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MARC Project 4:

Australian Children of Alcoholic Female Twins

Wendy S. Slutske, Valerie S. Knopik,
Theodore Jacob, Michael T. Lynskey, & Anne Glowinski

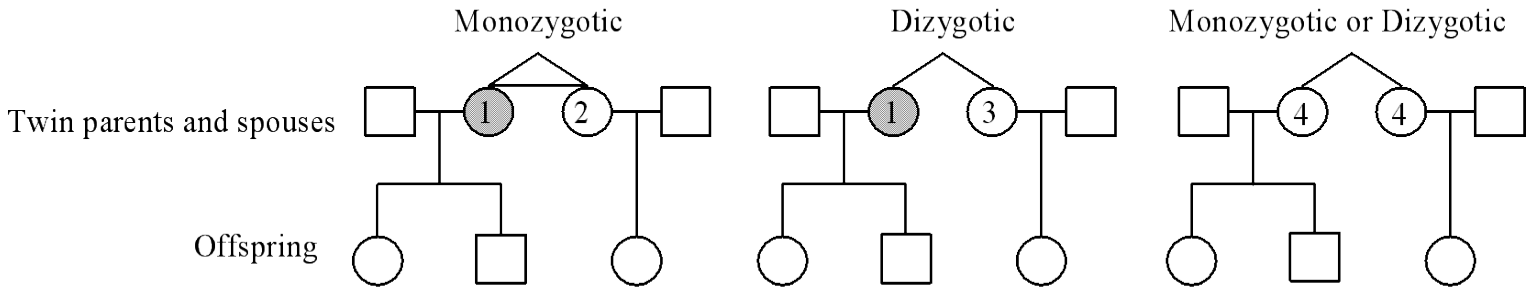
Background

- Although it has been widely embraced by the treatment community, and certainly has a great deal of intuitive appeal, it has been difficult to demonstrate empirically a (non-genetic) consequence of being reared by an alcoholic parent.
- One critical test for demonstrating an important environmental effect of being reared by an alcoholic parent is to compare the rates of adverse outcomes among the biological offspring of an alcoholic parent to the rates of adverse outcomes among the biological offspring of the unaffected monozygotic cotwin of the alcoholic parent.
- The major aim of this project is to determine whether being raised by an alcoholic parent, in particular an alcoholic mother, increases the risk of adverse outcomes in the offspring after controlling for genetic transmission, and to identify mediators and modifiers of risk-outcome relationships.

Limitations of Previous Research

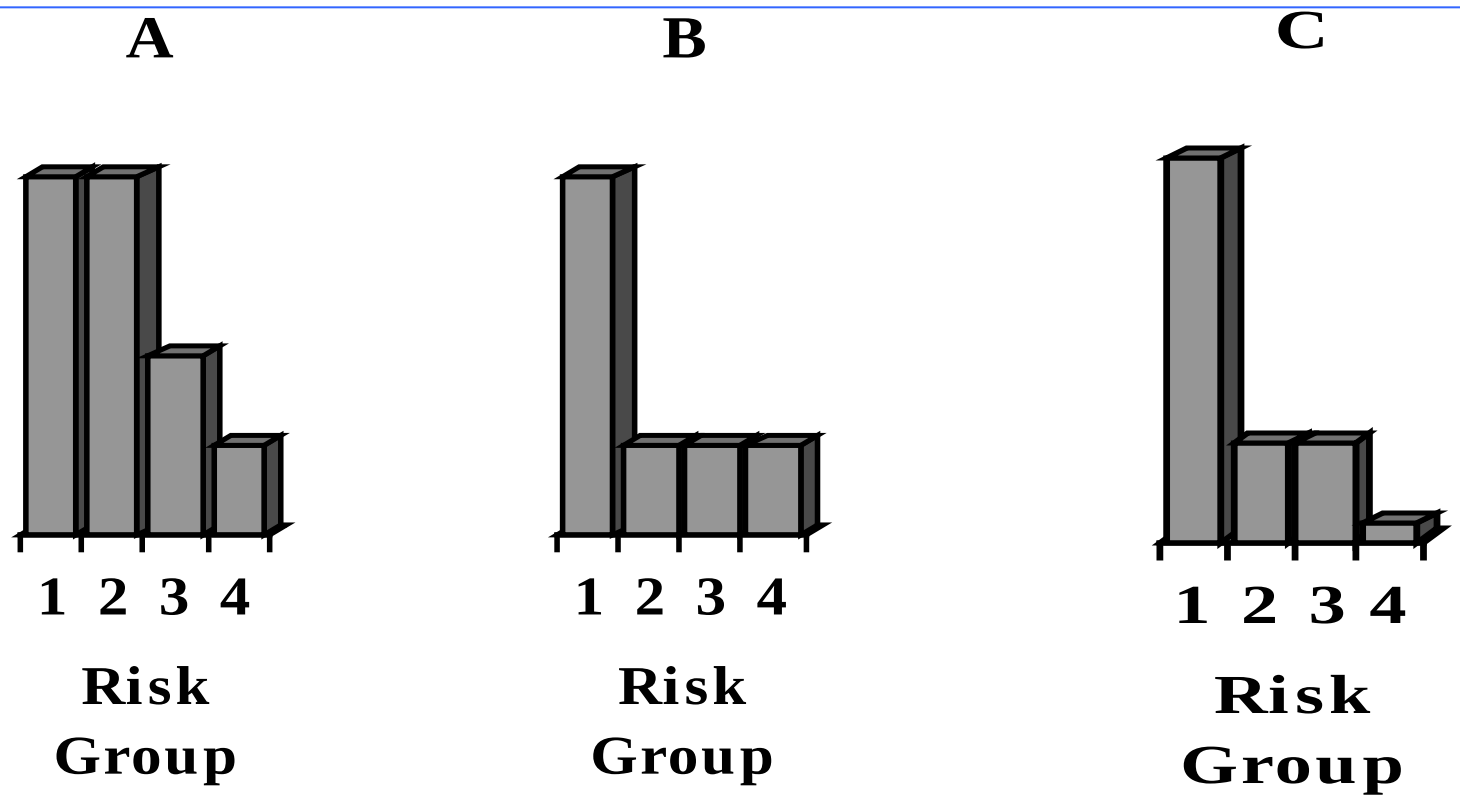
- Family studies have demonstrated that offspring of alcoholic parents are at higher risk for adverse outcomes than offspring of nonalcoholic parents, but it is impossible to determine from such studies whether this is due to genetic or environmental transmission of risk.
- Twin studies have generally led to the conclusion that family environmental influences do not play a major role in the familial transmission of alcoholism risk. However, in the twin design the estimate of family environmental effects only includes those that are independent of genetic effects.
- Adoption studies have not consistently demonstrated that offspring of alcoholic adoptive parents are at higher risk for adverse outcomes than offspring of nonalcoholic adoptive parents. Adoption studies are ideal in theory but limited in practice due to the screening of adoptive parents, which results in a restriction in the range of environmental adversity to which adoptive offspring are exposed.
- There is a paucity of research focused on the risk of adverse outcomes for offspring of alcoholic mothers.

Offspring of Twins Research Design



Genetic Effects	High	High	High	Intermediate	Low	Low
Familial Environment Effects	High	Low	High	Low	Low	Low
Genotype x Environment Interaction Effects	High	Low	High	Low	Very Low	Very Low

Above are pedigree diagrams of the three types of twin-families included in this study of offspring of twins (shaded circles represent female twins with a history of alcohol use disorder (alcohol dependence (AD) or alcohol abuse (AB) -- AUD): families with at least one monozygotic female twin with a history of AUD, families with at least one dizygotic female twin with a history of AUD, and monozygotic or dizygotic twin families in which both female twins are unaffected with AUDs (control families).



Above are hypothetical results of the risk of adverse outcomes among offspring of twins from different risk categories represented in the previous panel. Panel ‘A’ represents the risk to offspring when the familial transmission is solely due to genetic effects, panel ‘B’ represents the risk to offspring when the familial transmission is solely due to family environmental effects, and panel ‘C’ represents the risk to offspring when the familial transmission is largely due to genotype x family environmental effects. All panels assume statistical control for paternal psychopathology.

Data Collection

- Data collection for this project is being done at the Queensland Institute of Medical Research in Brisbane, Australia.
- Female twin pairs from the different risk categories have been identified from previous large twin interview surveys.
- Female twin pairs are administered structured psychiatric telephone interviews in which they report about themselves, their biological offspring ages 7-22, and the father of the offspring. Fathers of the offspring are administered structured psychiatric telephone interviews in which they report about themselves.
- All offspring ages 11 and older are interviewed.
- Follow-up interviews with offspring are conducted every two years for a maximum of four interviews over the entire course of the 10-year study.

Key Constructs Assessed

In addition to collecting information about alcohol use and alcohol use disorders among all participants, we are assessing constructs related to three hypothesized pathways of the genetic and environmental transmission of alcoholism risk:

- Deviant socialization pathway
  - impaired parenting, family disruption
  - deviant peers
  - academic failure, childhood ADHD, oppositional behavior, and conduct problems
- Negative affect pathway
  - childhood stressors (physical and sexual abuse, traumatic events)
  - personality trait of neuroticism
  - internalizing disorders (depression and anxiety)
- Pharmacological vulnerability pathway
  - initial sensitivity to alcohol
  - drinking motives, alcohol expectancies

We are currently in year 8 of this project.

By the end of year 10, we expect the following sample sizes:

Risk group	Mothers	Offspring
1 - Mother AUD (AD or AB)	332	512
2 - Mother unaffected, MZ cotwin AUD	101	179
3 - Mother unaffected, DZ cotwin AUD	104	171
4 - Mother unaffected, cotwin unaffected	654	1023
Total	1191	1879

Recent projects have focused on the relationship between maternal AUD and offspring externalizing behavior problems.

Data have been analyzed based on the interviews with 536 mothers of 922 offspring.

Risk group	Mothers	Offspring
1 - Mother AUD (AD or AB)	145	231
2 - Mother unaffected, MZ cotwin AUD	41	67
3 - Mother unaffected, DZ cotwin AUD	38	61
4 - Mother unaffected, cotwin unaffected	312	563
Total	536	922

Rates of ADHD among offspring from different risk groups

Risk group	% with ADHD	Odds ratio
1a – Mother alcohol dependent (AD)	10.1	2.53*
1b - Mother alcohol abuse (AB)	9.2	1.85
2 - Mother unaffected, MZ cotwin AUD	11.9	3.16**
3 - Mother unaffected, DZ cotwin AUD	1.6	0.32
4 - Mother unaffected, cotwin unaffected	4.8	1.00

These results are consistent with a genetic transmission explanation of the increased risk of ADHD among the offspring of alcoholic mothers (Knopik et al., *Psychological Medicine*, 2006).

Rates of conduct problems among offspring from different risk groups

Risk group	% with CP	Odds ratio
1a – Mother alcohol dependent (AD)	13.1	2.43*
1b - Mother alcohol abuse (AB)	9.9	1.75
2 - Mother unaffected, MZ cotwin AUD	14.9	2.82*
3 - Mother unaffected, DZ cotwin AUD	1.6	0.27
4 - Mother unaffected, cotwin unaffected	5.9	1.00

These results are consistent with a genetic transmission explanation of the increased risk of conduct problems among the offspring of alcoholic mothers (Knopik et al., in preparation).

A major focus of these projects has also been to examine the effect of prenatal exposure to alcohol and tobacco among offspring of alcoholic mothers.

The following two tables illustrate that:

1) Maternal smoking during pregnancy is strongly associated with ADHD and CP among children of alcoholic mothers.

2) Even after controlling for the genetic risk conferred by an alcoholic mother, there remained a strong association between maternal smoking during pregnancy and offspring ADHD and CP.

3) The evidence for a genetic transmission explanation for the increased risk of ADHD and CP among the offspring of alcoholic mothers was substantially reduced after controlling for the effect of smoking during pregnancy.

Maternal AUD, smoking during pregnancy, and offspring ADHD

	ADHD					
		Unadjusted			Adjusted	
	%	OR	95% CI		OR	95% CI
Mother AD	10.1	**2.53***	**1.14-5.59**			
Mother AB	9.2	1.85	0.88-3.90		**2.47***	**1.09-5.59**
Mother UN, MZ cotwin AD/AB	11.9	**3.16***	**1.38-7.20**			
Mother UN, DZ cotwin AD/AB	1.6	0.32	0.04-2.59		0.64	0.07-5.50
Mother UN, Cotwin UN	4.8	1.00	--		1.00	--
Mother never smoked	3.6	1.00	--		1.00	--
Mother smoked, not during pregnancy	5.1	1.57	0.67-3.67		0.72	0.23-2.22
Mother smoked,1st trimester only	9.5	**3.02***	**1.16-7.89**		1.88	0.45-7.81
Mother smoked beyond 1st trim., 1-15 cigs	6.8	2.07	0.79-5.42		0.54	0.16-1.83
Mother smoked beyond 1st trim., 16+ cigs	24.3	**9.47****	**4.74-18.95**		**3.83***	**1.09-13.45**
Mother drank <11 days during pregnancy, never heavily	7.1	1.00	--			
Mother drank 11-35 days, never heavily	6.6	0.91	0.43-1.95			
Mother drank 36+ days, never heavily	1.3	0.17	0.02-1.17			
Mother drank heavily, 1-10 days	2.9	0.38	0.05-2.69			
Mother drank heavily, 11+ days	10.5	1.29	0.29-5.80			

Knopik et al., 2006

Maternal AUD, smoking during pregnancy, and offspring conduct problems

	CP				
	Unadjusted			Adjusted	
	OR	95% CI		OR	95% CI
Mother AD	**2.43***	**1.18-5.00**		1.60	0.73-3.53
Mother AB	1.75	0.79-3.92		1.46	0.62-3.44
Mother UN, MZ cotwin AD/AB	**2.82***	**1.16-6.83**		2.38	0.94-5.83
Mother UN, DZ cotwin AD/AB	0.27	0.04-1.99		0.26	0.05-1.93
Mother UN, Cotwin UN	1.00	--		1.00	--
Mother never smoked	1.00	--		1.00	--
Mother smoked, not during pregnancy	1.63	0.72-3.68		1.49	0.63-3.40
Mother smoked,1st trimester only	2.47	0.97-6.32		1.81	0.65-5.02
Mother smoked beyond 1st trim., 1-15 cigs	**3.24****	**1.61-6.51**		**2.83****	**1.29-6.19**
Mother smoked beyond 1st trim., 16+ cigs	**6.30****	**2.63-15.07**		**5.12****	**2.12-12.37**
Mother drank <11 days during pregnancy, never heavily	1.00	--			
Mother drank 11-35 days, never heavily	0.91	0.43-1.95			
Mother drank 36+ days, never heavily	0.17	0.02-1.17			
Mother drank heavily, 1-10 days	0.38	0.05-2.69			
Mother drank heavily, 11+ days	1.29	0.29-5.80			

Knopik et al., in preparation