Heterogeneity Gene x Environment Interaction

Boulder Workshop, June 2022

Hermine H. Maes
with credit to many workshop faculty, Sarah Medland, Brad Verhulst, Marleen de Moor, Conor Dolan

Heterogeneity/Interaction Questions

- Univariate Analysis: What are the contributions of genetic (additive or dominance) and environmental (shared or unique) factors to the variance of a phenotype of interest?
- Are the contributions of genetic and environmental factors equal for different groups, such as sex, race, ethnicity; or for different levels of covariates, such as SES, environmental exposure, etc.?

Group Membership

Comparison	Concordant group membership	Discordant group membership
gender	MZ & DZ: MM & FF pairs	DZ: opposite sex pairs
nationality	MZ & DZ: OZ & US pairs	
environment	MZ & DZ: urban & rural pairs	MZ & DZ: urban/ rural pairs
age/cohort	MZ & DZ: young & old pairs	

- Differences in magnitude of effects (quantitative)
  - Are contributions of genetic/environmental factors greater/smaller in one groups versus another?
- Differences in nature of effects (qualitative)
  - Do different genetic/environmental factors influence trait in two groups?

Genes & Environment

GxE vs rGE

Br. J. math. statist. Psychol. (1977), **30**, 1–42 *Printed in Great Britain* 1

1977

A progressive approach to non-additivity and genotype–environmental covariance in the analysis of human differences.

L. J. Eaves, Krystyna Last, N. G. Martin and J. L. Jinks

Heredity (1978), **41** (3), 249-320

1978

MODEL-FITTING APPROACHES TO THE ANALYSIS OF HUMAN BEHAVIOUR

L. J. EAVES, KRYSTYNA A. LAST, P. A. YOUNG and N. G. MARTIN*
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Received 10.i.78

1987

Acta Genet Med GemelloI36:5·20 (1987)

Prospects for Detecting Genotype X Environment Interactions in Twins with Breast Cancer

N.G. Martin[1], L.J. Eaves, A.C. Heath
Department of Human Genetics, Medical College of Virginia, Richmond, USA

Eaves et al 1978 Heredity

(ii) *The use of twins in tests of scale*

Twins provide the best experimental design for some purposes. The detection of genotype-environment ($G \times E$) interaction usually requires the replication of genotypes either in the same or in different environments. Thus, identical twins form a natural experiment for studying some kinds of $G \times E$. More generally they also enable us to look at the properties of the scale of measurement.

These and other related problems were discussed by Eaves *et al.* (1977) who distinguished between "systematic" and "unsystematic" sources of non-additivity. Systematic non-additive effects included genetical non-additivity (*e.g.* directional dominance, in which the non-additive effects of loci operate to enhance the expression of the trait in a uniform direction, as might be expected for a trait showing a linear relationship with reproductive fitness) and genotype environmental-interactions, in which sensitivity to environmental factors is related in a systematic way to the average performance of the genotypes in a range of environments. Although both types of directional non-additivity can result in skewness in the distribution of phenotypes in a population, their effects may, under some circumstances, be separable with twin data.

Eaves et al 1978 Heredity

Jinks and Fulker (1970) suggested that systematic genotype-environment interactions might be detected by investigating the form of any relationship between the mean scores of monozygotic twin pairs and either the within-pair standard deviations (*i.e.* the absolute intra-pair differences) or the variances. Ideally, the relationship should be examined with twins reared apart to prevent the confounding of genotype-environment interactions with interactions between environmental differences within pairs and the family environment but, since such pairs are rare, we usually have to be satisfied with tests based on twins reared together.

Since the variation within pairs also reflects errors of measurement, an examination of the mean-standard deviation relationship for MZ twins is of psychometric interest because significant trends may indicate the points on a chosen scale of measurement where discrimination is most or least effective. Very few raw scales of psychological measurement are free of some kind of systematic non-additivity. This may be attributable to the inability of the test to discriminate effectively between individuals at certain points on the scale, often at the extremes.

Martin et al 1987 Acta GMG

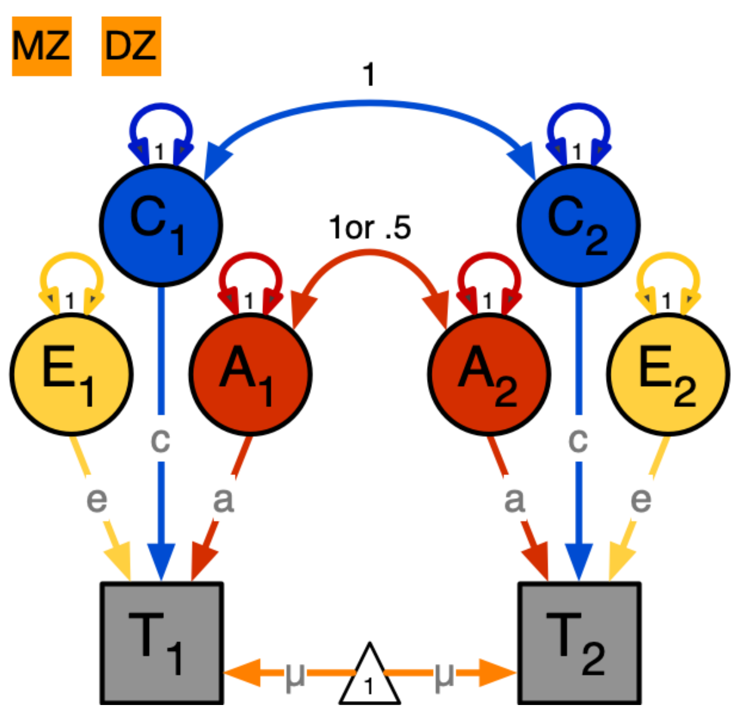
Because there are many questions about the design and power of the proposed study, it was decided to simulate it in some detail in order to assess the consequences of various sampling strategies. Key questions to be answered include:

1) What is the power to detect main effects of the measured and residual genotype (G_m and G_r) and the measured and residual environment (E_m and E_r) and all six of their two way interactions?
2) Is there an advantage in including controls, even if measured environmental indices (E_m) are not available for them (as would be the case if we used husbands as controls)?
3) What is the power of the study when 1) we assume that we can measure (or obtain an index of) liability, and 2) only affection status for individuals is known?
4) How are estimates and power affected by different assumptions about ascertainment? In particular, how are they affected if ascertainment differs in MZ and DZ twins?

$VA = a^2 = \boldsymbol{\sigma}^2 A$

Standard ACE Model

- When we fit ACE model we assume model holds in population ($\mathbf{r_Z}$=1 for MZ & 0.5 for DZ)



$$\mathbf{P_i - \mu = a{*}A_i + e{*}E_i}$$

Means

	Twin 1	**Twin 2**
1	μ	μ

Covariance

	Twin 1	**Twin 2**
T1	VA+VC+VE	**rz***VA+VC
T2	**rz***VA+VC	VA+VC+VE

- Phenotypic variable ~ N(**μ**, **VA**+**VE**+**VC**) normally distributed with mean **μ** and variance **VA**+**VE**(+**VC**)

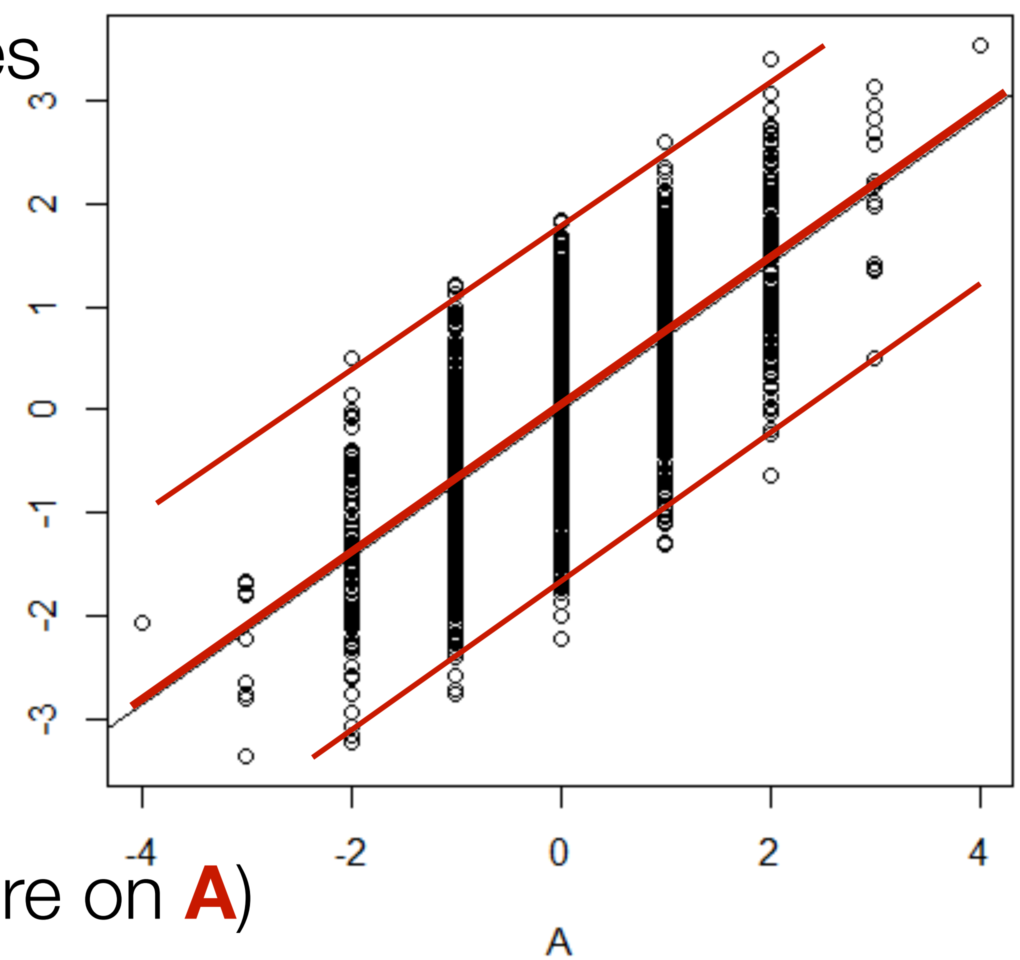
Testing for Heterogeneity

- What if two populations, e.g., males and females?
  - main effect of sex (moderator) on phenotype **μ**f ≠ **μ**m?
  - interaction effect of sex by **A**, **E** (sex as moderator of **A** &| **E** variances): **VAf** ≠ **VAm** and / or **VEf** ≠ **VEm**?
- If source of “heterogeneity” ignored, estimates of **μ**, **VE**, **VA** are biased
- Include source of heterogeneity, moderator, in model
  - If moderator is binary – multigroup model
  - If moderator is continuous – moderation model

Homoskedastic Model

- **E** is constant over levels of **A**

Phenotypic scores



Environmental dispersion

Variance of **E** given **A** score

$$P_i - \mu = a * A_i + e * E_i$$

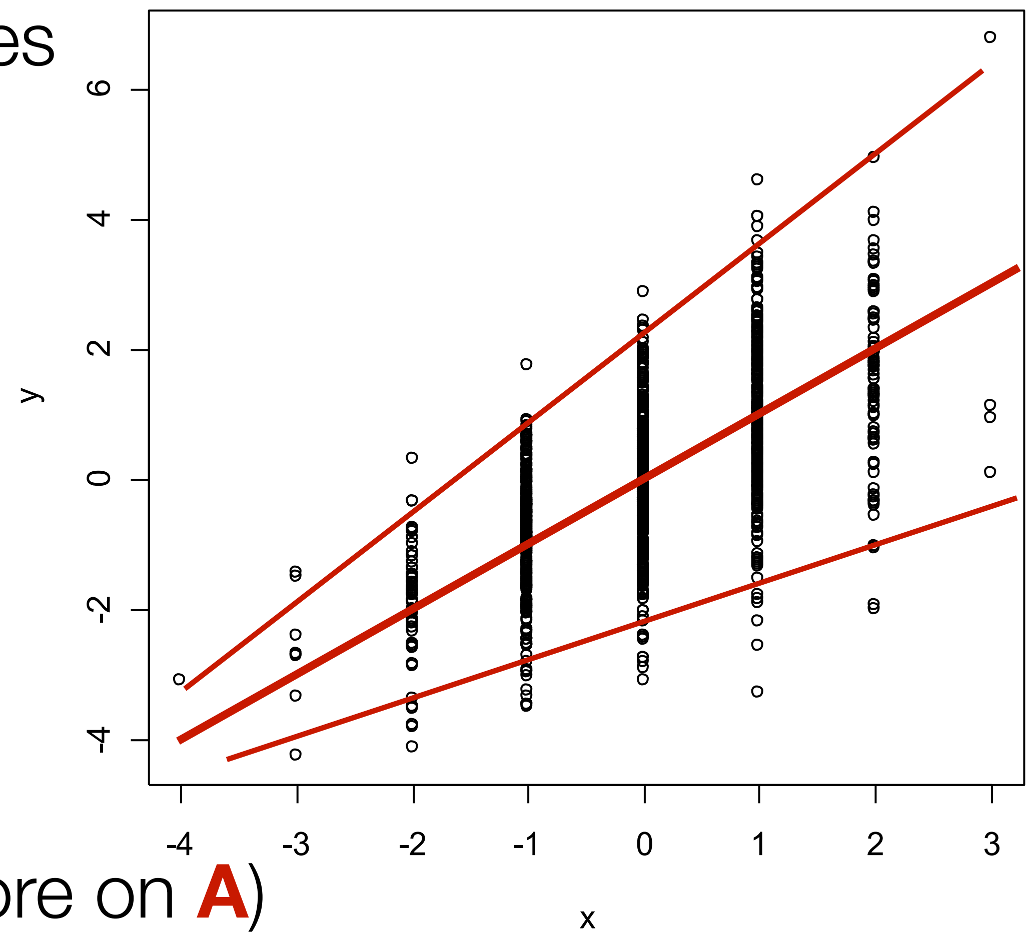
Genetic level (score on **A**)

- Environmental effects **E** are the same given any **A**

Heteroskedastic Model

- **G** x **E** as genetic control of sensitivity to different environments: heteroskedasticity

Phenotypic scores



Environmental dispersion

Variance of **E** given **A** score

$e=f_e(A)$ or $VE=g_e(A)$

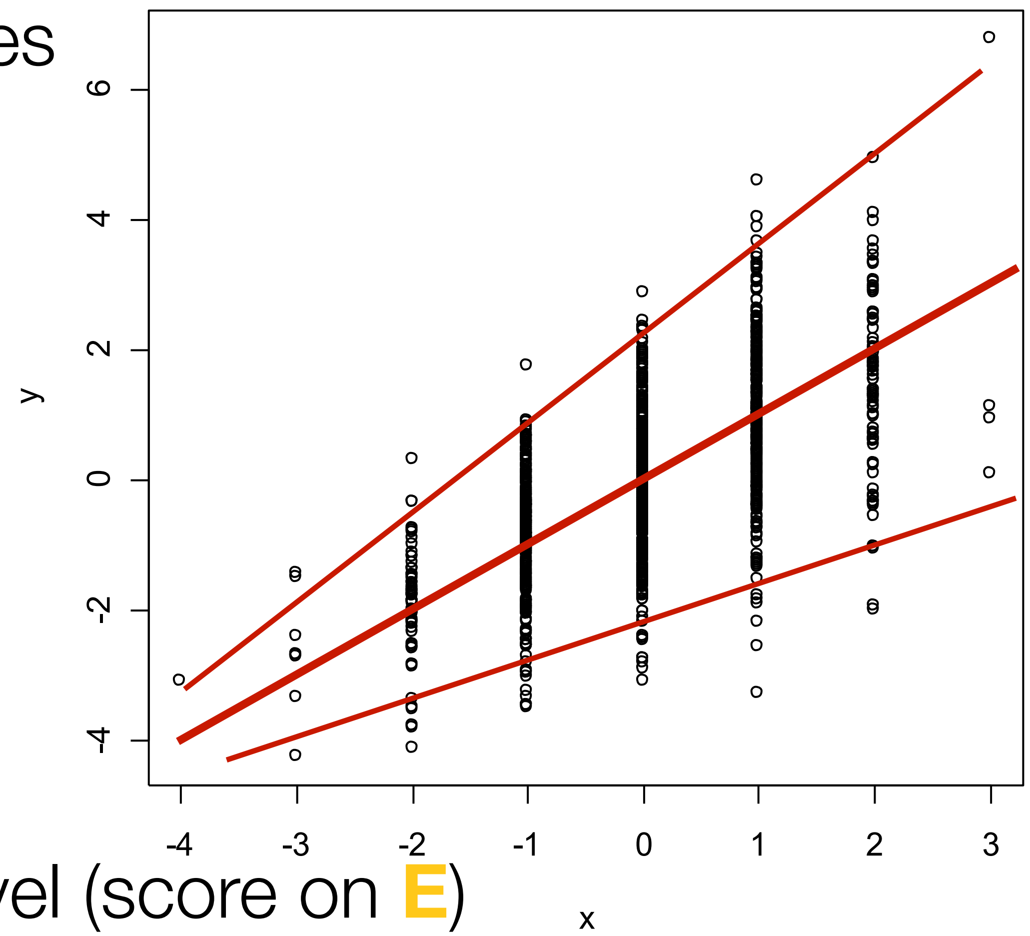
Genetic level (score on **A**)

- Environmental effects **E** systematically vary with **A**

Heteroskedastic Model

- **G** x **E** as environmental control of genetic effects: heteroskedasticity

Phenotypic scores



Genetic dispersion

Variance of **A** given **E** score

$a=f_a(E)$ or $VA=g_a(E)$

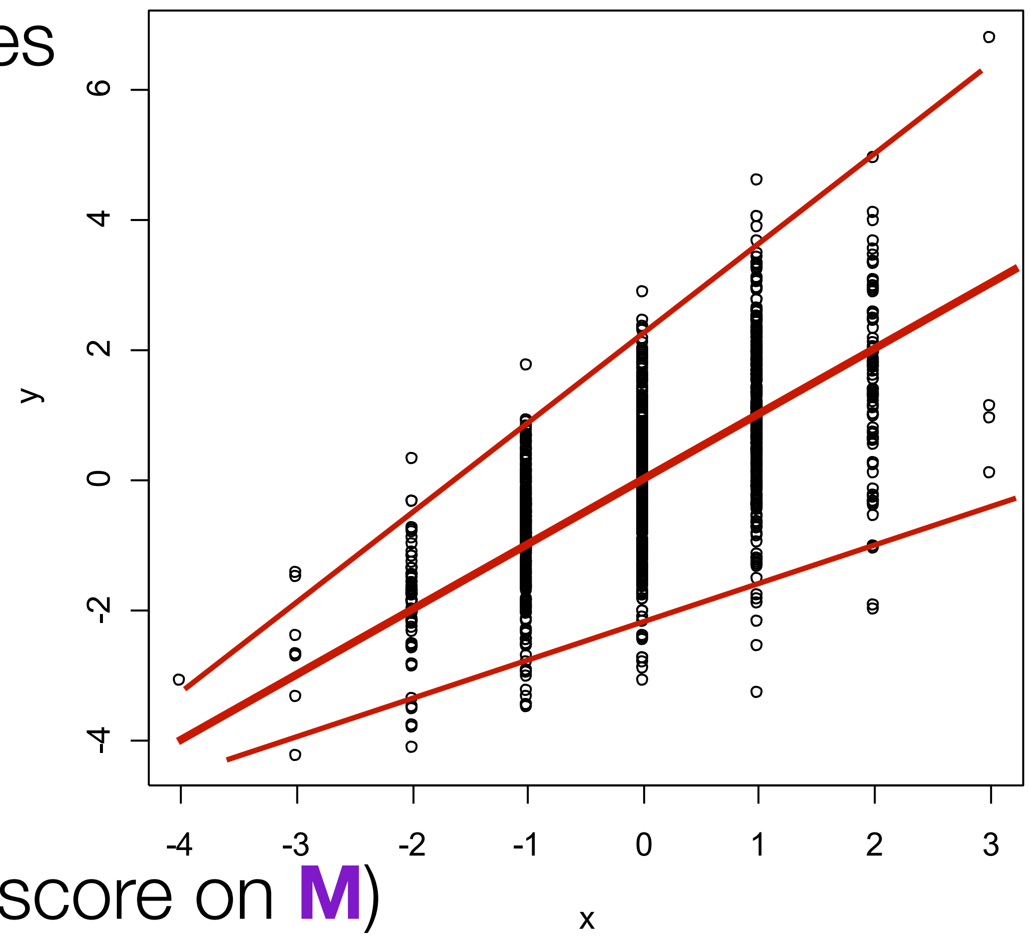
Environmental level (score on **E**)

- Genetic effects **A** systematically vary with **E**

Moderation

- moderation of effects (**A**, **C**, **E**) by measured moderator **M**: heteroskedasticity

Phenotypic scores



Moderator level (score on **M**)

Variance of **A** or/and **E** given **M** score

$a=f_a(M)$ or $VA=g_a(M)$

$c=f_c(M)$ or $VC=g_c(M)$

$e=f_e(M)$ or $VE=g_e(M)$

- Genetic effects **A** systematically vary with **M**

Gene-Environment Interaction

- **GxE**
  - genetic control of sensitivity to the environment
  - environmental control of gene expression
- Examples:
  - Does heritability of IQ depend on SES?
  - Does heritability of ADHD change as a function of age?
  - Does genetic variance for drinking depend on parental monitoring?

Gene-Environment Correlation

- **rGE**
  - genetic control of exposure to the environment
  - environmental control of gene frequency
- Examples:
  - Active rGE: Children with high IQ read more books
  - Passive rGE: High IQ parents give their children books
  - Reactive/Evocative rGE: Children with ADHD are treated differently by their parents

Binary Moderator: Multigroup Approach

- Is magnitude of genetic influences on trait the same in two or more groups? **VA1** = **VA2** ?
- Examples of binary moderators:
  - **A** effects moderated by sex = Sex **x** **A** interaction
  - **A** moderated by marital status: Unmarried women show greater levels of genetic influence on depression (Heath et al 1998)
  - **A** moderated by religious upbringing: A effects on personality trait of disinhibition diminished by religious upbringing (Boomsma et al 1999)

GxE Application: binary moderator

Twin Research (1998) 1, 119–122

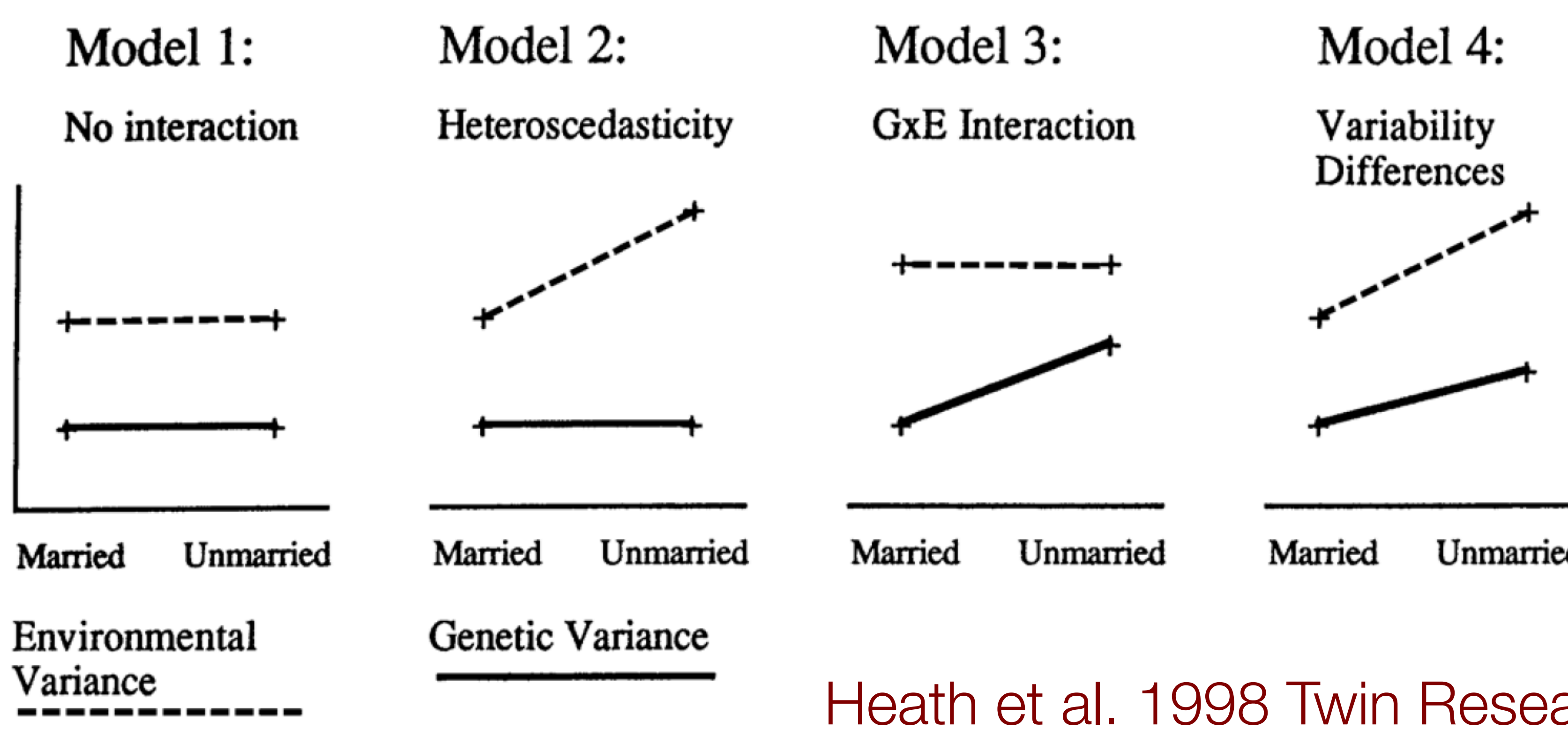
http://www.stockton-press.co.uk/tr

Interaction of marital status and genetic risk for symptoms of depression

Andrew C Heath[1], Lindon J Eaves[2] and Nicholas G Martin[3]

[1]Department of Psychiatry, Washington University, St Louis
[2]Virginia Institute of Psychiatric and Behavioral Genetics, Richmond, USA
[3]Queensland Institute of Medical Research, Brisbane, Australia

Depression scores (DSSI) were available for 1232 MZ and 751 DZ female twin pairs who completed a mailed questionnaire. Pairs were divided into those concordant for being in a marriage-like state, concordant for having no partners, and those discordant. The pattern of twin correlations differed according to marital status. Our results suggest that having a marriage-like relationship acts as a protective factor in reducing the impact of inherited liability to symptoms of depression in the general population.



Heath et al. 1998 Twin Research

GxE Application: binary moderator

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

DI Boomsma[1], EJC de Geus[1], GCM van Baal[1] and JR Koopmans[2]

[1]Department of Biological Psychology, Vrije Universiteit, Amsterdam, The Netherlands

Information on personality, on anxiety and depression and on several aspects of religion was collected in 1974 Dutch families consisting of adolescent and young adult twins and their parents. Analyses of these data showed that differences between individuals in religious upbringing, in religious affiliation and in participation in church activities are not influenced by genetic factors. The familial resemblance for different aspects of religion is high, but can be explained entirely by environmental influences common to family members. Shared genes do not contribute to familial resemblances in religion. The absence of genetic influences on variation in several dimensions of religion is in contrast to findings of genetic influences on a large number of other traits that were studied in these twin families. Differences in religious background are associated with differences in personality, especially in Sensation Seeking. Subjects with a religious upbringing, who are currently religious and who engage in church activities score lower on the scales of the Sensation Seeking Questionnaire. The most pronounced effect is on the Disinhibition scale. The resemblances between twins for the Disinhibition scale differ according to their religious upbringing. Receiving a religious upbringing seems to reduce the influence of genetic factors on Disinhibition, especially in males.

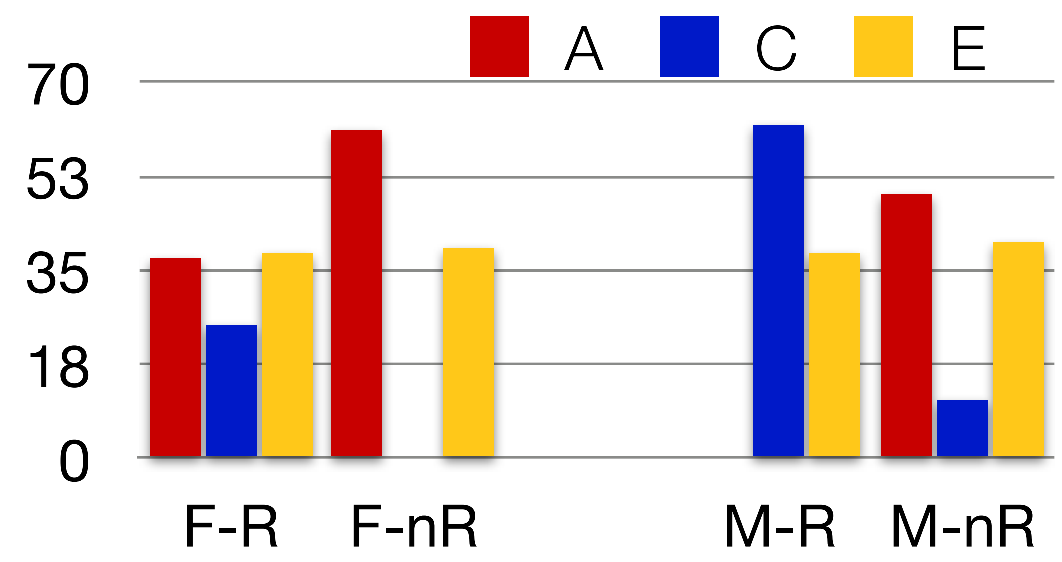


Table 5B Percentage of variance in Disinhibition explained by additive genetic factors (A), common (C) and unique environment (E) for males and females as a function of religious upbringing; parameter estimates with 95% confidence intervals in parentheses

	Mean	A	C	E
Fem, religious	29.45	37 (22–55)	25 (09–37)	38 (32–46)
Fem, non-religious	31.86	61 (07–67)	00 (00–48)	39 (32–51)
Male, religious	34.21	00 (00–22)	62 (43–69)	38 (31–45)
Male, non-religious	36.53	49 (14–69)	11 (00–40)	40 (32–51)

Boomsma et al. 1999 Twin Research

Heterogeneity - Moderation

- Some variables have many categories:
  - socioeconomic status, education
- Some variables are continuous:
  - age, parental monitoring
- Grouping variables into high/low categories loses lots of information
- Does magnitude of genetic and environmental variance change linearly with moderator?

G x E: Environment = Moderator

- Micro-Environment (unmeasured, random) E & C in twin models
- Macro-Environment (measured, ?”fixed”) SES, life events, exposure, smoking(?)

- Independent (of genotype)
- Correlated with genotype -
  - of individual (“active/evocative”) or
  - of relatives (“passive”)

Assumptions about Moderator

- Moderator is measured environmental variable
- “Environmental” measures display genetic variance
  - See Plomin & Bergeman, 1991
  - See Kendler & Baker, 2006

BEHAVIORAL AND BRAIN SCIENCES (1991) 14, 373–427
Printed in the United States of America

The nature of nurture: Genetic influence on “environmental” measures

Robert Plomin[a] and C. S. Bergeman[b]

Psychological Medicine, 2007, **37**, 615–626. © 2006 Cambridge University Press
doi:10.1017/S0033291706009524 First published online 19 December 2006 Printed in the United Kingdom

REVIEW ARTICLE

Genetic influences on measures of the environment: a systematic review

KENNETH S. KENDLER[1,2*] AND JESSICA H. BAKER[1,3]

Conclusion. Genetic influences on measures of the environment are pervasive in extent and modest to moderate in impact. These findings largely reflect ‘actual behavior’ rather than ‘only perceptions’. Etiologic models for psychiatric illness need to account for the non-trivial influences of genetic factors on environmental experiences.

Thank you Lindon