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

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

*Kathleen Ries Merikangas, Ph.D.*

*Senior Investigator*

*Section on Developmental Genetic Epidemiology*



# In recognition of the scientific contributions of Samuel B. Guze

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- **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**

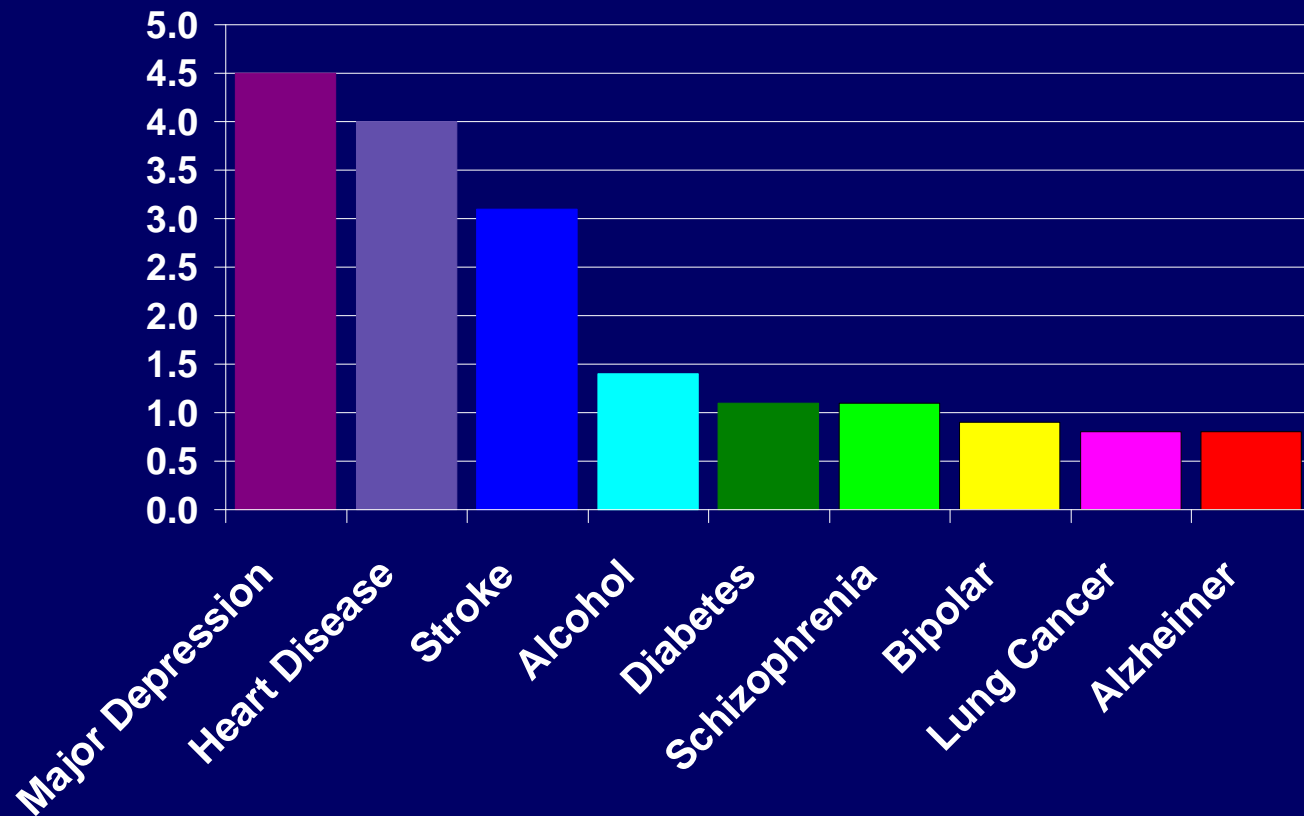


# Goals

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- **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

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| 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; 1<sup>st</sup> 5000 cases*

*NES = National Epidemiologic Survey on Alcohol and Related Conditions, Grant et al*

# Comorbidity of Alcoholism and Mood Disorders in Community Studies

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



# Comorbidity of Alcoholism and Anxiety Disorders in Community Studies

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| 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**

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*(Median Odds Ratio)*

|                 | <b>Use</b> | <b>Drug<br/>Problems</b> | <b>Dependence</b> |
|-----------------|------------|--------------------------|-------------------|
| <b>Mood</b>     | <b>2.2</b> | <b>3.1</b>               | <b>3.5</b>        |
| <b>Anxiety</b>  | <b>1.9</b> | <b>2.5</b>               | <b>4.0</b>        |
| <b>Behavior</b> | <b>3.3</b> | <b>5.7</b>               | <b>5.6</b>        |

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

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|                | Affective Dx | Anxiety Dx |
|----------------|--------------|------------|
| <b>Alcohol</b> |              |            |
| New Haven      | 40 %         | 38 %       |
| San Juan       | 42 %         | 42 %       |
| <b>Drug</b>    |              |            |
| 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.

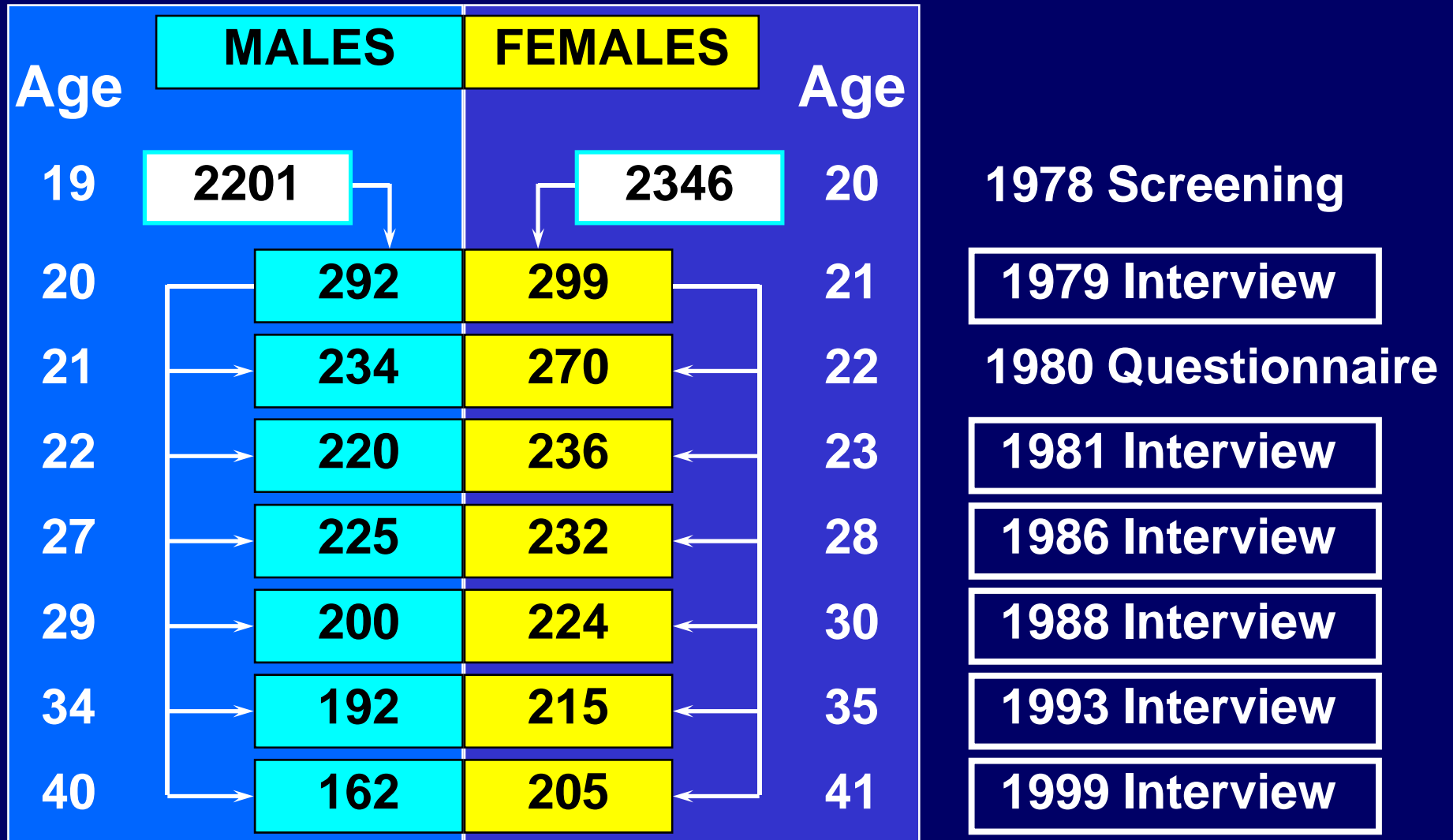
## **Prospective Studies**

# Zurich Cohort Study of Young Adults

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- **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)



# Statistical Methods

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- 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

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|            | ALCOHOL                |                 |
|------------|------------------------|-----------------|
|            | Abuse                  | Dependence      |
|            | <i>Odds Ratio (CI)</i> |                 |
| 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

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|                | <b>Alcohol Abuse</b>   | <b>Dependence</b>        |
|----------------|------------------------|--------------------------|
|                | <i>Odds Ratio (CI)</i> |                          |
|                | <b>ALCOHOL</b>         |                          |
|                | <b>6.3 (2.9,13.6)</b>  | <b>7.6 (2.7, 21.7)</b>   |
|                | <b>CANNABIS</b>        |                          |
| <b>Smoking</b> | <b>8.6 (4.7,15.9)</b>  | <b>40.4 (11.2,144.9)</b> |

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

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|                | CANNABIS               |                       |
|----------------|------------------------|-----------------------|
|                | Use                    | Abuse/Dep             |
| <b>Alcohol</b> | <i>Odds Ratio (CI)</i> |                       |
| Abuse          | <b>1.7 (1.2, 4.1)</b>  | <b>2.2 (0.7,6.9)</b>  |
| Dependence     | <b>3.8 (0.8, 4.1)</b>  | <b>4.1 (1.0,15.8)</b> |

# Results of Community Surveys

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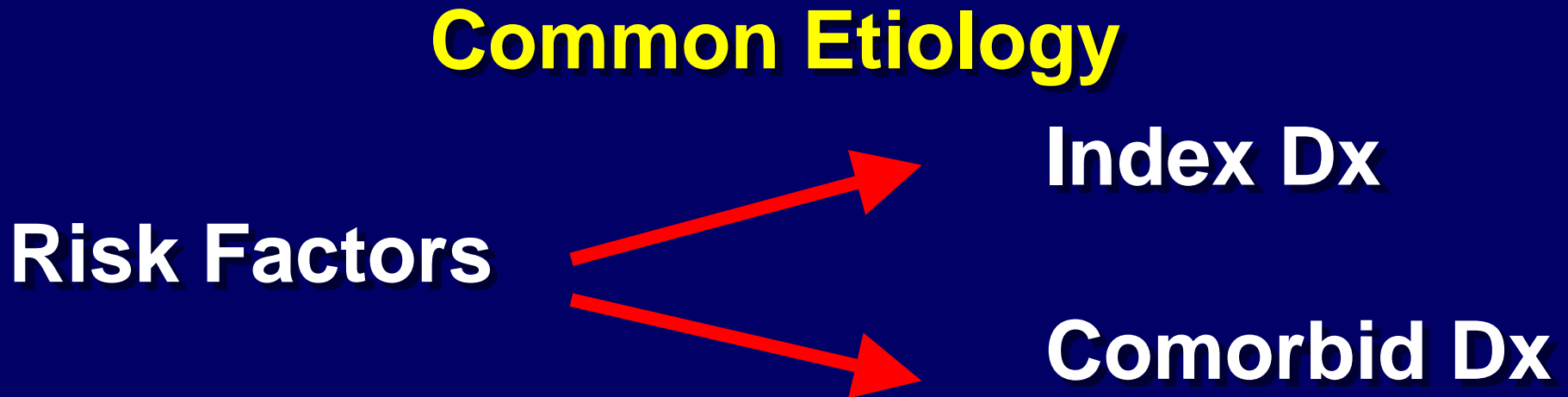
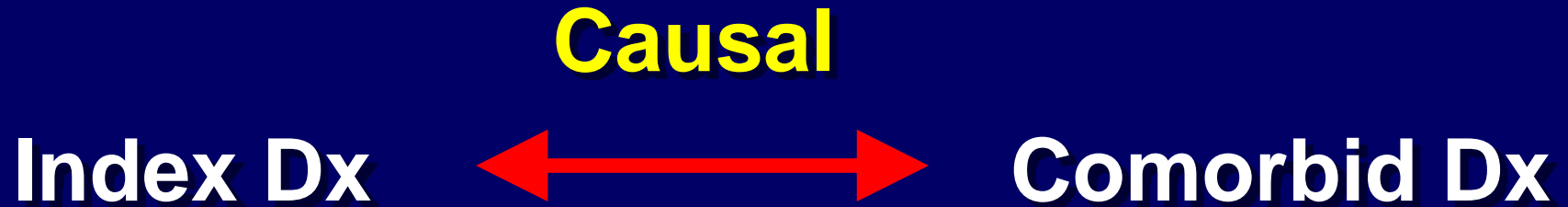
- **Mood disorders are more strongly associated with alcohol dependence than with alcohol abuse**
- **The bipolar subtype has a significantly larger association with alcoholism than major depression**

# What are the potential explanations for comorbidity?

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- 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



**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

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## 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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**K.R. Merikangas**

**K. Conway**

**B. Fenton**

**J. Merikangas**

**N. Risch**

**D. Stevens**

**P. Szatmari**

**S. Avenevoli**

**L. Dierker**

**C. Grillon**

**M. Preisig**

**B. Rounsaville**

**M. Stolar**

**H. Zhang**



# Yale Comorbidity Family Study : Sample

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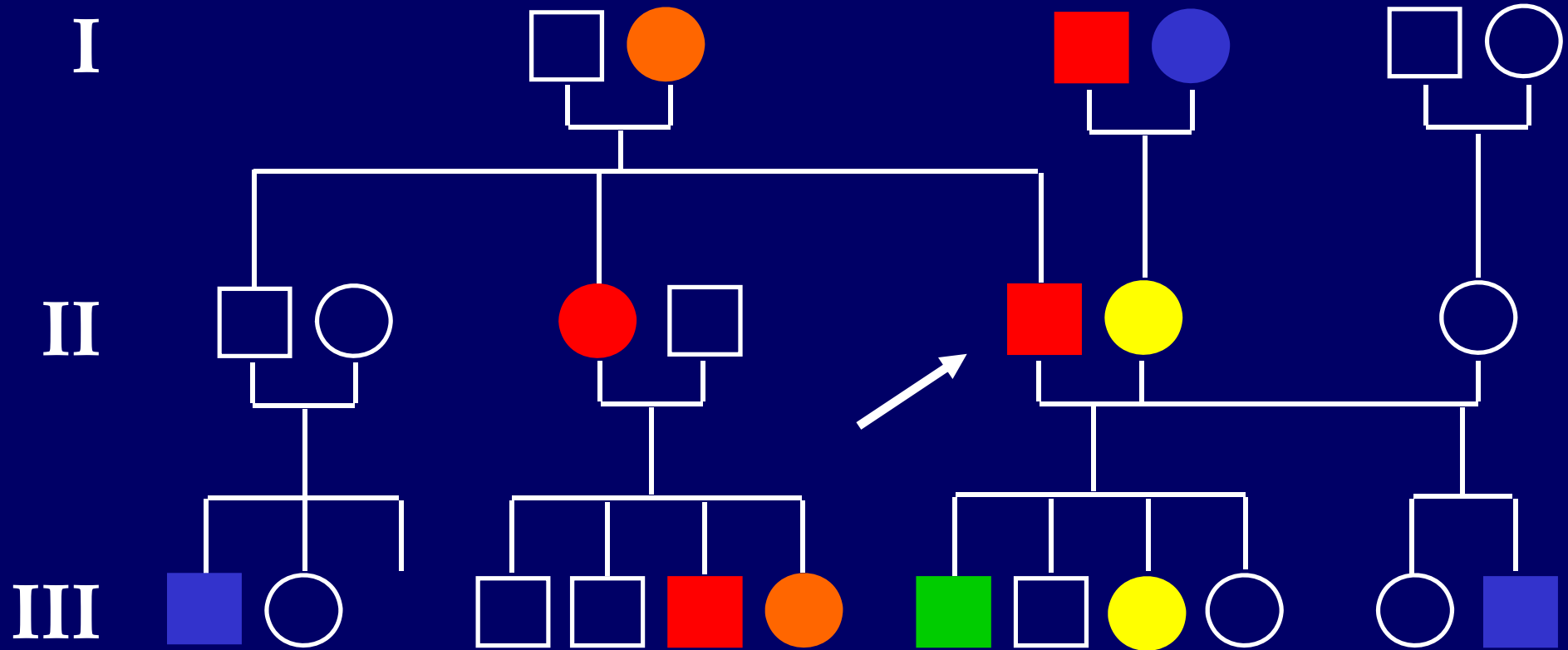
Probands ( N=262)

**Drug Alcohol Anxiety Control**

|                        |            |            |            |            |
|------------------------|------------|------------|------------|------------|
| <b>N of Probands</b>   | <b>87</b>  | <b>89</b>  | <b>76</b>  | <b>61</b>  |
| <b>Sex (Males %)</b>   | <b>58</b>  | <b>71</b>  | <b>26</b>  | <b>43</b>  |
| <b>Age (Mean Yrs.)</b> | <b>36</b>  | <b>40</b>  | <b>40</b>  | <b>41</b>  |
| <b>N of Relatives</b>  | <b>604</b> | <b>408</b> | <b>359</b> | <b>255</b> |

**Relatives ( N = 1626)**

# What disorder runs in this family?



Orange square: BIPOLAR

Red square: ALCOHOLISM

Green square: DRUG ABUSE

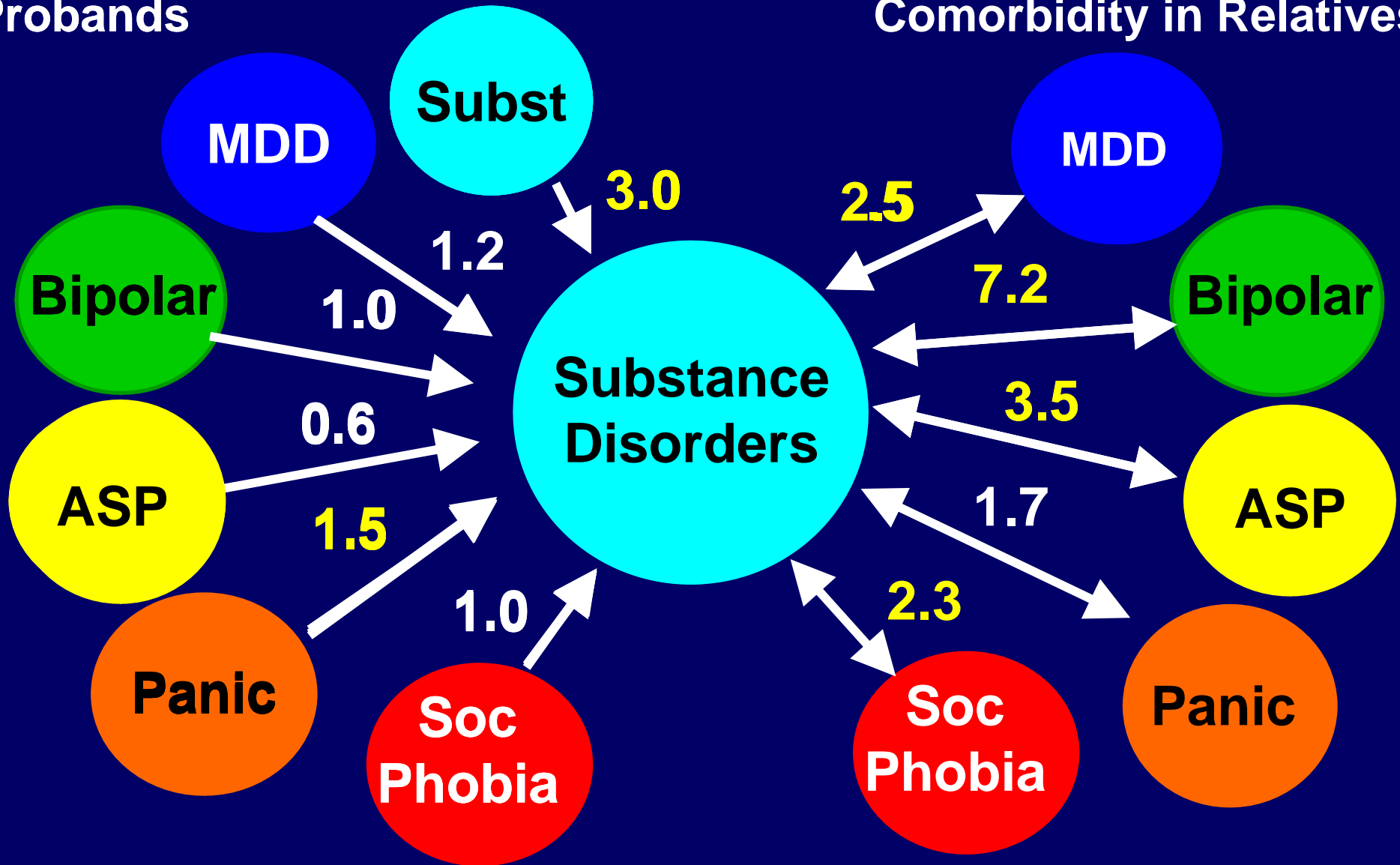
Yellow square: ANXIETY

Blue square: DEPRESSION

# Substance Disorders in Relatives

Probands

Comorbidity in Relatives



# **Mechanisms for Comorbidity: Yale Family Study**

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## **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

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| Variable         | OR  | 95% CI    |
|------------------|-----|-----------|
| Latent Familial  | 8.4 | 1.2- 58.5 |
| <b>PROBANDS</b>  |     |           |
| 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  |
| <b>RELATIVES</b> |     |           |
| Anxiety          | 1.5 | 0.9- 2.9  |
| Alcohol Dep      | 4.3 | 2.0- 9.2  |
| Antisocial       | 3.7 | 1.3-10.6  |

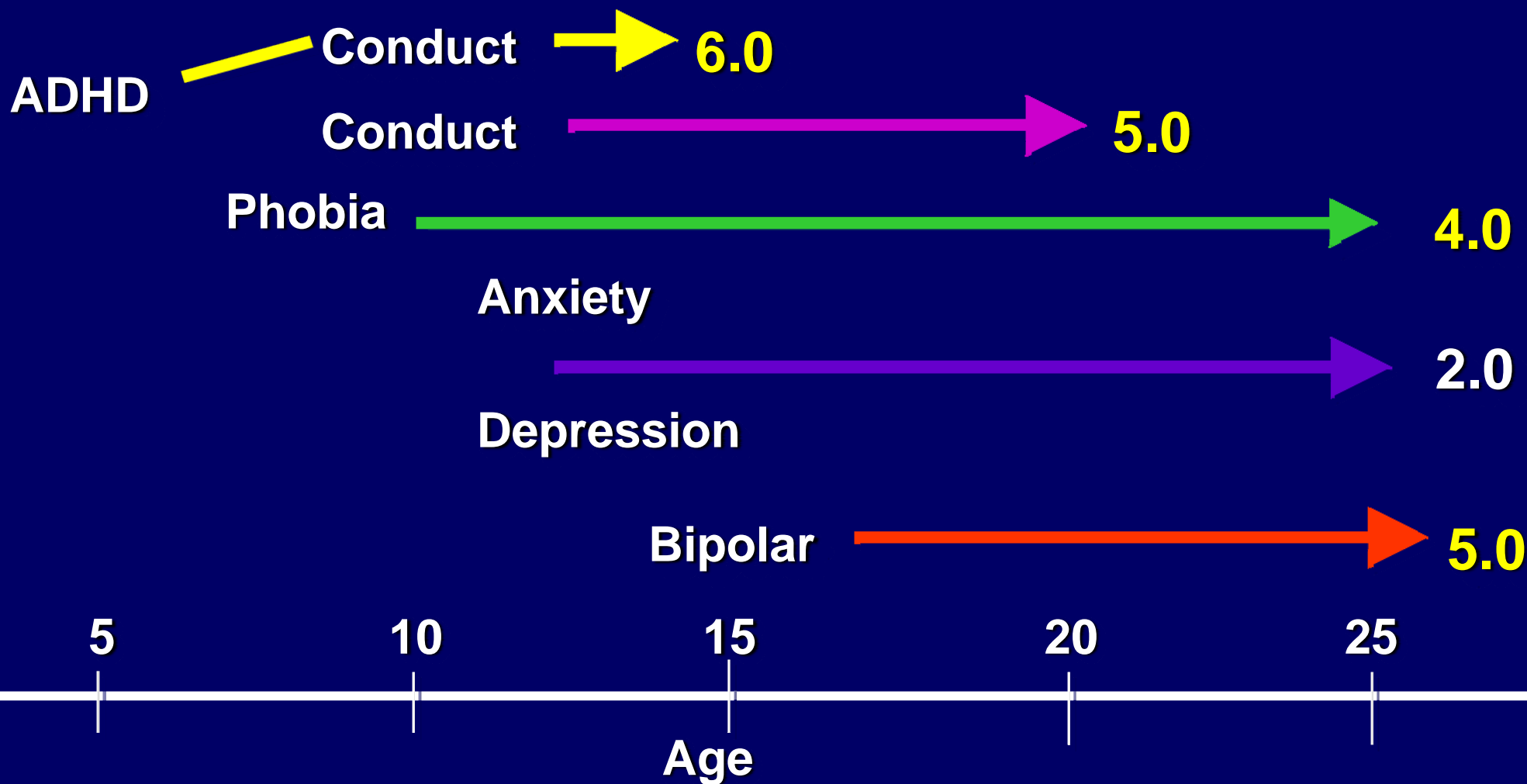
# Yale High Risk Study: Age and Sex of Sample at Wave I

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## Proband Group

|  | <b>Substance<br/>+Anxiety<br/>N=39</b> | <b>Anxiety<br/>N=58</b> | <b>Substance<br/>N= 38</b> | <b>Normal<br/>N = 57</b> |
|--|--|-------------------------|----------------------------|--------------------------|
| <b>Age<br/>(% <math>\geq</math>12)</b> | <b>51.3</b>                            | <b>46.6</b>             | <b>50.0</b>                | <b>49.1</b>              |
| <b>Sex<br/>(% male)</b>                | <b>53.8</b>                            | <b>55.2</b>             | <b>50.0</b>                | <b>45.6</b>              |
|  |  |                         | <b>Total N = 203</b>       |                          |

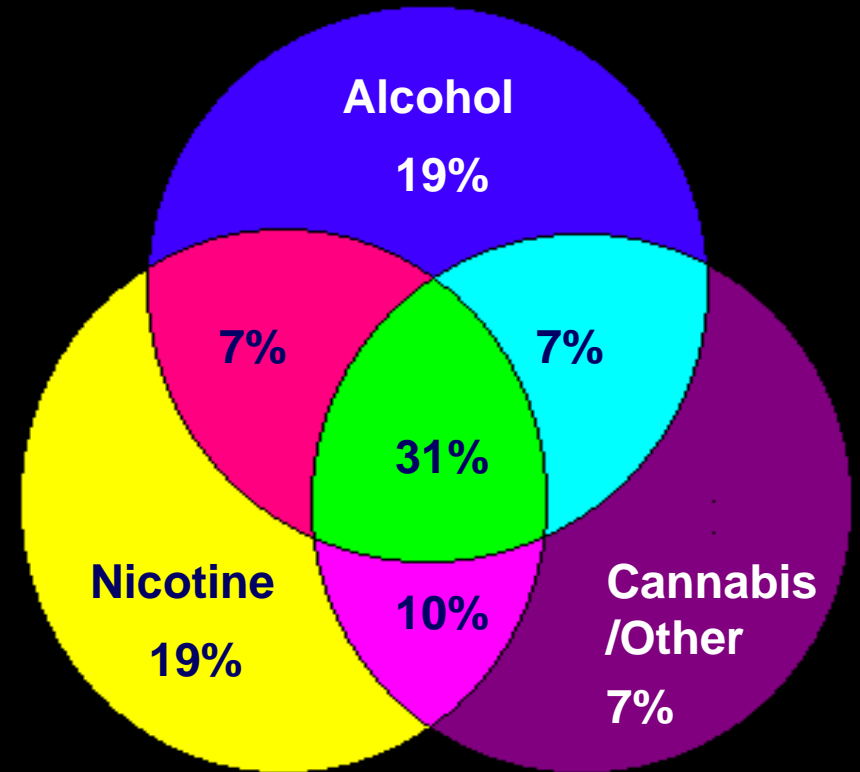
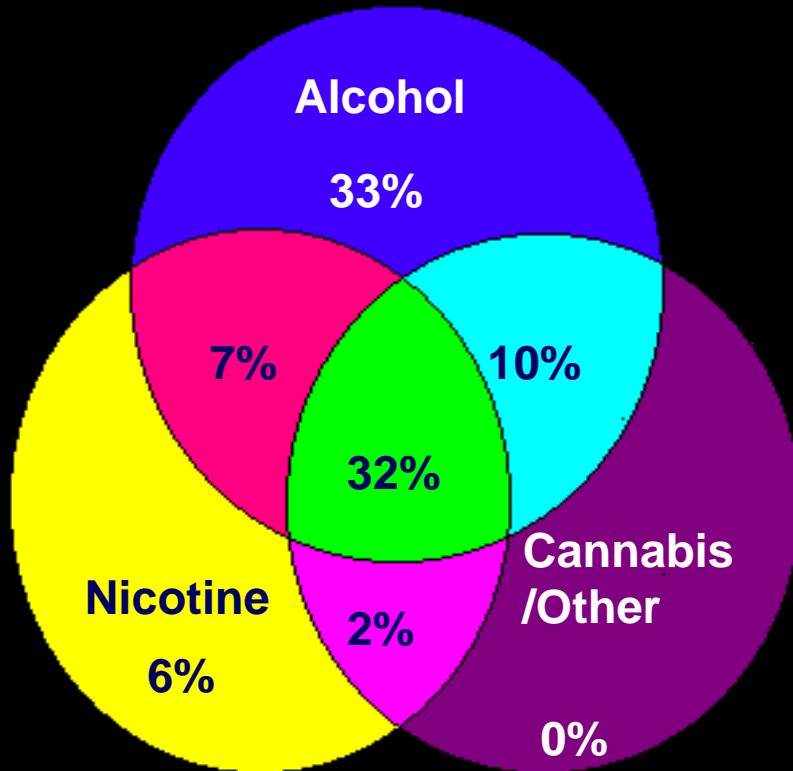
# Pathways to Substance Disorders through Psychopathology (Relative Risk)



# 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)

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| Pre-existing Dx | Use        | Adjusted Risk Ratio |            |
|-----------------|------------|---------------------|------------|
|                 |            | Substance 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        |
| <b>ANY DX</b>   | <b>1.3</b> | <b>3.0</b>          | <b>5.7</b> |

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

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|                           | <i>Attributable Risk</i> |                 |
|---------------------------|--------------------------|-----------------|
|                           | <b>Use</b>               | <b>Disorder</b> |
| <b>Family History</b>     | <b>20%</b>               | <b>12%</b>      |
| <b>Premorbid Disorder</b> | <b>20%</b>               | <b>18%</b>      |
| <b>BOTH</b>               | <b>32%</b>               | <b>20%</b>      |

# Summary

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- **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 conditions 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

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- **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

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