The Genetic Epidemiology of Substance Abuse

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TABLE 1. Four Major Paradigms of Psychiatric Genetics

Paradigm	Samples Studied	Method of Inquiry	Scientific Goals
1. Basic genetic epidemiology	Family, twin, and adoption studies	Statistical	To quantify the degree of familial aggregation and/or heritability
2. Advanced genetic epidemiology	Family, twin, and adoption studies	Statistical	To explore the nature and mode of action of genetic risk factors
3. Gene finding	High-density families, trios, case-control samples	Statistical	To determine the genomic location and identity of susceptibility genes
4. Molecular genetics	Individuals	Biological	To identify critical DNA variants and trace the biological pathways from DNA to disorder

Paradigm 1- Basic Genetic Epidemiology - What Have We Learned?

- Genetic factors play a substantial role in the etiology of Substance Use Disorders (AD).
- Heritability – the proportion of individual differences in a particular disorder or trait in a particular population that results from genetic differences between individuals.
- Heritability estimates typically in the range of 50-60%
- How does this compare to other psychiatric and biomedical disorders?

Heritability Of Psychiatric Disorders

Heritability	Psychiatric Disorders	Other Important Familial Traits
~zero		Language Religion
20-40%	Anxiety disorders, Depression, Bulimia, Personality Disorders	Myocardial Infarction, Normative Personality, Breast Cancer, Hip Fracture
40-60%	Alcohol Dependence Drug Dependence	Blood Pressure, Asthma Plasma cholesterol, Prostate Cancer, Adult-onset diabetes
60-80%	Schizophrenia Bipolar Illness	Weight, Bone Mineral Density
80-100%	Autism	Height, Total Brain Volume

How Consistent are the Estimates of Heritability of AD Across Space and Time?

- Heritability is not a characteristic of a disorder – rather it is a feature of a disorder in a specific population at a specific time.
- We will look quickly at twin studies of AD and other SUDs.

Genetic & environmental proportions of variance in alcoholism estimated from studies of male twins

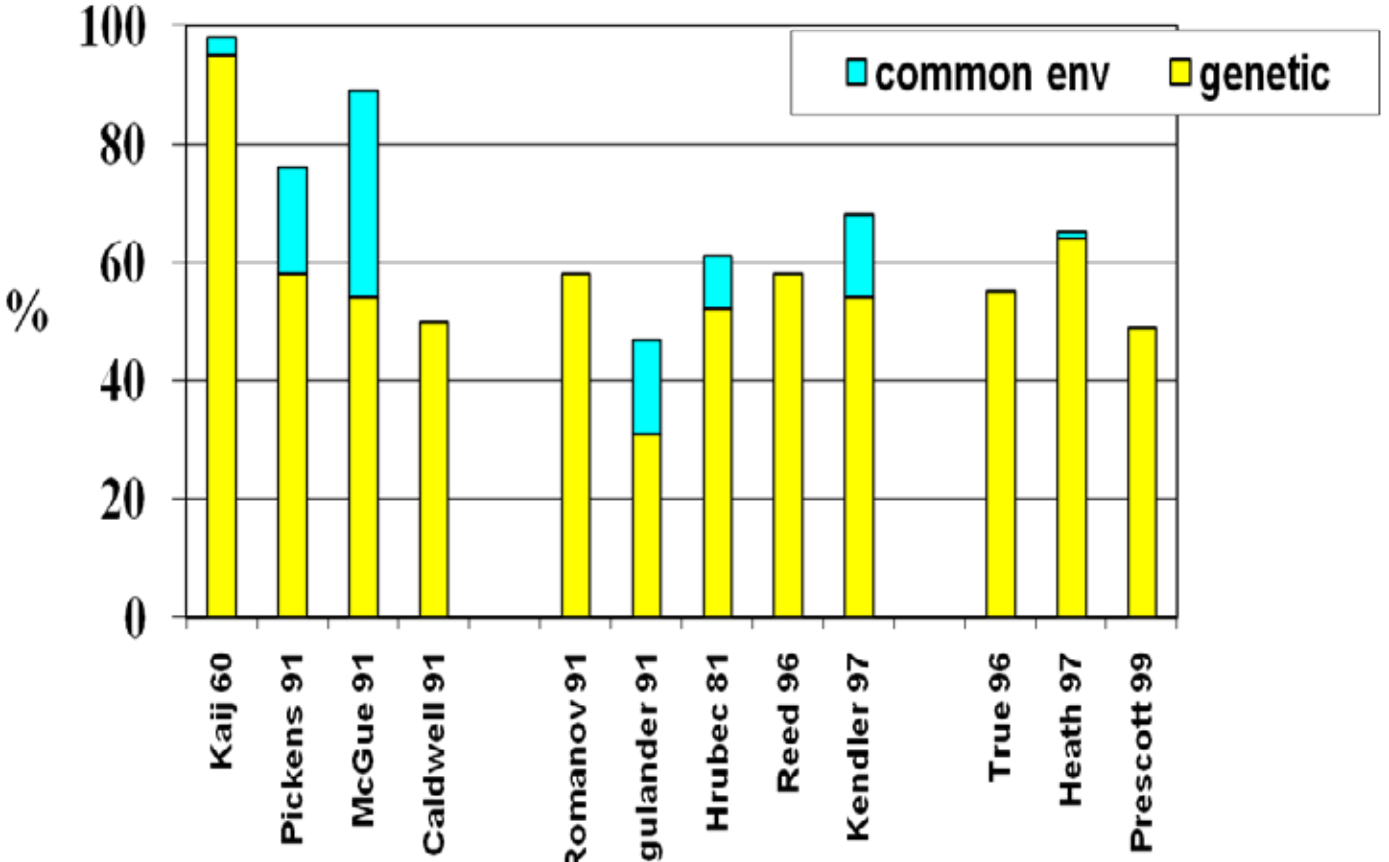
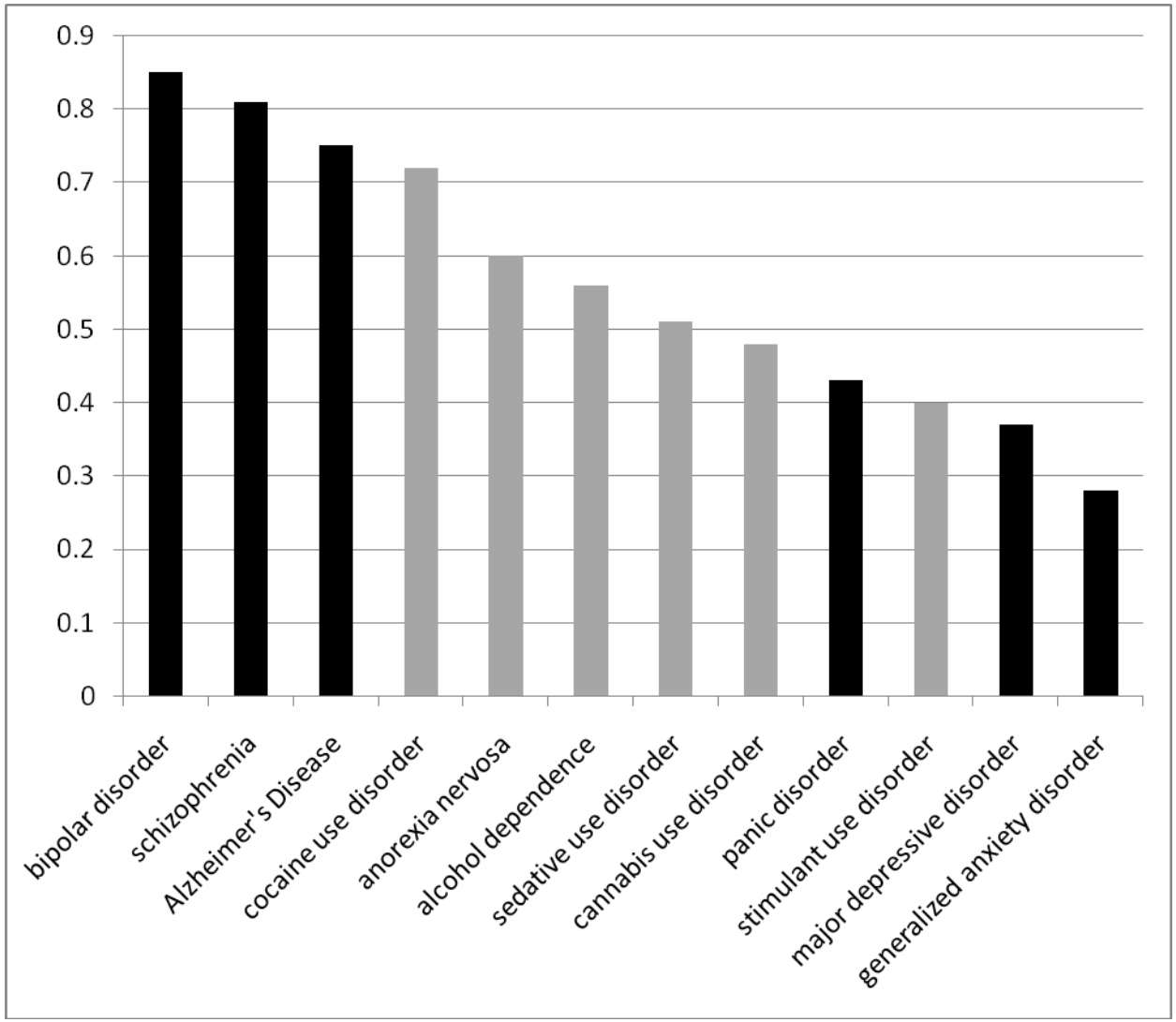


Figure 2a, *Prescott, Maes & Kendler, 2005*

Summary Slide

- Based on published meta-analyses or ones we did ourselves (with Joe Bienvenu) – pretty large CIs.
- Main results of non-alcohol SUDs from two studies – VATSPSUD and Vietnam Era twin study. Some reports from the Australian and Norwegian registiries.


0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
bipolar disorder
schizophrenia
Alzheimer's Disease
cocaine use disorder
anorexia nervosa
alcohol dependence
sedative use disorder
cannabis use disorder
panic disorder
stimulant use disorder
major depressive disorder
generalized anxiety disorder

How Consistent are the Estimates of Heritability of AD Across Time?

- Swedish Temperance Board Registration Data – 8,935 pairs of male-male twins born 1902-1949.

How Consistent are the Estimates of Heritability of AD Across Space and Time?

- Swedish Temperance Board Registration Data – 8,935 pairs of male-male twins born 1902-1949.
- Complete birth cohort.
- Sweden underwent several dramatic changes.
- Income increased 6-fold
- Government experimented with changes in governmental control of access to alcohol.

How Consistent are the Estimates of Heritability of AD Across Space and Time?

- In 1917, Sweden adopted a nationwide alcohol rationing system that strictly limited the amount of alcohol that an individual was permitted to purchase. An individual's official limit varied according to sex, age, and financial situations, and was, for men older than 25 years, usually between 1 and 3 L of hard liquor per month.

Table 2. Sample Size, Prevalence, Probandwise Concordance, and Tetrachoric Correlation for TBR in Swedish Monozygotic and Dizygotic Male-Male Twin Pairs by Birth Cohort*

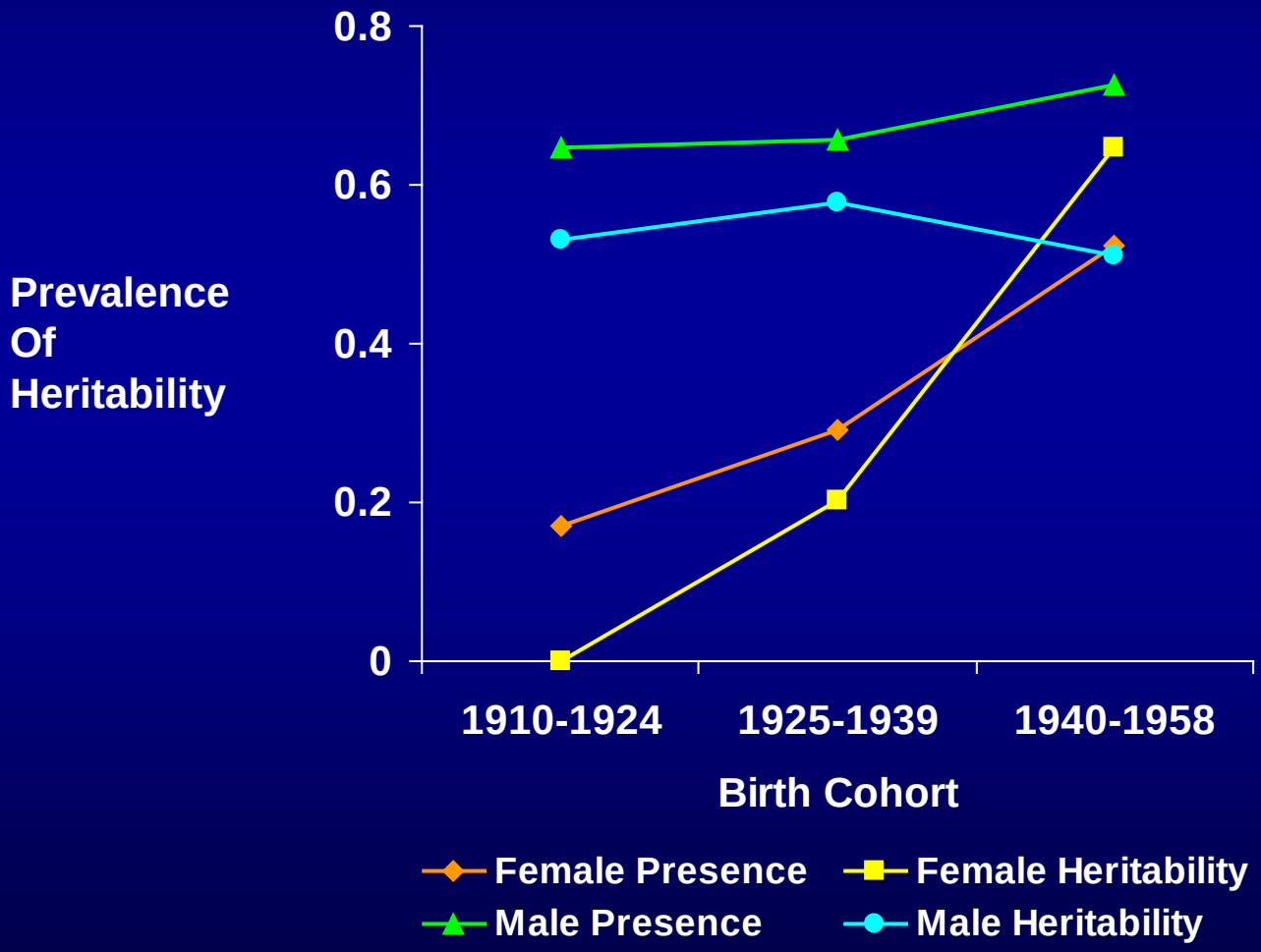
	Monozygotic Twins				Dizygotic Twins			
Birth Years†	No. of Pairs	Prevalence	Probandwise Concordance	*r*	No. of Pairs	Prevalence	Probandwise Concordance	*r*
1902-1949	**3185**	0.132	0.479	+ 0.669	**5750**	0.146	0.328	+ 0.409
1902-1917	799	0.128	0.500	+ 0.701	1500	0.159	0.347	+ 0.418
1918-1930	791	0.141	0.502	+ 0.688	1534	0.147	0.293	+ 0.340
1931-1942	842	0.138	0.438	+ 0.603	1507	0.136	0.323	+ 0.421
1943-1949	753	0.120	0.478	+ 0.688	1209	0.140	0.355	+ 0.470

Interactions between gender, culture and genes – the role of social factors to constrain behavior.

- Tobacco consumption and year of birth in Swedish twins.
- Study done with Nancy Pedersen on the SATSA sample.
- Study males and females separately

Prevalence And Heritability Of Regular Tobacco Use

Three Birth Cohorts Of Men And Women In Sweden



How Consistent are the Estimates of Heritability of SUDs Across Space and Time?

- So, to the best of our knowledge, the heritability of AD is relatively robust – across multiple European populations living in Australia, North American and Europe and across a half century of Swedish history that saw dramatic changes in that country.
- But a quite different picture is seen for regular smoking behavior with a large gene x cohort interaction in women.
- Know much less about results for other psychoactive substance abuse and dependence.

Paradigm 2- Advance Genetic Epidemiology

- Many questions relevant to SUDs
- Begin with question of multivariate models –
- What is the relationship between the genetic and environmental risk factors for SUDs and for psychiatric disorders?

Paradigm 2- Advance Genetic Epidemiology – Multivariate Models

- Examine this question in 2,111 personally interviewed young adult members of the Norwegian Institute of Public Health Twin Panel. Statistical analyses were performed with the Mx and Mplus programs.

Paradigm 2- Advance Genetic Epidemiology – Multivariate Models

- Replicating earlier results from our Virginia twin analyses and from the Minnesota group, SUDs are genetically part of the externalizing group of disorders.

Paradigm 2- Advance Genetic Epidemiology – Multivariate Models

- Let’s drill down deeper into the relationship between AD and SUD to directly address the question of the specificity or non-specificity of genetic risk factors for AD.

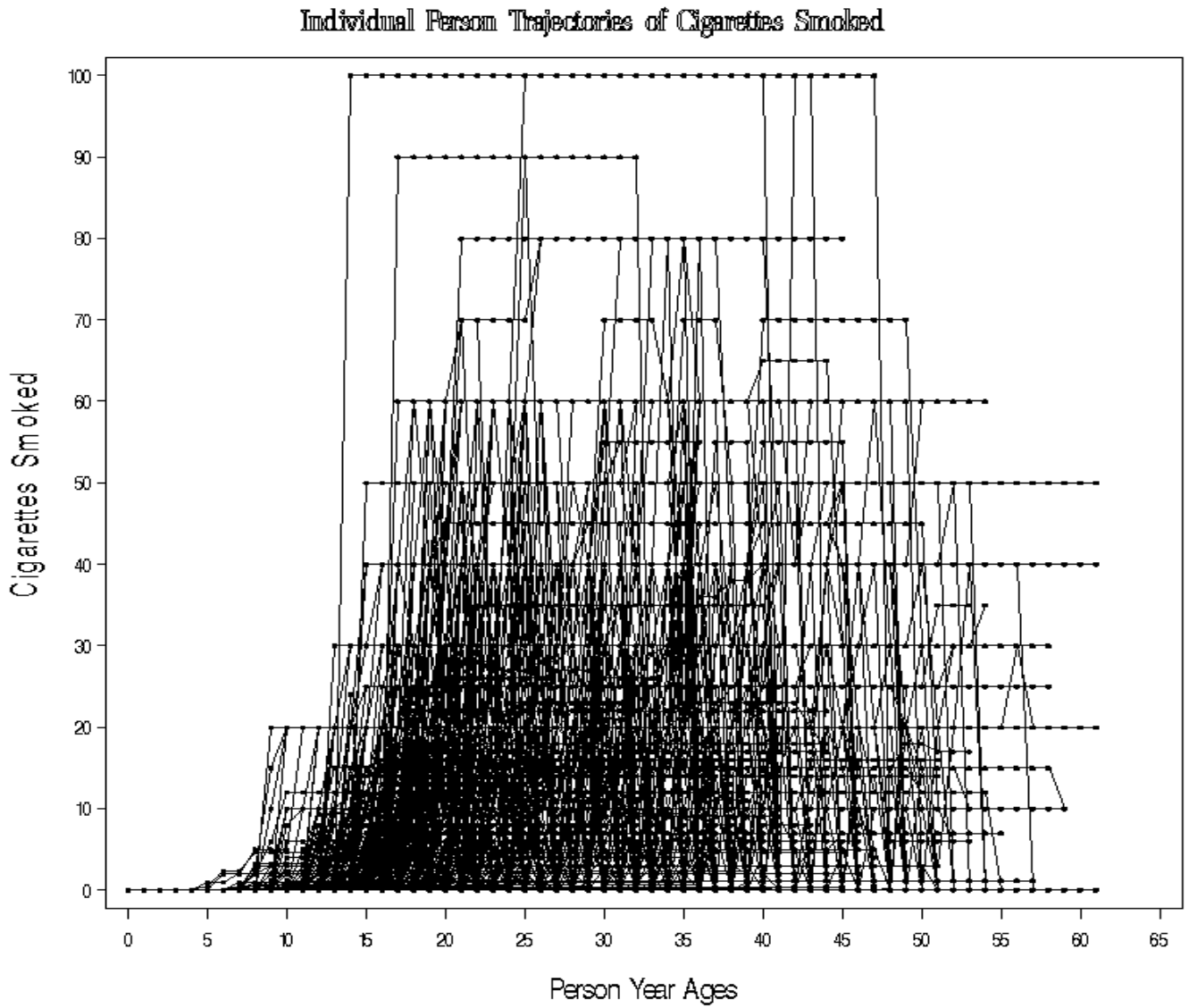
Paradigm 2- Advance Genetic Epidemiology – Multivariate Models

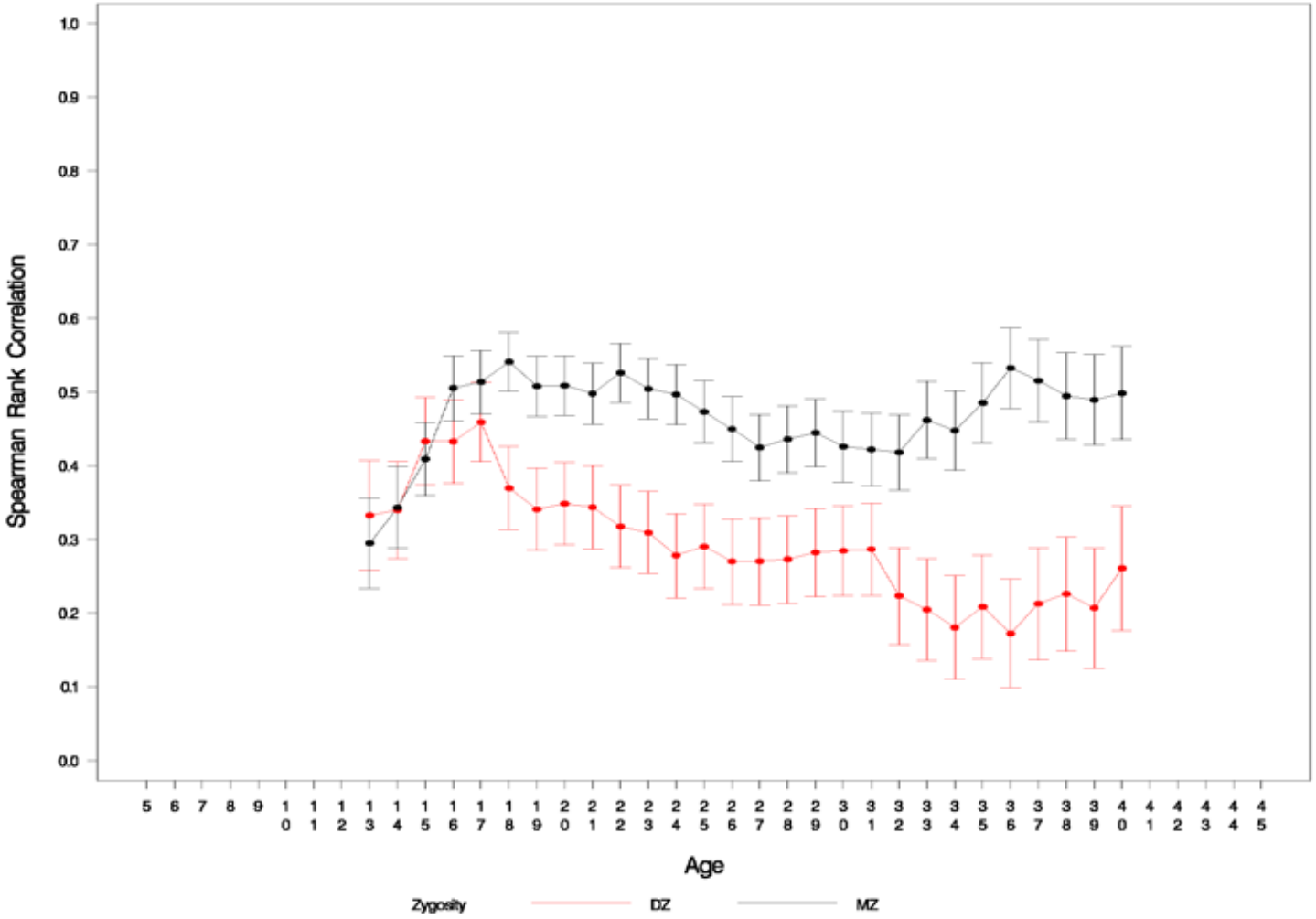
- Similar to prior analyses from this sample, these results suggest that ~ 70% of heritabiity for AD is shared (this time with other drugs of abuse) and 30% unique to AD.
- For cocaine dependence, for example, 85% of total heritability is shared with other drugs and 15% is unique.
- In general, pretty clear that non-specific genetic effects outweigh specific effects.

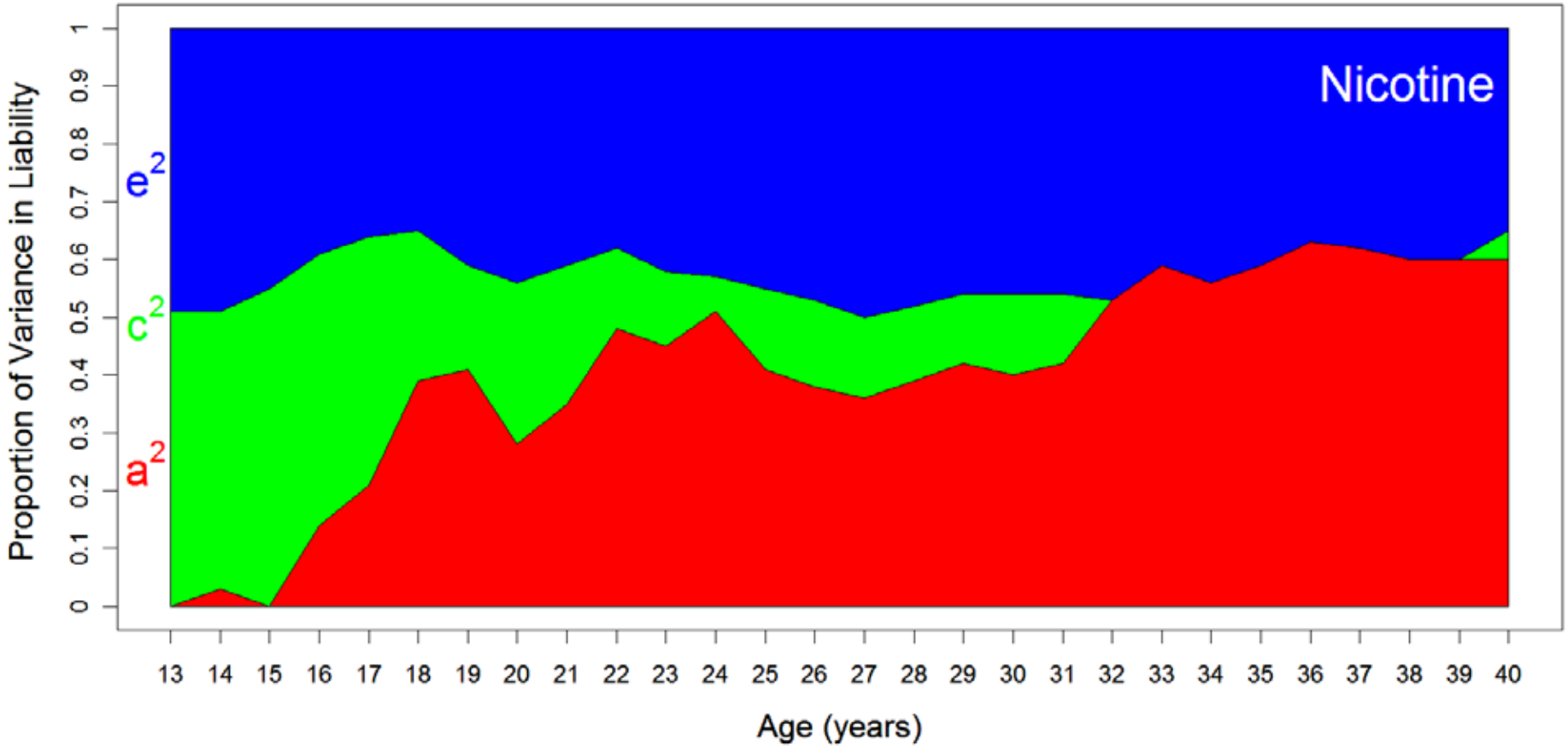
Paradigm 2- Advance Genetic Epidemiology – Development

- Genes and environment act through time.
- Focus on alcohol intake in 1796 members of male-male pairs from the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders.
- Assessed retrospectively using a life-history calendar.

NICOTINE

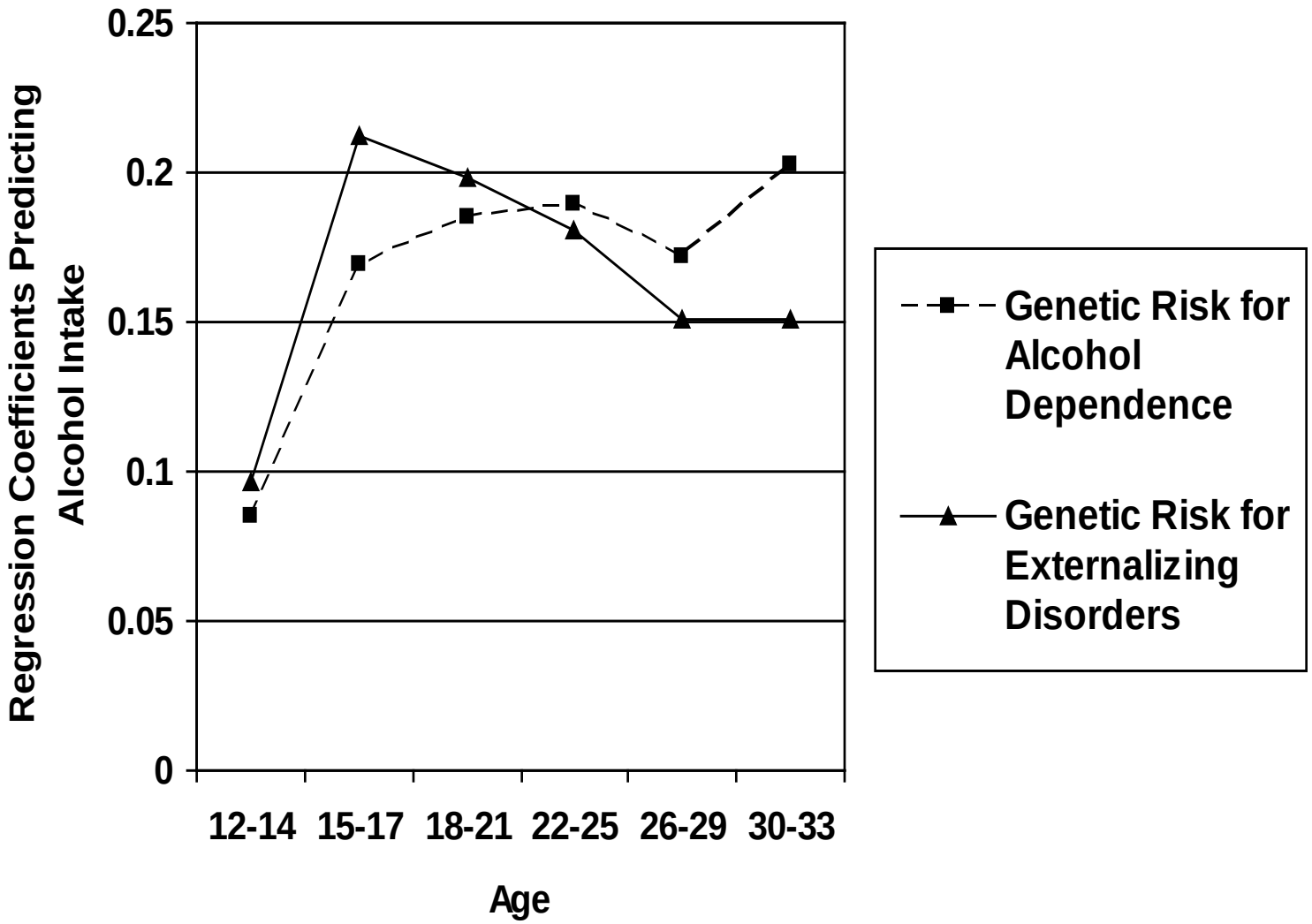

Individual Person Trajectories of Cigarettes Smoked
Cigarettes Smoked
0
10
20
30
40
50
60
70
80
90
100
0
5
10
15
20
25
30
35
40
45
50
55
60
65
Person Year Ages


Spearman Rank Correlation
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45
Age
Zygosity
DZ
MZ


Nicotine
e^2
c^2
a^2
Proportion of Variance in Liability
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40
Age (years)

Paradigm 2- Advance Genetic Epidemiology – Development

- One more developmental question –
- Do we see differential developmental changes in the impact of specific genetic risk factors for AD versus non-specific risk factors for externalizing disorders.
- Again ~ 1700 males from VATSPSUD


Regression Coefficients Predicting Alcohol Intake
0.25
0.2
0.15
0.1
0.05
0
12-14
15-17
18-21
22-25
26-29
30-33
Age
Genetic Risk for Alcohol Dependence
Genetic Risk for Externalizing Disorders

Paradigm 2- Advance Genetic Epidemiology

- Twin-family designs – ask a new set of questions.

FIGURE 1. Path Diagram of the Full Twin Family Model for Alcoholism[a]

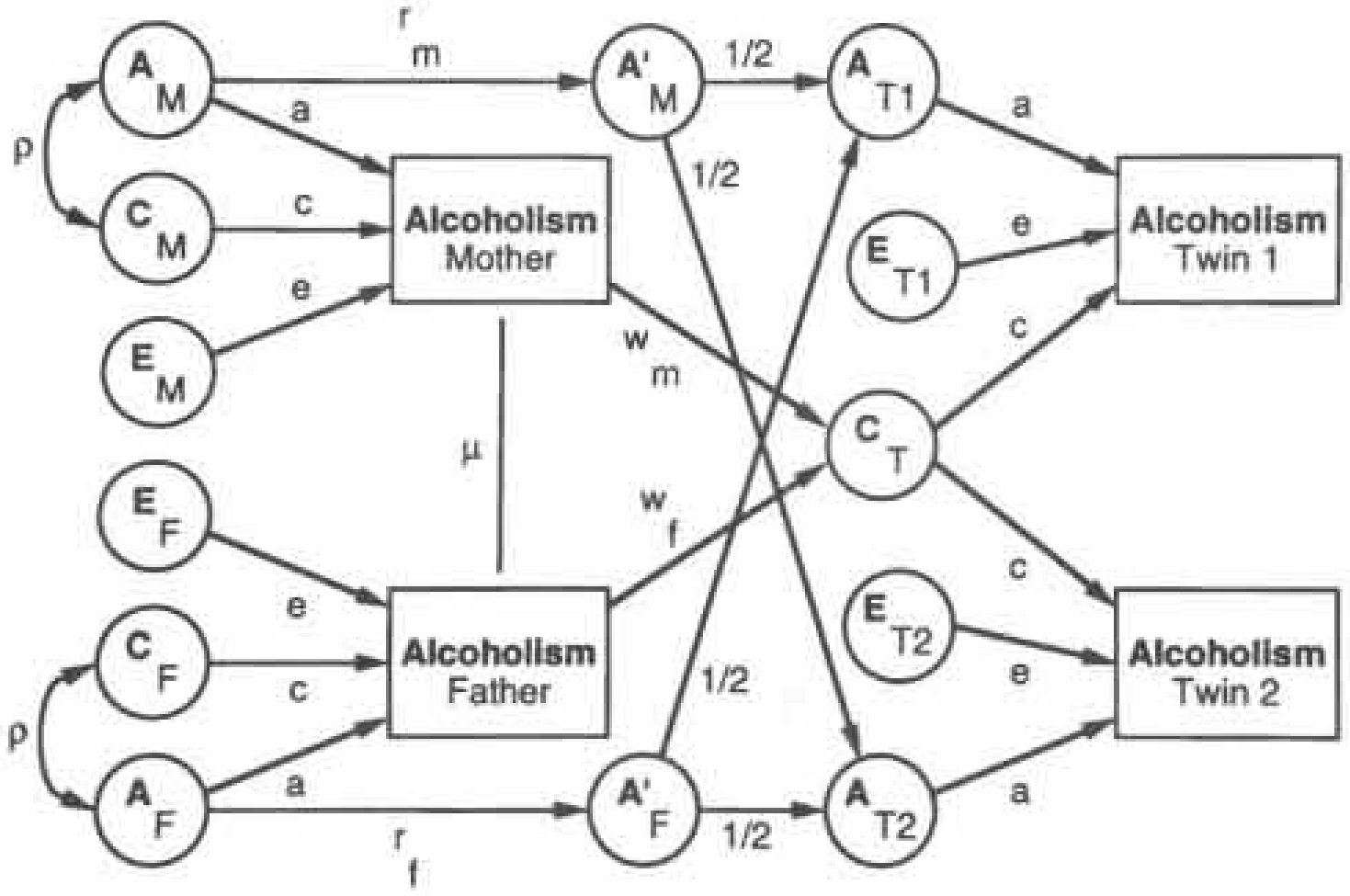
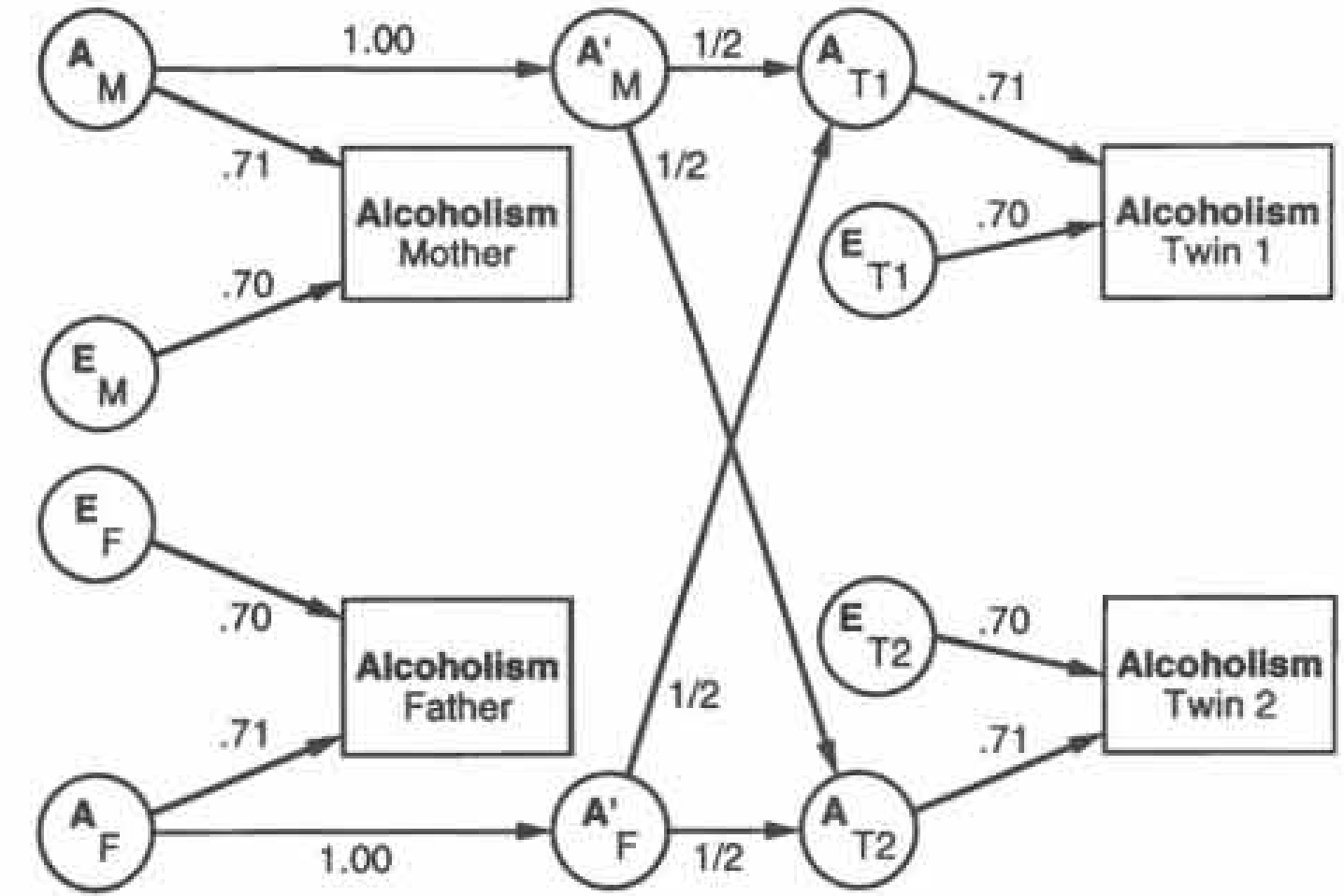


FIGURE 2. Parameter Estimates for the Best-Fitting Model Applied to Narrowly Defined Alcoholism (With Tolerance or Dependence)[a]



Paradigm 2- Advance Genetic Epidemiology

- How to capture the conditionality of genetic influences on SUDs.
- No initiation, no chance to express genetic risk.
- How to model?
- CCC model – causal, contingent, common pathway.

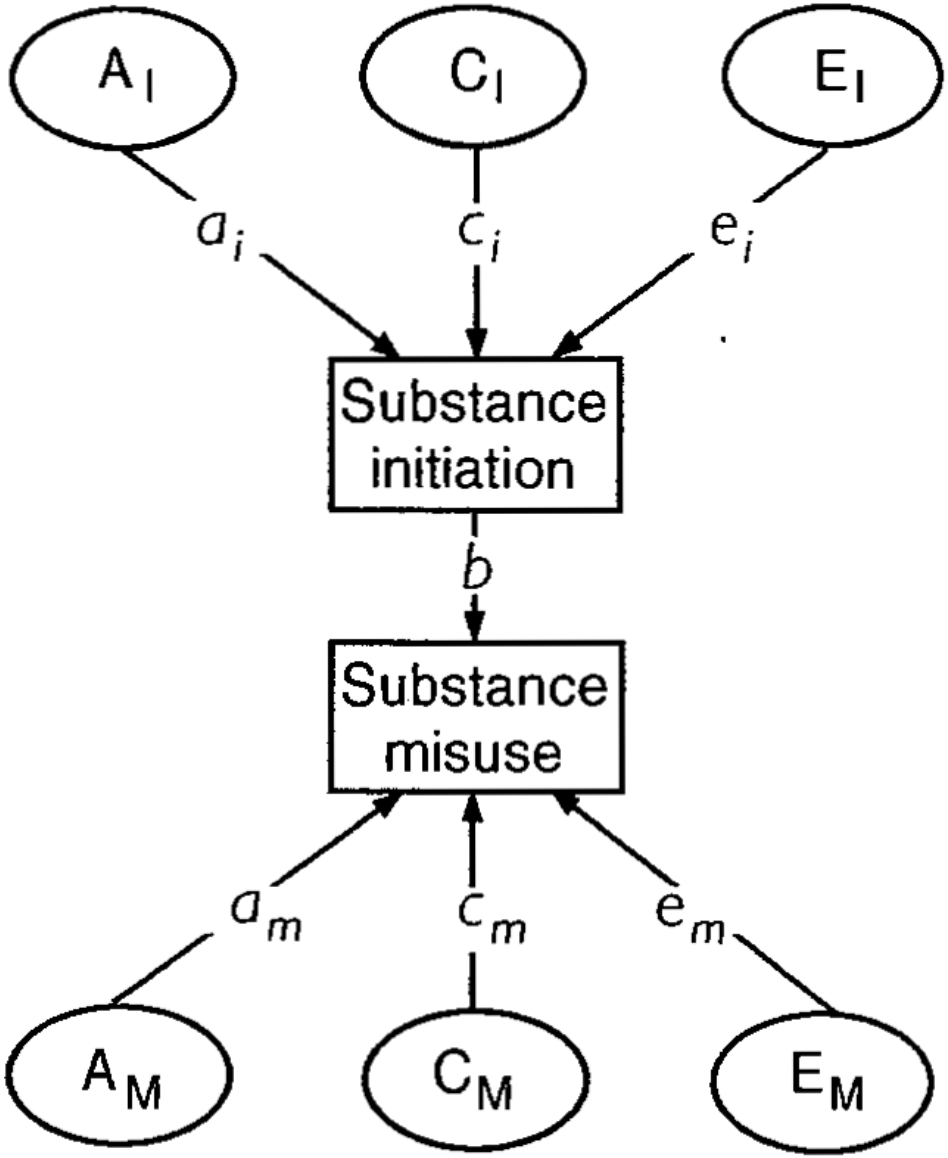


Fig. 1 A bivariate twin model for substance initiation and subsequent substance misuse.

Table 3 Parameter estimates and 95% confidence intervals (95% CI) for the full and best-fit models for illicit substance initiation and subsequent misuse

Substance	Model	Estimate (E)/95% CI	a_i^2	c_i^2	e_i^2	b^2	a_m^2	c_m^2	e_m^2
Any	I	E	0.49	0.28	0.23	0.53	0.23	0.00	0.24
		CI	0.21–0.81	0.14–0.53	0.16–0.30	0.19–0.77	0.00–0.48	0.00–0.08	0.06–0.46
	V	E	0.49	0.28	0.23	0.53	0.23	–	0.24
		CI	0.21–0.81	0.14–0.53	0.16–0.30	0.19–0.77	0.03–0.48	–	0.06–0.40
Cannabis	I	E	0.46	0.29	0.25	0.66	0.17	0.00	0.17
		CI	0.18–0.77	0–0.54	0.20–0.32	0.32–0.94	0–0.41	0–0.25	0–0.40
	V	E	0.46	0.29	0.25	0.66	0.17	–	0.17
		CI	0.18–0.77	0–0.54	0.20–0.33	0.32–0.94	0–0.41	–	0–0.40

Paradigm 2- Advance Genetic Epidemiology – Gene x Environment Interaction

- Definition – the impact of genetic risk factors on disease risk is dependent on the history of environmental exposures. OR
- – the impact of environment risk factors on disease risk is dependent on genotype.
- Probably no area of psychiatric genetics research that is more controversial and artifact prone.
- A range of conceptual and statistical issues - Buyer beware!

Gene x Environment Interaction

- Just show one classical example – in type I (adult non-ASPD) alcoholism from Cloninger's Swedish adoption studies.
- Risk only high in subjects at high genetic risk and exposed to high risk environment.

Table 3. Confirmatory Cross-Fostering Analysis: Severe Type 1 Alcohol Abuse in 577 Men From Replication Study Classified According to Stockholm Study Discriminant Functions

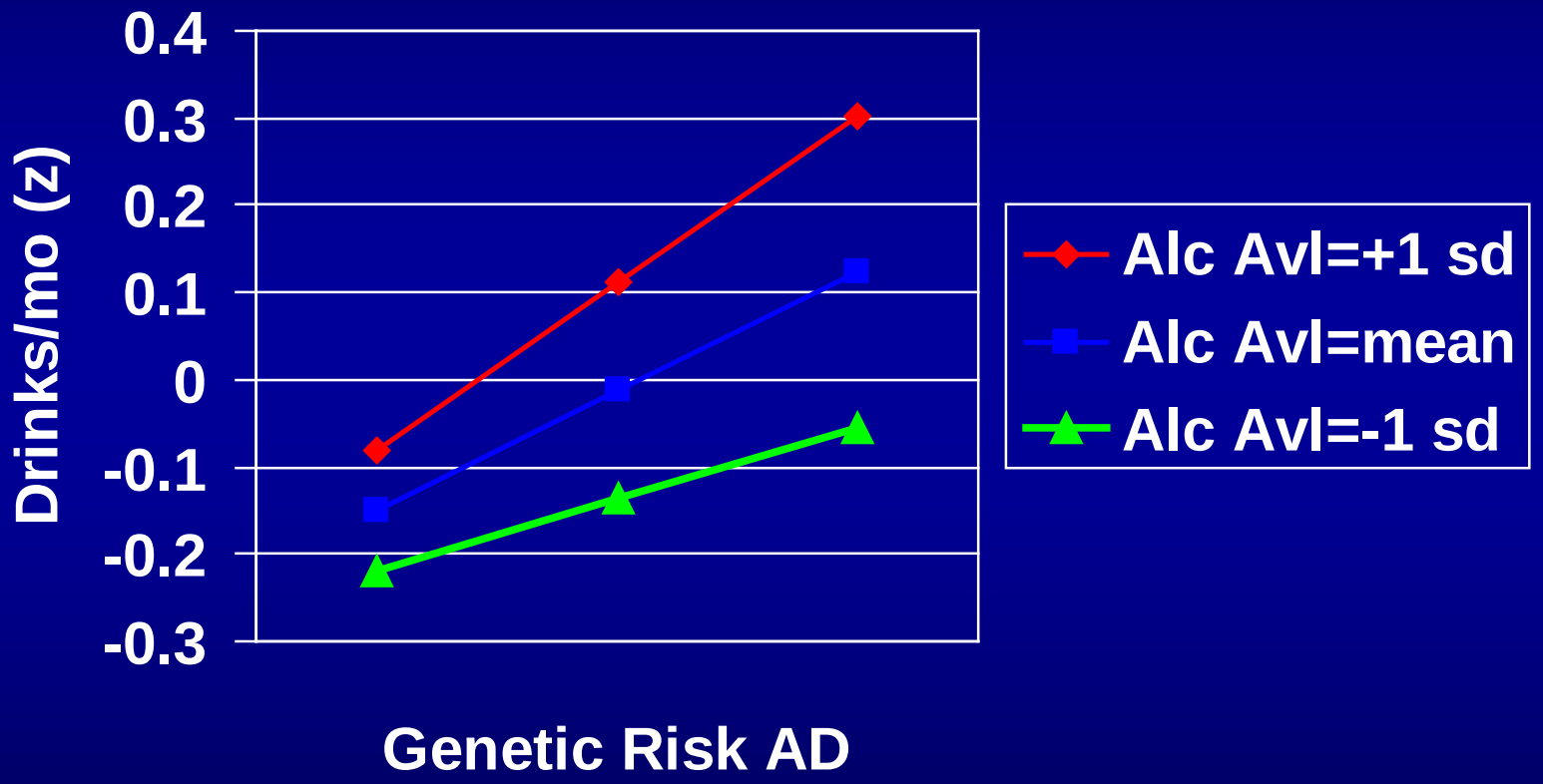
Type 1 Genetic Background	Severe Environmental Background	Stockholm Men		Replication Men	
		No.	% Severe	No.	% Severe
No	No	376	4.3	363	3.0
No	Yes	72	4.2	44	2.3
Yes	No	328	6.7	135	3.0
Yes	Yes	86	11.6*	35	11.4*

**Risk was significantly increased compared with all others in the Stockholm study (odds ratio, 2.4; 95% confidence interval, 1.1-4.9) and in the replication study (odds ratio, 4.2; 95% confidence interval, 1.3-13.5).*

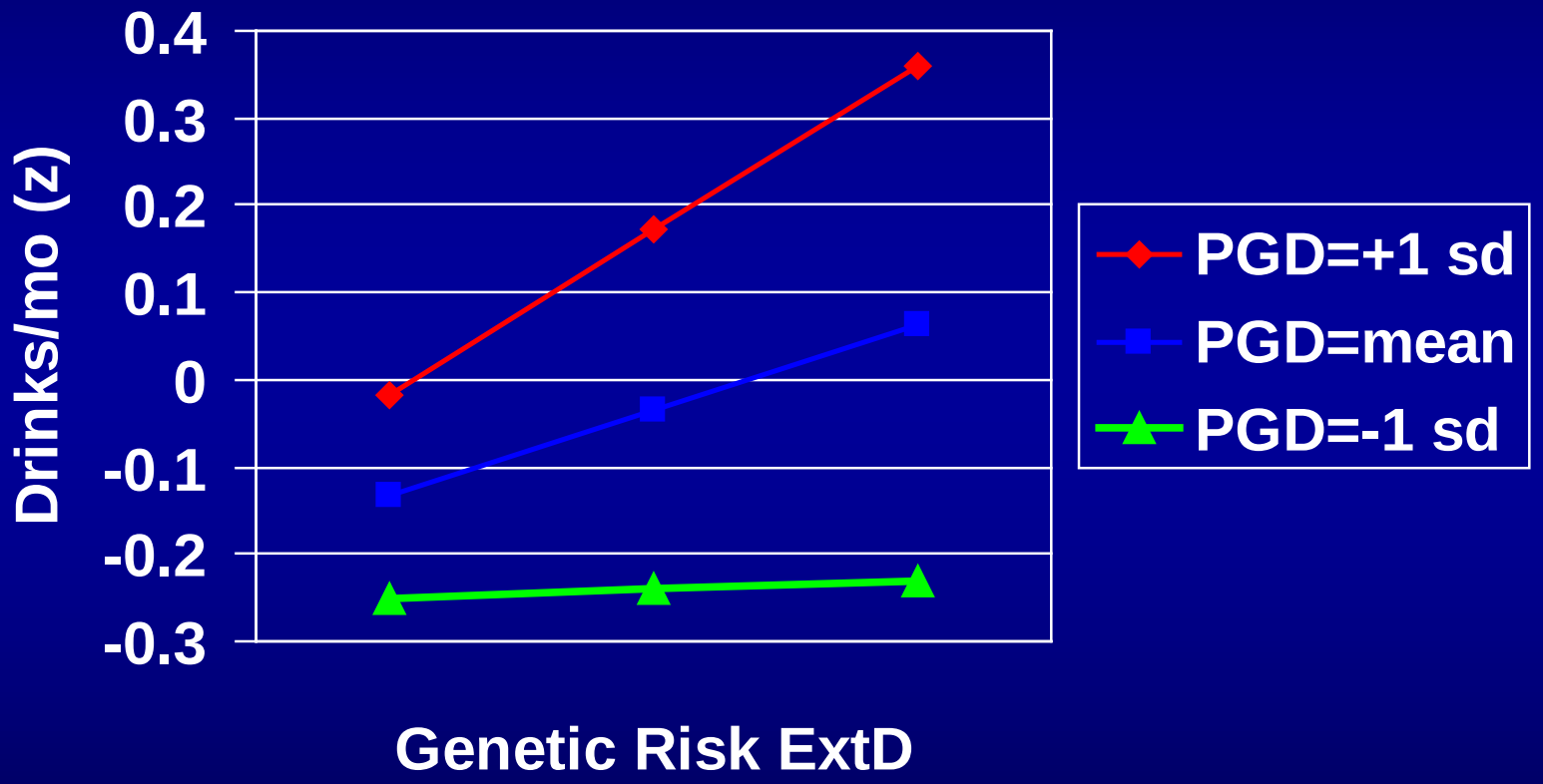
Paradigm 2- Advance Genetic Epidemiology – Gene x Environment Interaction

- Again ~ 1700 males from VATSPSUD
- Asked – would the heritability of alcohol consumption in adolescence be modified by key environmental risk factors
  - Alcohol Availability
  - Peer Deviance
  - Prosocial Behaviors

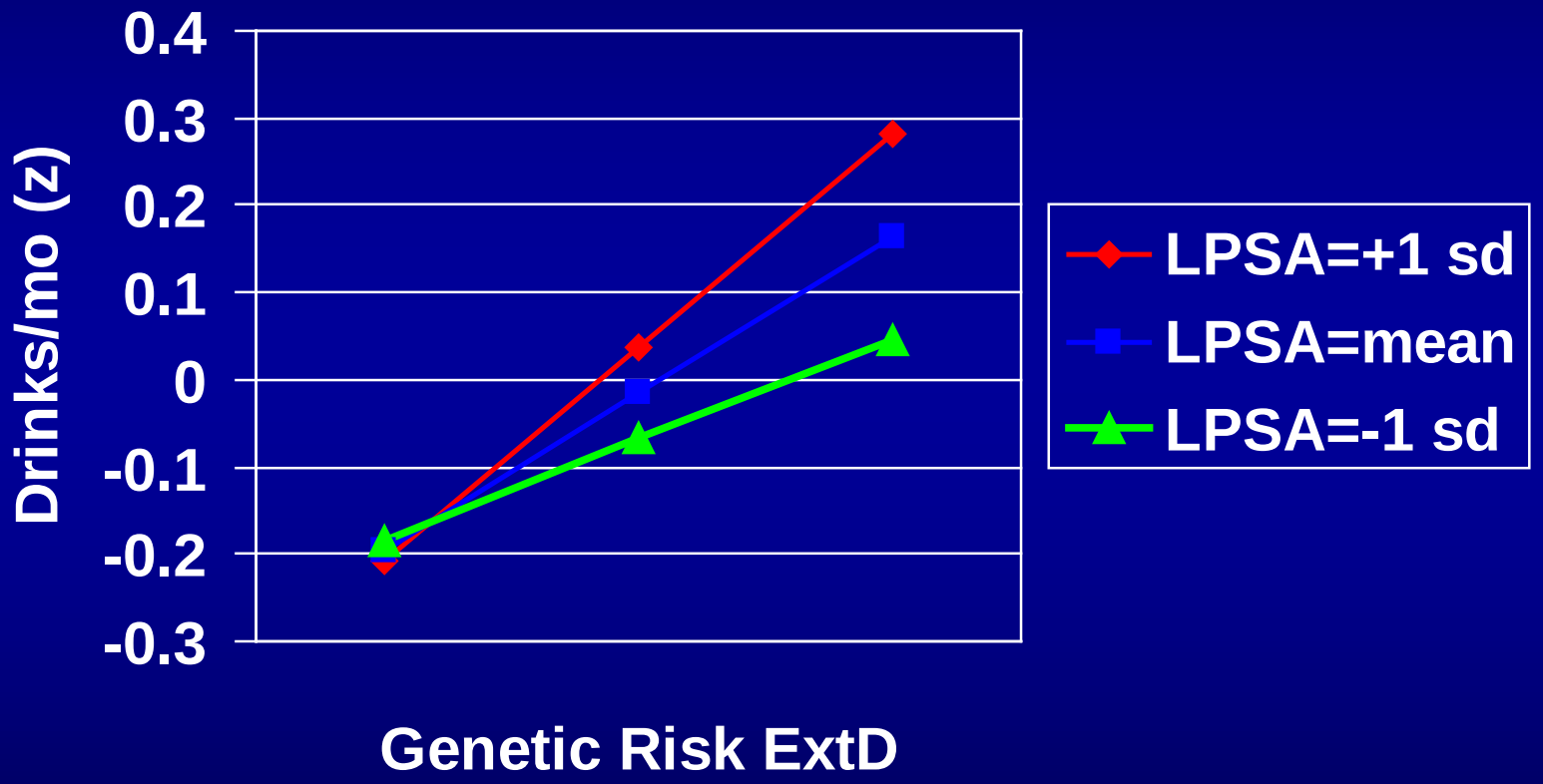
Alcohol Availability 12-14



Peer Group Deviance 12-14



Lack of Prosocial Activities 12-14



Paradigm 2- Advance Genetic Epidemiology – Gene x Environment Interaction

- Many other interesting G x E findings for alcohol use.
- A few other examples many from the work of my colleague Danielle Dick.
- One general theme – Genetic effects on alcohol use are more pronounced when social constraints are minimized and/or when the environment permits easy access to alcohol and/or encourage its use.

Gene-Environment Interaction Alcohol Use

- Marital Status (Heath et al., 1989)
- Religiosity (Koopmans et al., 1999)
- Urban/rural residency (Rose et al., 2001)
- Neighborhood characteristics (Dick et al., 2001)
- Parenting/Peers (Dick et al., 2006, 2007)

Gene- Environment Correlation

- Better termed **genetic control of sensitivity to the environment**.
- Time is too limited to give details.
- My sense is that this process is of substantial importance in mediating the impact of genetic risk factors on SUDs.
- That is, in part, genes impact on risk for SUDs by increasing the chances that individuals seek out high risk environments which expose them to substances of abuse and encourage them in their use and misuse.

Paradigm 2- Advance Genetic Epidemiology

- Integrated etiologic models.
- To just get a start looking at causal pathways.

Paradigm 2- Advance Genetic Epidemiology – Integrative Developmental Model

- Evidence for two etiologic pathways characterized by genetic and temperamental factors and by psychosocial adversity.

Paradigm 2- Advance Genetic Epidemiology – Multivariate Model for DSM-IV Criteria for AD

- Attempted to distinguish two hypotheses.
- 1. Each of the seven AD criteria index the same set of risk genes so that the diagnosis of AD is genetically homogeneous.
- 2. The DSM-IV syndrome of AD is genetically heterogeneous, arising from multiple sets of risk genes that are each reflected by a distinct set of diagnostic criteria.
  - Rodent studies suggest relatively distinct set of risk genes for different alcohol-related traits.

Paradigm 2- Advance Genetic Epidemiology – Multivariate Model for DSM-IV Criteria for AD

- Long arduous task of complex model fitting.
- 7,548 personally interviewed male and female twins from the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders
- Had to take account of the fact that lots of people did not meet our screening criteria and skipped out of the alcohol section.
- This is the best fit model --

Paradigm 2- Advance Genetic Epidemiology – Multivariate Model for DSM-IV Criteria for AD

- This is the best fit model –
- Robustly supported second hypothesis – evidence for three genetic factors, which we tentatively called:
  - heavy use and tolerance
  - loss of control with alcohol associated social dysfunction
  - withdrawal and continued use despite known problems.

8 Major Conclusions

- 1. SUDs are substantially heritable and heritability estimates for AD appear to be relatively stable across time and space. For smoking, we have evidence of potentially strong gene x cohort effects.
- 2. Roughly 2/3rds of genetic risk factors for AD and other SUDs are not-disorder specific but are shared with other forms of substance abuse and with other externalizing disorders generally.

- 3. In early adolescence, siblings resemblance for alcohol, nicotine and cannabis consumption is entirely due to environmental factors. With increasing age, we see an increasing degree of genetic influence.
- 4. For at least AD, we do not have strong evidence from GE models for parent-offspring environmental transmission.
- 5. Genes for AD appear to be rather substantially moderated by environmental exposures, especially those which either relax social constraints and/or permit easy access to alcohol and/or encourage its use.

Conclusions

- 6. G-E correlation is probably an important etiologic factor in SUDs. Genes can impact on SUDs via outside the skin pathways.
- 7. I presented one very rough integrated etiologic model for AD – showing how genetic/termpermental and environmental adversity pathways might inter-relate in the etiology.
- 8. DSM-IV criteria for AD appear, from a genetic perspective, to be etiologically complex reflecting multiple dimensions of genetic risk. Would we see the same for other SUDs?

Key Collaborators

- Mike Neale PhD
- Danielle Dick PhD
- Carol Prescott PhD
- Hermine Maes PhD
- Lindon Eaves PhD
- Charles Gardner PhD
- Steve Aggen PhD
- John Myers MA
- Ted Reichborn-Kjennerud MD

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