Moderation of covariance among family members

Moderation of means

(in twin-sib studies)

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Thanks to Lindon Eaves

Faculy drive: dorret\2010 Thursday morning

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Kendler and Eaves (1986): Several mechanisms explain variation in a trait or in liability to disorder

- genes and environment contribute additively

- genes and environment interact: genes control sensitivity to the environment, or: the environment controls gene expression

- genes and environment are correlated: passive, active or reactive correlations

Moderation of covariance = Gene-environment Interaction (GEI) (not the same as GE correlation)

"No aspect of human behavior genetics has caused more confusion and generated more obscurantism than the analysis and interpretation of the various types of non-additivity and non-independence of gene and environmental action and interaction...".

Eaves L et al. A progressive approach to non-additivity and genotype–environmental covariance in the analysis of human differences.
British J Mathematical Statistical Psychology, 1977, 30:1

This statement may be as true today as thirty years ago.

Definitions

- Genetic additivity (A): the effects of alleles sum within and across loci
- Genetic non-additivity (Dominance): interaction of the effects of alleles within loci, not shared between parents and offspring
- Genetic non-additivity (Epistasis): interaction of the effects of alleles across loci

- Environment-environment interaction: ExE, CxC, CxE

- Additivity of genes and environment: P = G + E

- Gene-environment interaction: P = G + E + GEI

Genotype-Environment Interaction:
Are genetic effects larger in some subgroups than in others?
This is difficult to test in practice because it is rare that we will have strong a priori reasons for expecting genetic effect to be restricted to any specific subgroup.

Clayton D, McKeigue PM (2001). Epidemiological methods for studying genes and environmental factors in complex diseases. Lancet 358, 1356–60

Example GE non-additivity: Disinhibition

Twin Research (1999) 2, 115–125

http://www.stockton-press.co.uk/tr

A religious upbringing reduces the influence of genetic factors on disinhibition: Evidence for interaction between genotype and environment on personality

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Example GE non-additivity: Disinhibition

- I like wild “uninhibited” parties
- Keeping the drinks full is the key to a good party
- A person should have considerable sexual experience before marriage
- I like to have new and exciting experiences and sensations even if they are a little unconventional or illegal
- I feel best after a couple

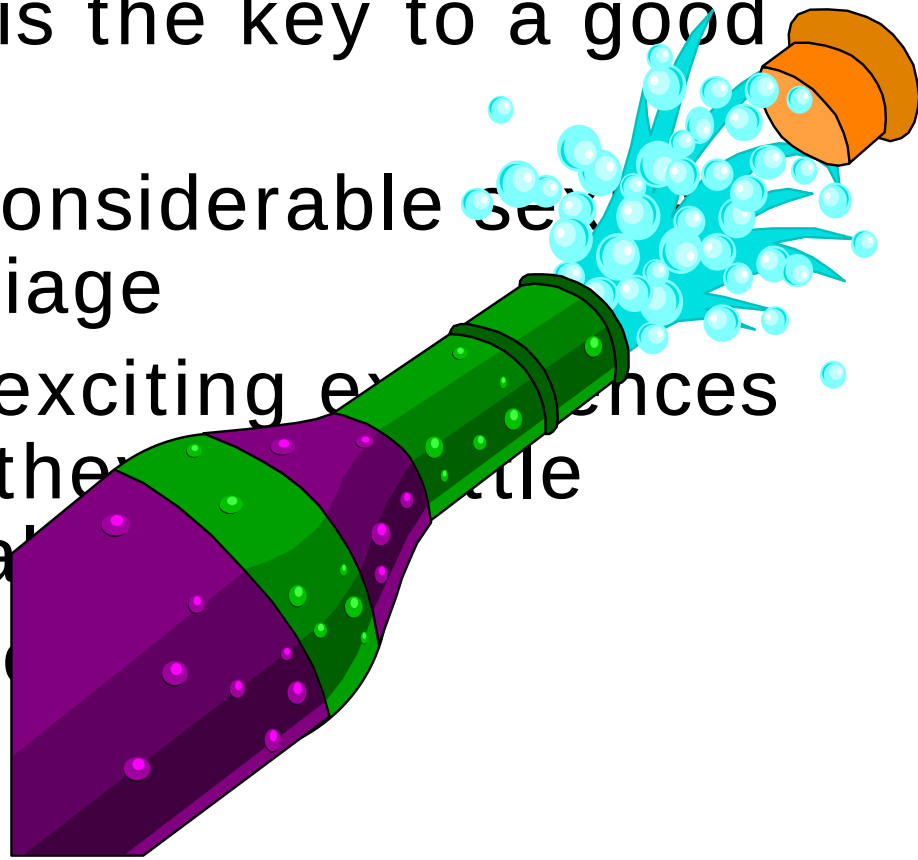


Table 3 Religion (upbringing, currently religious and religious practice) and personality in twin families (father, mother, son, daughter)

	Religious upbringing				*Religious yes/no*				*Religious practice*			
	Fa	*Mo*	*So*	*Da*	*Fa*	*Mo*	*So*	*Da*	*Fa*	*Mo*	*So*	*Da*
Anxiety[49,50]	–	–	–	–	?	–	?	?	–	?	–	?
Depression[51]	–	–	–	?	?	?	Y	?	?	–	?	?
Neuroticism[52]	Y	–	–	–	Y	–	–	–	Y	–	–	Y
Somatic complaints[52]	–	–	–	Y	–	–	–	?	–	–	–	Y
Thrill and adventure seeking[53–55]	–	–	–	Y	Y	–	–	Y	Y	?	–	Y
Experience seeking[53–55]	?	–	?	Y	Y	Y	Y	Y	?	Y	Y	Y
Boredom susceptibility[53–55]	–	–	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Disinhibition[53–55]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Extraversion[52]	–	–	–	?	–	–	–	–	Y	Y	–	Y
Anger[56,57]	–	–	–	?	–	–	–	–	–	–	–	–
Test attitude[52]	–	–	–	–	–	Y	Y	–	Y	Y	Y	–

Y = P<0.05, ? = P<0.10, – = P>0.10

For all scales (except Test Attitude) that show a significant effect of religion, the effect was always in the same direction: religious Ss, Ss with a religious upbringing and Ss actively involved in religious activities scored lower on all scales. The only exception was the Test Attitude (‘Lie’) Scale on which they scored higher.

	Religious upbringing			
	Fa	*Mo*	*So*	*Da*
Anxiety[49,50]	–	–	–	–
Depression[51]	–	–	–	?
Neuroticism[52]	Y	–	–	–
Somatic complaints[52]	–	–	–	Y
Thrill and adventure seeking[53–55]	–	–	–	Y
Experience seeking[53–55]	?	–	?	Y
Boredom susceptibility[53–55]	–	–	Y	Y
Disinhibition[53–55]	Y	Y	Y	Y
Extraversion[52]	–	–	–	?
Anger[56,57]	–	–	–	?
Test attitude[52]	–	–	–	–

Y = P<0.05, ? = P<0.10, – = P>0.10

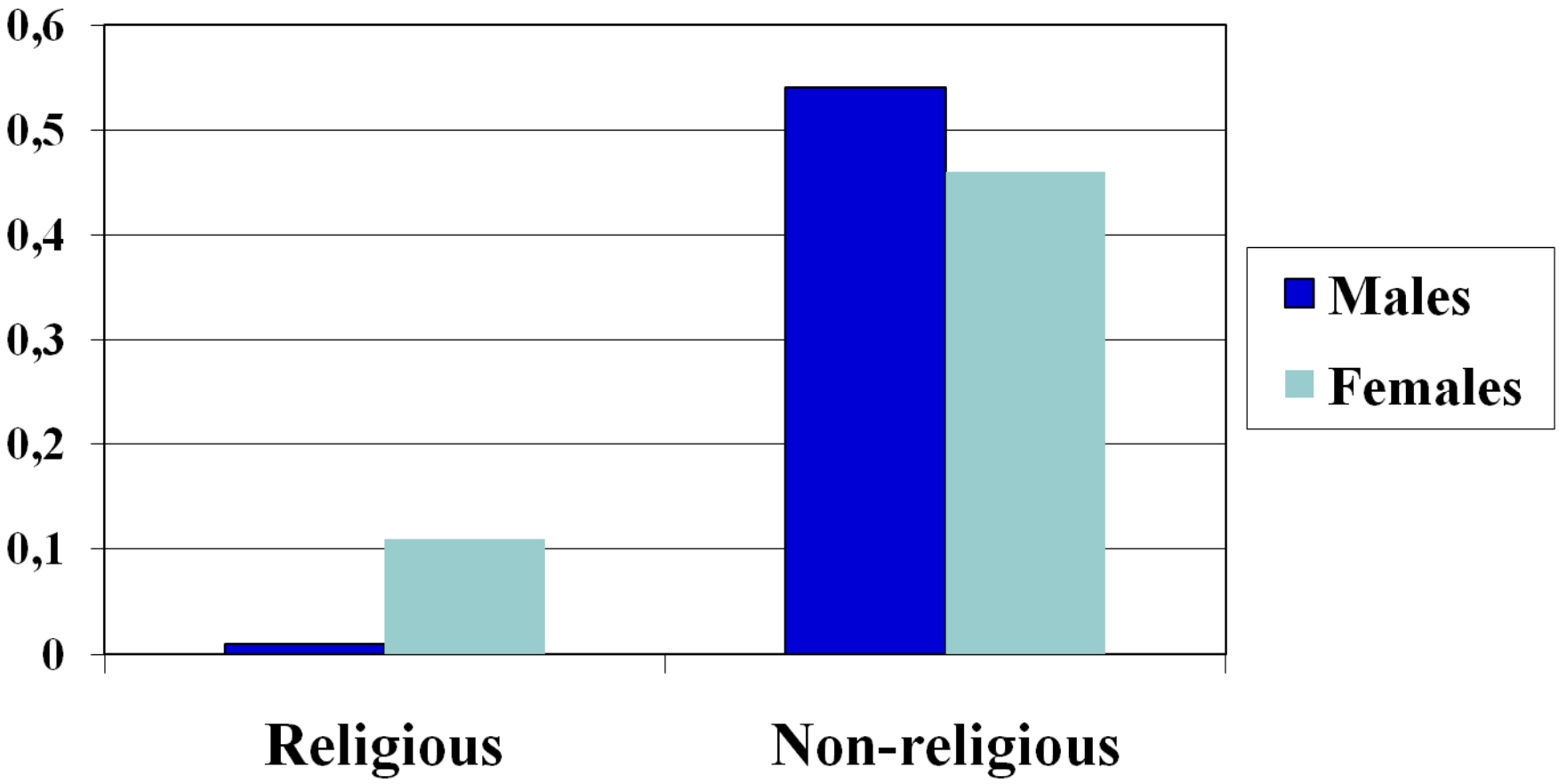
Example non-additivity: gene-environment interaction: Disinhition

Twin resemblances (correlations) for Disinhibition as a function of religious upbringing

	MZM	*DZM*	*MZF*	*DZF*	*DOS*
Religious	0.62	0.62	0.61	0.50	0.38
Non-religious	0.62	0.35	0.58	0.35	0.30

- Religious: MZM = 149, DZM = 124, MZF = 227, DZF = 169,DOS = 259 pairs
- Non-relig: MZM = 143, DZM = 123, MZF = 188, DZF = 151, DOS = 214 pairs

Heritability of Disinhibition in 1974 adolescent Dutch twin pairs as a function of religious upbringing

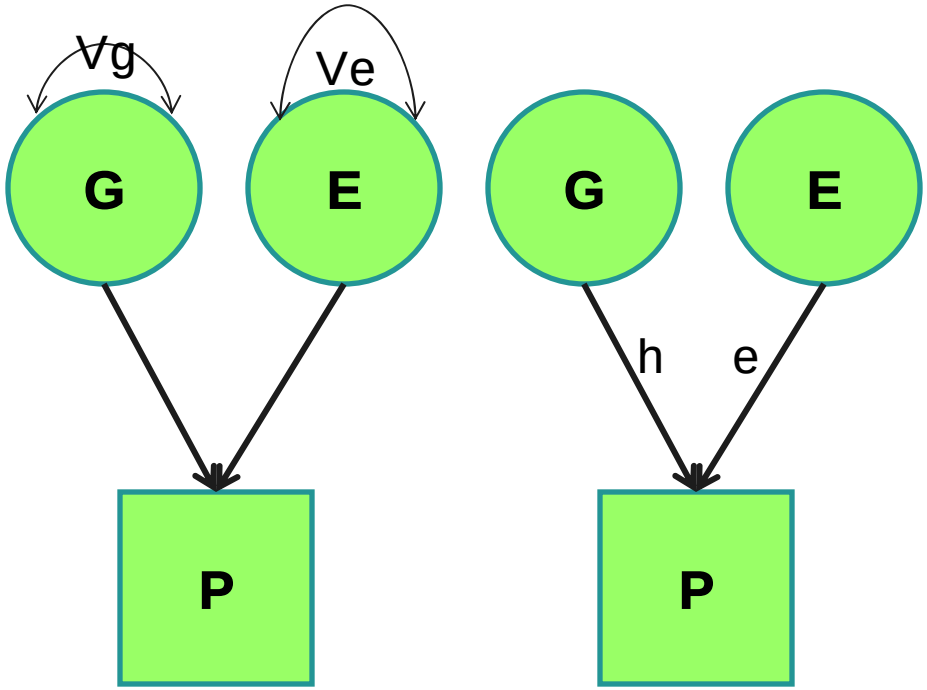


Boomsma et al. (1999) Twin Res 2, 115-125; from a special issue on religion

Phenotype is a function of genotype and environment

P = G + E

P = hG +eE



P is an observed value (it can also be a residual after the effect of another variable has been taken out).

G and E are factor scores (unobserved values for each individual in the study).

Some environments cause a stronger expression of the genotype -> h (or Vg) takes different values in different environments.

Phenotype is a function of genotype and environment

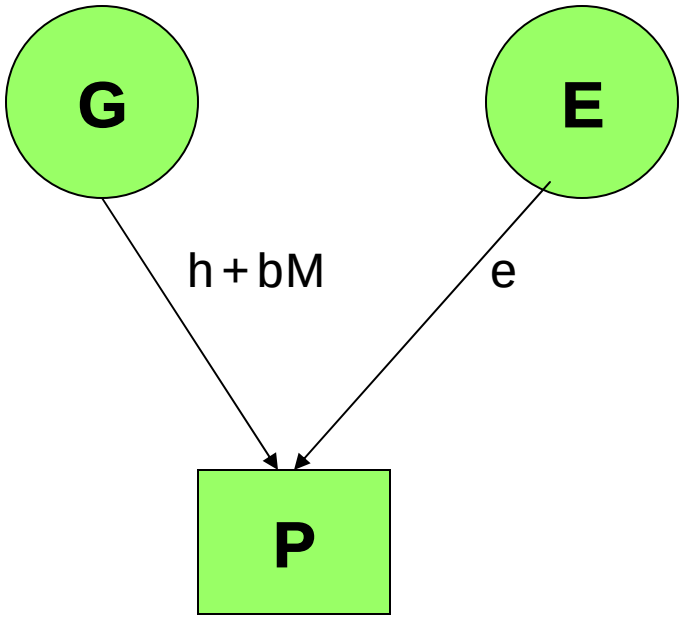
P = G + E

P = G + E + GEI

Assume that the relevant environment is absence or presence to exposure (0 or 1); it then follows that the exposed group should score higher on the Phenotype, than the non-exposed group.

- Suppose M (moderator) takes values 0 or 1 (i.e. 2 groups)

- For Ss with M = 0: P = hG + eE
- For Ss with M = 1: P = (h+bM)G +eE = hG+bMG + eE



At the individual level

- All Ss come from the same population; i.e. no population substructures (based on G or E)
- G uncorrelated with E
- Within each group G has mean zero and variance unity; then mean values of P will differ, because of formula above (this is why the effect of M on mean also needs to be modeled)
- The variance between the 2 groups also will differ (because the genetic variance (and heritability) is larger in the exposed group

- The moderator also can be a continuous variable (e.g. age)
- The phenotype can also be a categorical trait
- There may be alternative explanations for positive findings

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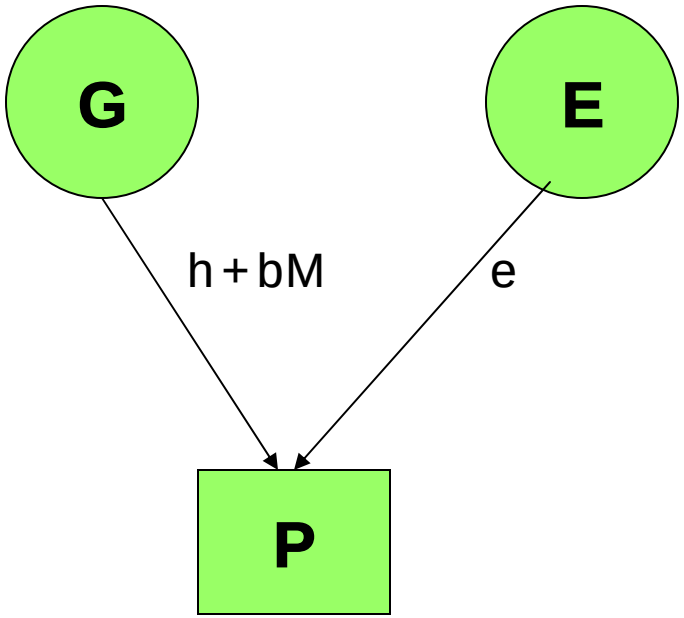

At the individual level

- Purcell S. Variance components models for gene-environment interaction in twin analysis. Twin Res. 2002, 554-71.
- Eaves LJ. Genotype x Environment interaction in psychopathology: fact or artifact? Twin Res Hum Genet. 2006, 1-8.
- Medland SE, Neale MC, Eaves LJ, Neale BM. A note on the parameterization of Purcell's G x E model for ordinal and binary data. Behav Genet. 2009, 220-9.
- DS Falconer. Introduction to Quantitative Genetics

P = G + E (+ GEI)

(phenotype is a function of genotype and environment)

Var (P) = Var (G) + Var (E)

Var (P) = Var (G) + Var (E) [+ Var (GEI)]

Var (P) = Var (G) + Var (E) [+ 2 cov (GE)]: GE correlated

Heritability = Var(G) / Var(P)

This has been a discussion of GEI when E is measured and G is latent

If GEI is not modeled

GxE → ends up as "E"

GxC → ends up as "G" ; see Purcell (2002)

The expected twin covariances are:

$$Cov(T1,T2) = a^2Cov(A1, A2) + c^2Cov(C1, C2) + e^2Cov(E1, E2) + i^2Cov(A1C1, A2C2)$$

$= a^2 + c^2 + i^2$ *for MZ twins*

$= a^2/2 + c^2 + i^2/2$ *for DZ twins*

More GEI

Heritability differs as a function of E: is this a quantitative difference? (are the *same* genes are expressed to a larger extent?)

Or does the exposure lead to the expression of *different* genes?

How to address this question?

Measure the same Ss under different conditions (or longitudinally); or include MZ and DZ twins discordant for exposure.

Do genes and environment interact?

Measured environment:
Does the environment control gene expression?

Are there differences in trait heritability conditional on environmental exposure? (test of covariance structure).

In the Disinhibition example exposure was measured and genotype was a *latent* variable.

Do genes and environment interact?

Measured genotypes and environment:

Does the effect of a particular (measured) genotype depend on the environment?

Lots of research on the SERT polymorphism (serotonin transporter gene). The promotor region of the gene contains a polymorphism with "short" and "long" repeats: 5-HTT-linked polymorphic region (5-HTTLPR or SERTPR). The short allele has 14 repeats of a sequence while the long allele has 16 repeats. The short variation leads to less transcription.

The Personality Assessment Inventory-Borderline Features (PAI-BOR) Scale

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Heritability of Bordeline Disorder Personality Features (BDPF) 42% (Distel et al. 2007)

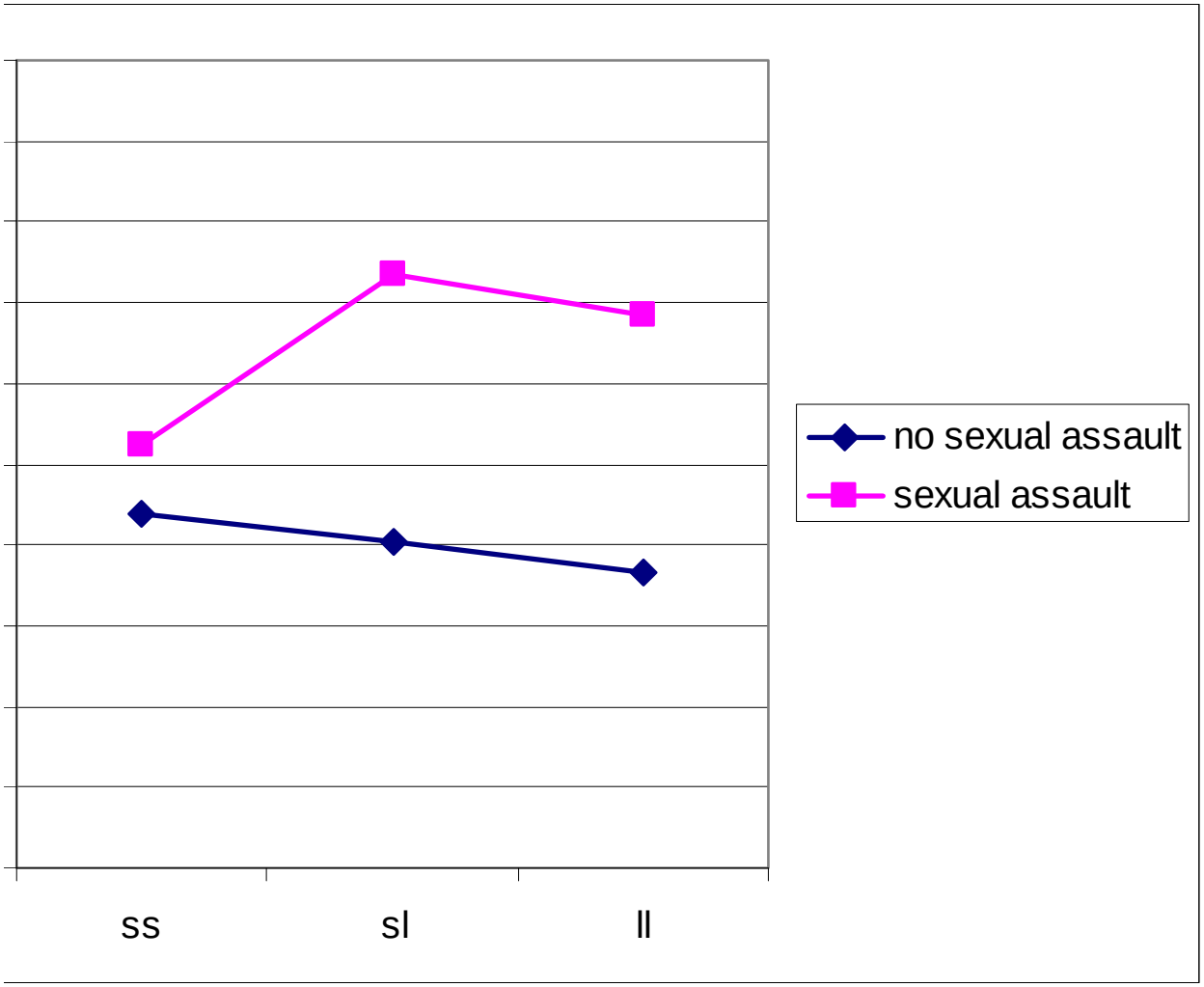
The survey included a question about ever having experienced a sexual crime (rape, sexual abuse).

The answers were dichotomized (“no” – “yes”).

SERT *short/long* promotor polymorphism was assessed in 1049 Ss from 399 families (329 parents & 801 offspring).

In the genotyped sample, 72 Ss reported sexual assault (lifetime) and 976 individuals reported no sexual abuse.

Interaction SERT and sexual abuse



In the no abuse group, SERT genotype did not influence BPDF scores.

In the abuse group, the *s/s* genotype was protective

(this is usually the at-risk genotype for depression).

It is it likely to have GEI without G main effect?

Note: different question from the one about mean differences between exposure groups.

In an analysis of genotype (e.g. SS, SL, LL) and environment (0, 1) we test for main effect of genotype, environment and their interaction (e.g. ANOVA). Should we look at the interaction if the main effects are NS?

ARCHIVAL REPORTS

Gene × Environment Interactions at the Serotonin Transporter Locus

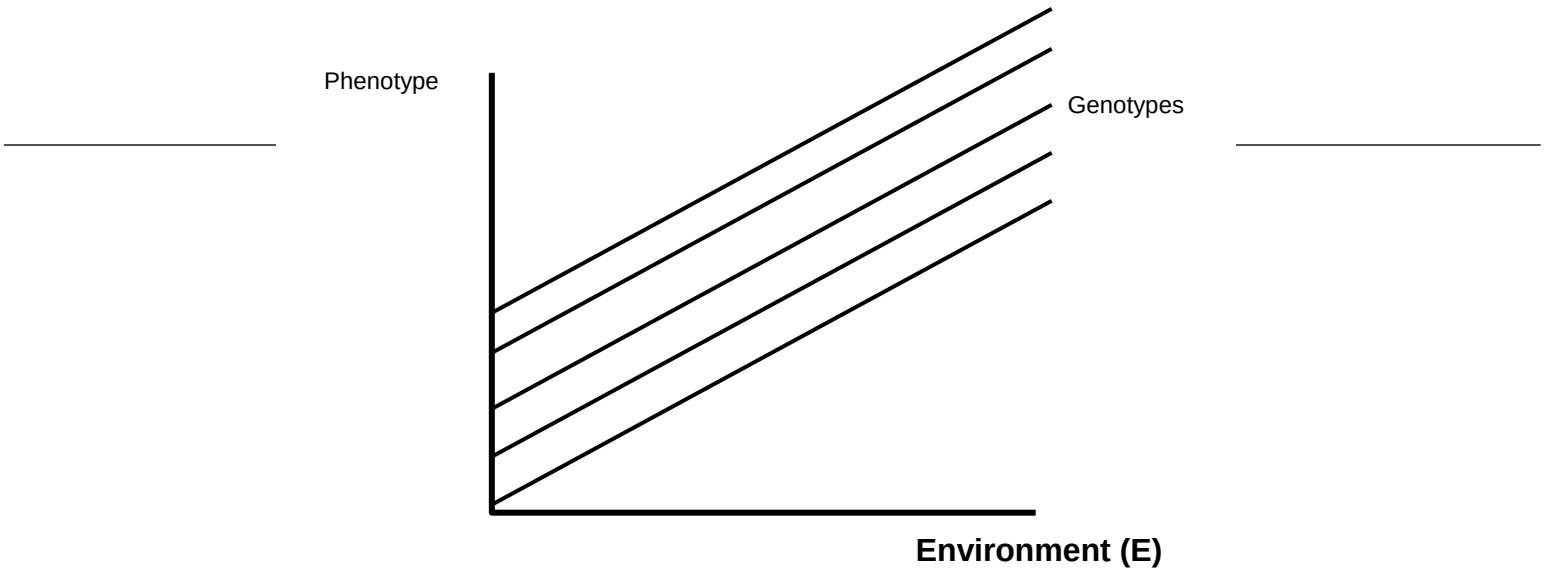
Marcus R. Munafò, Caroline Durrant, Glyn Lewis, and Jonathan Flint

Biol Psychiatry 2008

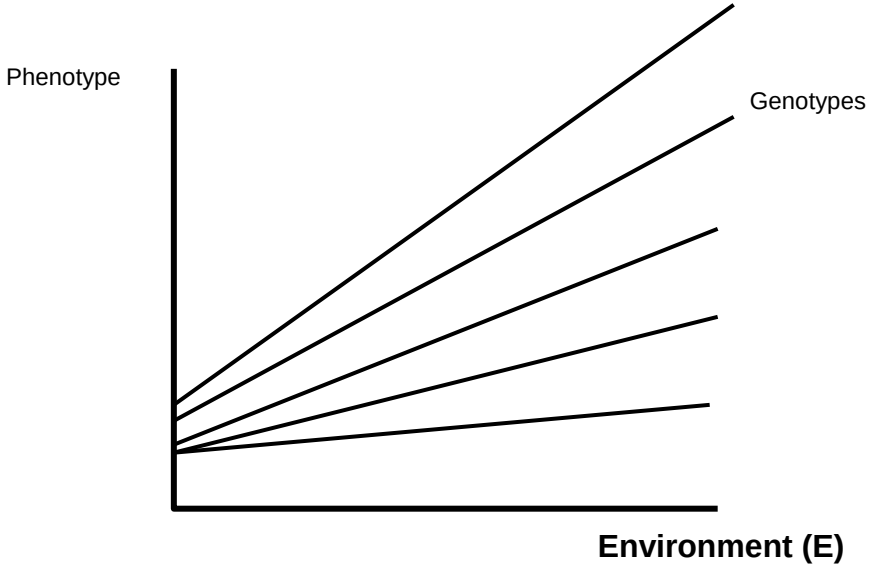
…. When the proportion of environmentally exposed individuals is quite low, the size of the interaction effect will be larger than the size of the genetic main effect, because data from the unexposed individuals dominate the genetic main effect and overwhelm the signal from the exposed individuals.

In this case it would be possible, with a small sample, to detect an interaction effect and not a genetic main effect.

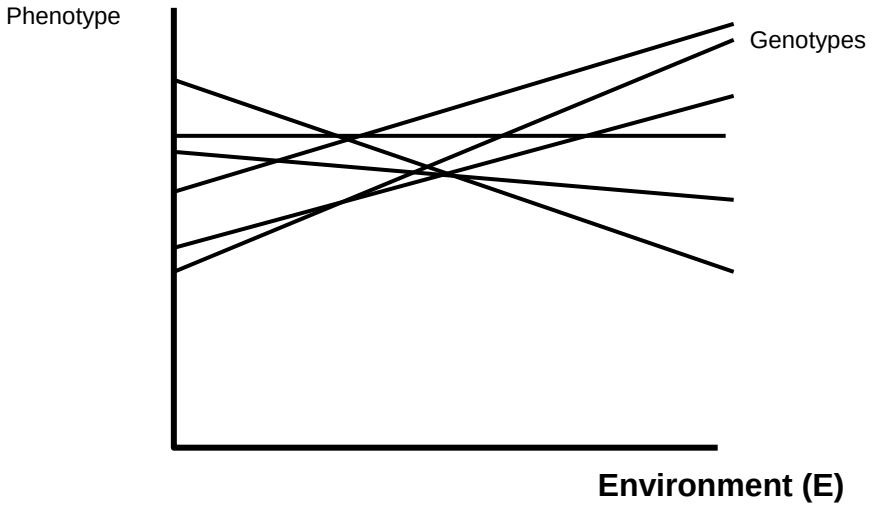
a. No GxE



b. “Scalar” GxE



c. “Non-scalar” GxE

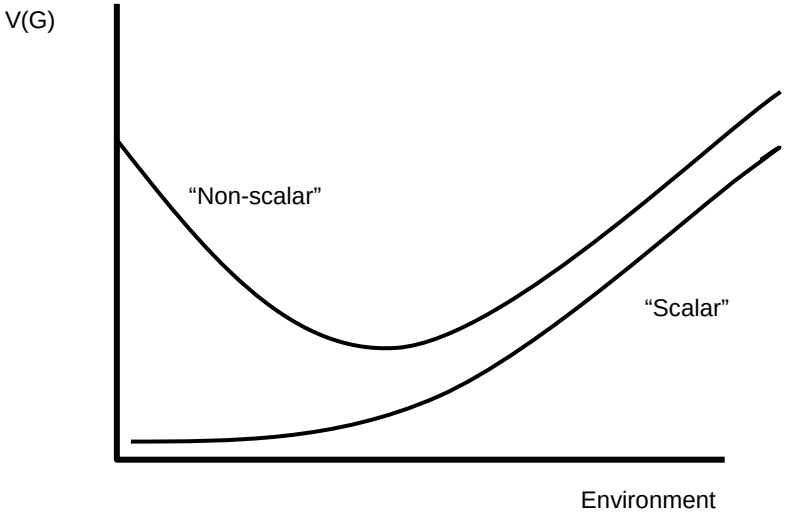


“Main effect of E and G?”

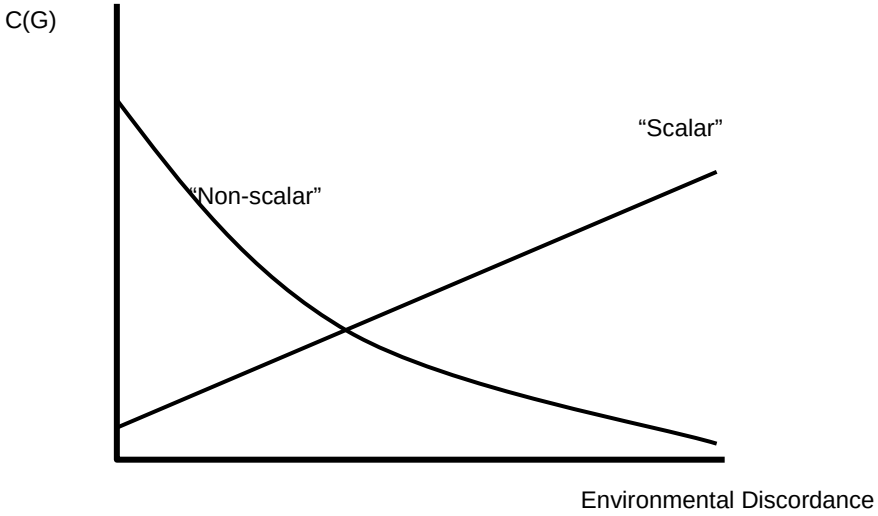
- b is constant in “a”-> Main effects of G and E but no GxE
- Average b is positive in “b”-> Main effects of G and E and GxE
- Average b is zero in “c” GxE but no main effects of E.
- The main effects of G in “c” will depend on the cross-over point.

i.e. The contribution of main effects and interaction depends critically on the mean and variance of the regression of individual genotypes on environment. [Note also that the expected (genetic) covariance between relatives as a function of environment depends on the (genetic) covariance between slopes and elevation.]

a. Genetic Variance Under GxE

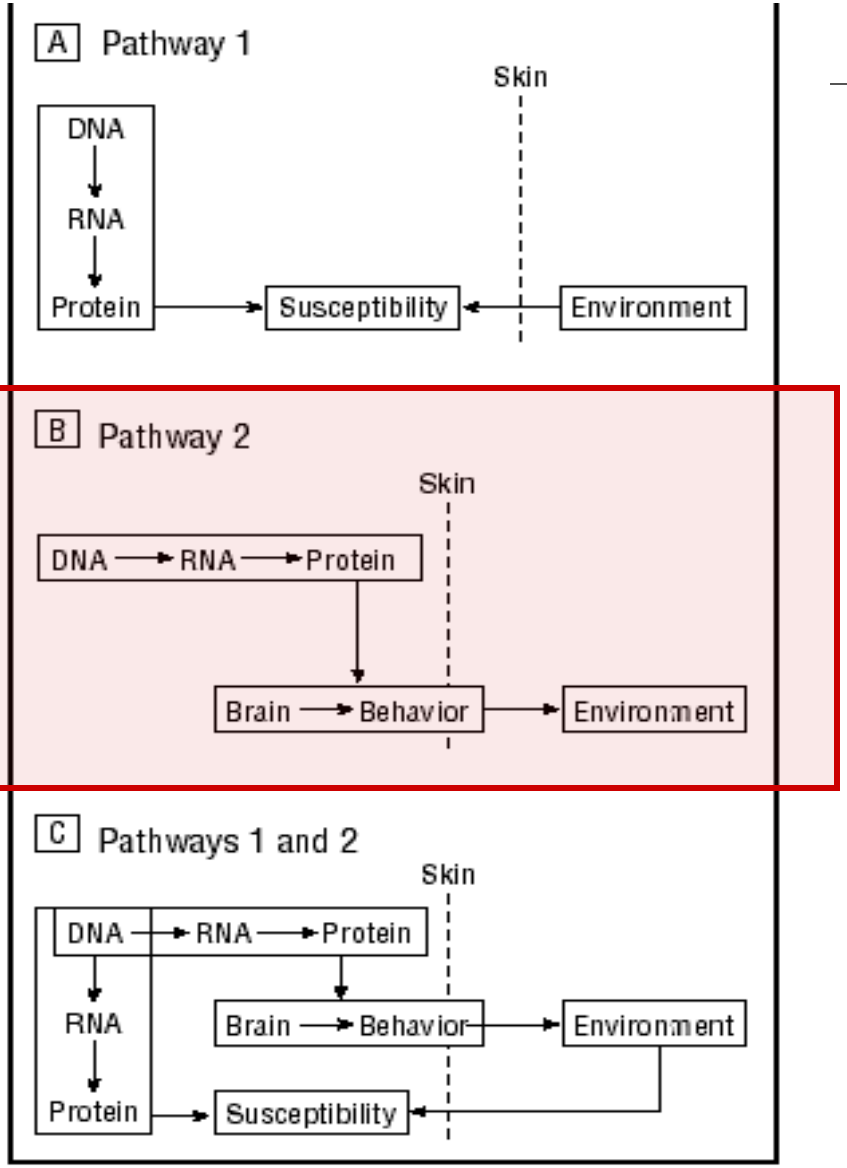


b. Genetic Covariance Under GxE



Genetic variance conditional on environment in “a”, depends on mean and variance of response slopes in previous slide.

Genotype x Environment Correlation



A: traditional view: Genes and environment add up

B: Genes determine exposure to the environment

C: Combined model

(Kendler, 2001, Archives General Psychiatry)

GE correlation

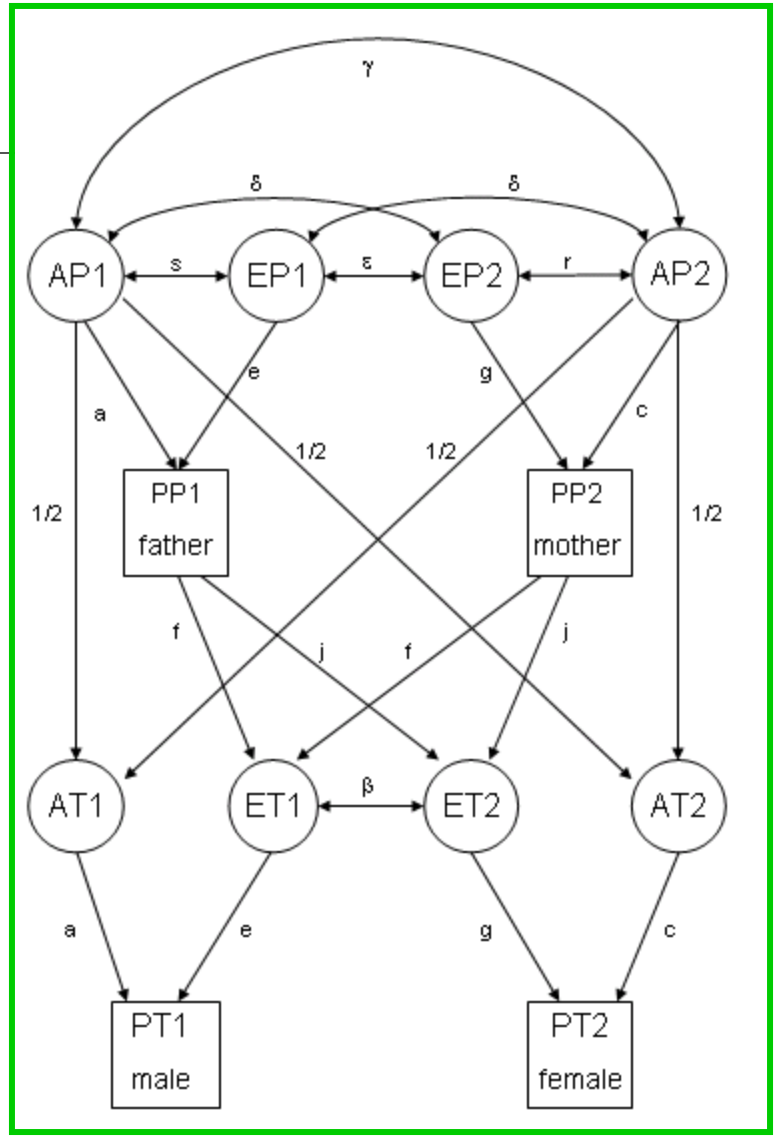
- The detection of GE interaction may be difficult when GE correlation is present
- GE correlation: non-random occurrence of genotypes in environments
- Different mechanisms:
  - Passive: kids receive both G and E
  - Reactive: environment reacts to genotype
  - Active: genotype “seeks out” environment

Extended twin designs

Twin and parents:

(Assortative mating)

Genetic transmission *plus*
Cultural transmission -> GE correlation



Example: association depression and life events

- Gene-environment correlation
  - An individual's genetic make-up influences depression and life events
- Causality:
  - Life events influence depression
  - Depression influences the risk for life events

Example

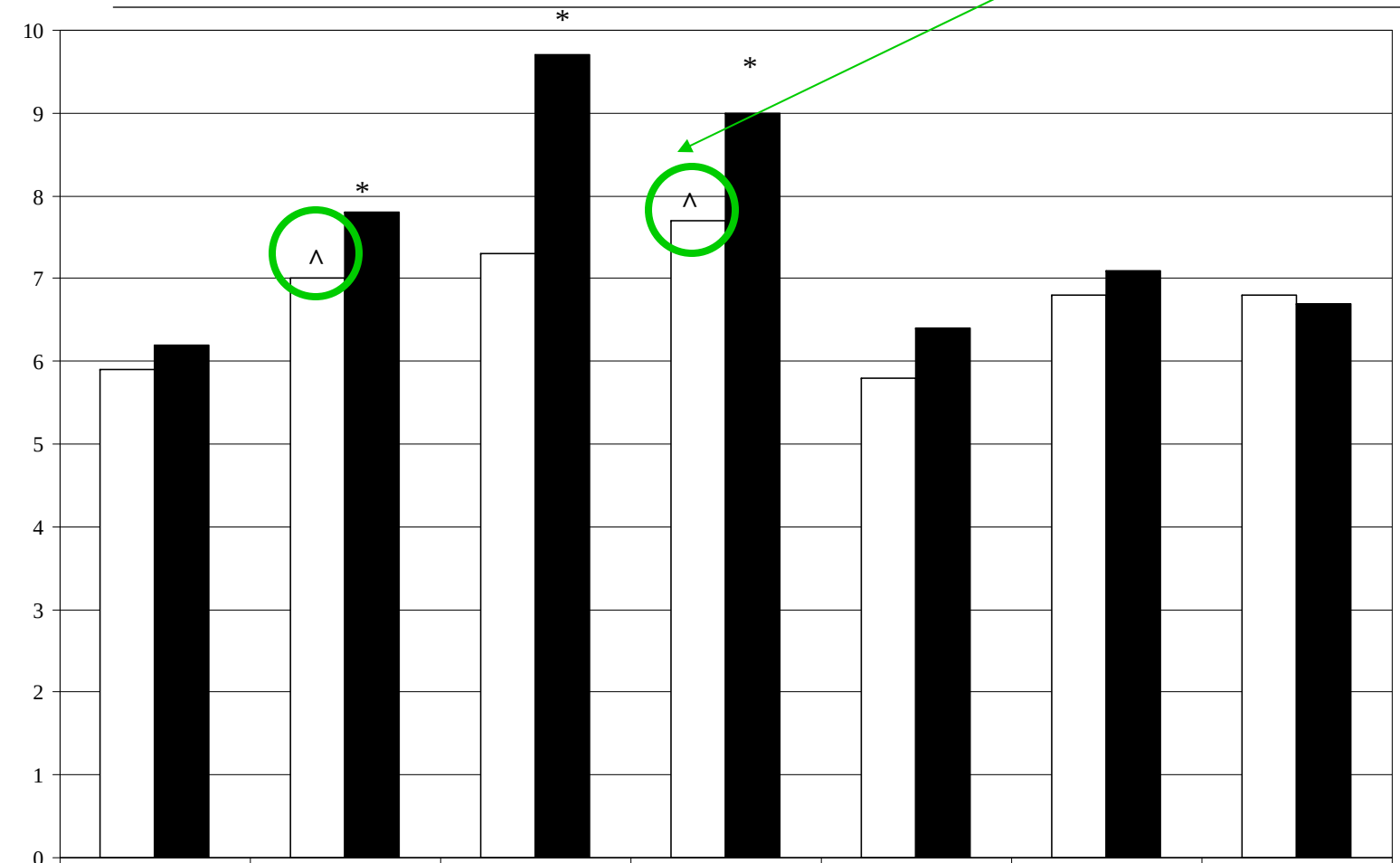
Two measures:

- Time 1:
  - depression
- Time 2:
  - depression
  - life events

- **causal analyses:**
  - Comparison scores before and after life events (mixed model)
  - Comparison scores at T1 between subjects exposed and non-exposed to life events
- **Gene-environment correlation:**
  - Co-twin control method: compare differences between discordant MZ pairs, discordant DZ pairs and unrelated subjects

Life events and depression

Before the life event happened already an increase in depression

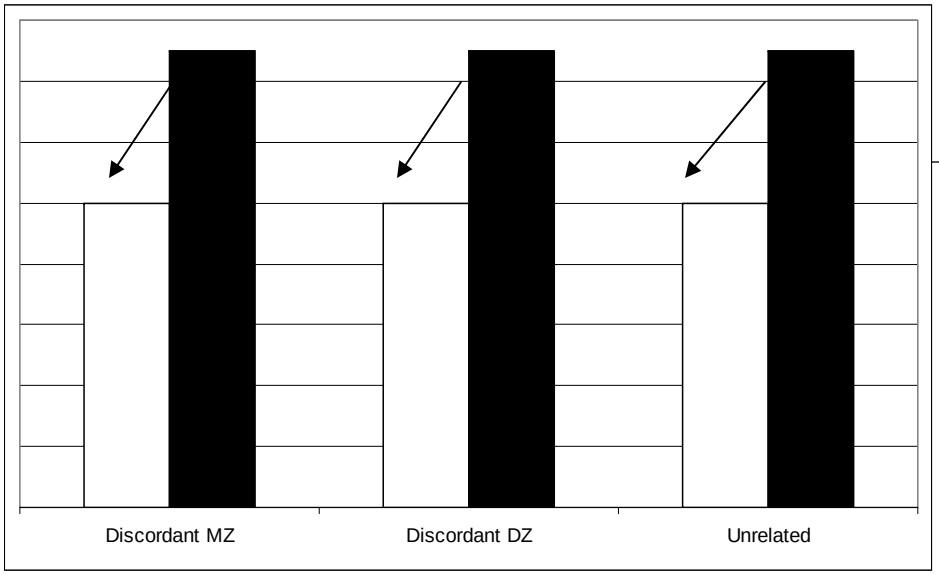


	No events (N=2246)	Any event (N=539)	Illness / injury self (N=107)	Divorce/break-up (N=139)	Accident (N=91)	Robbery (N=236)	Violent assault (N=28)
□ T1	5.9	7	7.3	7.7	5.8	6.8	6.8
■ T2	6.2	7.8	9.7	9	6.4	7.1	6.7

Discordant twin design

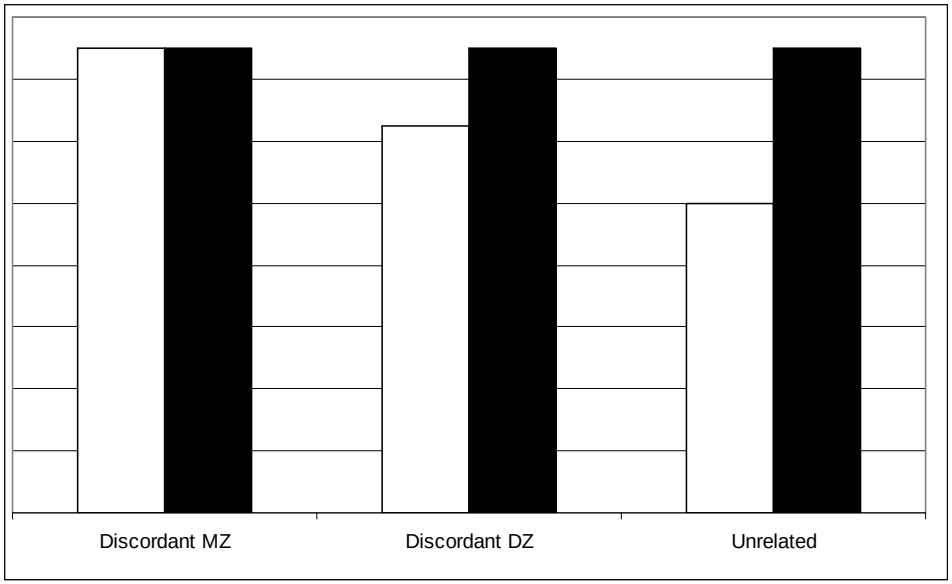
- Compare depression scores *within pairs* discordant for exposure to life events
- 3 groups:
  - MZ pairs, DZ pairs, unrelated pairs
- If the association of depression and LE is due to GE correlation the within-pair differences in depression in these 3 groups will not be the same

Expected scores in exposed ■ and non-exposed Ss □



No gene-environment correlation:

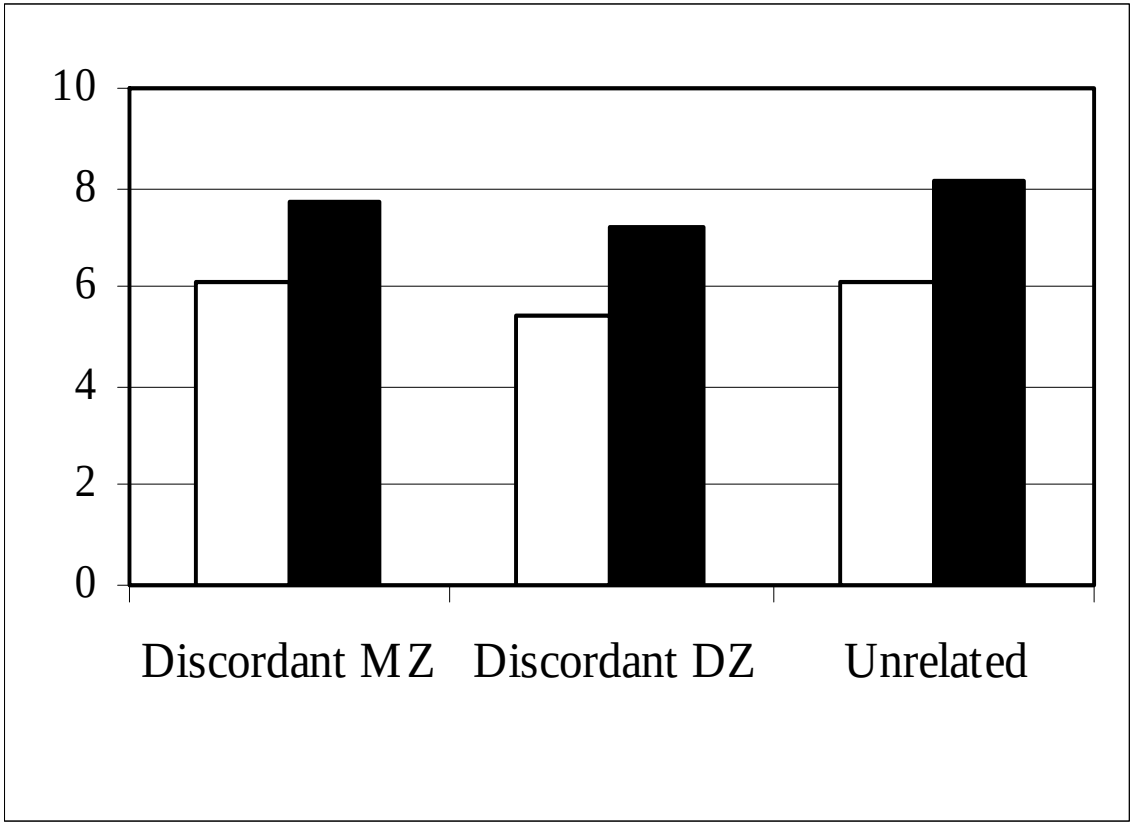
Similar differences between exposed and unexposed subjects in discordant MZ, DZ and unrelated subjects



Gene environment correlation:

- differences in unrelated > differences in DZ > differences in MZ.
- Unexposed subjects differ from each other

Exposure to life events one year ago and depression; no differences between 3 groups



No gene-environment correlation

Middeldorp CM, Cath DC, Beem AL, Willemsen G, Boomsma DI. Life events, anxious depression and personality: a prospective and genetic study. Psychol Med. 2008

If rGE is not modeled (see also Purcell 2002)

Correlation between A and C acts like C; correlation between A and E acts like A.

GE interaction

- May exist
- Not easy to find
- GxC may be even harder to find
- Other phenomena (GE correlation, causality) need to be taken into account

Class Example: parental divorce and adolescent's perception of family function

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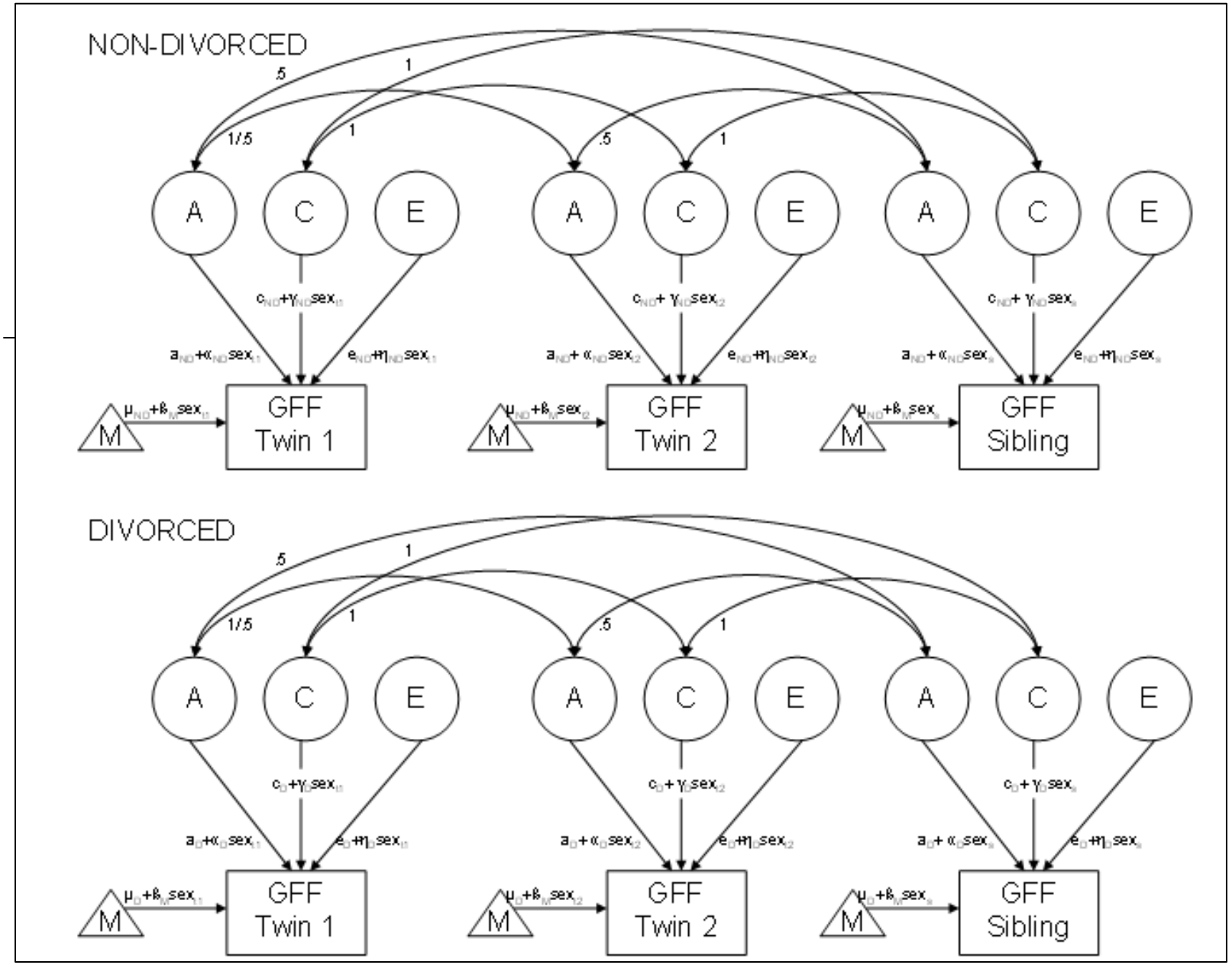
We will

- include sibs of twins in the analyses
- heterogeneity ("multi group") for divorce / non-D

After coffee:

- test for GEI with divorce as moderator
- Include effect of divorce on the means
- Include effect of other (continuous) covariates
- Test for GEI with a continuous moderator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