it is possible that adolescent behavioral disinhibition precipitates a lifetime pattern of marijuana use, or that persistent behavioral disinhibition has an influence at each step of marijuana use development (initiation, increase to regular use, desistance of use). We are also unable to draw causal conclusions because early marijuana use and legal issues surrounding it could contaminate our risk indicators. Lastly, since many constructs exist under the umbrella term of externalizing psychopathology, our definition of behavioral disinhibition is one of several possible (see Derringer et al., 2015). We selected this definition to ensure comparable content and assessments in Colorado and Minnesota, but it is possible that results would differ if alternative indicators were used.

*Conclusions*

Adolescent behavioral disinhibition can be robustly and replicably represented as a confirmatory factor model. Adolescent behavioral disinhibition is related to expected use at age ~16.5 and the increase in use across adolescence and early adulthood. Exploratory analyses indicate that adolescent behavioral disinhibition is also related to the decline in marijuana use in adulthood. Additive-genetic effects explain much of the correlation between adolescent behavioral disinhibition and use at initiation and change in use. Differences in the biometric decomposition of the change in marijuana use highlight the importance of environmental context to heritability estimates.

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## Appendix

Table A1.1: List of retained and excluded symptoms from each diagnostic system for Attention Deficit Hyperactivity Disorder

| DSM-3R: Minnesota | DSM-IV: Colorado | **Status** |
|---|---|---|
| Often fidgets with hands or feet or squirms in seat (in adolescents, may be limited to subjective feelings of restlessness) | Often fidgets with hands or feet or squirms in seat | Retained |
| Has difficulty remaining seated when required to do so | Often leaves seat in classroom or in other situations in which remaining seated is expected | Retained |
| Is easily distracted by extraneous stimuli | Is often easily distracted by extraneous stimuli | Retained |
| Has difficulty awaiting turn in games or group situations | Often has difficulty awaiting turn | Retained |
| Often blurts out answers to questions before they have been completed | Often blurts out answers before questions have been completed | Retained |
| Has difficulty following through on instructions from others (not due to oppositional behavior or failure of comprehension), e.g., fails to finish chores. | Often does not follow through on instructions and fails to finish school-work, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions). | Retained |
| Has difficulty sustaining attention in tasks or play activities | Often has difficulty sustaining attention in tasks or play activities | Retained |
| Often shifts from one uncompleted activity to another | | Excluded |
| Has difficulty playing quietly | Often has difficulty playing or engaging in leisure activities quietly | Retained |
| Often talks excessively | Often talks excessively | Retained |
| Often interrupts or intrudes on others, e.g., butts into other children's games | Often interrupts or intrudes on others (e.g., butts into conversations or games | Retained |
| Often does not seem to listen to what is being said to him or her | Often does not seem to listen when spoken to directly | Retained |
| Often loses things necessary for tasks or activities at school or at home (e.g., toys, pencils, books, assignments) | Often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools) | Retained |
| Often engages in physically dangerous activities without considering possible consequences (not for the purpose of thrill-seeking), e.g., runs into street without looking | Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness) | Retained |
| | Often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities | Excluded |
| | Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework) | Excluded |
| | is often forgetful in daily activities | Excluded |
| | Is often "on the go" or often acts as if "driven by a motor" | Excluded |
| | Often has difficulty organizing tasks and activities | Excluded |

Table A1.2: List of retained and excluded symptoms from each diagnostic system for Conduct Disorder

| DSM-3R: Minnesota | DSM-IV: Colorado | Status |
|---|---|---|
| Has stolen without confrontation of a victim on more than one occasion (including forgery) | Has stolen items of nontrivial value without confronting a victim (e.g., shoplifting, but without breaking and entering; forgery) | Retained |
| Has run away from home overnight at least twice while living in parental or parental surrogate home (or once without returning) | Has run away from home overnight at least twice while living in parental or parental surrogate home (or once without returning for a lengthy period) | Retained |
| Often lies (other than to avoid physical or sexual abuse) | Often lies to obtain goods or favors or to avoid obligations (i.e., cons others) | Retained |
| Has deliberately engaged in fire-setting | Has deliberately engaged in fire setting with the intention of causing serious damage | Retained |
| Is often truant from school (for older person, absent from work) | Is often truant from school, beginning before age 13 years | Retained |
| Has broken into someone else's house, building, or car | Has broken into someone else's house, building, or car | Retained |
| Has deliberately destroyed others' property (other than by fire-setting) | Has deliberately destroyed others' property (other than by fire setting) | Retained |
| Has been physically cruel to animals | Has been physically cruel to animals | Retained |
| Has forced someone into sexual activity with him or her | Has forced someone into sexual activity | Excluded |
| Has used a weapon in more than one fight | Has used a weapon that can cause serious physical harm to others (e.g., a bat, brick, broken bottle, knife, gun) | Retained |
| Often initiates physical fights | Often initiates physical fights | Retained |
| Has stolen with confrontation of a victim (e.g., mugging, purse-snatching, extortion, armed robbery) | Has stolen while confronting a victim (e.g. mugging, purse snatching, extortion, armed robbery) | Retained |
| Has been physically cruel to people | Has been physically cruel to people | Retained |
| | Often bullies, threatens, or intimidates others | Excluded |
| | Often stays out at night despite parental prohibitions, beginning before age 13 years | Excluded |

Table A1.3: List of retained and excluded symptoms from each diagnostic system for Alcohol Dependence

| DSM-3R: Minnesota | DSM-IV: Colorado | Status |
|---|---|---|
| Substance often taken in larger amounts or over a longer period than the person intended | The substance is often taken in larger amounts or over a longer period than was intended | Retain |
| Persistent desire or one or more unsuccessful efforts to cut down or control substance use | There is a persistent desire or unsuccessful efforts to cut down or control substance use | Retain |
| A great deal of time spent in activities necessary to get the substance (e.g., theft), taking the substance (e.g., chain smoking), or recovering from its effects | A great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), use the substance (e.g., chain-smoking), or recover from its effects. | Retain |
| Frequent intoxication or withdrawal symptoms when expected to fulfill major role obligations at work, school, or home (e.g., does not go to work because hung over, goes to school or work "high," intoxicated while taking care of his or her children). | Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; neglect of children or household | Retain |
| Frequent intoxication or withdrawal symptoms when substance use is physically hazardous (e.g., drives when intoxicated). | Recurrent substance use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by substance use) | Retain |
| Important social, occupational, or recreational activities given up or reduced because of substance use | Important social, occupational, or recreational activities are given up or reduced because of substance use | Retain |
| Continued substance use despite knowledge of having a persistent or recurrent social, psychological, or physical problem that is caused or exacerbated by the use of the substance (e.g., keeps using heroin despite family arguments about it, cocaine-induced depression, or having an ulcer made worse by drinking) | The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., current cocaine use despite recognition of cocaine-induced depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption). | Retain |
| Marked tolerance: need for markedly increased amounts of the substance (i.e., at least a 50% increase) in order to achieve intoxication or desired effect, or markedly diminished effect with continued use of the same amount | Tolerance, as defined by either of the following: (a) a need for markedly increased amounts of the substance to achieve intoxication or desired effect (b) markedly diminished effect with continued use of the same amount of the substance. | Retain |
| Characteristic withdrawal symptoms (see specific withdrawal syndromes under Psychoactive Substance-induced Organic Mental Disorders) or substance often taken to relieve or avoid withdrawal symptoms | Withdrawal, as manifested by either a) the characteristic withdrawal syndrome for the substance (refer to Criteria A and B of the criteria sets for Withdrawal from the specific substances) or b) the same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms | Retain |
| | Recurrent substance-related legal problems (e.g., arrests for substance-related disorderly conduct | Exclude |
| | Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g., arguments with spouse about consequences of intoxication, physical fights) | Exclude |

Table A2: Results of regressions to residualized behavioral disinhibition indicator symptom counts before analyses

| Minnesota | | | | | |
|---|---|---|---|---|---|
| Phenotype | Predictor | β | Std. Error | t | p |
| ADHD | Sex | -.206 | .02 | -9.69 | $1.0\times10^{-16}$ |
| | Cohort (17) | -5.645 | 9.0 | -.63 | .53 |
| | Cohort (ES) | -.496 | .82 | -.61 | .55 |
| | Age | 1.040 | 1.22 | .85 | .39 |
| | $Age^2$ | -.044 | .05 | -.84 | .40 |
| | Age:Cohort (17) | .415 | .62 | .68 | .50 |
| | Age:Cohort (ES) | .063 | .07 | .91 | .36 |
| Conduct Disorder | Sex | -.398 | .02 | -19.94 | $1.0\times10^{-16}$ |
| | Cohort (17) | -.327 | .65 | -.50 | .62 |
| | Age | -.975 | .60 | -1.64 | .10 |
| | $Age^2$ | .028 | .02 | 1.70 | .09 |
| | Age:Cohort (17) | .024 | .04 | .63 | .53 |
| Alcohol Dependence | Sex | -.161 | .02 | -9.81 | $1.0\times10^{-16}$ |
| | Cohort (17) | .136 | .63 | .22 | .83 |
| | Cohort (ES) | -1.091 | .60 | -1.83 | .07 |
| | Age | -.822 | .53 | -1.55 | .12 |
| | $Age^2$ | .026 | .01 | 1.74 | .08 |
| | Age:Cohort (17) | -.007 | .04 | -.21 | .84 |
| | Age:Cohort(ES) | .060 | .03 | 1.75 | .08 |
| Colorado | | | | | |
| Phenotype | Predictor | β | Std. Error | t | p |
| ADHD | Sex | .109 | .03 | 4.21 | $2.6\times10^{-5}$ |
| | Cohort | -.033 | 1.00 | -.03 | .97 |
| | Age | -.036 | .18 | -.20 | .84 |
| | $Age^2$ | .002 | .01 | .43 | .67 |
| | Age:Cohort | -.003 | .08 | -.04 | .97 |
| Conduct Disorder | Sex | .243 | .02 | 11.48 | $1.0\times10^{-16}$ |
| | Cohort | -2.252 | .65 | -3.48 | $5.2\times10^{-4}$ |
| | Age | .750 | .26 | 2.93 | $3.5\times10^{-3}$ |
| | $Age^2$ | -.021 | .01 | -3.11 | $2.0\times10^{-3}$ |
| | Age:Cohort | .122 | .04 | 3.26 | $1.2\times10^{-3}$ |
| Alcohol Dependence | Sex | .120 | .02 | 5.42 | $6.5\times10^{-8}$ |
| | Cohort | -1.476 | .67 | -2.21 | .03 |
| | Age | .049 | .27 | .18 | .85 |
| | $Age^2$ | .002 | .01 | .23 | .82 |
| | Age:Cohort | .085 | .04 | 2.19 | .03 |

Note: For Colorado regressions, the Community Twin Sample was the reference cohort and the Longitudinal Twin Sample was the comparison cohort. For Minnesota regressions, the sample recruited at age 11 was the reference cohort and the samples recruited at age 17 and the Enrichment Study sample were the comparison cohorts (abbreviated as 17 and ES in table). Enrichment Sample twins conduct disorder symptoms were excluded from analysis.