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What twin studies teach us about the causes of alcoholism

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Contributions of Washington University to the study of complex diseases

Conceptual Models

heterogeneity, sex differences

Statistical Models

families, adoptees, twins, pedigrees

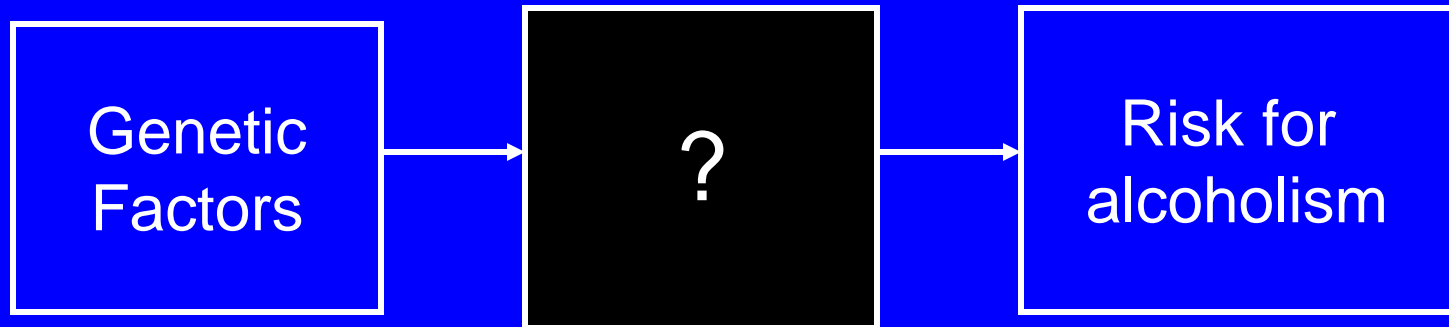
Tools

Structured interviews, reliable diagnostic
criteria

Why continue to study twins?

- Genetic influence on alcoholism already established
- Animal models offer experimental control; ability to study effects of particular loci
- Human molecular genetic research in progress
 - Candidate genes
 - Genome-wide scans

How do genes influence risk for alcoholism?



How do genes influence risk for alcoholism? many paths at many levels



Beyond Heritability

- *Twin Studies teach us:*

Biological boundaries between disorders

Confirmation or refutation of subtypes

Gene – environment interactions

Basis for sex differences

Nature of risk factors

Mechanisms of genetic transmission

Talk Overview

What twin studies teach us about:

- I. Alternative definitions of alcoholism
- II. Sex differences in genetic influences on alcoholism
- III. Nature of risk factors

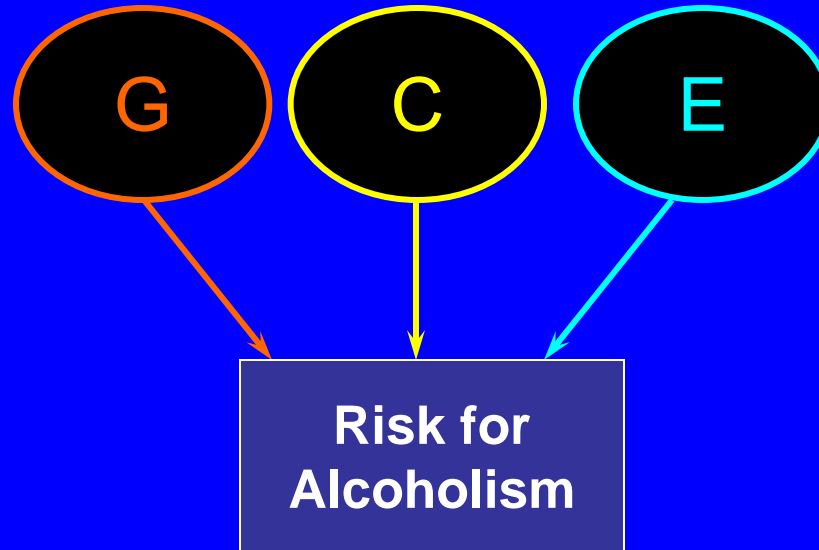
Part I.

Alternative definitions of alcoholism

Part I. Alternative definitions

- Goal: Develop a biologically relevant definition of alcoholism
- Method: Estimate heritabilities for alternative definitions and subgroups
- Examples from two twin studies

Sources of variation estimated in twin studies

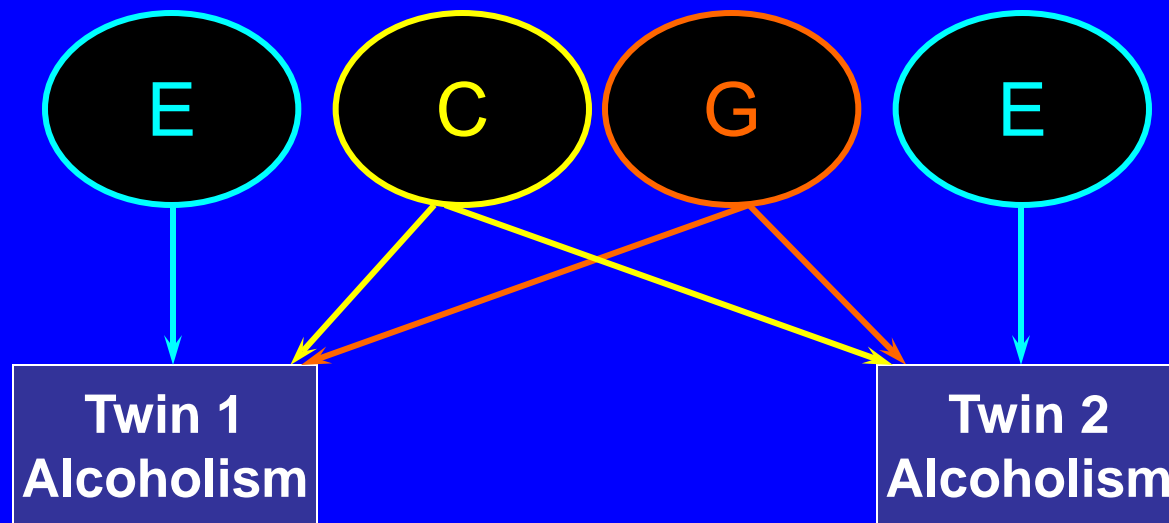


G = additive genetic

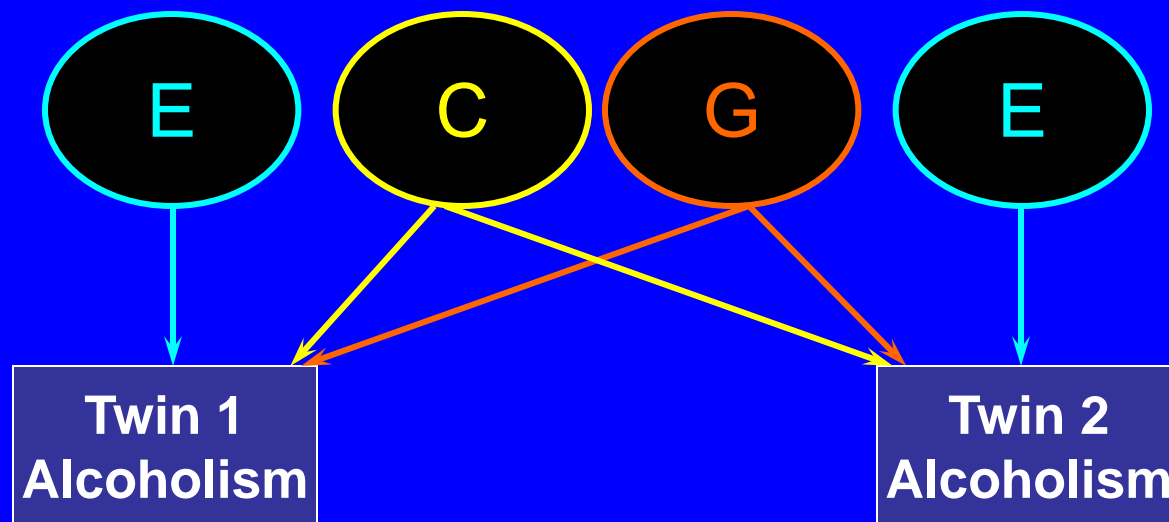
C = common environment (shared by twins in a pair)

E = individual-specific environment (not shared)

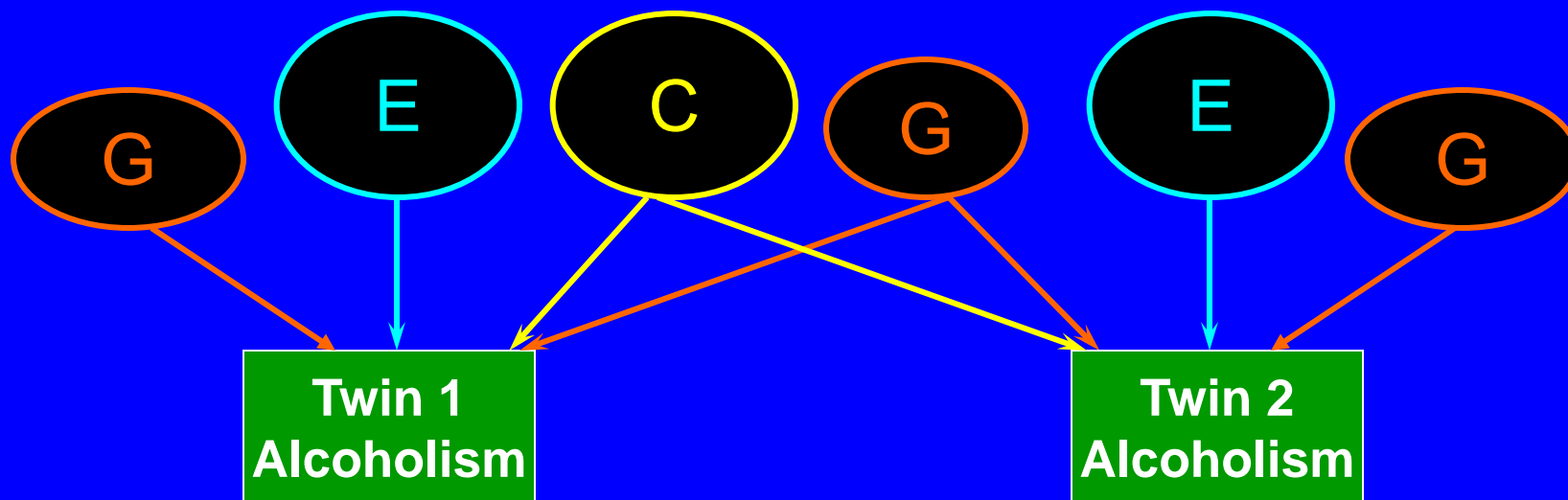
Sources of similarity and differences in Monozygotic (MZ) twin pairs



Monozygotic (MZ) twin pairs



Dizygotic (DZ) twin pairs



Study 1:

Washington University Twin Study

- Gottesman, Carey, Vogler, NIMH
 - With support from PROFESSORS GUZE & REICH
- Twins admitted to inpatient and outpatient psychiatric units and substance abuse treatment facilities in St. Louis area from 1981-1986
- “Best Estimate” diagnoses based on structured psychiatric interview, personality assessment & medical records
- Multiple diagnoses, comorbidity patterns
- 295 twin pairs

Washington University Twin Study Alcohol Sample Characteristics

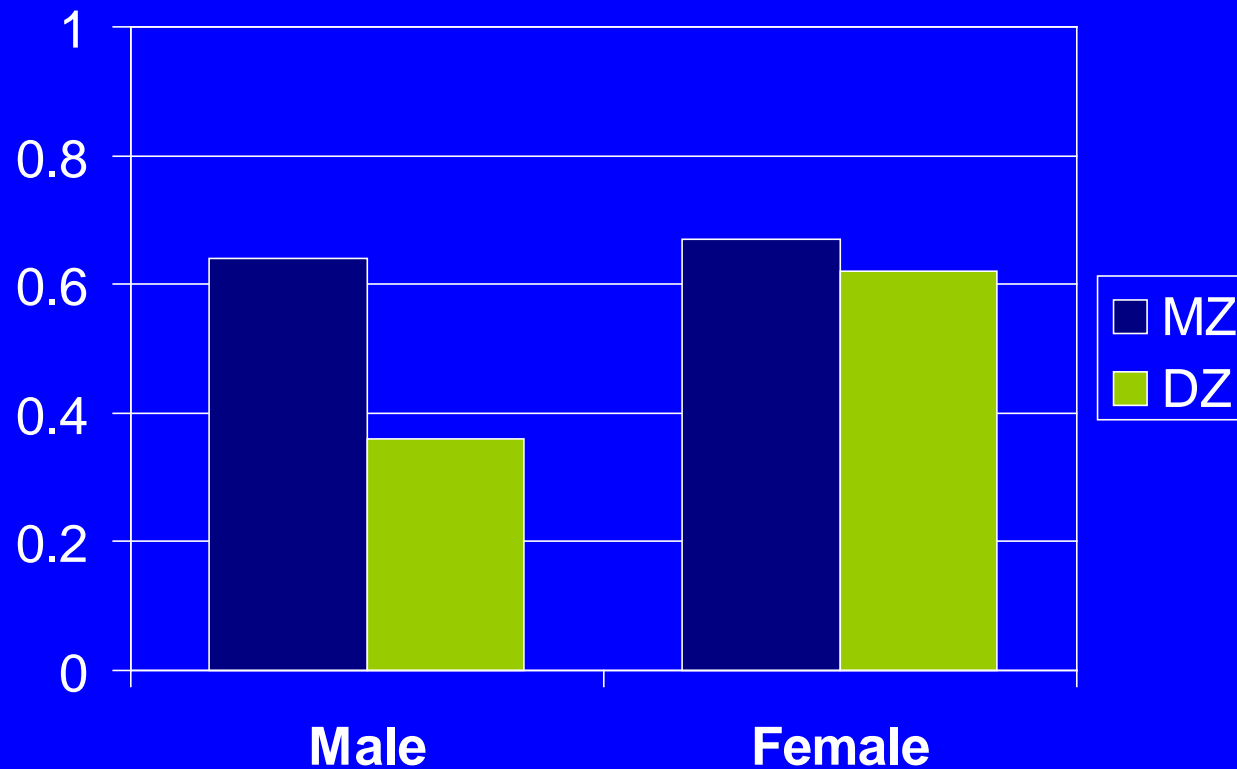
(Caldwell & Gottesman, 1991)

154 pairs in which the proband had an alcohol diagnosis (45 MZ, 50 DZS, 59 DZO)

Age: 15-74 years (mean=34.7, sd=12.1)

Ethnicity: 68% Caucasian, 32% African-American

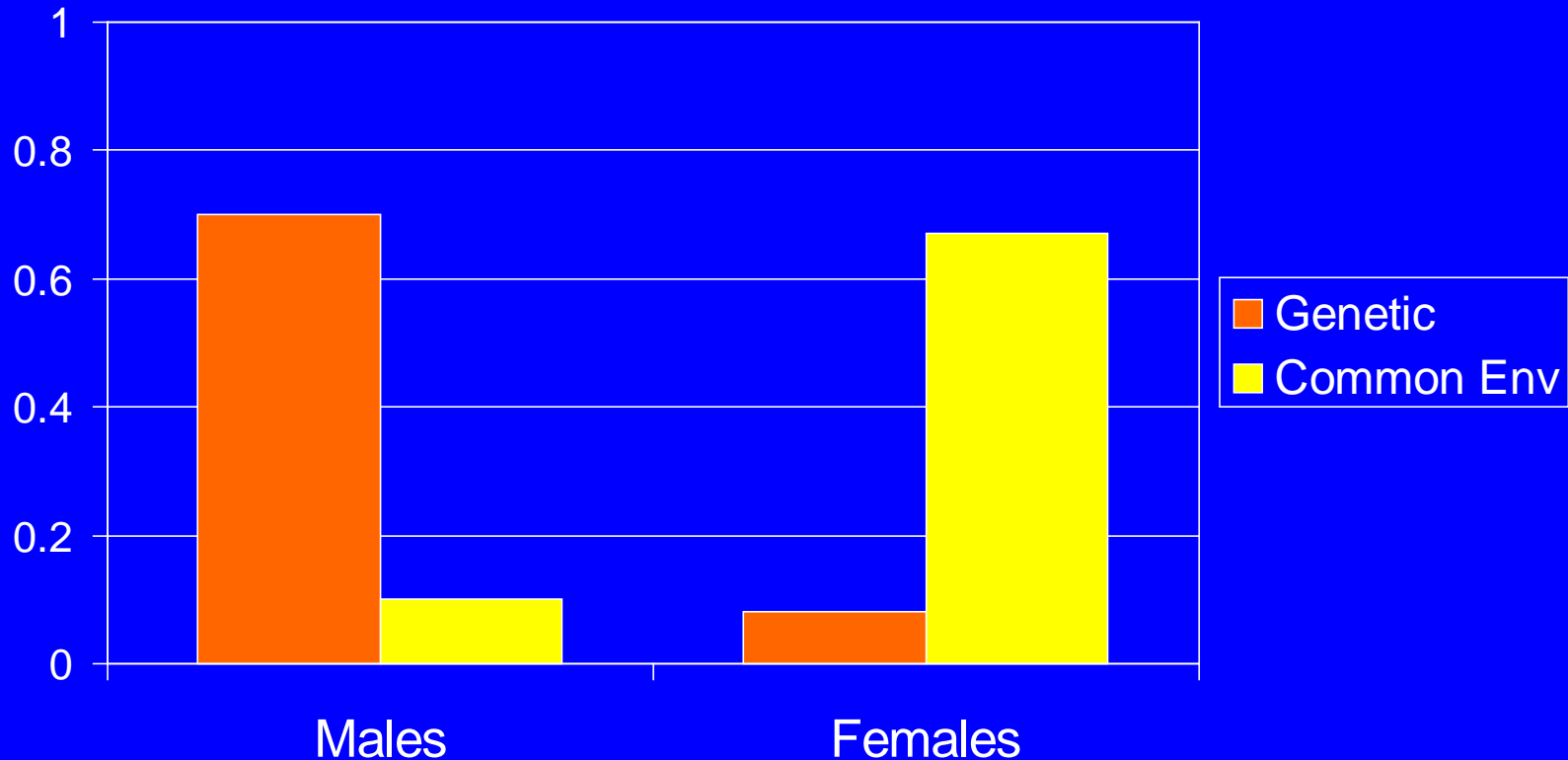
Twin pair resemblance for Alcohol Abuse/Dependence in the Washington University Twin Alcoholism Sample



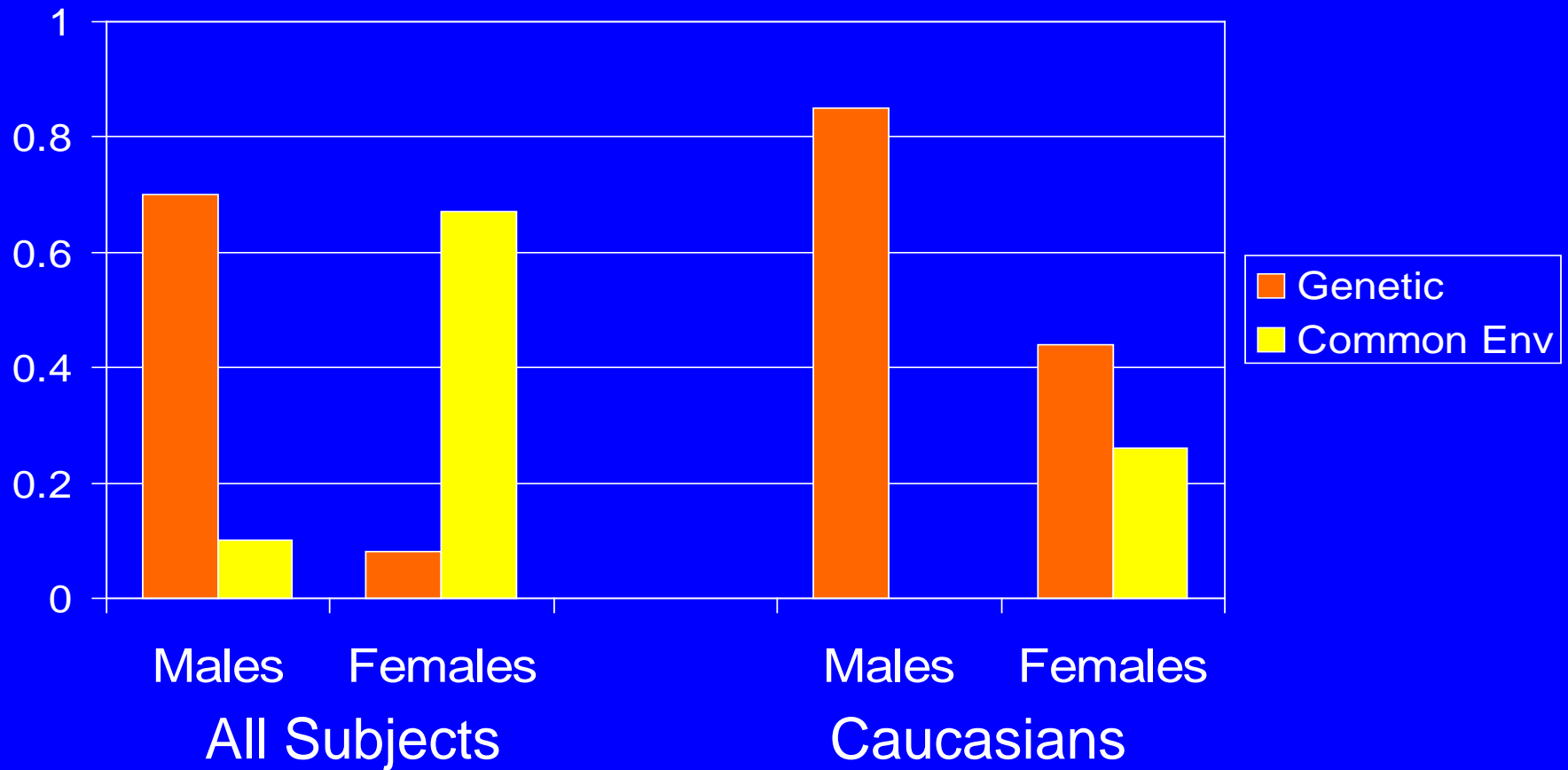
Male MZ > DZ ($p < .05$)

Values are tetrachoric correlations

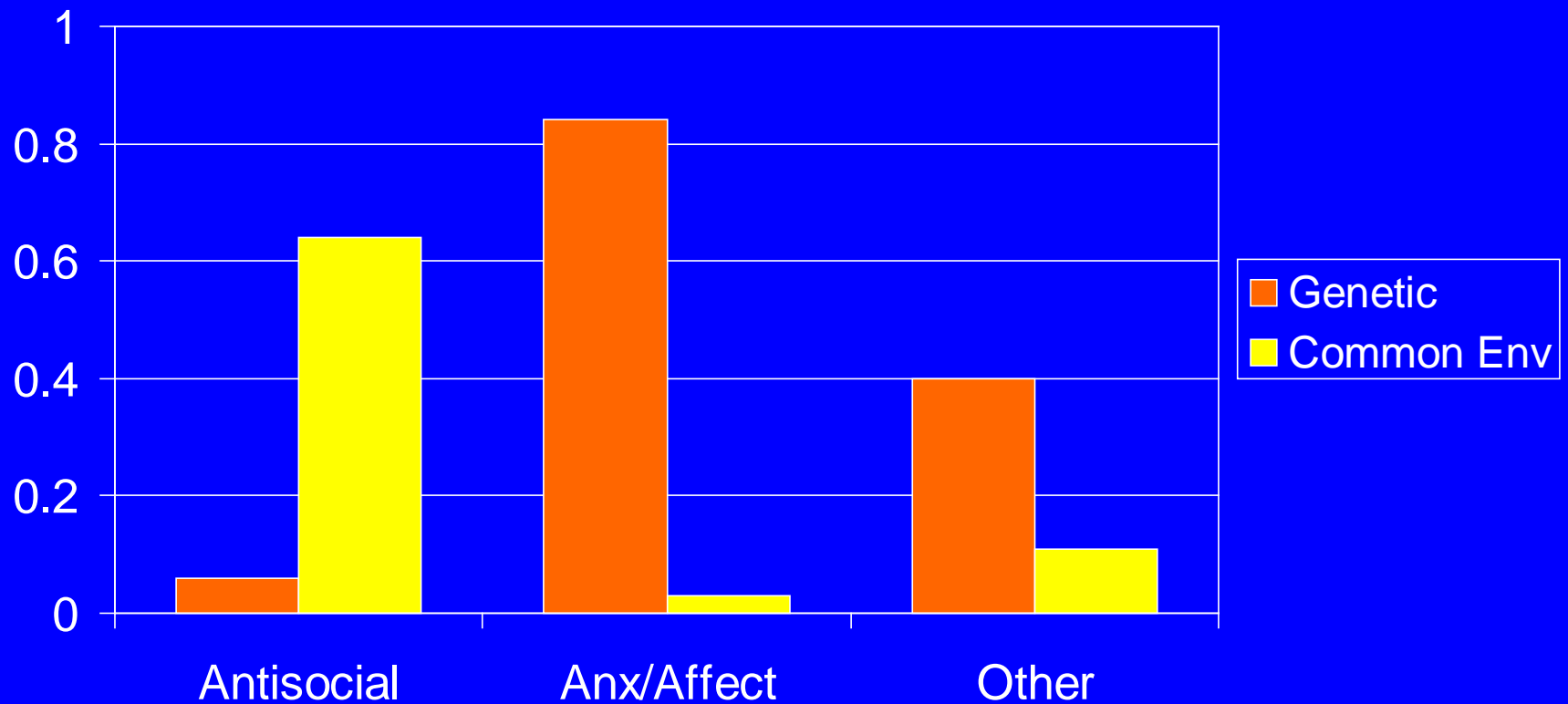
Proportions of Variance for Alcohol Abuse/Dependence In the Washington University Twin Sample



Proportions of Variance for Alcohol Abuse/Dependence by Gender and Ethnicity



Proportions of Variance for Alcohol Abuse/Dependence by Comorbidity Subgroup



Study 1: Conclusions

- Results are tentative but intriguing
- Lower heritability of ASP type not expected; perhaps a sampling effect
- Little twin research on ethnic variation in alcoholism – group differences probably more due to environmental than genetic differences

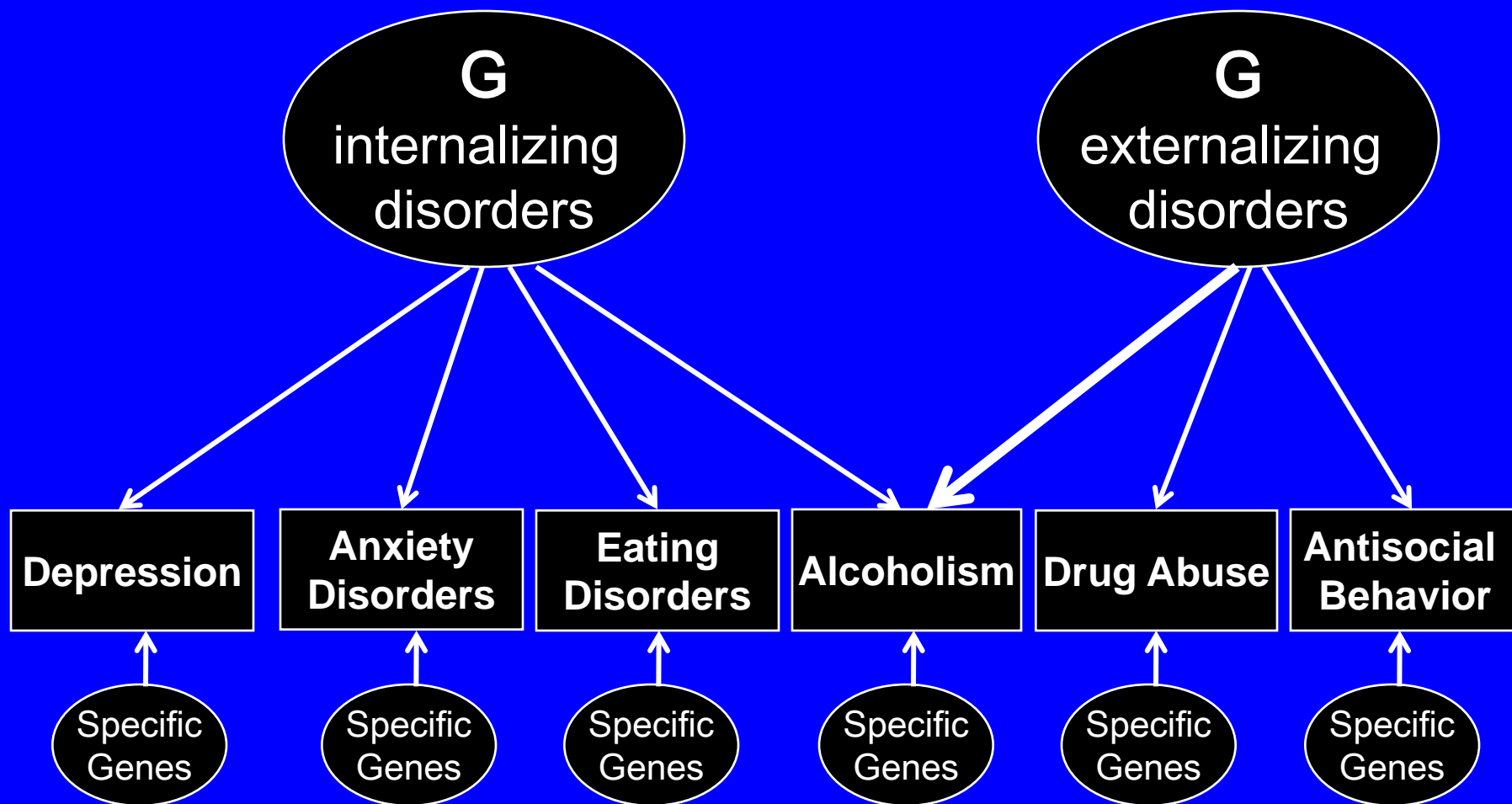
Study 2:

Alcoholism subtypes in the
Virginia Adult Twin Study of Psychiatric
& Substance Use Disorders

Design & Sample

- Kendler, Eaves, Neale, Heath & Kessler, 1985
NIMH, NIAAA, NIDA
- Twins identified from Virginia birth records
- Caucasian, born 1933-1975
- > 9,000 individuals, >4100 pairs
- Structured psychiatric interviews
- Up to 4 interviews: 1987 - 2004
(Kendler et al., 1992, Prescott & Kendler, 1999)

Alcoholism shares genetic overlap with both internalizing and externalizing disorders



e.g., Kendler, Prescott, Myers & Neale (2003) *Arch Gen Psychiatry* 60:929-37

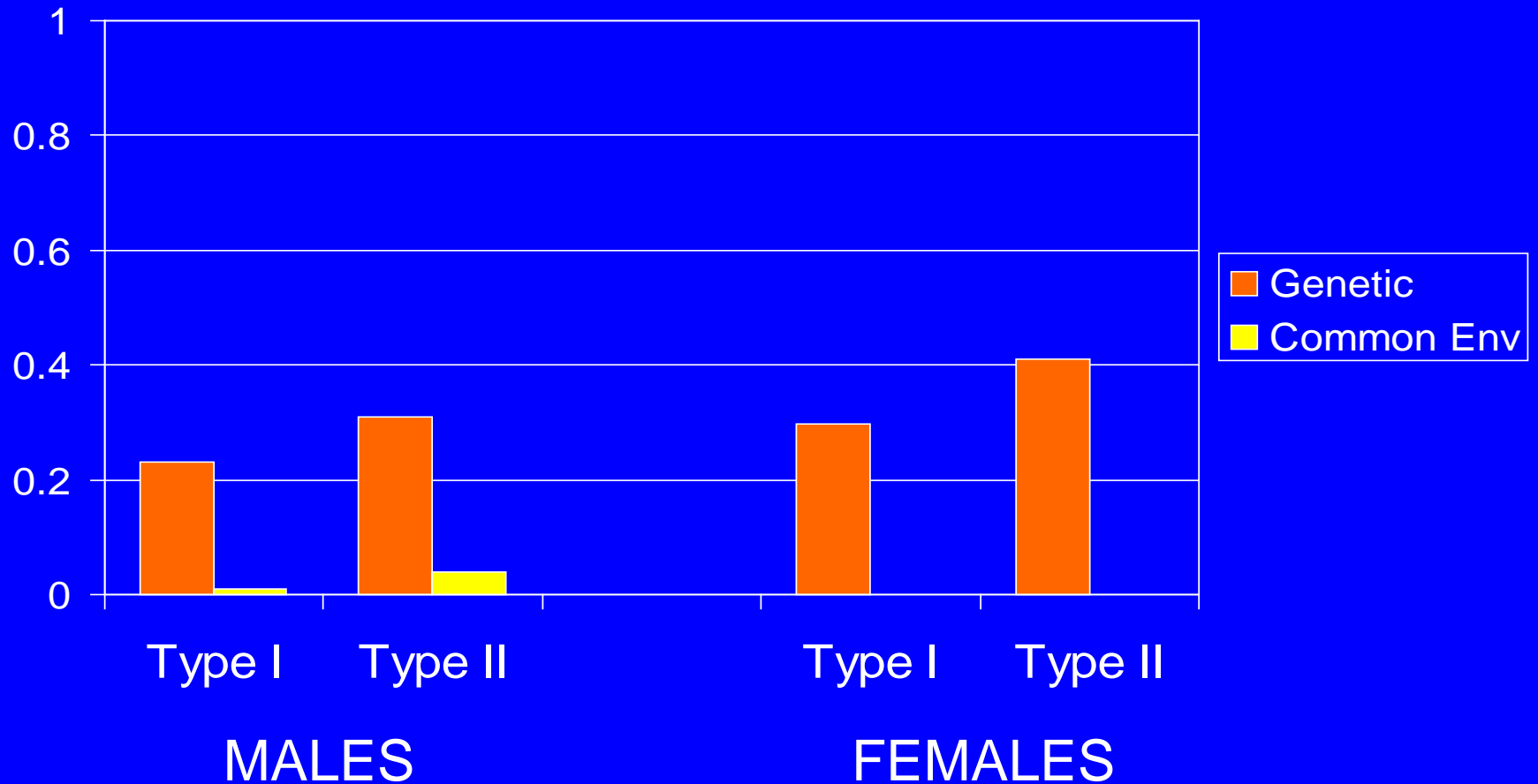
Study Goal: Estimate heritability for alcoholism subtypes

- Guided by Cloninger et al. Type I / II and Babor A/B classifications
- Dimensional approach – how closely a twin matches a subtype
- Based on features of alcoholism, personality traits, comorbid diagnoses, drinking motivations
- Drinking twin pairs (570 MZM, 481 DZM, 277 MZF, 222 DZF, 946 DZO)
- Prescott, Aggen & Kendler, *in preparation*

Creation of subtype scores

	Type I	Type II
Alcoholism features	Onset \geq 25, binge drinking, loss of control	Onset <25, inability to abstain, fights/arrests
Personality	Neuroticism (+), Novelty seeking (-)	Novelty seeking (+)
Comorbidity	Major depression, Anxiety disorders	Conduct disorder, Antisocial personality
Drinking motives	social anxiety, manage mood	social interaction, mental clarity

Proportions of variance for alcoholism subtypes



$$R(TI, TII) = .25$$

Study 2: Conclusions

- Likely to be etiologic heterogeneity based on clinical features and comorbidity
- Significant genetic contributions to both subtypes; perhaps stronger for Type II, but not overwhelming

Part II.

Sex Differences in Genetic Influences on Alcoholism

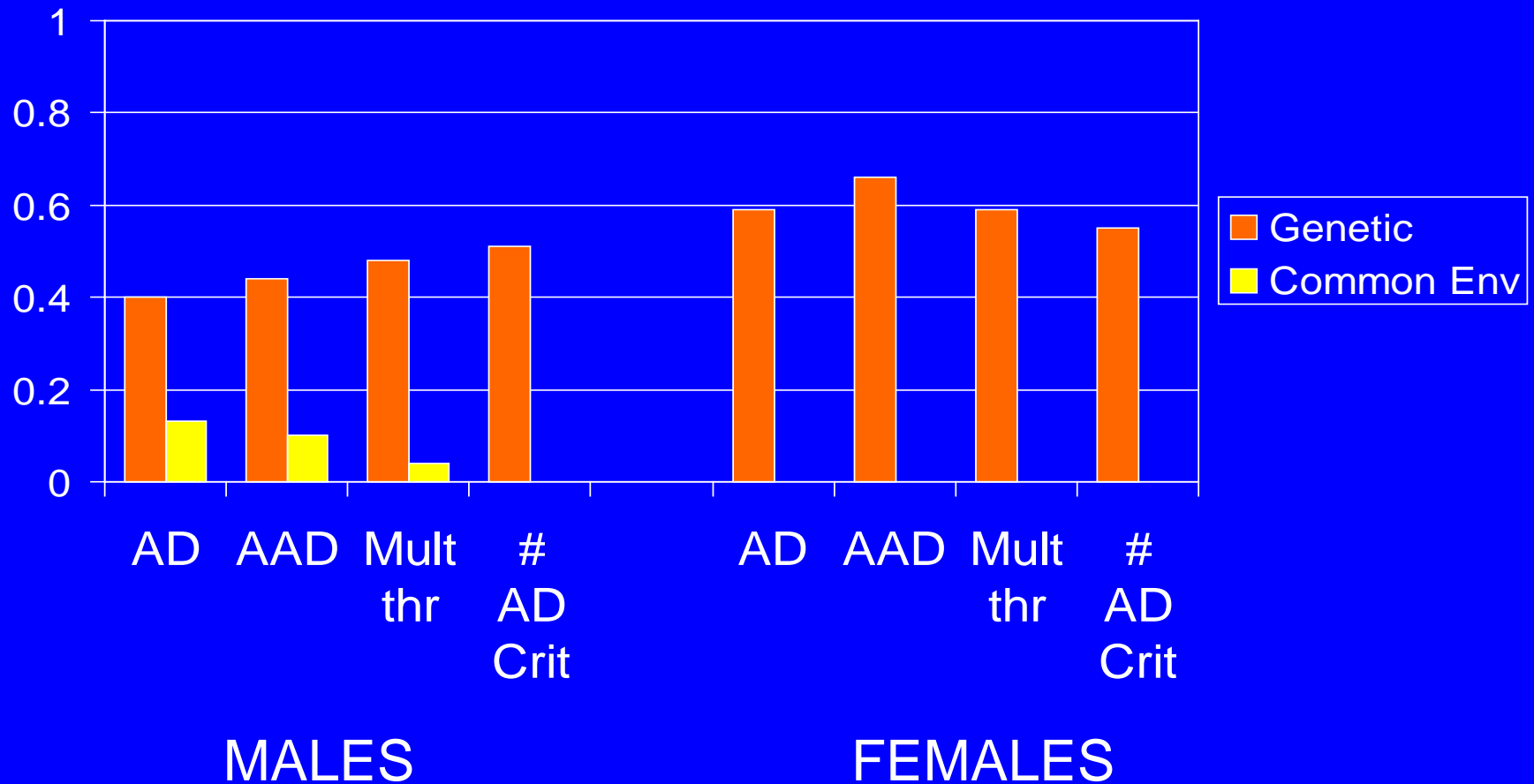
Part II. Sex Differences

- Is alcoholism less heritable in women?
- Do the same set of genes contribute to alcoholism in men and women?
- Is alcoholism in men genetically related to depression in women?

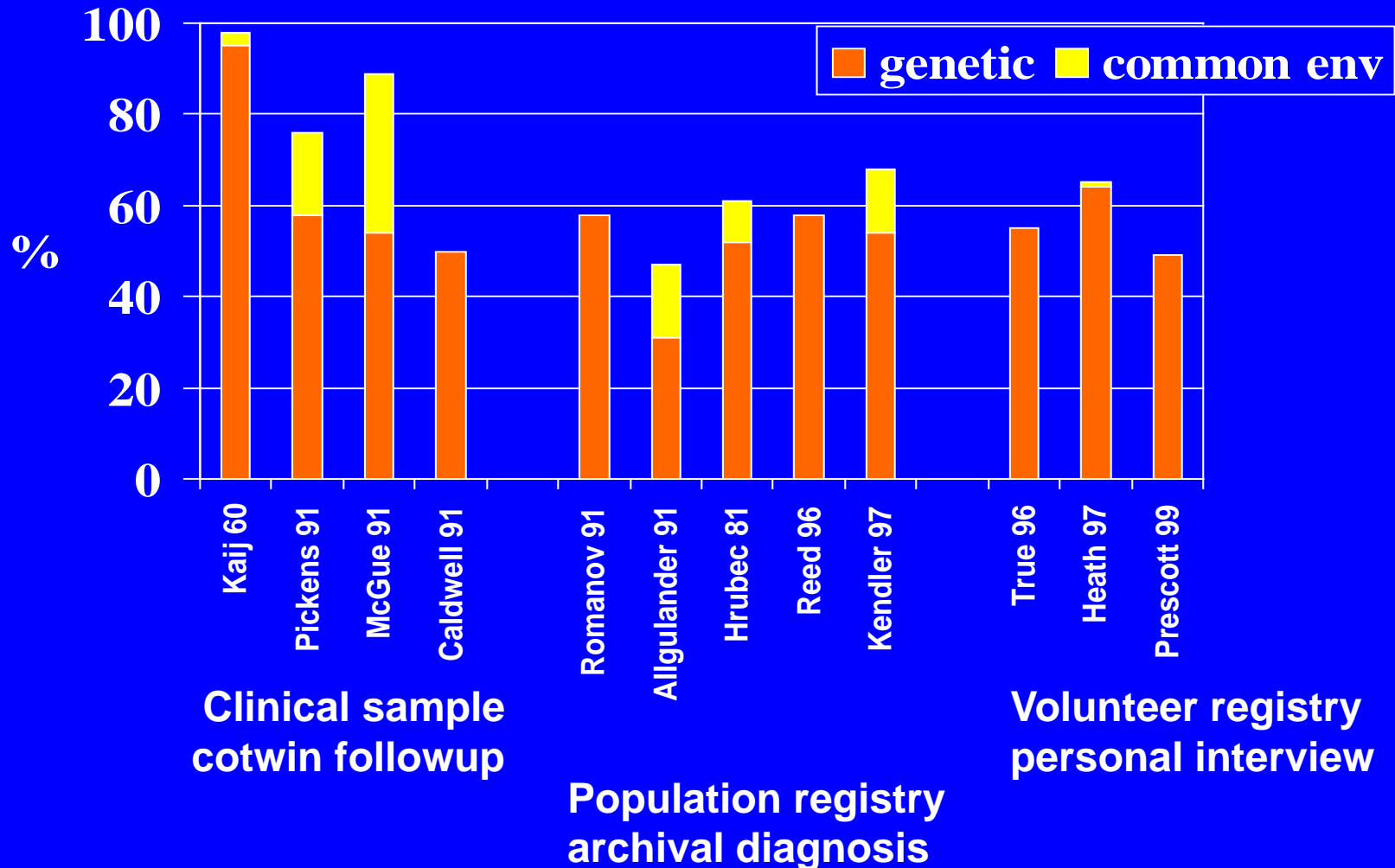
Study 3: Sex differences in genetic contributions to alcoholism

- VATSPSUD sample (MZF=683, DZF=474, MZM=863, DZM=654, DZO=1423)
- Two kinds of sex differences:
 - Magnitude of genetic effect: Compare male and female estimates
 - Sources of genetic effect: Compare similarity for alcoholism among DZ same-sex and DZ opposite-sex pairs

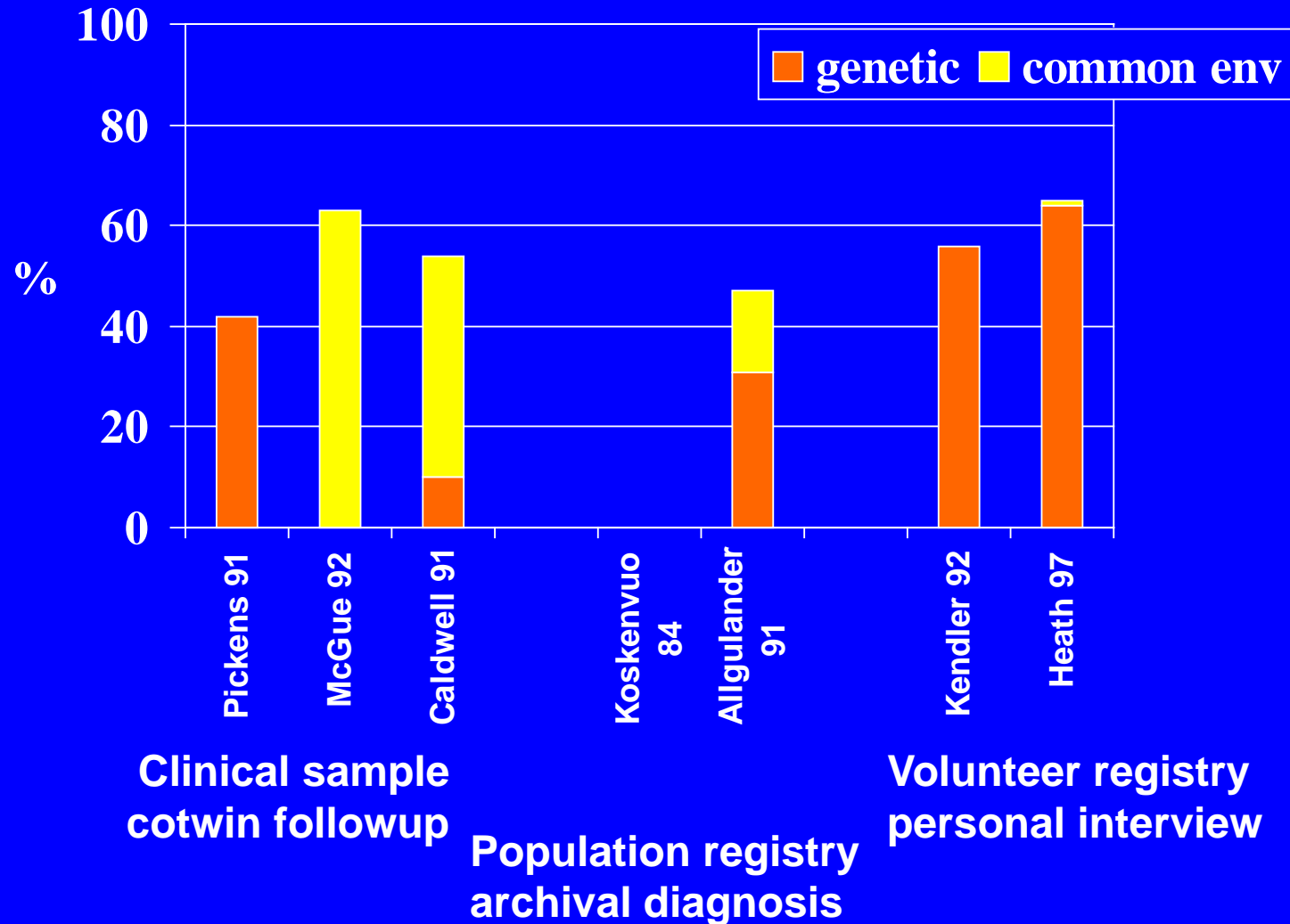
Proportions of variance for alternative definitions of alcoholism



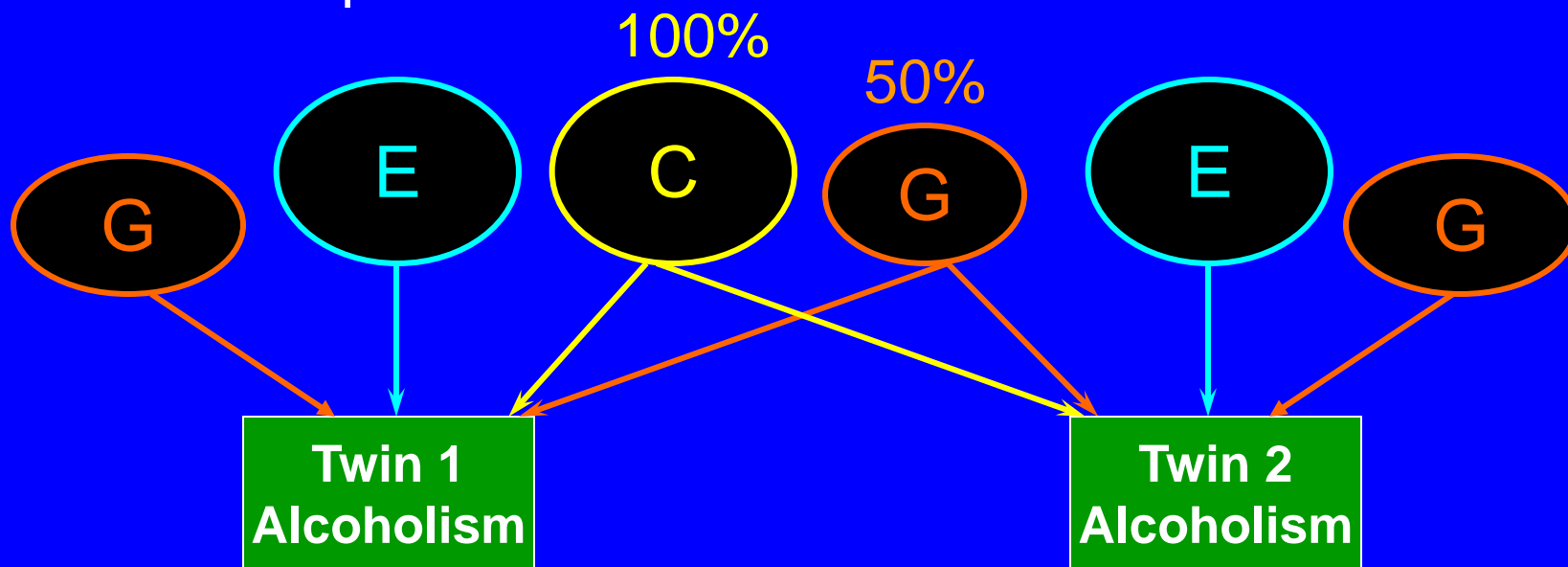
Genetic & environmental proportions of variance in alcoholism estimated from studies of male twins



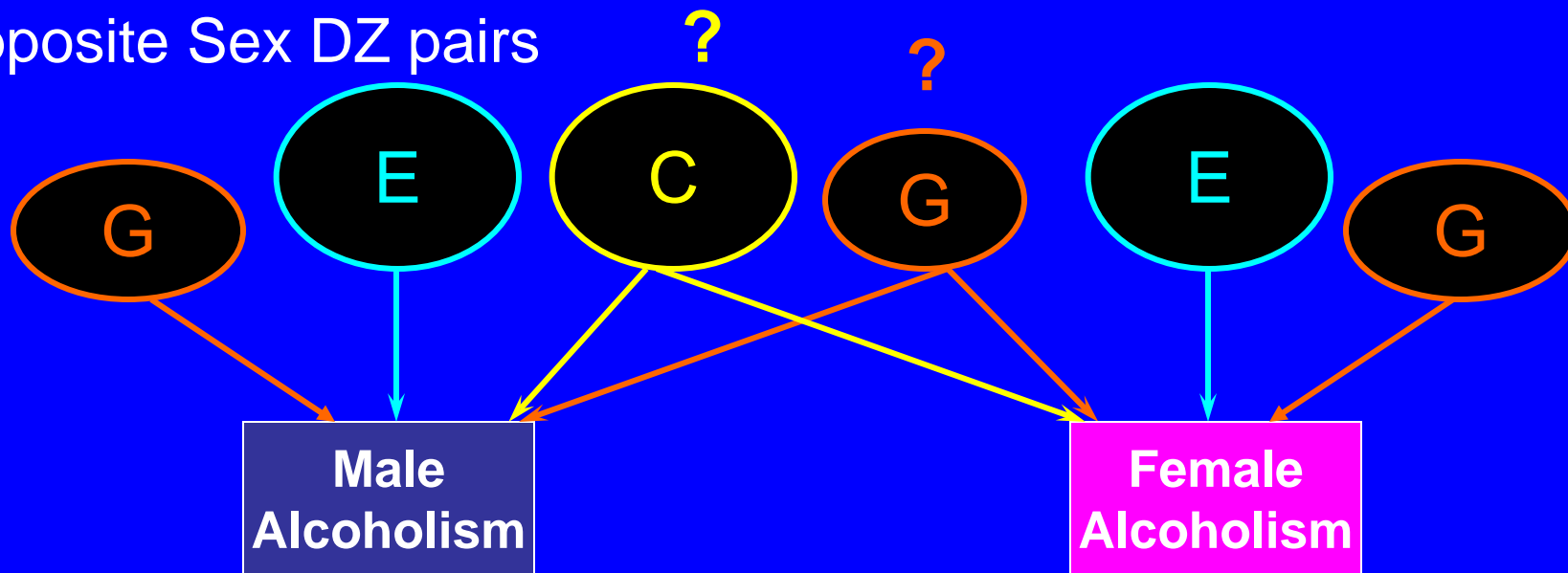
Genetic & environmental proportions of variance in alcoholism estimated from studies of female twins



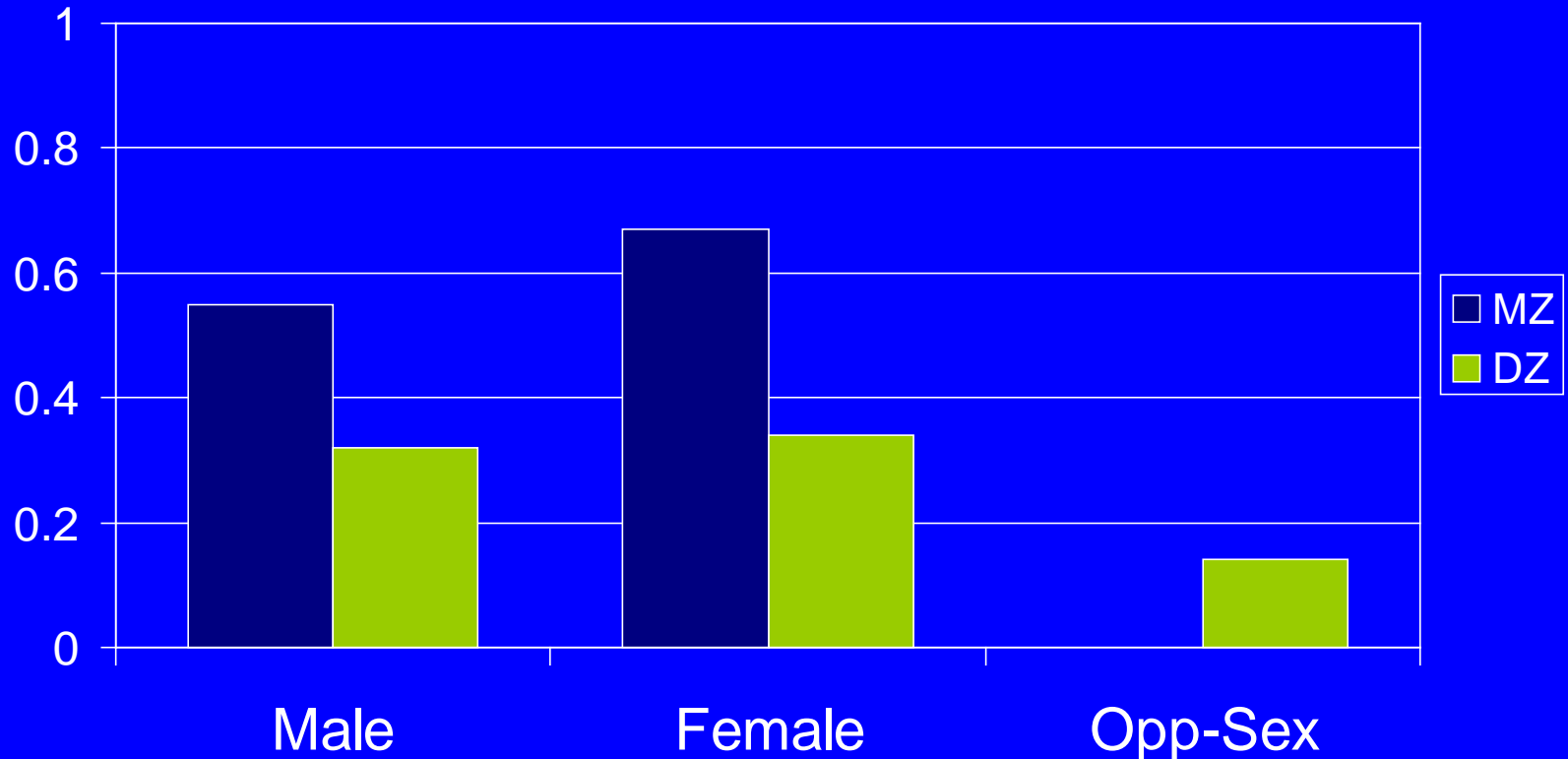
Same-Sex DZ pairs



Opposite Sex DZ pairs

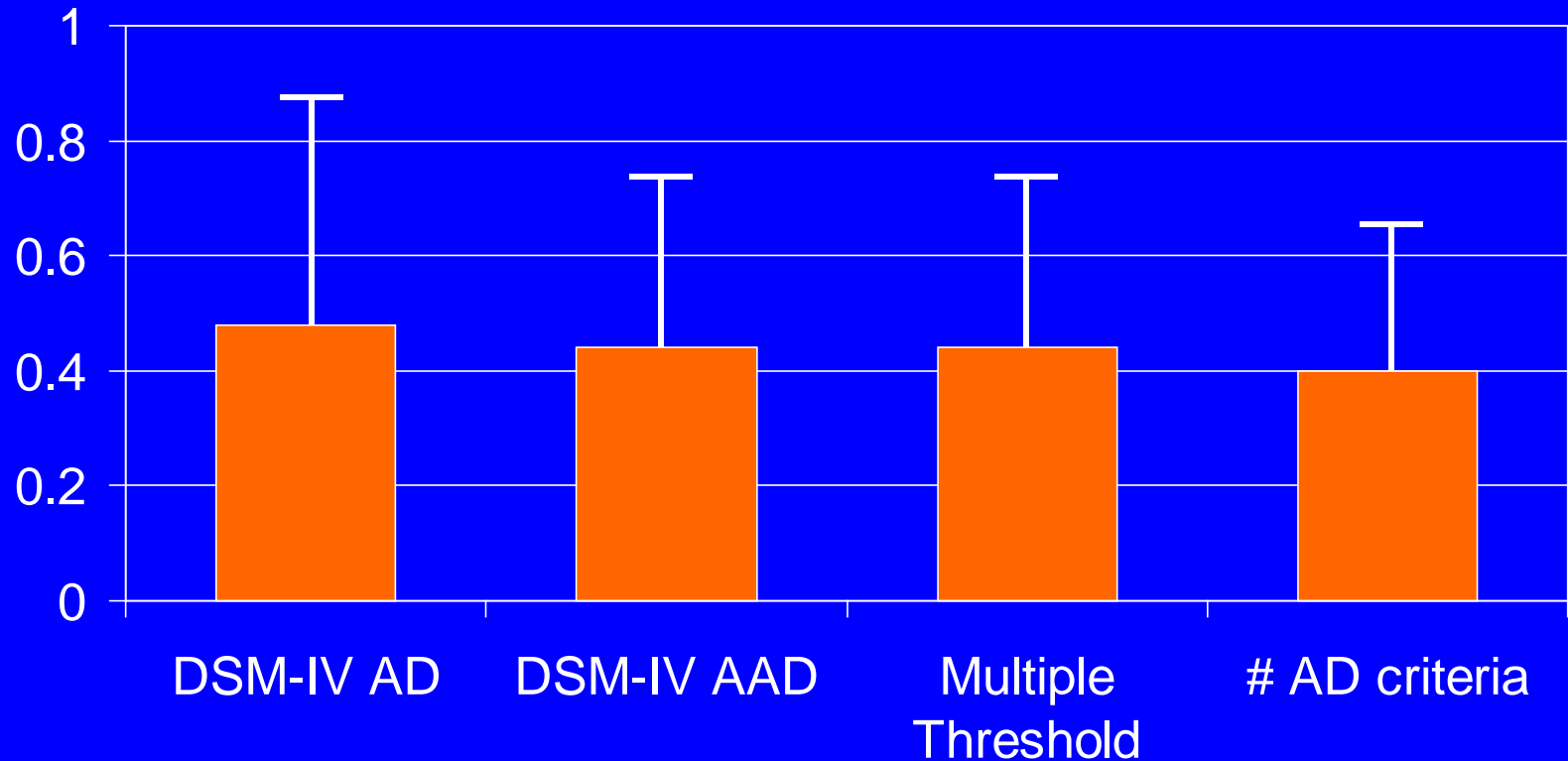


Twin-pair similarity for alcoholism is lower in opposite-sex twin pairs than same-sex DZ pairs



polychoric correlations for DSM-IV alcohol dependence

Estimated genetic overlap for alcoholism in men and women is significantly lower than 100%



Bars show 95% confidence boundary

Prescott, Aggen & Kendler (1999) *Alcoholism: Clin Exp Research* 23:1136-1144

Study 3 Conclusions

- Genetic contributions to alcoholism are of similar magnitude in men and women.
- Lower heritabilities for women in prior studies may be due to sampling differences
- Genetic factors which contribute to alcoholism are only partially overlapping in men and women (cf. Heath et al., 1997)
- Awaits replication: few studies have included adequate numbers of opposite-sex twin pairs

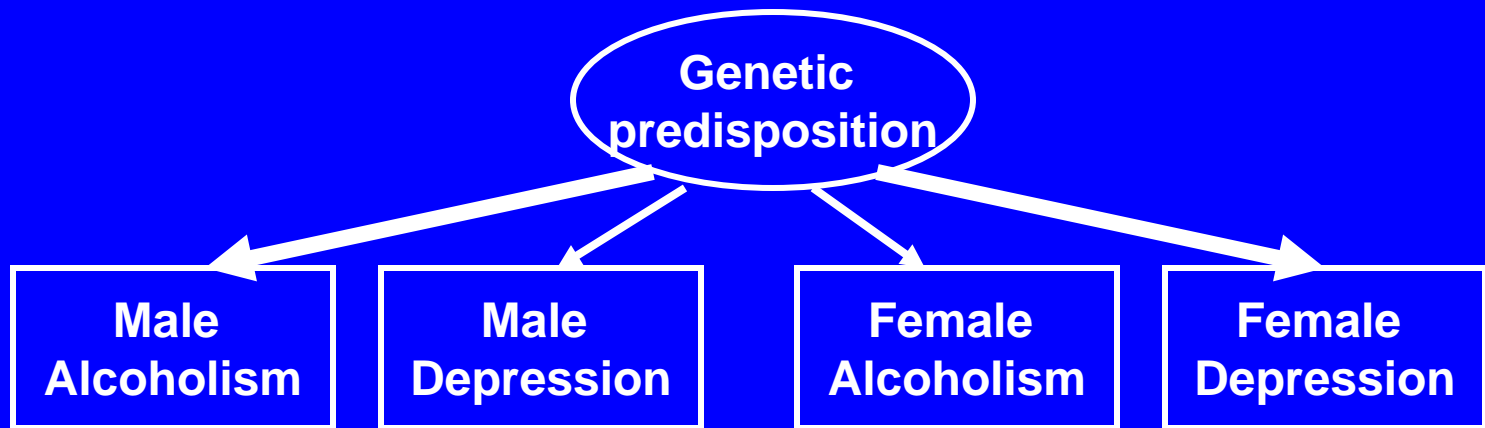
Study 4: Sex Differences and Alcoholism-Depression Comorbidity

- What is the basis for the alcoholism-depression overlap?
- Is alcoholism in men genetically related to depression in women?

Study Rationale

- Male:female ratio is ~2:1 for alcoholism and 0.5:1 for depression
- Alcoholism & depression co-occur within individuals, and run together in families
- Depression spectrum hypothesis: alcoholism in men and depression in women are alternative manifestations of the same genetic vulnerability (e.g., Winokur & Coryell, 1991)

Depression-spectrum hypothesis:
Alcoholism and depression have the same genetic
basis in men and women

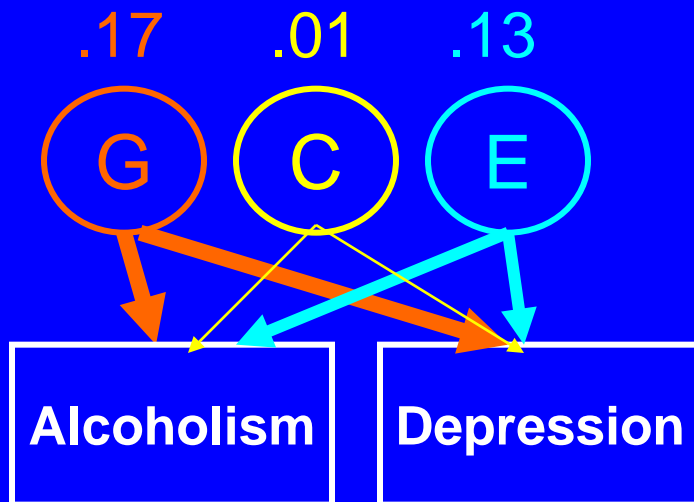


Study Method

- VATSPSUD sample
- Tested 5 alternative models
- Each makes different predictions about the alcoholism-depression correlation for males, females and twin pairs of each zygosity type
- from Prescott, Aggen & Kendler (2000) *Archives of General Psychiatry* 57:803-811

Estimated genetic and environmental contributions to alcoholism-depression comorbidity

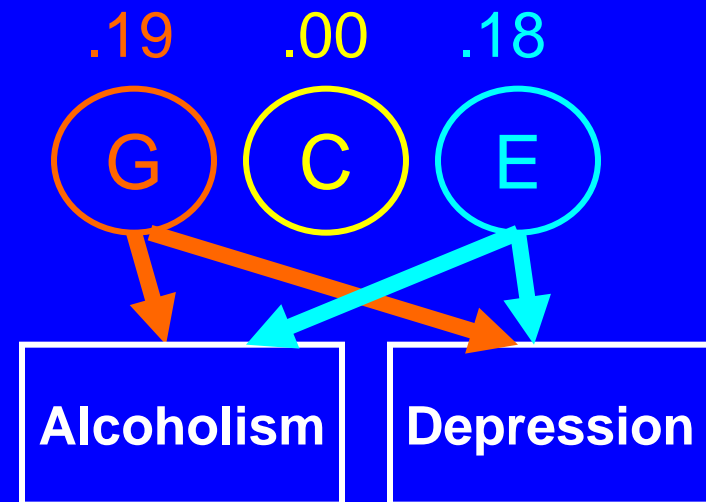
MALES



Total overlap = .31

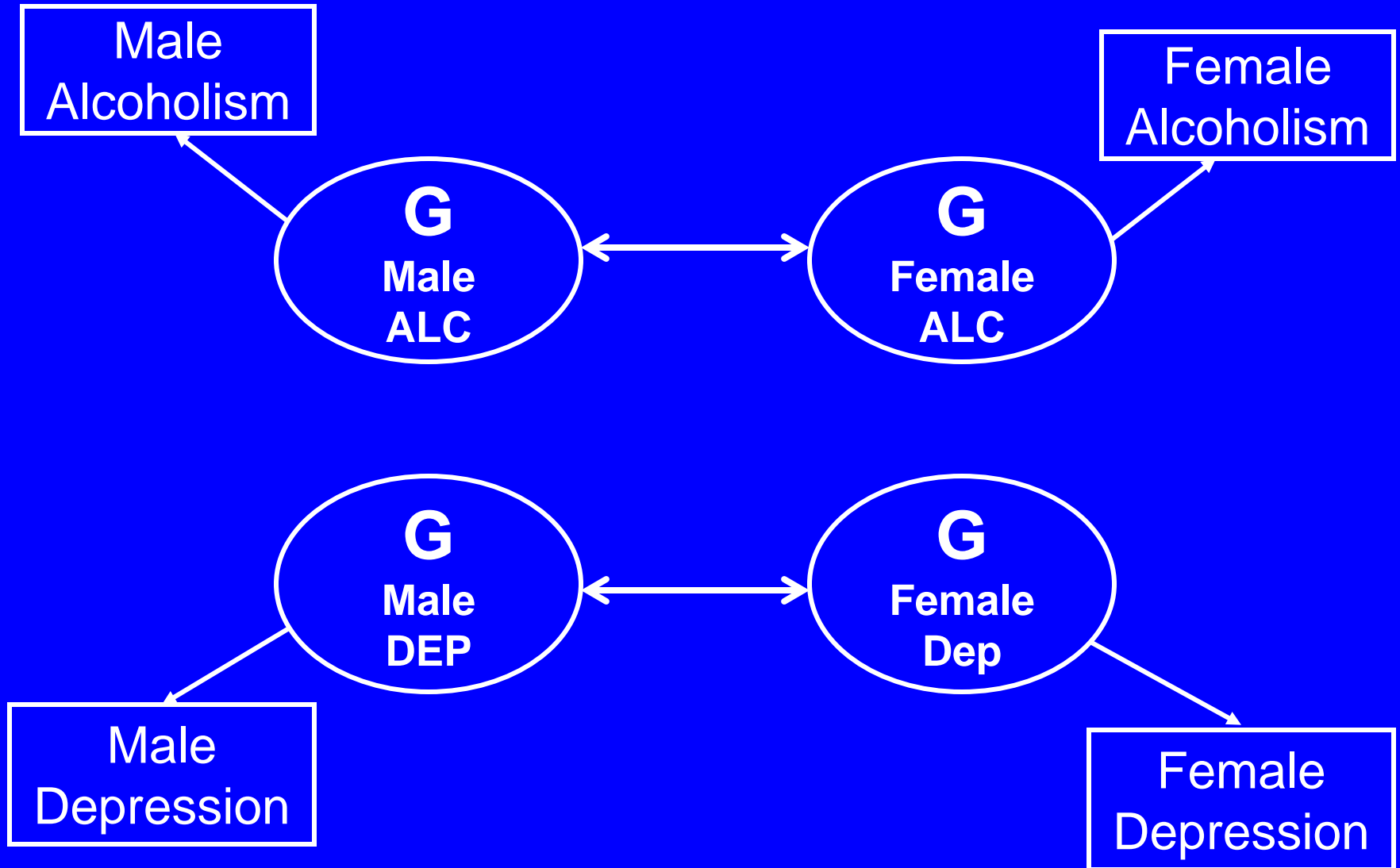
Standard error = .05

FEMALES

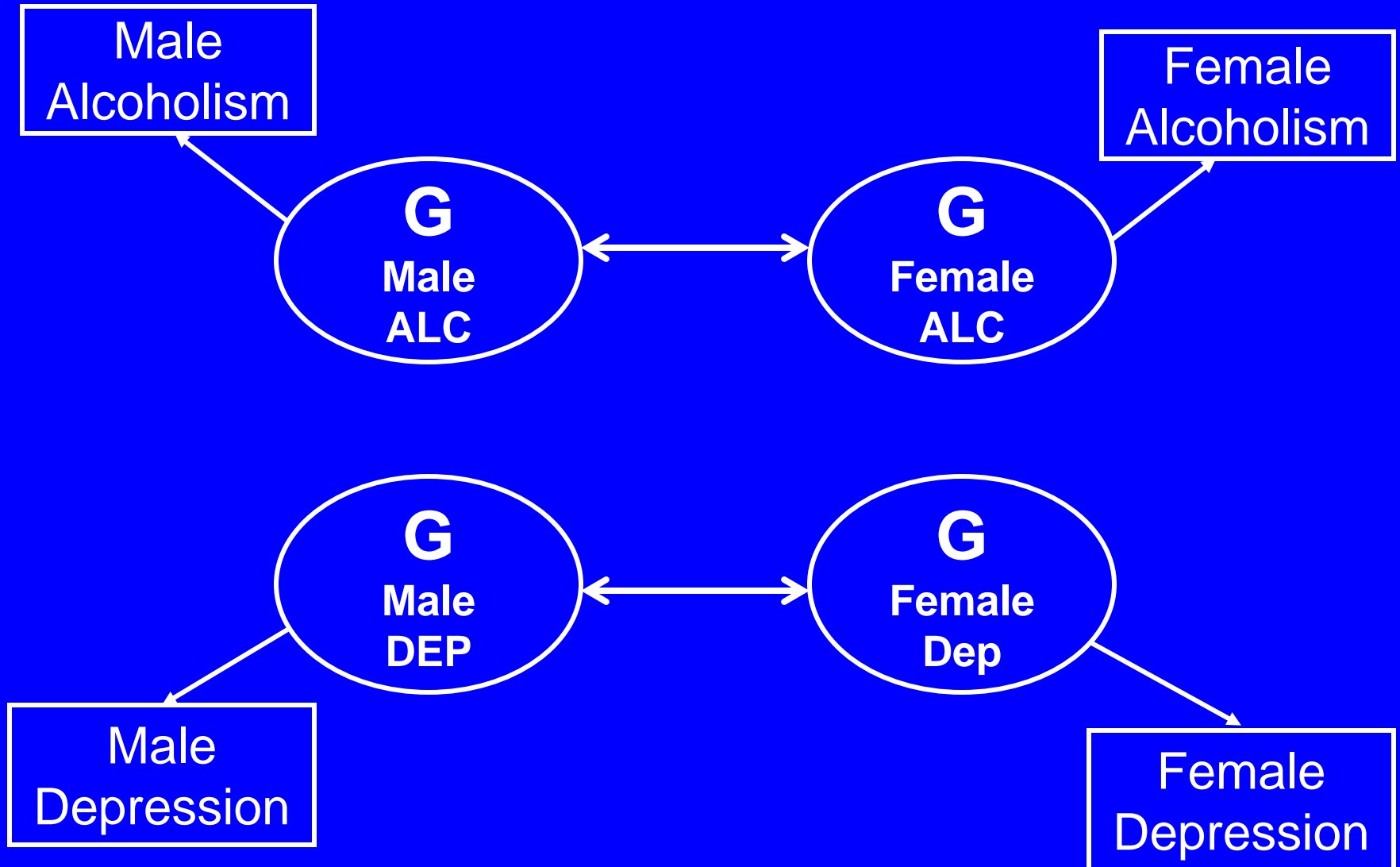


Total overlap = .37

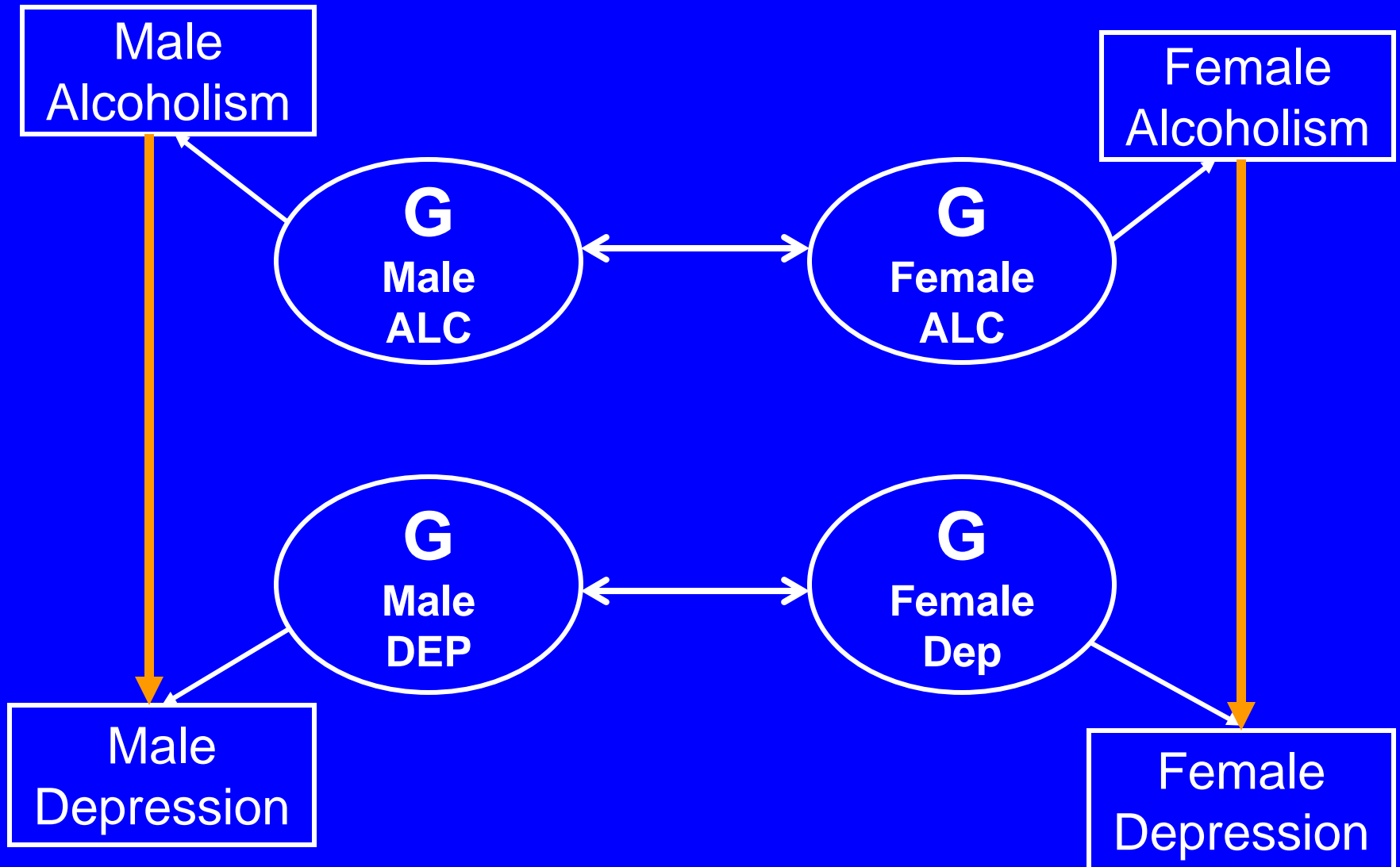
Null Model: No genetic overlap between alcoholism & depression



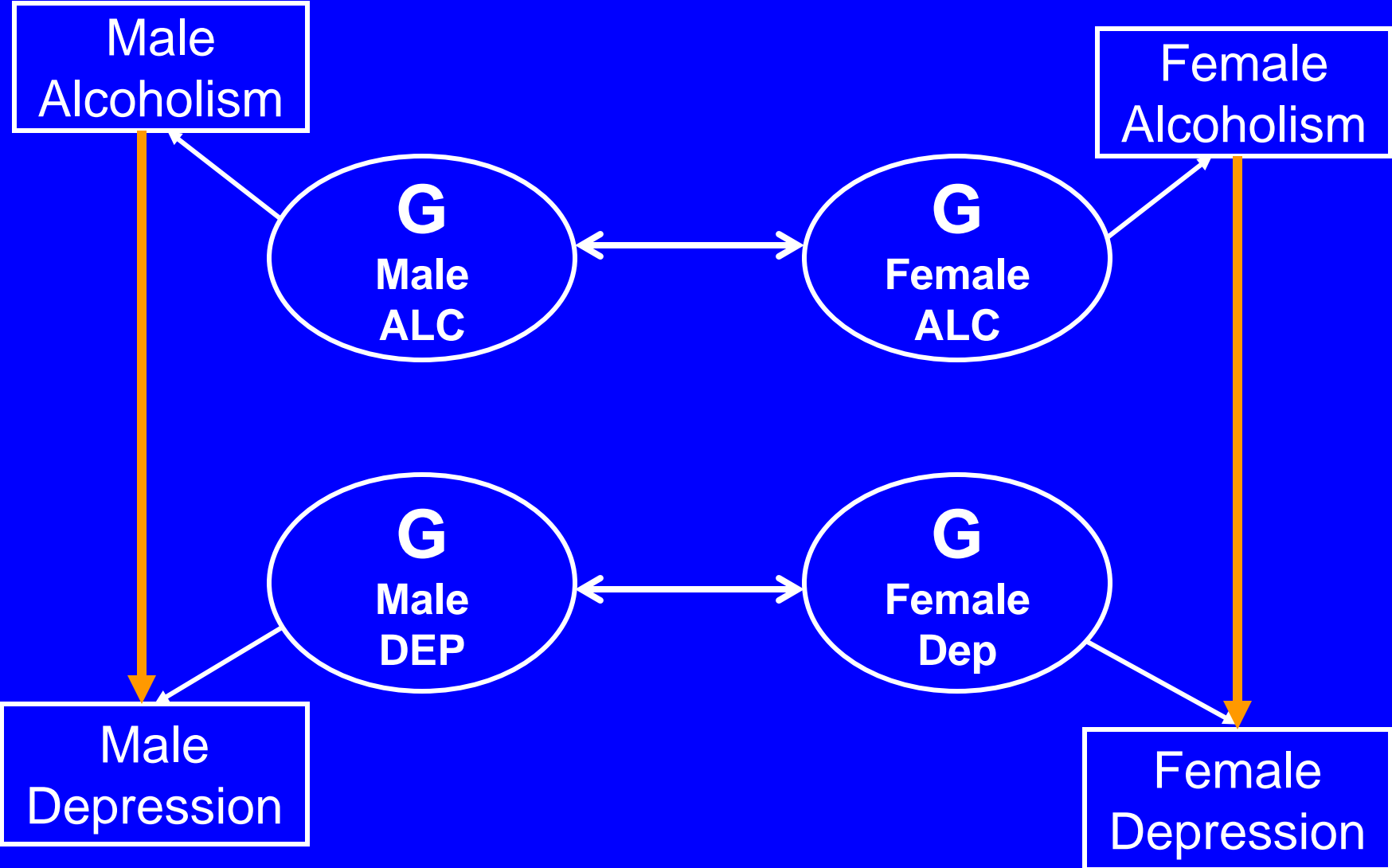
Null Model: No genetic overlap between alcoholism & depression -- REJECTED



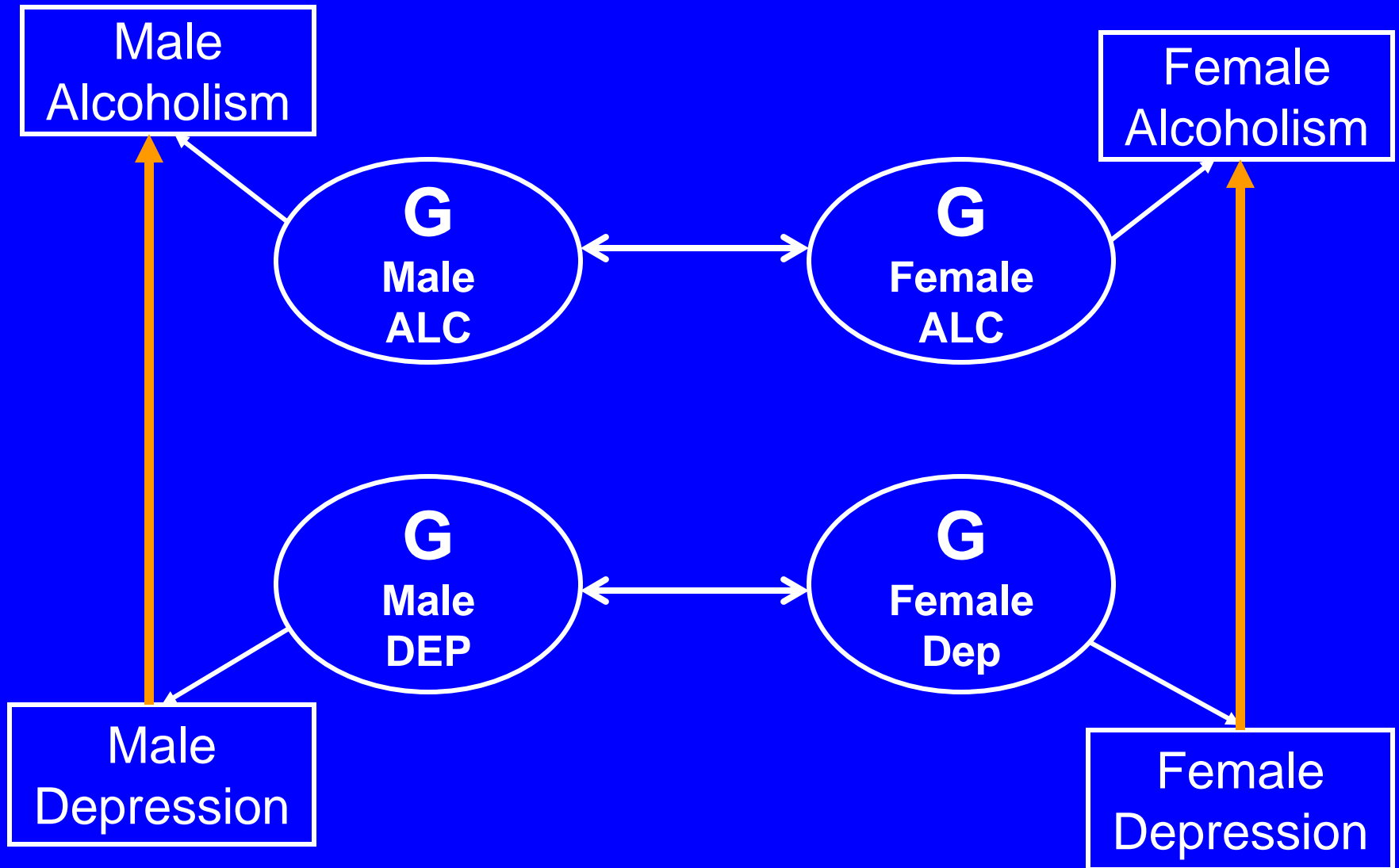
Model 1: Alcoholism leads to depression



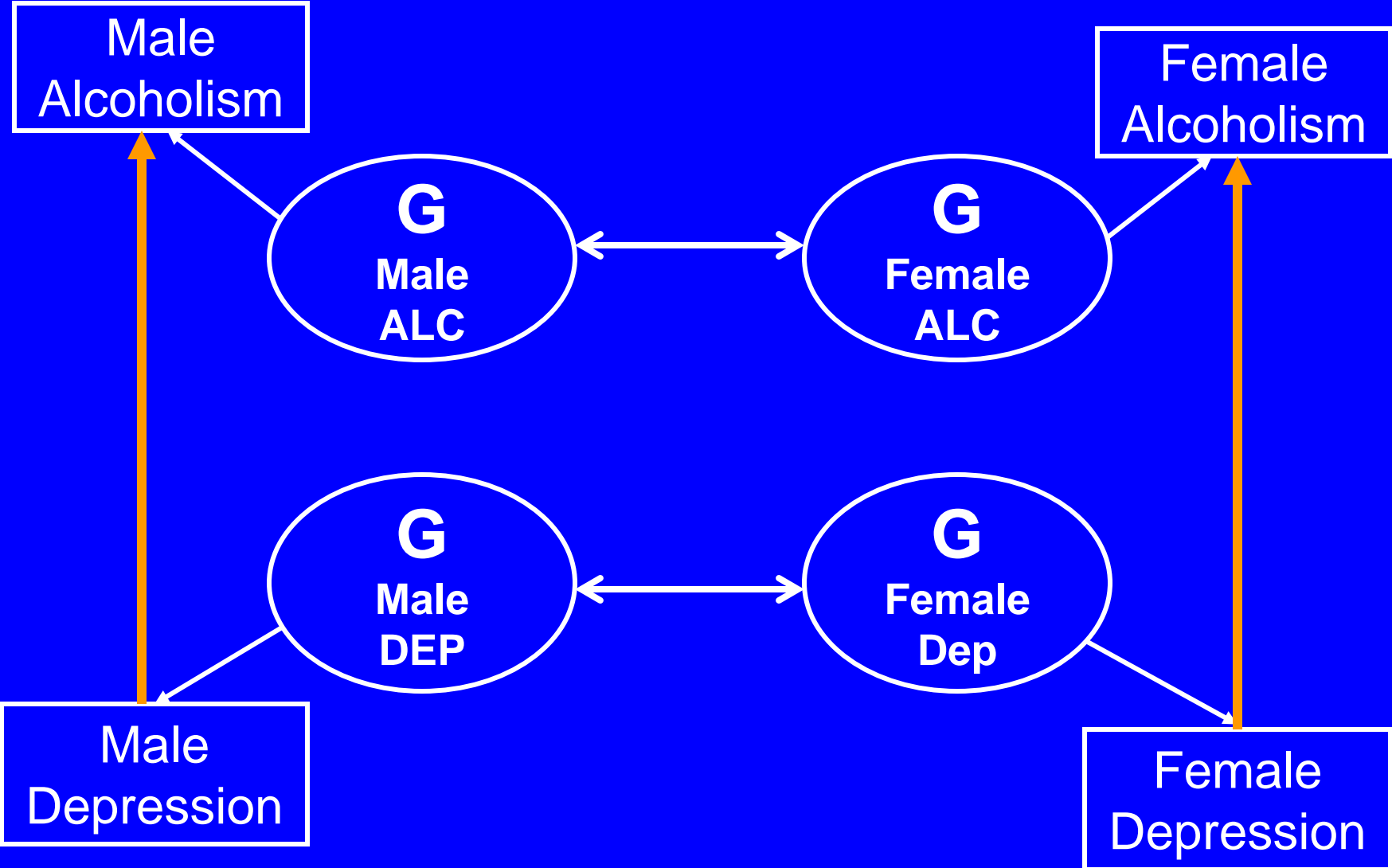
Model 1: Alcoholism leads to depression -- REJECTED



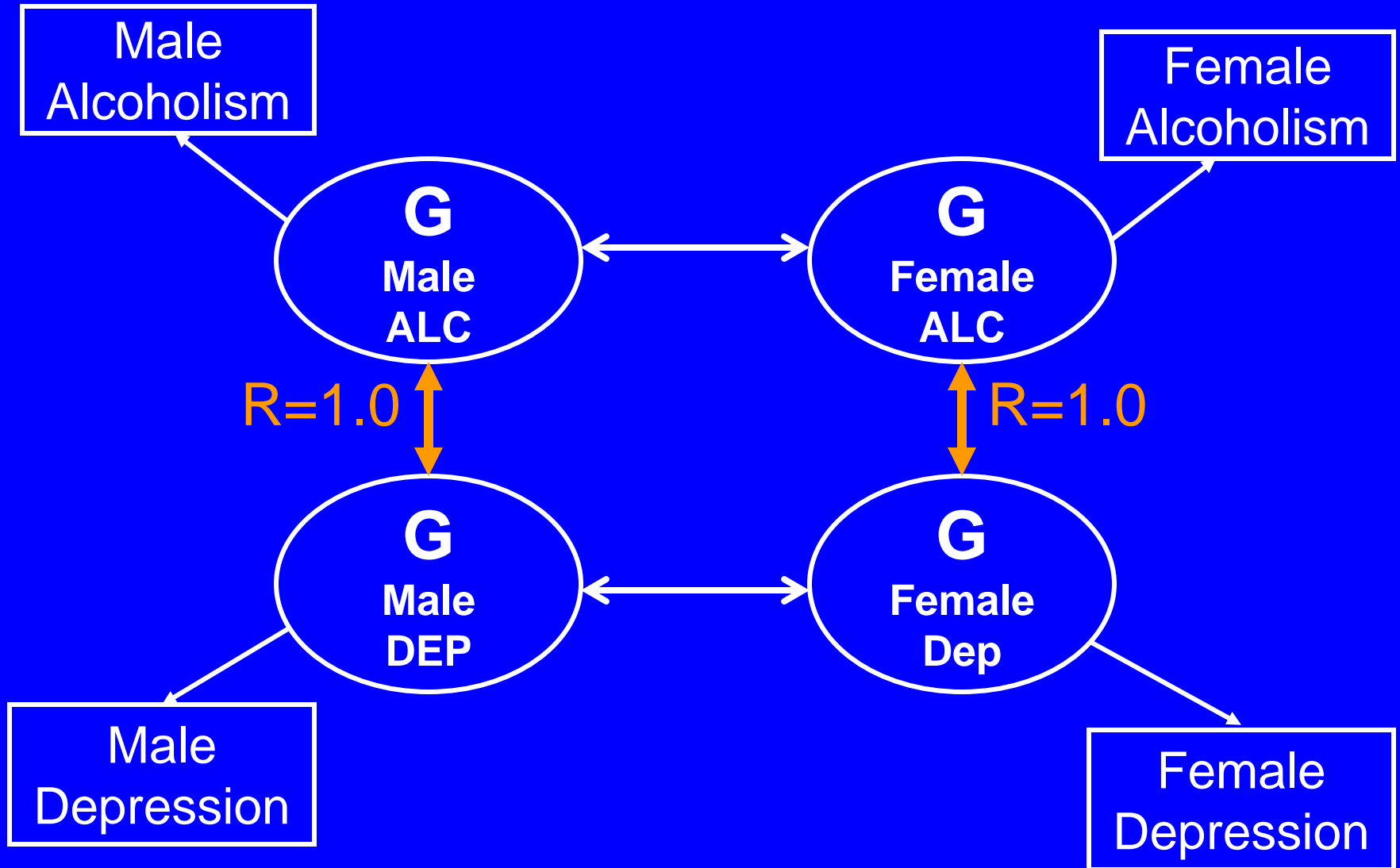
Model 2: Depression leads to alcoholism



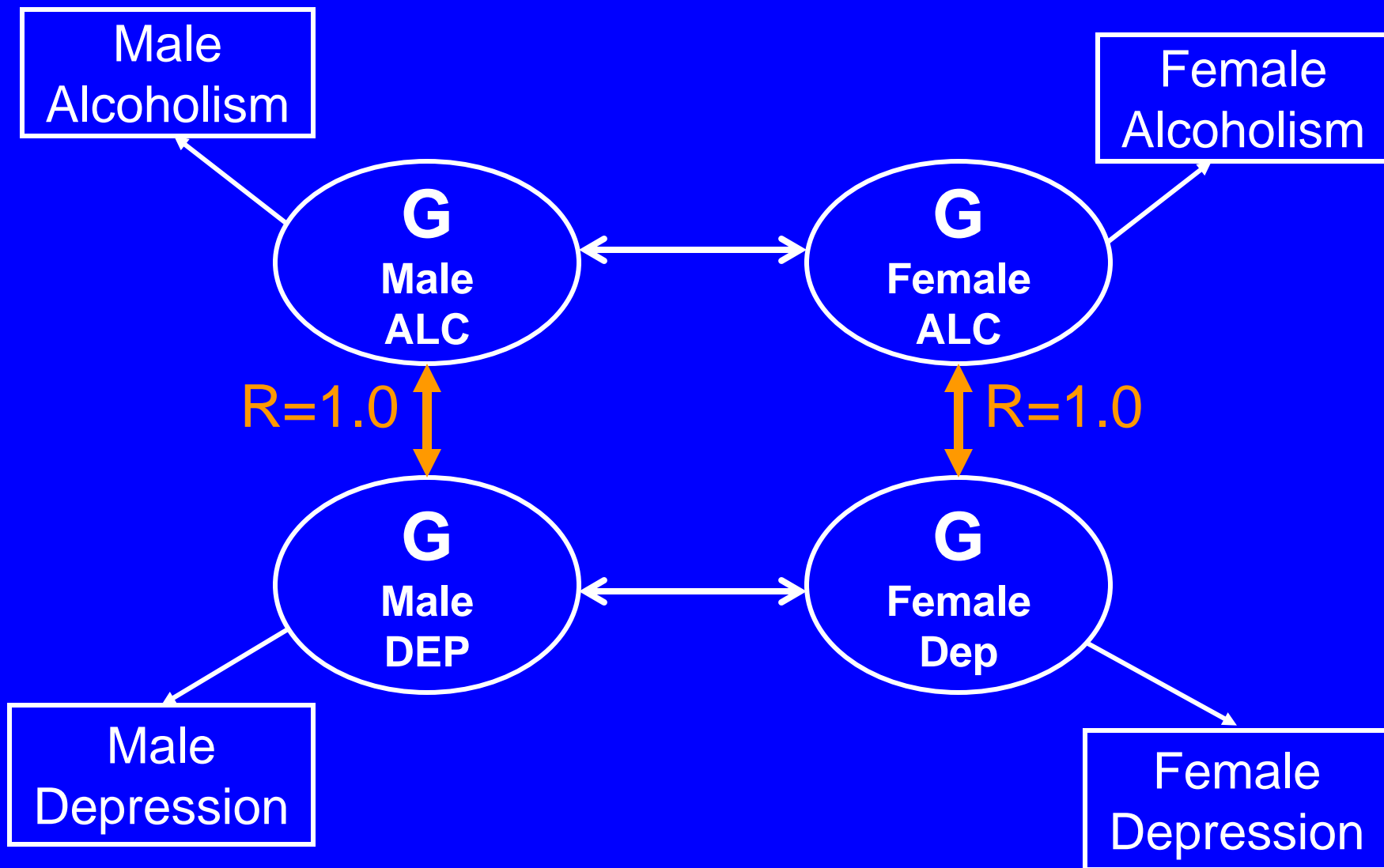
Model 2: Depression leads to alcoholism -- REJECTED



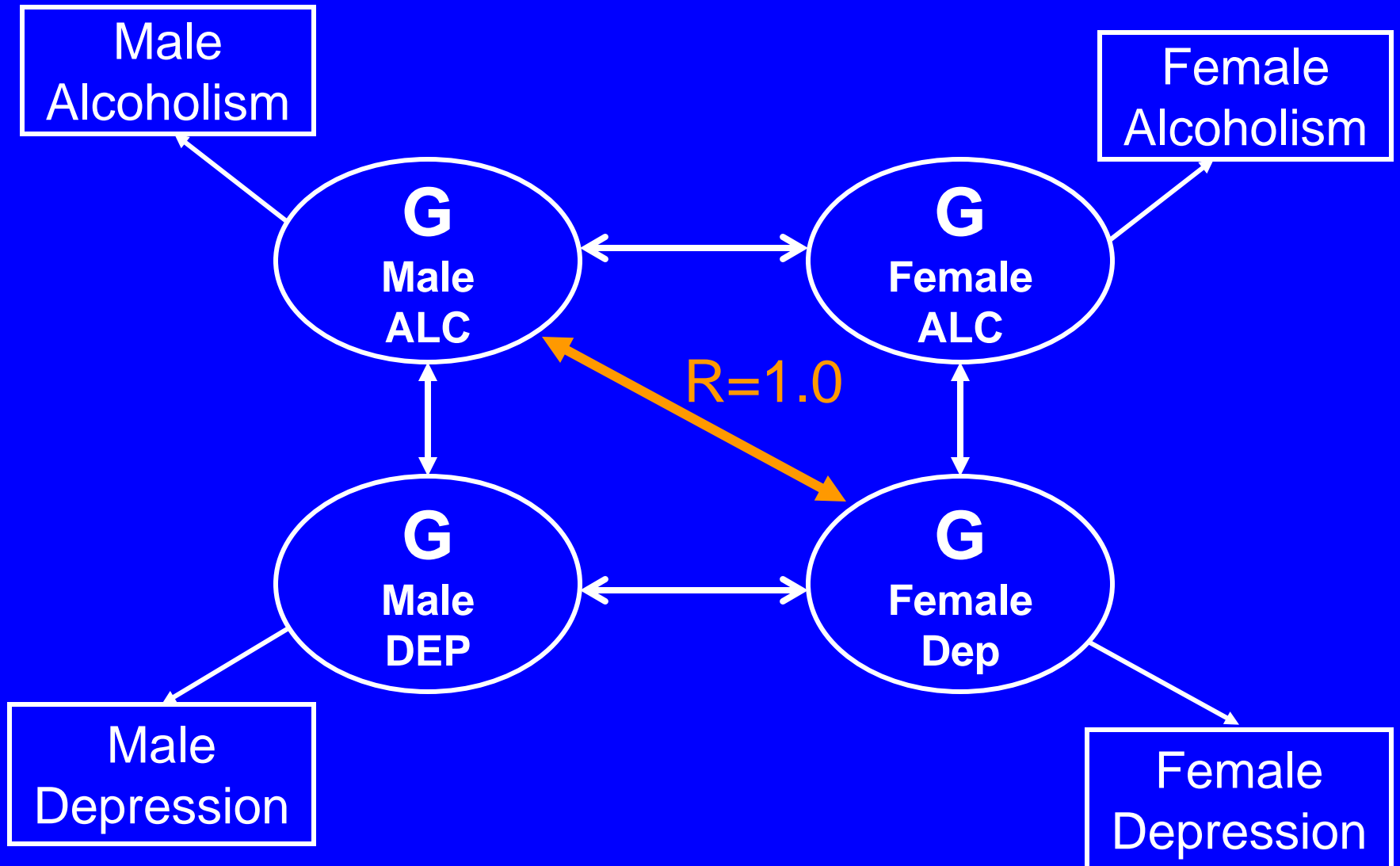
Model 3: Depression and alcoholism are the same thing genetically



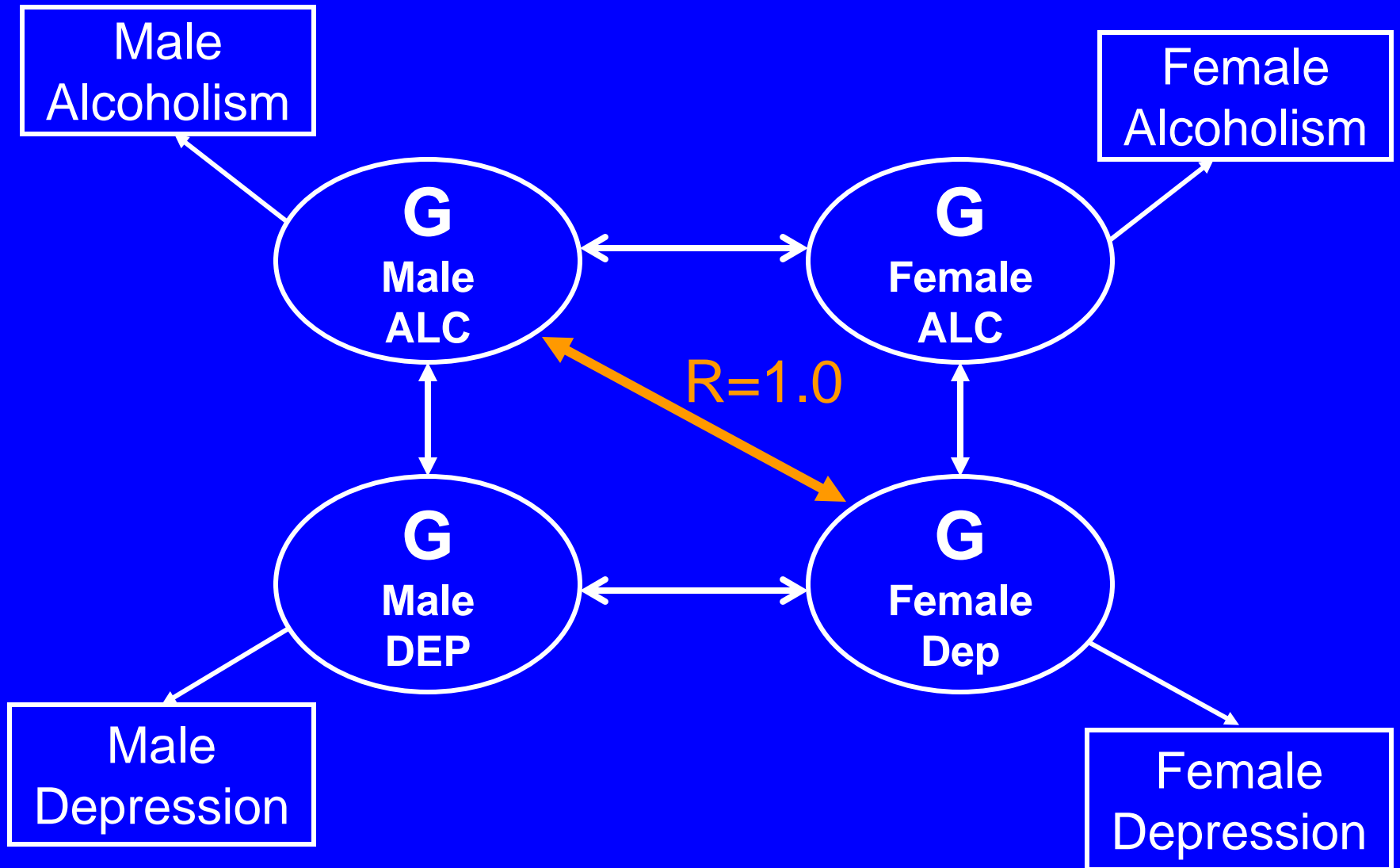
Model 3: Depression and alcoholism are the same thing genetically -- REJECTED



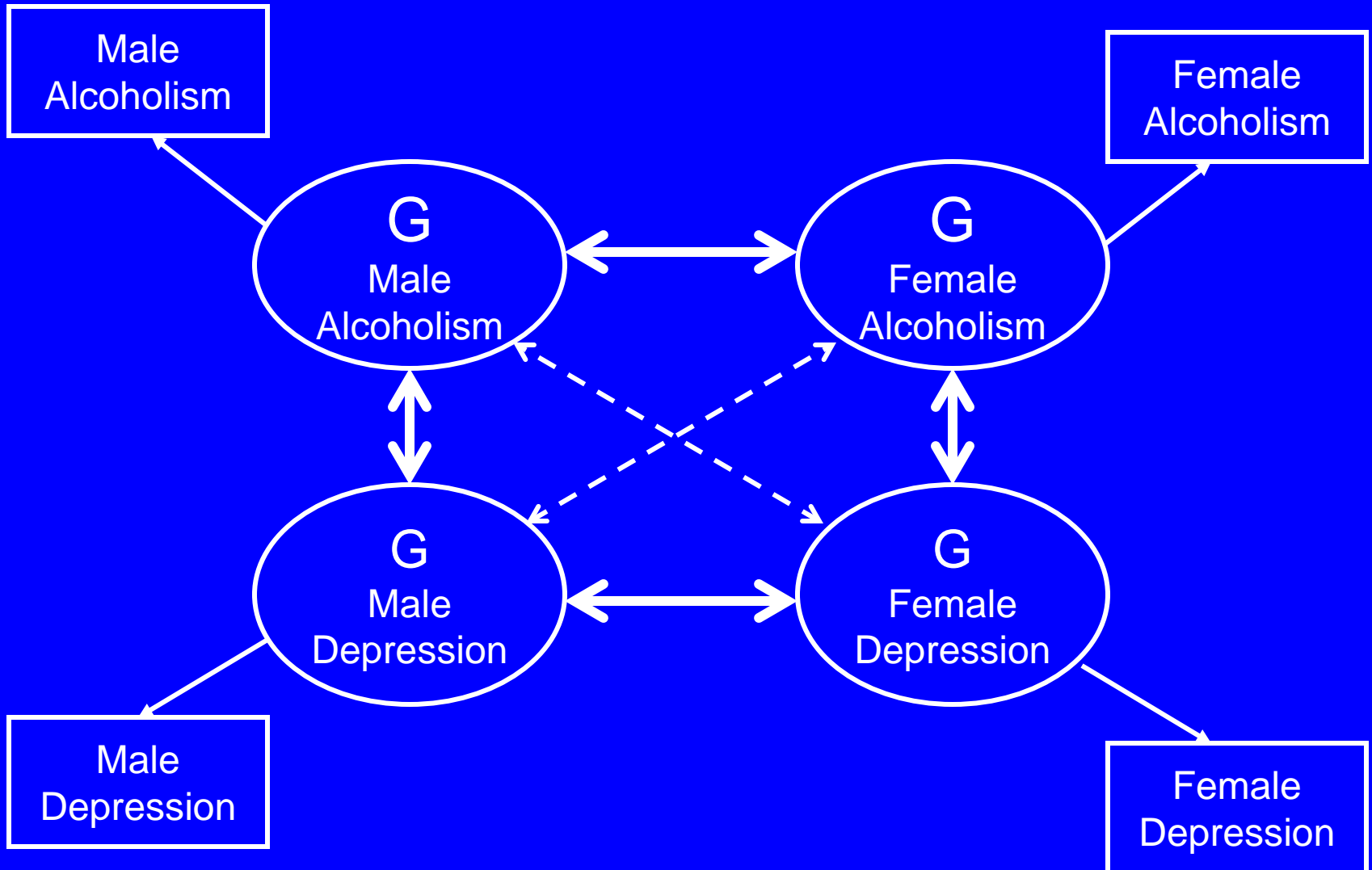
Model 4: Depression Spectrum Hypothesis



Model 4: Depression Spectrum Hypothesis -- REJECTED



Result: Alcoholism and Depression are genetically correlated *within*, but not *across* sexes



Study 4: Conclusions

- Alcoholism-depression comorbidity is attributable to both genetic and individual-specific environment
- Alcoholism and depression run in families because of genetic overlap, not environmental
- Alcoholism in men does not arise from the same genetic predisposition as depression in women

Part III.

Evaluating Risk Factors for Alcoholism

Part III. Risk Factors

Many factors are associated with increased risk for alcoholism

Are they causal?

Twin data applied to two examples:

- Loss of a parent during childhood
- Early age at first drink

Part III. Method

- Evidence for association between risk factor and alcoholism
- Alternative hypotheses
- Data from VATSPSUD used to evaluate competing models

Study 5:

How does loss of a parent during
childhood increase risk
for alcoholism during adulthood?

Kendler, Neale, Prescott, Kessler, Heath, Corey & Eaves
(1996) *Psychological Medicine*, 26:79-95

Alternative explanations for an association between parental loss during childhood and alcoholism during adulthood

Causal hypothesis:



Alternative explanations for an association between parental loss during childhood and alcoholism during adulthood

Causal hypothesis:

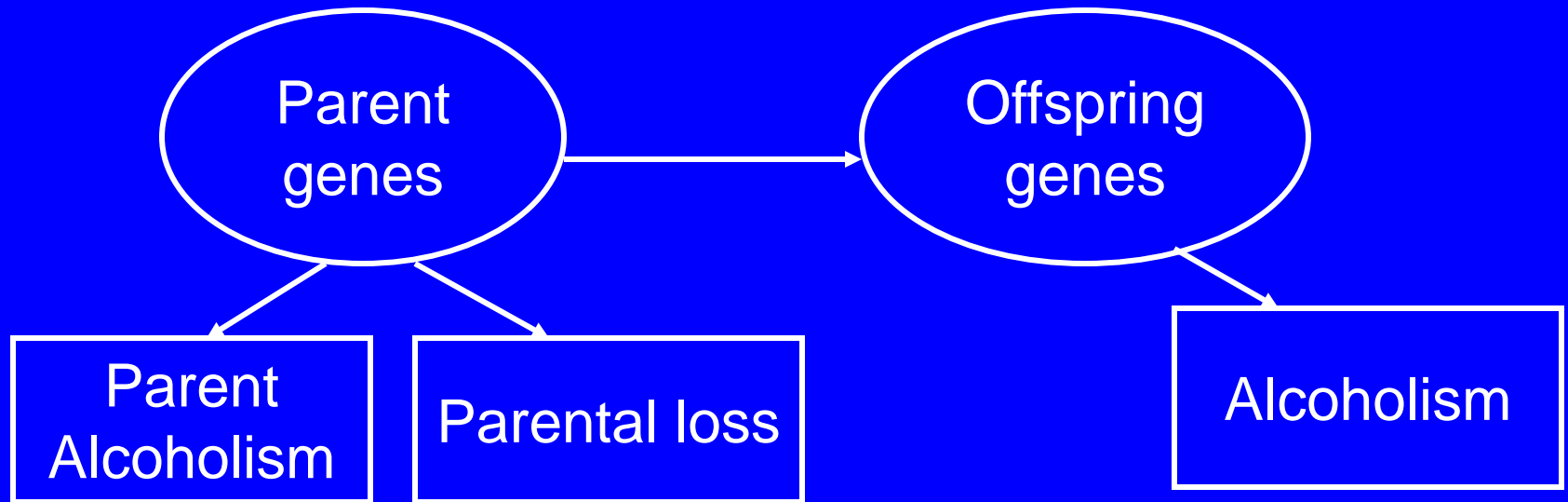


Both twins experience loss, predicted pair similarity for alcoholism:

$$R_{MZ} = R_{DZ}$$

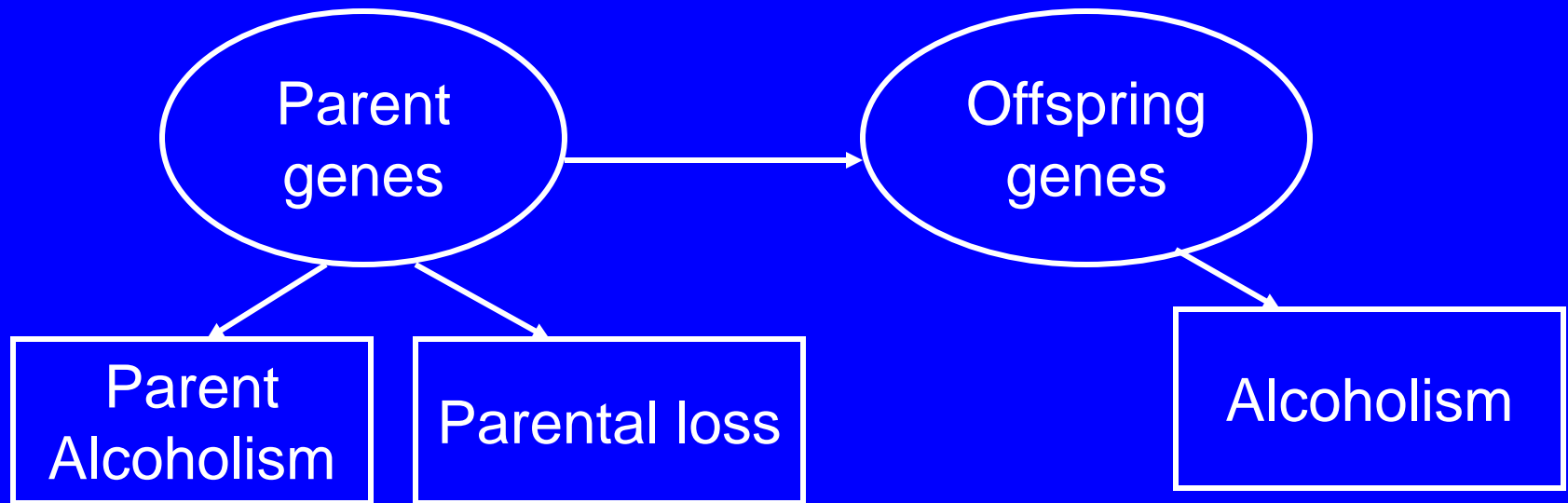
Alternative explanations for an association between parental loss during childhood and alcoholism during adulthood

Correlated hypothesis:



Alternative explanations for an association between parental loss during childhood and alcoholism during adulthood

Correlated hypothesis:



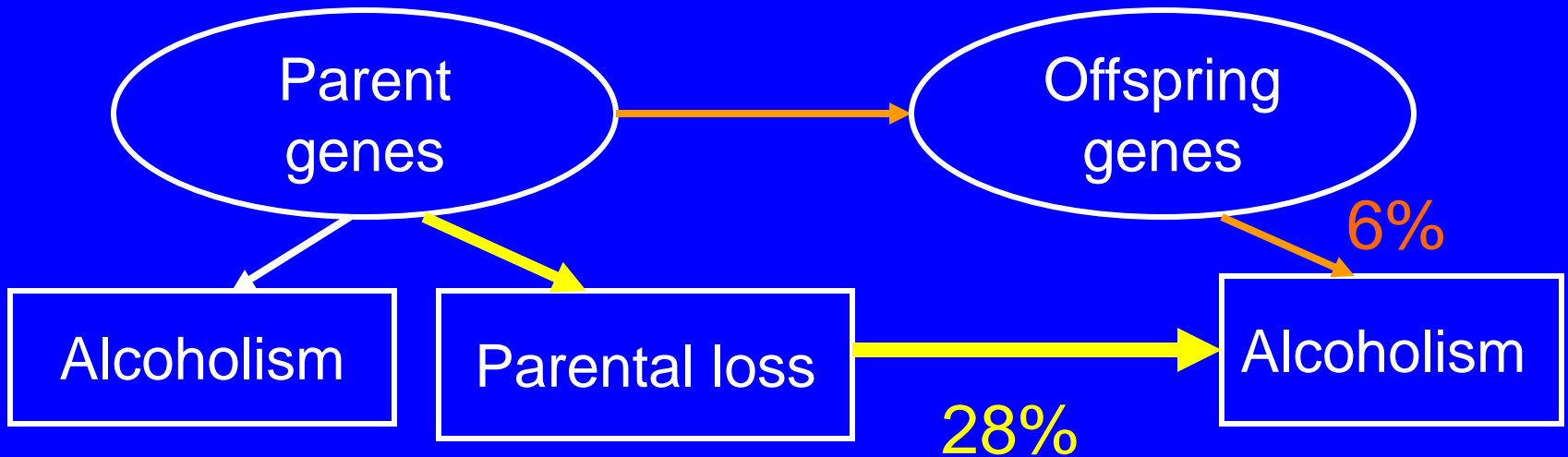
MZ and DZ pairs differ in degree to which they inherit parent's predisposition to alcoholism;
Predicted pair similarity for alcoholism: $R_{MZ} > R_{DZ}$

Method

- Data on alcoholism from female twins and their parents
- 17.5% of twins experienced loss of parent before age 17
- Loss due to death (6.1%) or divorce (12.1%)
- Analysis used structural models for twins and parents, using parental loss as a measured component of family environment

Results

Both models were supported



Study 5: Conclusion

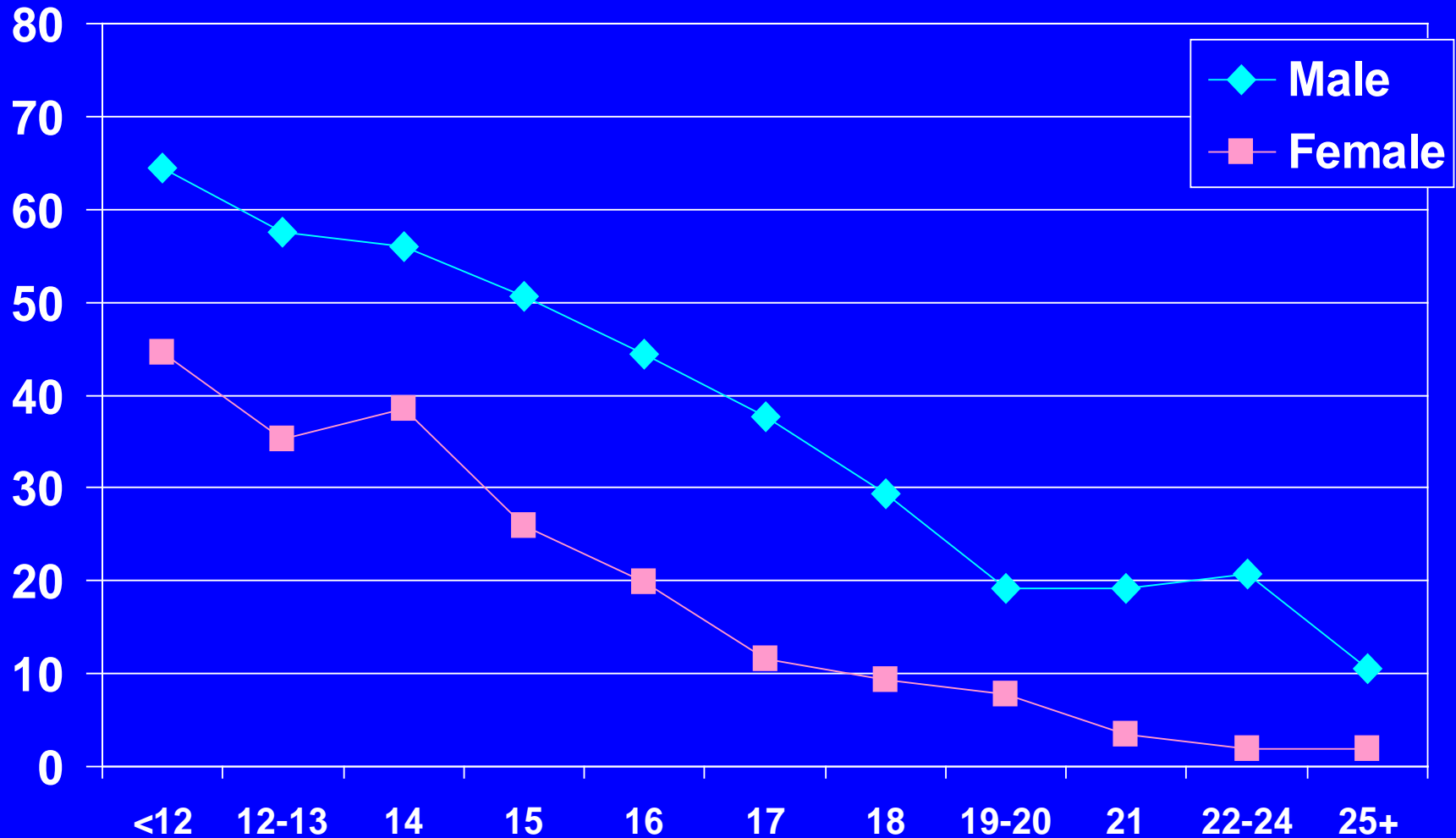
The association between parental loss and alcoholism occurs because of both the environmental effects of parental loss and the genetic transmission of alcoholism risk

Study 6:

Does early drinking
increase risk for alcoholism?

Prescott & Kendler (1999) *Alcohol Clin Exp Res* 23:101-107

Lifetime prevalence of DSM-IV alcohol abuse/dependence by age at first drink



N= 8,746 adult twins

Causal explanation for the association between early drinking and risk for alcoholism



Causal explanation for the association between early drinking and risk for alcoholism



Implication:

Delaying drinking will reduce risk for alcoholism

Causal explanation for the association between early drinking and risk for alcoholism



Implication:

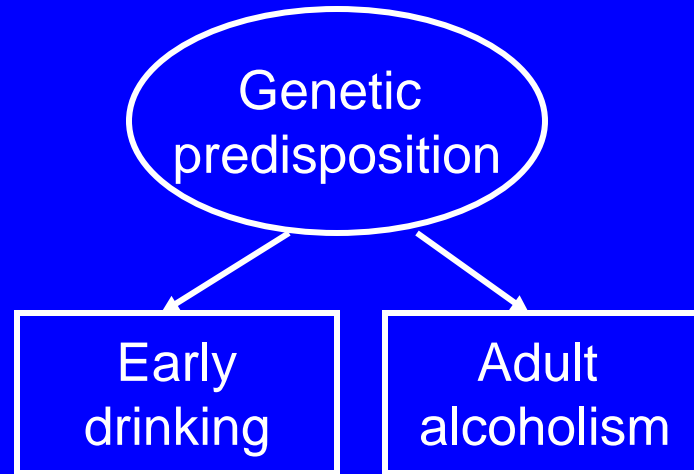
Delaying drinking will reduce risk for alcoholism

Prediction:

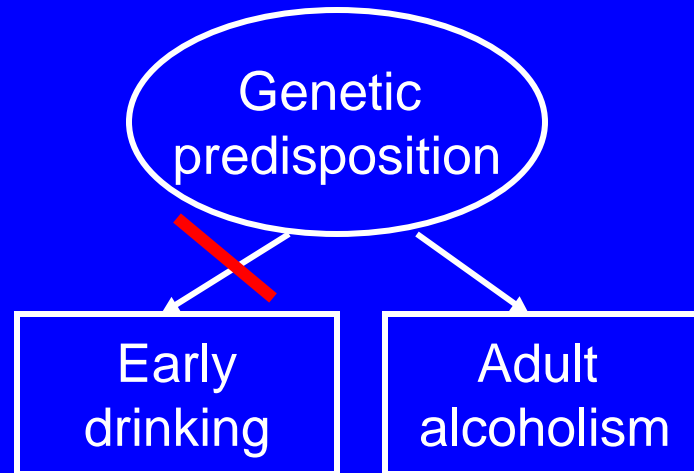
Twin 1 early drinking increases Twin 1 risk

Twin 1 early drinking not directly associated with Twin 2 risk

Common cause explanation for the association between early drinking and risk for alcoholism



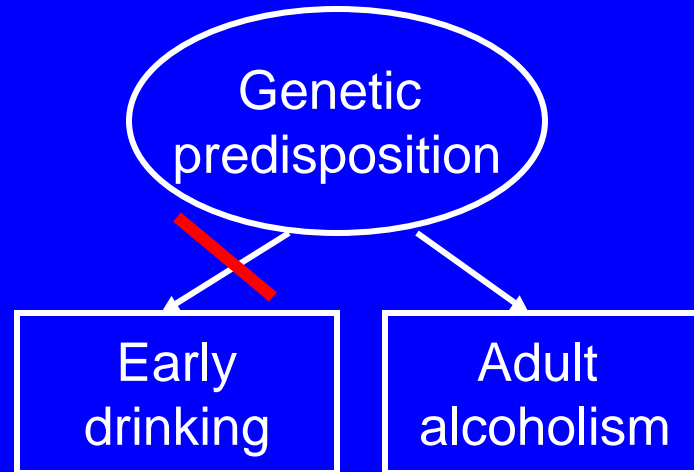
Common cause explanation for the association between early drinking and risk for alcoholism



Implication:

Delaying first drink may not reduce risk for alcoholism

Common cause explanation for the association between early drinking and risk for alcoholism



Implication:

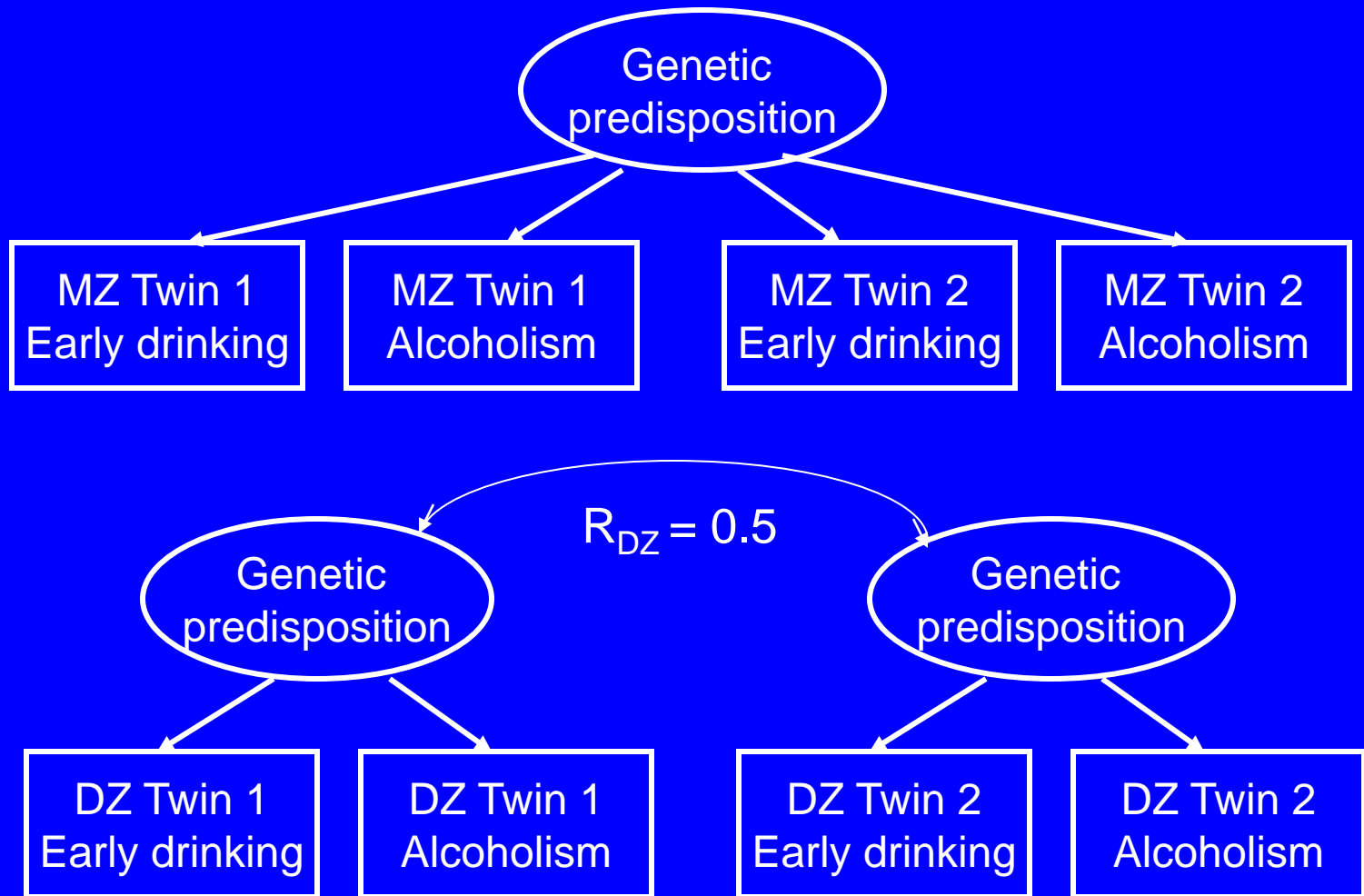
Delaying first drink may not reduce risk for alcoholism

Predictions:

Twin 1 early drinking associated with higher risk for Twin 1 and Twin 2

Correlation of Twin 1 drinking and Twin 2 risk will be higher in MZ pairs than DZ pairs

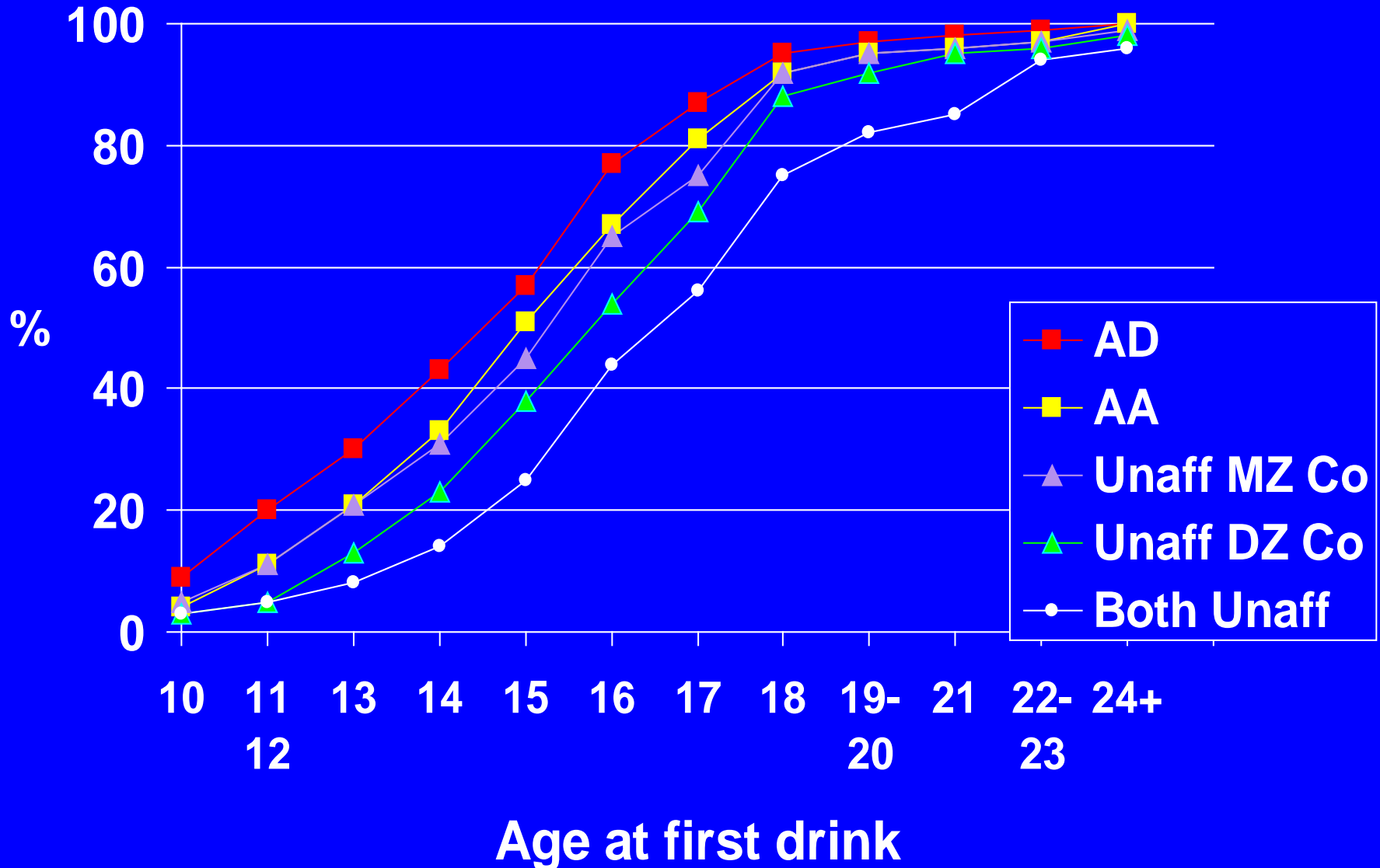
Prediction based on Common Cause Explanation:
Twin 1 early drinking increases Twin 1 risk and Twin 2 risk
Twin 2's risk will be higher in MZ pairs than DZ pairs



Statistical Analysis

- Bivariate structural models for twin pairs
- Discrete time survival models of onset-diagnosis relation, using cotwin drinking age as a covariate

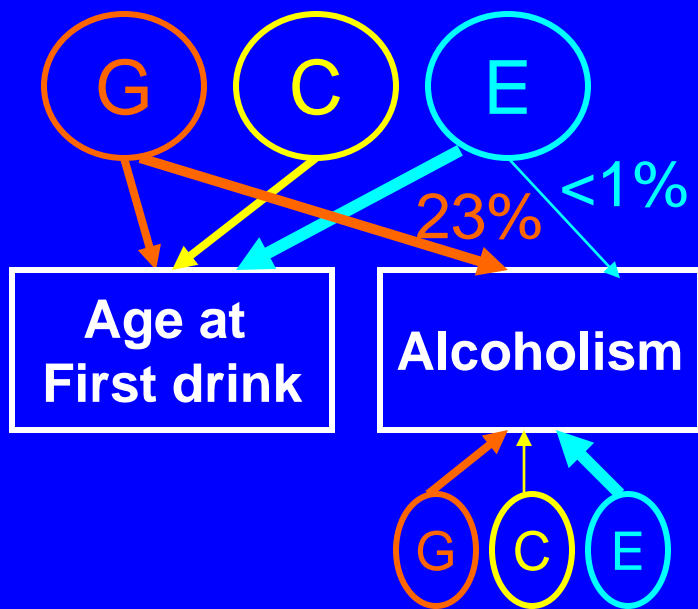
Cumulative distribution of drinking onset by diagnosis of affected twin and unaffected cotwins



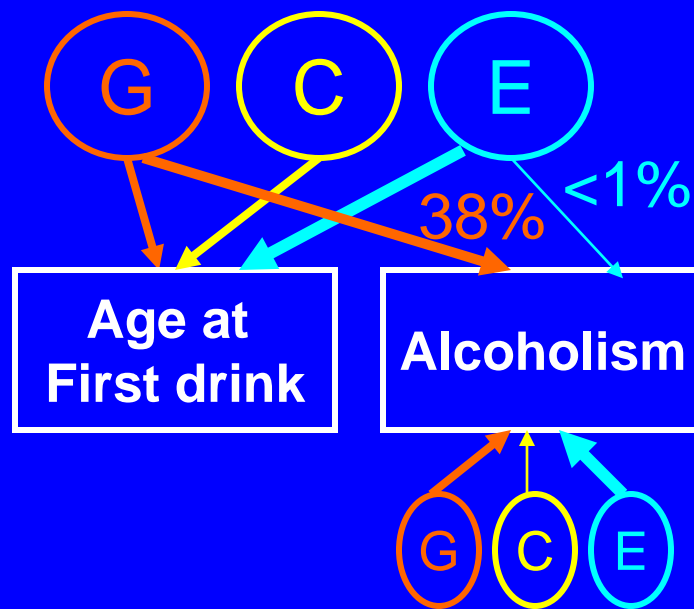
Results are consistent with the common cause model

Estimated proportion of risk for alcoholism which overlaps with early drinking

MALES = 23%



FEMALES = 39%



Based on DSM-IV Alcohol Abuse/Dependence;
Standard error for genetic estimates <5%

Study 6: Conclusions

- Age at first drink is an index of genetic risk for alcoholism
- Delaying first drink may not reduce risk for alcoholism
- Other targets for intervention may be more effective
- BUT: Delaying adolescent drinking may have other benefits!

Final Summary: What twin studies teach us about the etiology of alcoholism

- Biologically-relevant definitions of alcoholism
 - Refining the phenotype for molecular genetic studies
- Clarify specificity or generality of genetic influence
 - Subtypes may be etiologically distinct
 - Basis for comorbidity is complex
- Sources for sex differences
 - Alcoholism is not less genetic in women, but is different
- Evaluating risk factors
 - Don't rush to causal interpretations

Other things twin studies can teach us about the etiology of alcoholism

- Moderation: Gene-Environment Interactions
- Mediation: How genetic variation is translated into alcoholism risk
- Genetic contributions to development: continuity and change

Collaborators & Colleagues

- VCU

Ken Kendler

Lindon Eaves

Mike Neale

Steve Aggen

Jonathan Kuhn

Kristen Jacobson

Chuck Gardner

Linda Corey

- Elsewhere

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Rebecca Cross

John Horn

Ron Kessler

Connie Caldwell

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Greg Carey

Lenn Murrelle

VATSPSUD

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Barbara Brooke, Patsy Waring

Data Quality – Katharine Gagarin, Karen Hough, Justine Jones,
Paige McCleary, Beth Patton, Karen Petersen, Toni Phillips

Database Management – Indrani Ray

Data Entry – Cheryl Smith

Administrative support – Stacey Garnett, Lou Hopkins, Becky Gander

60+ Interviewers

9000+ TWINS