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Genetic epidemiologic approaches to understanding of comorbidity of substance abuse and psychiatric disorders

Kathleen Ries Merikangas

Genetic Epidemiologic Approaches to Understanding of Comorbidity of Substance Abuse and Psychiatric Disorders

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Section on Developmental Genetic Epidemiology

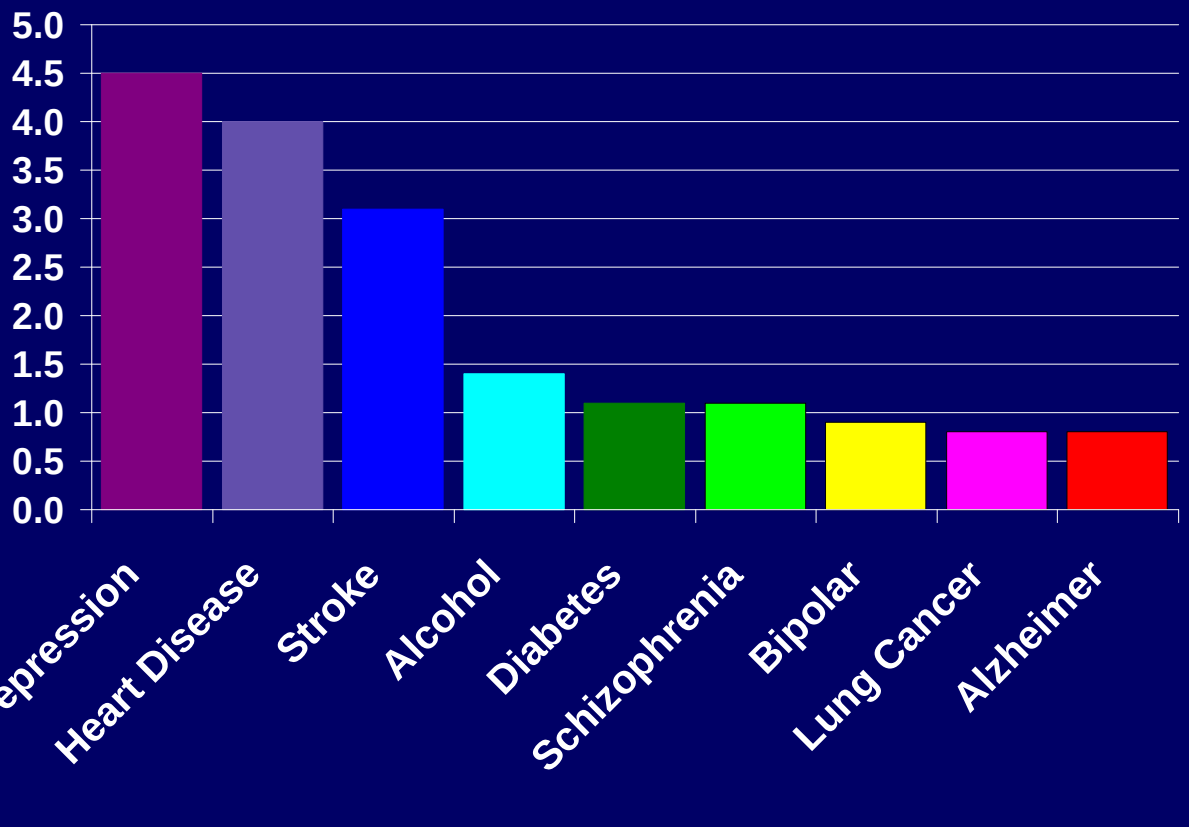
In recognition of the scientific contributions of Samuel B. Guze

- Emphasis on empiricism in psychiatry
- Validation of criteria for psychiatric disorders
  (Robins E. & Guze, S. Am J Psychiatry, 1970)
- Application of family studies to investigate subtypes and overlap between syndromes
- Integration of clinical work and research

Goals

- Population-based data on comorbidity
- Familial patterns of co-aggregation to illustrate genetic epidemiologic approach
- Patterns of co-occurrence and order of onset among high risk youth
- Clinical and research implications

Diseases with Greatest Global Burden : % Total Disability Adjusted Life Years



World Health Organization, 2002

Guze SB *Psychiatr Clin North Am.* 1990 Dec;13(4):651-9.
Secondary depression: observations in alcoholism, Briquet's syndrome, anxiety disorder, schizophrenia, and antisocial personality. A form of **comorbidity**?

Patterns of Comorbidity in the Community

12-month Prevalence of Substance Use Disorders in National Surveys of United States

Site	NCS-R	NES
Alc Abuse	3.8	4.7
Alc Dep	1.9	3.8
Drug Abuse	1.8	1.4
Drug Dep	0.7	0.6
Any Sub Abuse	9.4	9.4

NCS = National Comorbidity Survey Replication, Kessler et al; 1st 5000 cases
NES = National Epidemiologic Survey on Alcohol and Related Conditions, Grant et al

Comorbidity of Alcoholism and Mood Disorders in Community Studies

Author (yr)	Subtype	Alc Abuse	Alc Dep
Brady (92)	BPI	3.0	5.5
	BPII	3.9	3.1
	MDD	0.9	1.6
Kessler (90)	Mania	0.3	9.7
	MDE	1.0	2.7
Grant (04)	Mania	1.4	5.7
	Hypomania	1.7	5.2
	MDE	1.2	3.7

Comorbidity of Alcoholism and Anxiety Disorders in Community Studies

Author (yr)	Subtype	Alc Abuse	Alc Dep
Brady (92)	BPI	3.0	5.5
	BPII	3.9	3.1
	MDD	0.9	1.6
Kessler (90)	Mania	0.3	9.7
	MDE	1.0	2.7
Grant (04)	Mania	1.4	5.7
	Hypom	1.7	5.2
	MDE	1.2	3.7

International Consortium in Psychiatric Epidemiology:

Comorbidity of Drug and Psychiatric Disorders across Sites

(Median Odds Ratio)

	Use	Drug Problems	Dependence
Mood	2.2	3.1	3.5
Anxiety	1.9	2.5	4.0
Behavior	3.3	5.7	5.6

Substance Abuse/Dependence Lifetime Comorbidity in Puerto Rican in San Juan and New Haven

	Affective Dx	Anxiety Dx
Alcohol		
New Haven	40 %	38 %
San Juan	42 %	42 %
Drug		
New Haven	48 %	49 %
San Juan	40 %	44 %

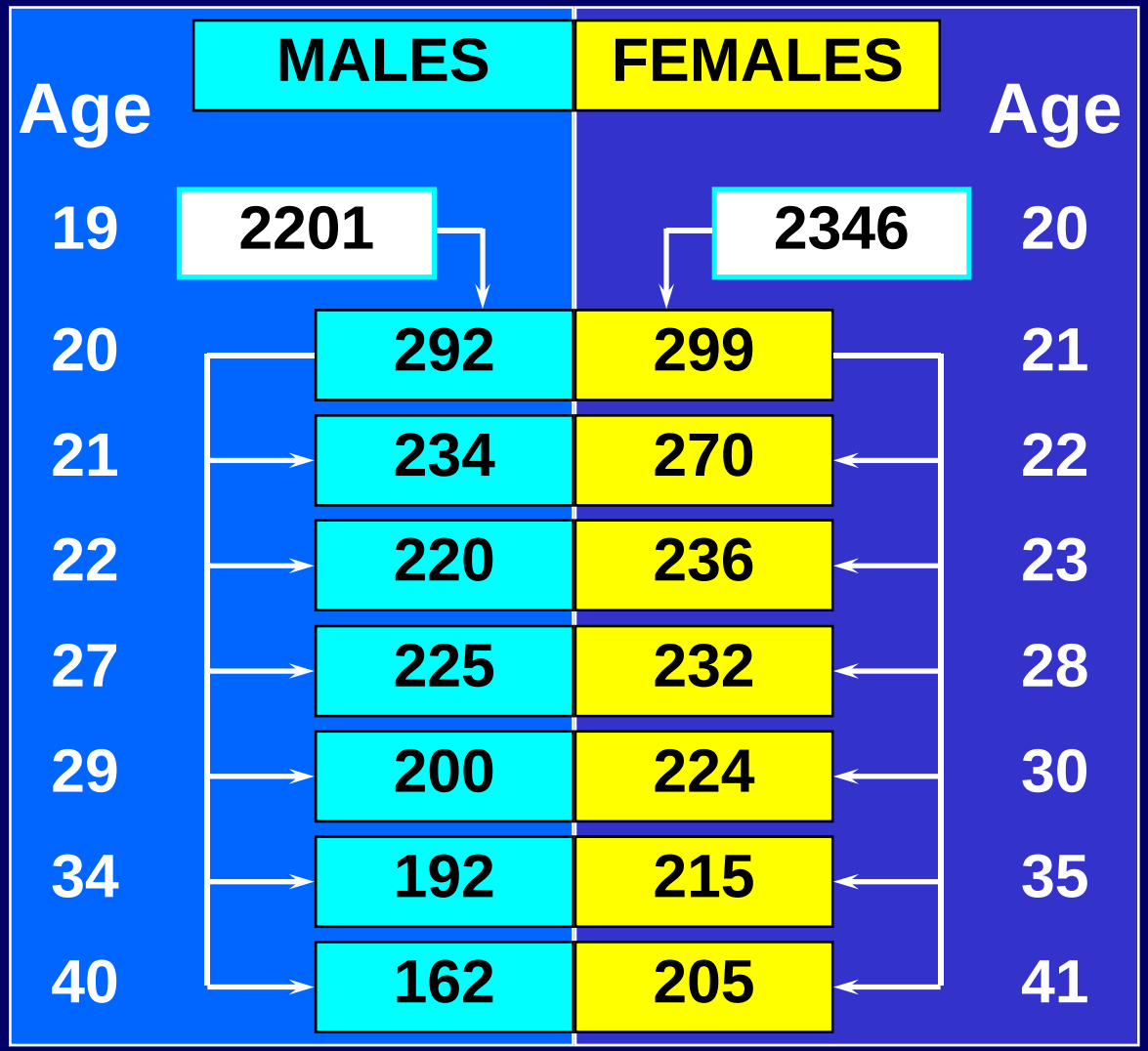
Guze SB. Semin Psychiatry. 1970 Nov;2(4):392-402. The role of follow-up studies: their contribution to diagnostic classification as applied to hysteria.

Prospective Studies

Zurich Cohort Study of Young Adults

- Sample from general community of Zurich, Switzerland
- Methods:
  - Diagnostic interview for psychiatric and somatic disorders
  - Comprehensive assessment of risk factors and correlates
  - Evaluation of spectrum of expression of mental disorders in the community

Zurich Cohort Study (1978-1999)



1978 Screening

1979 Interview

1980 Questionnaire

1981 Interview

1986 Interview

1988 Interview

1993 Interview

1999 Interview

Statistical Methods

- **Regression models were fit using generalized ordinal logistic models that yield an odds ratio for each cut-point in the ordinal outcome (Stata).**
- **The odds ratios represent the relative odds of being above the cut-point *(e.g., alcohol abuse or dependence vs. none or use; and alcohol dependence vs. none, use, or abuse).***
- **These cut-points may be regarded as diagnostic thresholds.**

Mood Disorders as Predictors of Alcohol Abuse/Dependence

	ALCOHOL	
	Abuse	Dependence
	Odds Ratio (CI)	
Major Dep	1.3 (0.6,2.9)	2.2 (0.7, 7.2)
Manic Sx	2.4 (1.2, 4.8)	4.4 (1.5,12.7)
Bipolar II	9.1 (2.7,31.2)	21.0 (6.6,67.5)

Smoking as Predictor of Alcohol and Cannabis Abuse or Dependence

	Alcohol	
	Abuse	Dependence
	Odds Ratio (CI)	
	ALCOHOL	
Smoking	6.3 (2.9,13.6)	7.6 (2.7, 21.7)
	CANNABIS	
	8.6 (4.7,15.9)	40.4 (11.2,144.9)

Alcohol Use Disorders as Predictors of Cannabis Use/ Abuse/ Dependence

	CANNABIS	
	Use	Abuse/Dep
Alcohol	*Odds Ratio (CI)*	
Abuse	1.7 (1.2, 4.1)	2.2 (0.7,6.9)
Dependence	3.8 (0.8, 4.1)	4.1 (1.0,15.8)

Results of Community Surveys

- Mood disorders are more strongly associated with alcohol dependence than with alcohol abuse
- The bipolar subtype has a significantly larger association with alcoholism than major depression

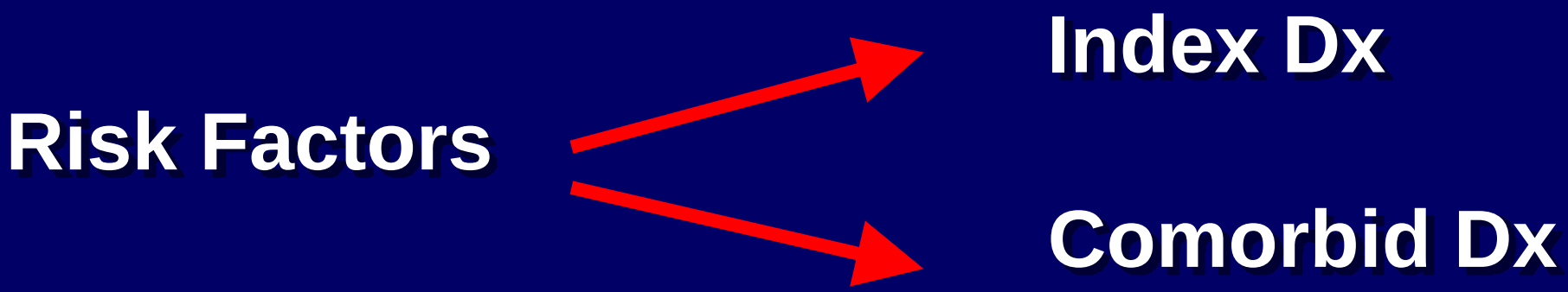
What are the potential explanations for comorbidity?

- Comorbidity is a marker of severity of the index disorder
- Different syndromes are developmentally different manifestations of the same underlying pathogenesis
- Comorbid disorder is a consequence of another index disorder, or vice versa
- Comorbid disorders are alternate manifestations of the same underlying familial liability

Sources of Comorbidity

Causal

Common Etiology



Guze SB, Cloninger CR, Martin RL, Clayton PJ.
Br J Psychiatry. 1986 Jul;149:17-23.
A **follow-up and family study** of Briquet's syndrome.

Family Study of Explanations for Comorbidity

Mechanisms for Comorbidity: Family Studies

Common Etiology

Increased risk of "comorbid" disorder alone among relatives of probands with index disorder

Causal (Precursor of Consequence)

Increased risk of "comorbid" disorder only in combination with same index disorder

Investigators: Yale Family Study of Comorbidity of Substance Disorders & Psychopathology

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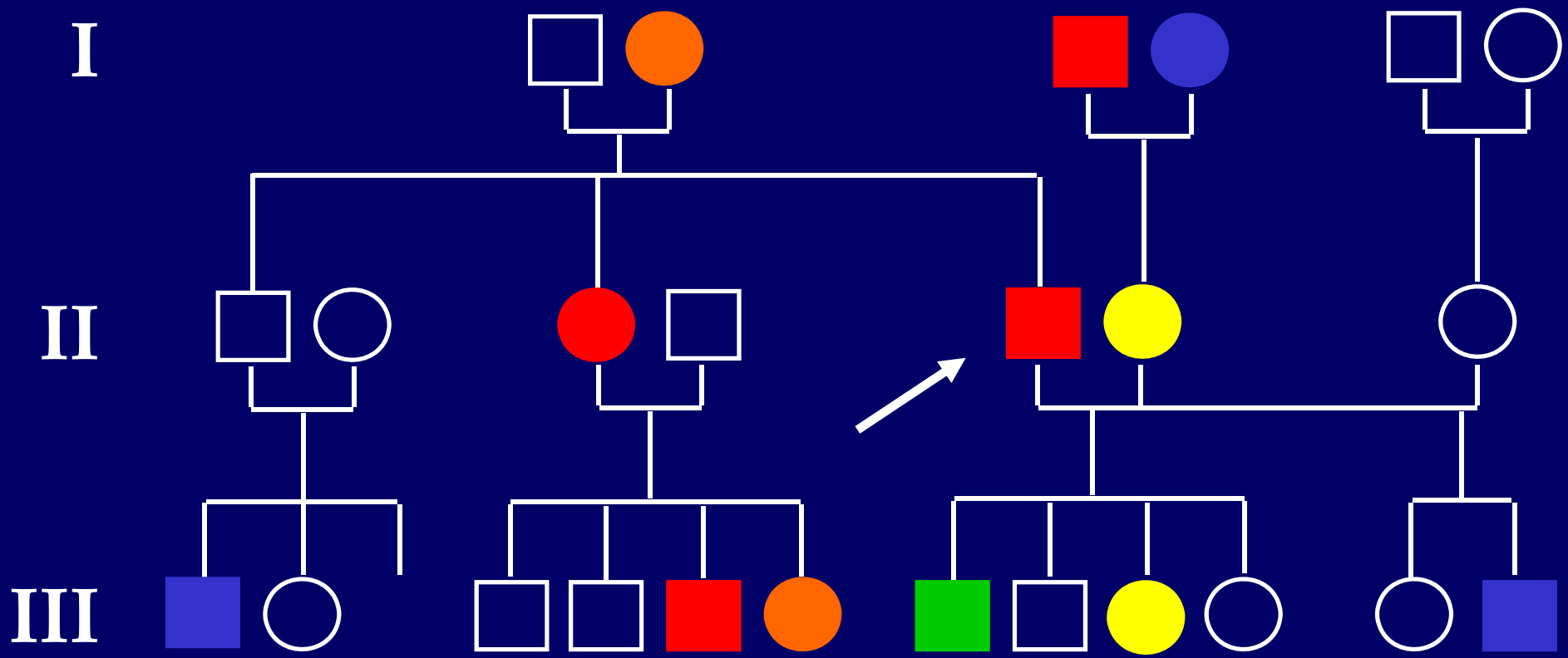
Yale Comorbidity Family Study : Sample

Probands (N=262)

	Drug	Alcohol	Anxiety	Control
N of Probands	87	89	76	61
Sex (Males %)	58	71	26	43
Age (Mean Yrs.)	36	40	40	41
N of Relatives	604	408	359	255

Relatives (N = 1626)

What disorder runs in this family?



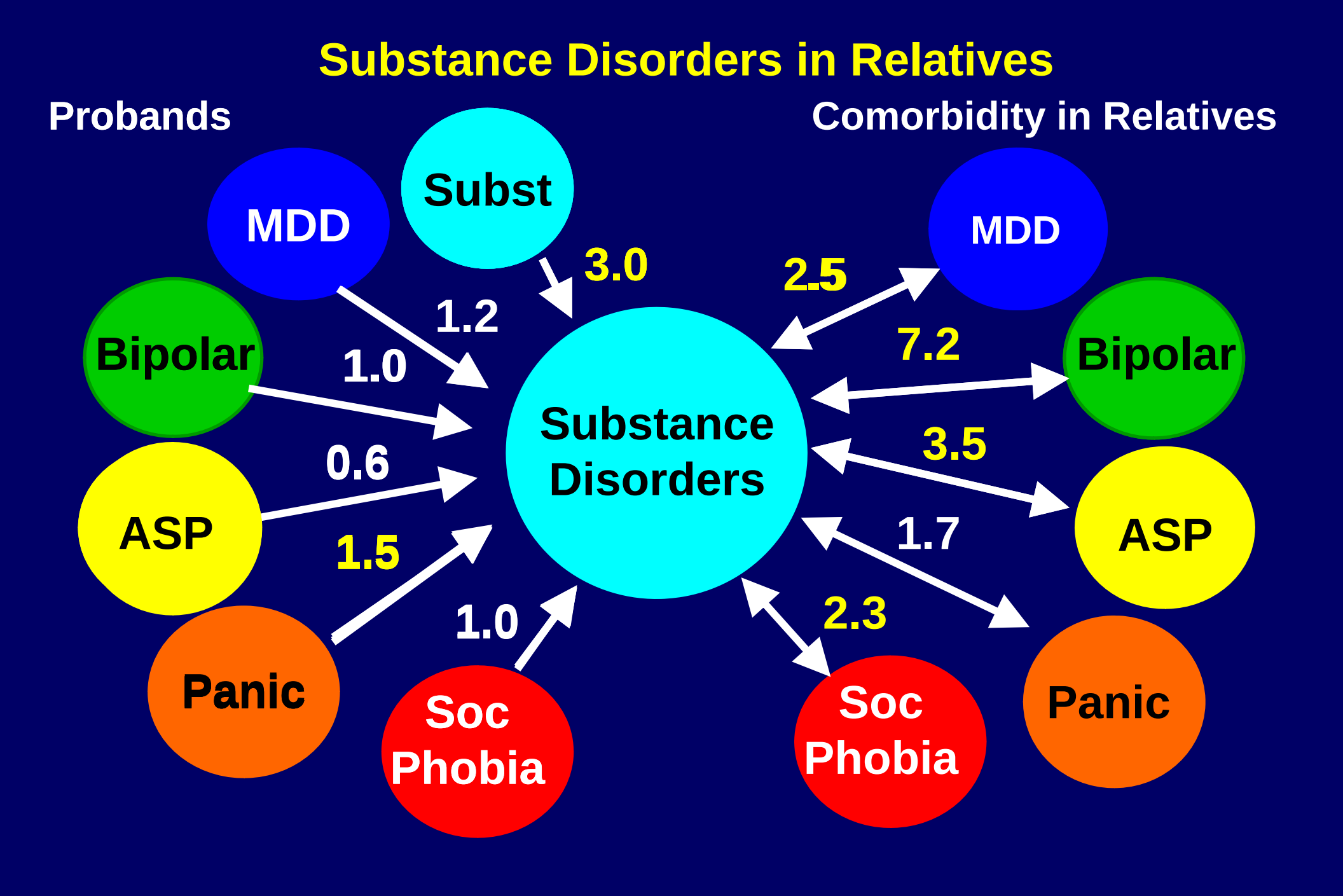
BIPOLAR

ALCOHOLISM

DRUG ABUSE

ANXIETY

DEPRESSION


Substance Disorders in Relatives
Probands
Comorbidity in Relatives
MDD
Subst
Bipolar
ASP
Panic
Soc Phobia
Substance Disorders
MDD
Bipolar
ASP
Panic
Soc Phobia
3.0
1.2
1.0
0.6
1.5
1.0
2.5
7.2
3.5
1.7
2.3

Mechanisms for Comorbidity: Yale Family Study

Common Etiology

Panic, Major Depression & Substance Use Disorders have shared underlying etiologic factors.

Causal (Precursor of Consequence)

The familial associations between Social Phobia, Bipolar Disorder & Behavior Disorders with Substance Use Disorders are independent, despite the high magnitude of comorbidity between them.

Common familial liability for cannabis and alcohol dependence

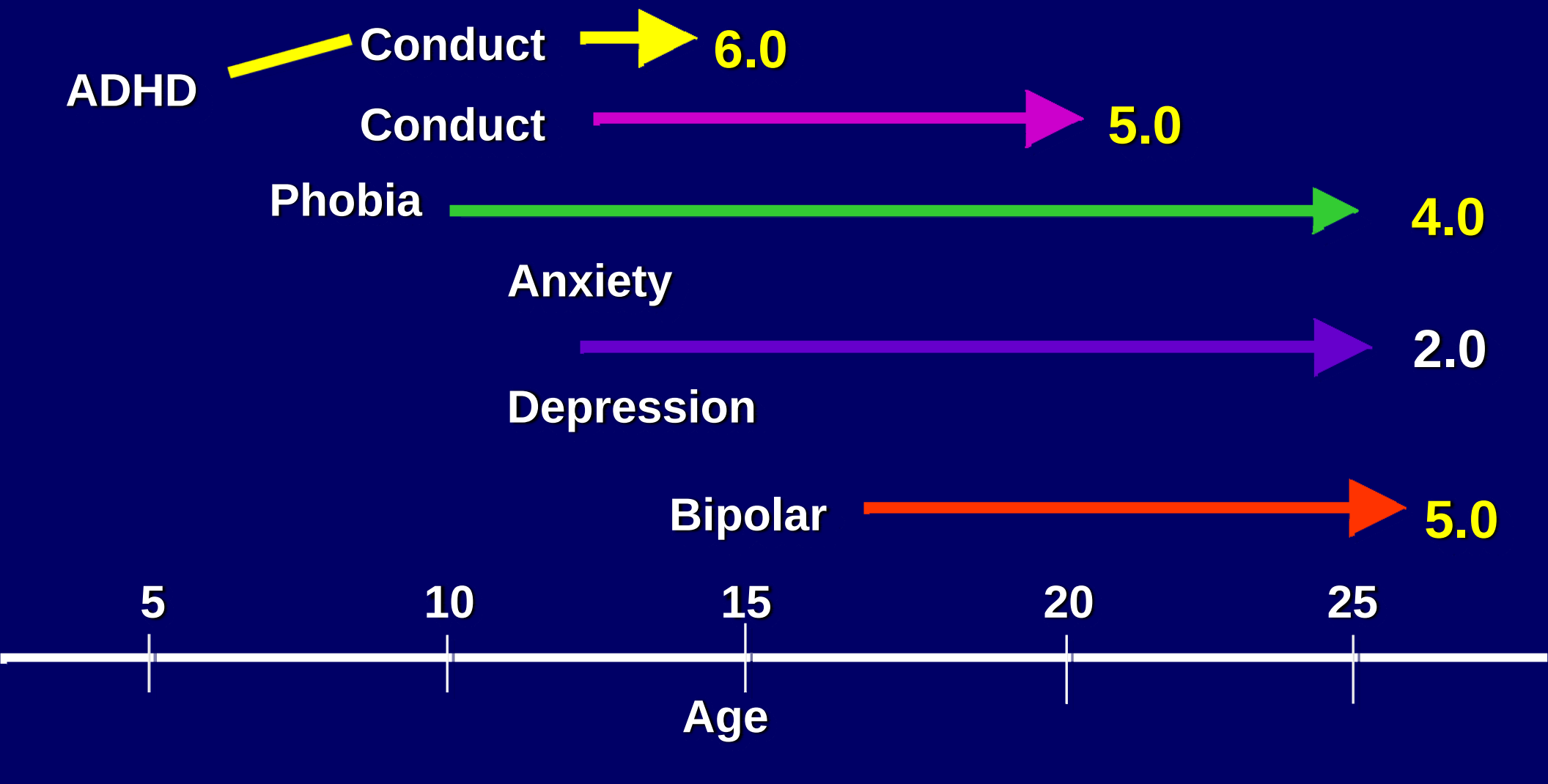
Variable	OR	95% CI
Latent Familial	8.4	1.2- 58.5
PROBANDS		
Anxiety	0.7	0.4- 1.5
Depression	0.9	0.5- 1.7
Antisocial	0.4	0.1- 1.4
Alcohol Dep	2.6	1.2- 5.5
RELATIVES		
Anxiety	1.5	0.9- 2.9
Alcohol Dep	4.3	2.0- 9.2
Antisocial	3.7	1.3-10.6

Yale High Risk Study: Age and Sex of Sample at Wave I

	Proband Group			
	Substance +Anxiety N=39	Anxiety N=58	Substance N= 38	Normal N = 57
Age (% ≥12)	51.3	46.6	50.0	49.1
Sex (% male)	53.8	55.2	50.0	45.6

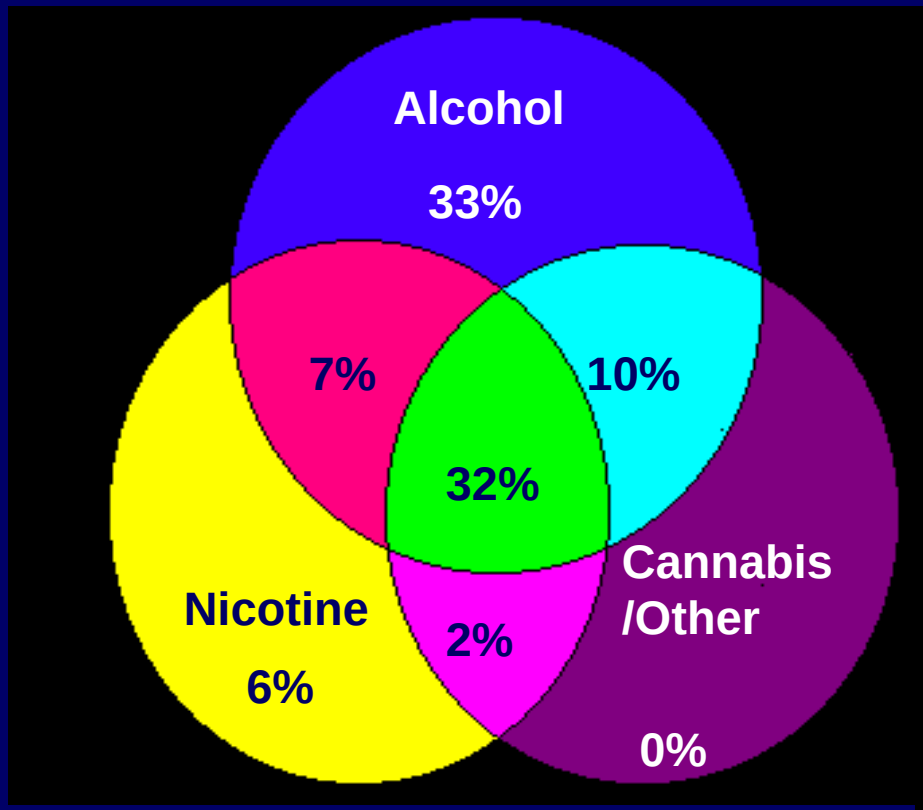
Total N = 203

Pathways to Substance Disorders through Psychopathology (Relative Risk)

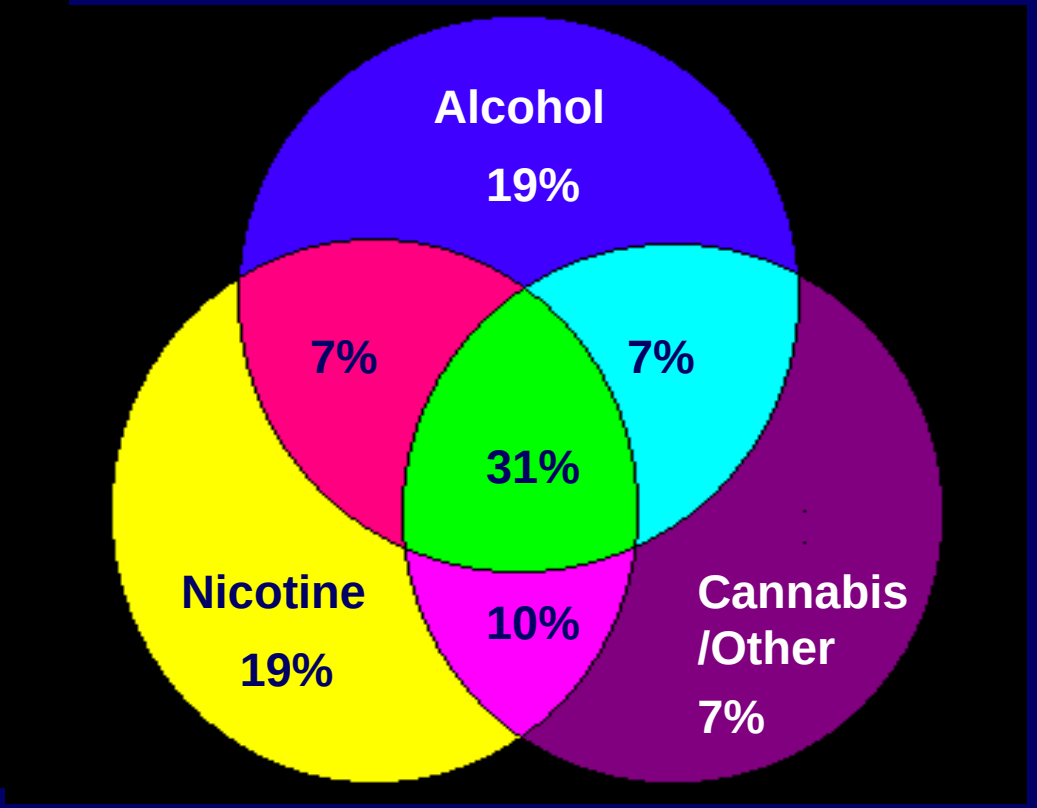


Overlap in Use and Abuse/Dependence on Specific Substances among Offspring

Use



Abuse/Dependence



Prospective Association between Psychiatric and Substance Use Disorders by Ages 13-23 (N=203)

Adjusted Risk Ratio

	Substance		
Pre-existing Dx	Use	Abuse	Dependence
Affective	0.6	1.7	3.2
Conduct	4.2	6.0	6.0
Oppositional	4.2	3.3	4.1
ADHD	0.9	2.0	3.6
Anxiety	0.9	1.9	5.5
ANY DX	1.3	3.0	5.7

Impact of Parental History and Premorbid Psychopathology on Substance Use and Disorders

	Attributable Risk	
	Use	**Disorder**
Family History	**20%**	**12%**
Premorbid Disorder	**20%**	**18%**
BOTH	**32%**	**20%**

Summary

- Mood and anxiety disorders co-occur with alcohol and drug dependence in both clinical and community surveys
- Alcoholism is largely transmitted independently of most other comorbid considitions with the exception of panic and cannabis use disorder
- The onset of bipolar syndromes and social anxiety tend to precede that of alcohol problems.

Implications

- **Etiology:** Identification of pathways and risk factors for the development of substance use disorders
- **Treatment:** Integration of psychiatric symptoms/syndromes in defining treatment strategies; Family-based approaches
- **Prevention:** Intervention in psychiatric syndromes may reduce incidence of substance use disorders; Offspring of substance abusers are important target for prevention

Clinic-based Prevention Opportunities

- **Offspring of parents in treatment for mental illness**
- **Incorporation of potential sequelae of primary disorders in treatment**
  (e.g., Geller, et al, 1998)