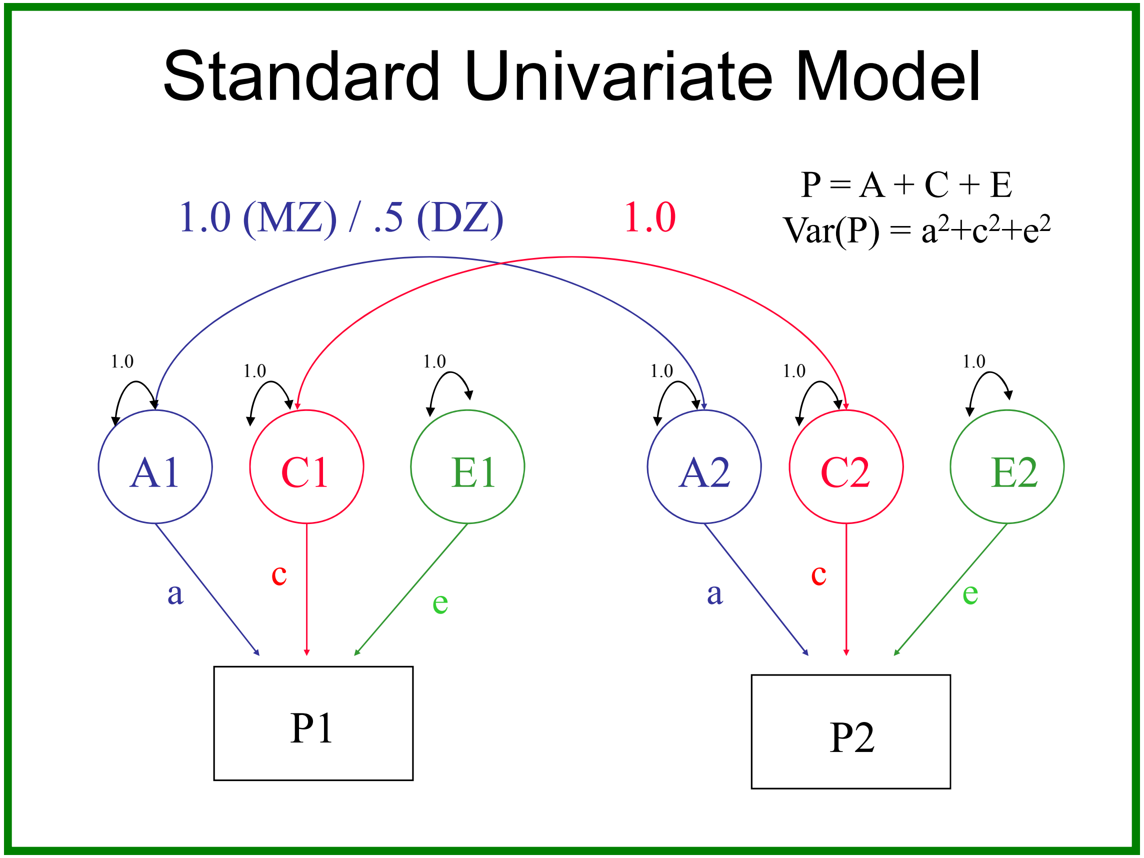
Gene-Environment Interaction & Correlation

Danielle Dick & Danielle Posthuma

Leuven 2008

Interplay between genes & environment

- Contribution of genes and environment is additive



Interplay between genes & environment

- Contribution of genes and environment is additive
- Genes and environment are correlated: genes alter the exposure to relevant environmental factors
- Genes and environment interact:
    - Genes control sensitivity to the environment,
    - The environment controls gene expression

Eaves LJ (1984) Genetic Epidemiology, 215-228
Kendler KS, Eaves, LJ (1986) *Am J Psychiatry,* 279-289

Gene-Environment Correlation

1. Passive rGE – genetically related parents provide a rearing environment that is correlated with the child's genotype

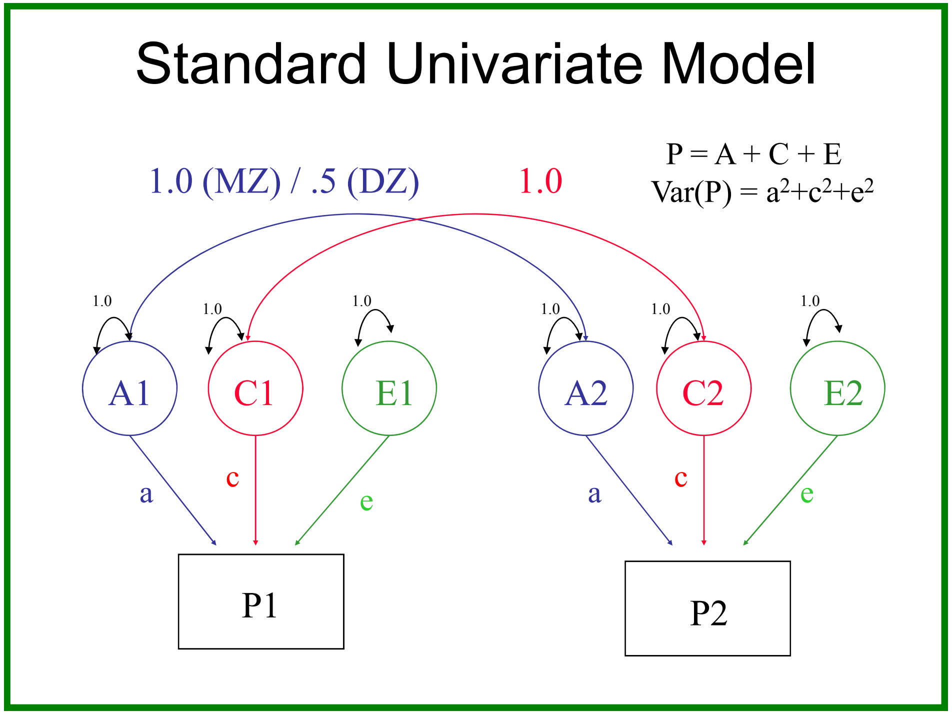
2. Evocative rGE – children receive responses from others that are influenced by their genotype and interpret them differently (reactive)

3. Active rGE – people's choice of environments are influenced by their genotype (niche-picking)

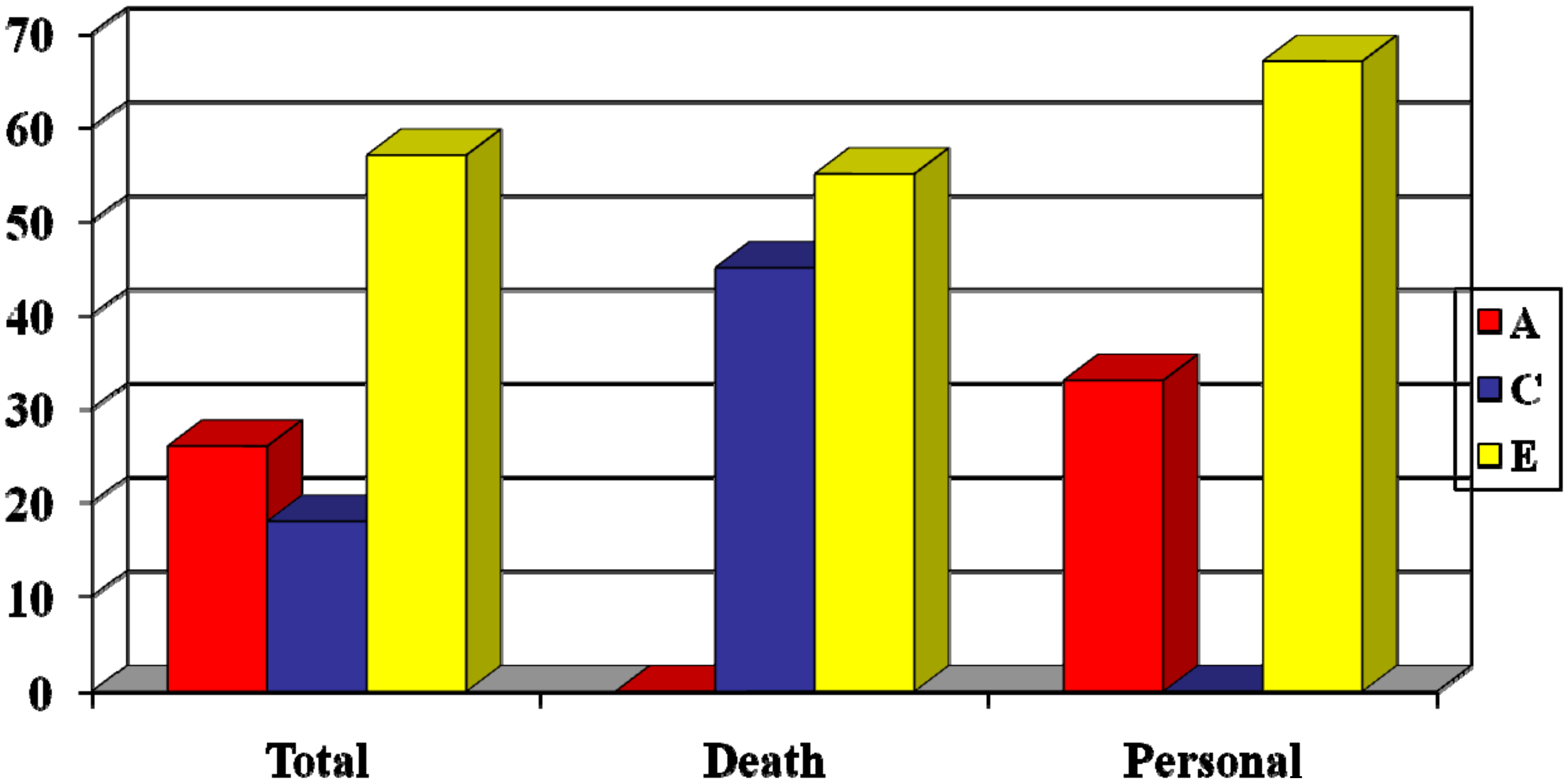
How to Model Genetic Influences on Environmental Traits?

How to Model Genetic Influences on Environmental Traits?

- The same way we study any other phenotype!

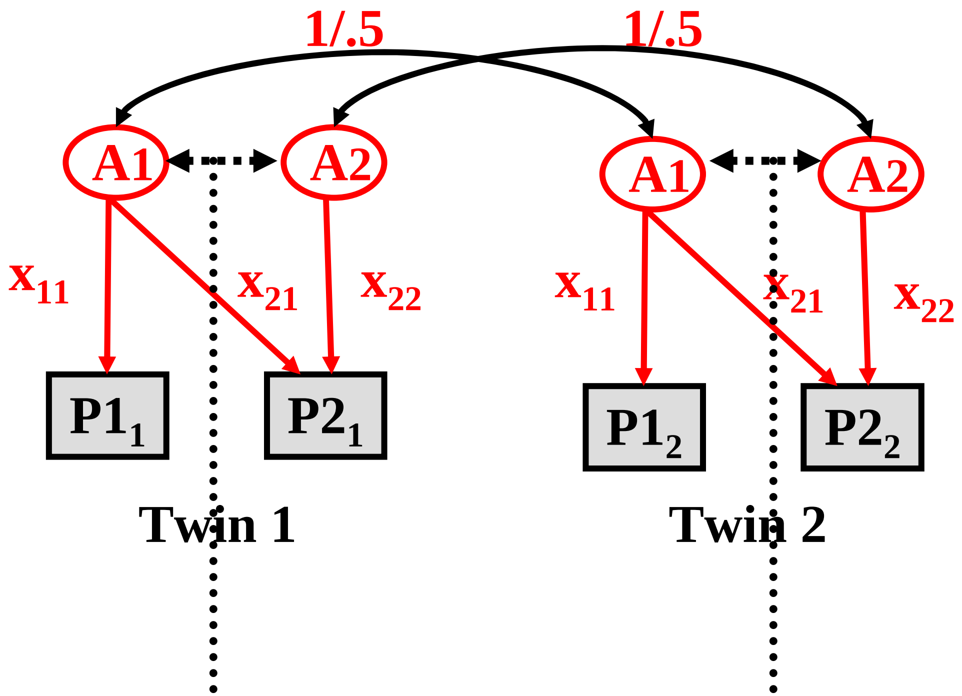


A Twin Study of Life events
(Kendler et al., 1993)



Death/illness/crisis happened to someone close to you/natural disaster
Personal – marital or financial problems, robbed/assaulted

Genetic correlation



$$r_g = \frac{x_{21}x_{11}}{\sqrt{x_{11}^2 * (x_{21}^2 + x_{22}^2)}}$$

Matrix Function in Mx: O = \stnd(A)

Implications of active and evocative rGE

- Some genetic effects are indirect, operating through effects on environmental risk
- If present, heritability estimates will be misleadingly high
- Some effects of adverse environments are genetically mediated
- Genes are involved in individual differences in environmental risk exposure

Gene-Environment Interaction

- *Genetic control of sensitivity to the environment*
- *Environmental control of gene expression*

- Bottom line: nature of genetic effects differs among environments

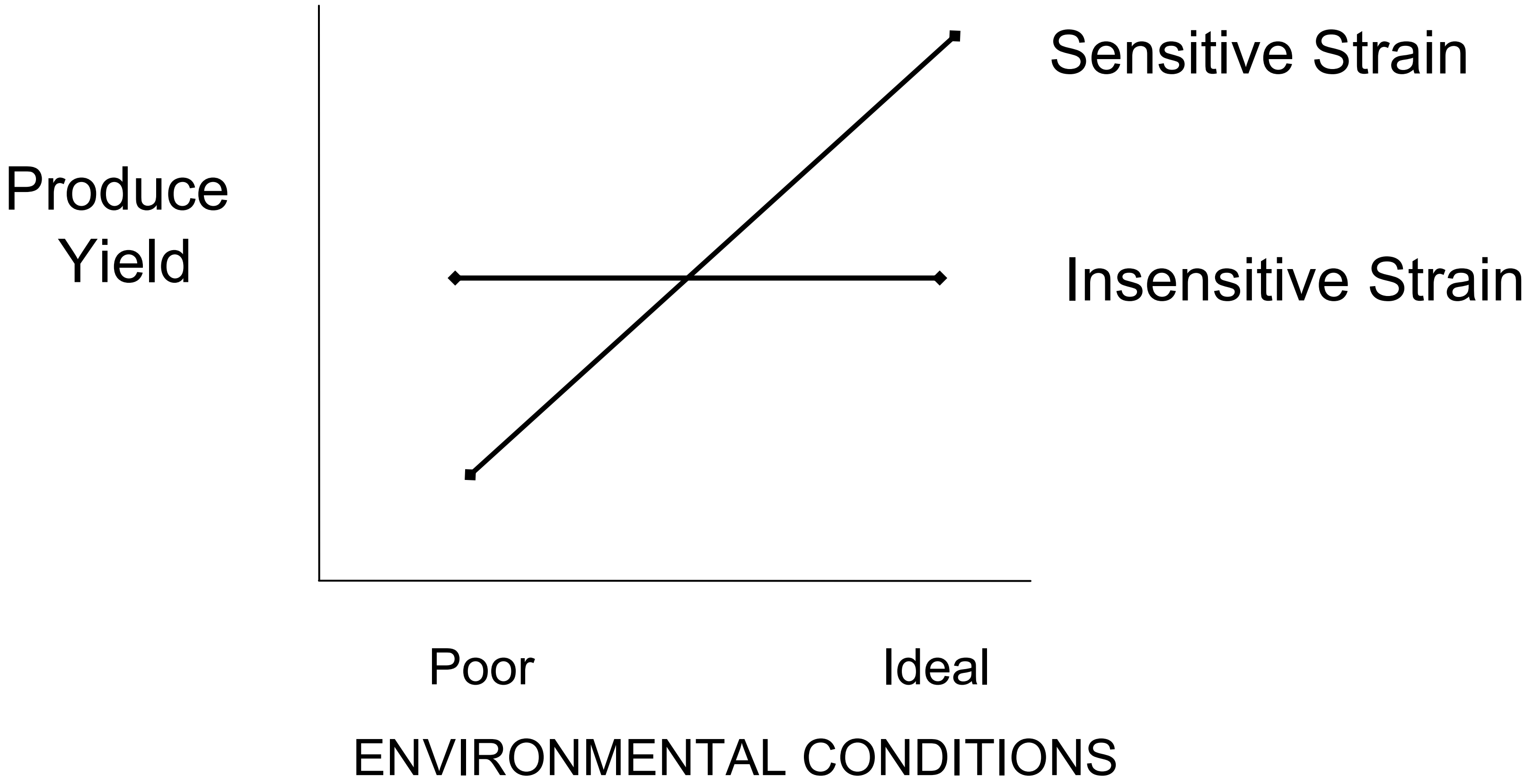
Gene-Environment Interaction

- *First observed by plant breeders:*
  - – Sensitive strains – did great under ideal conditions (soil type, sunlight, rainfall),

    but very poorly under less than ideal circumstances

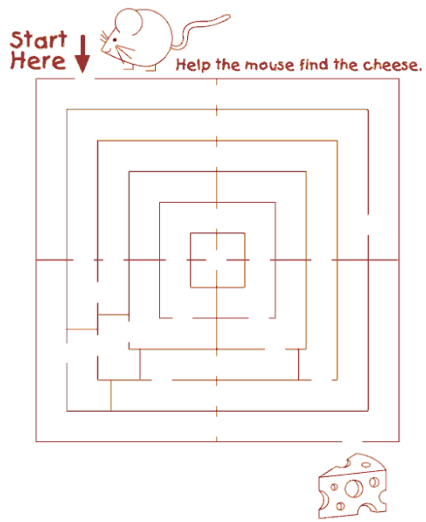
  - – Insensitive strains – did OK regardless of the condition; did worse under ideal conditions but better under poor conditions

Conceptualizing Gene-Environment Interaction

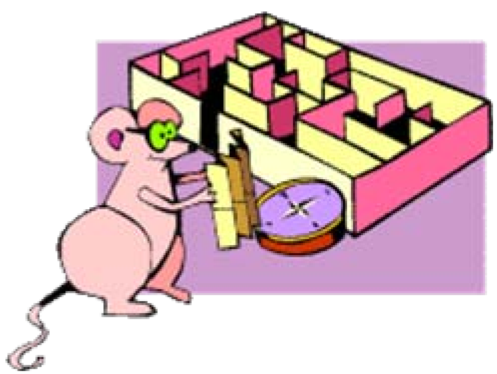


G-E Interaction Animal Studies

Maze
"Dull"



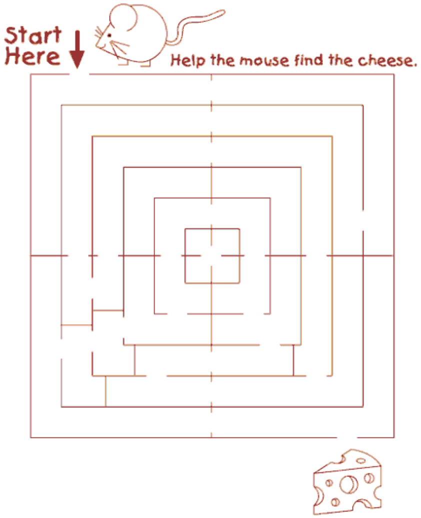
Maze
"Bright"



(Cooper & Zubeck, 1958)

G-E Interaction Animal Studies

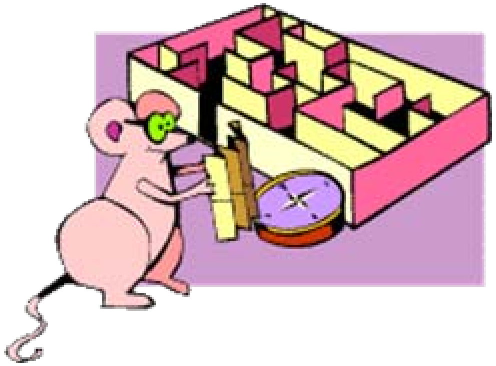
Maze
“Dull”



Impoverished
Environment

Enriched
Environment

Maze
“Bright”



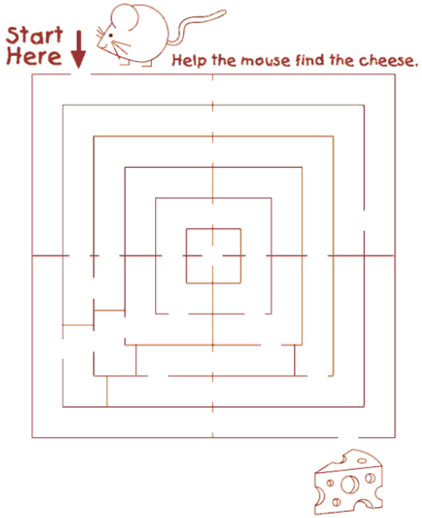
Impoverished
Environment

Enriched
Environment

(Cooper & Zubeck, 1958)

G-E Interaction Animal Studies

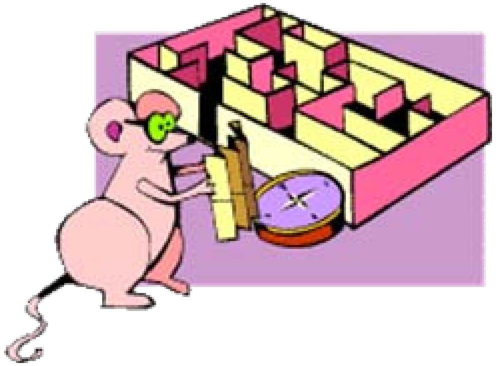
Maze "Dull"



Impoverished Environment → No change

Enriched Environment → Improvement

Maze "Bright"



Impoverished Environment → Poorer Performance

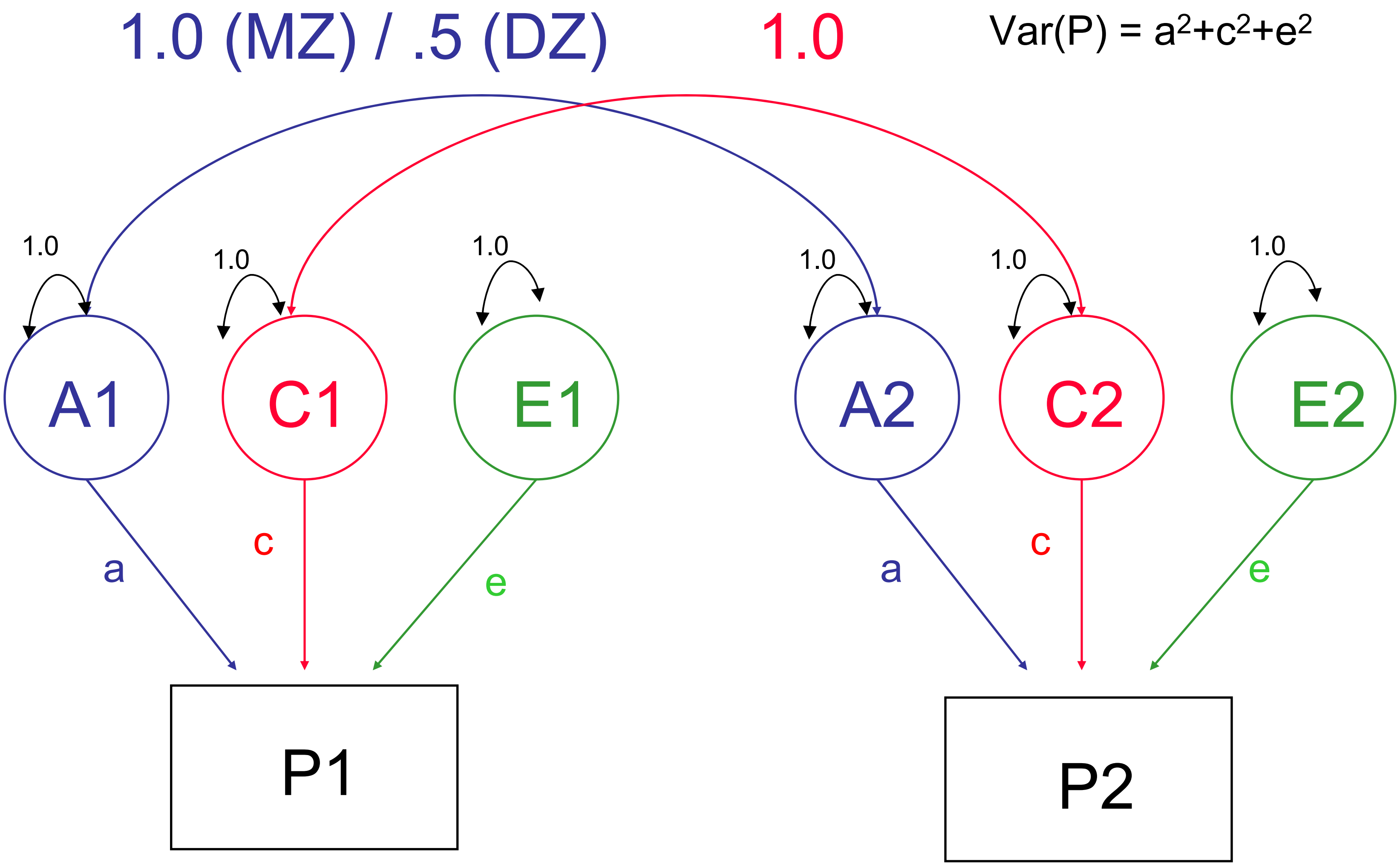
Enriched Environment → No change

(Cooper & Zubeck, 1958)

Standard Univariate Model

$P = A + C + E$

$Var(P) = a^2+c^2+e^2$



Contributions of Genetic, Shared Environment, Genotype x Shared Environment Interaction Effects to Twin/Sib Resemblance

	Shared Environment	Additive Genetic Effects	Genotype x Shared Environment Interaction
MZ Pairs	1	1	$1 \times 1 = 1$
DZ Pairs/Full Sibs	1	½	$1 \times ½ = ½$

Contributions of Genetic, Shared Environment, Genotype x Shared Environment Interaction Effects to Twin/Sib Resemblance

	Shared Environment	Additive Genetic Effects	Genotype x Shared Environment Interaction
MZ Pairs	1	1	1 x 1 = 1
DZ Pairs/Full Sibs	1	½	1 x ½ = ½

In other words—if gene-(shared) environment interaction is not explicitly modeled, it will be subsumed into the A term in the classic twin model.

Contributions of Genetic, Unshared Environment, Genotype x Unshared Environment Interaction Effects to Twin/Sib Resemblance

	Unshared (Unique) Environment	Additive Genetic Effects	Genotype x Unshared Environment Interaction
MZ Pairs	0	1	0 x 1 = 0
DZ Pairs/Full Sibs	0	½	0 x ½ = 0

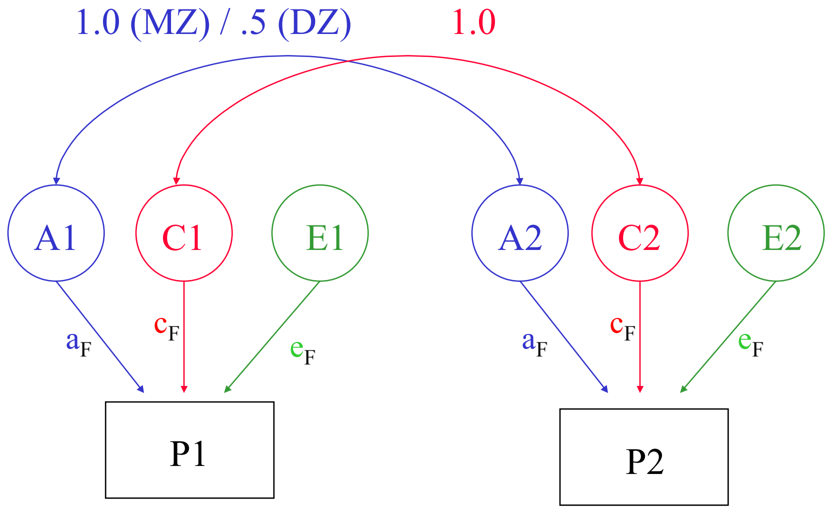
If gene-(unshared) environment interaction is not explicitly modeled, it will be subsumed into the E term in the classic twin model.

Ways to Model Gene-Environment Interaction in Twin Data

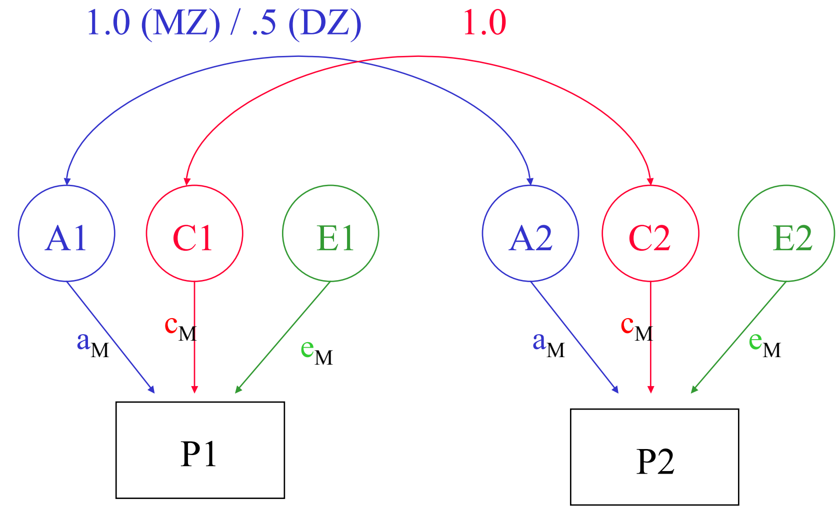
- Multiple Group Models
  - (parallel to testing for sex effects using multiple groups)

Sex Effects

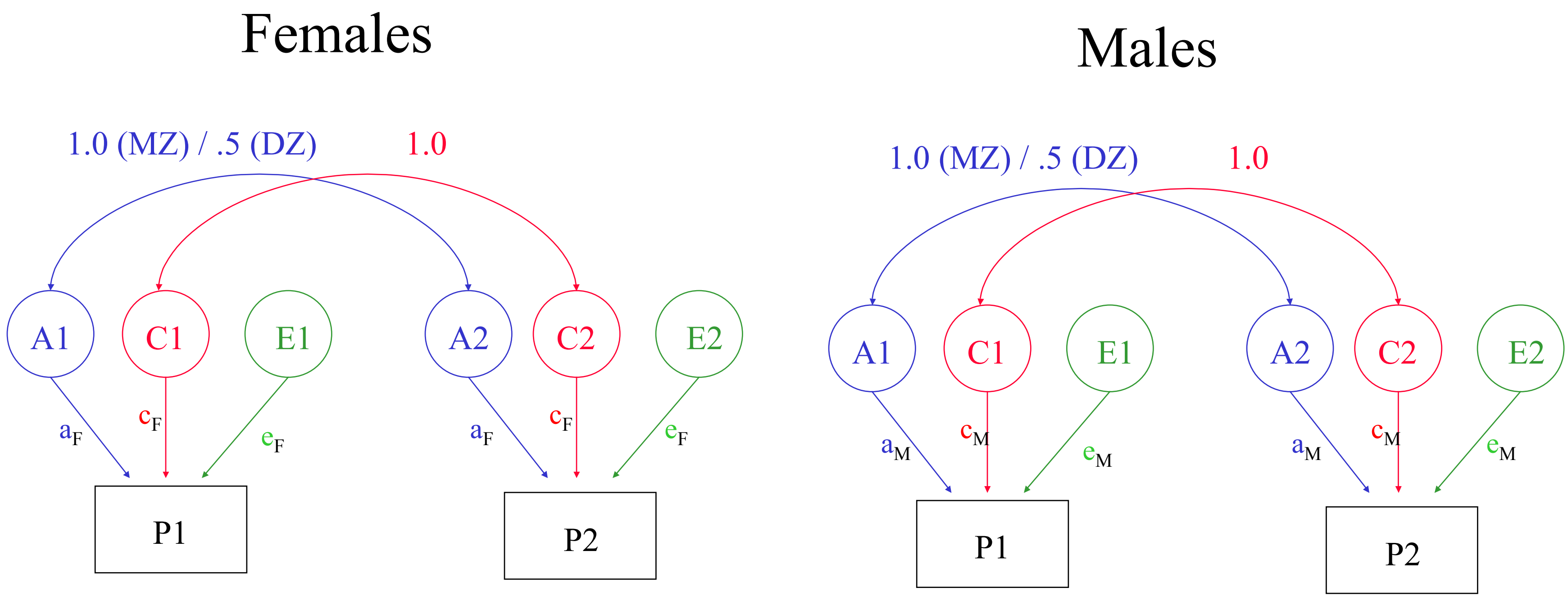
Females



Males

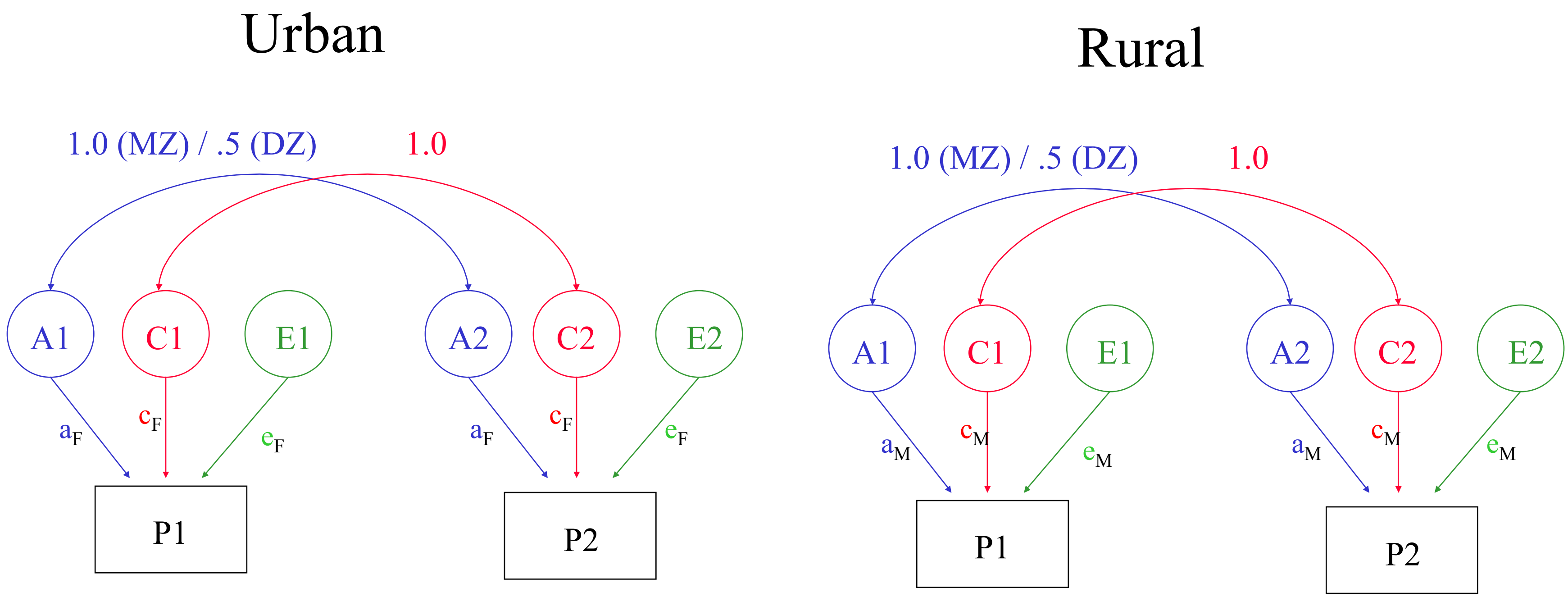


Sex Effects



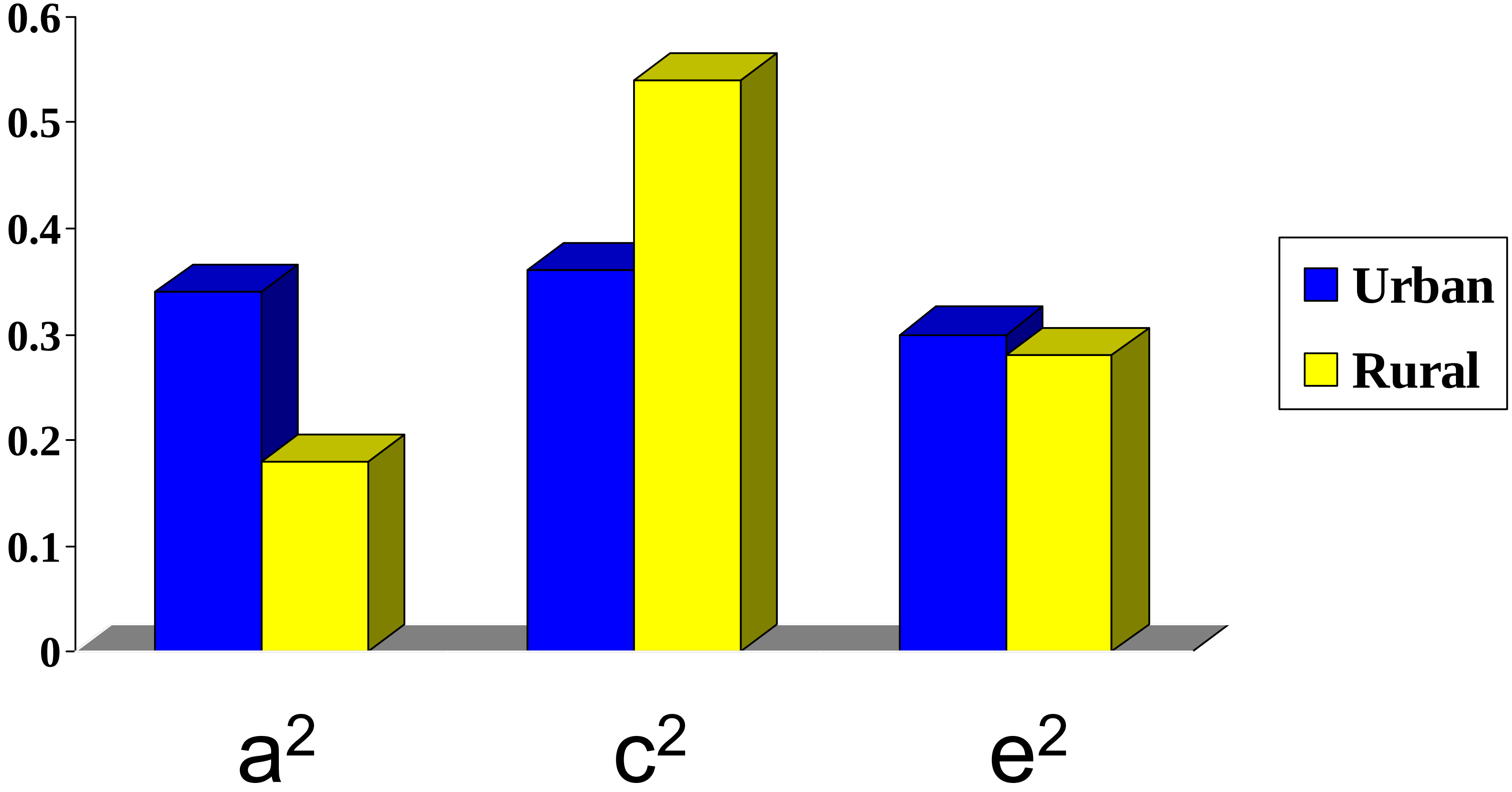
$a_F = a_M$? $c_F = c_M$? $e_F = e_M$?

GxE Effects



$a_U = a_R$? $c_U = c_R$? $e_U = e_R$?

Influences on Alcohol Use at Age 16: Urban/Rural Interaction



Rose et al., 2001, *ACER*

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

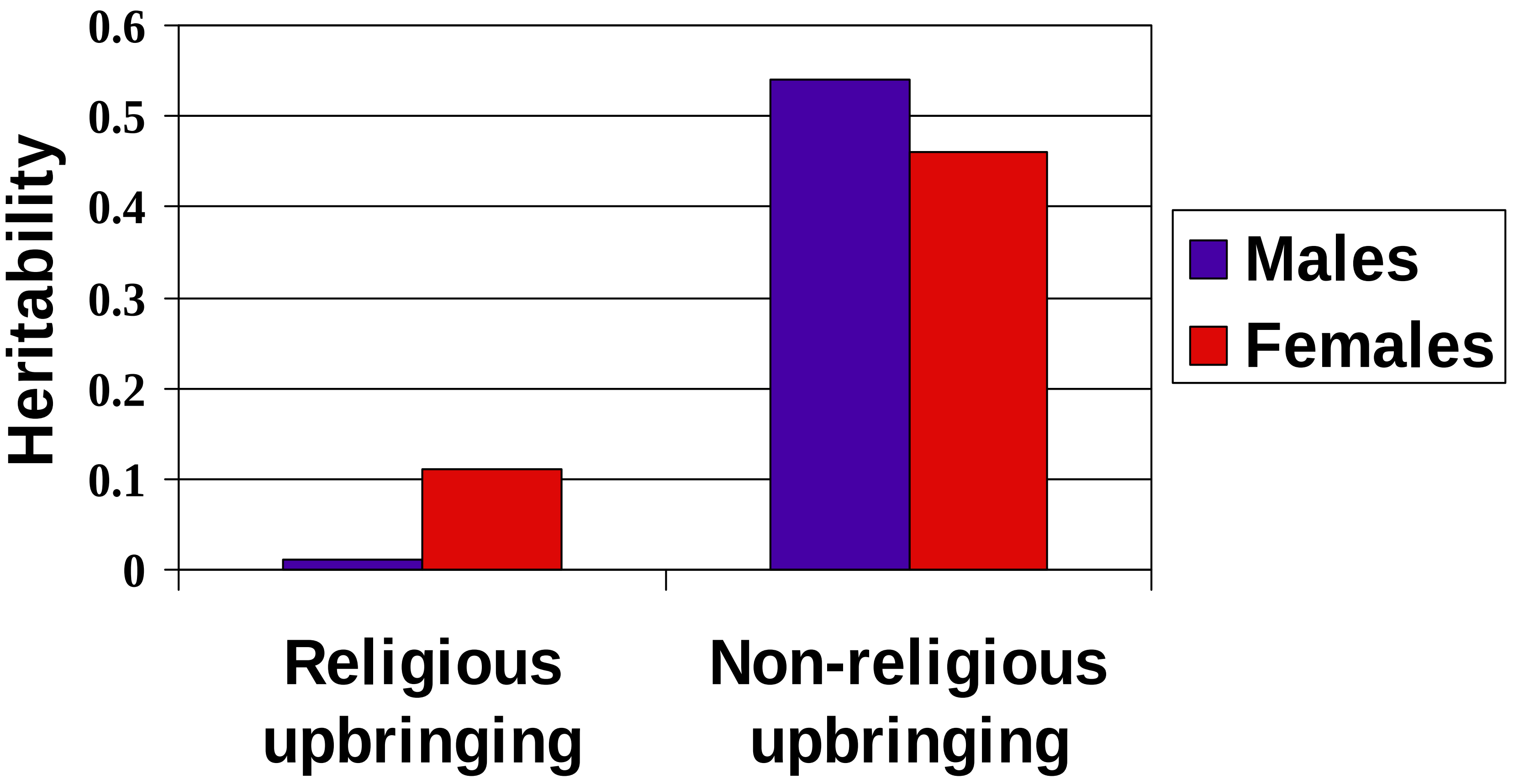
DI Boomsma[1], EJC de Geus[1], GCM van Baal[1] and JR Koopmans[2]

[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.

Keywords: genotype × environment (G × E) interaction, twins, religion, personality, sensation seeking

Heritability of Disinhibition estimated from Dutch twin pairs stratified by religious / non-religious upbringing



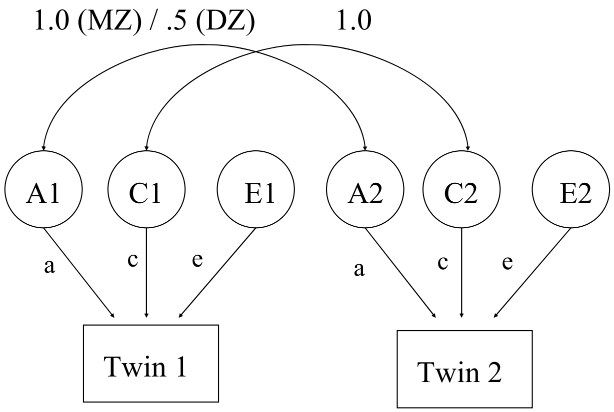
Problem:

- Many environments of interest do not fall into groups
  - Regional alcohol sales
  - Parental warmth
  - Parental monitoring
  - Socioeconomic status

    - Grouping these variables into high/low categories potentially loses a lot of information

- **Classic Twin Model:**

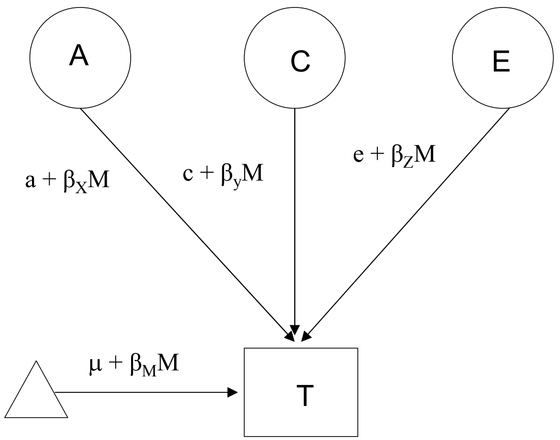
  $Var(T) = a^2 + c^2 + e^2$



- **Moderation Model:**

  $Var(T) =$

  $(a + \beta_X M)^2 + (c + \beta_Y M)^2 + (e + \beta_Z M)^2$



Purcell 2002,
Twin Research

$$\text{Var (T)} = (a + \beta_X M)^2 + (c + \beta_Y M)^2 (e + \beta_Z M)^2$$

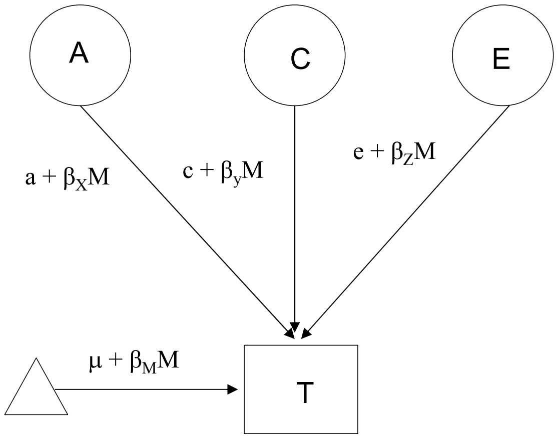
Where M is the value of the moderator and

Significance of β_X indicates genetic moderation

Significance of β_Y indicates common environmental moderation

Significance of β_Z indicates unique environmental moderation

B_M indicates a main effect of the moderator on the mean



‘Definition variables’ in Mx

- General definition: Definition variables are variables that may vary per subject and that are not dependent variables
- In Mx: The specific value of the def var for a specific individual is read into a matrix in Mx when analyzing the data of that particular individual

‘Definition variables’ in Mx

create dynamic var/cov structure

- Common uses:

1. As covariates/effects on the means (e.g. age and sex)

2. To model changes in variance components as function of some variable (e.g., age, SES, etc)

Definition variables used as covariates

General model with age and sex as covariates:

$$y_i = \alpha + \beta_1(\text{age}_\text{i}) + \beta_2(\text{sex}_\text{i}) + \varepsilon$$

Where $\boldsymbol{y_i}$ is the observed score of individual *i*, α is the intercept or grand mean, $\boldsymbol{\beta_1}$ is the regression weight of age, $\textbf{age}_\textbf{i}$ is the age of individual *i*, $\boldsymbol{\beta_2}$ is the deviation of males (if sex is coded 0= female; 1=male), $\textbf{sex}_\textbf{i}$ is the sex of individual *i*, and ε is the residual that is not explained by the covariates (and can be decomposed further into ACE etc).

Standard model

- Means vector

$$\begin{pmatrix} m & m \end{pmatrix}$$

- Covariance matrix

$$\begin{pmatrix} a^2 + c^2 + e^2 & \\ Za^2 + c^2 & a^2 + c^2 + e^2 \end{pmatrix}$$

Allowing for a main effect of *X*

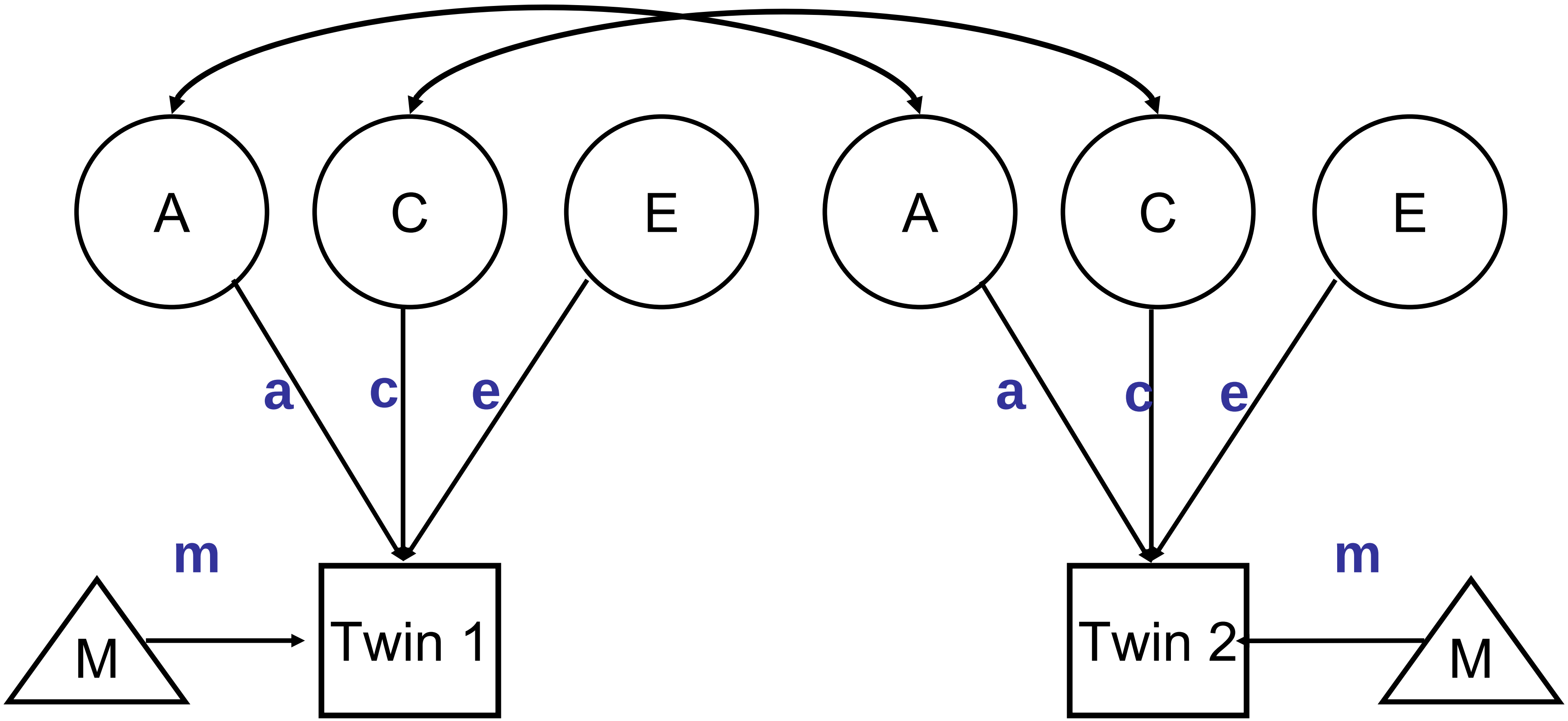
- Means vector

$$\begin{pmatrix} m+\beta X_{1i} & m+\beta X_{2i} \end{pmatrix}$$

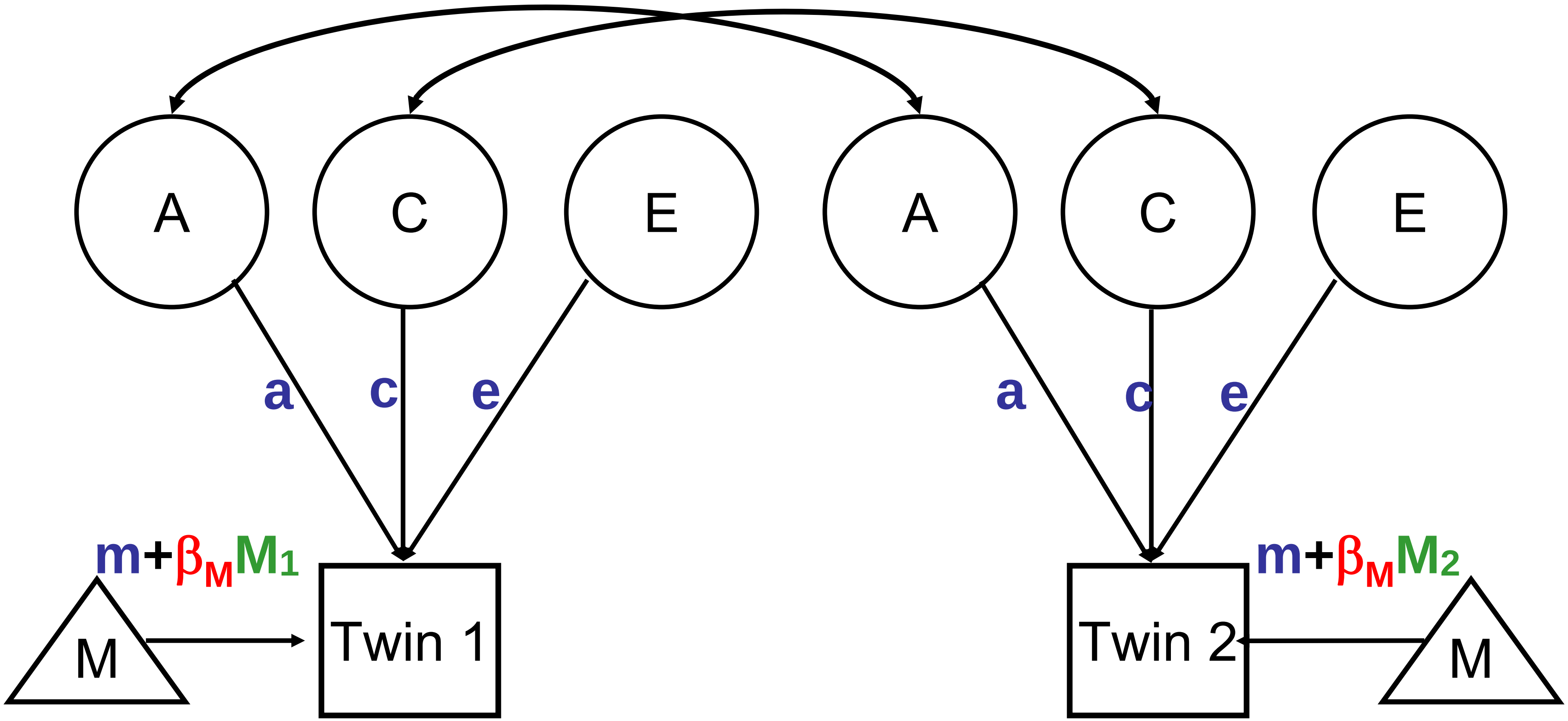
- Covariance matrix

$$\begin{pmatrix} a^2+c^2+e^2 & \\ Za^2+c^2 & a^2+c^2+e^2 \end{pmatrix}$$

Model-fitting approach to GxE



Adding Covariates to Means Model



‘Definition variables’ in Mx

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- Common uses:

1. As covariates/effects on the means (e.g. age and sex)

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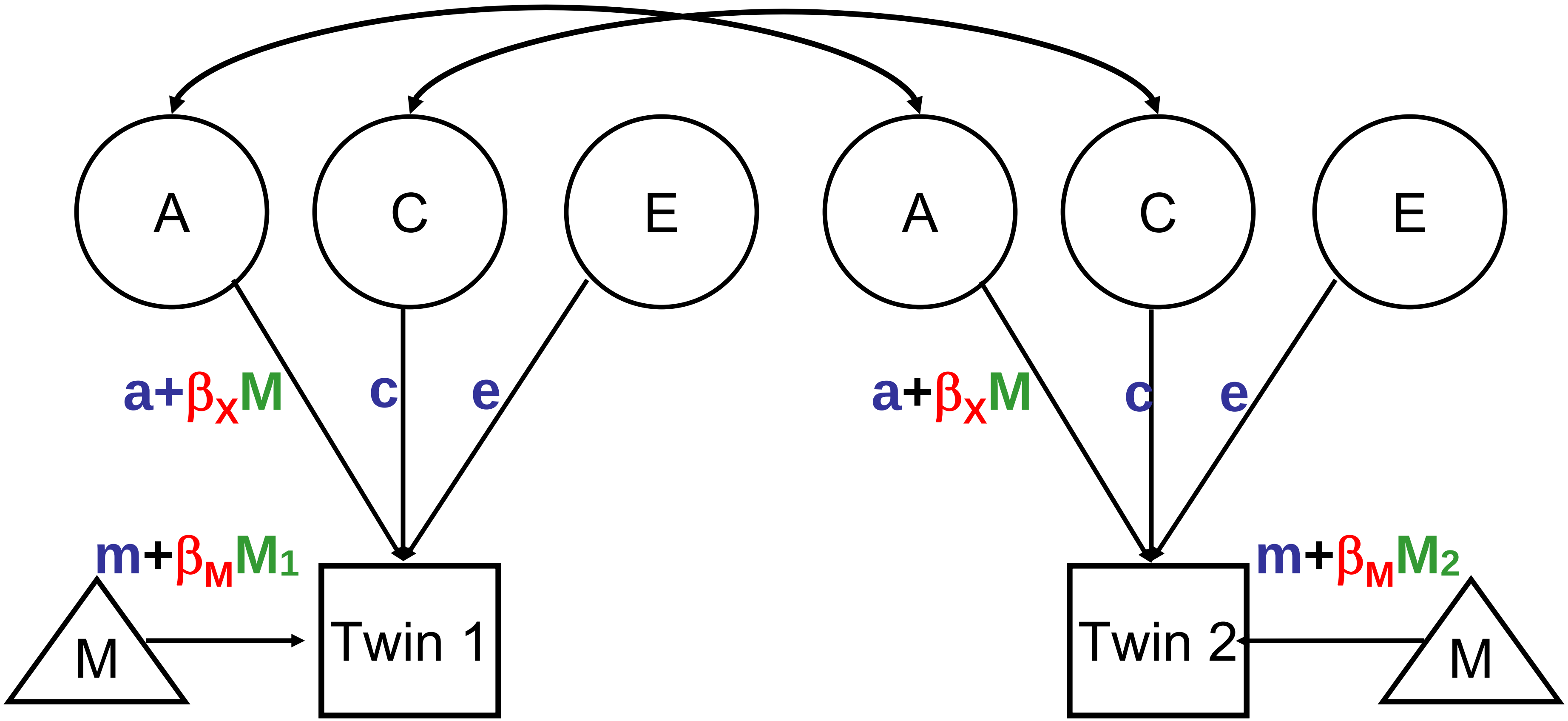
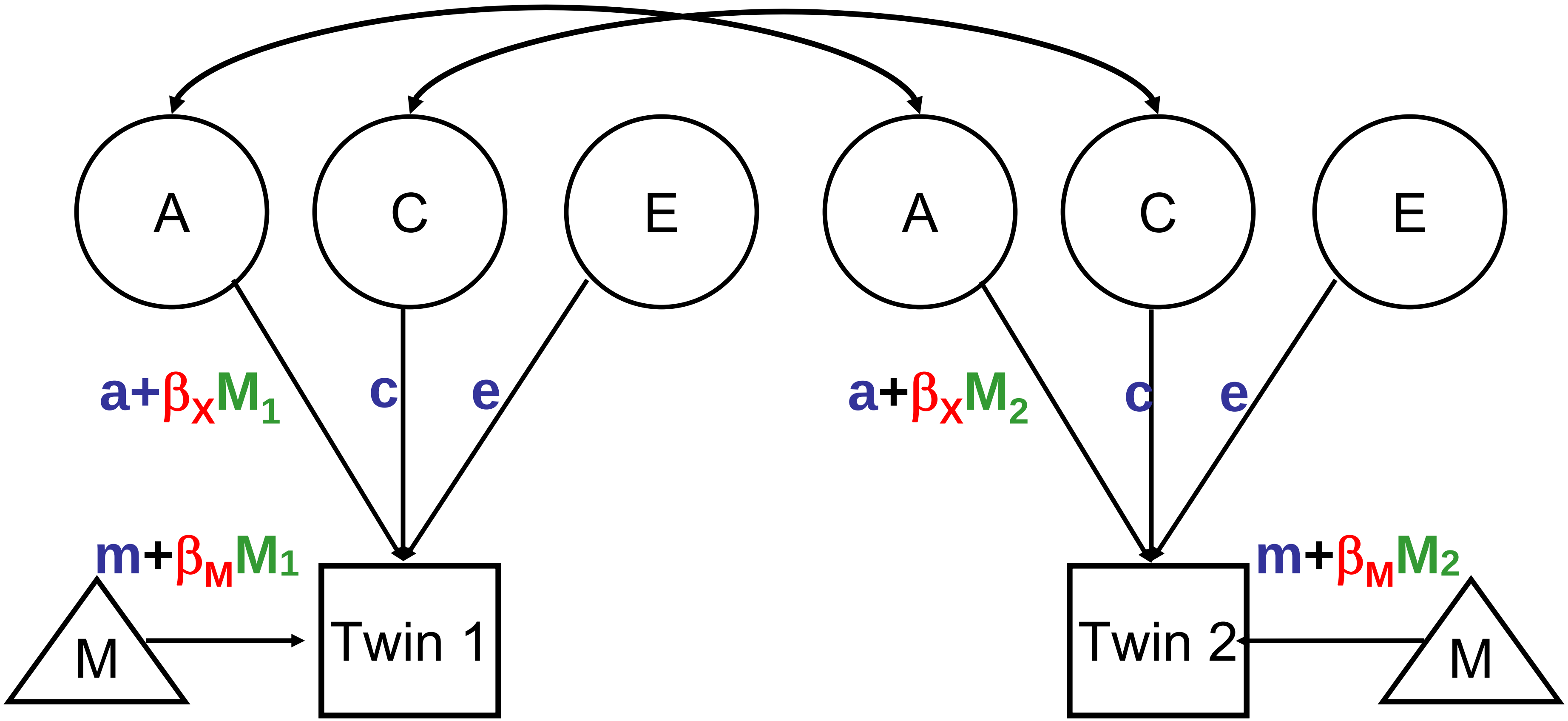
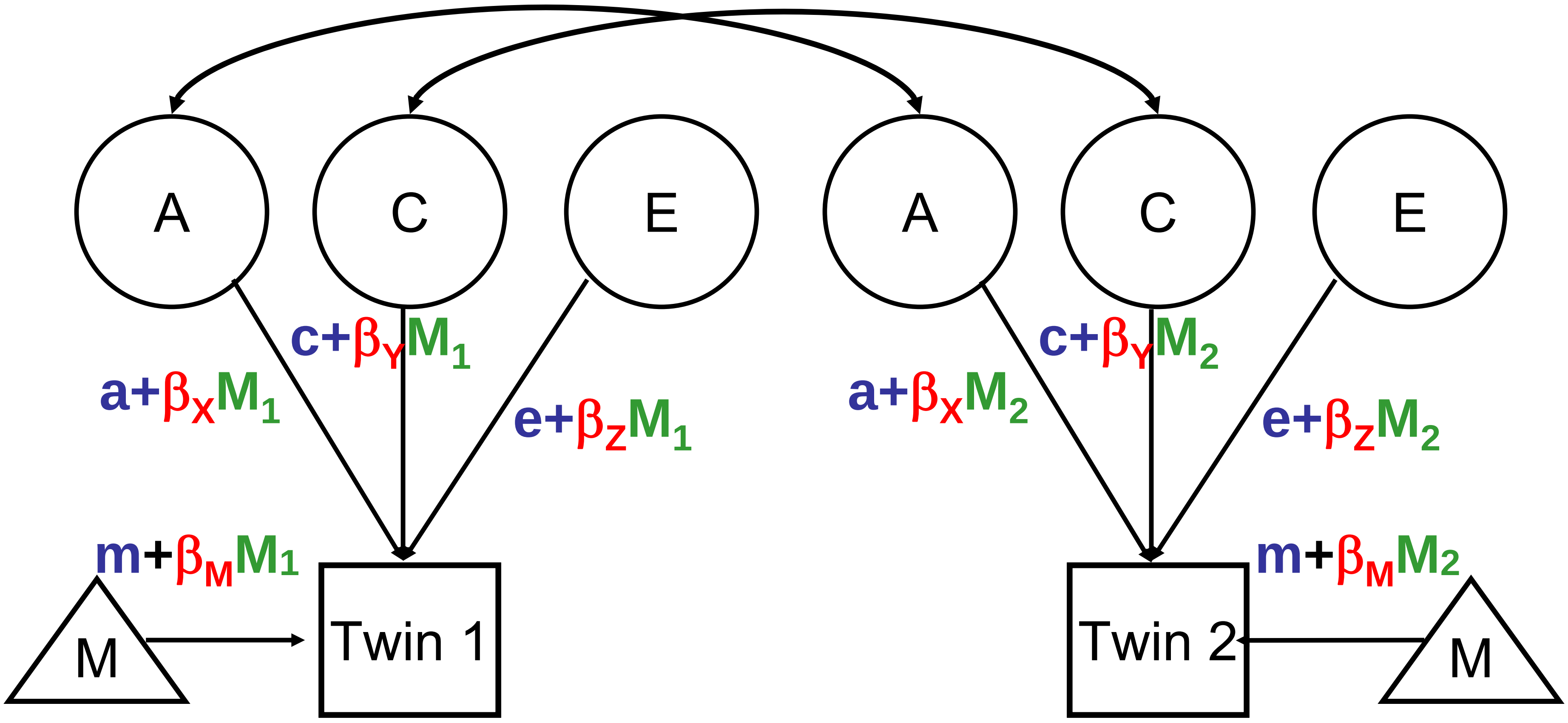
Model-fitting approach to GxE



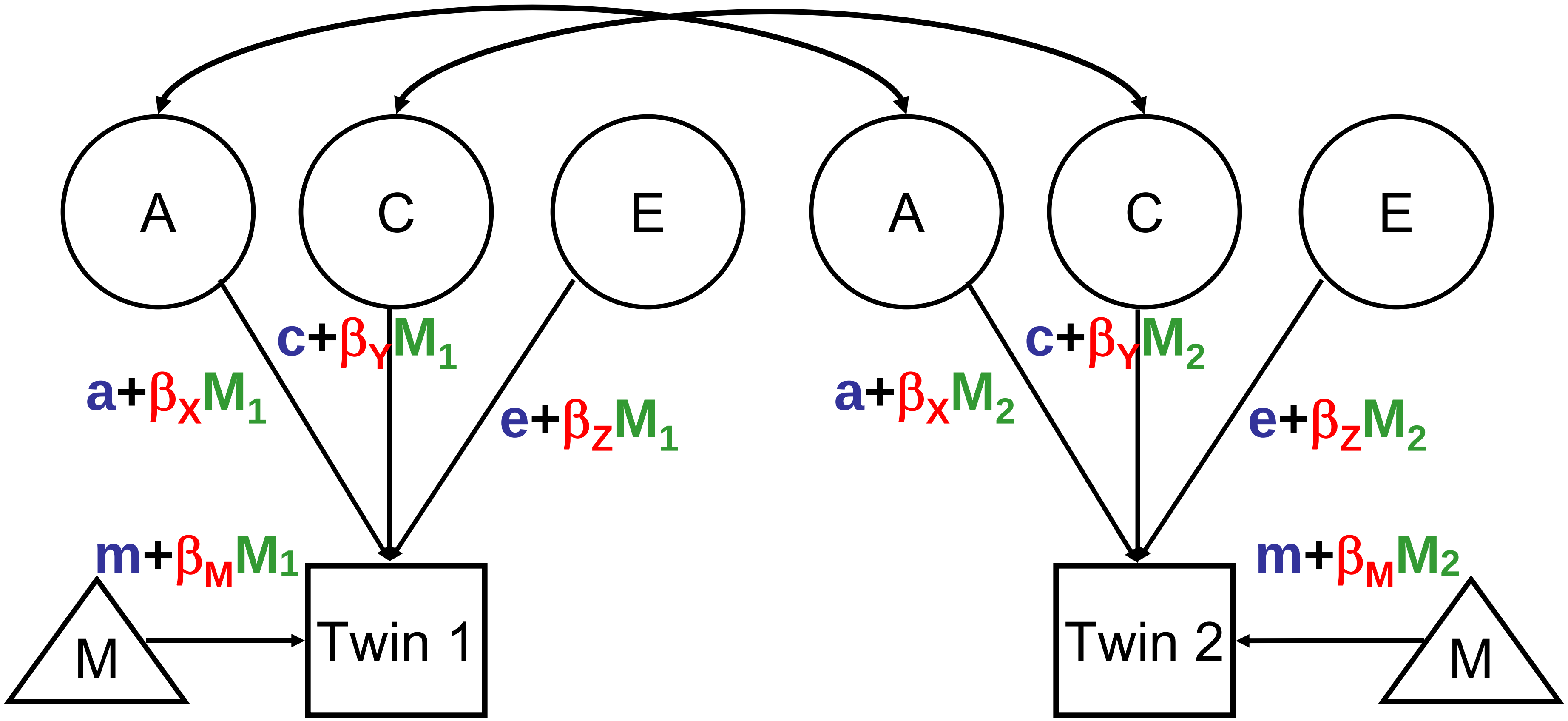
Individual specific moderators



E x E interactions

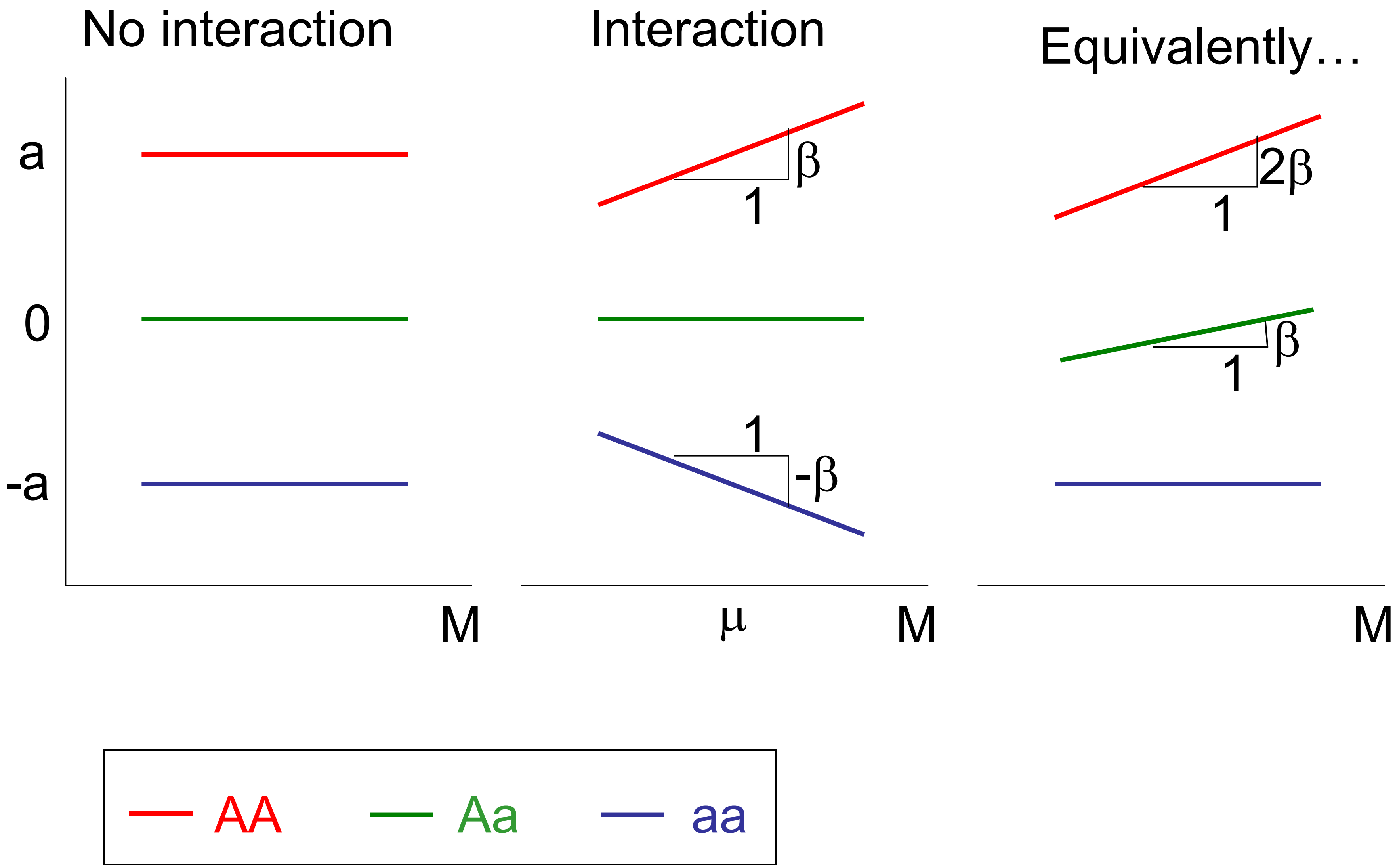


ACE - XYZ - M

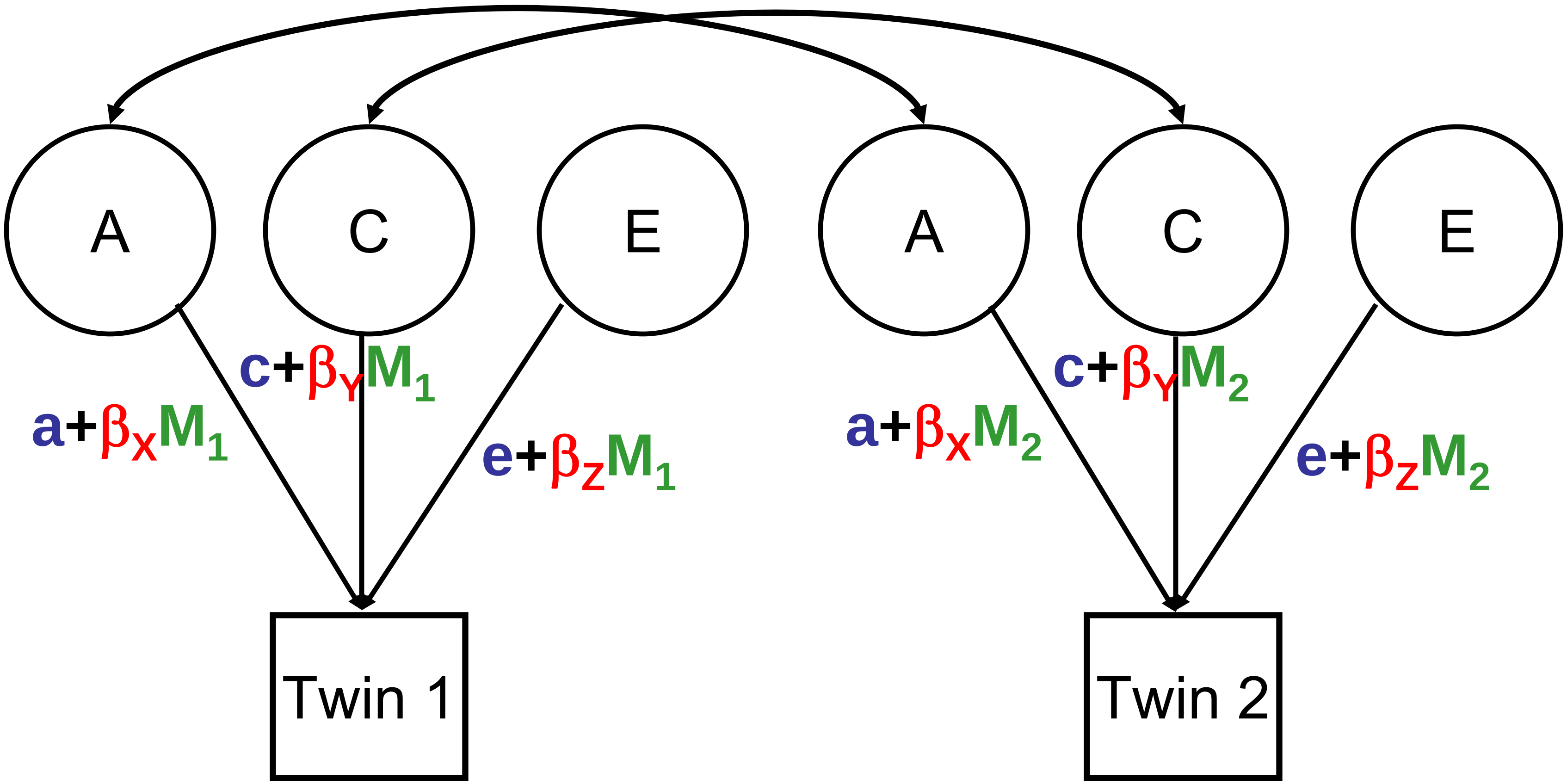


Main effects and moderating effects

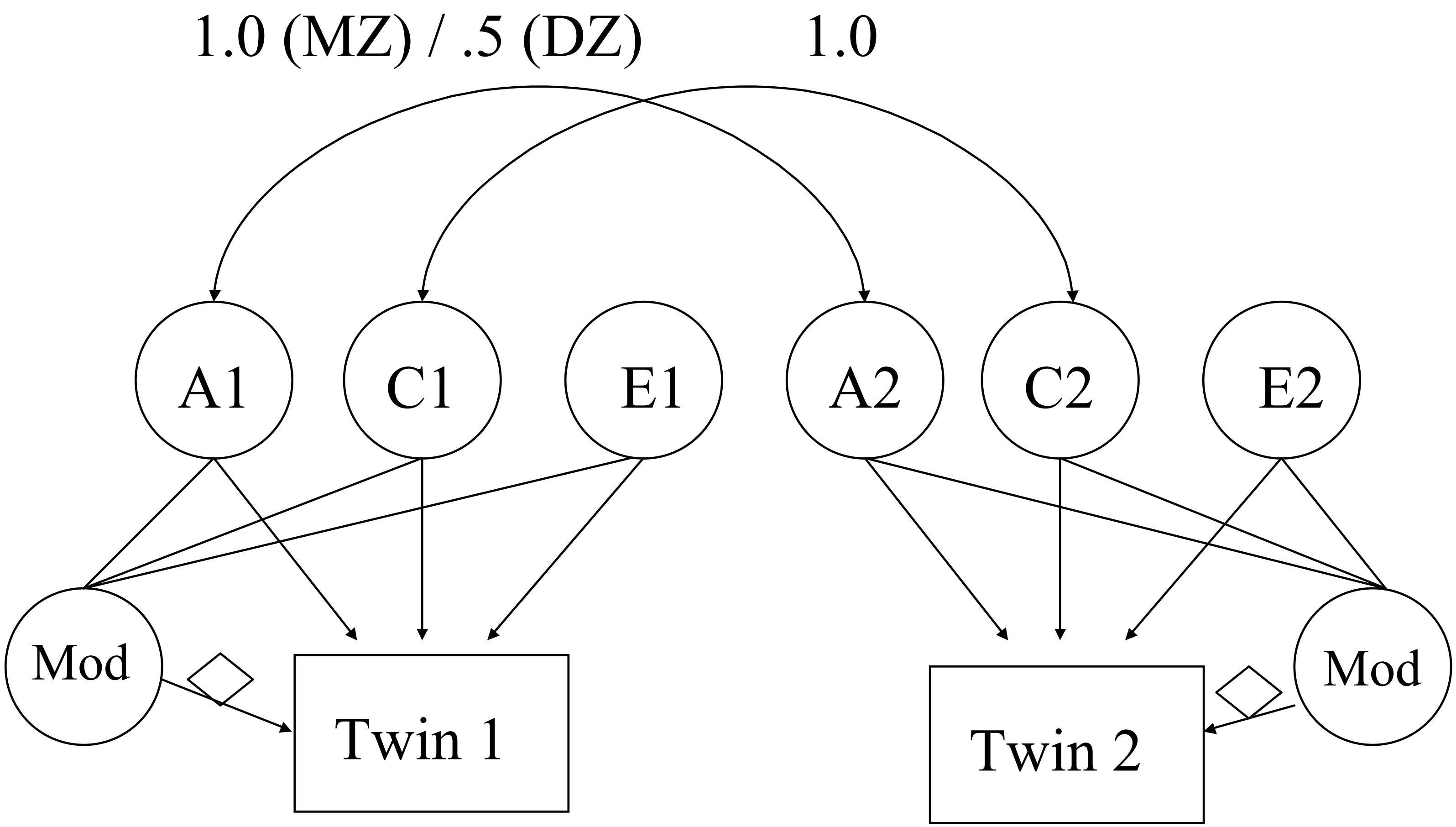
Biometrical G × E model



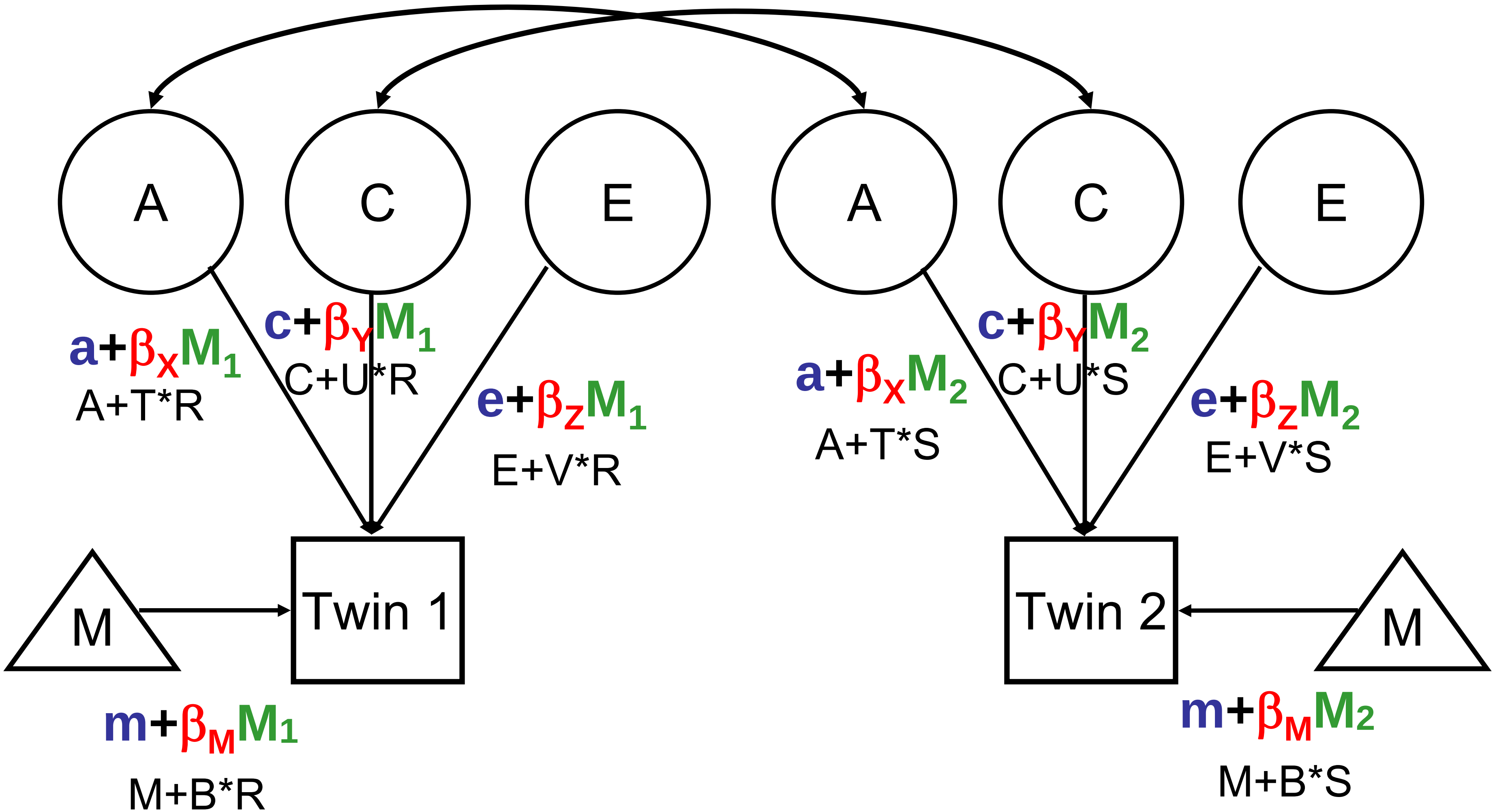
Moderation using Mx Script



Definition Variables in Mx



Matrix Letters as Specified in Mx Script



Practical - 1

- Fit GxE script
  - Is main effect of moderator significant?
  - Is A moderation significant?
  - Is C moderation significant?
  - Is E moderation significant?

Fit GxE script: Results

	-2LL	df	ΔLL	Δdf	p
Full Model					
Drop Main effect of Moderator					
Drop A Moderation					
Drop C Moderation					
Drop E Moderation					

Practical

- Fit GxE script
  - Is main effect of moderator significant?
    - Drop B 1 1 1
  - Is A moderation significant?
    - Drop T 1 1 1
  - Is C moderation significant?
    - Drop U 1 1 1
  - Is E moderation significant?
    - Drop V 1 1 1

Results

	-2LL	df	ΔLL	Δdf	p
Full Model	845.847	1119			
Drop Main effect of Moderator	846.434	1120	0.587	1	0.444
Drop A Moderation	857.056	1120	11.209	1	0.001
Drop C Moderation	847.443	1120	1.596	1	0.206
Drop E Moderation	947.697	1120	101.85	1	0.000

Practical - 2

- Calculate
  - What is genetic variance, common environmental variance, unique environmental variance
    - when there is no moderation?
    - at different levels of the moderator (calculate for -1.5,1.5)

$$\mathrm{Var}\,(T) = (a + \beta_X M)^2 + (c + \beta_Y M)^2\ (e + \beta_Z M)^2$$

Calculate Variances

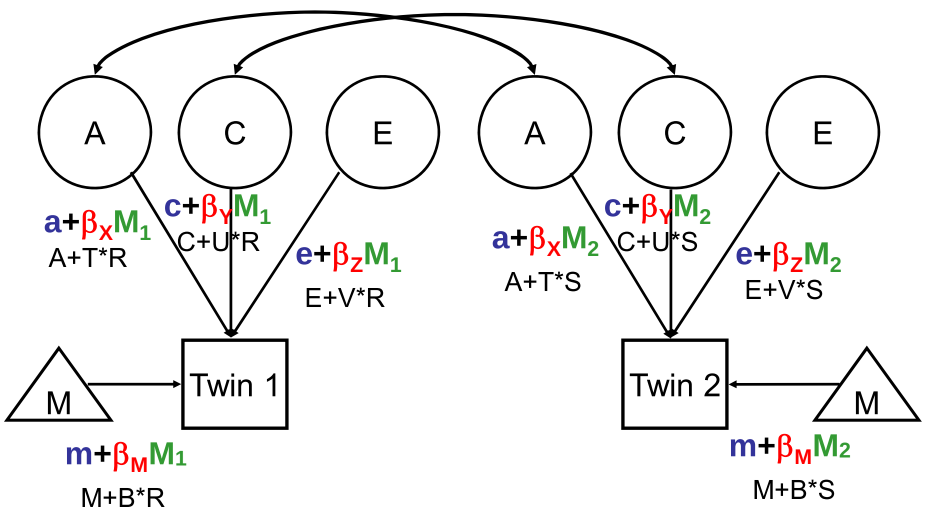
Squared variance components

Moderator values	A	C	E
-1.5			
0			
1.5			

Calculate Variance Components

$$Var\ (T) = (a + \beta_X M)^2 + (c + \beta_Y M)^2\ (e + \beta_Z M)^2$$

Matrix Letters as Specified in Mx Script

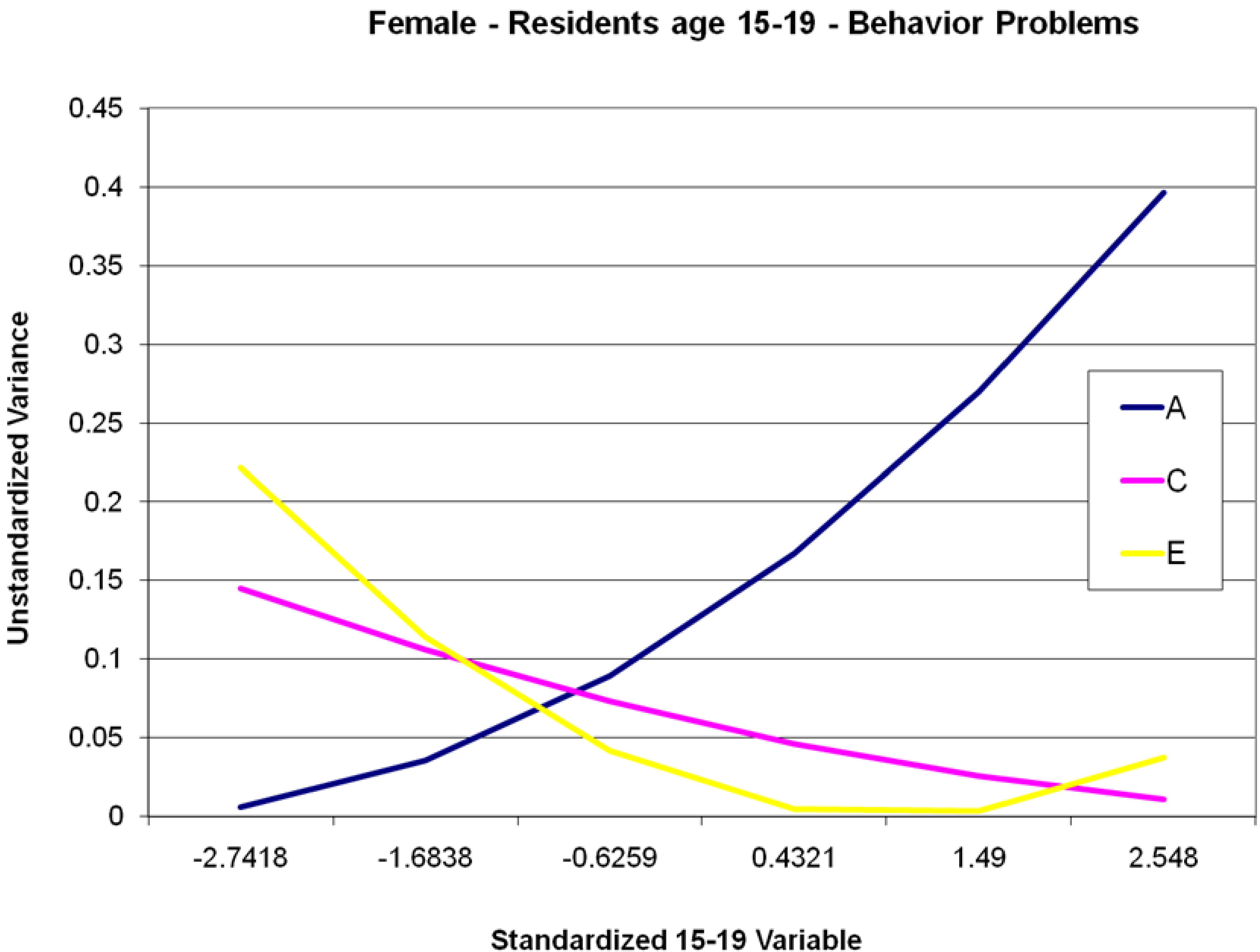


A	0.364
C	0.2375
E	0.1259
T	0.1042
U	-0.0522
V	-0.1259

Genetic variance: $(.364 + (.1042*1.5))^2$

Squared variance components

Moderator values	A	C	E
-1.5	0.043139	0.09973	0.099068
0	0.132496	0.056406	0.015851
1.5	0.270712	0.025345	0.003963


Female - Residents age 15-19 - Behavior Problems
Unstandardized Variance
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
-2.7418
-1.6838
-0.6259
0.4321
1.49
2.548
Standardized 15-19 Variable
A
C
E

Final Things to Consider

Unstandardized versus standardized effects

	ENVIRONMENT 1		ENVIRONMENT 2	
	Unstandardized Variance	Standardized Variance	Unstandardized Variance	Standardized Variance
Genetic	60	0.60	60	0.30
Common environmental	35	0.35	70	0.35
Unique environmental	5	0.05	70	0.05
Total variance	100		200	

Final Things to Consider

- Unstandardized versus standardized effects
- Don’t forget about theory!

- http://pngu.mgh.harvard.edu/~purcell/gxe/