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Common and Unique Genetic Contributions to Conduct Disorder and Two Stages of Alcohol Dependence Development in Women

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Abstract

Genetic and environmental influences on conduct disorder (CD), early age at first alcohol use, and alcohol dependence (AD) were examined in a sample of adolescent and young adult women. Analyses revealed a high degree of genetic overlap among the three phenotypes as well as heritable components unique to the alcohol outcomes and specific to AD. Results provide additional evidence of common genetic contributions to CD, early alcohol initiation, and AD in females, but suggest distinctions in sources of variance on alcohol outcomes at different stages in the course of AD development.

Background

CD has consistently been linked to AD as well as early age at first alcohol use. Early alcohol initiation has in turn been identified as a risk factor for AD. Genetically-informative investigations have revealed evidence of common heritable influences on alcohol outcomes and CD, but changes in the impact of CD over the course of AD development remain largely unexplored. Further, the bulk of research in this area has focused solely on male samples and thus the importance of externalizing disorders for the development of AD in women is relatively unknown.

Aims

- To assess the degree to which genetic and environmental liability to CD are shared with early age at first drink and AD development in women.
- Further, to determine whether heritable influences on AD are fully accounted for by genetic contributions common to early initiation of alcohol use and CD.

Participants

- 3,633 female twins from the Missouri Adolescent Female Twin Study (MOAFTS)
- **MOAFTS** is a longitudinal study of alcohol use disorders and associated psychopathology in female adolescents and young adults (PI: Heath)
- 86% Caucasian, 14% African-American
- Mean age at Wave 4 assessment: 21.6 years of age (range=18–29)
- Prevalence of CD: 4.2%

Assessment Protocol

Telephone interviews using the Semi-Structured Assessment for the Genetics of Alcoholism (Bucholz et al., 1994) were used to derive:

Alcohol Outcomes (Wave 4)

- Lifetime alcohol use
- Age at first drink
- DSM-IV AD diagnosis

DSM-IV Conduct Disorder (Baseline & Wave 4)

- Participants >18 years at baseline (33.7% of the sample) were not re-assessed at Wave 4. For all other cases, CD was derived from Wave 4 assessments.

Alcohol Outcomes by CD Status

	CD Status	
	+	-
Alcohol Use	96.1%	85.0%
Age at First Drink		
<= 15 years (early)	63.7%	32.4%
16-17 years	24.0%	36.4%
>= 18 years	12.3%	31.2%
Alcohol Dependence	6.8%	28.3%

Age at Alcohol Use Initiation and AD Status

Age at First Drink	AD Status	
	+	-
<= 15 years	15.9%	84.1%
16-17 years	7.5%	92.5%
>= 18 years	3.7%	96.3%

Age at First Drink in Alcohol-Dependent Participants

	<= 15 years	16-17 years	>= 18 years
AD +	58.5%	29.1%	12.4%

Logistic Regression Analyses

- Logistic regression analyses (adjusted for familial clustering) provided initial estimates of the associations between CD, early age at first alcohol use, and AD.

Conduct Disorder and Early Age at First Drink

- CD was associated with elevated risk for early initiation of alcohol use (OR = 4.14; CI: 2.91 – 5.91).

Conduct Disorder and Alcohol Dependence

- CD predicted AD (OR = 4.80; CI: 3.30 – 6.98).

Early Age at First Drink and Alcohol Dependence

- Early age at first alcohol use was associated with increased risk for AD (OR = 3.06; CI: 2.37 – 3.95).

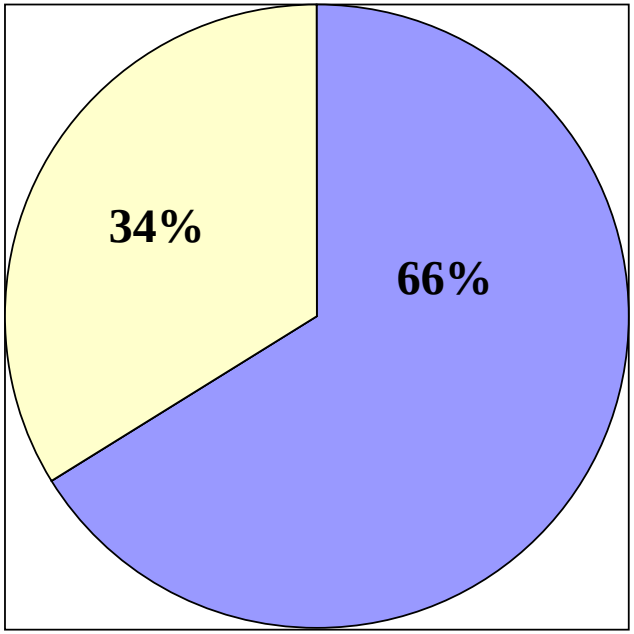
Data Analysis: Partitioning Variance in CD and Alcohol Outcomes

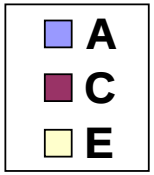
- Standard univariate genetic analyses were conducted to partition variance into additive genetic (A), shared environmental (C), and unique environmental (E) components for each of the three phenotypes.
- A trivariate Cholesky decomposition model was constructed based on results of the best-fitting univariate models.
- The trivariate model allowed for genetic influences that impact all three phenotypes (A1), additional genetic influences that impact only early alcohol use and AD (A2), and genetic influences unique to AD (A3).

Univariate Models of CD and Alcohol Outcomes:

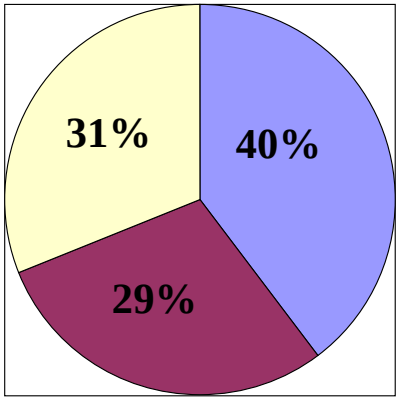
Proportion of variance accounted for by A, C, and E

Conduct Disorder

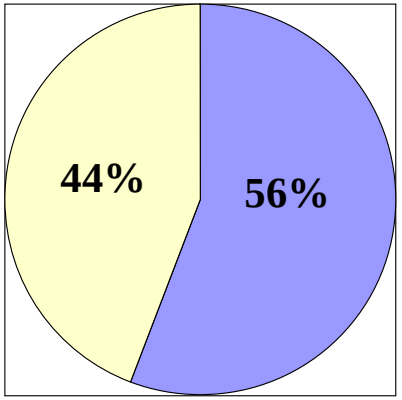




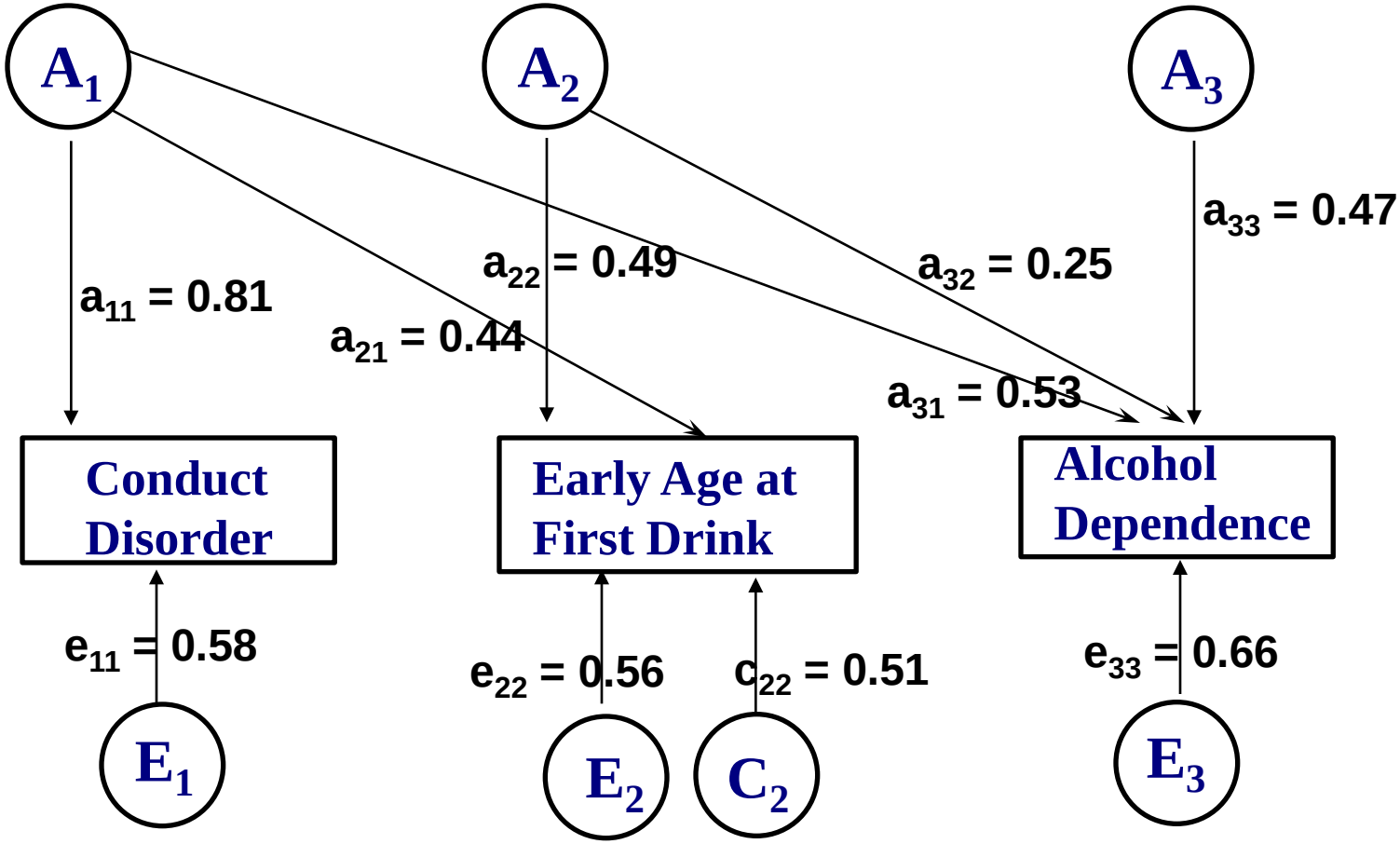
Early Age at First Drink



Alcohol Dependence



Trivariate Cholesky Decomposition Model: CD, Early Age at First Drink, and AD



CD, Early Age at First Drink, and AD

- Substantial heritable contributions were found for all three phenotypes, but shared environmental influences were only evident in early age at first drink.
- Genetic correlations were high between all three phenotypes:

  CD-early age at first drink: **r = 0.66**

  Early age at first drink-AD: **r = 0.72**

  CD-AD: **r = 0.71**
- In addition to overlapping sources of genetic variation among CD, early alcohol use, and AD, additional heritable influences were found that were specific to the two alcohol outcomes and that were unique to AD.

Conclusions

- Results provide further evidence for the genetic link between CD and alcohol outcomes in females (Slutske et al., 1998) and extend this literature by demonstrating the association at two stages of AD development.
- The considerable but incomplete overlap in genetic sources of variation between early alcohol use and AD suggests both continuity in the influence of some genetic factors across stages of AD development as well as the possibility of stage-specific heritable influences on transitions in the course of alcohol use.

Future Directions

- In an effort to characterize the association between CD and the pathway to AD using a genetically informative design, the present model will be expanded upon in two ways:
- First, additional milestones (e.g., onset of problem alcohol use) will be examined in combination with initiation of alcohol use and onset of AD.
- Second, progression to AD will be modeled using rate of transitions between milestones to better capture the dynamic nature of AD development.