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EARLY ONSET ALCOHOL USE: ITS ASSOCIATION WITH LATER RISK OF ALCOHOL DEPENDENCE: RETROSPECTIVE FINDINGS FROM AUSTRALIA

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INTRODUCTION

In the early 1980s, Lee Robins noted an association between early onset of use of alcohol or illicit drugs ("substance use") and subsequent risk of dependence. This association has been rediscovered and replicated many times, and is seen consistently for early alcohol use as well as other drug use.

There remains controversy, however, about how this association comes about. At one extreme, it has been hypothesized that excessive alcohol use during early adolescence may have effects on the still developing brain that "prime" an adolescent drinker for later problems with alcohol. At the other extreme, it has been argued, with some supporting data (Prescott & Kendler), that since genetic factors play an important role in determining differences in alcohol dependence risk, early onset of alcohol use may merely be a trait that is more common in those at hightened genetic risk.

One way to investigate these and alternative possibilities is by studying twin pairs. In this poster, we investigate this possibility using data from a large adult twin cohort, who reported retrospectively about their problems with alcohol, and about critical drinking milestones (age at first alcohol use, age at first intoxication, age at first regular alcohol use). This is an Australian twin cohort, who are living in a country that is very tolerant of heavy drinking.

SAMPLE

The data that we presented here are from a panel of Australian twins, born 1964-71, who were volunteered by their parents to take part in research, in 1980-82. The twins were recruited through the Australian school systems, and through media appeals. They were first surveyed as young adults in 1989-1990, by mailed questionnaire, and were recontacted and invited to complete a telephone diagnostic interview in 1996-2000.

Out of a total of 4245 twin pairs, there were 235 pairs who were never successfully retraced, and 17 pairs for whom no current contact information could be found. Excluding these pairs, and excluding twins who were deceased, incapacitated, or never assigned for interview, interviews were successfully completed with 83.4% of twins, including both twins from 2723 pairs, and one twin only from an additional 761 pairs.

ASSESSMENT

Twins completed a diagnostic telephone interview, adopted for telephone administration from, an instrument commonly used in alcohol research, the SSAGA, which included assessments of:

(1) history of alcohol dependence and alcohol abuse;

(2) current (past-12-month) alcohol consumption patterns, alcohol consumption patterns during heaviest drinking period, and maximum alcohol consumption in a single day;

(3) ages at critical alcohol use milestones;

(4) history of smoking and tobacco dependence, including ages at tobacco use milestones;

(5) history of illicit drug use, a brief screen for illicit drug abuse or dependence, and ages at first illicit drug use;

(6) history of major depression and suicidality;

(7) history of childhood conduct disorder.

ALCOHOL USE EXPERIENCES

This Australian cohort is characterized by near universal alcohol use, with widespread heavy alcohol use.

Fewer than 1% of men, and fewer than 1% of women, were lifetime abstainers.

90% of men reported drinking 9 or more standard drinks in a single day at least once.

70% of women reported drinking 7 or more standard drinks in a single day at least once.

By age 35, we project that 96% of men and 88% of women would have drunk to intoxication at least once (Kaplan-Meier curve)

By age 16, 29% of women had already been intoxicated; by age 17, 28%.

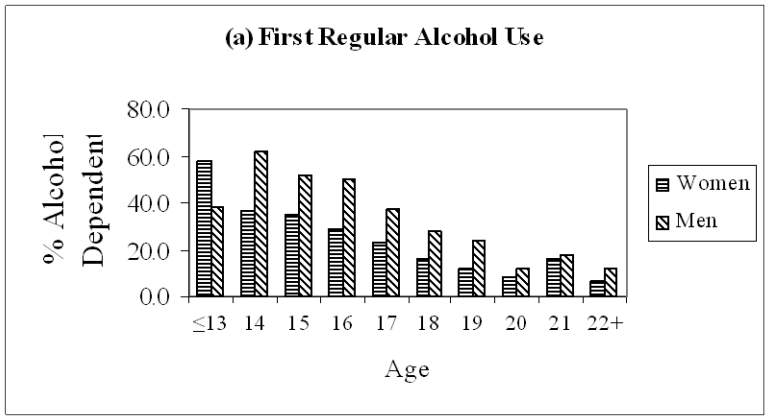
By age 16, 36% of men had already been intoxicated; by age 17, 41%.

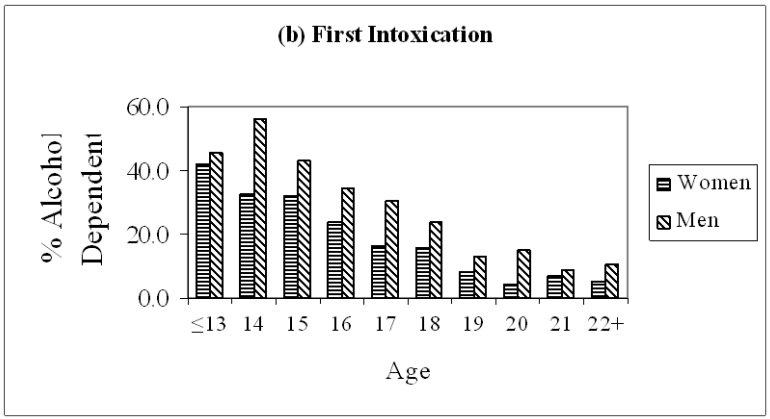
EARLY ONSET OF ALCOHOL DEPENDENCE RISK

Figure 1 shows the associations between early onset of (a) regular alcohol use (using monthly for six months or longer) and (b) drinking to intoxication, and later reporting of alcohol-related problems that meet diagnostic criteria for alcohol dependence (DSM-IV).

In general, in both women and men, the earlier the onset of either drinking to intoxication, or regular drinking, the higher the probability of reporting a history of alcohol dependence.

Figure 1. Probability of reporting a history of alcohol dependence as a function of (a) recalled age at onset of first regular (monthly) alcohol use, or (b) recalled age at first intoxication.





Age at first regular alcohol use

	(a) First regular alcohol use		(b) First intoxication	
	% Alcohol dependent		% Alcohol dependent	
Age	Women	Men	Women	Men
≤13	57.7	37.9	41.6	45.5
14	36.7	62.5	32.5	56.5
15	34.9	51.8	31.7	43.3
16	29.0	49.9	23.5	34.3
17	22.6	37.7	16.3	30.7
18	16.4	28.1	15.5	23.5
19	12.2	24.0	8.0	13.2
20	8.8	12.0	4.5	15.0
21	16.1	17.7	6.9	9.0
22+	6.9	11.5	5.1	10.5

RISK OF ALCOHOL DEPENDENCE AS A FUNCTION OF EARLY ONSET REGULAR DRINKING OR DRINKING TO INTOXICATION, AND OF YEARS OF "AT RISK" DRINKING.

An individual who began drinking at age 16 has, by age 26, had 10 years in which problems with alcohol may emerge. An individual who delays drinking until age 21 has had only 5 years in which alcohol problems could emerge. Statisticians refer to this as the problem of statistical censoring – the association between early onset of alcohol use and probability of reporting a history of alcohol dependence could arise merely because we were assessing those with late-onset drinking at an earlier point in their drinking careers.

To address this possibility, we rescaled the data from Figure 1 in terms of years of "at risk" drinking, where at risk drinking was defined to begin at the earlier of the ages at which someone first drank regularly, or first drank to intoxication.

This is illustrated in Figure 2 for women with onset of drinking to intoxication on or before versus after age 16 (since age at first intoxication proved to be the better predictor of alcohol dependence risk in women). Figure 2 still shows robust evidence for a higher risk of alcohol dependence in women who first got drunk by age 16, compared to other women.

A similar pattern is seen for men in Figure 3. Here we compare men with onset of regular alcohol use on or before versus after age 16 (since age at onset of regular alcohol use was a better predictor of alcohol dependence risk in men). Again, we still see a substantially elevated rate of alcohol dependence in those with onset on or before 16.

Figure 2. **Cumulative incidence of DSM-IV alcohol dependence as a function of years of at-risk drinking in women with versus without onset of first drinking to intoxication at or before age 16.**

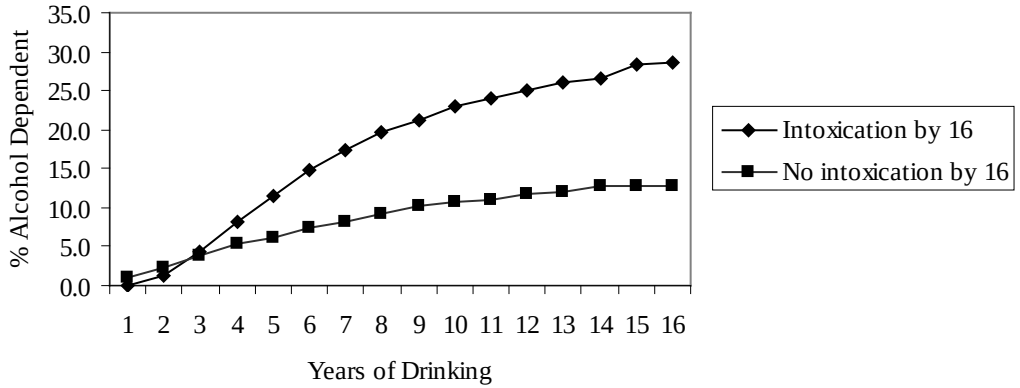
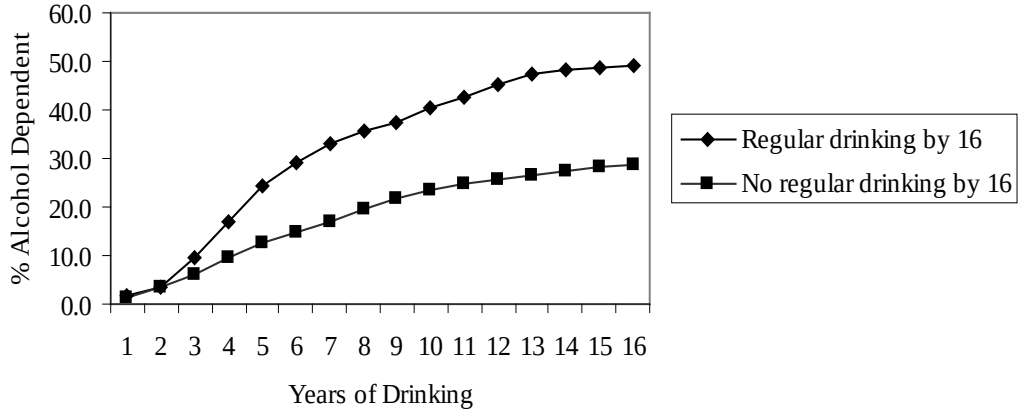


Figure 3. **Cumulative incidence of DSM-IV alcohol dependence as a function of years of at-risk drinking in men with versus without onset of regular drinking at or before age 16.**



ROLE OF PSYCHIATRIC AND OTHER RISK FACTORS

It is a well established finding in the alcoholism literature that history of childhood conduct problems (behaviors such as fire-setting or vandalism), and history of depression, are predictive of increased risk of alcohol dependence. If these same variables are also predictive of early onset at-risk drinking, this could create an artefactual association between early onset of at-risk drinking, and risk of alcohol dependence. To explore this possibility, we included these measures, as well as information about early onset smoking and early onset marijuana use, in a Cox regression analysis (see Table 1).

Reported in Table 1 are hazard ratios which, in non-technical terms, may be thought of as the ratio of the risk to someone with a risk factor (e.g. onset of regular alcohol use at or before 13), and someone without (onset of regular alcohol use after age 18). For example, men who reported onset of regular alcohol use at ages 14-16 had a 2.5 fold increased risk of alcohol dependence, as did women who reported onset of regular alcohol use at or by 13. (In fact, men with onset before 13 do not show any increase in risk, although this group of individuals is small).

Table 1. Association between early alcohol use (and other milestones) and onset of alcohol dependence. Hazard ratios estimated under a Cox regression model, using years of at-risk drinking (defined as years since onset of the earlier of regular drinking or drinking to intoxication).

Women		Hazard Ratio	Men		Hazard Ratio
Drinking to intoxication at/by 13		2.42	Drinking to intoxication at/by 13-15		1.35[NS]
	at 14 or 15	2.44		at 16 or 17	1.32[NS]
	at 16	2.19		at 18	1.35[NS]
	at 17 or 18	1.93	Regular alcohol use at/by 13		1.20[NS]
Regular alcohol use at/by 13		2.48		at 14-16	2.52
	at 14 or 15	1.51		at 17	2.26
	at 16	1.66		at 18	1.84
	at 17 or 18	1.59	Conduct disorder	- narrow	2.36
Conduct disorder	- narrow	2.13		- broad (relaxed age criteria)	1.97
	- broad (relaxed age criteria)	1.54		- broad (relaxed impairment)	1.70
	- broad (relaxed impairment)	1.83		- 2 conduct problems	1.39
	- 2 conduct problems	1.23[NS]	Major depression	- narrow	1.52
Major depression	- narrow	1.79		- broad	1.46
	- broad	1.27[NS]	Marijuana use by 18		1.15[NS]
Marijuana use by 18		1.49	Any smoking by 18		1.24
Regular smoking by 18		1.21[NS]	Regular smoking by 18		1.52

[NS] Not statistically significant

EARLY ONSET ALCOHOL USE VERSUS OTHER RISK FACTORS

Several conclusions can be drawn from Table 1:

(1) **History of conduct disorder or conduct problems did predict increased risk of alcohol dependence, in women as well as men, even when we controlled for early alcohol use milestones.**

(2) **History of depression was also associated with increased risk for women, this was only true for narrowly defined depression, where we required evidence that problems were severe enough for the woman to seek professional help. For men, this was true for both broad and narrow depression (perhaps because Australian men with depression were less likely to seek professional help).**

(3) **Controlling for these psychiatric risk factors, early onset of drinking to intoxication was not predictive of increased alcohol dependence risk in men, but was predictive of increased alcohol dependence risk in women (risk ratios 1.9-2.4)**

(4) **Controlling for these psychiatric risk factors, early onset of regular alcohol use <u>was</u> predictive of increased risk of alcohol dependence in women as well as men.**

COTWIN-CONTROL COMPARISONS

Finally, Table 2 shows associations between early onset of regular alcohol use, or drinking to intoxication in twin pairs who were discordant for early onset of at risk drinking. In these analyses, we again controlled for history of depression and history of conduct disorder.

We found no evidence for genetic effects on age at onset of regular drinking (data not shown), hence for this variable we pool data from monozygotic and same sex dizygotic twin pairs. We find:

(a) onset of regular drinking by age 16 was not significantly predictive of increased risk of alcohol dependence in women or men. However, 95% confidence intervals were somewhat broad, so we could not exclude an important effect.

(b) onset of regular drinking by age 18 was strongly associated with increased risk in men (a 4.5 fold increase) but not significantly in women.

Since we did find evidence for genetic effects on age at first intoxication (data not shown), for this variable we report results separately by twin pair zygosity as well as by gender. We find:

(c) Drinking to intoxication in women by age 16, in MZ female pairs, was significantly associated with increased risk of alcohol dependence. In men, this association did not reach statistical significance.

(d) Onset of drinking to intoxication by age 18 was significantly predictive of increased risk of alcohol dependence in dyzygotic pairs only.

Table 2. Cotwin-control analysis of the association between early drinking to intoxication, or early regular alcohol use, and DSM-IV alcohol dependence, in doubly discordant twin pairs. Conditional odds ratios, and 95% confidence interval, are reported.

	Alcohol dependent twin was early user/drunk	Non-dependent twin was early user/drunk	Adjusted[a] Odds Ratio	95% CI
Regular drinking by 16				
Female like-sex	34	21	1.20[NS]	0.66-2.19
Male like-sex	55	29	1.51[NS]	0.90-2.53
Regular drinking by 18				
Female like-sex	48	25	1.60[NS]	0.95-2.68
Male like-sex	50	11	4.59	2.23-9.45
Intoxication by 16				
MZF	33	16	1.97	1.04-3.75
MZM	26	18	1.35[NS]	0.69-2.61
DZF	31	17	1.46[NS]	0.76-2.81
DZM	36	21	1.35[NS]	0.70-2.62
Intoxication by 18				
MZF	14	5	2.30[NS]	0.78-6.80
MZM	11	3	3.17[NS]	0.83-12.07
DZF	24	6	3.70	1.41-9.68
DZM	18	4	3.60	1.05-12.29

[a] **Controlling for depression, conduct disorder and other risk factors included in Table 1.**

CONCLUSIONS

These analyses lead us to the following conclusions:

(a) Early onset of regular alcohol use, or early onset of drinking to intoxication, during the teen years, is associated with increased risk of alcohol dependence (Figure 1). This remains true even when we correct for years of "at-risk" drinking (Figure 2). Early onset of regular drinking was more strongly predictive in men; early onset of drinking to intoxication was more strongly predictive in women, unless onset of regular drinking was very early (by age 13: Table 1).

(b) The association between early onset of regular drinking and alcohol dependence risk in men remained significant when known psychiatric risk-factors were controlled for. Further more, in male like-sex twin pairs discordant for onset of regular alcohol use by age 18, the early onset drinker was 4.5 times to report a history of alcohol dependence than the late onset drinker (Table 2).

In the Australian context, where 18 is the legal drinking age, these data are perhaps better conceptualized as either a protective effect of late-onset alcohol use, or, if the association is non-causal, with reduced risk associated with late onset alcohol use.

CONCLUSIONS - II

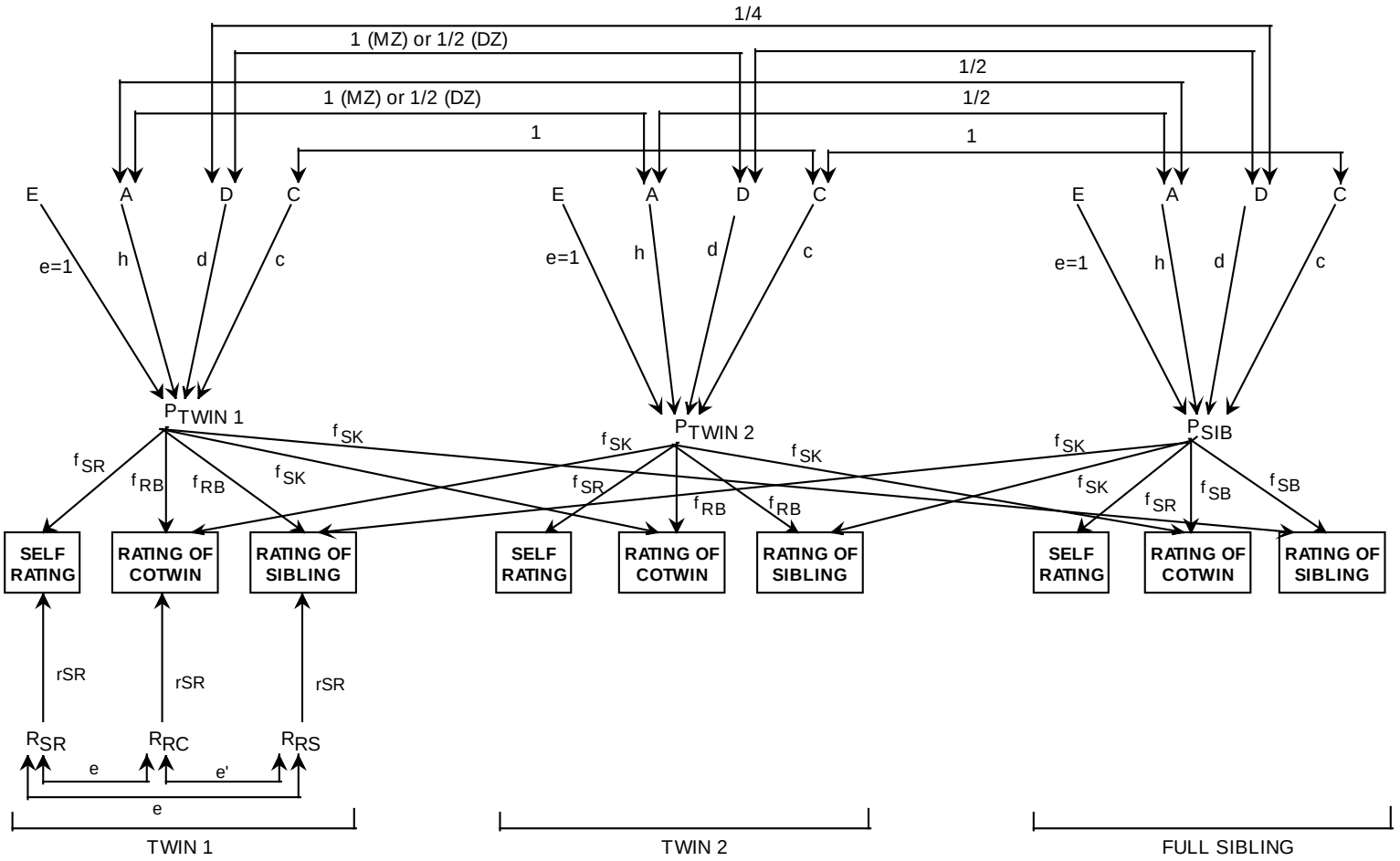
(c) **In women, both early onset drinking to intoxication, and early onset regular drinking, were predictive of increased risk, even when psychiatric risk-factors were controlled for (Table 1)**

(d) **In female like-sex pairs discordant for early onset of regular drinking, there was only a slight, non-significant increase in risk in the early-user, suggesting that shared environmental influences (e.g. peer influences, family, neighborhood or school effects) are important determinants of the association between early onset regular drinking, and heightened alcohol dependence risk: the early-onset-drinkers are more likely to come from high-risk environments (Table 2)**

(e) **In contrast, in female MZ pairs discordant for early onset drinking to intoxication (by age 16), the risk to the early user was almost double that to her twin sister who did not get drunk by age 16. Environmental influences not shared by twin sisters (e.g. boyfriends) may be more important here.**

(f) **In dizygotic pairs discordant for drinking to intoxication by age 18, the sibling who had been intoxicated by age 18 had a 3.5 fold increase in alcohol dependence risk compared to the sibling who did not. In this group however, since dizygotic twins are no more similar than ordinary brothers or sisters, genetic differences associated with differences in age at first intoxication may have contributed to this association.**

Figure 4.2 Reciprocal rating model for twin and sibling data (adapted from Heath et al, 1992)



NOTE: MZ = monozygotic, DZ = dizygotic, P = true phenotype, E = nonshared environmental deviation, A = additive genetic deviation, D = nonadditive genetic (dominance or epistatic) deviation; C = shared environmental deviation. Path coefficiently e, h, d and c represent the path regressions of P on E, A, D and C respectively. $R_{SR,}$ R_{RC} and R_{RS} represent measurement error (residual) effects on self-rating, rating of cotwin and rating of sibling, with corresponding paths r_{SR}, r_{RS}, r_{RS} (illustrated for twin 1 only). Paths from true phenotype (P) to self-rating, rating of cotwin or sibling (rater bias parameter) and rating by cotwin or sibling knowledge parameter) are *** by f_{SR}, f_{RB} and f_{SK} respectively.