of dependence for ten drug classes collected using the CIDI-SAM were combined into ten variants of a multiple substance dependence composite. Data were collected from 2792 adolescents and young adults between the ages of 11 and 26 in three community samples, consisting of twins and their siblings and matched nonadoptees, and a sample of adolescents and sollings selected as controls to a population of adolescents in each of the ten Dependence Vulnerability of COIOTALO, BOUIDET

Figure 4 shows the corresponding data for one of the Dependence Vulnerability of Contribution to the (genetically identical other full siblings), a contribution to the (genetically identical other full siblings), a and alcohol.

Analyses and Results, Continued

Analyses and Results, continued

Analyses and Results, continued over this age range, the number of substances tried to criterion increased other full siblings), a and alcohol.

Measure 3: The sum of symptoms across nine drug classes, excluding tobacco.

Analyses and Results, Continued

Analyses and Results, Continued

Table 1 shows the variance in each of the ten Dependence Vulnerability which non-genetic shithese measures. dependence. Each measure was gender- and age-corrected within the combined more for others). dependence composite that emphasizes depth is a better choice for QTL analysis.

Revisions to abstract: We are now using DSM-IV scoring for symptom Measure 8: The number of substance classes with at least one dependence counts and have increased our sample of adolescents and young adults to a total

## The Colorado Center on Antisocial Drug Dependence is a collaboration

between researchers at the University of Colorado at Boulder, and the University

of Colorado's Health Science Center in Denver. Clinical probands at residential dependence and antisocial personality/conduct disorder suggests the possibility of an underlying genetic vulnerability. A primary goal of the collaborative Center is to use data from genetically-informative unselected community samples to guide selection of phenotypes prior to genetic analyses using a selected sample. Crowley, Mikulich, Ehlers, Whitmore, & MacDonald (2001) have demonstrated that a substance dependence measure combined across substances strongly discriminates adolescent patients from community controls. The purpose of this presentation is to explore alternate formulations of a Dependence Vulnerability measure, exploring age and gender effects, and familial resemblance among

Between January, 1993 and March 15, 2001, we have conducted 3676 diagnostic interviews with community-based samples of twins, full siblings, and adoptive siblings recruited without regard to substance use or conduct disorder symptoms. Of these interviews, 1692 (46%) have been with female subjects. The subjects ranged in age from 11 through 25 years. The first sample consisted of 2026 twins and a near-in-age sibling if available. The second sample consisted of 720 participants in the Colorado Adoption Project (DeFries, Plomin, & Fulker, 1994), of whom 295 have been interviewed twice, once as adolescents, and once as young adults. The third sample consisted of adolescents and their siblings matched to adolescent probands in the treatment and outpatient facilities on the basis of ethnicity, gender, and age.

siblings in a combined, unselected sample of adolescents and young adults.

(CIDI-SAM) questions on tobacco, alcohol, and illicit substances were administered by a trained lay interviewer. Scoring algorithms based on whole life substance use were used to derive the number of Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV) dependence symptoms for each of ten drug classes: tobacco, alcohol, cannabis, stimulants, sedatives, cocaine, opioids, phencyclidine (PCP), hallucinogens, and inhalants. Ten possible variants of a Dependence Vulnerability measure were created from the lifetime symptom counts. The variants were designed to differ according to the substances excluded (none, tobacco, or tobacco and alcohol), whether the number of symptoms was adjusted for number of substances tried, and the threshold of number of symptoms per substance.

# Using unselected community samples to derive optimal multiple substance dependence phenotypes for genetic analysis

R. P. Corley, J. K. Hewitt, M. C. Stallings, & S. E. Young

Figure 3 shows the predicted age effects for boys and girls on the number of

substances tried to criterion as a function of age, along with the mean number of

substances tried by age category. The regression predictions for girls and boys

overlap substantially, and range from 0 substances at age 12 to around 2.5

Predicted Substances Tried by Gender and Actual Age Means

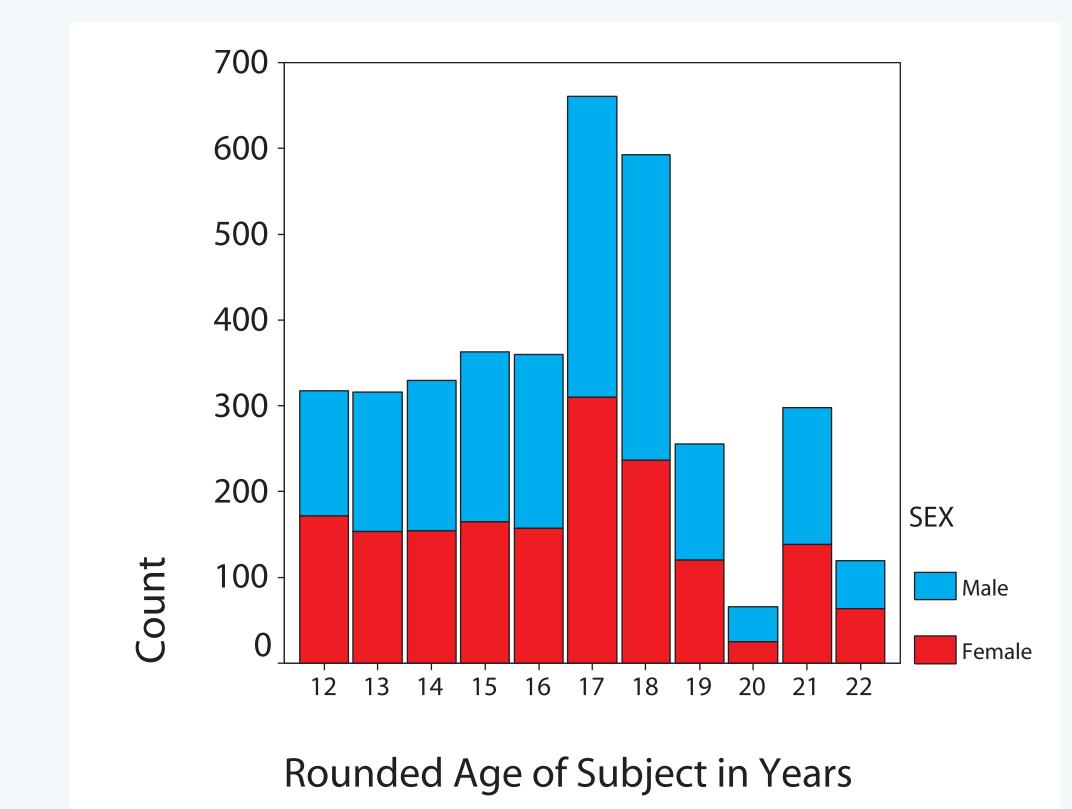
12 13 14 15 16 17 18 19 20 21 22

June 16-21, 2001

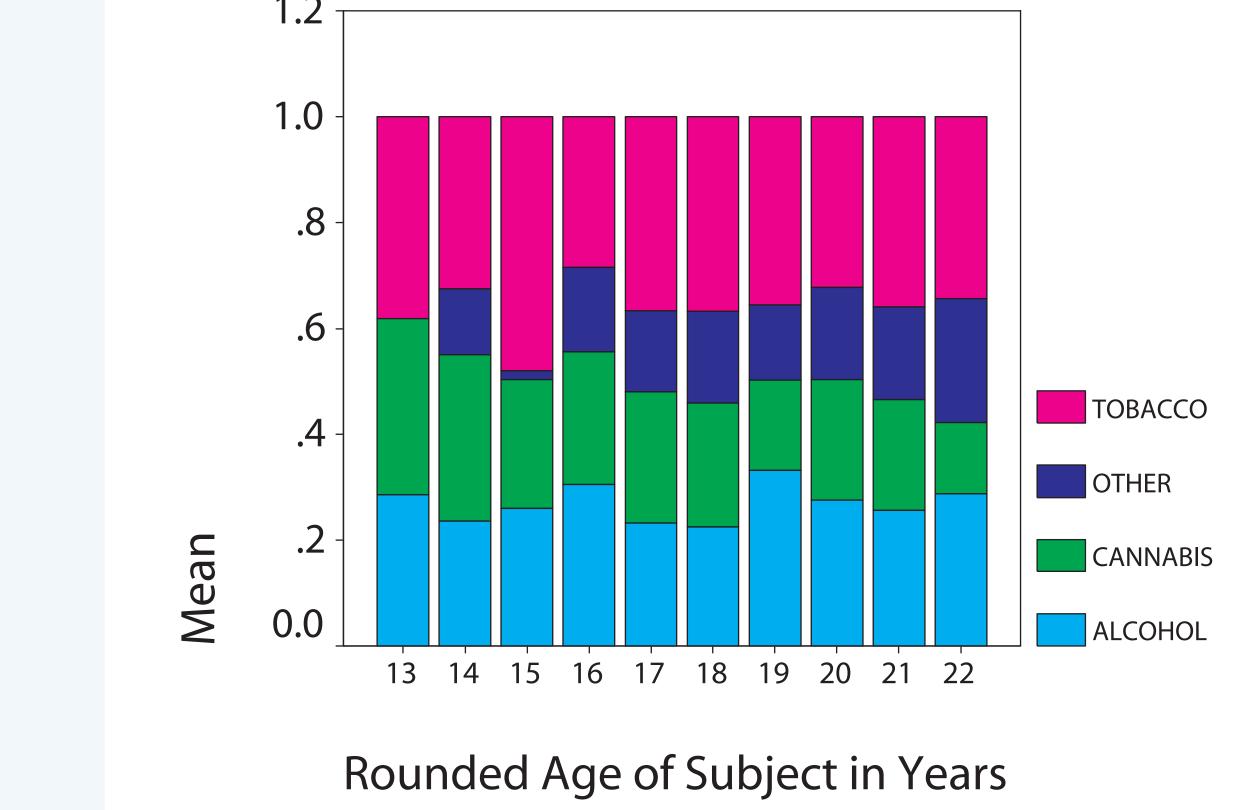
measures attributable to sex, and age within sex. Although the sex effect is sample. Results: All variants correlated 0.65 or greater, but depth variants that Measure 5: The average number of symptoms for each substance tried to Measure 6: The average number of symptoms for each substance tried to

> Measure 7: The number of symptoms for cannabis only. Measure 9: The number of substances with at least three dependence symptoms, Measure 10: The number of different symptoms found for at least one substance,

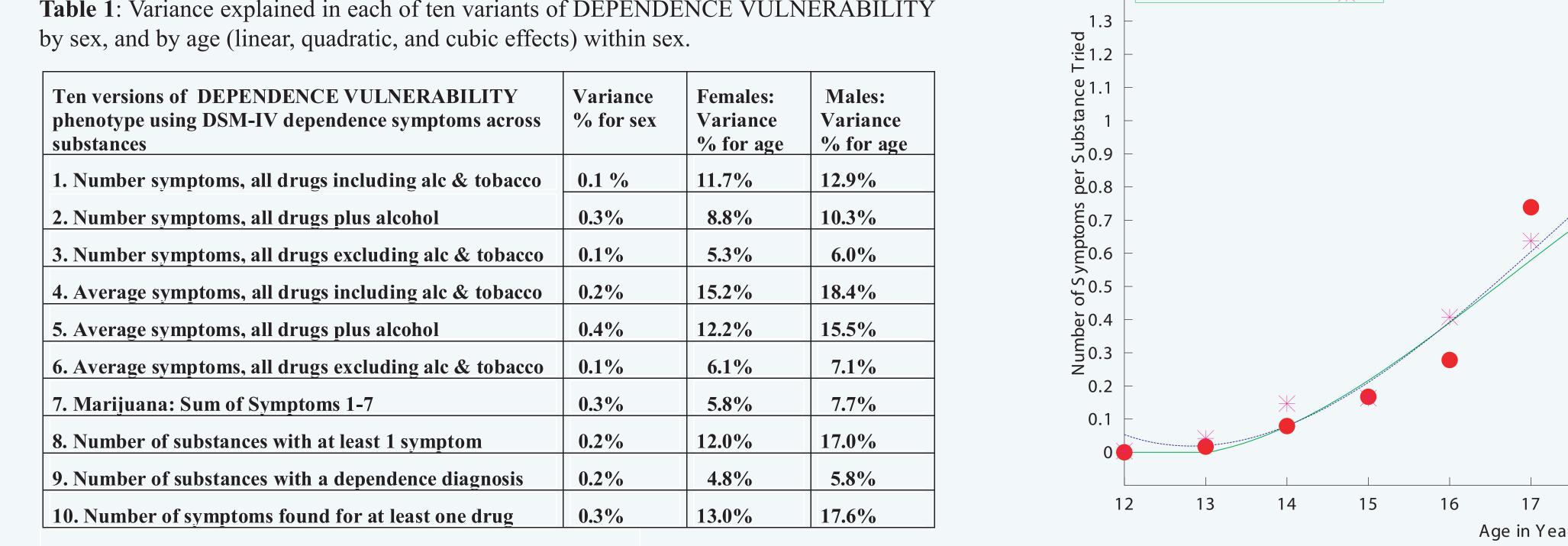
## 22.5 and 26 have been folded into the age 12 and age 22 age categories, respectively. Proportions of males and females are approximately equal across the age range, and all age categories except age 20 show at least 100 subjects.



The proportion of total symptoms by substance across the age range is shown one-third from tobacco, and the remainder from cannabis and other illicit



significant for each measure at least at the p < .05 level, the variance in the measures attributable to sex is relatively small (less than 0.5% for all measures). Predicted DSM-IV Average Dependence by Gender and Actual Age Means In contrast, age is a powerful predictor within each gender, with between 5% and 19% of the variance predictable by combined linear, quadratic, and cubic age. Table 1: Variance explained in each of ten variants of DEPENDENCE VULNERABILITY



measures both in their uncorrected form, and after correcting for the sex and age effects within sex. Because residuals after correction are still highly skewed, an additional rank-normalization transformation was performed. Both the uncorrected (below the diagonal) and corrected (above the diagonal) intercorrelations are high and significant, ranging from a low of 0.59 to a high of

(uncorrected scores below the diagonal; gender- and age-adjusted, normalized scores above uncorrected and corrected measures. diagonal) for 3674 unselected 11-25 year olds.

|            | 1.  | 2.  | <i>3.</i> | 4.  | <i>5</i> . | 6.  | <i>7</i> . | 8.  | 9.  | 10  |
|------------|-----|-----|-----------|-----|------------|-----|------------|-----|-----|-----|
| <i>1</i> . |     | .91 | .83       | .92 | .83        | .81 | .79        | .87 | .71 | .89 |
| 2.         | .95 |     | .88       | .86 | .93        | .85 | .83        | .93 | .78 | .97 |
| <i>3</i> . | .90 | .96 |           | .67 | .71        | .96 | .94        | .79 | .77 | .80 |
| 4.         | .85 | .76 | .63       |     | .91        | .68 | .66        | .87 | .59 | .89 |
| <i>5</i> . | .80 | .82 | .68       | .92 |            | .72 | .70        | .93 | .65 | .96 |
| 6.         | .77 | .78 | .79       | .73 | .77        |     | .97        | .78 | .72 | .80 |
| 7.         | .77 | .78 | .79       | .69 | .73        | .93 |            | .76 | .71 | .78 |
| 8.         | .89 | .89 | .82       | .76 | .78        | .72 | .71        |     | .59 | .95 |
| 9.         | .86 | .92 | .88       | .66 | .73        | .71 | .71        | .71 |     | .69 |
| 10.        | .89 | .88 | .78       | .87 | .92        | .83 | .82        | .88 | .77 |     |

subjects show some dependence symptoms by early adulthood for the substances

Table 3: Familial resemblance for ten DEPENDENCE VULNERABILITY measures

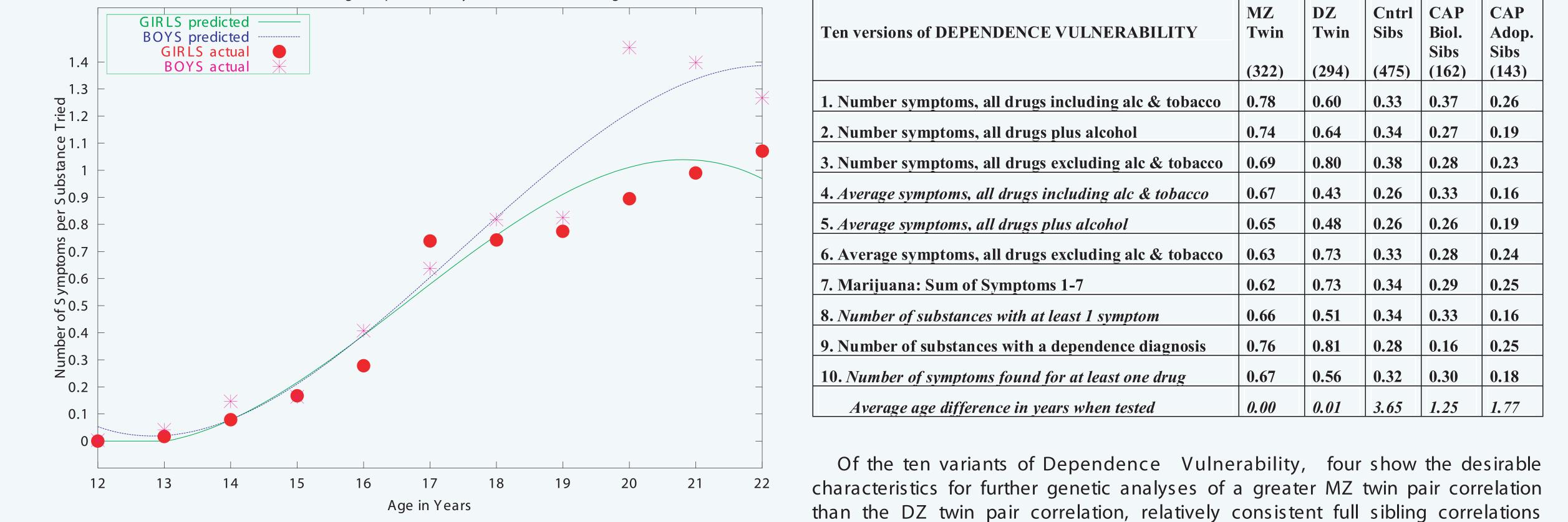


Table 2: Correlations among the ten DEPENDENCE VULNERABILITY measures

### Analyses and Results, continued

Table 3 shows familial resemblances for MZ twin pairs, DZ twin pairs, full siblings from the sample matched to treatment probands, and full and adoptive

|  | MZ    | DZ    | Cntrl | CAP        | CAP        |
|--|-------|-------|-------|------------|------------|
| Ten versions of DEPENDENCE VULNERABILITY               | Twin  | Twin  | Sibs  | Biol.      | Adop.      |
|  | (322) | (294) | (475) | Sibs (162) | Sibs (143) |
| 1. Number symptoms, all drugs including alc & tobacco  | 0.78  | 0.60  | 0.33  | 0.37       | 0.26       |
| 2. Number symptoms, all drugs plus alcohol             | 0.74  | 0.64  | 0.34  | 0.27       | 0.19       |
| 3. Number symptoms, all drugs excluding alc & tobacco  | 0.69  | 0.80  | 0.38  | 0.28       | 0.23       |
| 4. Average symptoms, all drugs including alc & tobacco | 0.67  | 0.43  | 0.26  | 0.33       | 0.16       |
| 5. Average symptoms, all drugs plus alcohol            | 0.65  | 0.48  | 0.26  | 0.26       | 0.19       |
| 6. Average symptoms, all drugs excluding alc & tobacco | 0.63  | 0.73  | 0.33  | 0.28       | 0.24       |
| 7. Marijuana: Sum of Symptoms 1-7                      | 0.62  | 0.73  | 0.34  | 0.29       | 0.25       |
| 8. Number of substances with at least 1 symptom        | 0.66  | 0.51  | 0.34  | 0.33       | 0.16       |
| 9. Number of substances with a dependence diagnosis    | 0.76  | 0.81  | 0.28  | 0.16       | 0.25       |
| 10. Number of symptoms found for at least one drug     | 0.67  | 0.56  | 0.32  | 0.30       | 0.18       |
| Average age difference in years when tested            | 0.00  | 0.01  | 3.65  | 1.25       | 1.77       |

than the DZ twin pair correlation, relatively consistent full sibling correlations across samples, and low adoptive sibling correlations relative to those for the full

### Substantial overlap exists between all these Dependence Vulnerability measures, as indicated by the high and significant correlations between both the

Gender is a relatively trivial, though significant, predictor for individual variation in the Dependence Vulnerability measures, but age contributes both significantly and substantially to individual variation. Age differences alone can contribute substantially to individual variation and need to be accounted for prior to Familial resemblance estimates from twins, full biological siblings, and adoptive siblings suggest that there are substantial familial effects that are shared by siblings regardless of degree of biological relatedness. However, certain of the Dependence Vulnerability measures do suggest possible genetic effects, among them versions 4 and 5 which adjust the total number of dependence symptoms for the number of substances tried to criterion (which may be more a function of non-genetic shared sibling effects), and version 8, which sums substances for which involvement is more than trivial. Conclusions about possible genetic contributions to Dependence Vulnerability based on non-clinical samples are only suggestive. The choice of a particular measure must be supported by evidence from clinical probands and their siblings

### Acknowledgements

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