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MARC Project 4: Australian children of alcoholic female twins

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ALCOHOLISM
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MARC Project 4:

Australian Children of Alcoholic Female Twins

Mary Waldron, Theodore Jacob, Wendy S. Slutske, Anne Glowinski, Nicholas Martin & Andrew Heath

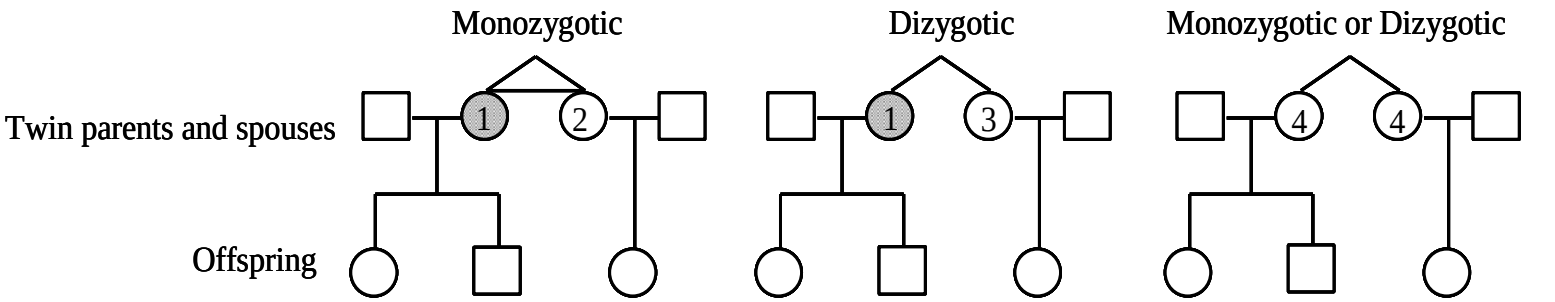
Background

- 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

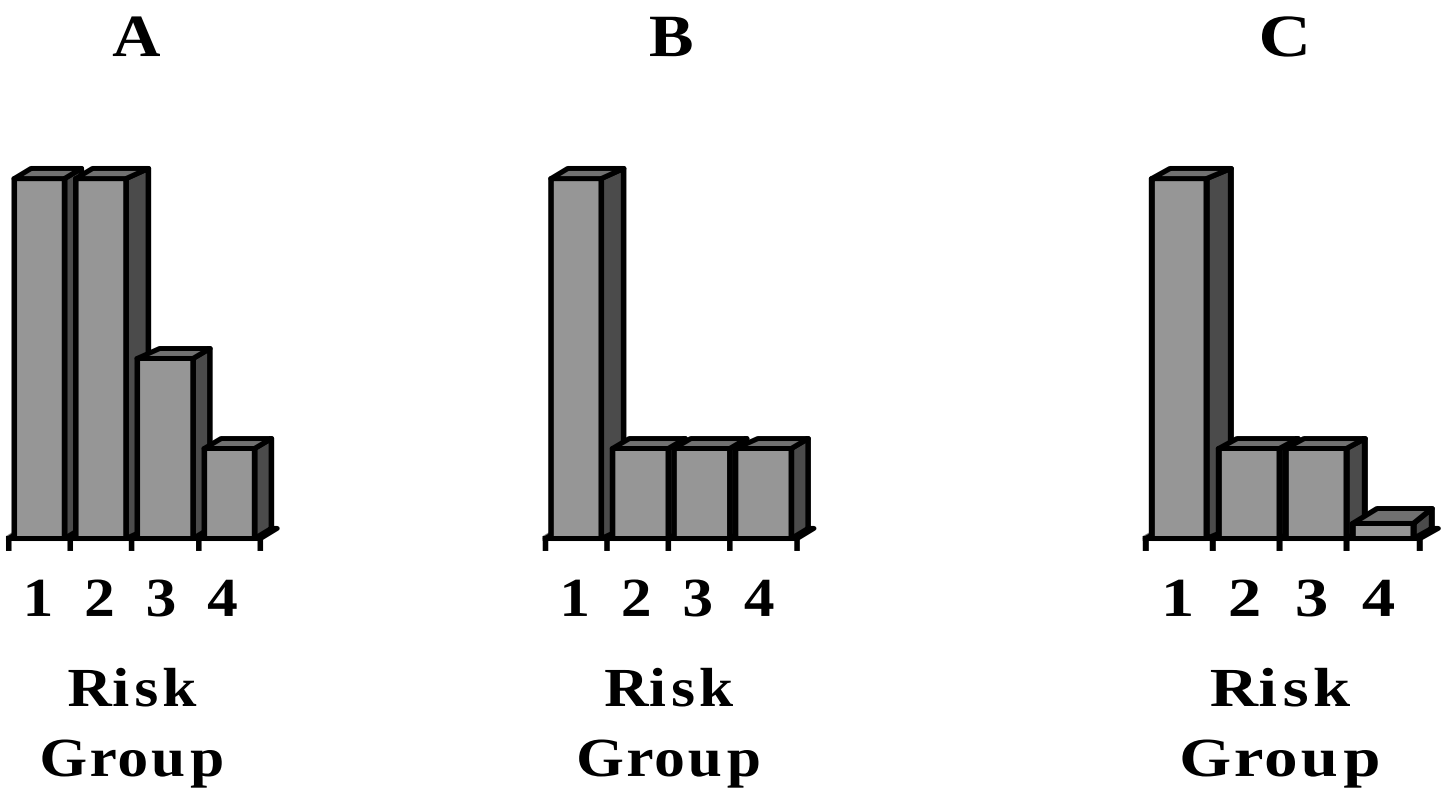
- Family studies have demonstrated that offspring of alcoholic parents are at higher risk for adverse outcomes than offspring of nonalcoholic parents, but it is impossible to determine from such studies whether this is due to genetic or environmental transmission of risk.
- Twin studies have generally 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 (parental separation and divorce)
  - 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

Substantive Findings

We use a lifespan perspective to consider how alcohol abuse or dependence in women impacts risks to the next generation.

Recent analyses focus on:

- Alcoholism and reproductive delay
- Assortative mating for alcoholism
- Exposure to alcohol/tobacco during pregnancy and childhood outcomes
  - ADHD Risk
  - Conduct Disorder Risk
- Parental alcoholism and marital separation and divorce
- Combined analyses of paternal alcoholism and risk of child externalizing and internalizing behavior

We are currently in year 10 of this project. As of 2008, we completed interviews with 951 parents (and an additional 207 cotwin informants, who provided updated alcoholism history information), with parent reports on 1731 offspring. We have also completed baseline and 2-year follow-up interviews with 1440 and 1090 11-year-old and older offspring, respectively, with two-year follow-ups still in progress

Numbers of twin mother and offspring interviews, as a function of maternal and cotwin's alcoholism status, combining cohorts 1 & 2:

				Maternal Interview		Offspring Interview				
						Baseline		Follow-up		Twin Sister Informant Interview
Risk group		Genetic Risk	Environmental Risk	Mothers	Offspring	11-14	15+	11-14	15+	
1a	Mother AD, cotwin any status	High	High	116	197	78	78	24	87	22
1b	Mother AB, cotwin any status	High	High	127	213	91	113	31	118	11
2	Mother UN, MZ cotwin AD/AB	High	Low	90	144	65	69	23	89	5
3	Mother UN, DZ cotwin AD/AB	Intermediate	Low	92	155	59	75	20	97	11
4a	Mother UN, cotwin UN (DZ pairs)	Low	Low	202	390	98	203	32	173	13
4b	Mother UN, cotwin UN (MZ pairs)	V. Low	Low	300	587	135	334	50	307	17
Risk group TBD				24	45	23	19	10	29	128
TOTAL				951	1731	549	891	190	900	207

Recent analyses have focused on the relationship between maternal smoking during pregnancy and child conduct problems, both with and without maternal alcoholism. Compared to control families where neither mother nor her twin sister has a history of alcohol use disorder, rates of problems are significantly elevated if there is a maternal history of alcohol dependence or alcohol abuse, but also for children of a non-alcoholic mother with an MZ twin sister who has a history of alcohol abuse or dependence. Controlling for maternal genetic risk of alcohol use disorder, maternal smoking during pregnancy beyond the 1st trimester and maternal heavy smoking beyond the 1st trimester (more than 15 cigarettes per day) remain strong predictors of risk of child conduct problems.

Association between maternal smoking during pregnancy and child conduct problems* with versus without adjustment for maternal alcoholism risk group.

	Unadjusted		Adjusted	
	OR	95% CI	OR	95% CI
1a. Mother AD	2.43	1.18-5.00	1.60	0.73-3.53
1b. Mother AB	1.75	0.79-3.92	1.46	0.62-3.44
2. Mother UN, MZ cotwin AD/AB	2.82	1.16-6.83	2.38	0.94-5.83
3. Mother UN, DZ cotwin AD/AB	0.27	0.04-1.99	0.26	0.05-1.93
4. Mother UN, cotwin UN	1.0	--	1.00	--
5. Mother never smoked	1.00	--	1.00	--
6. Mother smoked, not during pregnancy	1.62	0.72-3.66	1.49	0.65-3.40
7. Mother smoked, 1st trimester only	2.46	0.96-6.31	1.81	0.65-5.02
8. Mother smoked beyond 1st trimester, 1-15 cigs	3.24	1.61-6.51	2.83	1.29-6.19
9. Mother smoked beyond 1st trimester, 16+ cigs	6.30	2.63-15.07	5.12	2.12-12.37

*3+ CD Sx

An area of increasing emphasis in Project 4 is the domain of environmental risk exposures associated with parental marital separation and divorce.

The following table documents rates of early-onset alcohol use and of DSM-IV alcohol dependence in Australian cohort 2 twins as a function of parental alcoholism and parental marital separation (parental divorce in cohort 1 twins is too rare to permit comparable comparisons).

There is a striking three-way interaction of parental alcoholism, parental marital separation and offspring gender – separation from an alcoholic parent is indeed associated with a reduced risk of both early onset alcohol use, and of alcohol dependence, but only in male offspring.

Association between reported parental alcoholism and parental marital separation, and twin (i) early onset alcohol use (before age 15), and DSM-IV alcohol dependence history in female (F) and male (M) twins from Australian cohort 2.

			Outcomes in Twin Offspring			
			Early-onset Alcohol Use		Alcohol Dependence	
	N_F	N_M	F %	M %	F %	M %
Parental alcoholism and marital separation	213	146	16.0	17.8	25.8	32.9
Parental alcoholism, no marital separation	613	455	9.5	17.1	24.0	44.6
Parental marital separation, no parental alcoholism	224	191	8.3	14.1	14.3	29.3
No parental alcoholism, no parental separation	2363	1967	4.9	11.9	12.7	27.5

In preliminary analyses of data from 1225 Project 4 offspring, we find a significant association between parental separation and first cigarette use, onset of regular smoking, first alcohol use, and alcohol intoxication by age 12, and first use of cannabis. Adjusting for offspring CD and paternal alcohol dependence, parental separation remains a significant predictor of first alcohol use and alcohol intoxication by age 12, providing further support for the importance of parental separation as a risk-factor for offspring early use.

Hazard ratios (HR) and 95% CIs for onset of substance use as a function of maternal and cotwin AUD and parental separation allowing for age interaction (with and without adjustment for offspring CD and paternal AD).

	Unadjusted				Adjusted			
Onset/first use	Mother AUD+	MZ twin AUD+	DZ twin AUD+	Parental separation	Mother AUD+	MZ twin AUD+	DZ twin AUD+	Parental separation
Cigarettes	1.04 (.83-1.31)	1.41 (1.02-1.95)	1.10 (.78-1.54)	1.38 (1.10-1.72)	1.05 (.84-1.30)	1.39 (1.02-1.90)	1.06 (.75-1.50)	1.23 (.99-1.53)
Reg. Smoking	1.40 (.99-1.99)	1.87 (1.08-3.22)	1.30 (.73-2.28)	1.55 (1.11-2.17)	1.41 (1.01-1.98)	1.88 (1.12-2.16)	1.30 (.72-2.35)	1.20 (.86-1.68)
Alcohol	1.15 (.95-1.40)	1.32 (.96-1.83)	1.19 (.94-1.52)	1.29 (1.07-1.55)	1.14 (.94-1.37)	1.29 (.93-1.78)	1.15 (.90-1.48)	1.23 (1.03-1.48)
Intoxication								
≤ 12	⊤ 1.29 (1.02-1.62) ⊥	⊤ 1.33 (.94-1.88) ⊥	⊤ 1.26 (.91-1.74) ⊥	2.42 (1.41-4.15)	⊤ 1.26 (1.01-1.57) ⊥	⊤ 1.23 (.83-1.80) ⊥	⊤ 1.25 (.91-1.72) ⊥	2.13 (1.23-3.67)
> 12				1.23 (.98-1.55)				1.13 (.90-1.41)
Cannabis								
≤ 12	⊤ 1.24 (.90-1.71) ⊥	⊤ 1.70 (1.20-2.42) ⊥	⊤ 1.07 (.67-1.71) ⊥	⊤ 1.53 (1.14-2.04) ⊥	.96 (.46-1.98)	⊤ 1.60 (1.11-2.31) ⊥	⊤ 1.04 (.64-1.67) ⊥	⊤ 1.22 (.90-1.65) ⊥
> 12					1.28 (.94-1.76)			
Other Illicit Drugs								
≤ 12	⊤ 1.44 (.90-2.30) ⊥	⊤ 1.15 (.54-2.47) ⊥	⊤ 1.09 (.59-2.02) ⊥	3.11 (.43-22.43)	⊤ 1.36 (.86-2.17) ⊥	⊤ .95 (.42-2.11) ⊥	⊤ 1.10 (.60-2.00) ⊥	2.30 (.32-16.59)
> 12				1.42 (.92-2.20)				1.02 (.82-2.01)

Note: reference group = mother and cotwin AUD-

Recent analyses combine Project 4 with preliminary data from the Parental Alcoholism & Child Environmental Risk (PACER) study of male like-sex and opposite-sex twin pairs to examine genetic and environmental risks to offspring associated with maternal AUD or *paternal* AD. Together, twin parents from Project 4 and PACER completed the Child Behavior Checklist (CBCL) on 2492 biological offspring ages 7-22. Results of regression models predicting total, externalizing, and internalizing behavior problems from parental and co-twin AUD provide preliminary support for genetic transmission of risk for total problems and externalizing associated with parental alcoholism. Results for internalizing are mixed.

Total Behavior Problems

Groups 1,2 > 3,4

		Unadjusted			Adjusted		
	M (SD)	*Coef*	*SE*	*p*	*Coef*	*SE*	*p*
1. Parent AUD+	19.98 (20.75)	5.52[a]	1.30	.00	5.50[a]	1.30	.00
2. MZ co-twin AUD+	19.51 (20.09)	5.06[a]	2.02	.01	5.12[a]	2.02	.01
3. DZ co-twin AUD+	13.61 (12.45)	-.84[b]	1.16	.47	-.88[b]	1.16	.45
Constant	--	14.45	.62	.00	12.87	1.65	.00

Note. Reference group = parent and co-twin AUD-, *M(SD)* = 14.45 (16.36)

Externalizing Problems

Groups 1,2 > 3,4

		Unadjusted			Adjusted		
	M (SD)	*Coef*	*SE*	*p*	*Coef*	*SE*	*p*
1. Parent AUD+	5.79 (6.74)	1.64[a]	.42	.00	1.68[a]	.42	.00
2. MZ co-twin AUD+	5.58 (6.20)	1.44[a]	.64	.03	1.50[a]	.64	.02
3. DZ co-twin AUD+	3.88 (4.20)	-.27[b]	.39	.50	-.23[b]	.39	.55
Constant	--	4.14	.21	.00	2.38	.53	.00

Note. Reference group = parent and co-twin AUD-, *M(SD)* = 4.14 (5.77)

Internalizing Problems

Groups 1 > 3,4 and 2 > 4, but...

		Unadjusted			Adjusted		
	M (SD)	*Coef*	*SE*	*p*	*Coef*	*SE*	*p*
1. Parent AUD+	4.62 (5.76)	1.33[a]	.34	.00	1.37[a]	.35	.00
2. MZ co-twin AUD+	4.59 (6.19)	1.30[a,b]	.61	.03	1.32[a,b]	.61	.03
3. DZ co-twin AUD+	3.34 (3.76)	.05[b]	.35	.88	.09[b]	.35	.79
Constant	--	3.29	.16	.00	2.80	.47	.00

Note. Reference group = parent and co-twin AUD-, *M(SD)* = 3.29 (4.22)