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2003

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Recommended Citation

Jacob, T.; Heath, Andrew c.; Bucholz, Kathleen K.; Scherrer, J.; Waterman, B.; True, W. R.; Haber, R.; and Fu, Q., "Genetic and environmental influences on offspring alcoholism: New insights using a children-of-twins design" (2003). *Posters*. Paper 29 Samuel B. Guze Symposium on Alcoholism.

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GENETIC AND ENVIRONMENTAL INFLUENCES ON OFFSPRING ALCOHOLISM: NEW INSIGHTS USING A CHILDREN-OF-TWINS DESIGN

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Grant Support: This study was supported by grants AA11667, AA11822, and Center Grant AA11998 from the National Institute on Alcohol Abuse and Alcoholism and from a Merit Review Grant (TJ) from the Department of Veterans Affairs Medical Research Service, Washington, DC

ABSTRACT

Objective: The purpose of this study was to examine the genetic and environmental risk factors of alcoholism by means of the offspring of twins design.

Method: Detailed information regarding psychiatric and alcohol use, abuse, and dependence status (DSM-IV) was obtained from male MZ and DZ twins concordant or discordant for alcohol dependence, as well as from their spouses and offspring.

Results:

- Offspring of MZ and DZ twins with a history of alcohol dependence were significantly more likely to exhibit alcohol abuse and dependence than offspring of nonalcoholic fathers.
- Offspring of an alcohol abusing MZ twin whose cotwin was alcohol dependent were also more likely to exhibit alcohol dependence than were offspring of nonalcoholic twins.
- Offspring of nonaffected MZ twins whose cotwin was alcohol dependent were no more likely to exhibit alcohol abuse or dependence than were offspring of nonalcoholic twins.

Conclusions: Findings support the hypothesis that family environmental effects do make a difference in accounting for offspring outcomes. In particular, a low risk environment serves to moderate the impact of high genetic risk for the development of alcohol use disorders.

SPECIFIC AIMS

- 1. To determine the extent to which offspring of alcoholic twins compared to offspring of nonalcoholic cotwins differ in regards to alcohol use and abuse**

Prediction:

Prevalence of offspring alcohol abuse (AA)/dependence (AD) will be highest when children are reared by an alcoholic parent (MZ or DZ) and lowest when fathers exhibit no alcoholism and have no elevated genetic risk (father's cotwin is nonalcoholic).

SPECIFIC AIMS

2. To determine the relative importance of family genetic, family environmental, and nonshared environmental in accounting for offspring outcomes

Predictions:

- **Offspring with elevated genetic risk but lower environmental risk (unaffected father's with MZ or DZ cotwin is alcoholic) will exhibit lower rates of alcoholism than children of alcoholics (COAs).**
- **Rates of offspring alcoholism will be greater between COAs and children of unaffected DZ twins than between COAs and children of unaffected MZ twins (lower genetic risk)**

ETIOLOGY OF ALCOHOLISM

Two research traditions have contributed most significantly to understanding the etiology of alcoholism.

Psychosocial research studies

Have defined a number of key mediator (deviant socialization, affect regulation, and pharmacological vulnerability) and moderator mechanisms (socioeconomic factors, peer influences, young adult transition events) that account for (mediator) or qualify (moderator) the impact of family history on offspring outcome

Limitation: Separation of family genes from family environment has not been possible

Behavioral genetic studies

Have offered evidence that genetic influences account for 40-60% of variance in alcohol dependence risk, and the remaining variance is partly explainable in terms of shared family environmental effects

Limitation: Family environmental as well as nonshared environmental influences have been poorly articulated and measured

THE NEED FOR INTEGRATION

Both theoretical and methodological limitations require the need for an alternative genetic design. While it is evident that a genetic contribution exists in the contribution to alcoholism risk, it is also important to understand the environmental influences.

Stated otherwise, the next step is to understand how genetic effects are mediated and moderated by environmental influences

The **Offspring of Twins Design** provides a unique opportunity for testing what gene-environment correlations and gene x shared environment interaction effects exist.

OFFSPRING OF TWINS DESIGN

OFFSPRING RISK PROFILES

	GROUP 1		GROUP 2		GROUP 3		GROUP 4		GROUP 5		GROUP 6	
Parental Twinship	MZ or DZ		MZ		MZ		DZ		DZ		MZ or DZ	
Parental Alcohol Use	AD	AD	AD	AA	AD	Non	AD	AA	AD	Non	Non	Non
Offspring Genetic Risk	High	High	High	High	High	High	High	Moderate	High	Moderate	Low	Low
Offspring Environmental Risk	High	High	High	Moderate	High	Low	High	Moderate	High	Low	Low	Low

MZ = Monozygotic Twins

DZ = Dizygotic Twins

AD = Alcohol Dependence

AA = Alcohol Abuse

Non = Unaffected (No Dependence or Abuse)

PARTICIPANTS

Vietnam Era Twin Registry (VETR)

- **1213 Male twins (Mean age: 50)**
- **862 mothers (Mean age: 47)**
- **1270 offspring (age range: 12-26 years)**

ASSESSMENT DOMAINS

Data were obtained from Twins, Spouses, and Offspring regarding:

- **Alcohol-Related Behaviors**

- Alcohol dependence and Alcohol abuse

- Lifetime drinking history

- Family history of alcohol abuse/dependence

- Nicotine dependence, cannabis dependence and substance abuse

- **Psychiatric Status**

- Major depression and Mania

- Anxiety disorders

- Antisocial personality disorder

- Conduct disorder

- Oppositional defiant disorder

Outcome Differences Related to Genetic x Environmental Risk Status

Group 1 vs. Group 6:

High genetic/high environmental vs. low genetic/low environmental

**Compared to offspring of non-alcoholic fathers (Group 6) –
Offspring of MZ and DZ twins with a history of alcohol dependence
(Group 1: COAs) were significantly more likely to exhibit**

alcohol dependence	(OR=2.20; 95% CI:1.30-3.71)
alcohol abuse	(OR=1.74; 95% CI:1.15-2.62)
either abuse or dependence	(OR=1.98; 95% CI:1.37-2.86)

Outcome Differences Related to Genetic x Environmental Risk Status

Group 2 vs. Group 6:

High genetic/moderate environmental vs. low genetic/low environmental

**Compared to offspring of nonalcoholic fathers (Group 6) –
Offspring of an alcohol abusing MZ twin whose twin was alcohol
dependent (Group 2) were also more likely to exhibit**

alcohol dependence (OR=3.14; 95% CI:1.36-7.37)

either abuse or dependence (OR=2.61, 95% CI:1.30-5.22)

Outcome Differences Related to Genetic x Environmental Risk Status

Group 3 vs. Group 6:

High genetic/low environmental vs. low genetic/low environmental

Offspring of non-dependent, nonabusing fathers with an alcohol dependent MZ twin (Group 3) were at no greater risk for dependence or abuse than offspring of nonalcoholic fathers (Group 6).

Groups 4 & 5 vs. Group 6:

Similarly, offspring from Groups 4 and 5 were at no greater risk for alcohol dependence or alcohol abuse than offspring of nonalcoholic fathers (Group 6).

MAJOR FINDINGS & CONCLUSIONS

Use of the offspring of twins design offered a strong test of the hypothesis that family environmental effects do make a difference in accounting for offspring outcomes.

- 1. In the absence of an alcoholic family environment, even with the high genetic risk for the disorder, offspring alcoholism outcomes were similar to normal controls (both low genetic and low environmental risk).**
- 2. There seems to be no difference in impact on offspring of paternal alcohol dependence (Gp 1) and paternal alcohol abuse (Gp 2) as long as the father had a MZ alcohol dependent twin.**

MAJOR FINDINGS & CONCLUSIONS

- 1. If replicable and generalizable, the findings indicate that genetic risk (in many cases) becomes actualized only if there is some significant environmental sequella to the genetic vulnerability.**
- 2. Although we cannot yet specify particular family environmental factor(s) that account for these findings, the larger alcoholism literature suggests many plausible family environmental influences:**
 - impact of paternal AD on marital and parent-child relationships**
 - drinking models and drinking relevant cognitions and experiences**
 - family's economic well being.**

IMPLICATIONS/LIMITATIONS

Offspring in our sample have not yet passed through the major risk period: Since prevalence of alcohol use disorders is highest during the adolescent to young adult years, it may be difficult to differentiate offspring risk in terms of varying genetic and environmental risk profiles

Future follow-up of this sample will provide information regarding the expectation that those lower at risk will adopt non-problem drinking whereas those at higher risk will exhibit alcohol abuse or dependence