

Multiple Approaches to Studying Gene-Environment Interplay

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What is GE Interplay?

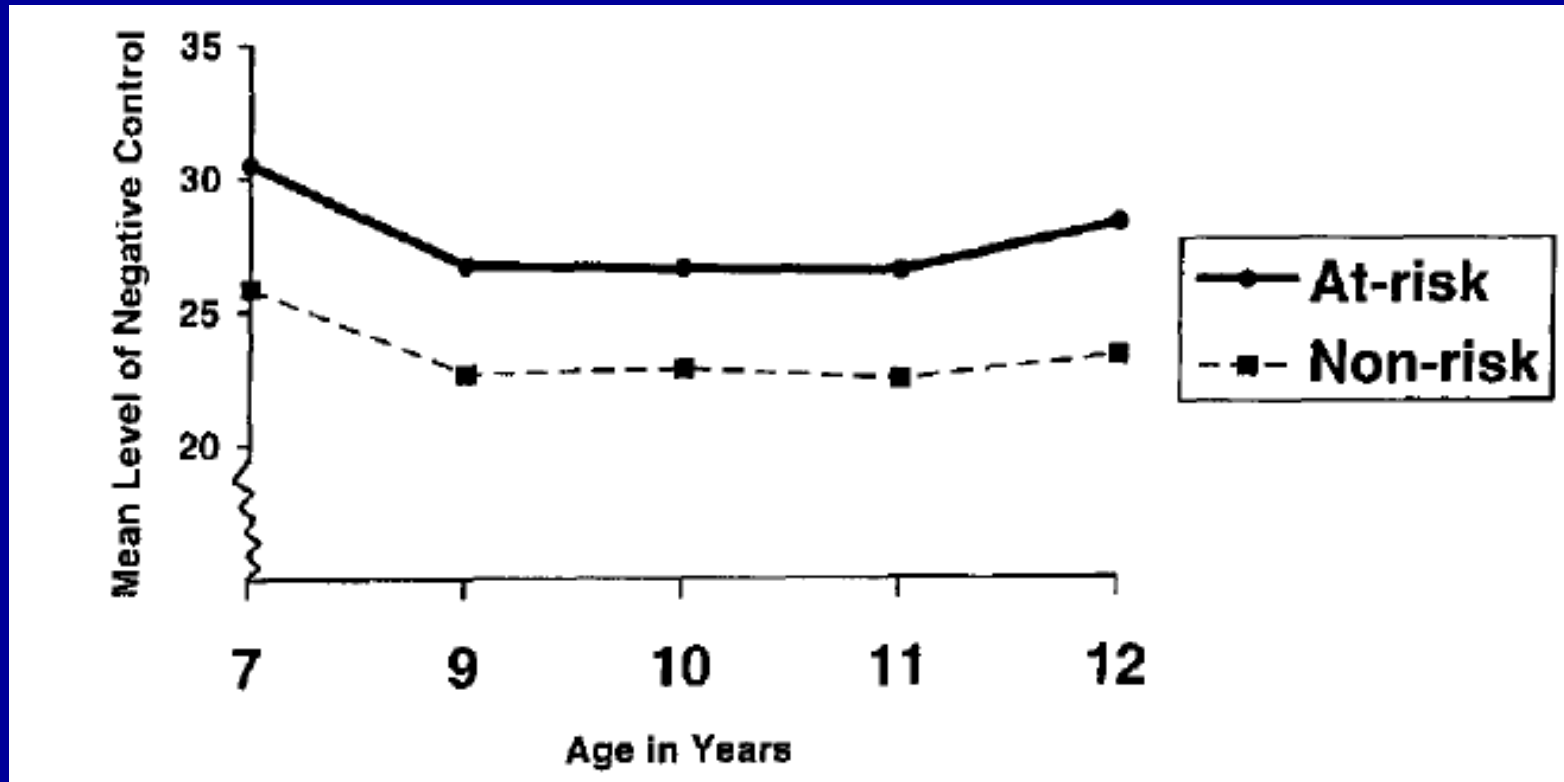
- Gene-environment correlation (rGE):
Individual differences in exposure to environments
 - Passive rGE, evocative rGE, active rGE
- Gene x environment interaction (GxE):
Individual differences in susceptibility to environments

Overview of Designs

- Sibling designs
 - Adoptees
 - MZ/DZ comparisons
 - Discordant MZ pairs
 - Children of twin designs
- Molecular genetics designs
 - Case control designs
 - Case only designs
 - Population studies
 - Discordant DZ pairs

Adoption Designs

- Eliminate passive rGE
 - Adoptive parents provide rearing environment, but not genetic material
- Estimate evocative rGE
 - Do adoptees at genetic risk evoke different responses from adoptive parents than adoptees not at genetic risk?

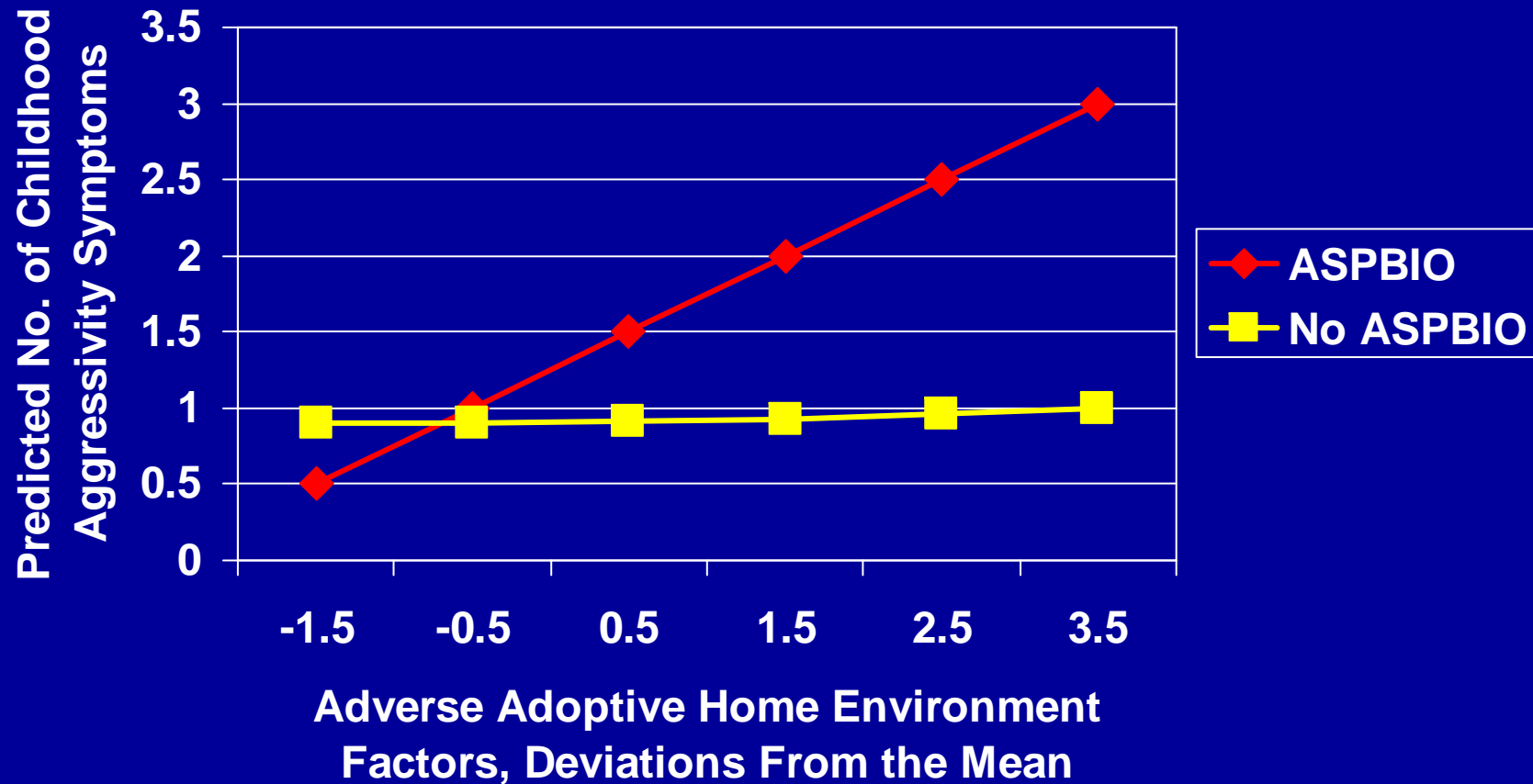


Data from O'Connor et al., 1998

Adoption Designs

- Estimate G x E
 - Genetic risk estimated based on biological parent data

Adoption Designs



Data from Cadoret et al., 1995

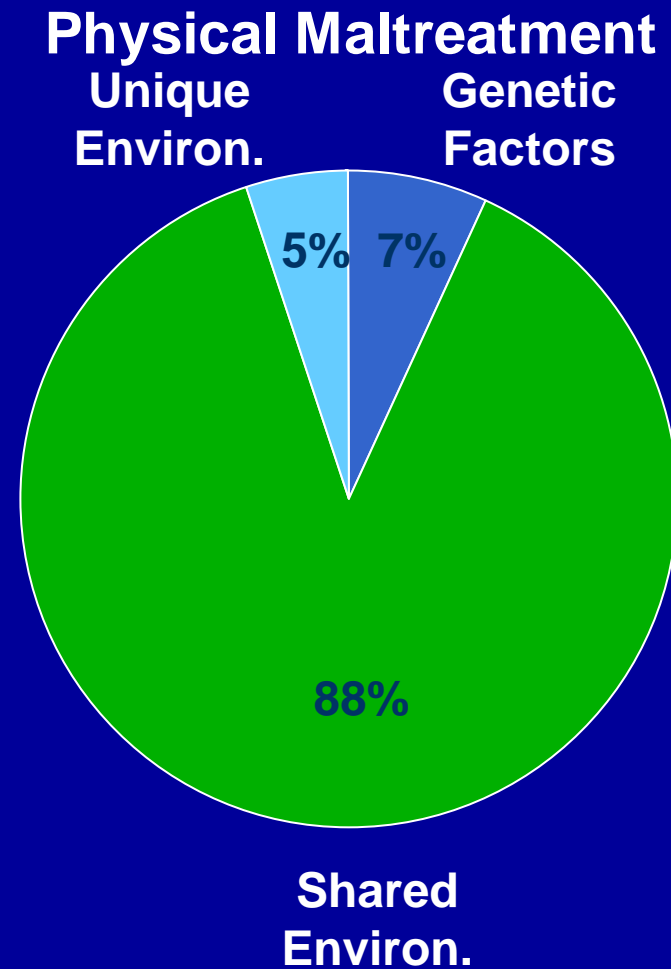
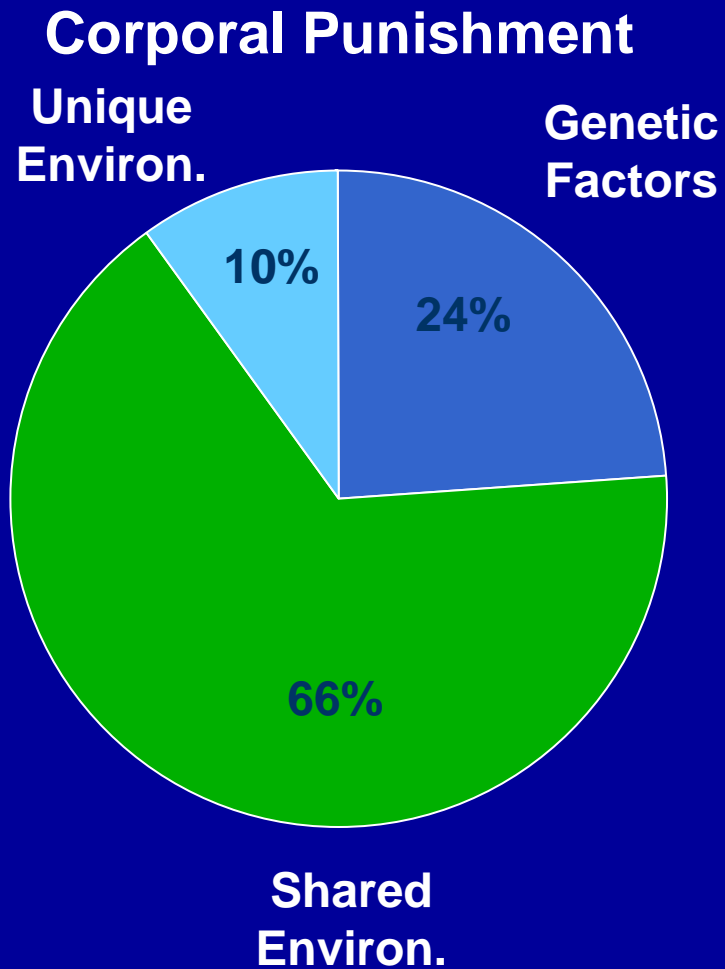
Adoption Designs

- Strengths: Genes and (between-family) environments are uncorrelated
 - Effects of between-family environments on behavior cannot be accounted for by passive rGE; assumptions of interaction models not violated
- Weaknesses:
 - Restricted range of family environments
 - Genetic risk inferred from biological parent data

MZ/DZ Twin Comparisons

- Evocative rGE: If the putative environment is heritable, this suggests that characteristics of the child are bringing about that environment

Child Characteristics Provoke Corporal Punishment, But Not Maltreatment



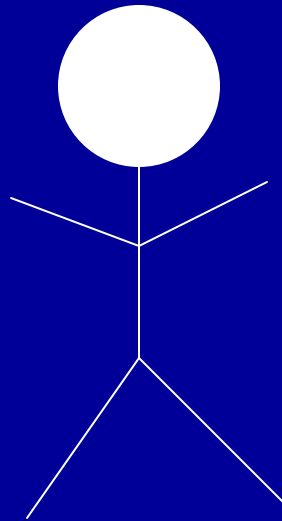
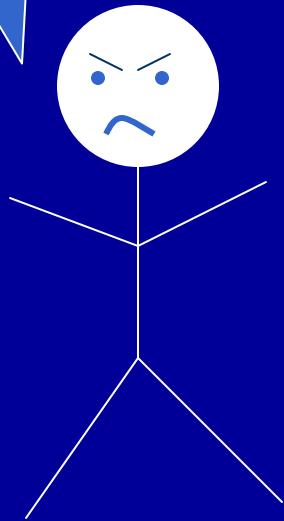
MZ/DZ Twin Comparisons

- Strengths
 - Estimates effects of all genes that account for variation in environmental experience
- Weaknesses
 - Doesn't specify which genetically-influenced characteristics of child influence environment or which genes specifically account for variation in environmental experience

MZ/DZ Twin Comparisons

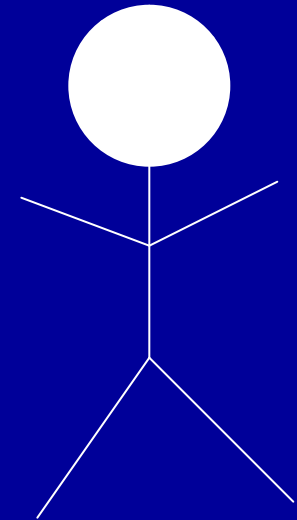
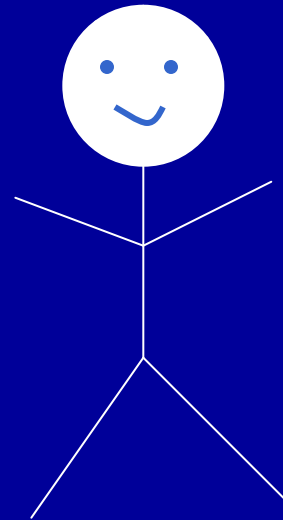
- G x E: Genetic risk for disorder can be inferred from pair's zygosity and co-twin's disorder status

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MZ,
Twin 1 has
Conduct Disorder

Twin 2 at
Highest risk

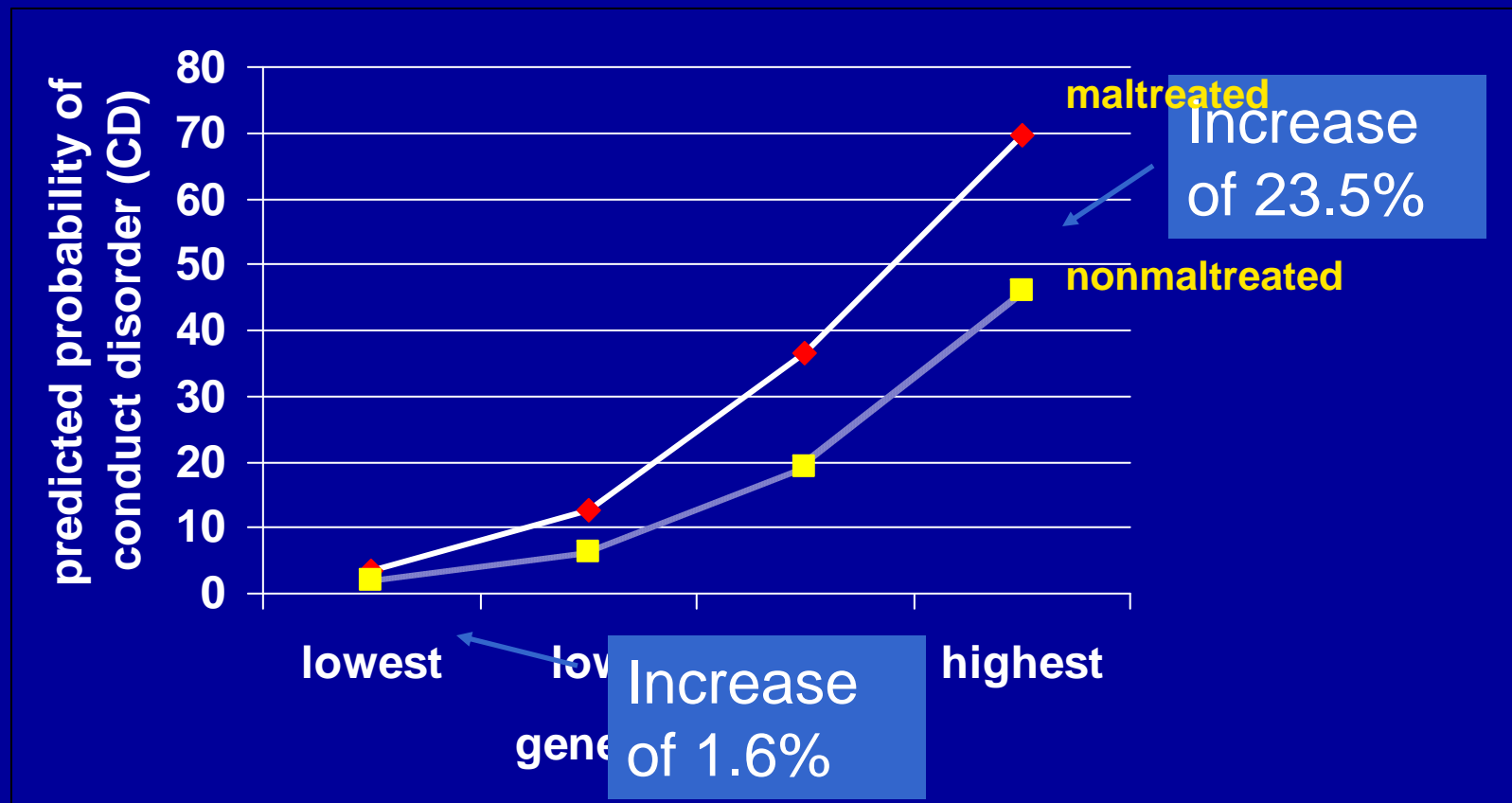


MZ,
Twin 1 no CD

Twin 2 at
Lowest risk

DZ + CD = med. high risk
DZ + no CD = med. low risk

Genetic Risk x Maltreatment



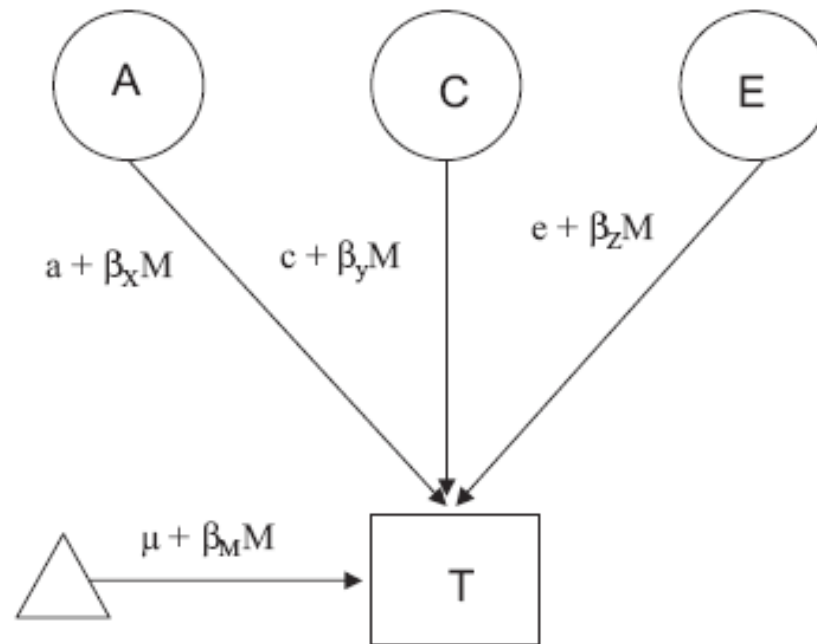


Figure 1. Moderation model. The latent variable A, represented in a circle, indicates additive genetic influences on the trait (T) of interest. C represents common (shared) environmental influences on the trait, and latent E represents unique environmental influences, which are uncorrelated between the twins. The triangle indicates the mean, or thresholds, for T and is necessary when modeling raw data. The standard paths a, c, and e, indicating the magnitude of effect of each latent variable on the trait, each include a β term, which indicates the significance of a measured moderator variable M on each of these genetic and environmental influences.

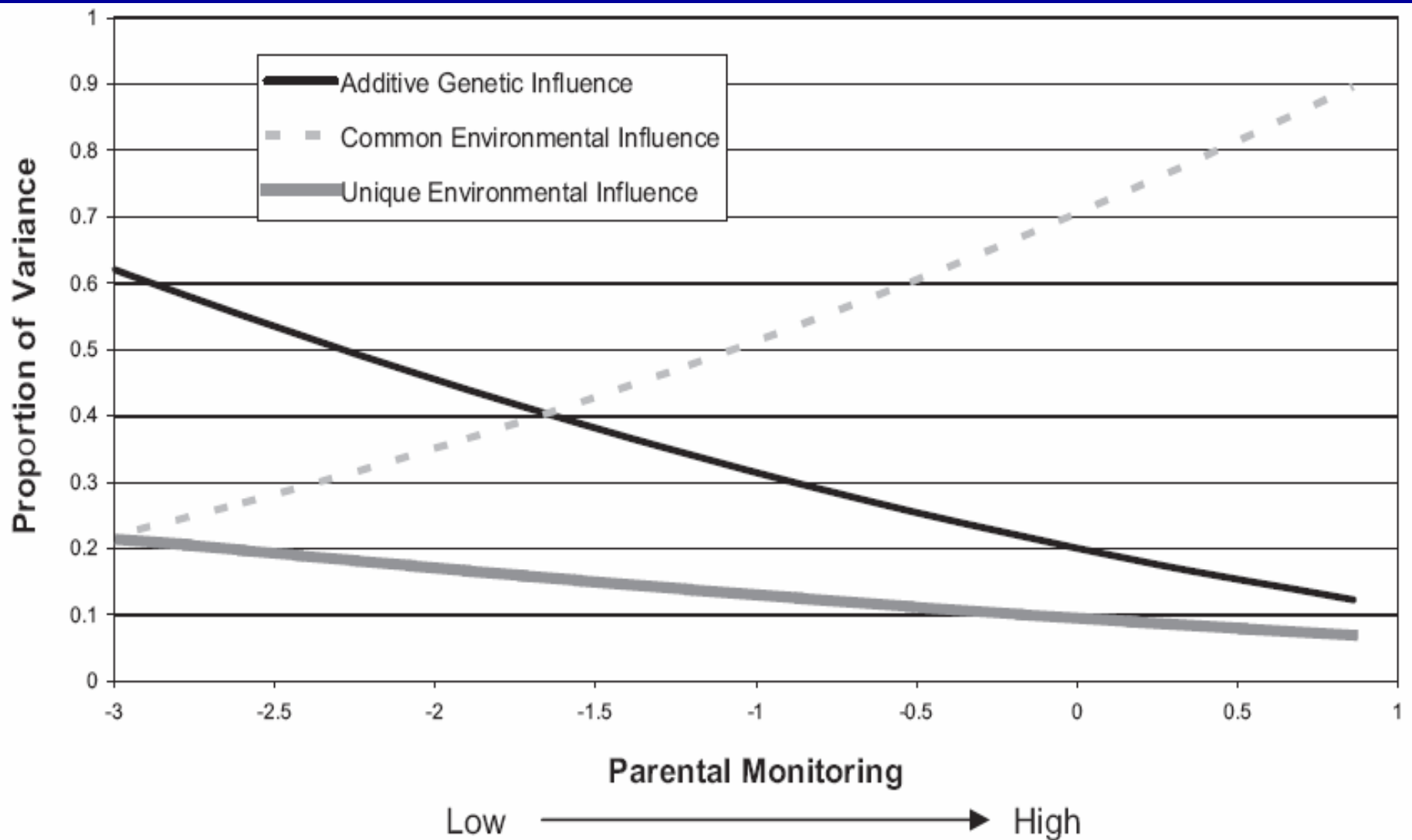


Figure 2. Proportions of changing variance in additive genetic effects, common environmental effects, and unique environmental effects on adolescent smoking across increasing levels of standardized parental monitoring scores.

MZ/DZ Twin Comparisons

- Strengths
 - Estimates effects of all genes that contribute to “genetic risk”
- Weaknesses
 - “Black box” measure of genetic risk
 - Scaling of genetic risk index
 - Analysis is most powerful if relying on discordant pairs

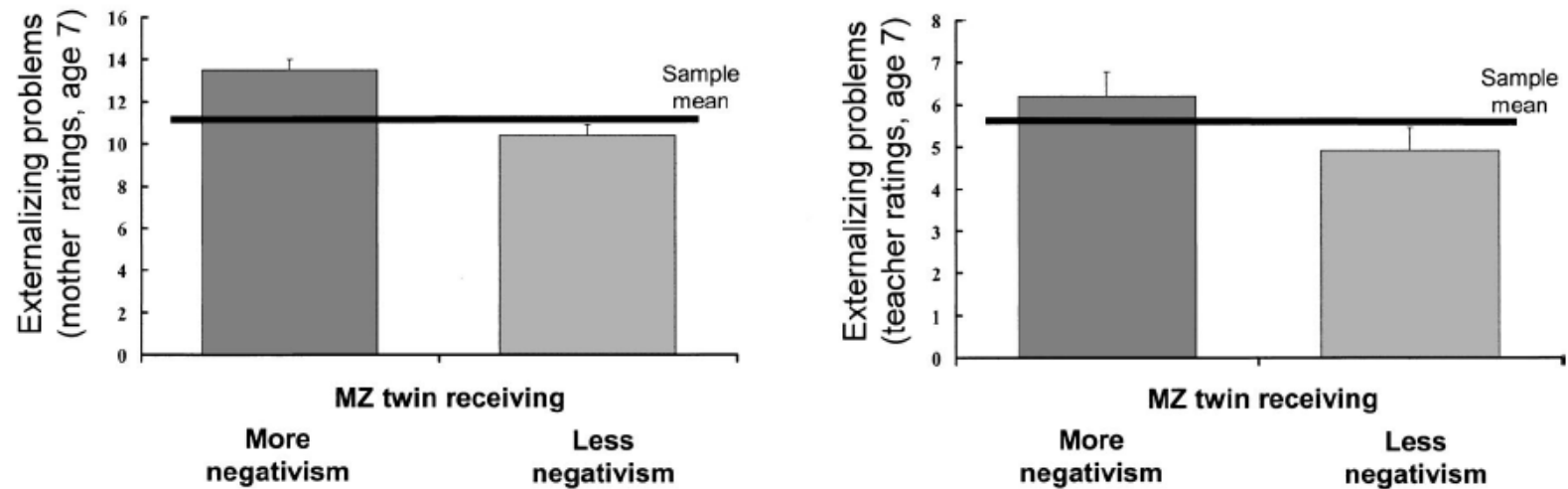
Discordant MZ Pairs

- MZ pairs share the same DNA and are raised within the same families
- Differences between MZ pairs must be due to experiences they don't share
 - Analysis rules out all forms of rGE

Discordant MZ Pairs

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CASPI ET AL.



From Caspi et al., 2004

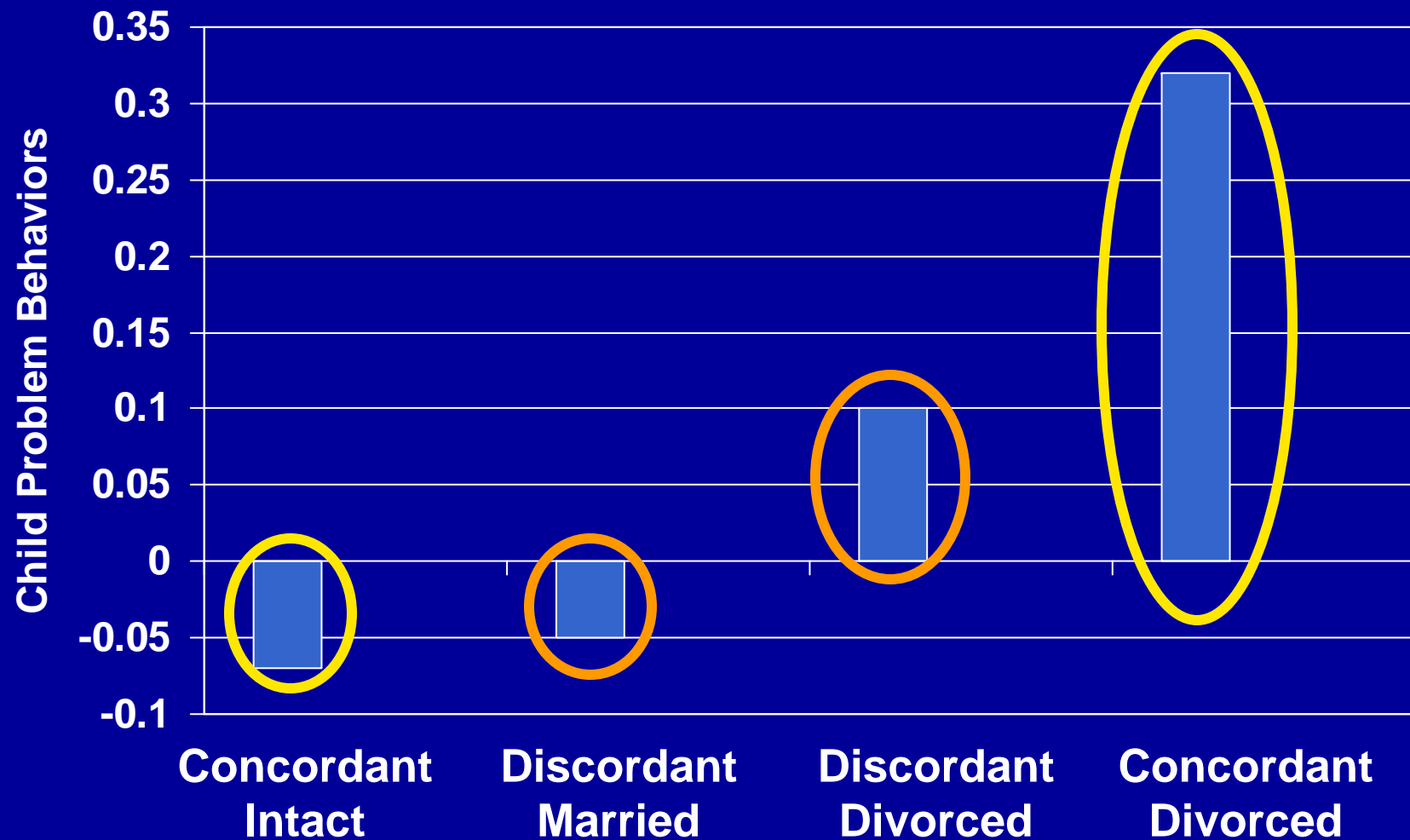
Discordant MZ Pairs

- Strengths
 - Can rule out all forms of gene-environment correlation
- Weaknesses
 - Difficulty identifying MZ twins who have very discordant experiences

Children of Twins Design

- Measure twin parents and their offspring
- If passive rGE accounts for association between child behavior problems and between-family environment, then cousins should have similar levels of behavior problems, regardless of differences in rearing environment

Children of Twins Design: Comparing Offspring of MZ Pairs



From D'Onofrio et al., 2005

Case Control Designs

- Select cases on the basis of disease status
- Select healthy controls
- Genotype cases and controls
- Measure their exposure to some environment

Effect of Cigarette Quantity on Bladder Cancer Risk Stronger Among NAT2 Slow Acetylators

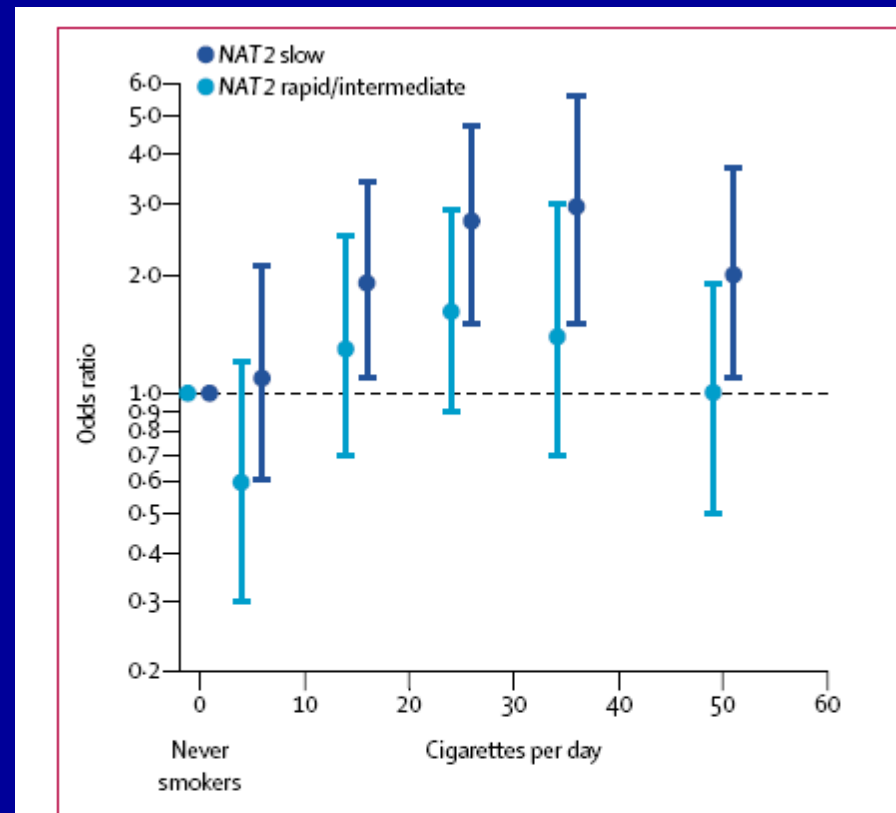


Figure 1: Association between smoking intensity (average number of cigarettes per day in categories of 10 cigarettes) and bladder-cancer risk compared with never smokers, stratified by NAT2 acetylation genotype
Odds ratios are from conventional logistic regression models adjusted for age, sex, region, smoking duration (<20 years, 20–29 years, 30–39 years, 40–49 years, ≥ 50 years), and smoking cessation (current/former smokers). Error bars represent 95% CI. p values for interaction are shown in table 3.

Case Control Studies

- Strengths
 - Adequate power to detect G x E
- Weaknesses
 - Environment often measured retrospectively, leading to rGE

Case Only Designs

- Select only individuals who have disorder (no control group)
- Measure genetic variation
- Measure variation in environmental exposure

Case Only Design

Table III. Relative risk (RR) and case-only analysis of interaction between the serotonin receptor 2A (*HTR2A*) +102T/C polymorphism genotype and antidepressant therapy in the occurrence of adverse effects and discontinuation of therapy.^[60] The reference group comprises subjects with genotype postulated not to increase risk (TT or TC) who received standard therapy (mirtazepine)

Treatment	<i>HTR2A</i> genotype	Cases ^a	No. of patients	Incidence (%)	RR (95% CI) ^b
Mirtazepine	TT or TC	13	86	15.1	1
	CC	6	38	15.8	R _g = 1.04 (0.43, 2.54)
Paroxetine	TT or TC	13	81	16.0	R _t = 1.06 (0.52, 2.15)
	CC	19	41	46.3	R _{tg} = 3.07 (1.68, 5.58)

a Case only odds ratio = $(19 \cdot 13)/(6 \cdot 13) = 3.17$ (95% CI 0.83, 12.74).

From Murphy et al., 2003

Population Studies

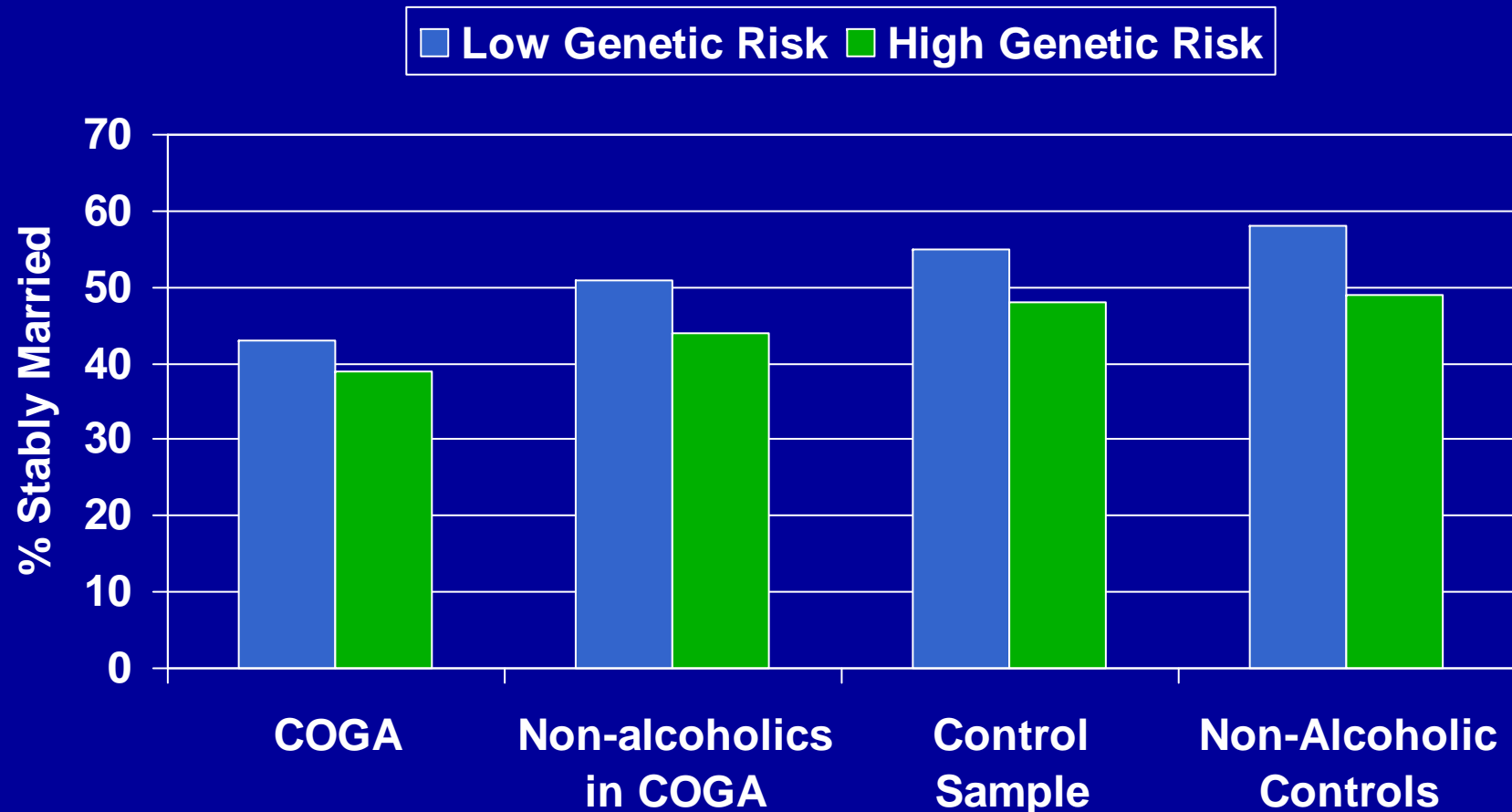
- Measure an environment of interest within a population
- Genotype a population sample
- Measure an outcome of interest within a population
- Test for main and interactive effects of genes and environments on outcome
- Test for rGE

Population Studies: G x E



From Caspi et al., 2003

Population Studies: rGE



All differences statistically significant at $p < .05$

From Dick et al., 2005

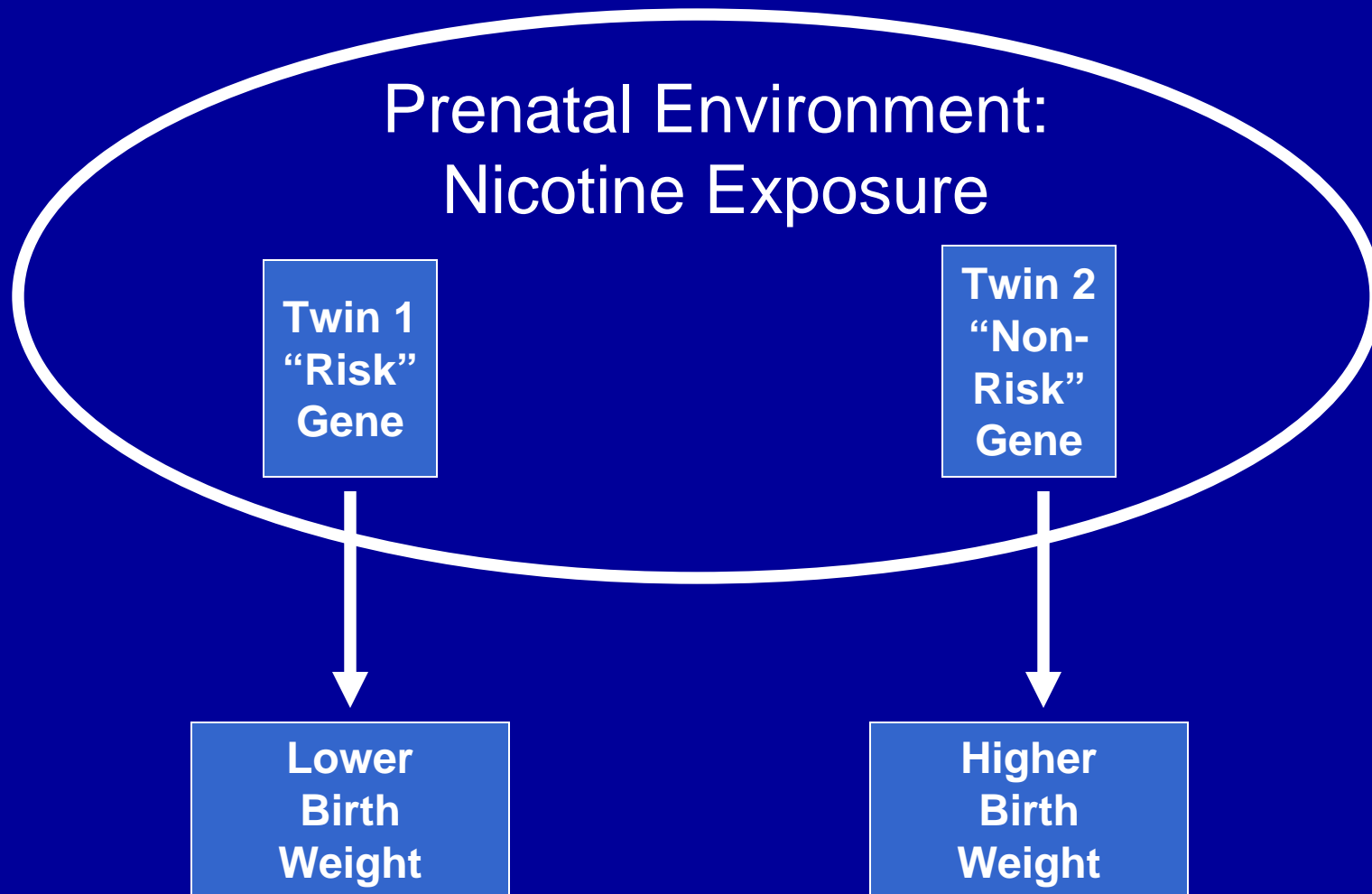
Population Studies

- Strengths
 - Generalizability
 - Broad range of environments
- Weaknesses
 - Low base rates for disease
 - Low power

Discordant DZ Pairs

- DZ twins are raised within the same family, but may differ genetically
- The effects of family-wide experiences (e.g., divorce) may vary as a function of genetic differences

Effect of Prenatal Nicotine Exposure on Birth Weight Varies as a Function of Genetic Makeup



Discordant DZ Pairs

- Strengths
 - DZ twins are same-age siblings
 - Controls for between-family environments
- Weaknesses
 - Prenatal environment not necessarily identical for DZ twins