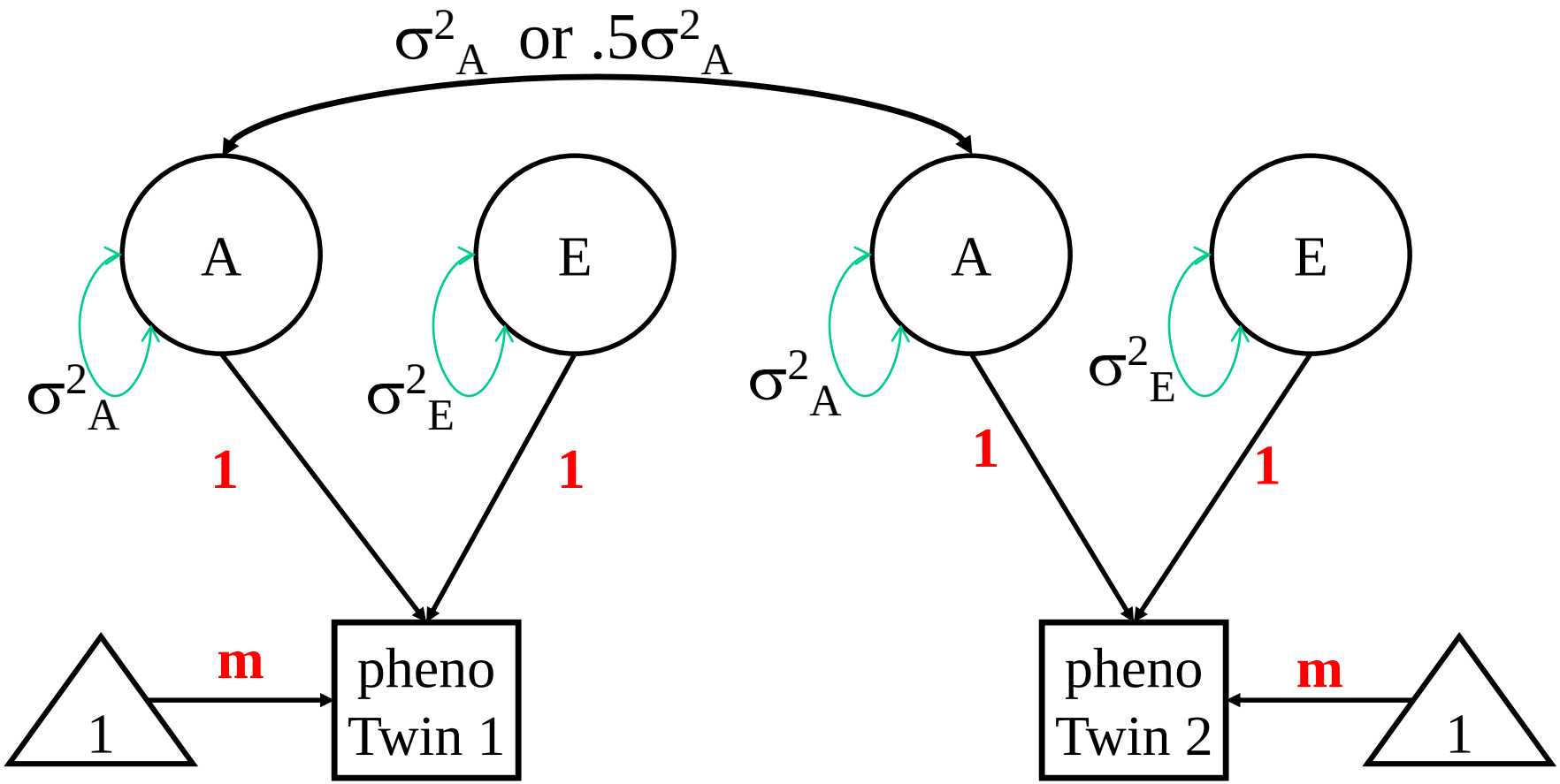
Continuously moderated effects of A,C, and E in the twin design

Conor V Dolan & Michel Nivard

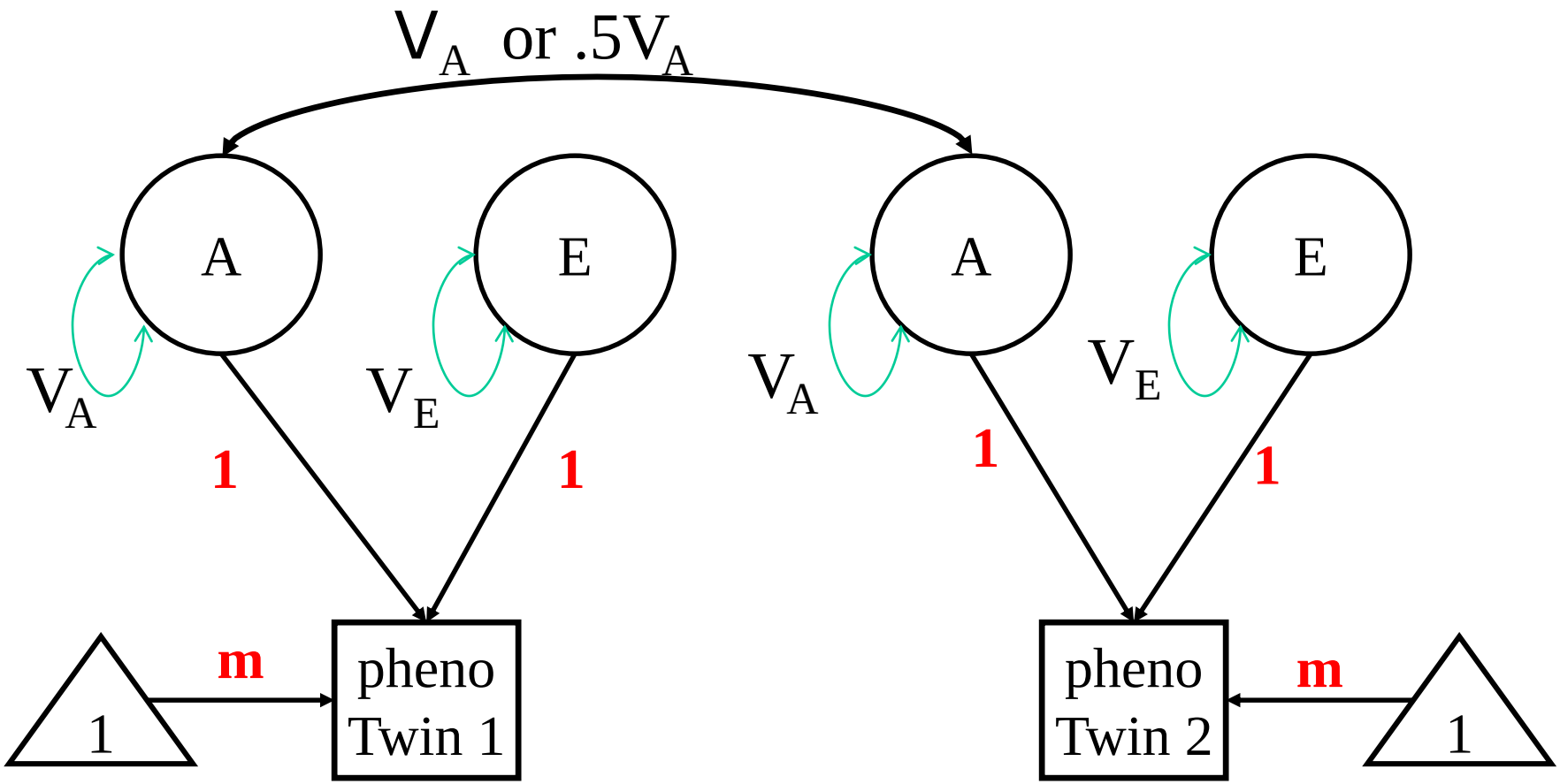
Boulder Twin Workshop
March, 2018

Standard AE model



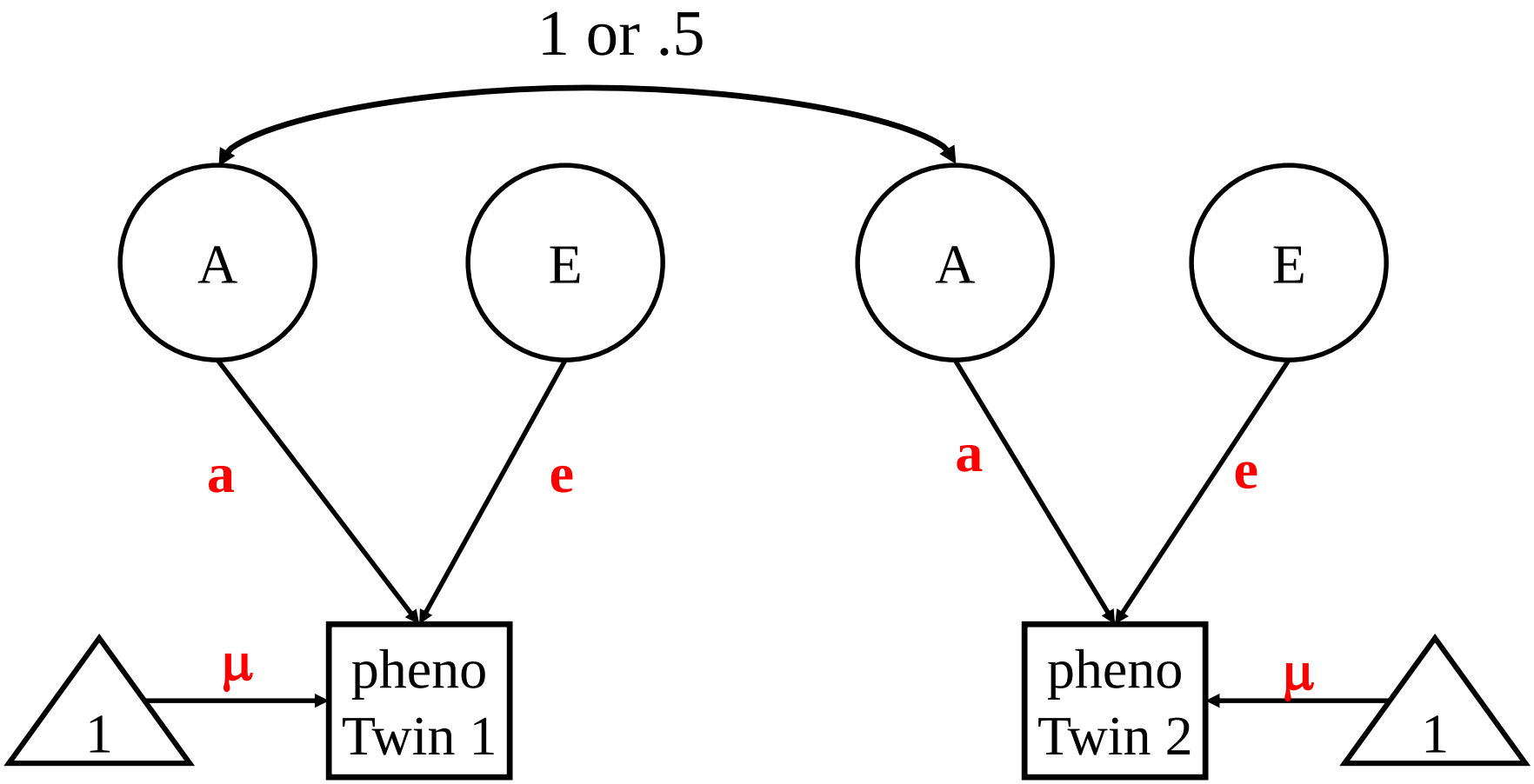
$$Ph_i - m = A_i + E_i$$

Standard AE model: Alt notation. $V_A = \sigma^2_A$



$$Ph_i - m = A_i + E_i$$

Standard AE model



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

When we fit this model we assume that the model holds in the population of interest (z=zygosity, mz or dz; r_z=1 or .5)

$$\boldsymbol{\Sigma}_z = \begin{matrix} \sigma^2_A + \sigma^2_E & r_z\sigma^2_A \\ r_z\sigma^2_A & \sigma^2_A + \sigma^2_E \end{matrix}$$

$$\boldsymbol{\mu} = \begin{matrix} \mu \\ \mu \end{matrix}$$

Phenotypic variable ~ $N(\mu, \sigma^2_A + \sigma^2_E)$ normally distributed with mean μ and variance $\sigma^2_A + \sigma^2_E$

What if we have two populations of interest, e.g., males and females?

* main effect of sex on phenotype $\mu_f \neq \mu_m$?

* sex by A, E interactions
(sex as moderator of A,E variances):
$\sigma^2_{Af} \neq \sigma^2_{Am}$ and / or $\sigma^2_{Ef} \neq \sigma^2_{Em}$?

If we ignore the source of "heterogeneity"
the estimates of μ, σ^2_E, σ^2_A are biased ... BAD!

What to do?

Include source of heterogeneity, moderator,
in the model:

Main effects of moderator $\mu_f \neq \mu_m$?
Interaction effects $\sigma^2_{Af} \neq \sigma^2_{Am}$ and / or $\sigma^2_{Ef} \neq \sigma^2_{Em}$?

If moderator is binary – multigroup model
If moderator is continuous – moderation model

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

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

1977

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

Acta Genet Med GemelloI36:5·20 (1987)

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

1987

N.G. Martin[1], L.J. Eaves, A.C. Heath

Department of Human Genetics, Medical College of Virginia, Richmond, USA

(Open)Mx

Michael C.Neale

& team

1994 - 2018

Twin Research Volume 5 Number 6 pp. 554- 571

Variance Components Models for Gene–Environment Interaction in Twin Analysis

2002

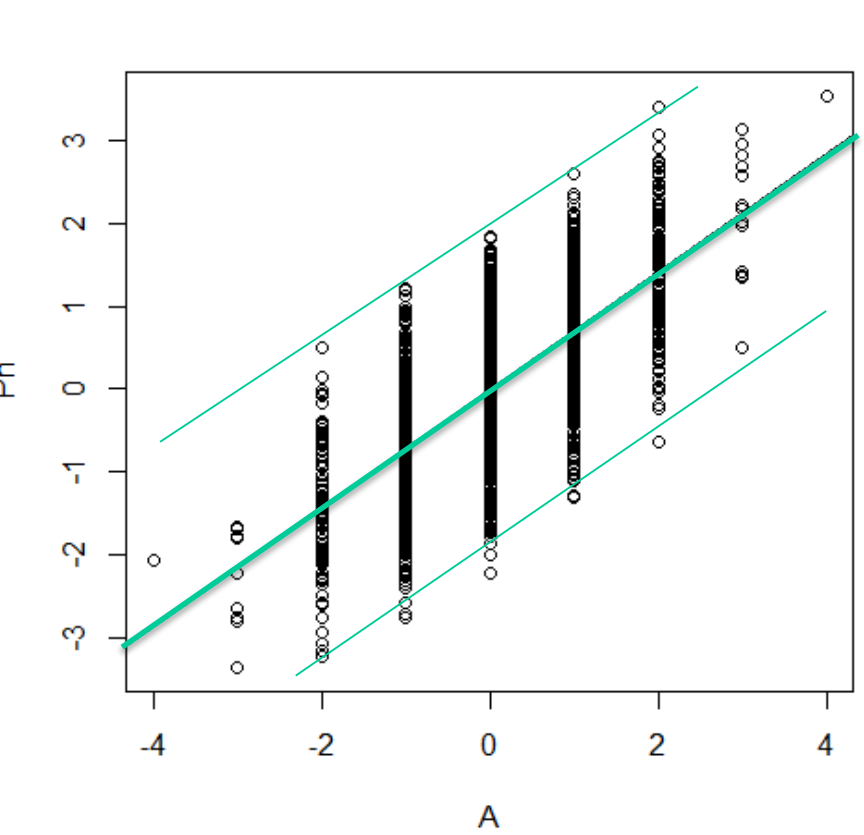
Shaun Purcell

Social, Genetic and Developmental Psychiatry Research Centre, Institute of Psychiatry, King's College, London, UK

MANY PAPERS Substantive & Methods

see
https://genepi.qimr.edu.au/staff/classicpapers/

What is moderation? What is GxE interaction



Phenotypic scores

Environmental Dispersion

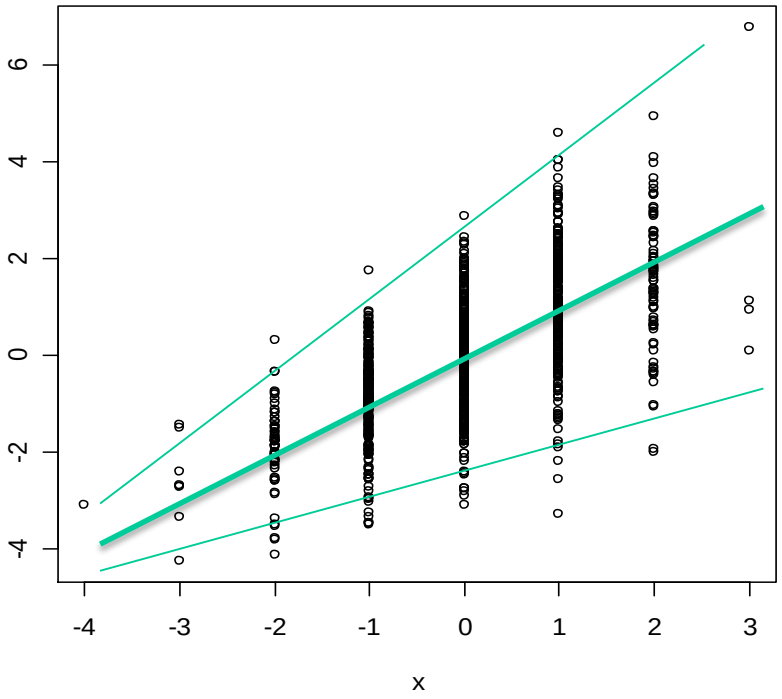
Variance of E given G score

Genetic level (score on A)

$$Ph_i - m = \mathbf{a}*A_i + \mathbf{e}*E_i$$

Homoskedastic model: **e** is **constant** over levels of A: environmental effects are the same given any A

Phenotypic scores



Environmental Dispersion

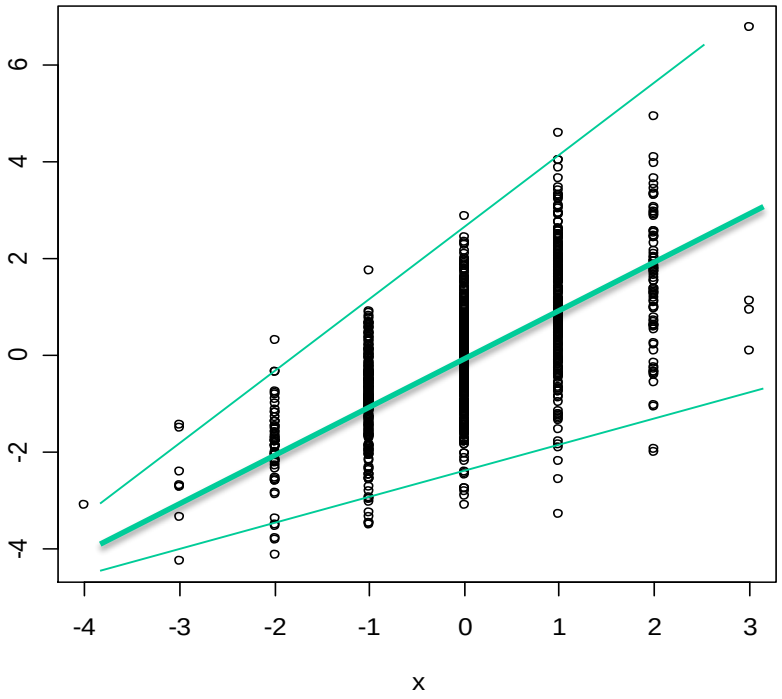
Variance of E given G score

Genetic level (score on A)

G x E as "genetic control" of sensitivity to different environments: heteroskedasticity **e**=$f_e(A)$ or $\sigma^2_E = g_e(A)$

Environmental effects (**E**) systematically vary with A

Phenotypic scores

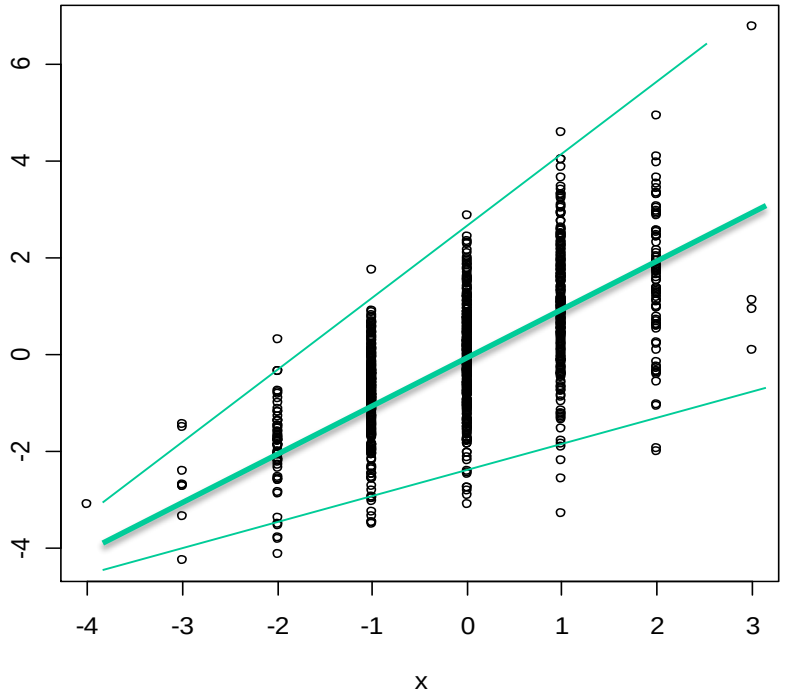


Conditional variance of A given E

Environmental level (score on E)

G x E as "environmental control" of genetic effects: heteroskedasticity (**a**=$f_a(E)$ or $\sigma^2_A = g_a(E)$).

Phenotypic scores



Genetic variance or (and) Environmental variance given M

Moderator level (score on moderator)

Moderation of effects (A,C,E) by measured moderator M: heteroskedasticity (**a**=$f_a(M)$, **c**=$f_c(M)$, **e**=$f_e(M)$ or ($\sigma^2_A = g_a(M)$, $\sigma^2_C = g_c(M)$, $\sigma^2_E = g_e(M)$).).

Sex X A interaction: Sex moderation of A effects

Is the magnitude of genetic influences on ADHD the same in boys and girls?

$\sigma^2_{Af} = \sigma^2_{Am}$?

Other examples binary moderators

A effects moderated by marital status:
Unmarried women show greater levels of genetic influence on depression (Heath et al., 1998).

A effects moderated by religious upbringing:
religious upbringing diminishes A effects on the personality trait of disinhibition (Boomsma et al., 1999).

Binary moderator: multigroup approach

Continuous moderation

Age as a moderator of standardized A, C, E variance components (Age x A,C,E interaction)

Research Article

aps ASSOCIATION FOR PSYCHOLOGICAL SCIENCE

Psychological Science
1–12
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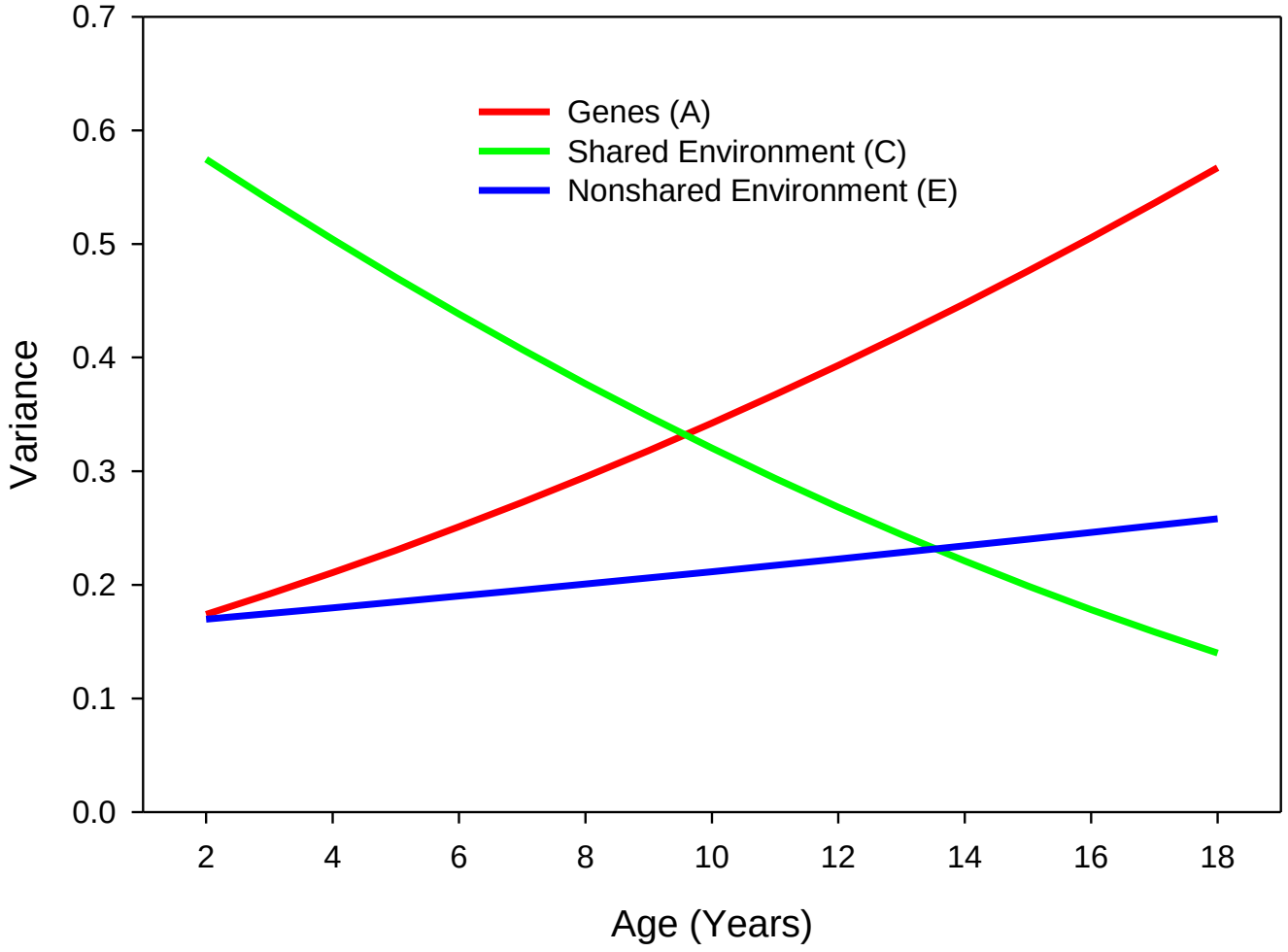
DOI: 10.1177/0956797615612727
pss.sagepub.com
SAGE

Large Cross-National Differences in Gene × Socioeconomic Status Interaction on Intelligence

Elliot M. Tucker-Drob[1,2] and Timothy C. Bates[3]
[1]Department of Psychology, University of Texas at Austin; [2]Population Research Center, University of Texas at Austin; and [3]Department of Psychology, University of Edinburgh



Tucker-Drob & Bates (2015)

A,C,E effects moderated by SES

PSYCHOLOGICAL SCIENCE

Research Article

SOCIOECONOMIC STATUS MODIFIES HERITABILITY OF IQ IN YOUNG CHILDREN

Eric Turkheimer, Andreana Haley, Mary Waldron, Brian D'Onofrio, and Irving I. Gottesman

PSYCHOLOGICAL SCIENCE

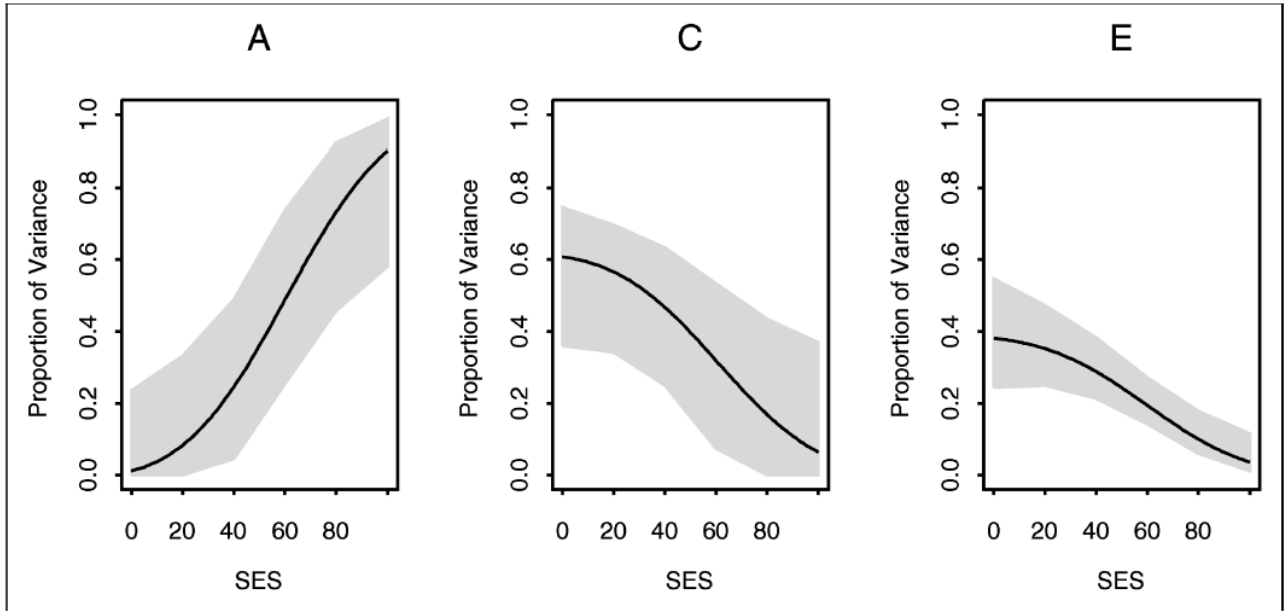


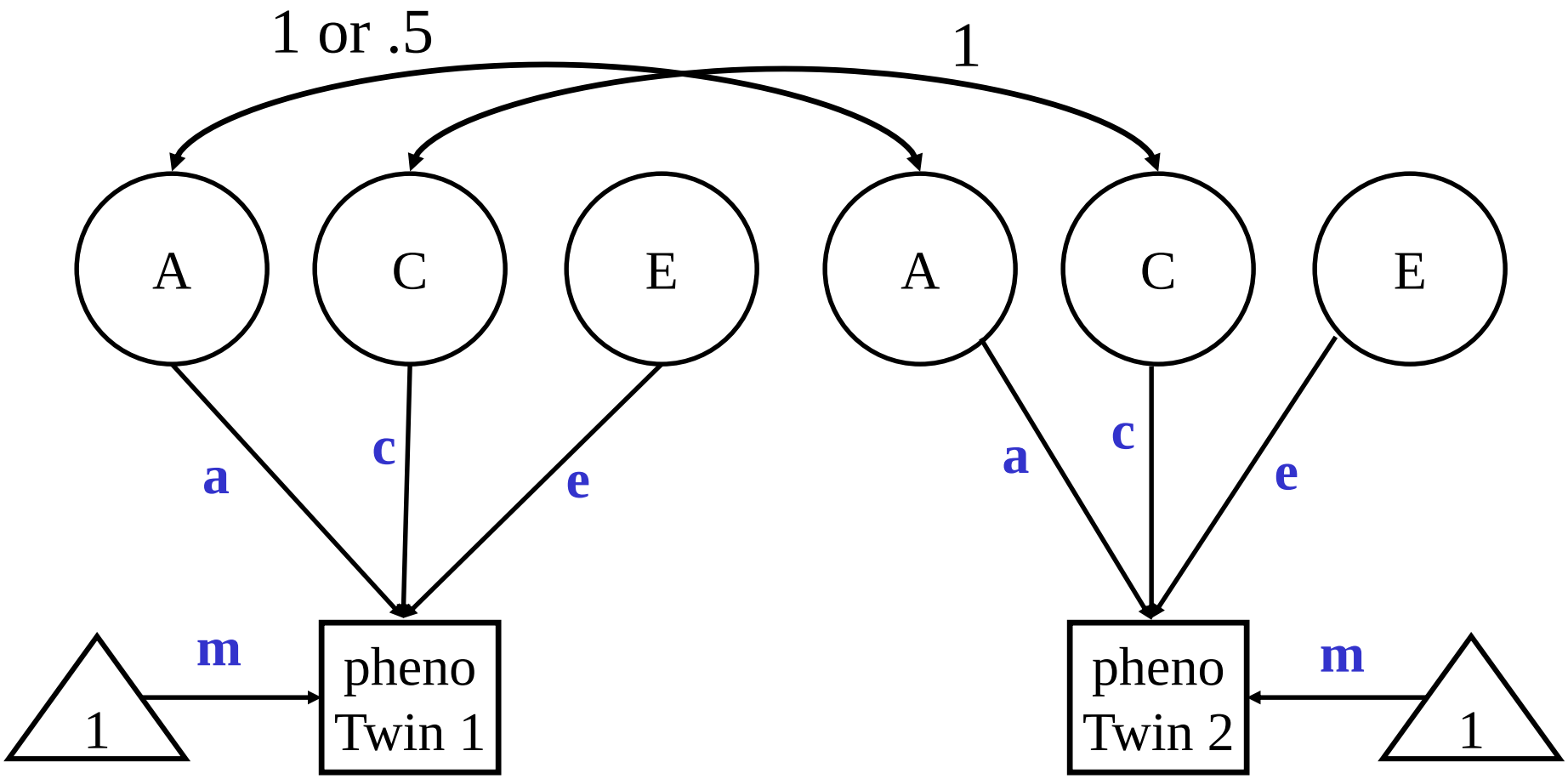
Fig. 3. Proportion of total Full-Scale IQ variance accounted for by A, C, and E plotted as a function of observed socioeconomic status (SES). Shading indicates 95% confidence intervals.

Continuous Moderators
not amenable to multigroup approach

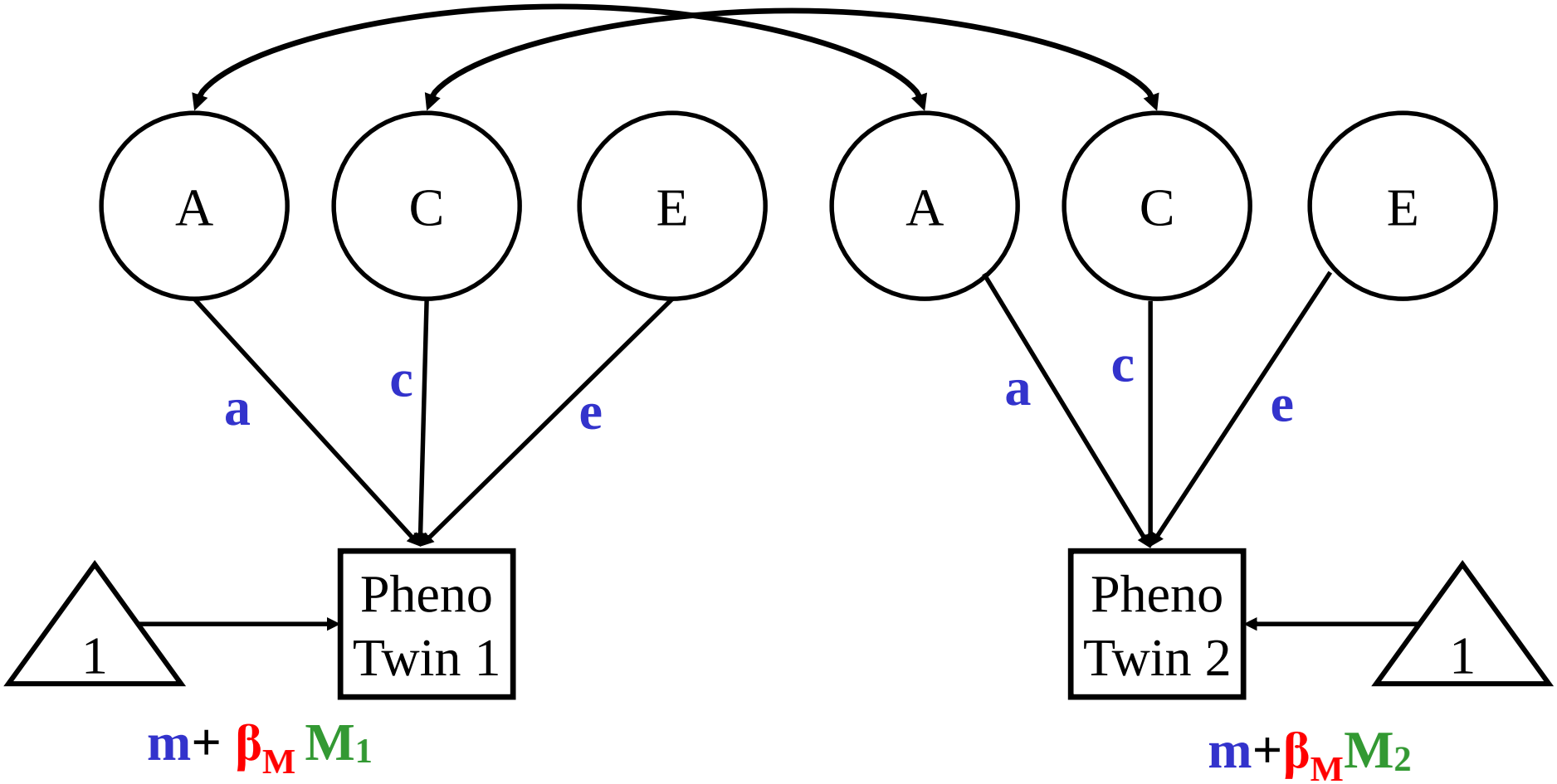
…

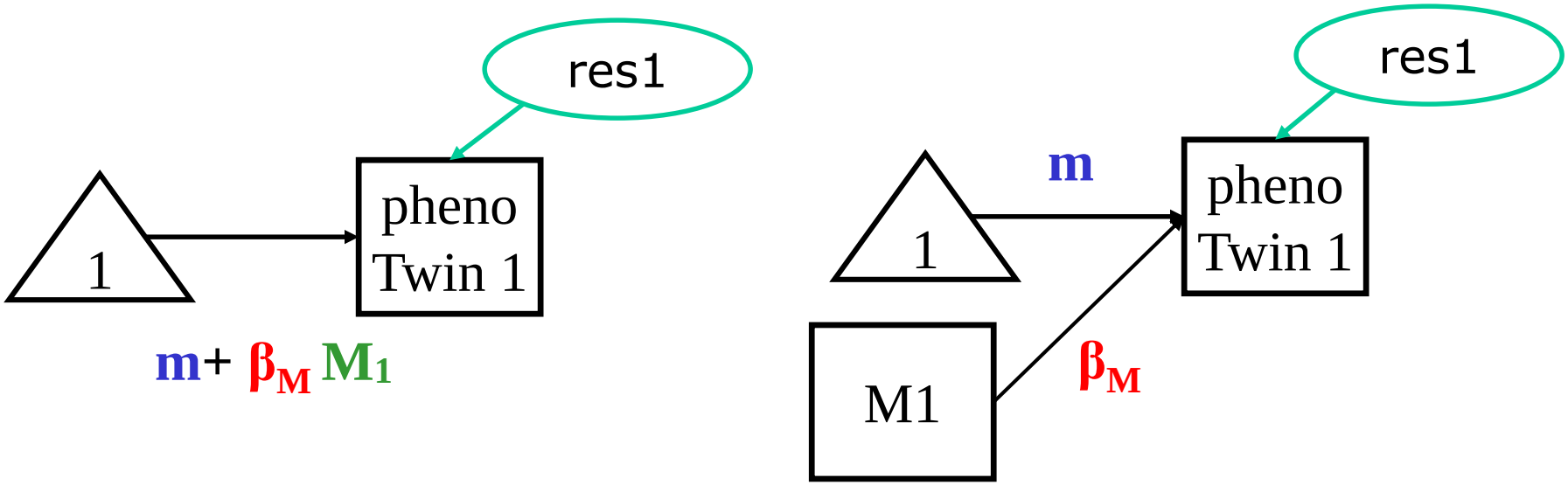
treat the moderator as continuous
(OpenMx and umx)

Standard ACE model



Standard ACE model + Main effect on Means





equivalent

The regression of Phenotype on M ...

pheno1 = **m**+ β_M M_1 + res1

What is left is the residual (res1), which is subject to (moderated) ACE modeling.

Summary stats (no moderator)

- Means vector

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

- Covariance matrix (r_z = r = 1 or ½)

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

Allowing for a main effect of the moderator M

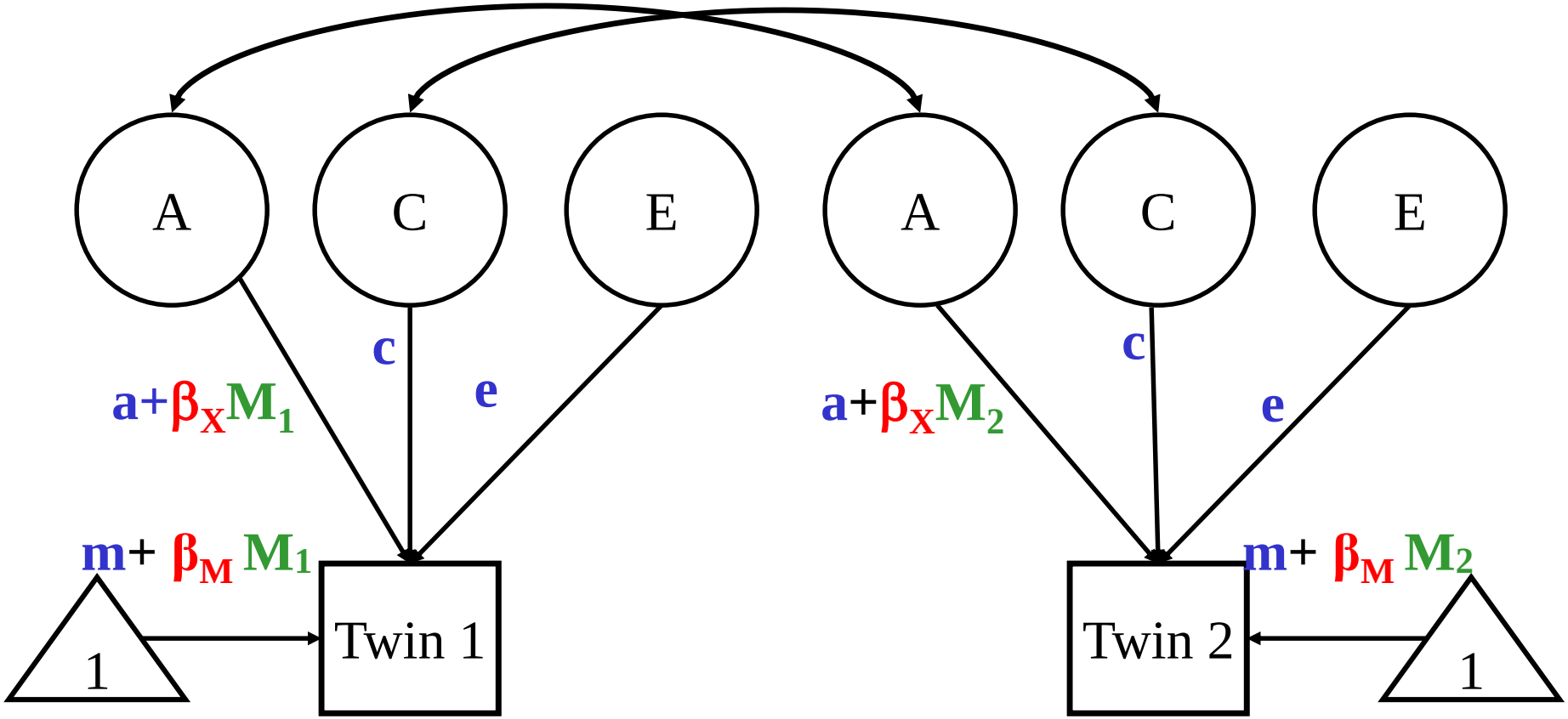
- Means vector (conditional on M)

$$\begin{pmatrix} m+\beta_{\mathrm{M}}M_{1i} & m+\beta_{M}M_{2i} \end{pmatrix}$$

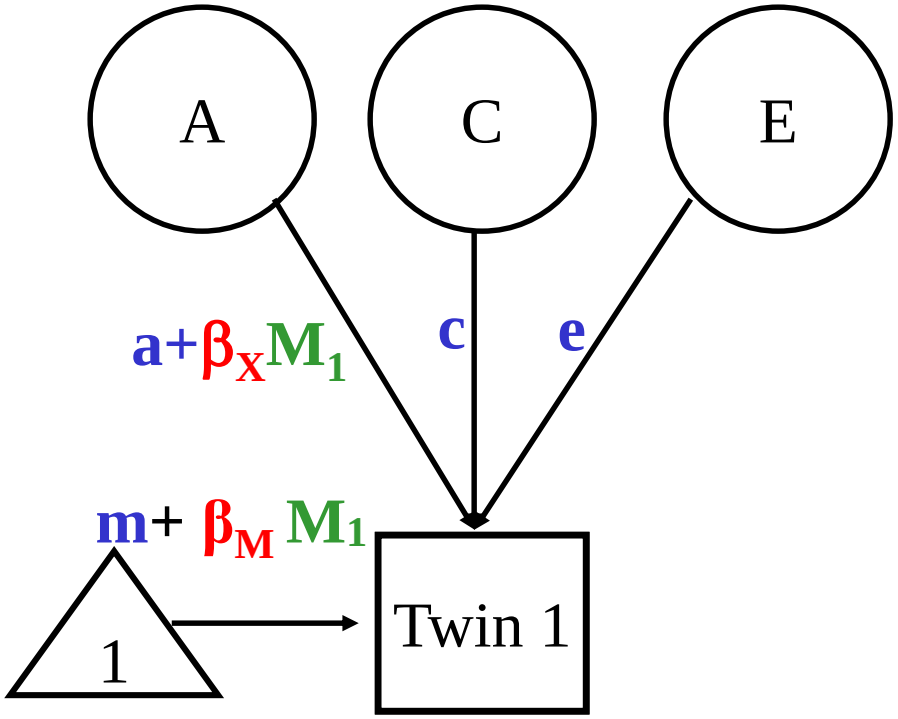
- Covariance matrix (r = 1 or r=½)

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

Standard ACE model + main effect and effect on A path



M has main effect + moderation of A effect ($a + \beta_M M_1$)

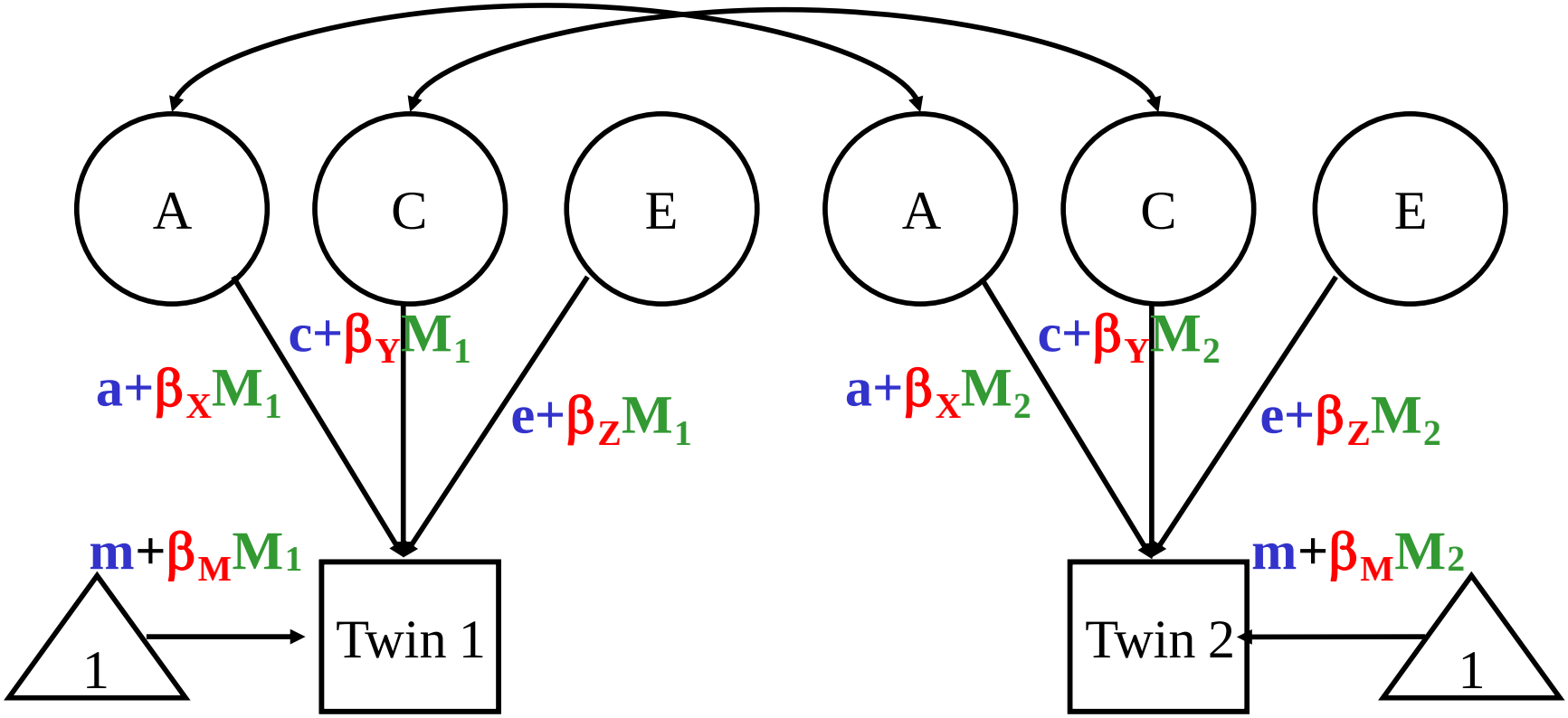


If M is binary (0/1) (instead of continuous)

M_1=0 → mean= **m** & A effect = **a**

M_1=1 → mean= **m**+ β_M & A effect = **a**+β_X

variance = $(a+\beta_X)^2$



- Main Effect on phenotype (linear regression)
- Effect path loadings: Moderation effects (A x M, C x M, E x M interaction)

Expected **variances**

Standard Twin Model:

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

Moderation Model:

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

P|M mean “the phenotype given a value on M” or “the phenotype conditional on M”

Expected MZ / DZ covariances

$$Cov(P_1,P_2|M)_{MZ} = (a + \beta_X M)^2 + (c + \beta_Y M)^2$$

$$Cov(P_1,P_2|M)_{DZ} = 0.5*(a + \beta_X M)^2 + (c + \beta_Y M)^2$$

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

$$h_{st}^2|M = (a + \beta_X M)^2 / \text{Var}(P|M)$$

$$c_{st}^2|M = (c + \beta_Y M)^2 / \text{Var}(P|M)$$

$$e_{st}^2|M = (e + \beta_Z M)^2 / \text{Var}(P|M)$$

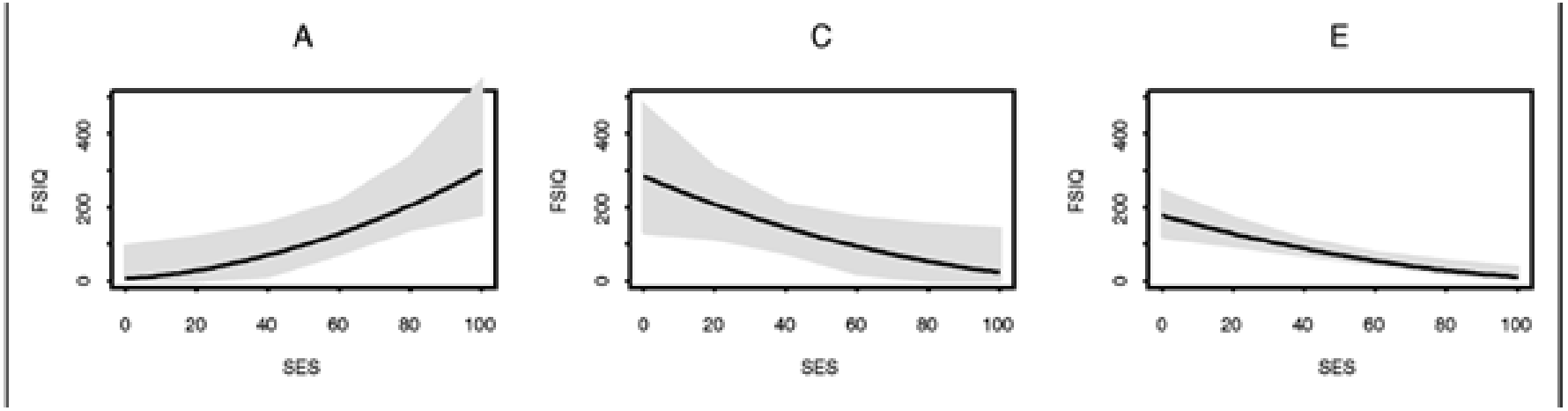
$$(h_{st}^2|M + c_{st}^2|M + e_{st}^2|M) = 1$$

Standardized conditional on value of M..

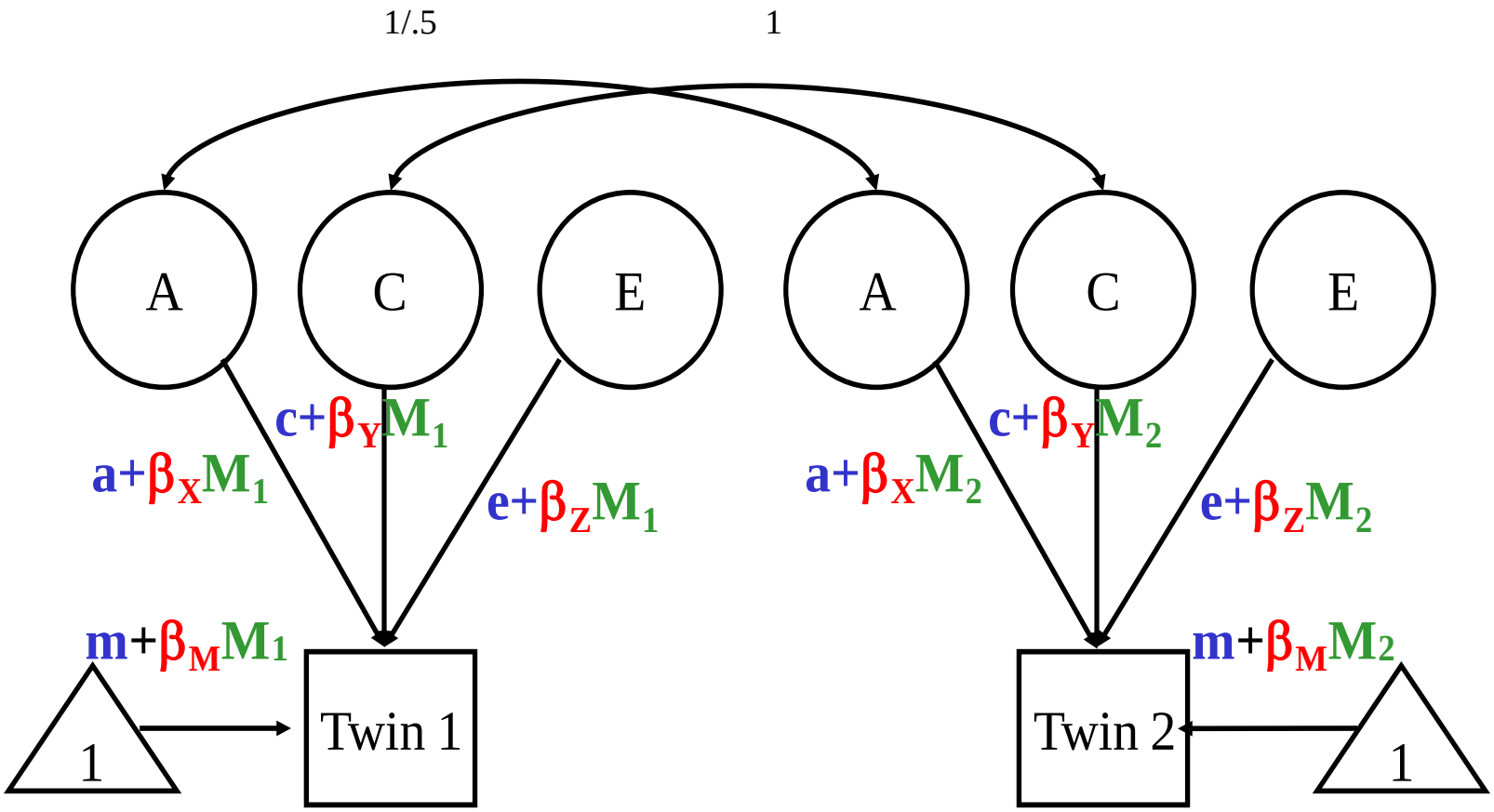
WARNING $h_{st}^2|M$ can vary with M while $\beta_X = 0$!

Turkheimer study SES

Moderation of **unstandardized** variance components

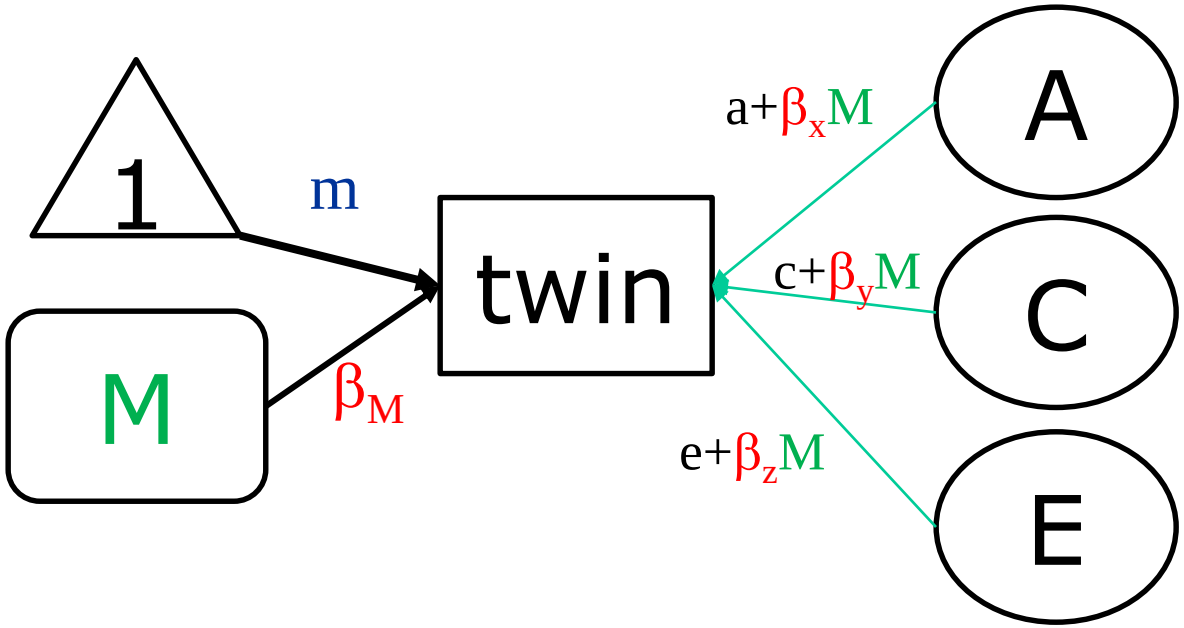


raw variance components good!



But what have we assumed concerning M?

The M is a measured variable



M is <u>environmental?</u>

(sociaal support, employment, marital status)

“Environmental” measures display genetic variance

See Kendler & Baker, 2006

Psychological Medicine, 2007, **37**, 615–626.
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]

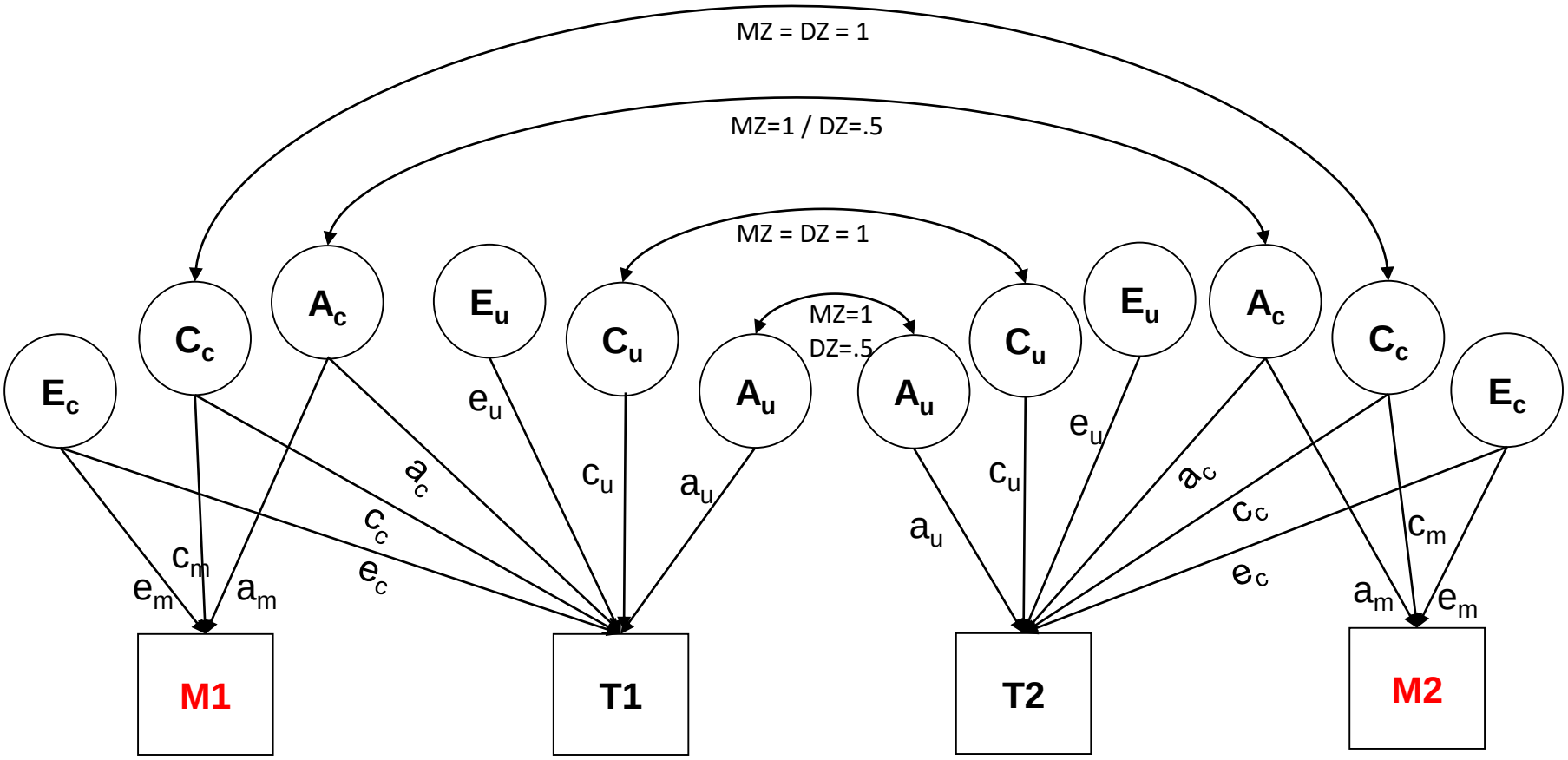
See Plomin & Bergeman, 199

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]

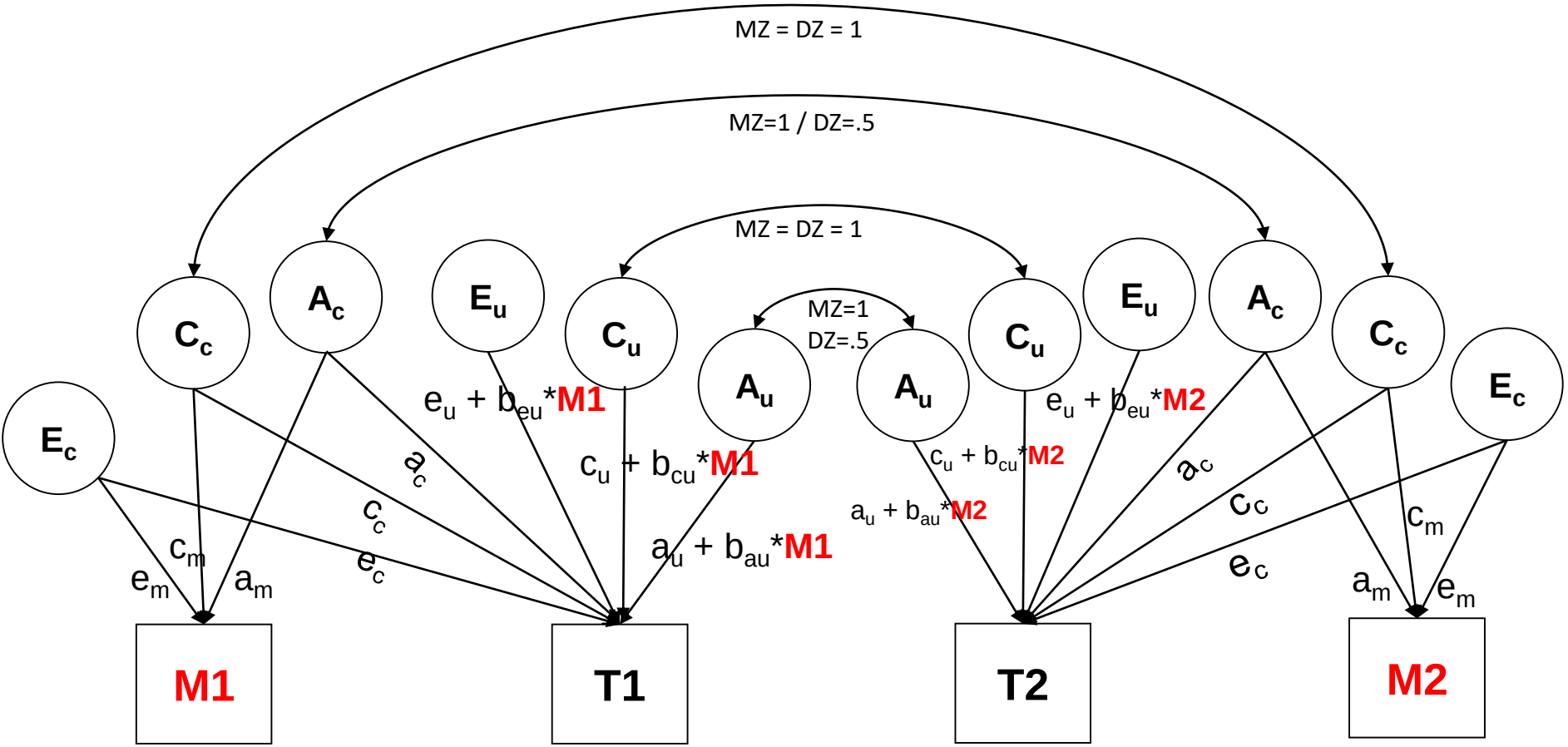
Full bivariate model



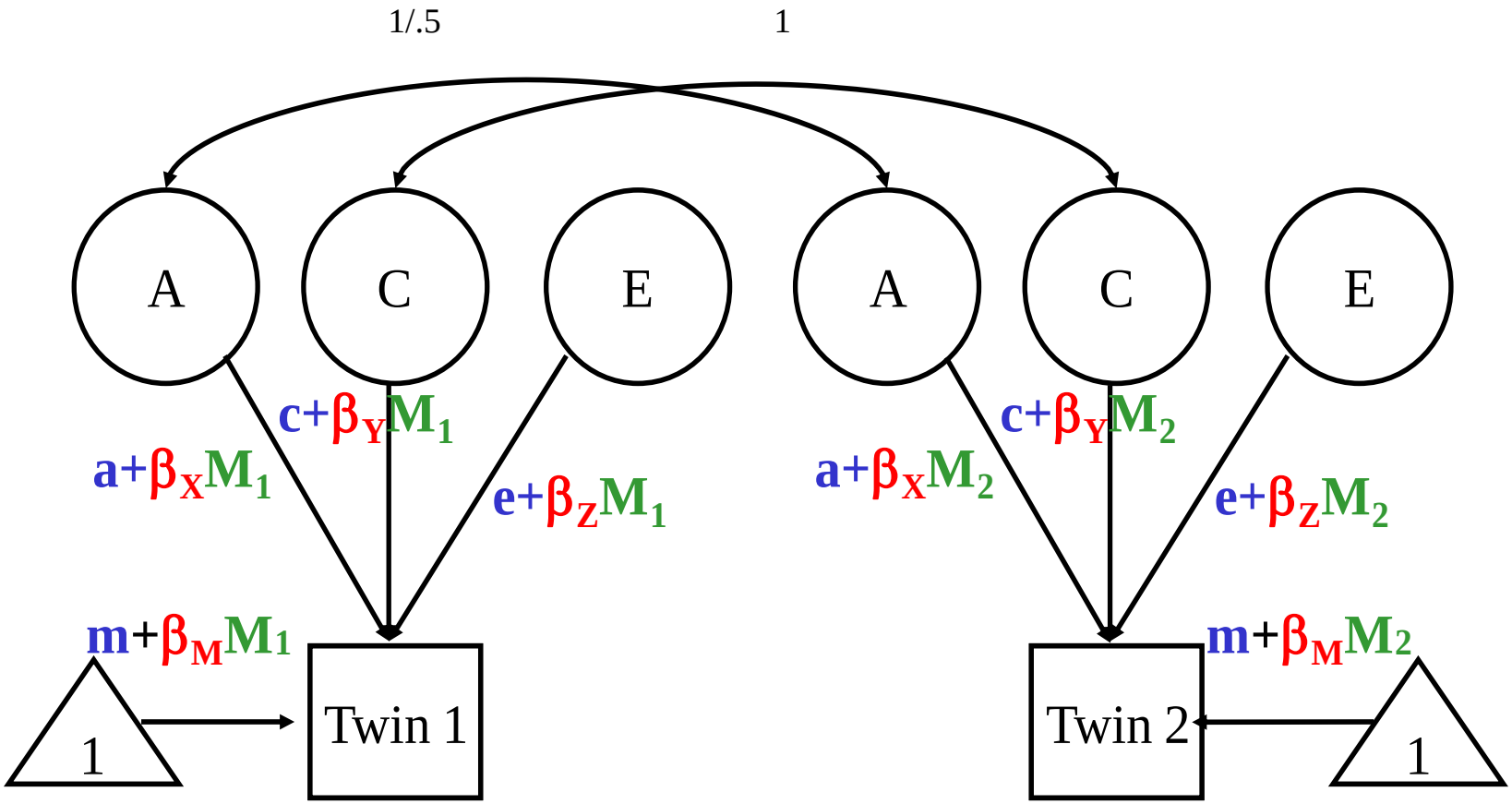
$$var(T) = \{e_c^2+c_c^2+a_c^2\} + \{e_u^2+c_u^2+a_u^2\}$$

shared with M unique to T

M with its own ACE + ACE cross loadings.

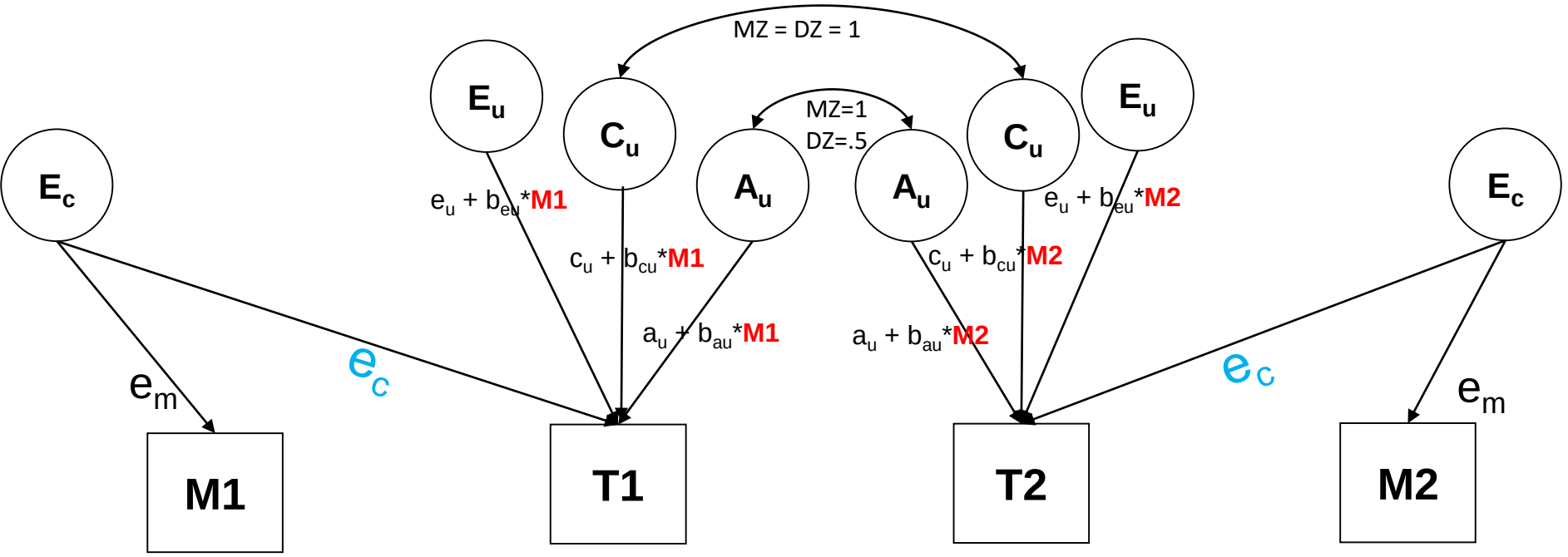


Can we treat M in this manner?

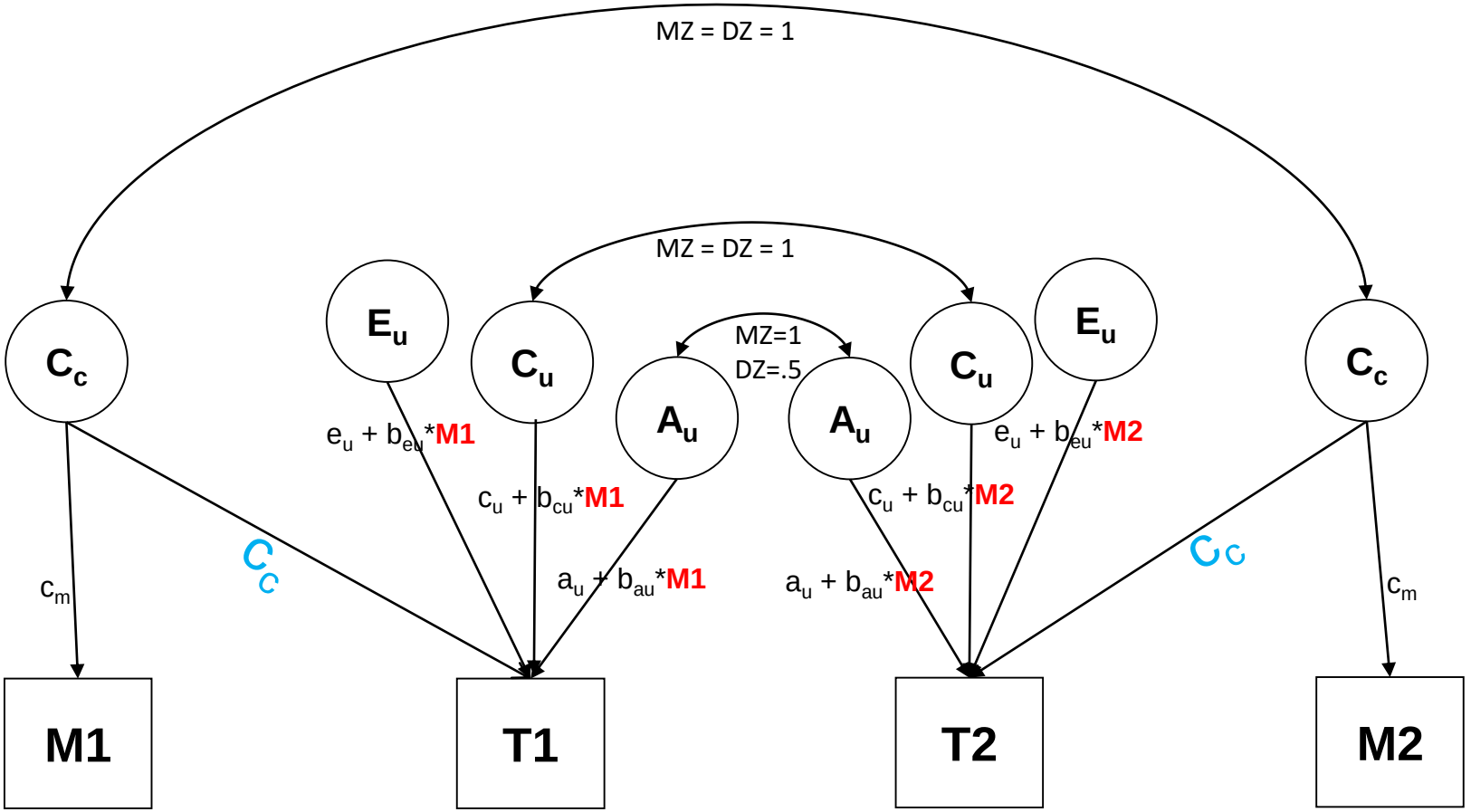


Not generally....

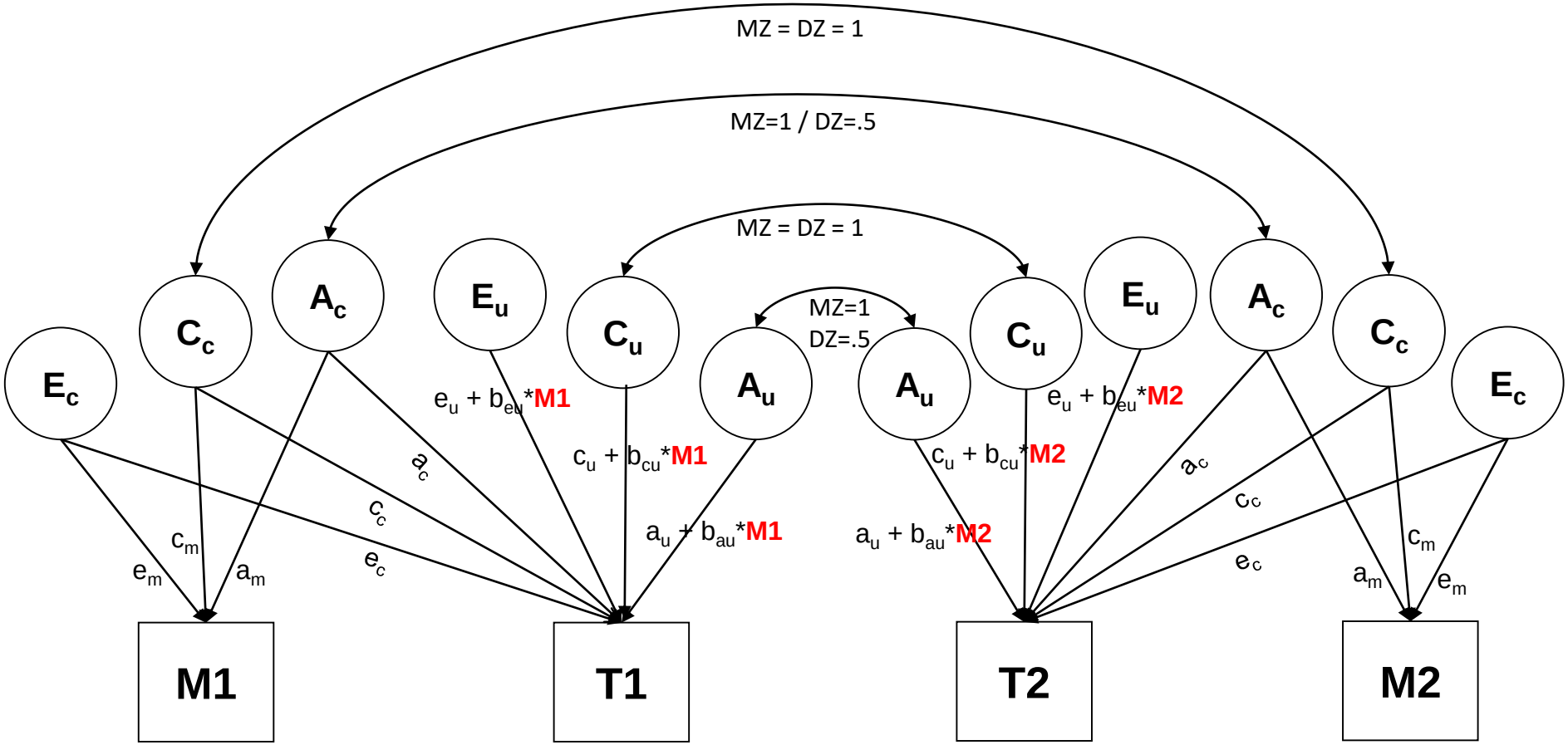
OK if #1: r(M1,M2) = 0

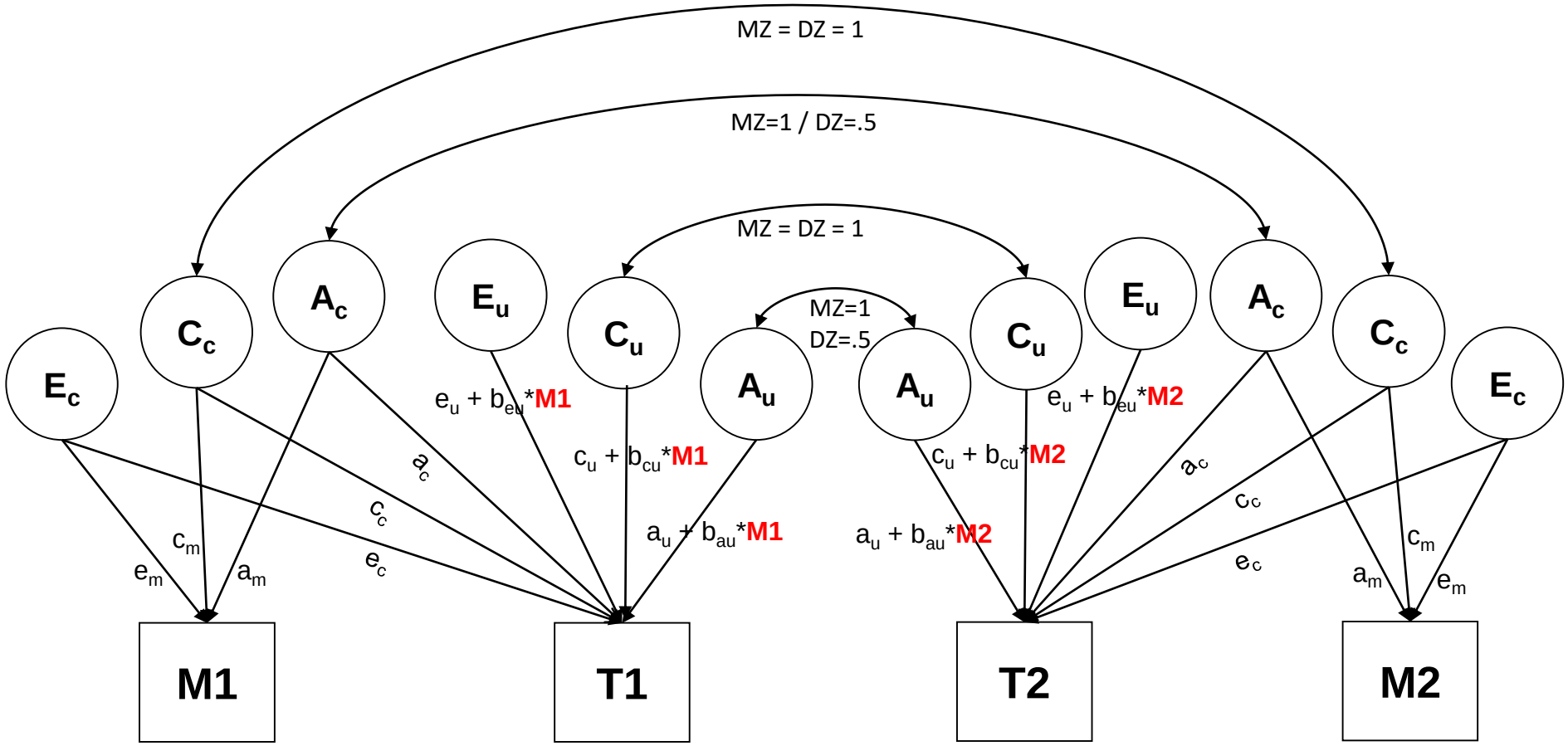


Ok if #2: r(M1,M2) = 1



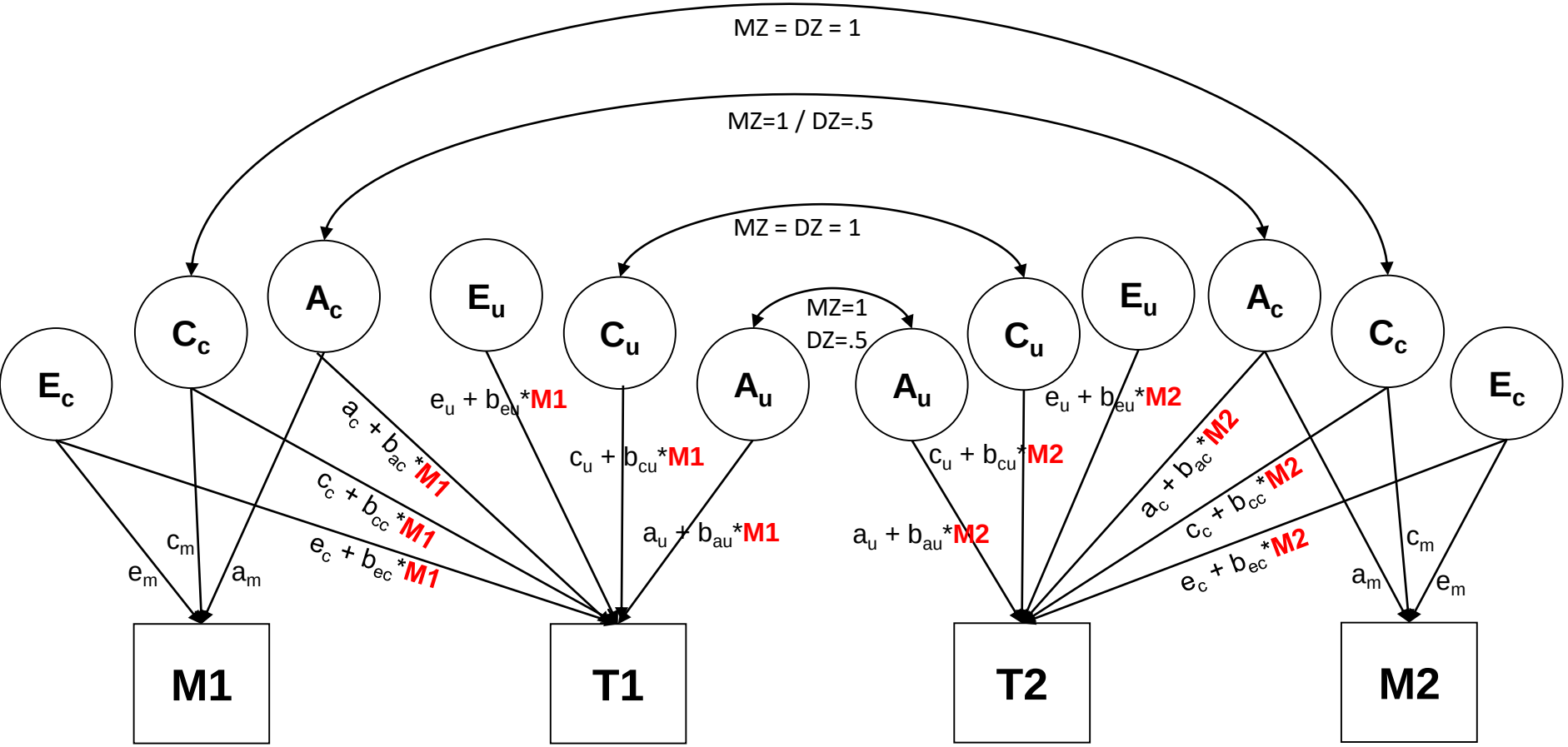
What to do otherwise? Fit model as shown:





But what about the common paths e_c c_c & a_c ....

Why only moderation of effect unique to T?



umx function available!

categorical data

- Continuous data
  - Moderation of means and variances
- Ordinal data
  - Moderation of thresholds and variances
  - See Medland et al. 2009

Behav Genet (2009) 39:220–229
DOI 10.1007/s10519-008-9247-7

BRIEF COMMUNICATION

A Note on the Parameterization of Purcell's G × E Model for Ordinal and Binary Data

Sarah E. Medland · Michael C. Neale ·
Lindon J. Eaves · Benjamin M. Neale

Non linear moderation? Extend the model from linear to linear + quadratic.

E.g., $e_c + b_{ec1}*\mathbf{M1} + b_{ec2}*\mathbf{M1^2}$

What about >1 number of moderators? Extend the model accordingly

$e_c + b_{ec1}$*__SES__ + b_{ec2}*__AGE__

With possible interaction:

$e_c + b_{ec1}$*__SES__ + b_{ec2}*__AGE__ + b_{ec3}*(__AGE__ *__SES__)

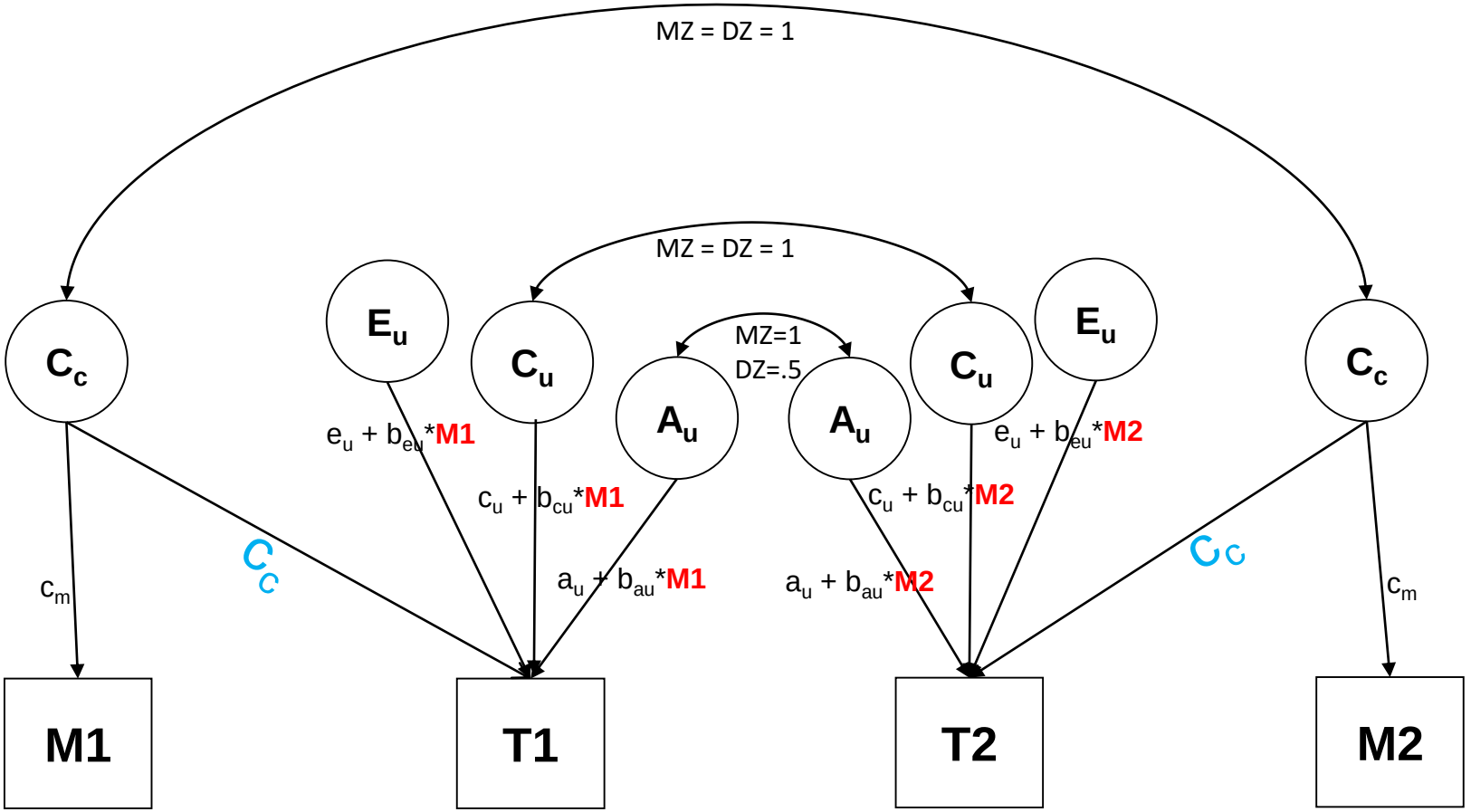
Michel Nivard Practical

- Replicate findings from Turkheimer et al. with twin data from NTR

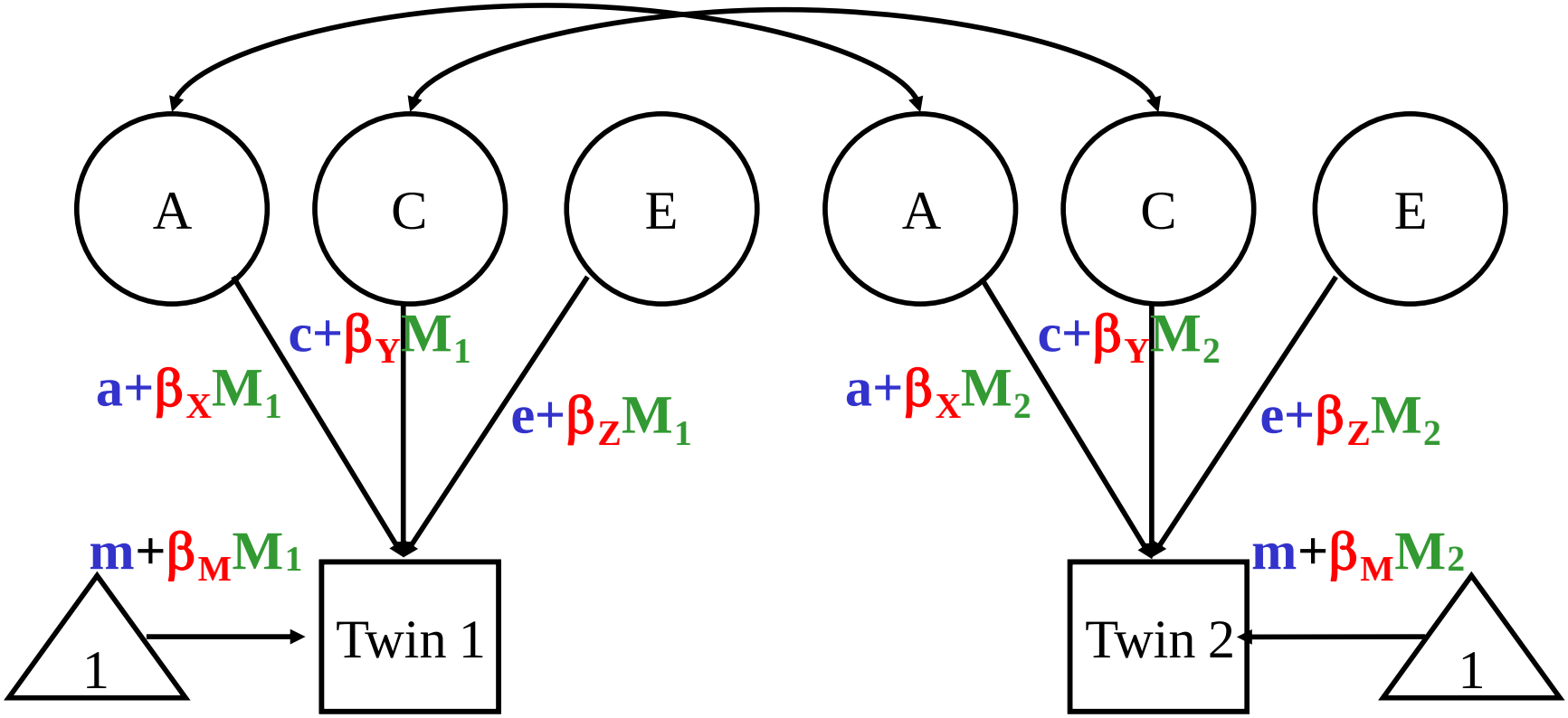
- Phenotype: FSIQ
- Moderator: SES in children
- cor(M1,M2) = 1

- Data: 205 MZ and 225 DZ twin pairs
- 5 years old

Ok if #2: r(M1,M2) = 1



SES = M



unx function available