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

Conor V Dolan & Sanja Franić (BioPsy VU)

Boulder Twin Workshop

March 4, 2014

Based on PPTs by Sophie van der Sluis & Marleen de Moor

Thanks to Neale family, Sarah Medland, & Brad Verhulst

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

Mx
MCNeale et al

Twin Research Volume 5 Number 6 pp. 554- 571

Variance Components Models for Gene–Environment Interaction in Twin Analysis

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

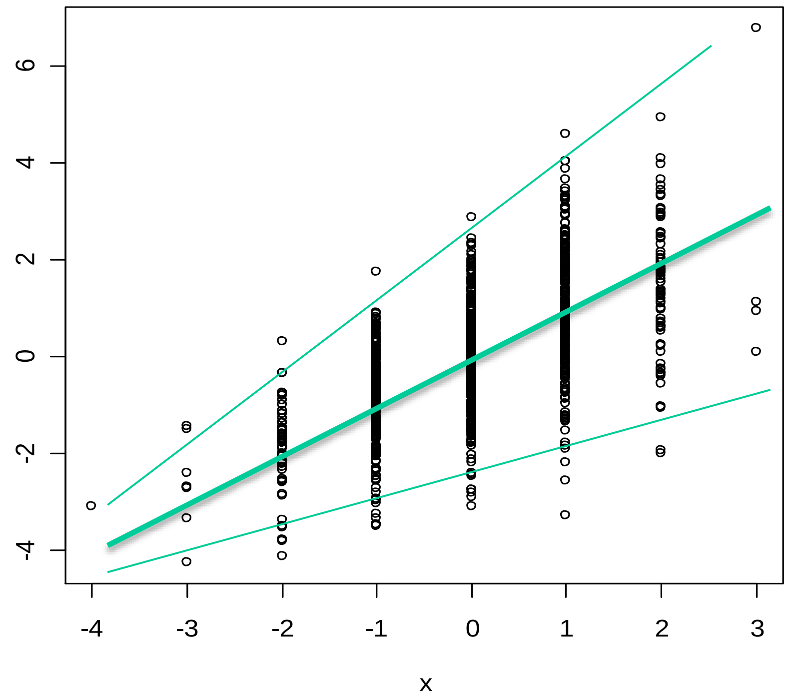
Behav Genet (2012) 42:170–186
DOI 10.1007/s10519-011-9480-3

ORIGINAL RESEARCH

A Note on False Positives and Power in G × E Modelling of Twin Data

Sophie van der Sluis · Danielle Posthuma ·
Conor V. Dolan

Phenotypic scores



Environmental Dispersion

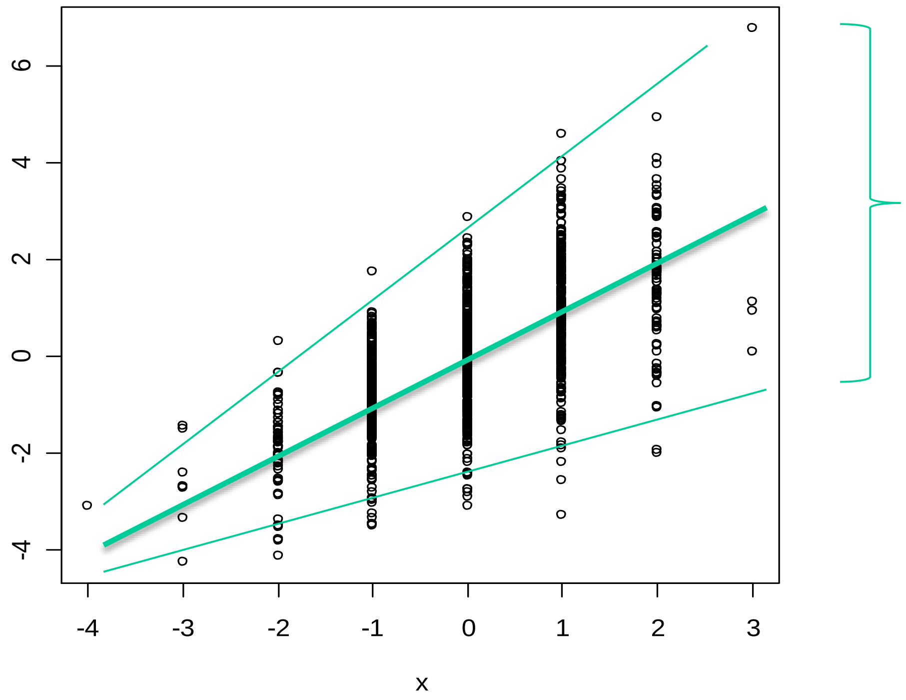
Variance of E given G score

Genetic level (score on A)

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

Not all heteroskedasticity is GxE!

Phenotypic scores



Genetic Dispersion

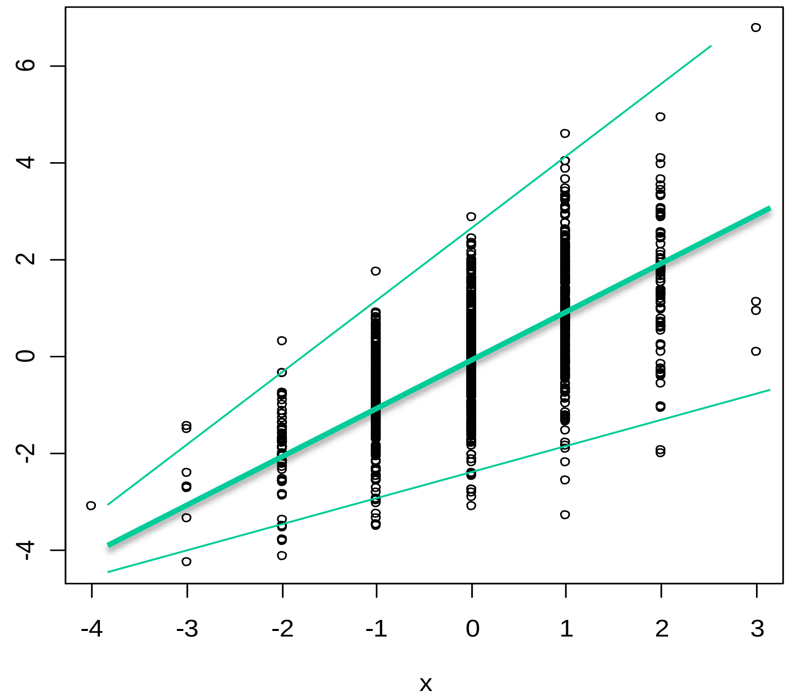
Conditional A variance

Environmental level (score on E)

G x E as "environmental control" of genetic effects: heteroskedasticity.

Not all heteroskedasticity is GxE!

Phenotypic scores



Genetic Dispersion

and / or

Environmental dispersion

Moderator level (score on moderator)

Moderation of effects (A,C,E) by measured moderator M: heteroskedasticity.

Not all heteroskedasticity is moderation!

Sex X A interaction: Moderation of A by sex

- Is the magnitude of genetic influences on ADHD the same in boys and girls?
- Do different genetic factors influence ADHD in boys and girls? (DZOS)

Moderation of A effects by binary variable with the bonus of the information provided by DZ opposite sex twins

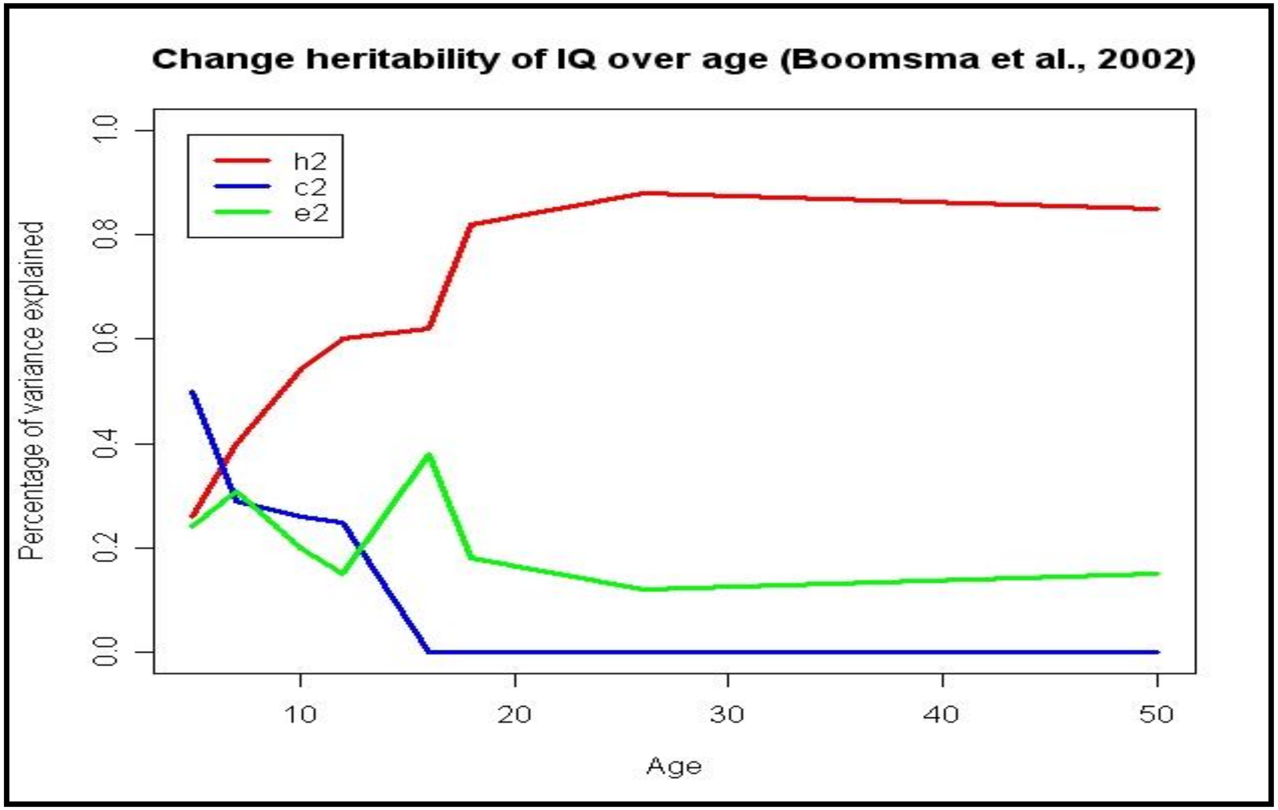
Other examples binary moderators

“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: A 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

A,C,E effects moderated by SES

PSYCHOLOGICAL SCIENCE

E. Turkheimer et al.

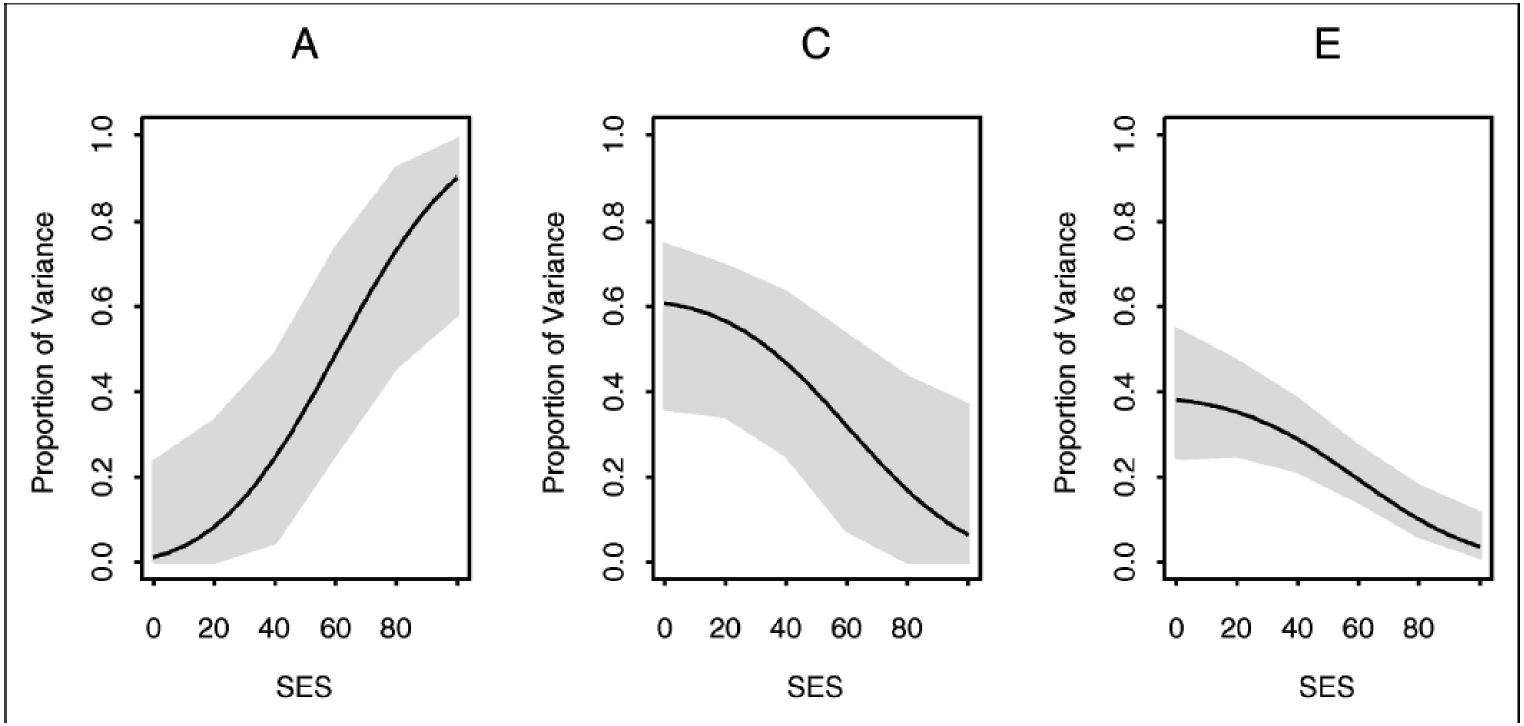


Fig. 3. Proportion of total Full-Scale IQ variance accounted for by A, C, and E plotted as a function of observed socioeconomic status (SES). Shading indicates 95% confidence intervals.

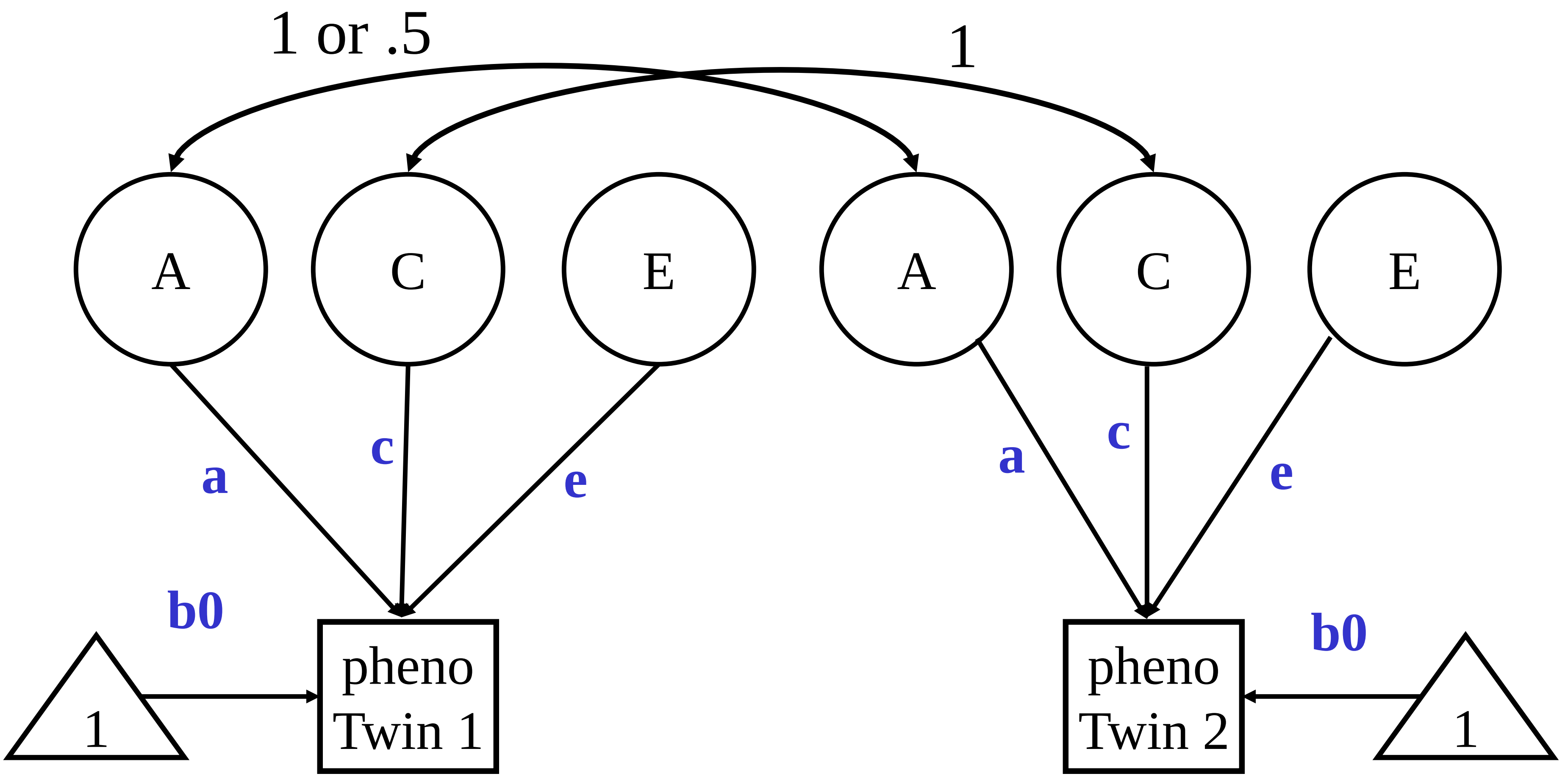
SES ordinal or continuous

Continuous Moderators
not amenable to multigroup approach

…

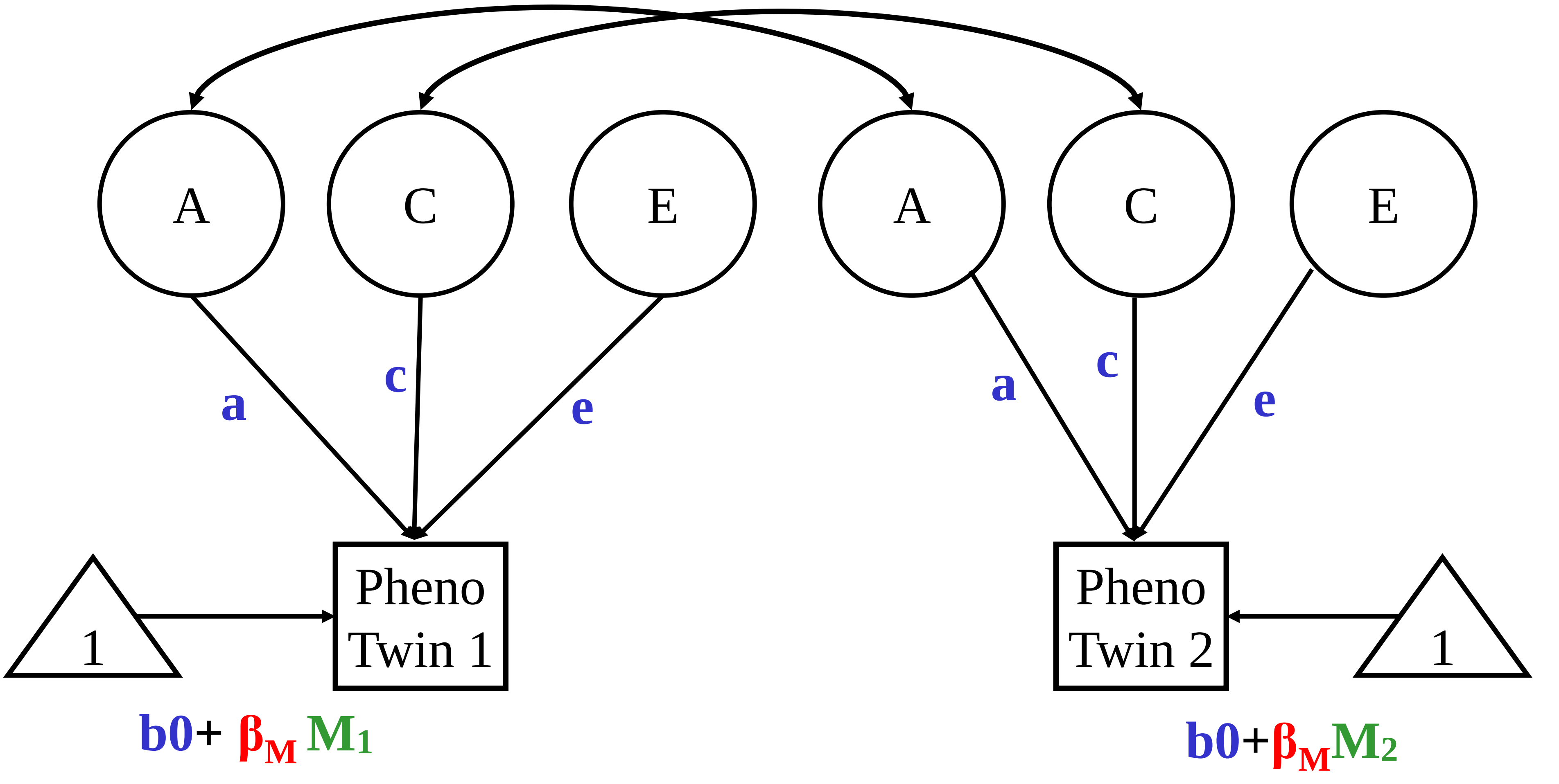
treat the moderator as continuous
(OpenMx)

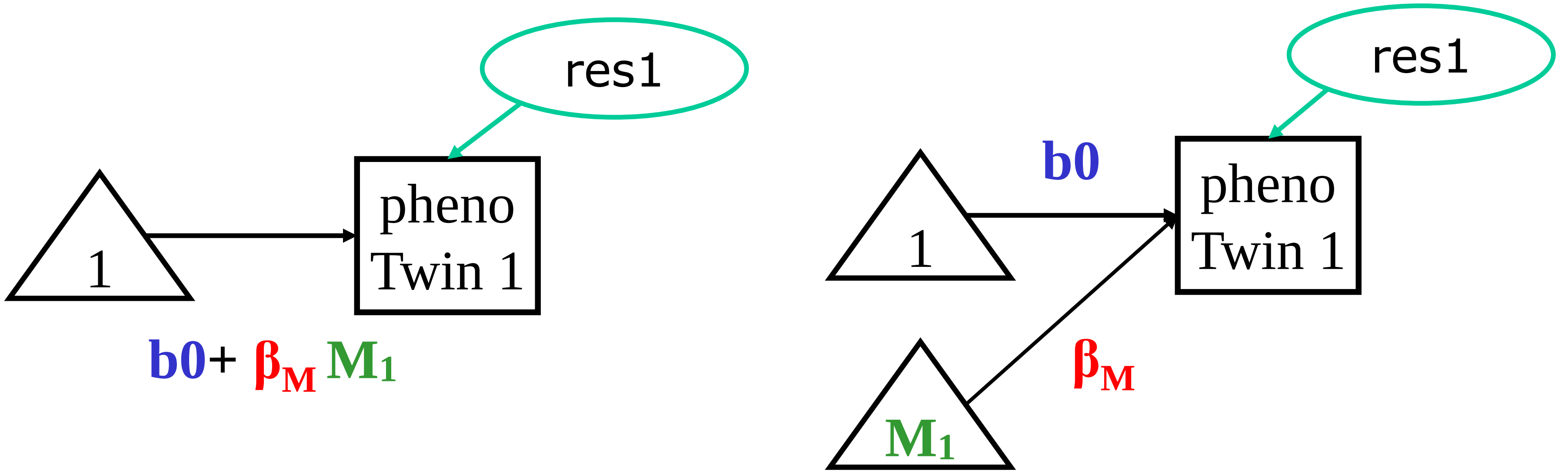
Standard ACE model



Regression on unit: just a way to estimate the mean.

Standard ACE model + Main effect on Means





equivalent

Actually: regression of Phenotype on M ...
What is left is the residual, subject to ACE modeling.

Why a triangle? Fixed regressors

Summary stats

- Means vector

$$\begin{pmatrix} \text{mean1} & \text{mean2} \end{pmatrix}$$

- Covariance matrix (r = 1 or r=1/2)

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

Allowing for a main effect of *X*

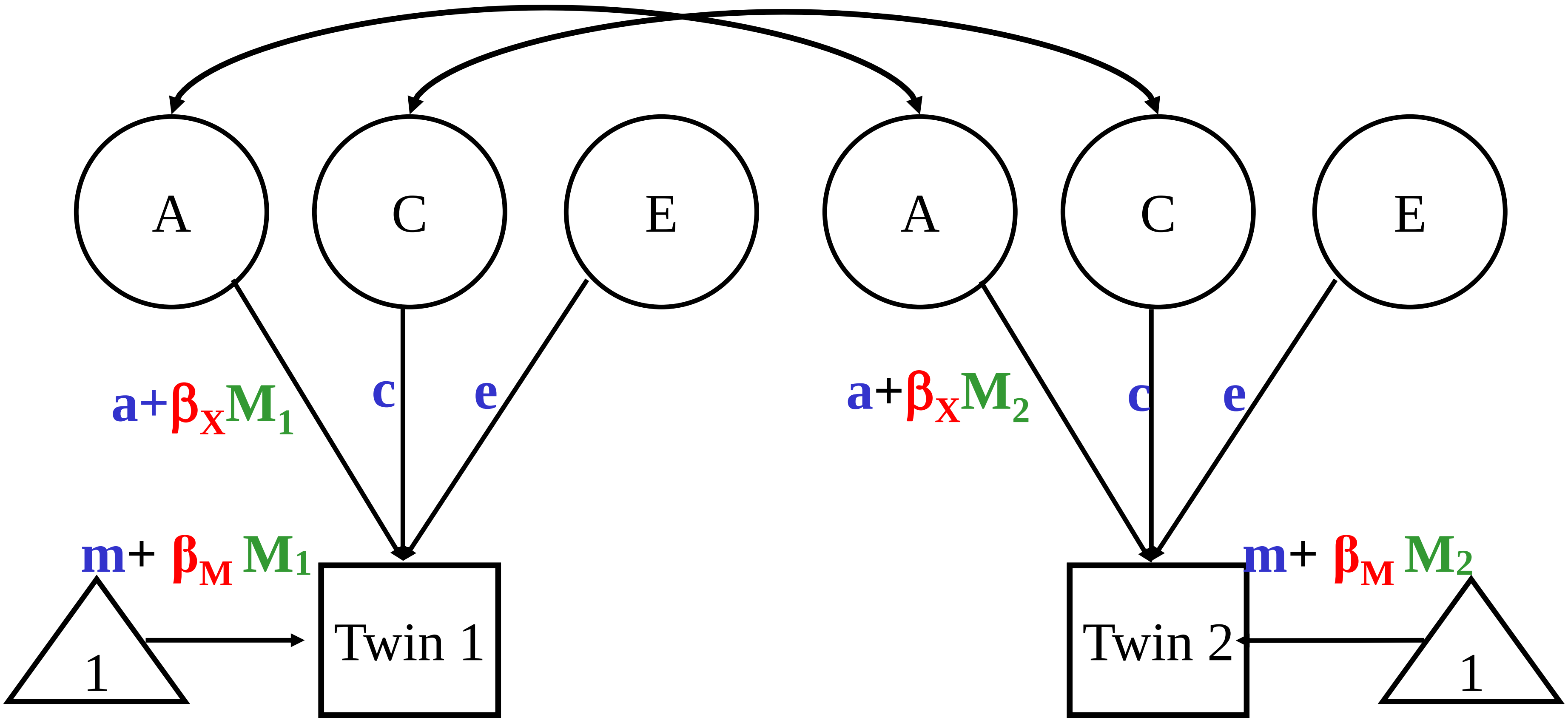
- Means vector

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

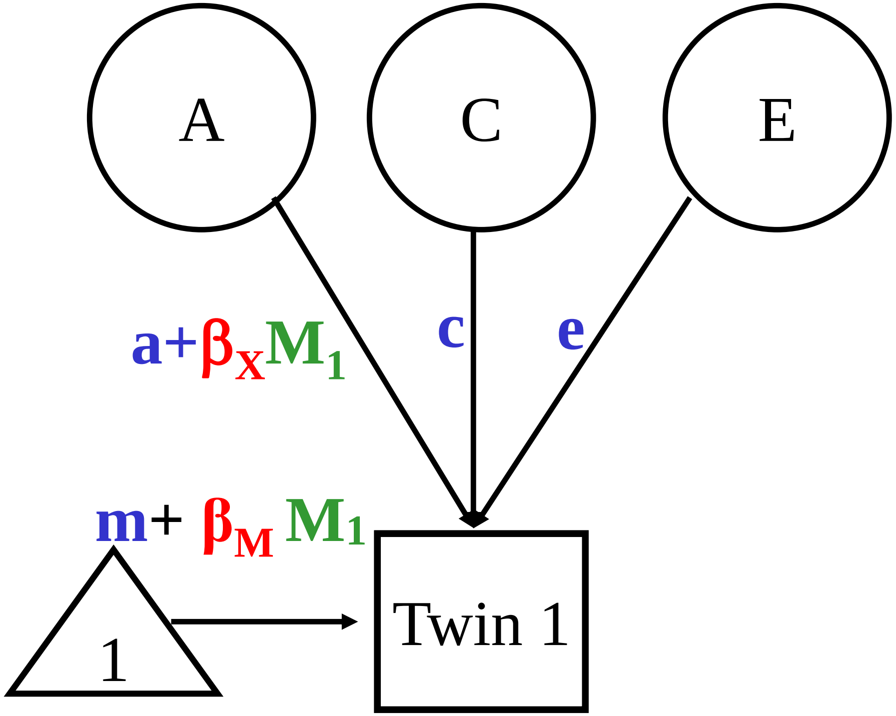
- Covariance matrix (r = 1 or r=1/2)

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

Standard ACE model + Effect on Means and a path



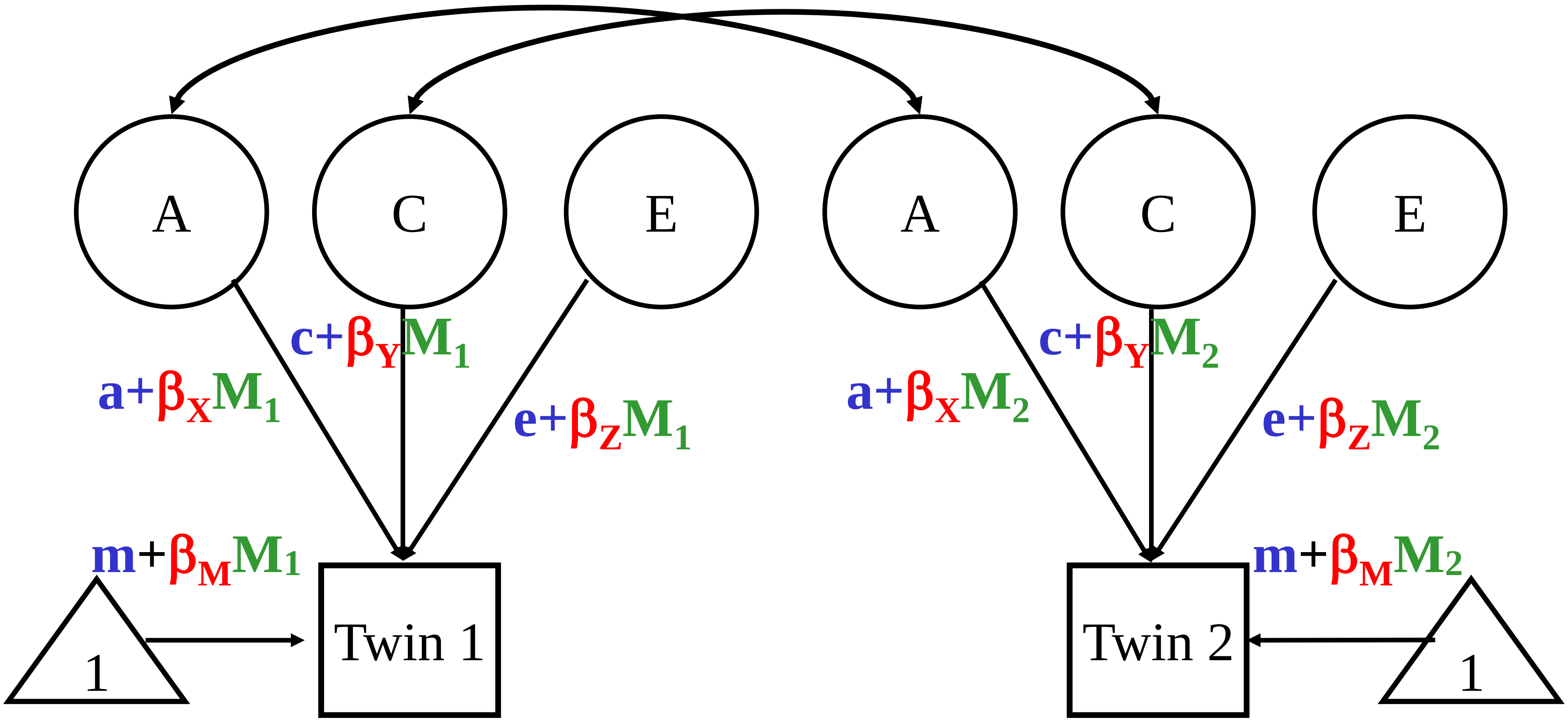
M has main effect on mean + moderation of A effect

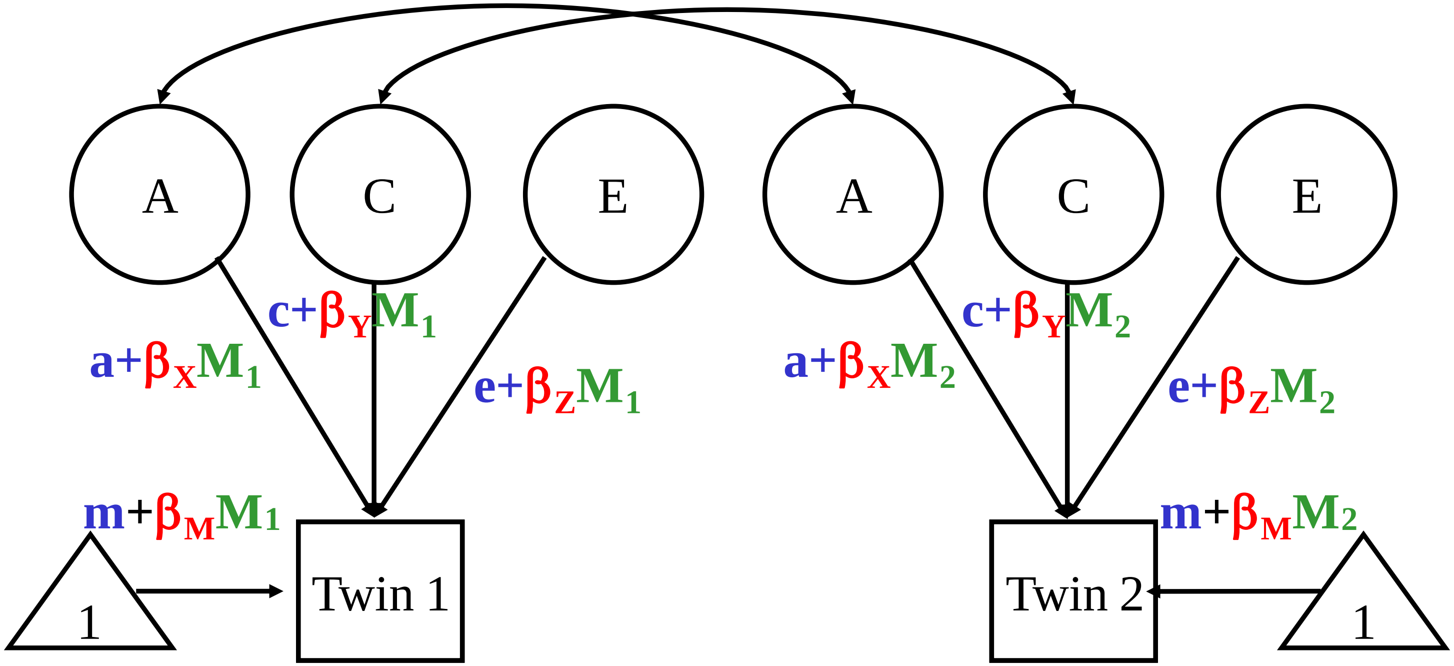


M1=0 -> mean= **m** & A effect = **a**

M1=1 -> mean= **m**+ $\beta_M M_1$ & A effect = $a+\beta_X M_1$

Standard ACE model + Effect on Means and a,c, & e paths





- Effect on means:
  - Main effects (regression of phenol on M)
- Effect on a/c/e 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:

$$Var\ (P|M) =$$

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

Expected MZ / DZ covariances

$$Cov(P_1,P_2|M)_{MZ} =$$

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

$$Cov(P_1,P_2|M)_{DZ} =$$

$$0.5*(a + \beta_X M)^2 + (c + \beta_Y M)^2$$

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

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

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

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

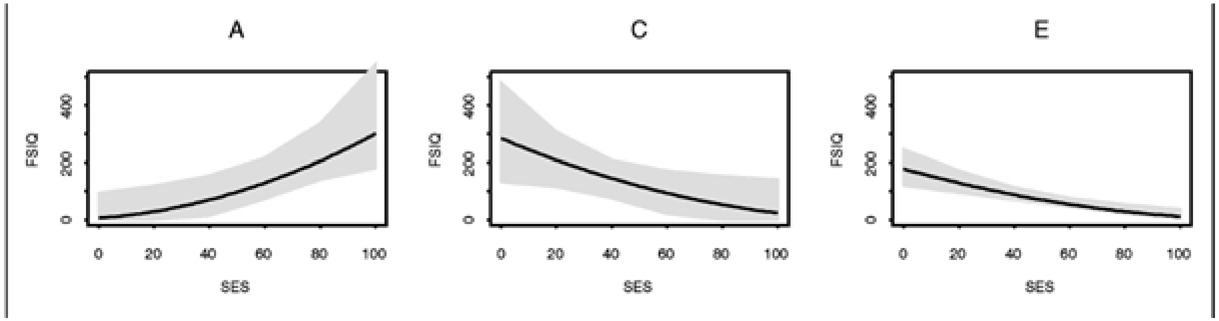
$$(h^2|M + c^2|M + e^2|M) = 1$$

Standardized conditional on value of M

Turkheimer study SES

Moderation of **unstandardized** variance components (top)

Moderation of **standardized** variance components (bottom)



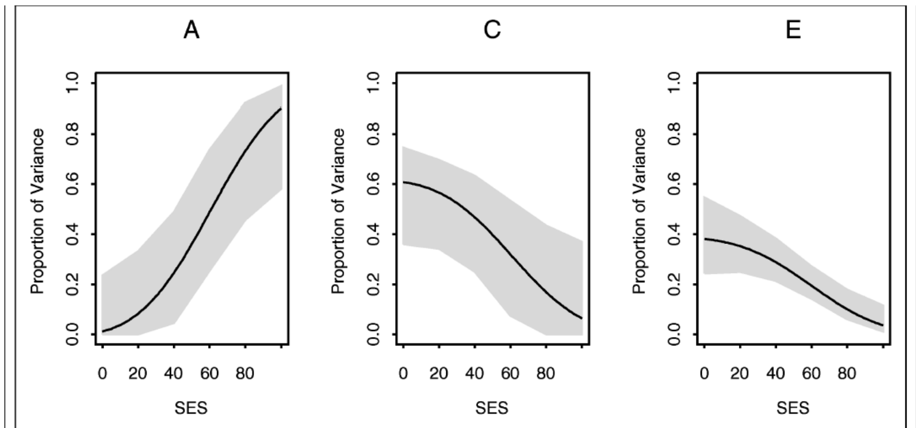
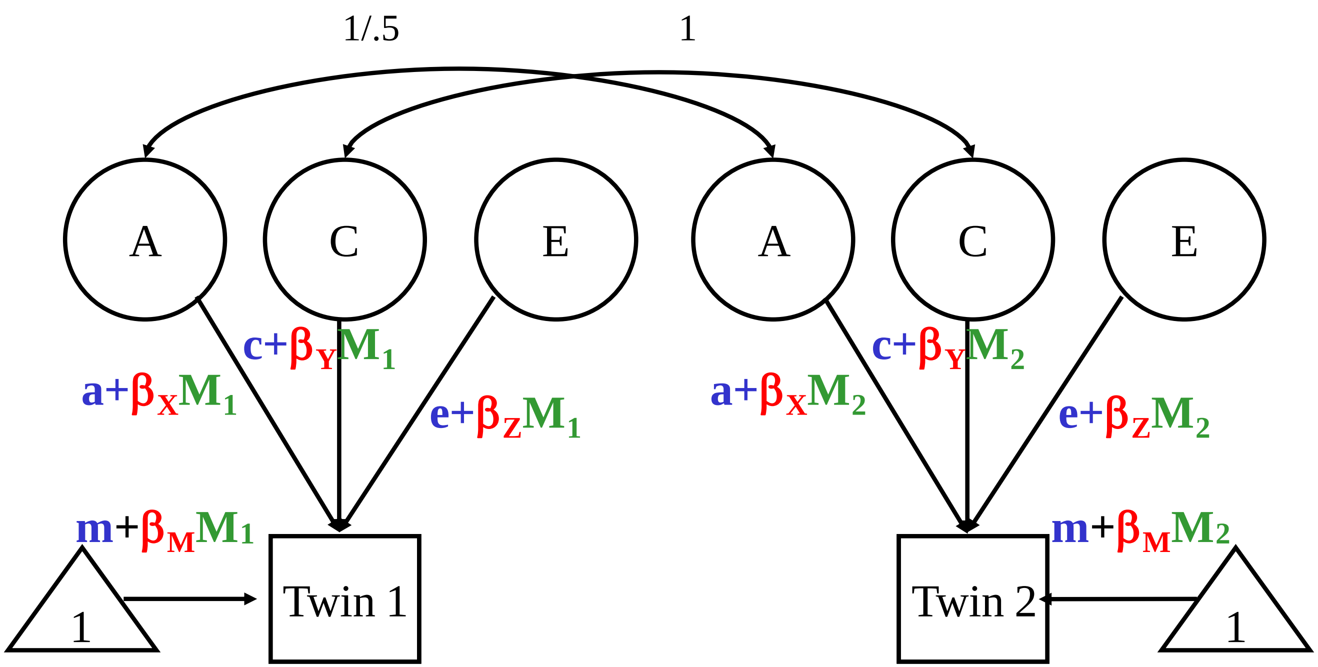
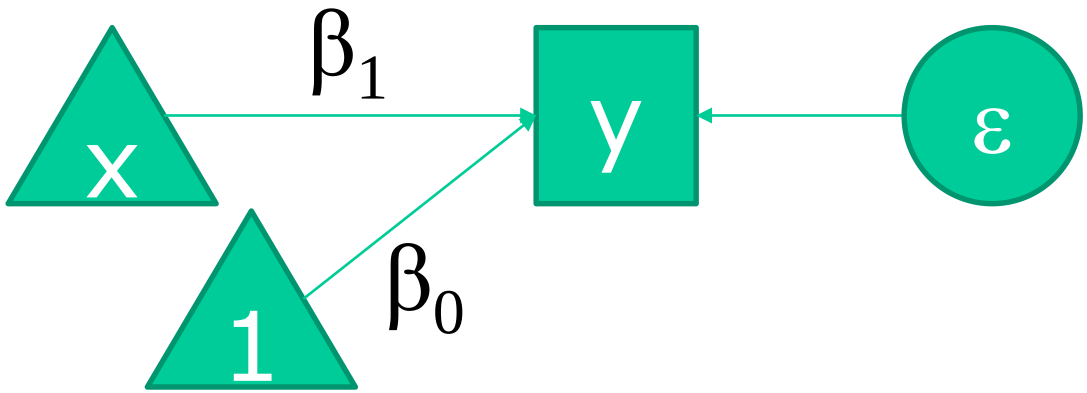


Fig. 3. Proportion of total Full-Scale IQ variance accounted for by A, C, and E plotted as a function of observed socioeconomic status (SES). Shading indicates 95% confidence intervals.



But what have assumed concerning M?

Fixed regressor

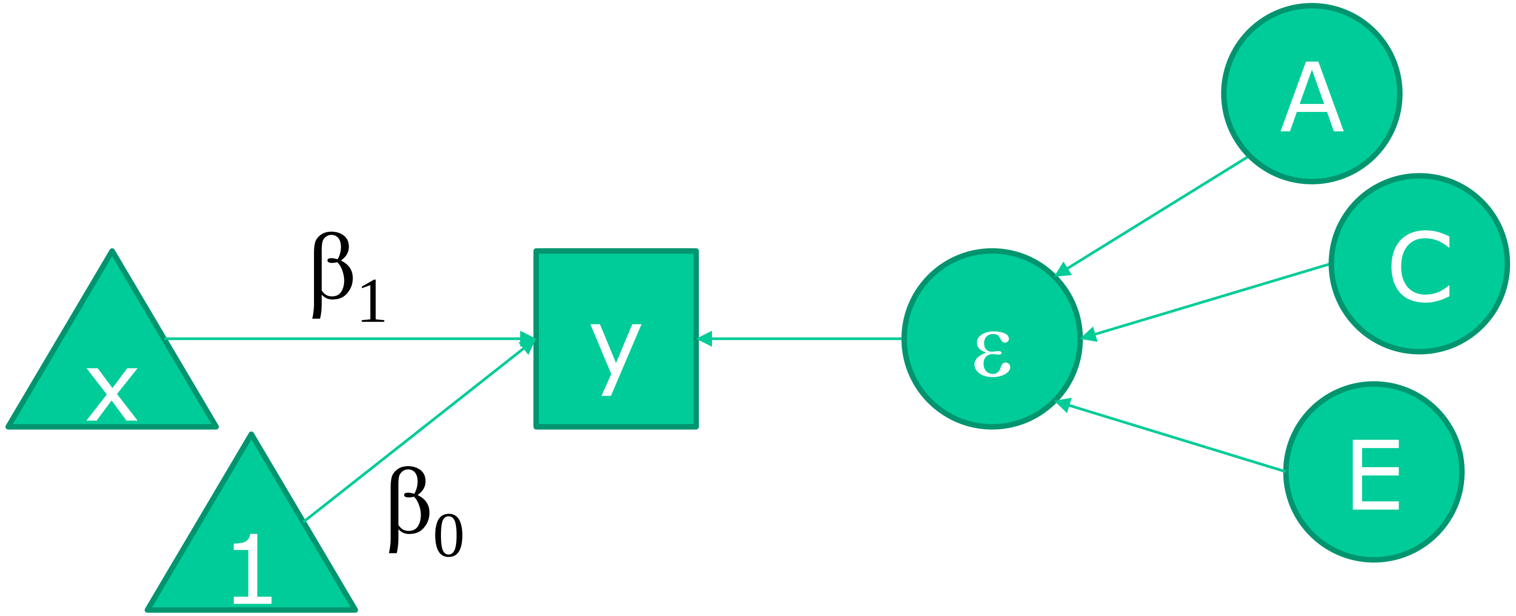


Assumption: $y|x^* \sim N(m_{y|x}, s_{y|x})$

$m_{y|x^*} = \beta_0 + \beta_1 x^*$

$s_{y|x^*} = s_\varepsilon$

Fixed regressor

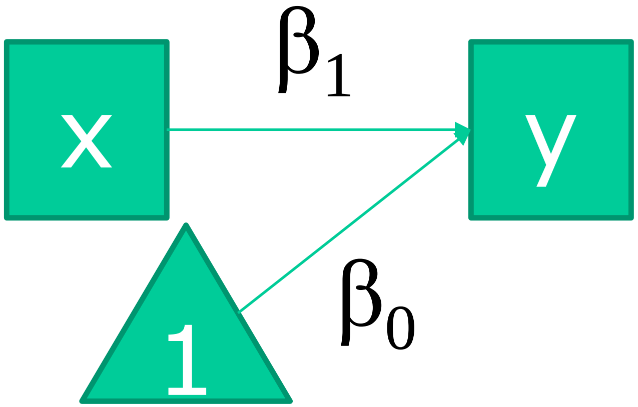


Assumption: $y|x^* \sim N(m_{y|x}, s_{y|x})$

$m_{y|x^*} = \beta_0 + \beta_1 x^*$

$s_{y|x^*} = s_\varepsilon$

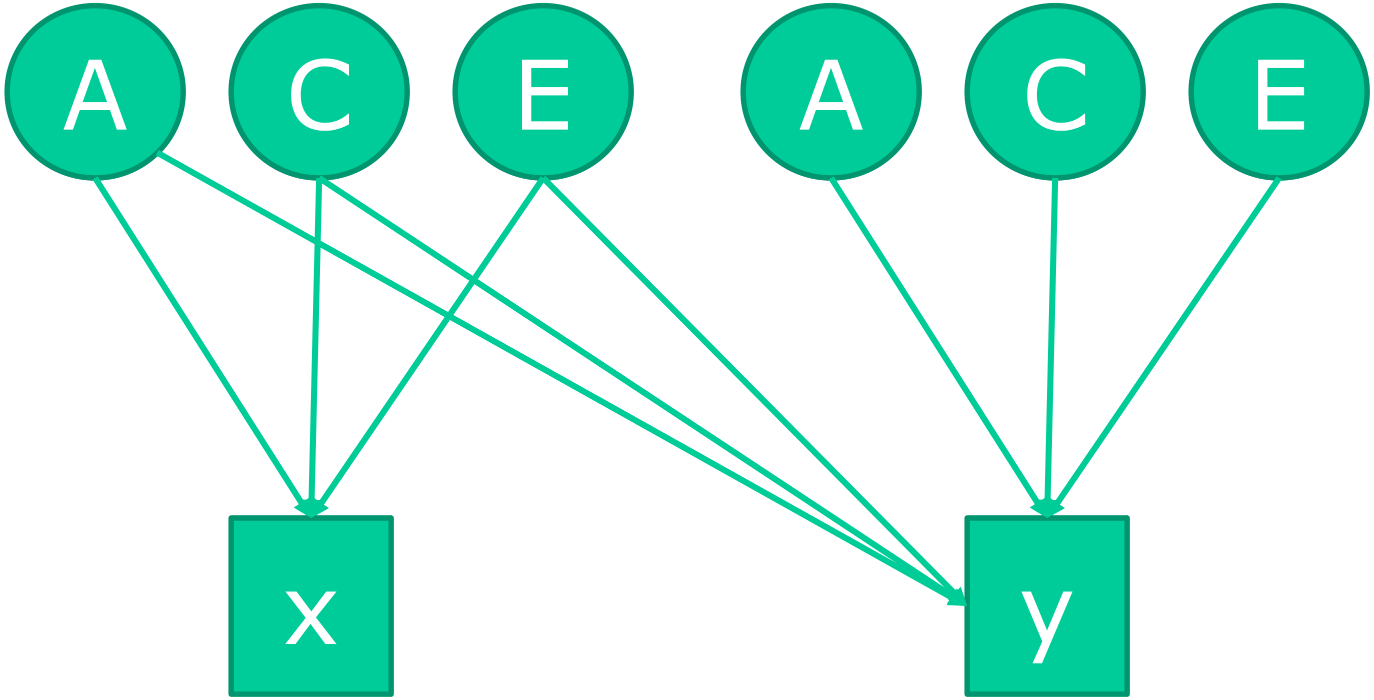
Random regressor



Assumption: $(y,x) \sim N(\boldsymbol{\mu}, \boldsymbol{\Sigma})$

"Random regressor not to be confused with Random effects regression (multilevel modeling)"

Bivariate distribution of X and Y



Regression of Y on X in terms of latent variables

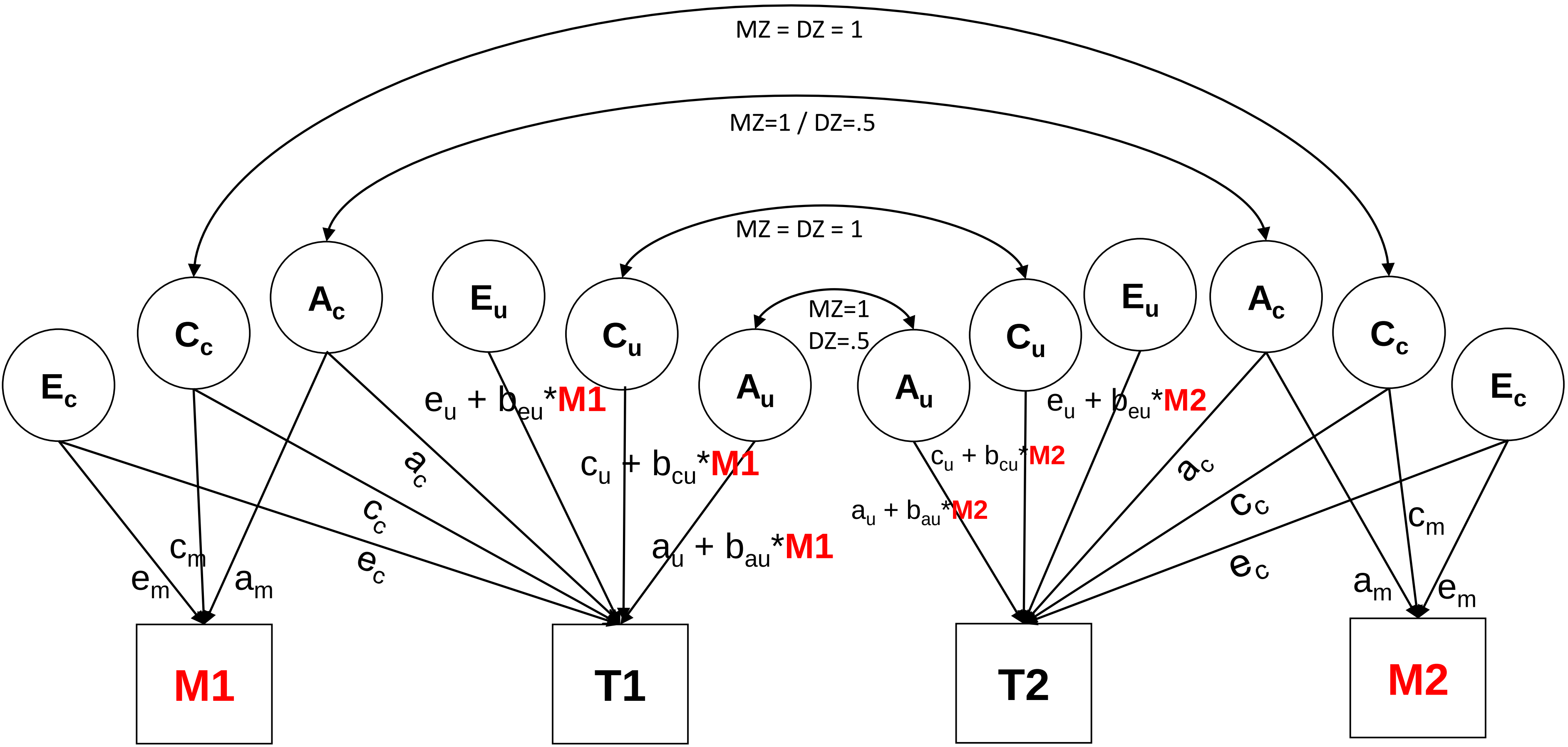
Assumption: $(y,x) \sim N(\boldsymbol{\mu}, \boldsymbol{\Sigma})$

M1,M2 (co)variance is not included in the model. M is a “fixed regressor”.

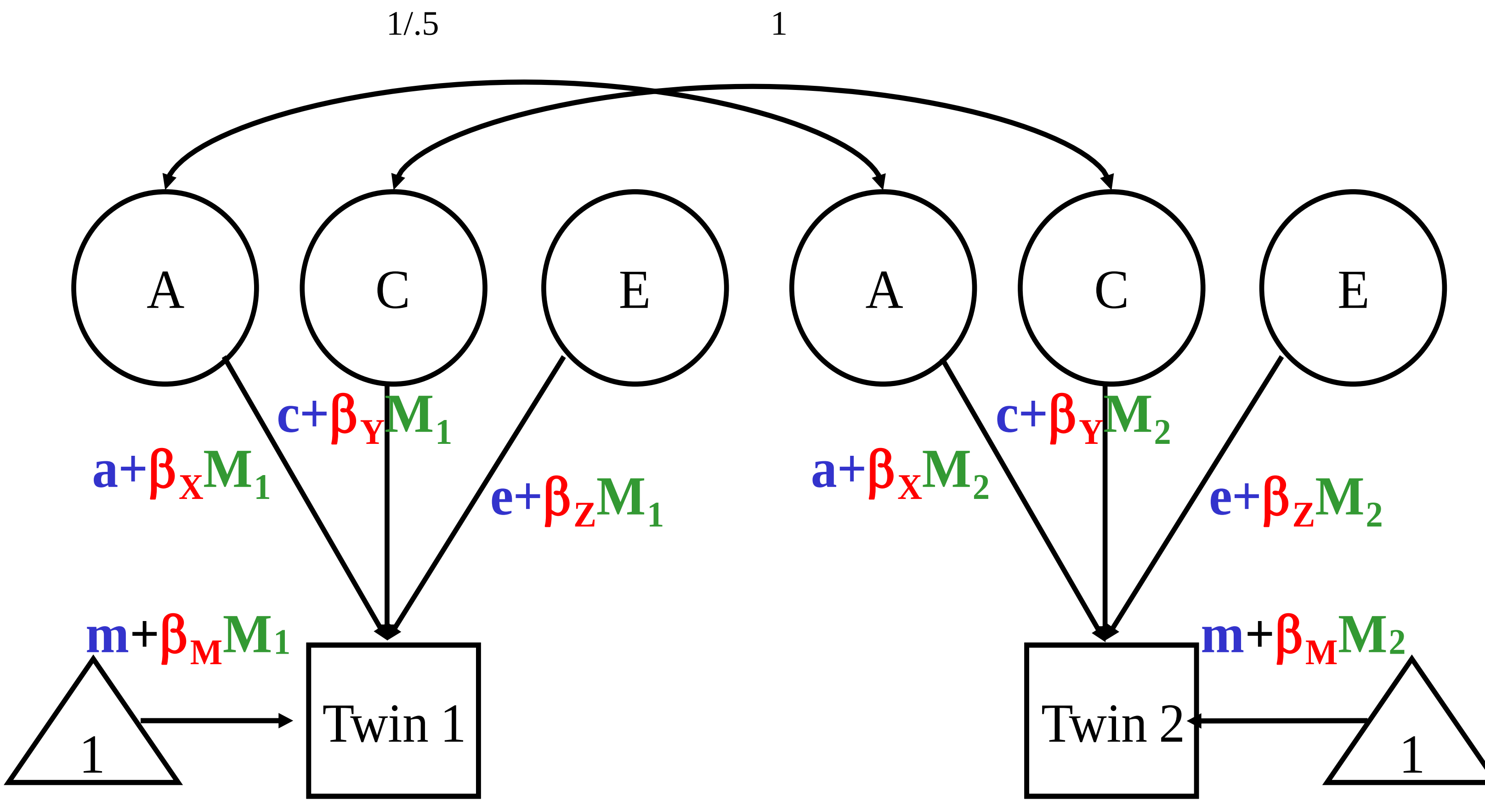
Phenotype = BMI
Moderator = Age .... A fixed regressor

Phenotype = BMI
Moderator = Intelligence ....
Can we treat Intelligence as a fixed fixed
In this context? Depends... on ...

M as a random regressor, with its own ACE + ACE cross loadings.

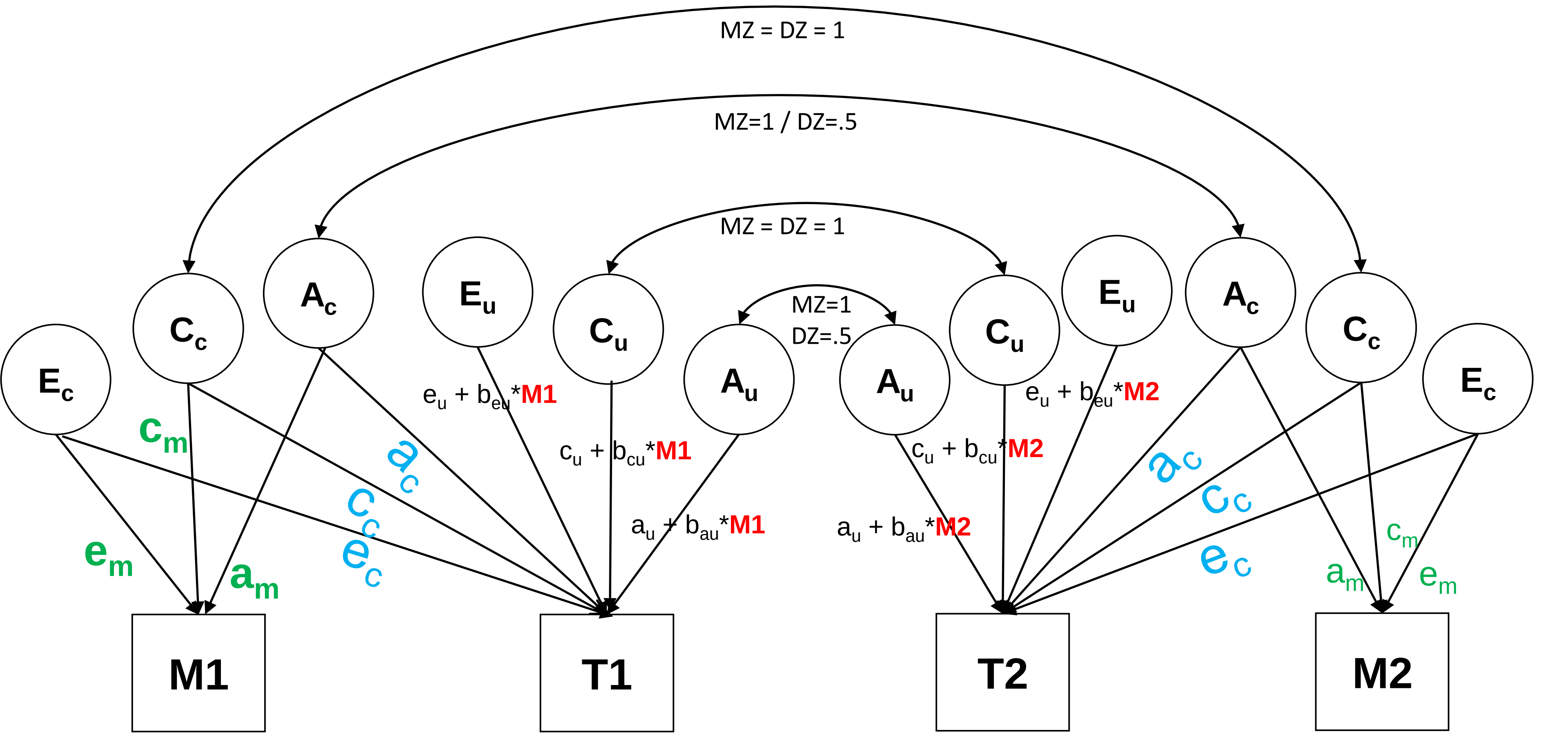


Can we treat M as a fixed effect in this manner?

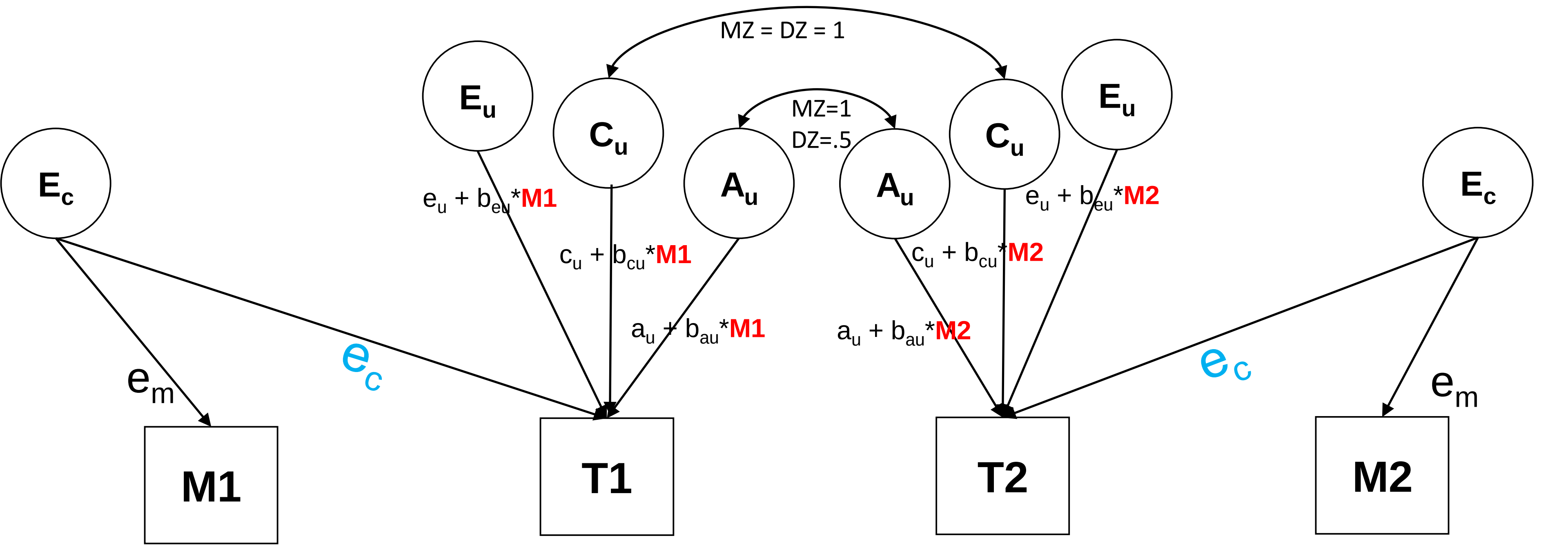


Not generally

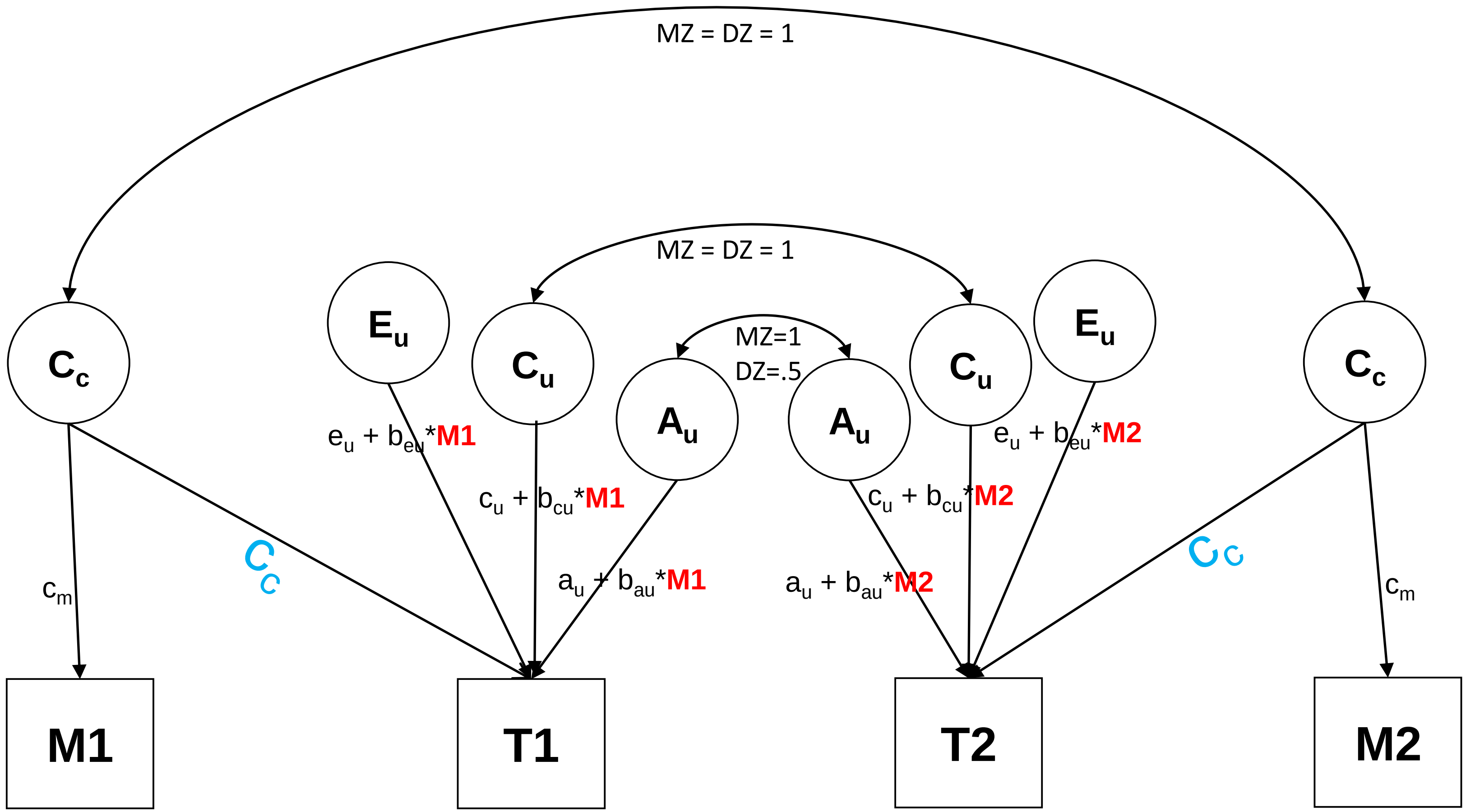
OK if #1: $a_c/a_m = c_c/c_m = e_c/e_m$



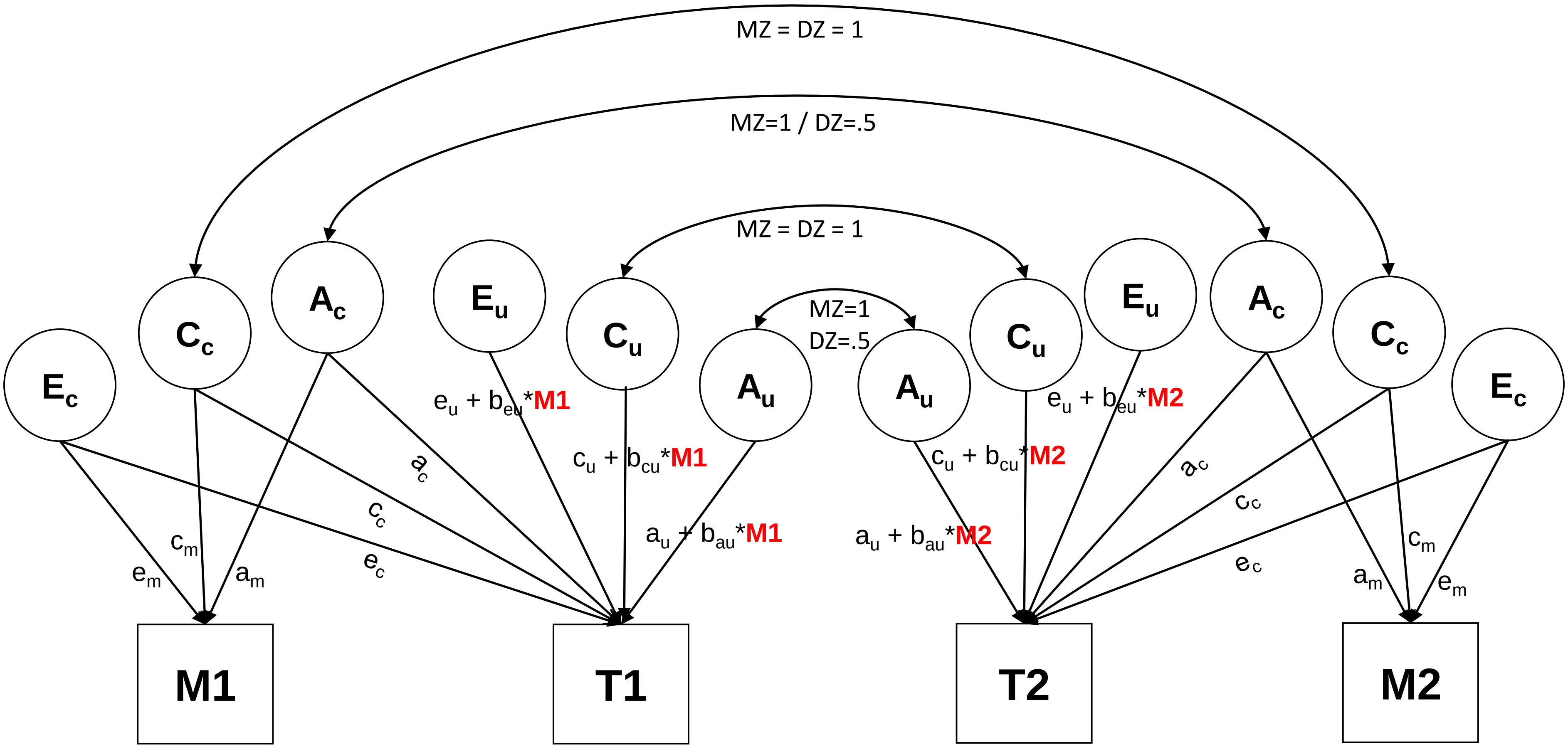
OK if #2: r(M1,M2) = 0

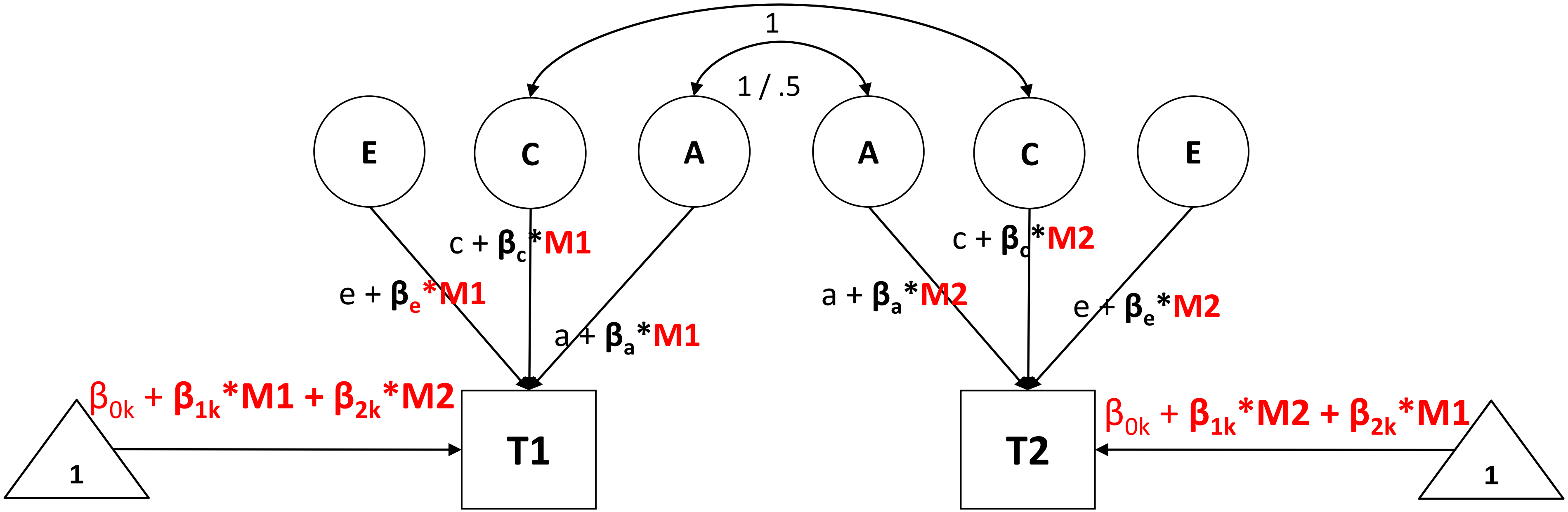


Ok if #3: r(M1,M2) = 1



What to do otherwise?





MZ:

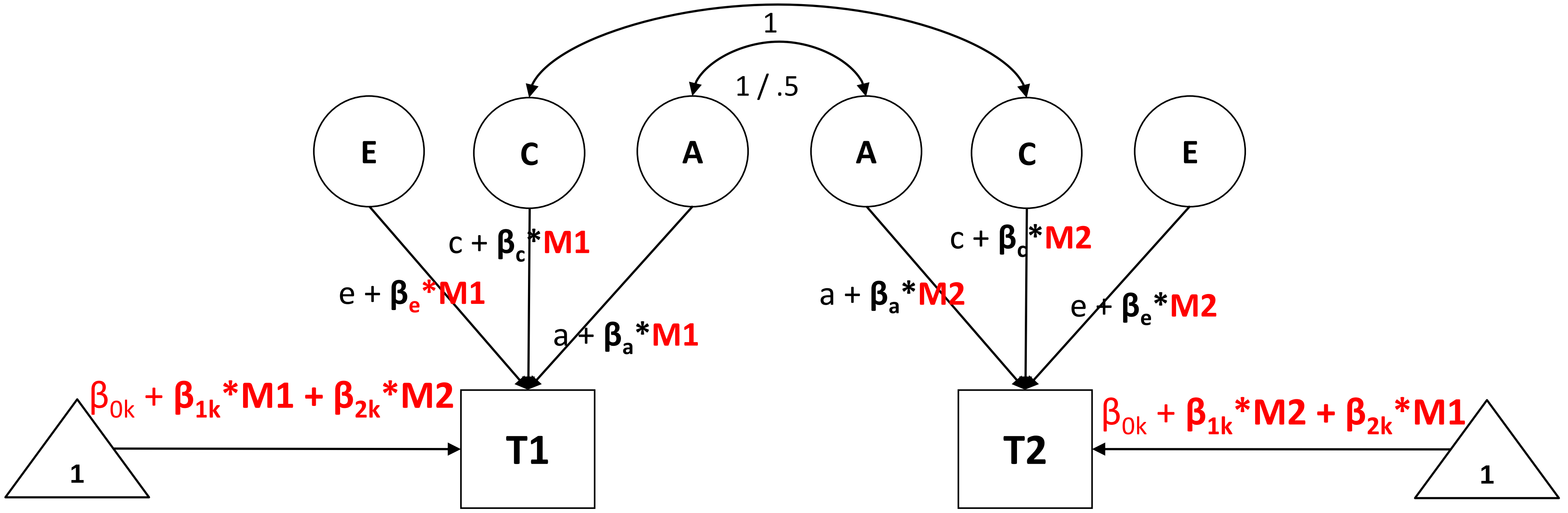
$$T1=\beta_{0,MZ} + \beta_{1,MZ}*M_1 + \beta_{2,MZ}*M_2$$

$$T2=\beta_{0,MZ} + \beta_{1,MZ}*M_2 + \beta_{2,MZ}*M_1$$

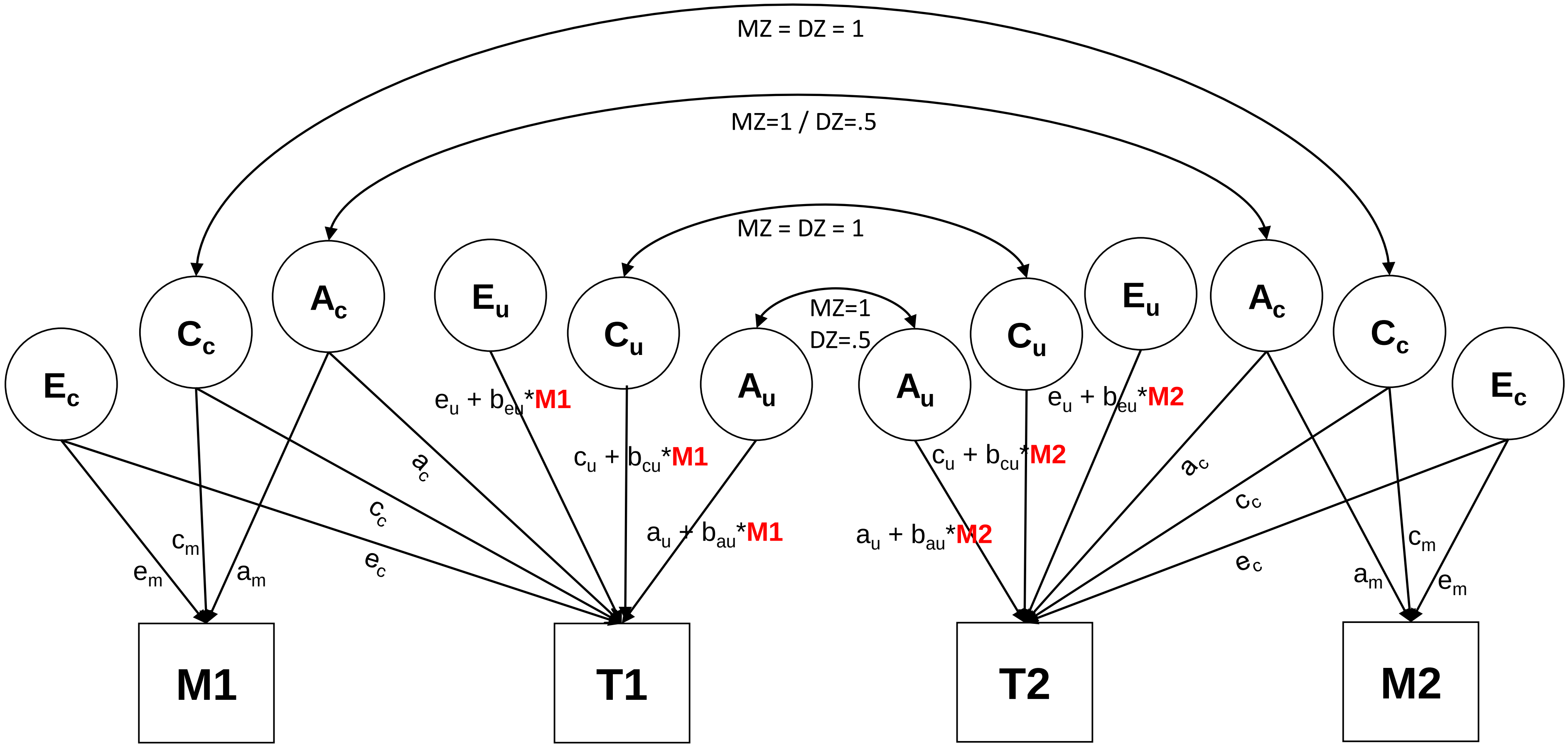
DZ:

$$T1=\beta_{0,DZ} + \beta_{1,DZ}*M_1 + \beta_{2,DZ}*M_2$$

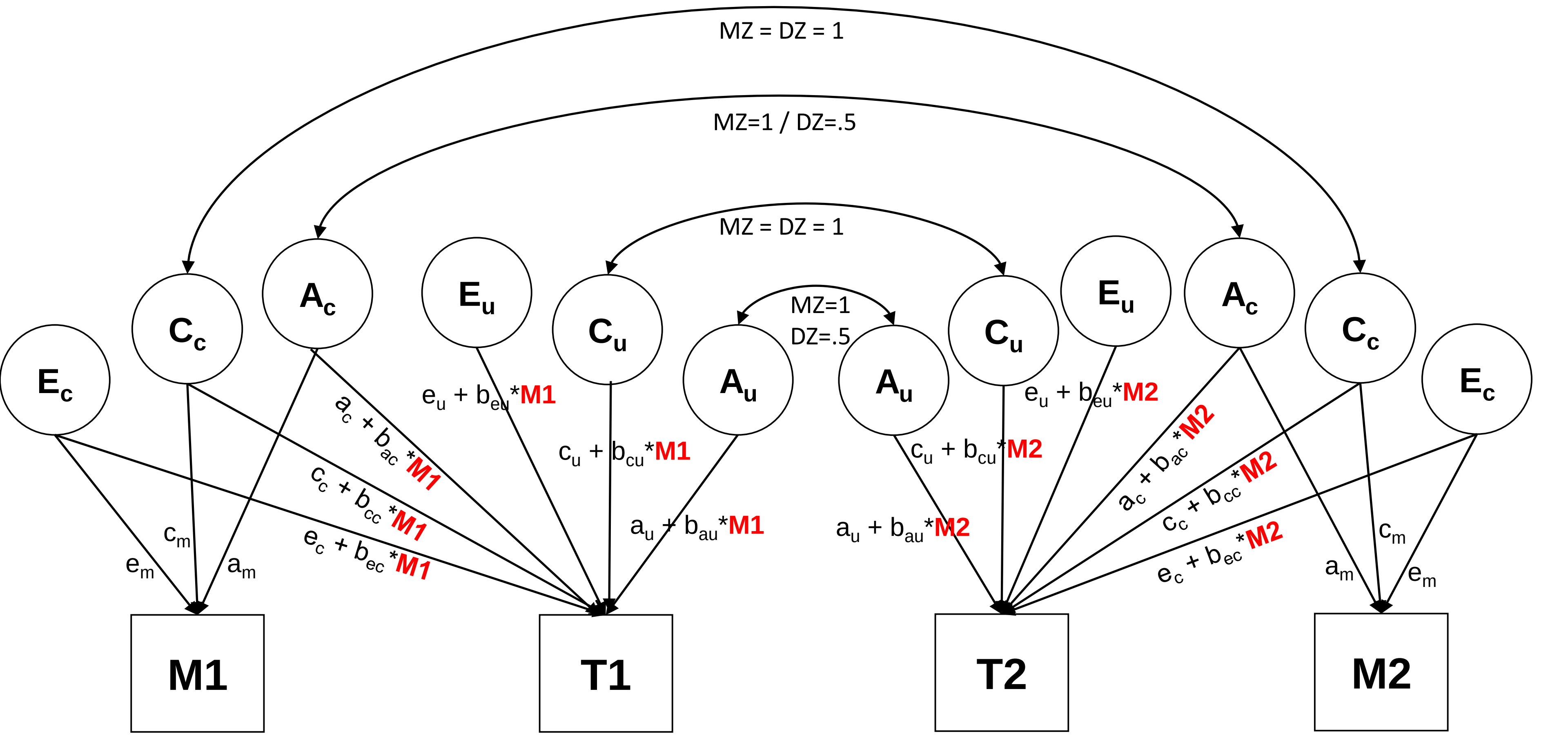
$$T2=\beta_{0,DZ} + \beta_{1,DZ}*M_2 + \beta_{2,DZ}*M_1$$



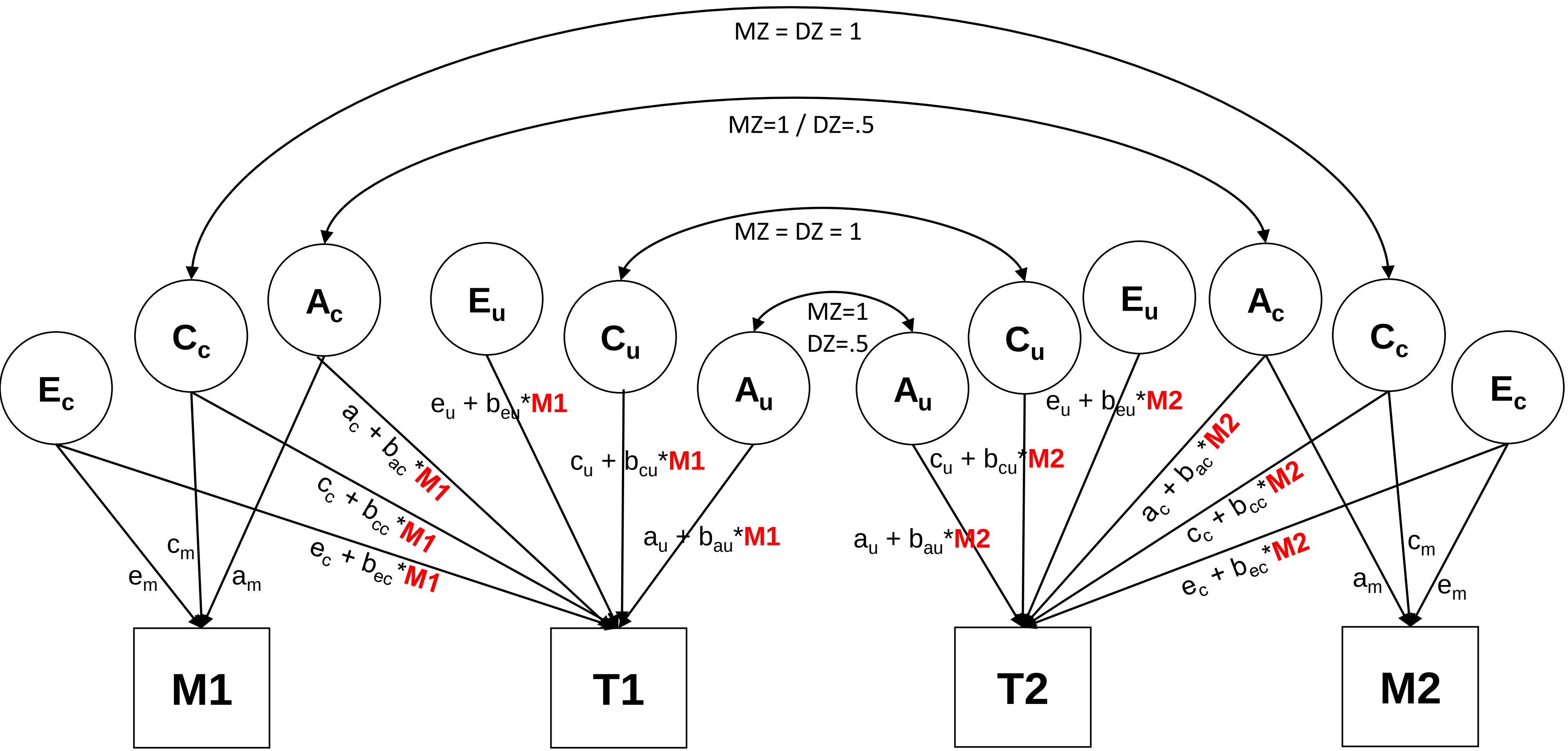
But what have assumed concerning the covariance between M and T?



MZ = DZ = 1
MZ=1 / DZ=.5
MZ = DZ = 1
MZ=1
DZ=.5
Ec
Cc
Ac
Eu
Cu
Au
Au
Cu
Eu
Ac
Cc
Ec
eu + beu*M1
cu + bcu*M1
au + bau*M1
au + bau*M2
cu + bcu*M2
eu + beu*M2
ac
cc
ec
cm
em
am
ac
cc
ec
cm
am
em
M1
T1
T2
M2



MZ = DZ = 1
MZ=1 / DZ=.5
MZ = DZ = 1
MZ=1
DZ=.5
Ec
Cc
Ac
Eu
Cu
Au
Au
Cu
Eu
Ac
Cc
Ec
em
cm
am
ac + bac*M1
cc + bcc*M1
ec + bec*M1
eu + beu*M1
cu + bcu*M1
au + bau*M1
au + bau*M2
cu + bcu*M2
eu + beu*M2
ac + bac*M2
cc + bcc*M2
ec + bec*M2
am
cm
em
M1
T1
T2
M2



M has to be treated as random and modeled appropriately (as shown)!

Conclusion:

Use standard fixed regression approach if

Cov(M,T) equally due to A,C,E

Cov(M1,M2) = zero

Cov(M1,M2) = one

Use extended fixed regression approach if

Cross paths are not moderated

Otherwise use full model.

A simpler conclusion:

ALWAYS USE FULL MODEL UNLESS Cor(M1,M2) = 1.

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?

$e_c + b_{ec1} * \mathbf{M1} + b_{ec2} * \mathbf{M1}^2$

What about >1 number of moderators

Extend the model accordingly

$$e_c + b_{ec1}*\textbf{SES} + b_{ec2}*\textbf{AGE}$$

What about >1 number of moderators and interaction Effects (sex X age) Extend the model accordingly...

e_c + b_{ec1}***SES** + b_{ec2}***AGE** +

b_{ec2}*(**AGE** ***SES**)

What about power given such extensions?

Do power calculation.... Exactly, by simulation, by exact simulation ?

Behav Genet (2008) 38:202–211
DOI 10.1007/s10519-007-9184-x

OpenAccess

ORIGINAL RESEARCH

Power Calculations Using Exact Data Simulation: A Useful Tool for Genetic Study Designs

Sophie van der Sluis · Conor V. Dolan ·
Michael C. Neale · Danielle Posthuma

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

Gene-Environment Correlation

rGE:

- Genetic control of exposure to the environment

Examples:

- ✓ Active rGE: Children with high IQ read more books
- ✓ Passive rGE: Parents of children with high IQ take their children more often to the library

Genetic control of exposure to the environment? “short hand”

Chain of causality?

A “causes” high IQ

high IQ “causes” interest in astronomy
join the astronomy club
study astronomy