Sex limitations and Moderation (*Interaction*) Models

Conor V Dolan & Eveline de Zeeuw

Boulder 2020

nature

BIOLOGY

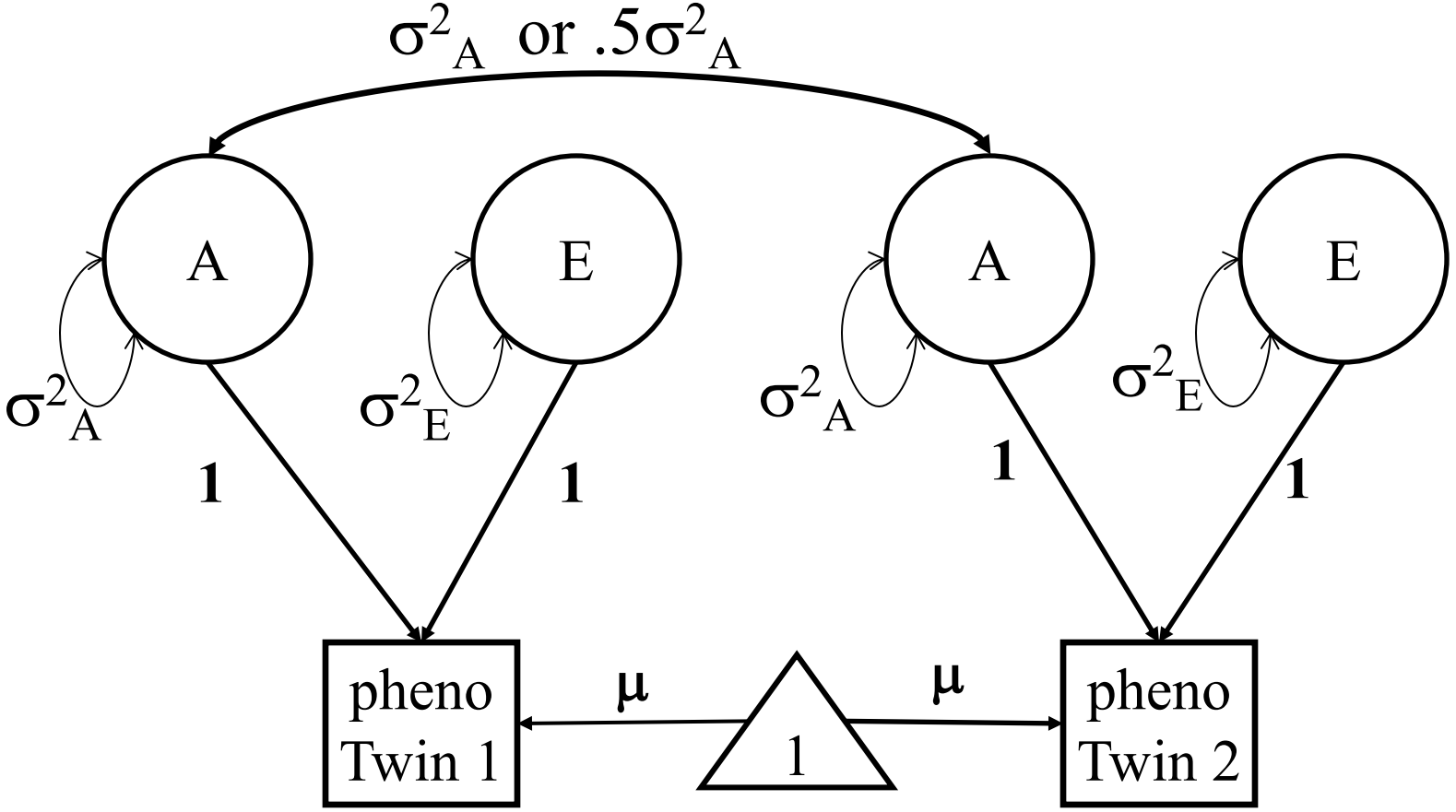
Sex Redefined: The Idea of 2 Sexes Is Overly Simplistic

Biologists now think there is a larger spectrum than just binary female and male

By Claire Ainsworth, Nature magazine on October 22, 2018

Standard AE model

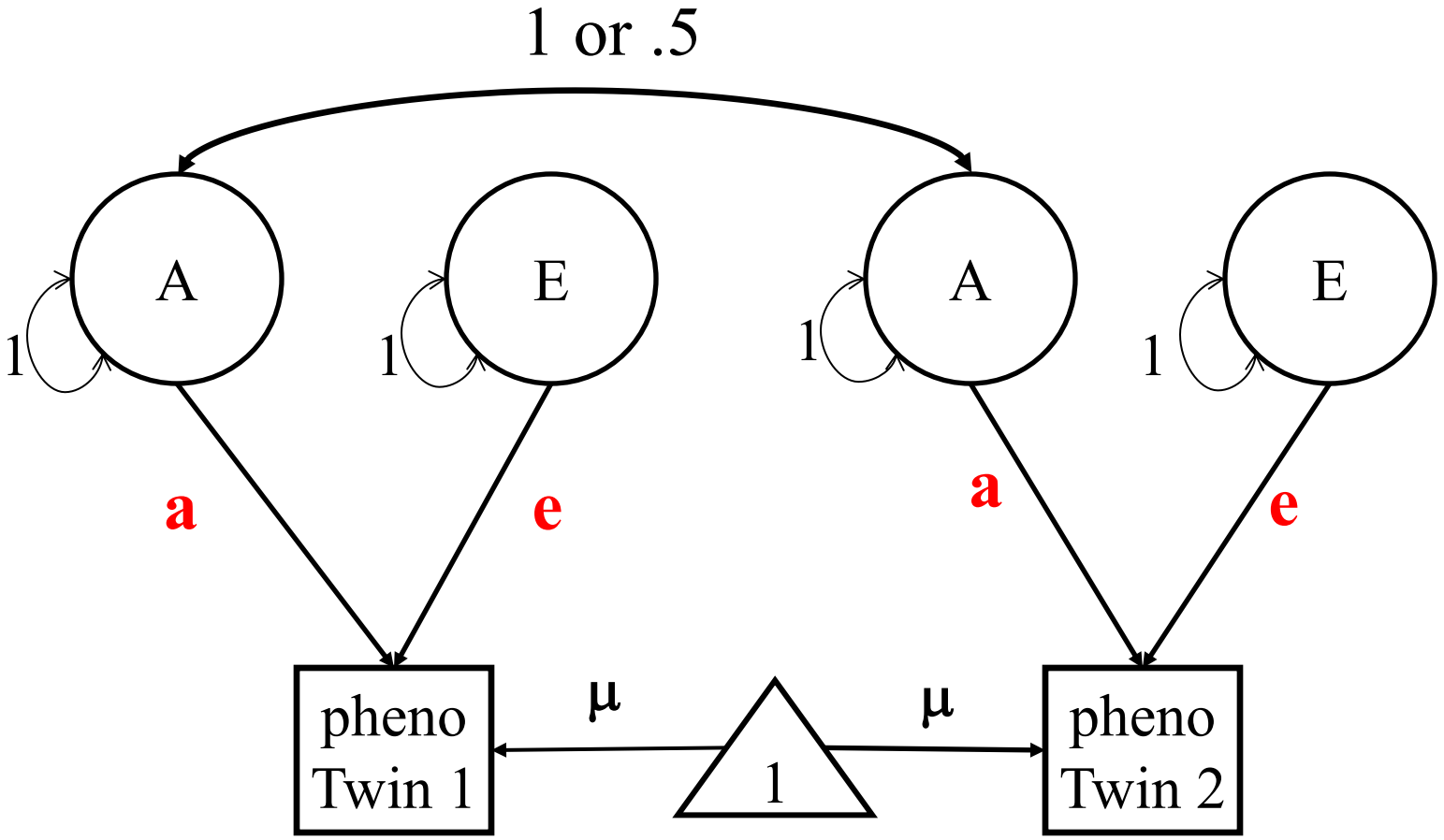
$$Ph_i - \mu = A_i + E_i$$



mean(Ph) = μ

var(Ph) = $\sigma^2_{Ph} = 1*\sigma^2_A*1 + 1*\sigma^2_E*1 = \sigma^2_A + \sigma^2_E$

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



mean(Ph) = μ

var(Ph) = $\sigma^2_{Ph} = V_{Ph} = a*1*a + e*1*e = a^2 + e^2$

Here's the ACE model (variance component):

$$\Sigma_{MZ} = \begin{matrix} \sigma^2_A + \sigma^2_C + \sigma^2_E & \sigma^2_A + \sigma^2_C \\ \sigma^2_A + \sigma^2_C & \sigma^2_A + \sigma^2_C + \sigma^2_E \end{matrix}$$

$$\mu_{MZ} = \begin{matrix} \mu \\ \mu \end{matrix}$$

$$\Sigma_{DZ} = \begin{matrix} \sigma^2_A + \sigma^2_C + \sigma^2_E & \tfrac{1}{2}\sigma^2_A + \sigma^2_C \\ \tfrac{1}{2}\sigma^2_A + \sigma^2_C & \sigma^2_A + \sigma^2_C + \sigma^2_E \end{matrix}$$

$$\mu_{DZ} = \begin{matrix} \mu \\ \mu \end{matrix}$$

NOTE: When we fit this model we assume that the model holds in the **population of interest**.
- conceptually and statistically a big deal.

What if the population comprises two discernable (sub)populations of interest, e.g., males and females?

Main effect of sex on phenotype

Sex by A (genotype), E (environment) interactions

If we ignore the source of *heterogeneity*
the estimates of μ, σ^2_E, σ^2_A may be biased ...
and even the statistical tests may be affected .... BAD!

What to do?

Include *source of heterogeneity*, moderator, in the model (sex, age, ... ANY VARIABLE **THEORY** prescribes) to render testable the moderation effects.

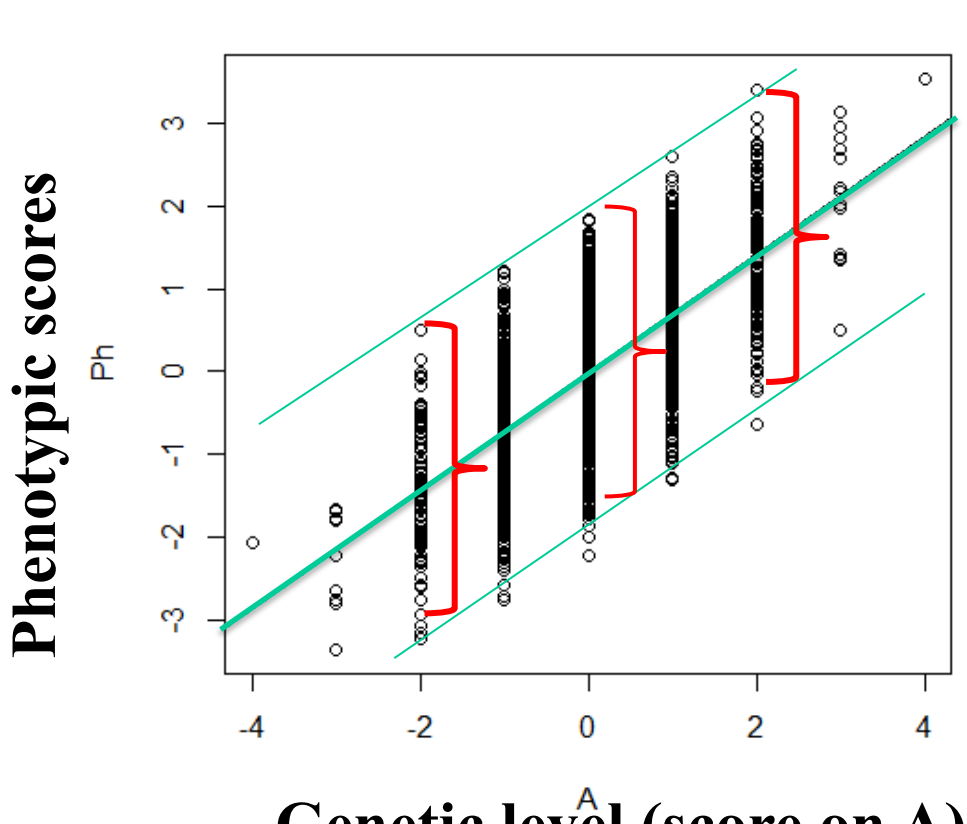
E.g., diathesis-stress model identifies childhood trauma as a moderator of genetic effects on depression.

Colodro-Conde L, et al. A direct test of the diathesis-stress model for depression. Mol. Psychiatry. 2018;23:1590–1596. doi: 10.1038/mp.2017.130.

What is moderation (a.k.a. interaction)?

To test it (using statistics), and we define it statistically.

no moderation ... homoskedatic....homogeneity

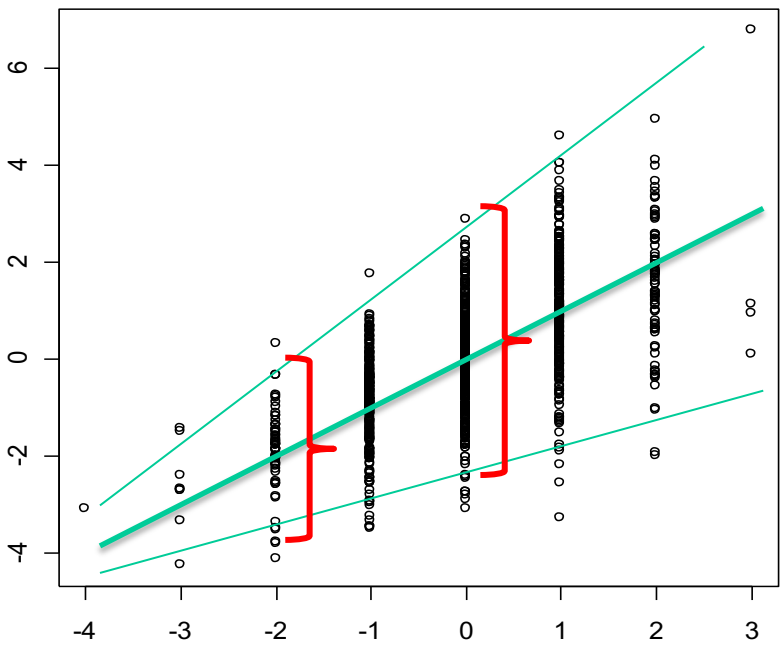


Environmental Dispersion

Variance of E given A score is ***approximately constant***

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

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



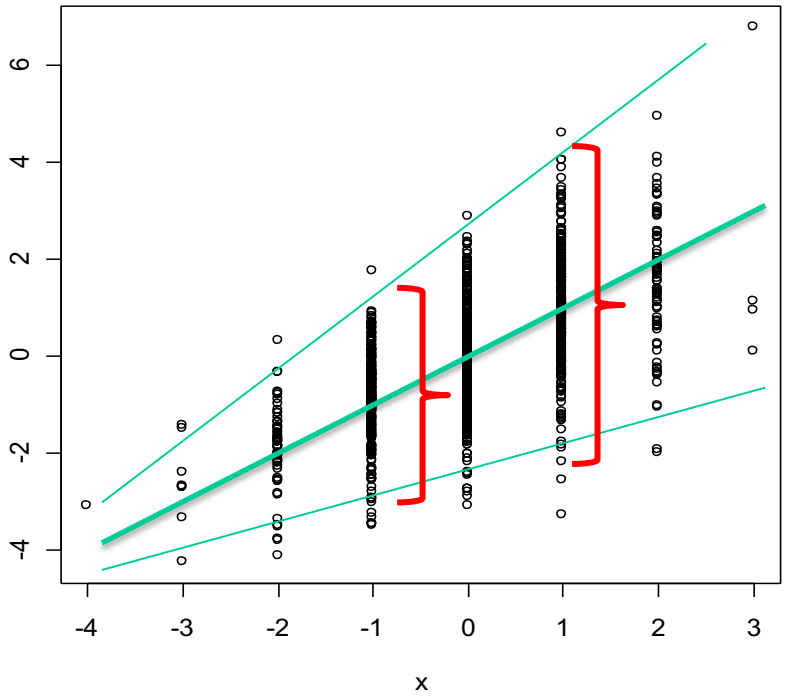
Environmental Dispersion

Variance of E given A score is ***not*** **constant**

A x E as "genetic control" of sensitivity to different environments: **heteroskedasticity (heterogeneity)**

e=f_e(A) or σ^2_E =g_e(A) -> Environmental effects (**E**) systematically vary with A. A moderator ...

Phenotypic scores

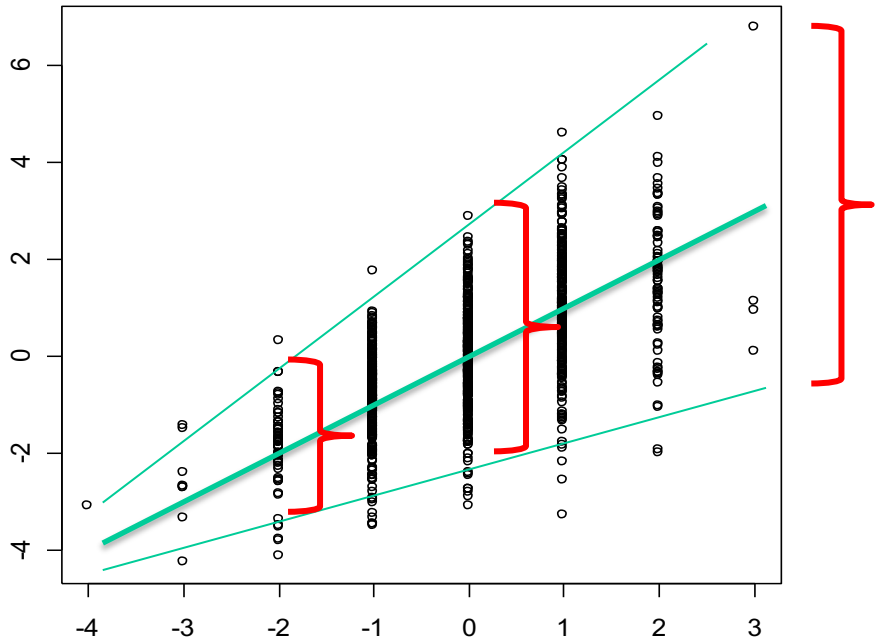


Conditional variance of A given E is ***not*** **constant**

Environmental level (score on E)

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

Phenotypic scores



Genetic variance or (and) Environmental (C and / or E) variance given M

Moderator level

(score on the measured 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

$\sigma^2_A = g_a(M)$, $\sigma^2_C = g_c(M)$, $\sigma^2_E = g_e(M)$

M moderaties the effects of A, C (or D) and E

Moderators are measured variables – may be binary

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

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

Sex (as a binary moderator)– discussed below .

Moderators are measured variables – may be continuous

Age as a moderator of 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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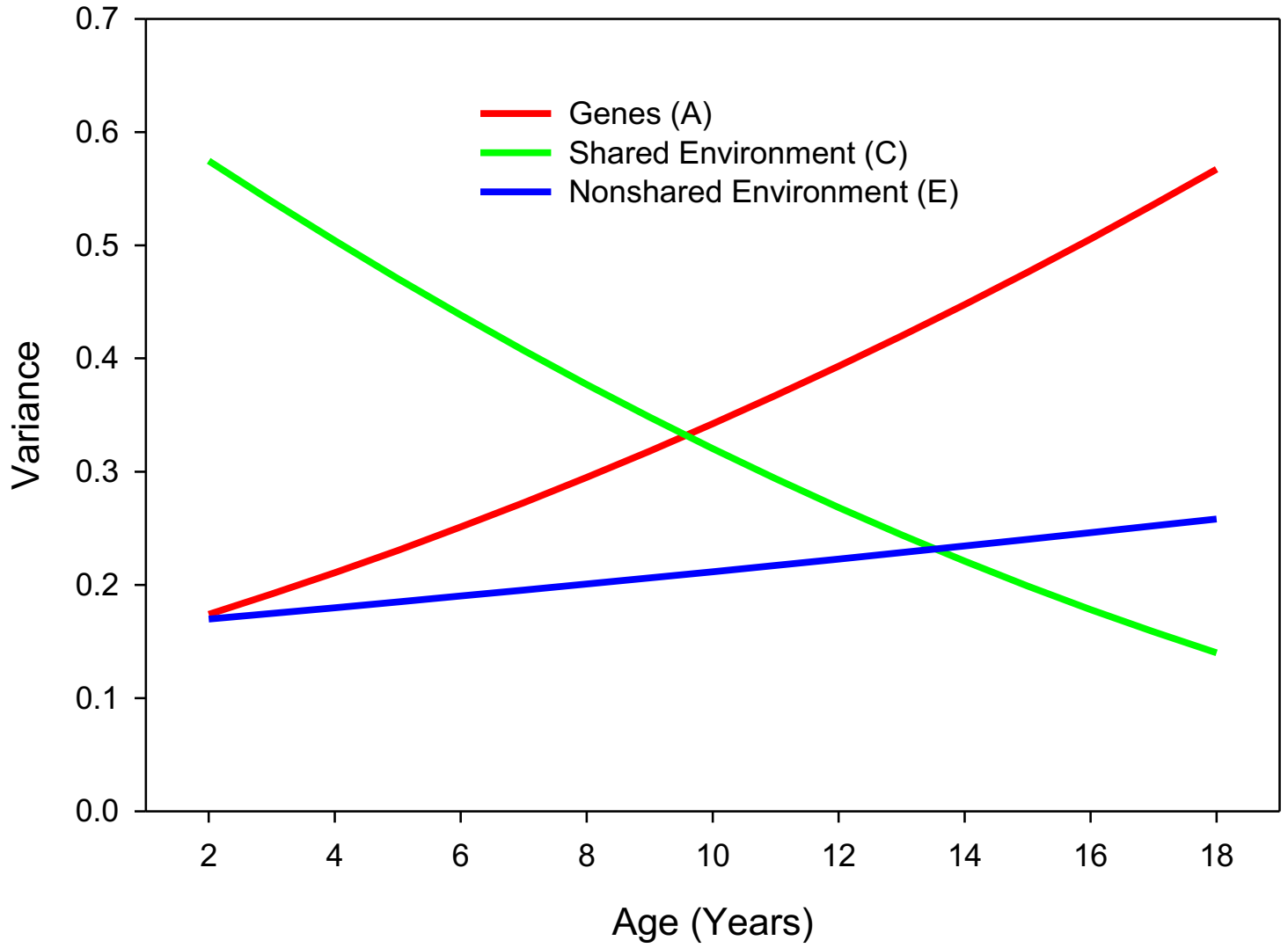
DOI: 10.1177/0956797615612727
pss.sagepub.com
SAGE

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

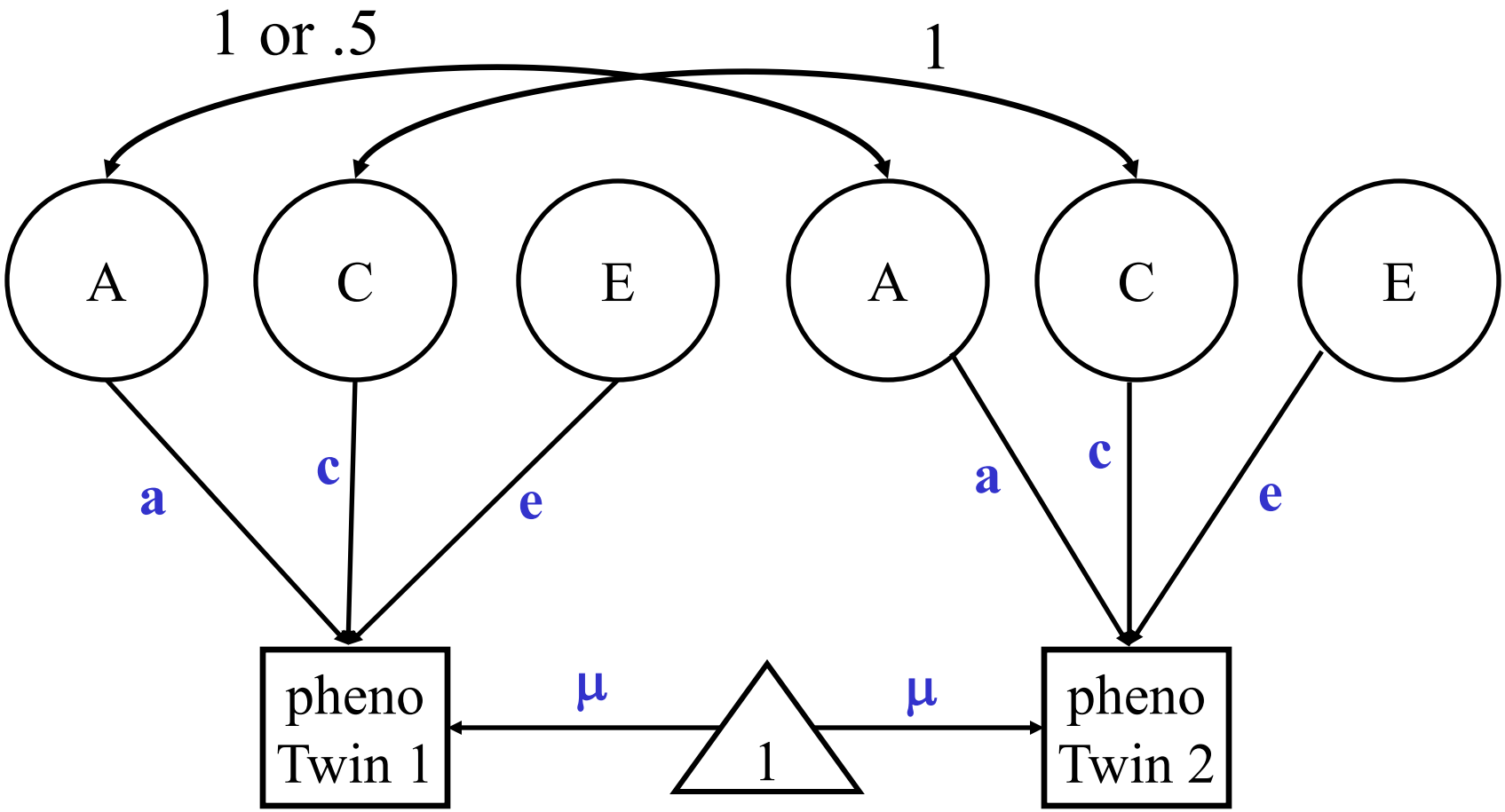
Elliot M. Tucker-Drob[1,2] and Timothy C. Bates[3]
[1]Department of Psychology, University of Texas at Austin; [2]Population Research Center, University of Texas at Austin; and [3]Department of Psychology, University of Edinburgh

Intelligence (western / us populations)

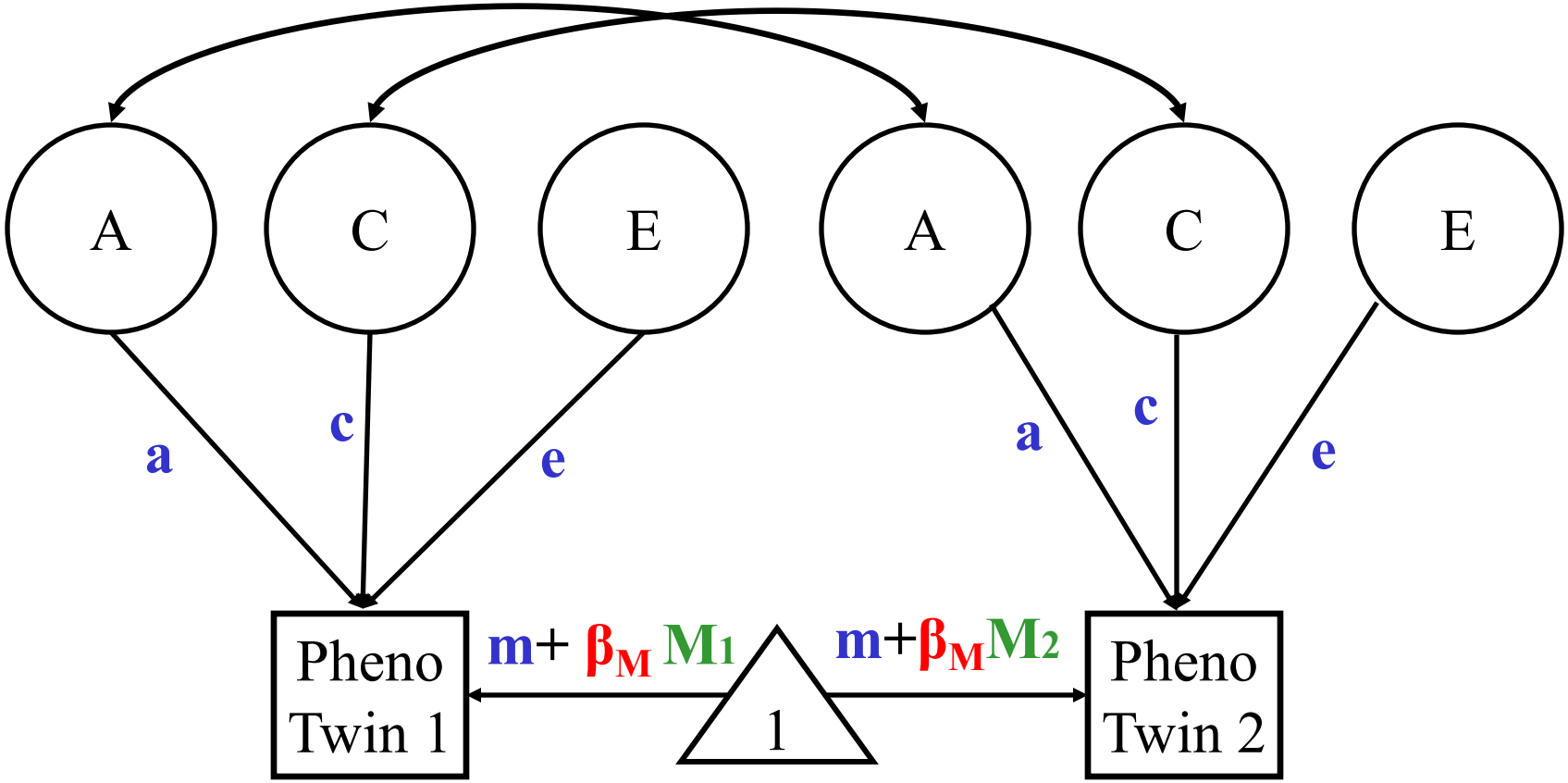


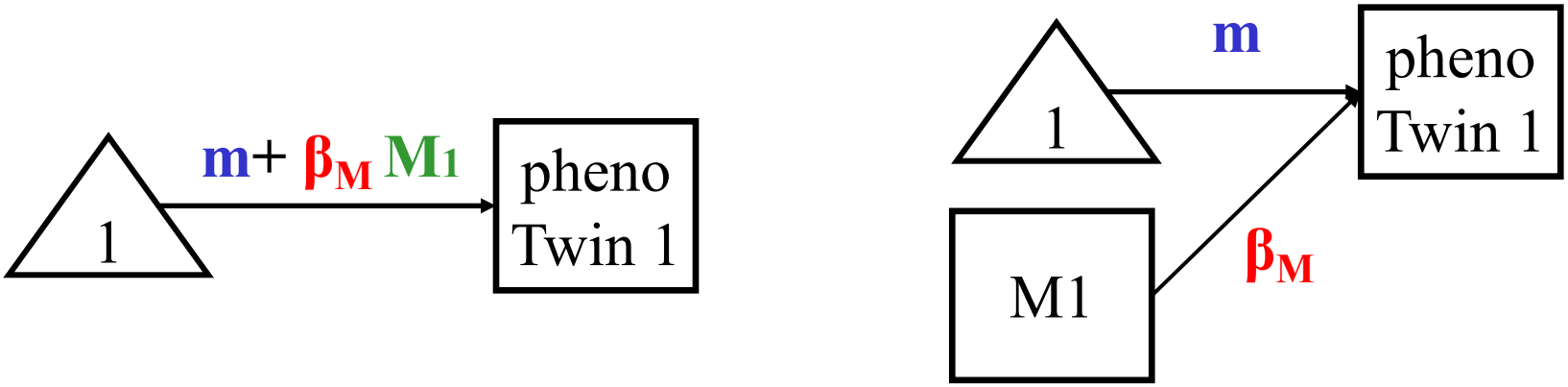
Tucker-Drob & Bates (2015)

ACE model (A,C,E standardized) continuous phenotype



ACE model +
Main effect on Means





equivalent

Two representations of the regression of Phenotype on M ...

$\text{Pheno}_i = \mathbf{m} + \boldsymbol{\beta}_M \mathbf{M1}_i + \text{residual}_i$

Summary stats (no moderator)

- Means vector

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

- Covariance matrix (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

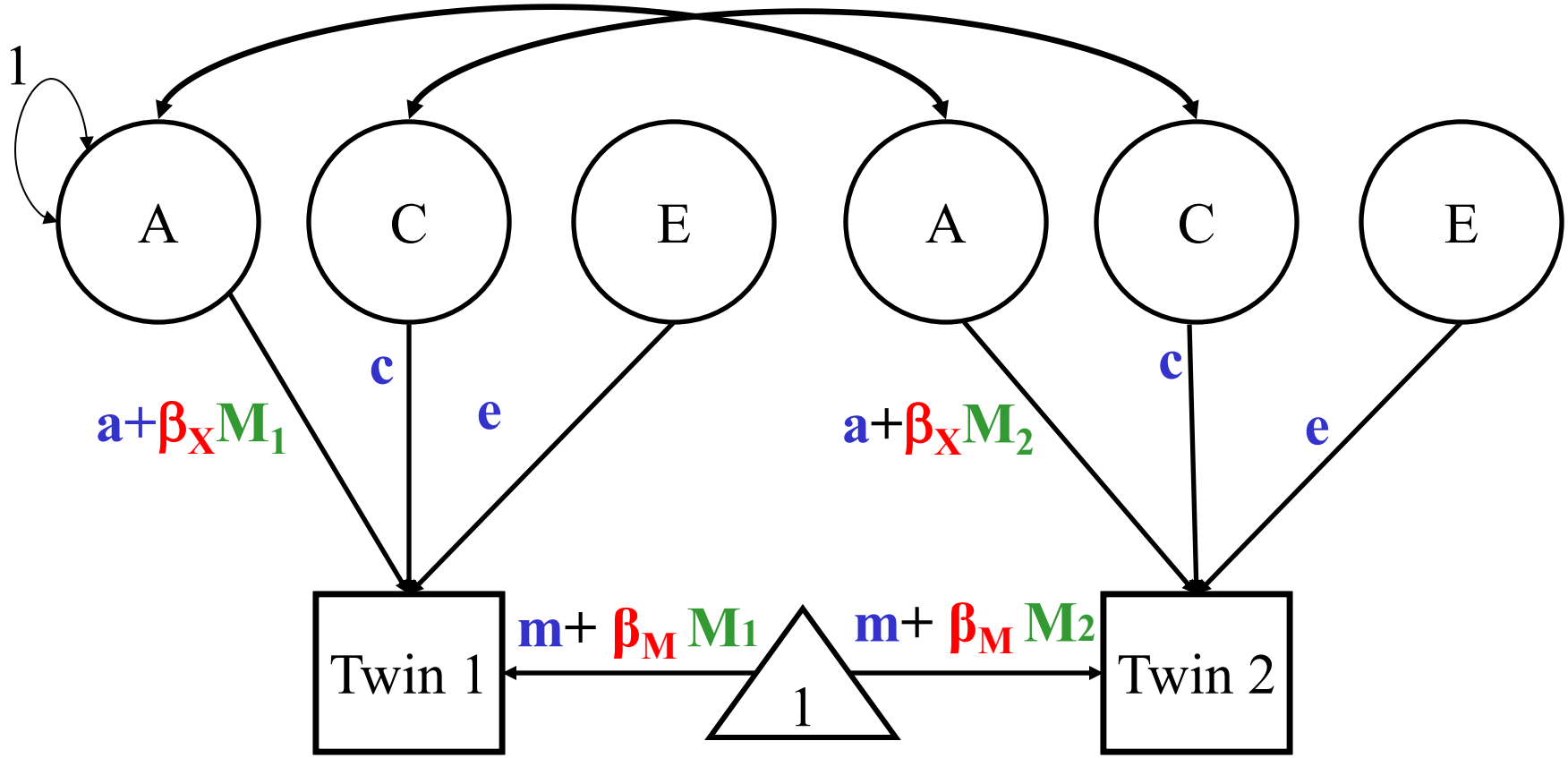
- Means vector (conditional on M)

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

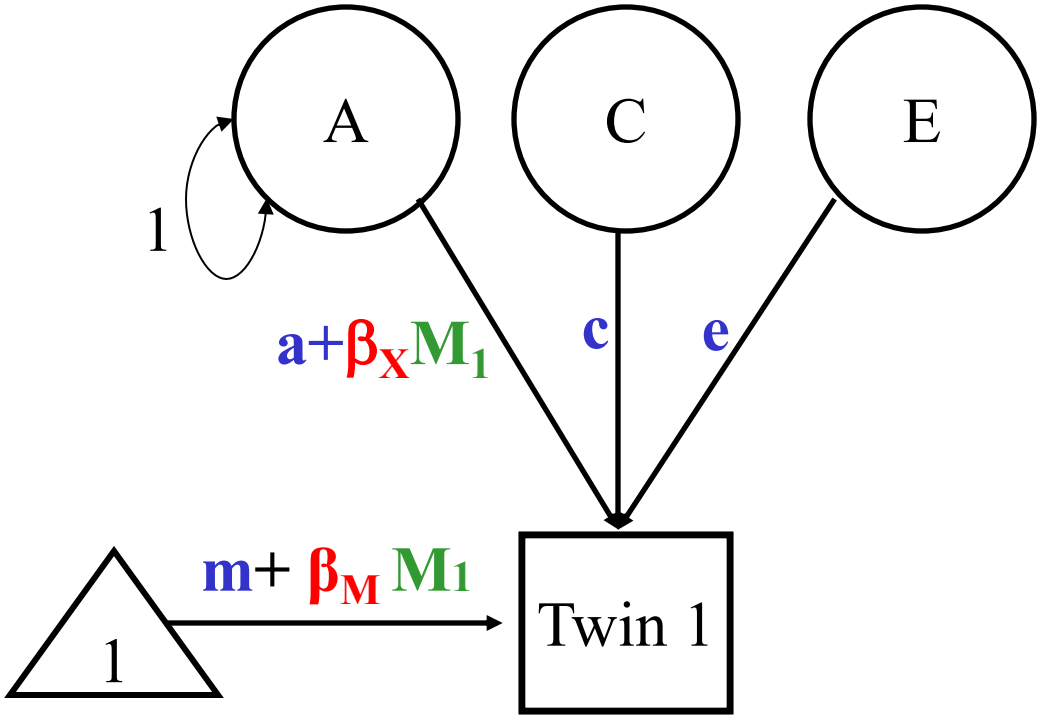
- Covariance matrix (r = 1 or r=½)

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

ACE model + main effect and effect on A path



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

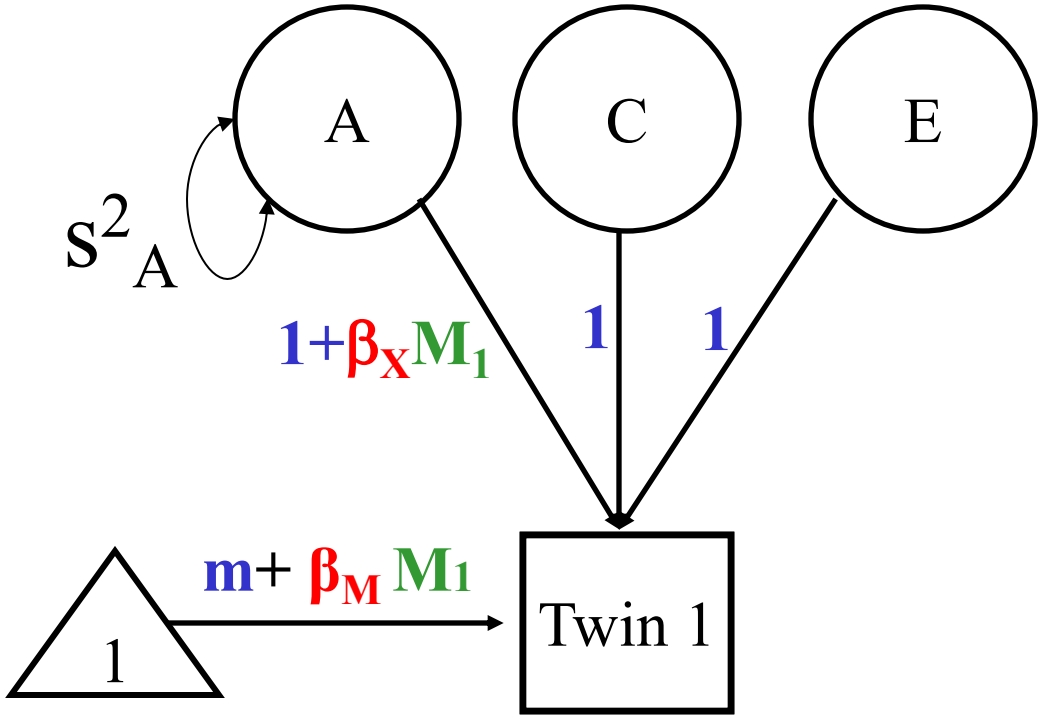


If M is binary (0/1) (instead of continuous)

M_1=0 → mean= **m** & s^2_A = $\mathbf{a}^2$

M_1=1 → mean= **m**+ β_M & s^2_A = $(\mathbf{a}+\beta_X M_1)^2$

Test of moderation: test of β_X

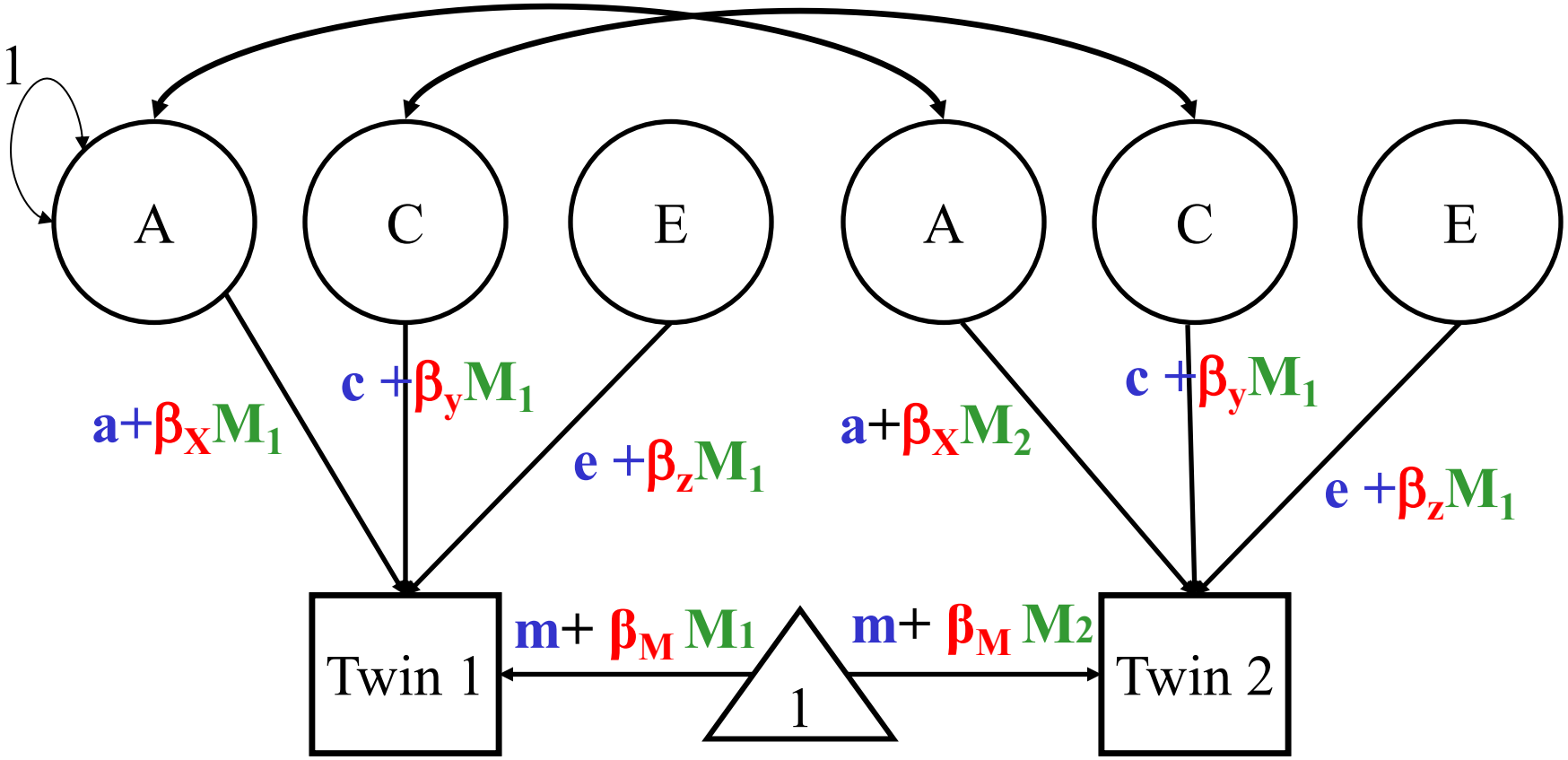


If M is binary (0/1) (instead of continuous)

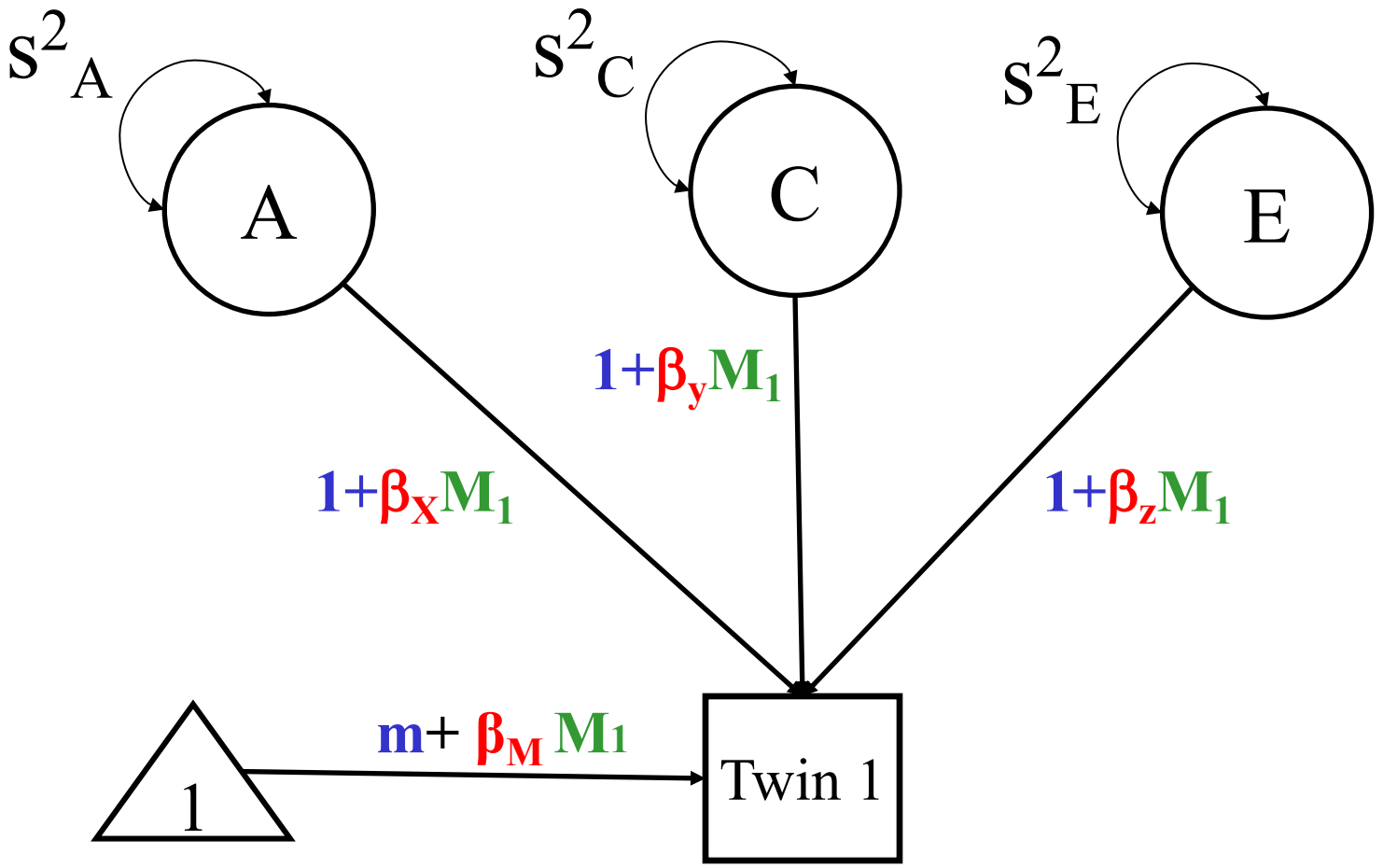
$M_1=0 \rightarrow$ mean= **m** & $s^2_A = s^2_A$

$M_1=1 \rightarrow$ mean= $m+\beta_M$ & $s^2_A = s^2_A (1+\beta_X)^2$

Test of moderation: test of β_X



- Main Effect on phenotype (linear regression)
- Effect path parameters: Moderation effects (A x M, C x M, E x M interaction).
- Test of moderation: Tests of β_x, β_y, β_z (3 df omibus test)



A variance component version (just the twin 1 member)

Conditional expected **variances**

Standard Twin Model:

$s^2_{Ph} = a^2 + c^2 + e^2$ or $s^2_A + s^2_C + s^2_E$

Moderation Model:

$Var(Ph|M) =$

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

$s^2_A(1 + \beta_X M)^2 + s^2_C(1 + \beta_Y M)^2 + s^2_E(1 + \beta_Z M)^2$

Ph|M mean "the phenotype given a value on M" or "the phenotype conditional on M"

Conditional expected MZ / DZ covariances

$$Cov(Ph_1,Ph_2|M)_{MZ} = (a+\beta_X M)^2 + (c+\beta_Y M)^2$$
$$Cov(Ph_1,Ph_2|M)_{DZ} = \tfrac{1}{2}(a+\beta_X M)^2 + (c+\beta_Y M)^2$$

$$Cov(Ph_1,Ph_2|M)_{MZ} = s^2_A(1+\beta_X M)^2 + s^2_C(1+\beta_Y M)^2$$
$$Cov(Ph_1,Ph_2|M)_{DZ} = \tfrac{1}{2}s^2_A(1+\beta_X M)^2 + s^2_C(1+\beta_Y M)^2$$

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

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

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

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

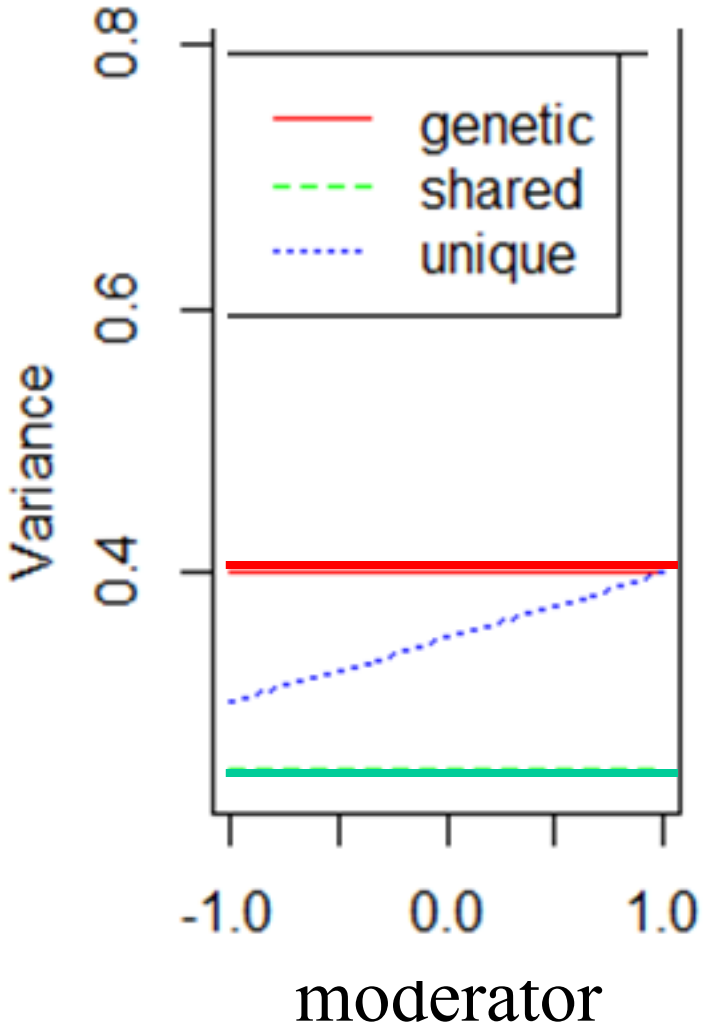
$$(h_{st}^2|M + c_{st}^2|M + e_{st}^2|M) = 1$$

Standardized conditional on value of M..

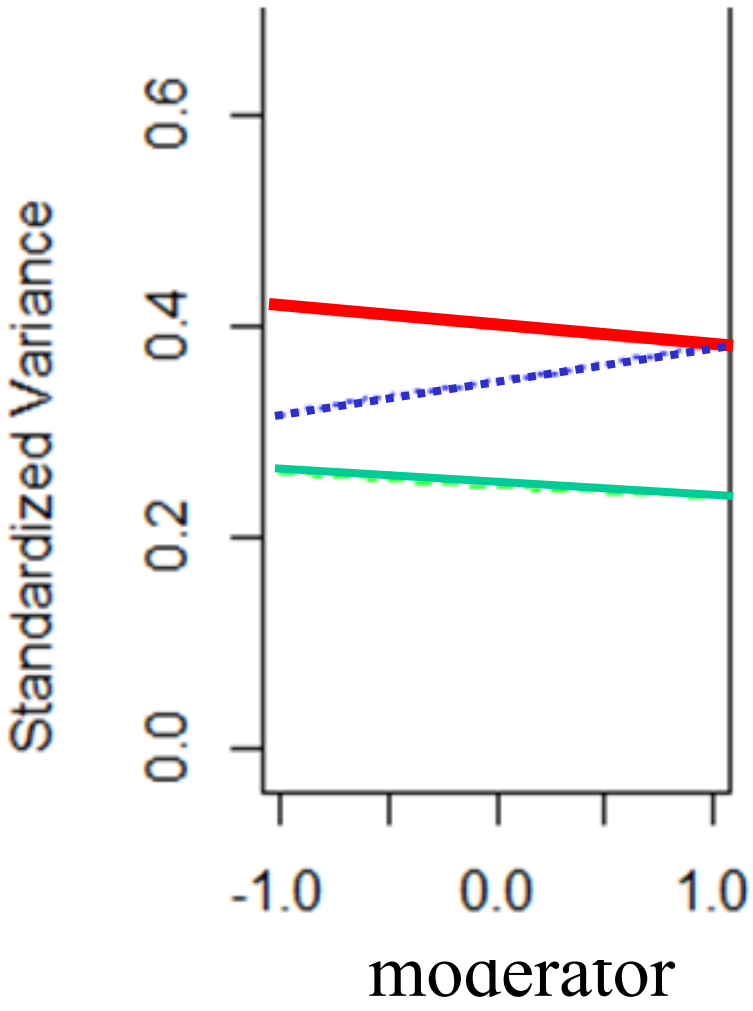
But $h_{st}^2|M$ can vary with M while $\beta_X = 0$!

same applies to $c_{st}^2|M$ and $e_{st}^2|M$

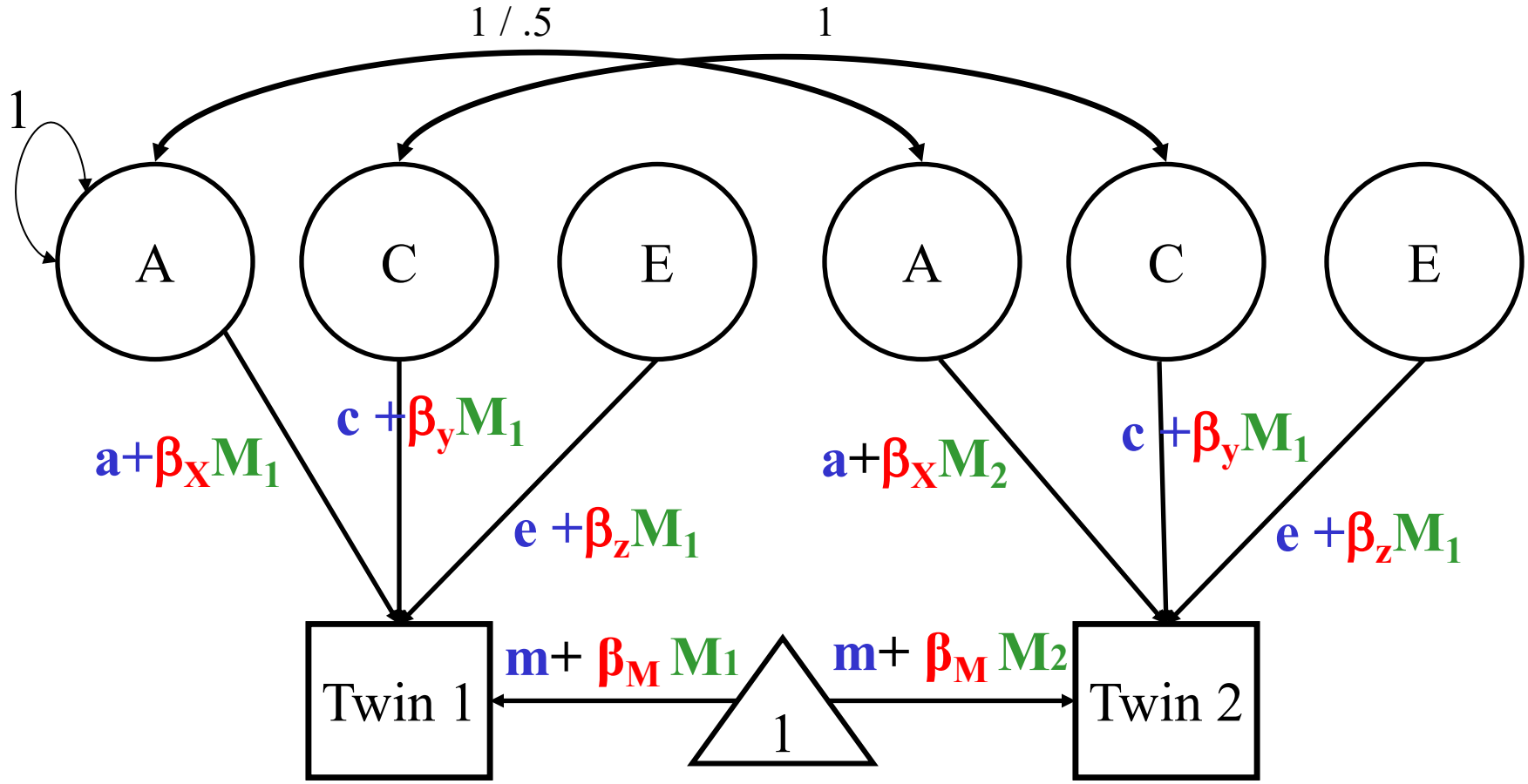
only e moderated
(umx plots)



a,c moderated? nope!
(umx plots)

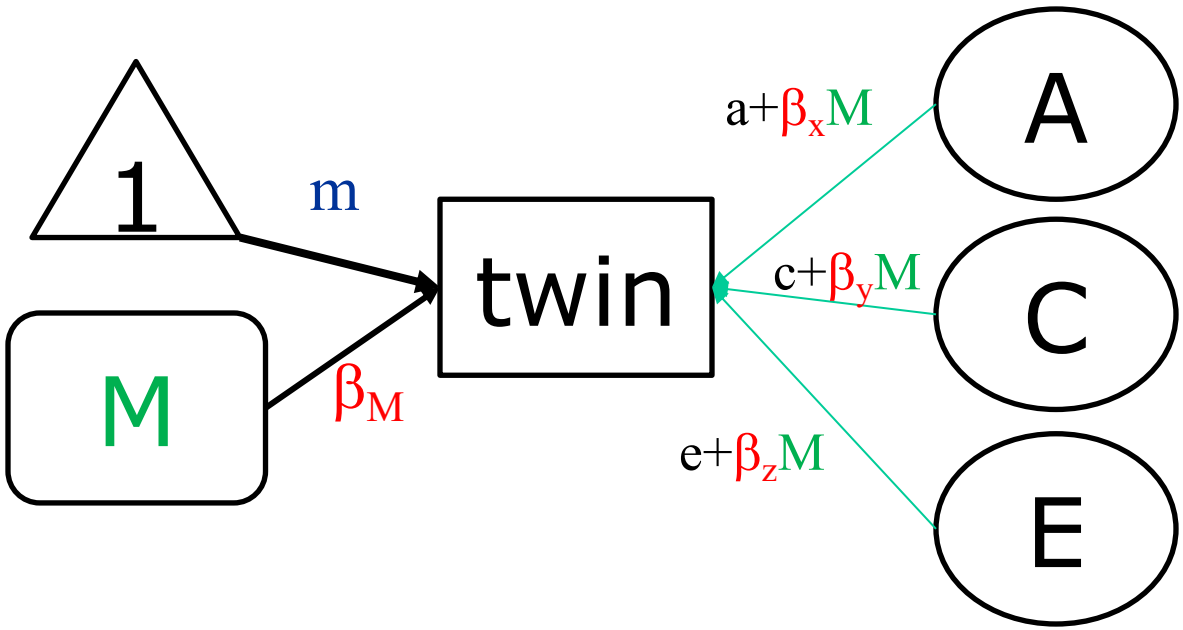


R code in the slide notes

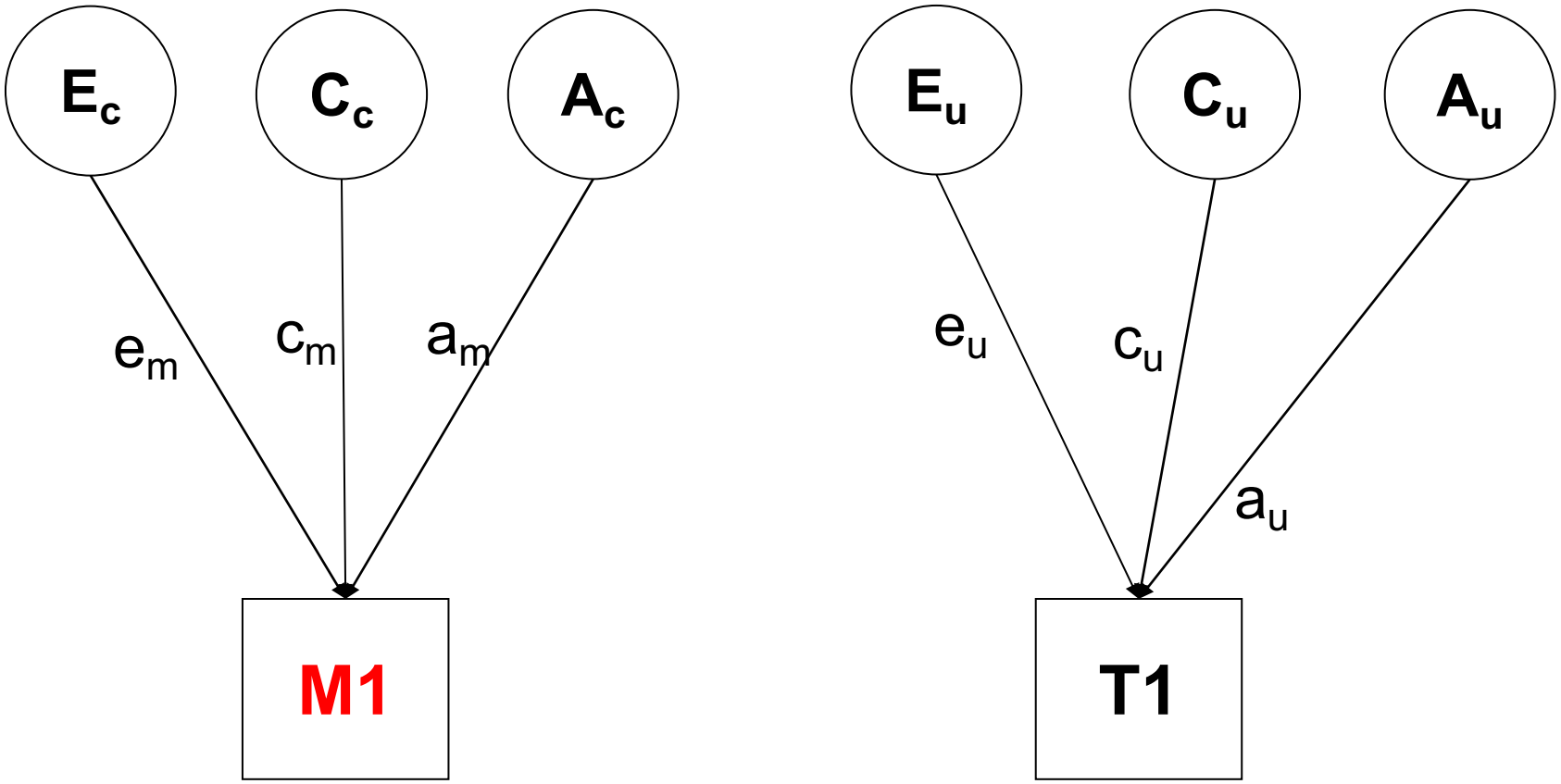


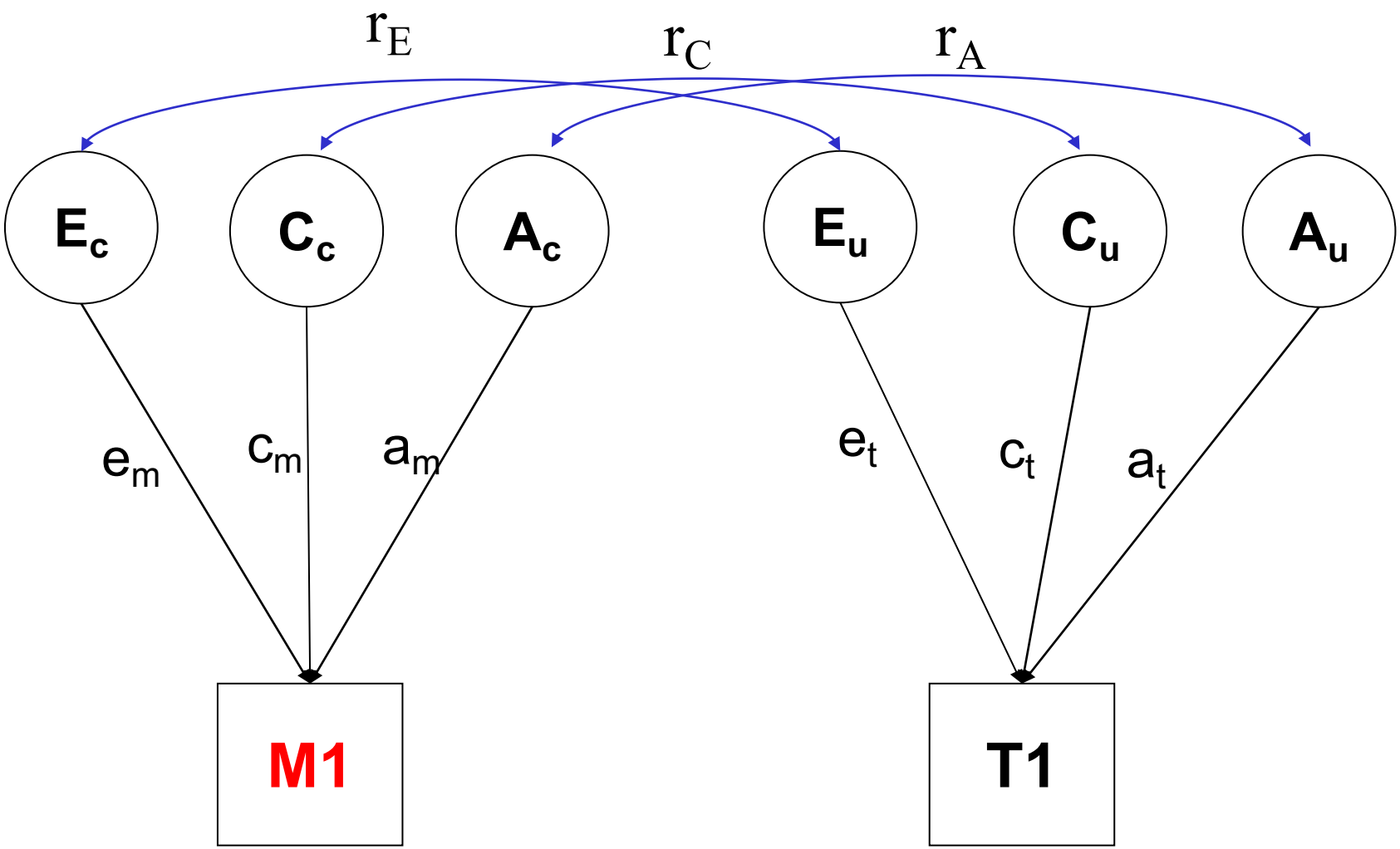
But what have we assumed concerning M?
So far treated like a definition variable (and a fixed regressor).

The M is a measured variable



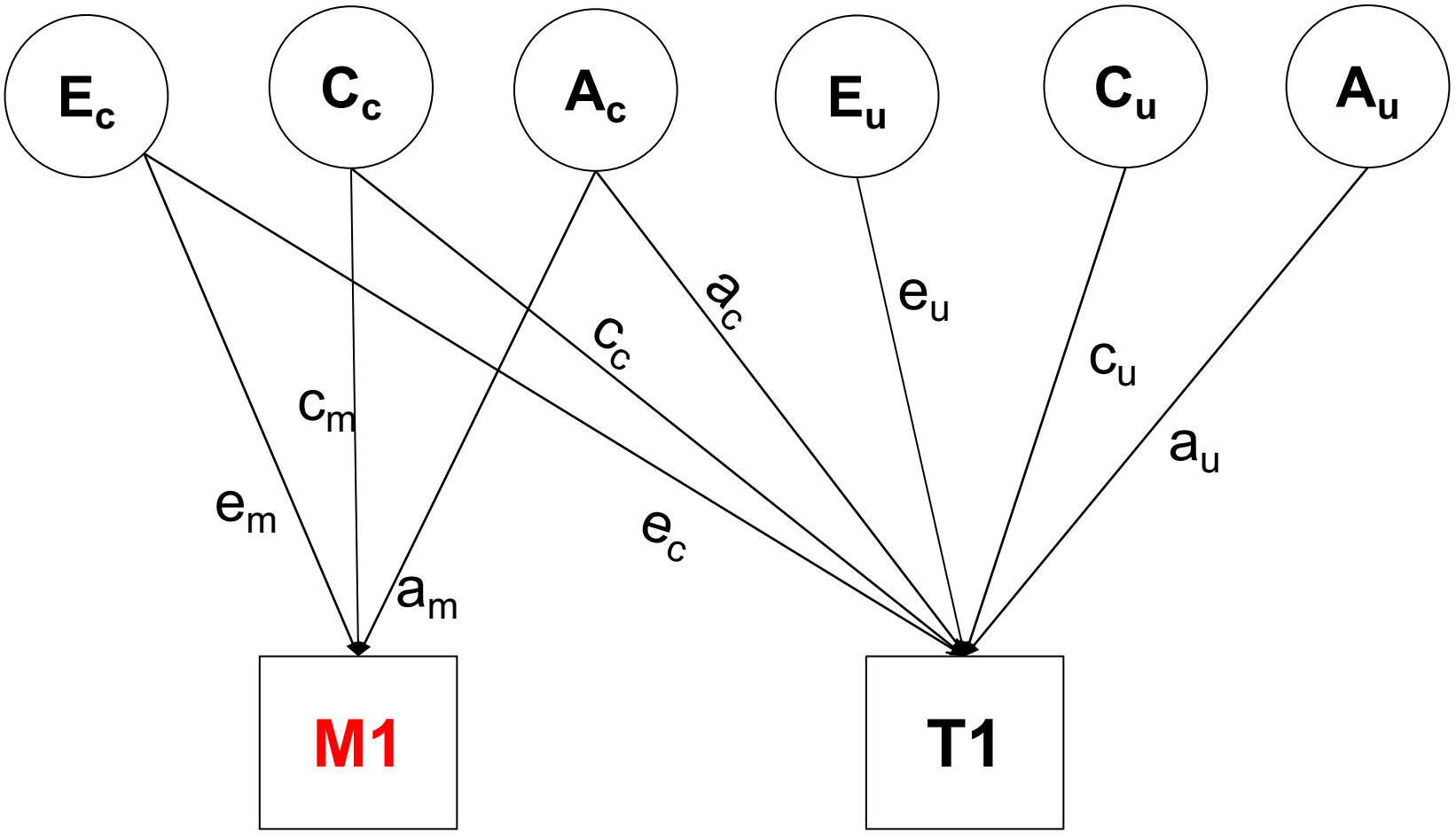
M is <u>environmental?</u>
Sociaal support? Employment status?
Marital status? (No No and No).
The weather (yes)


E_c
C_c
A_c
e_m
c_m
a_m
M1
E_u
C_u
A_u
e_u
c_u
a_u
T1



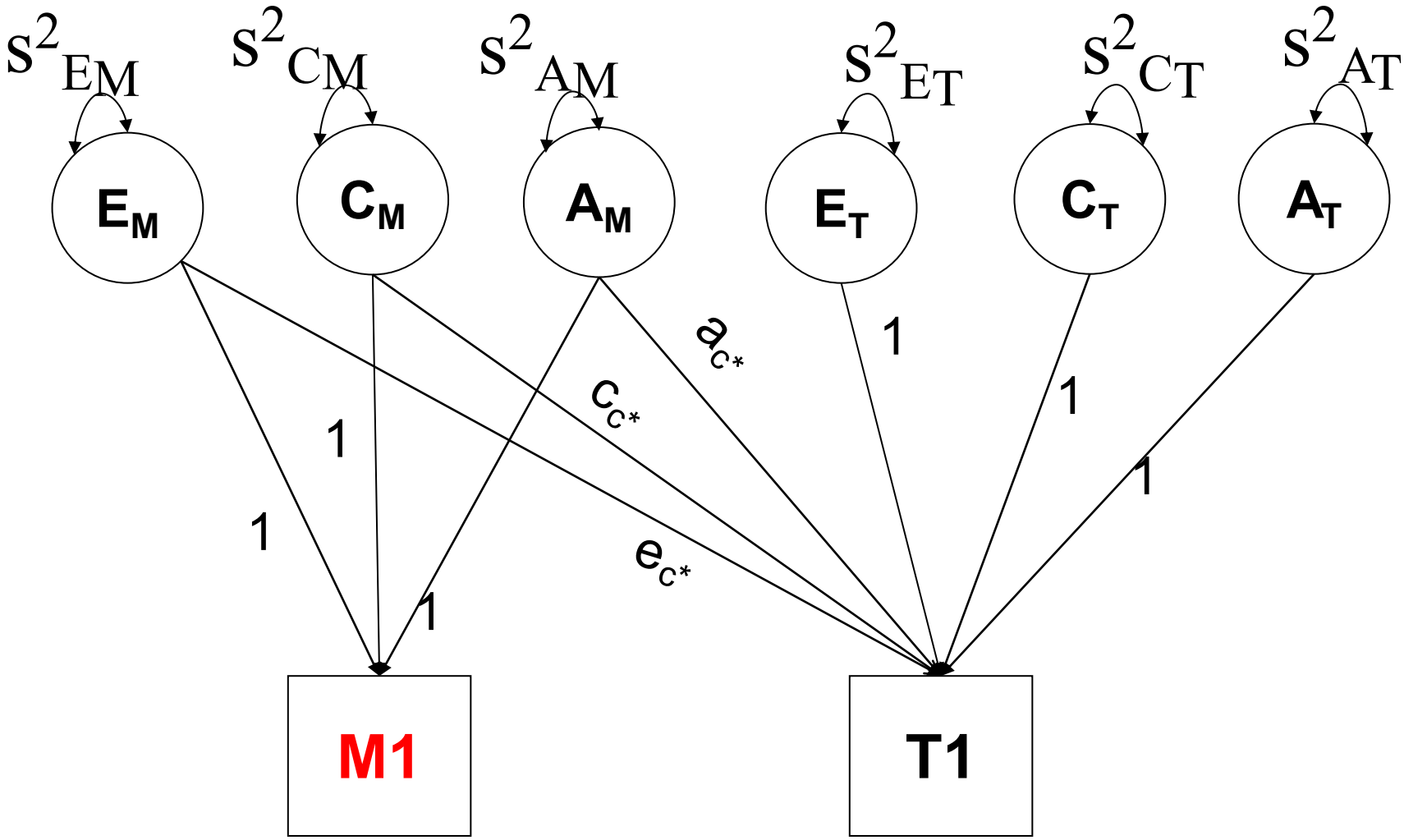
$$\text{cov}(M1,T1) = a_m r_E a_t + c_m r_C c_t + e_m r_E e_t$$

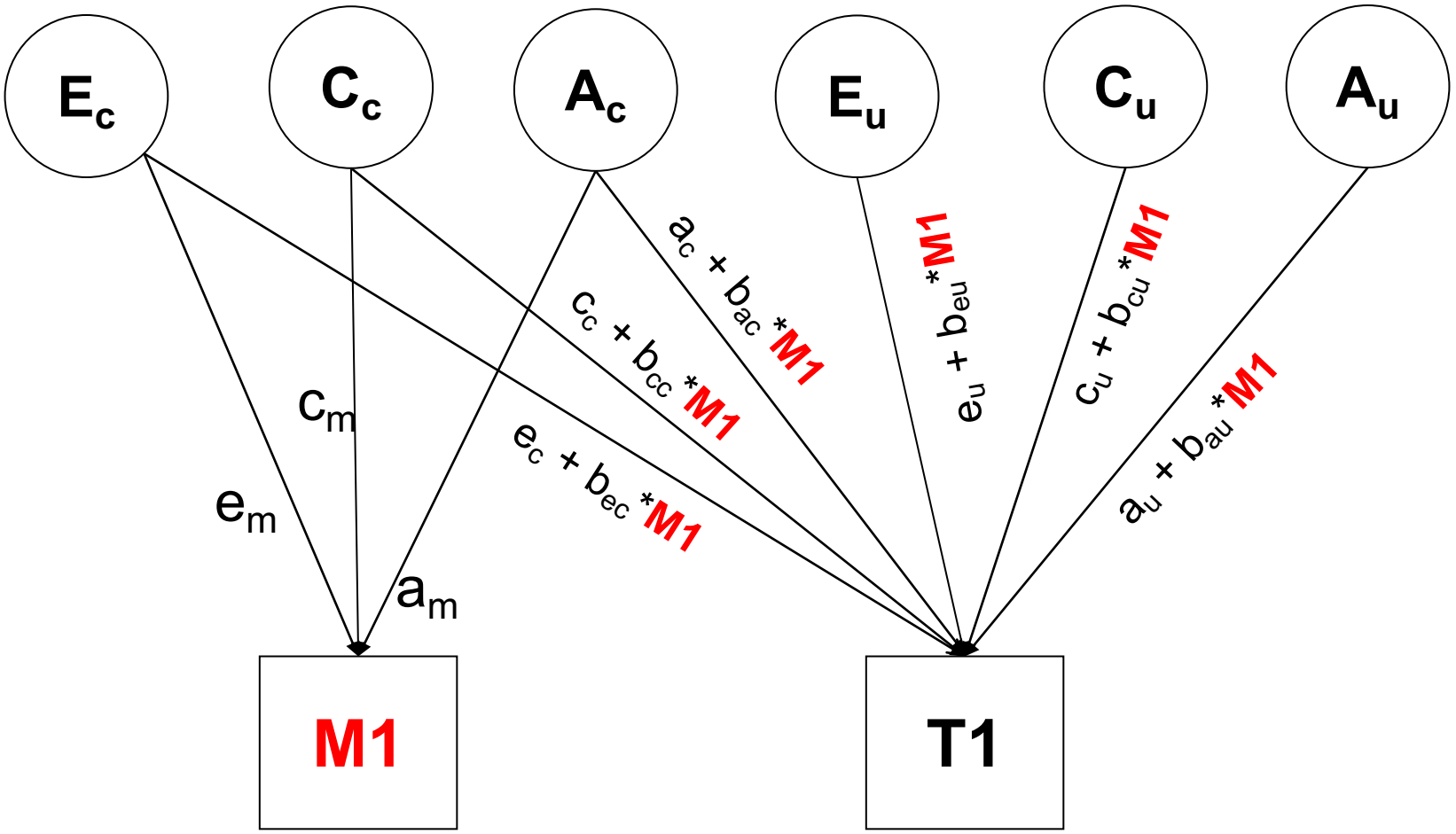
$$\text{var}(T1) = a_t^2 + c_t^2 + e_t^2$$



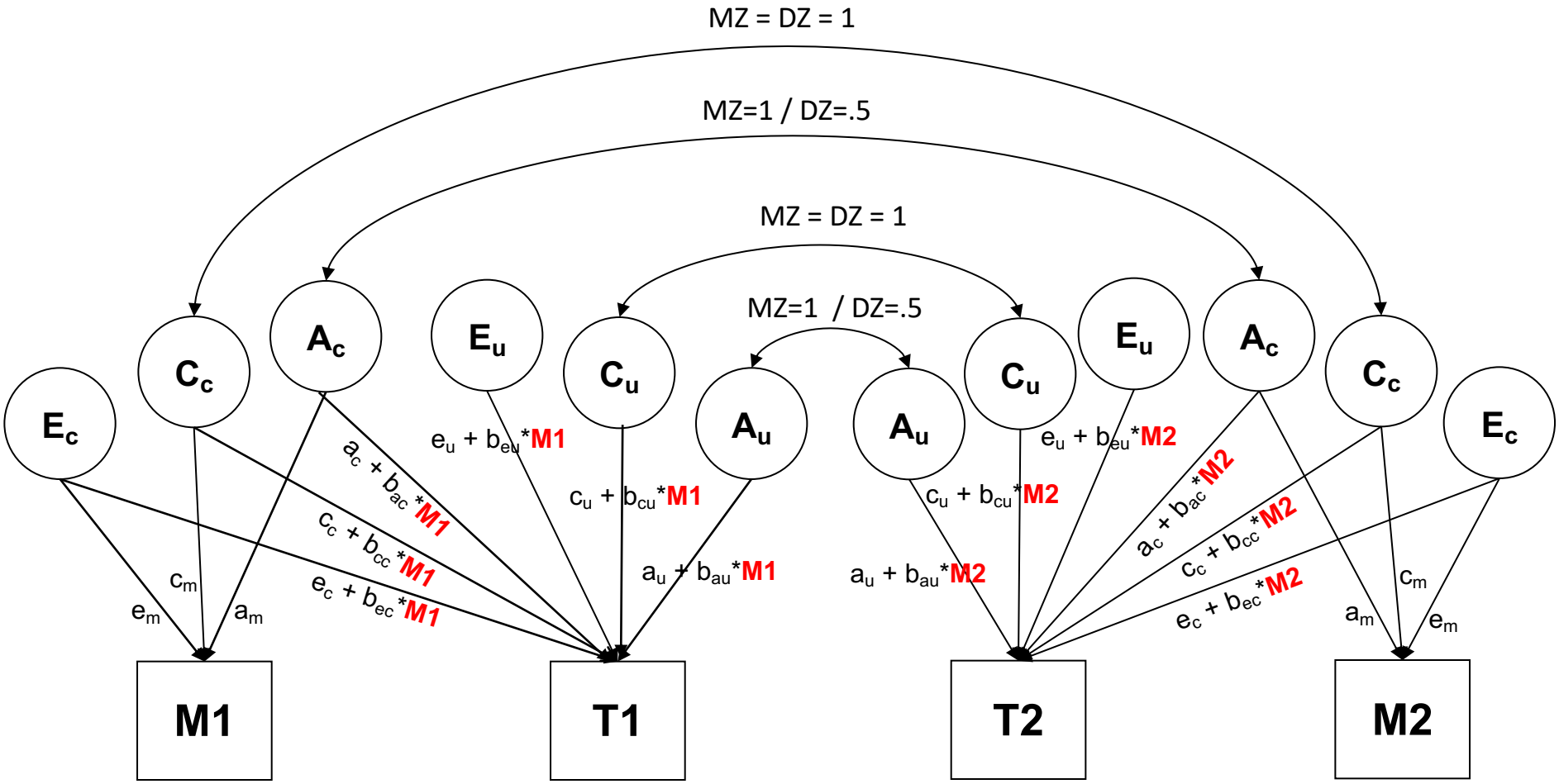
$$\text{cov}(M1,T1) = a_m a_c + c_m c_c + e_m e_c$$

$$\text{var}(T1) = e_c^2 + c_c^2 + e_c^2 + e_u^2 + c_u^2 + e_u^2$$


s^2_{EM}
s^2_{CM}
s^2_{AM}
s^2_{ET}
s^2_{CT}
s^2_{AT}
E_M
C_M
A_M
E_T
C_T
A_T
a_{c*}
c_{c*}
e_{c*}
1
1
1
1
1
1
1
M1
T1



$$\text{var}(T1|\ \mathbf{M1}) = (e_c + b_{ec}*\mathbf{M1})^2 + (c_c + b_{cc}*\mathbf{M1})^2 + (a_c + b_{ac}*\mathbf{M1})^2 + (e_u + b_{eu}*\mathbf{M1})^2 + (c_u + b_{cu}*\mathbf{M1})^2 + (a_u + b_{au}*\mathbf{M1})^2$$



umx function available!

ORIGINAL ARTICLE

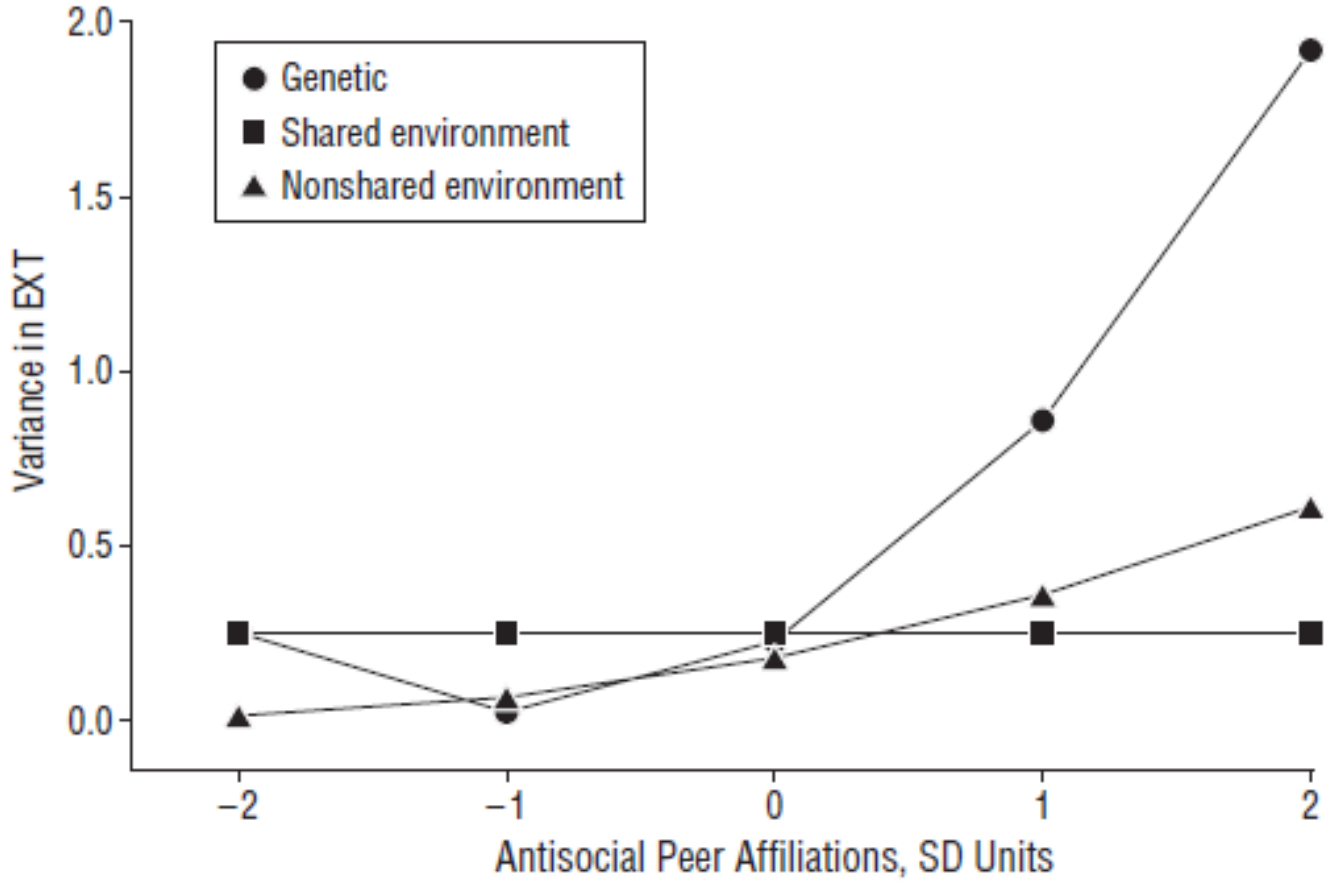
Environmental Adversity and Increasing Genetic Risk for Externalizing Disorders

Brian M. Hicks, PhD; Susan C. South, PhD; Ana C. DiRago, MA; William G. Iacono, PhD; Matt McGue, PhD

Phenotype: externalizing behavior

Moderators: academic achievement and engagement, antisocial and prosocial peer affiliations, mother-child and father-child relationship problems, and stressful life events.

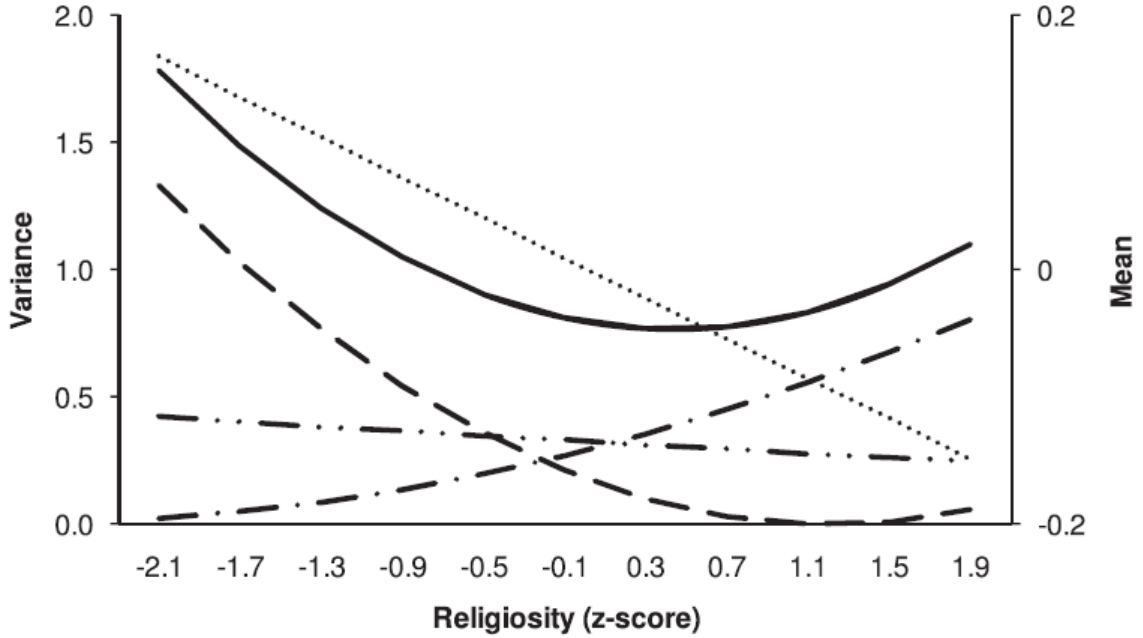
Arch Gen Psychiatry. 2009;66(6):640-648


Genetic
Shared environment
Nonshared environment
Variance in EXT
2.0
1.5
1.0
0.5
0.0
−2
−1
0
1
2
Antisocial Peer Affiliations, SD Units

Alcoholism: Clinical and Experimental Research
Vol. 34, No. 9
September 2010

The Moderating Effect of Religiosity on the Genetic Variance of Problem Alcohol Use

Tanya M. M. Button, John K. Hewitt, Soo H. Rhee, Robin P. Corley, and Michael C. Stallings



What about non-linear moderation? E.g., extend the model from linear to linear + quadratic.

$e_c + b_{ec1}$*__M1__ $+ b_{ec2}$*__M1__^{2}

What about >1 moderators?

Extend the model accordingly

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

What about categorical data?

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

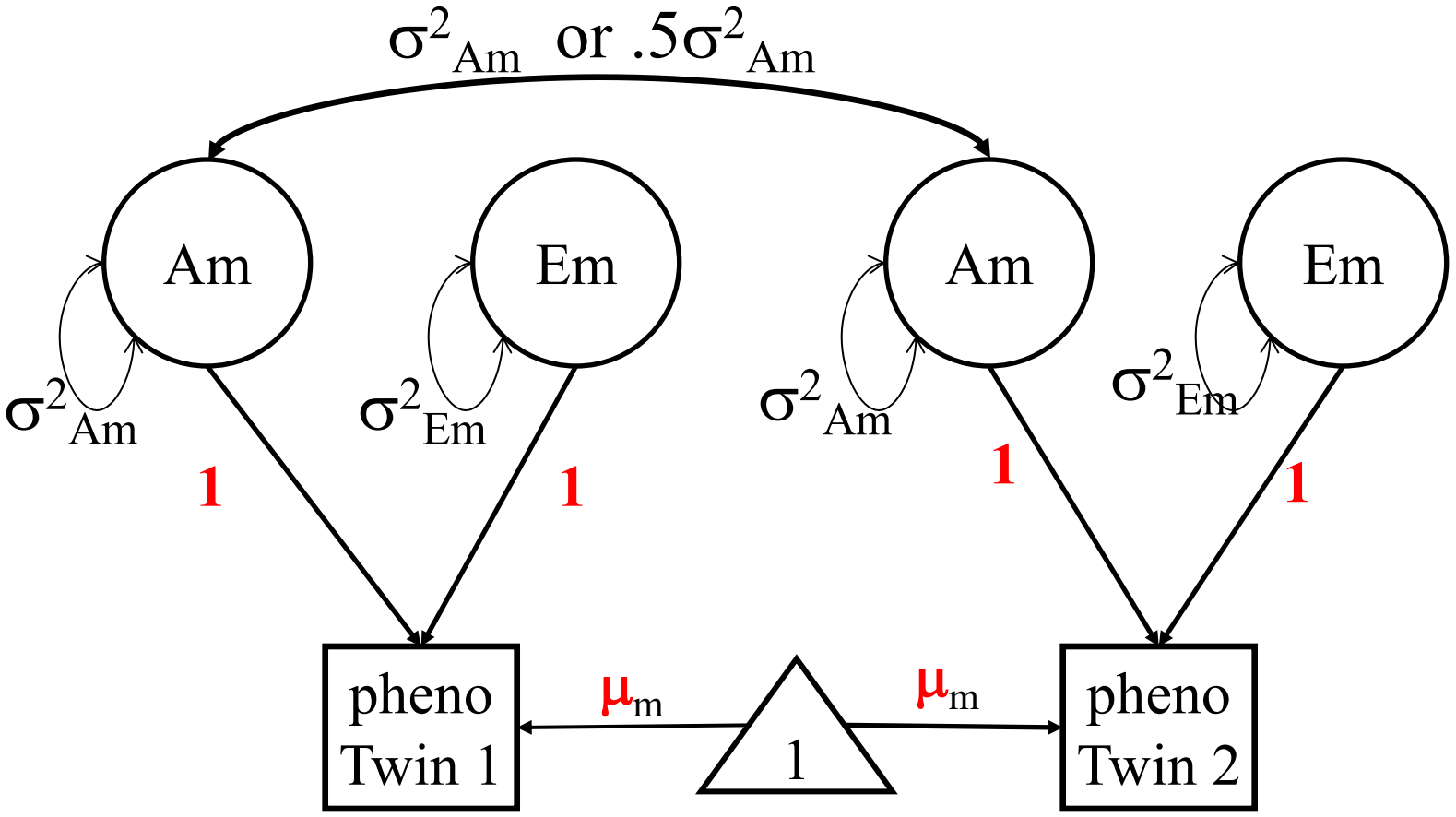
Sarah E. Medland · Michael C. Neale · Lindon J. Eaves · Benjamin M. Neale

Sex special case.... DZOS!

... offer unique means to test hypotheses concerning genetic effects.

5 groups MZM, DZM, MZF, DZF, DZOS

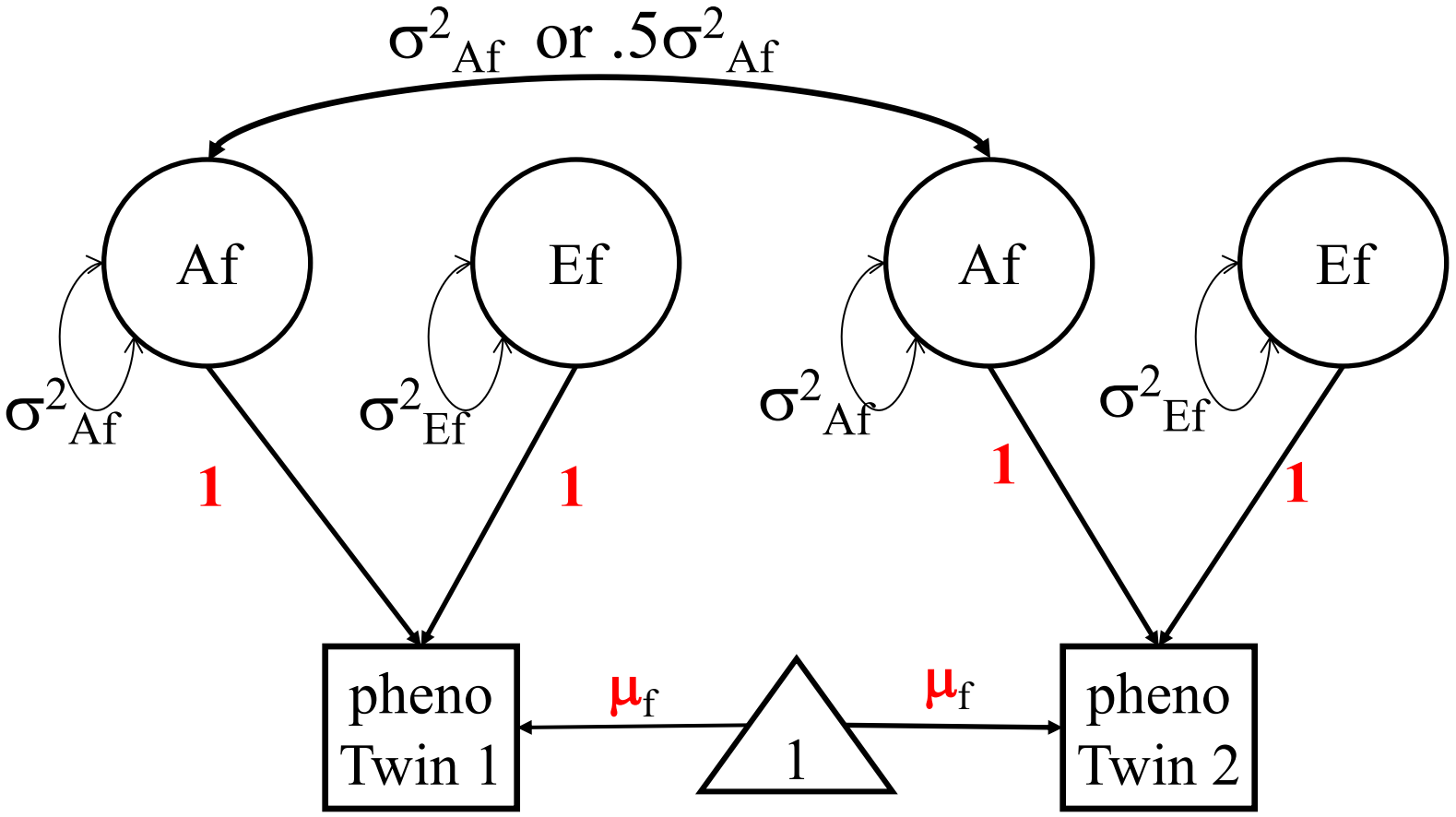
Considered in a 5 group model



$\text{mean}(Ph_m) = \mu_m$

$\text{var}(Ph_m) = \sigma^2_{Ph} = \sigma^2_{Am} + \sigma^2_{Em}$

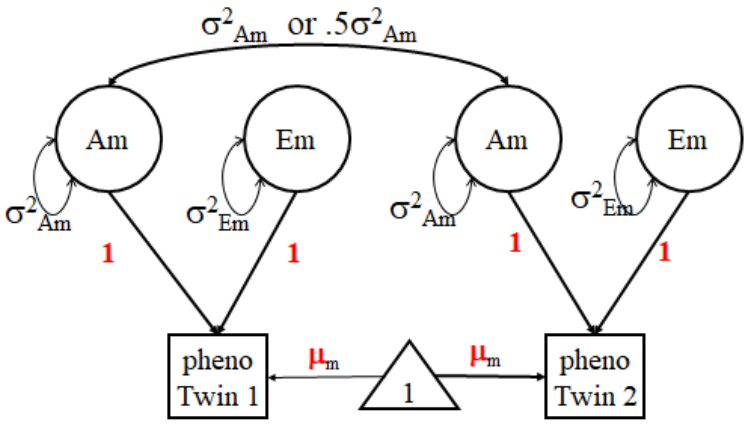
Males twins



$\text{mean}(Ph_f) = \mu_f$

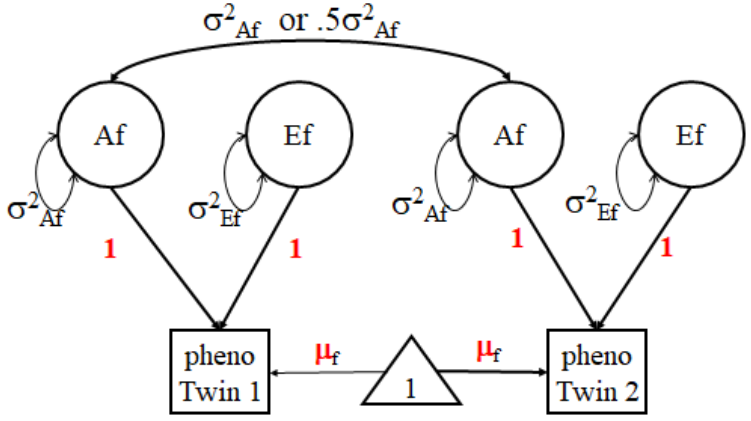
$\text{var}(Ph_f) = \sigma^2_{Ph} = \sigma^2_{Af} + \sigma^2_{Ef}$

Females twins



mean(Ph_m) = μ_m
var(Ph_m) = σ^2_{Ph} = σ^2_{Am} + σ^2_{Em}

Males twins



mean(Ph_f) = μ_f
var(Ph_f) = σ^2_{Ph} = σ^2_{Af} + σ^2_{Ef}

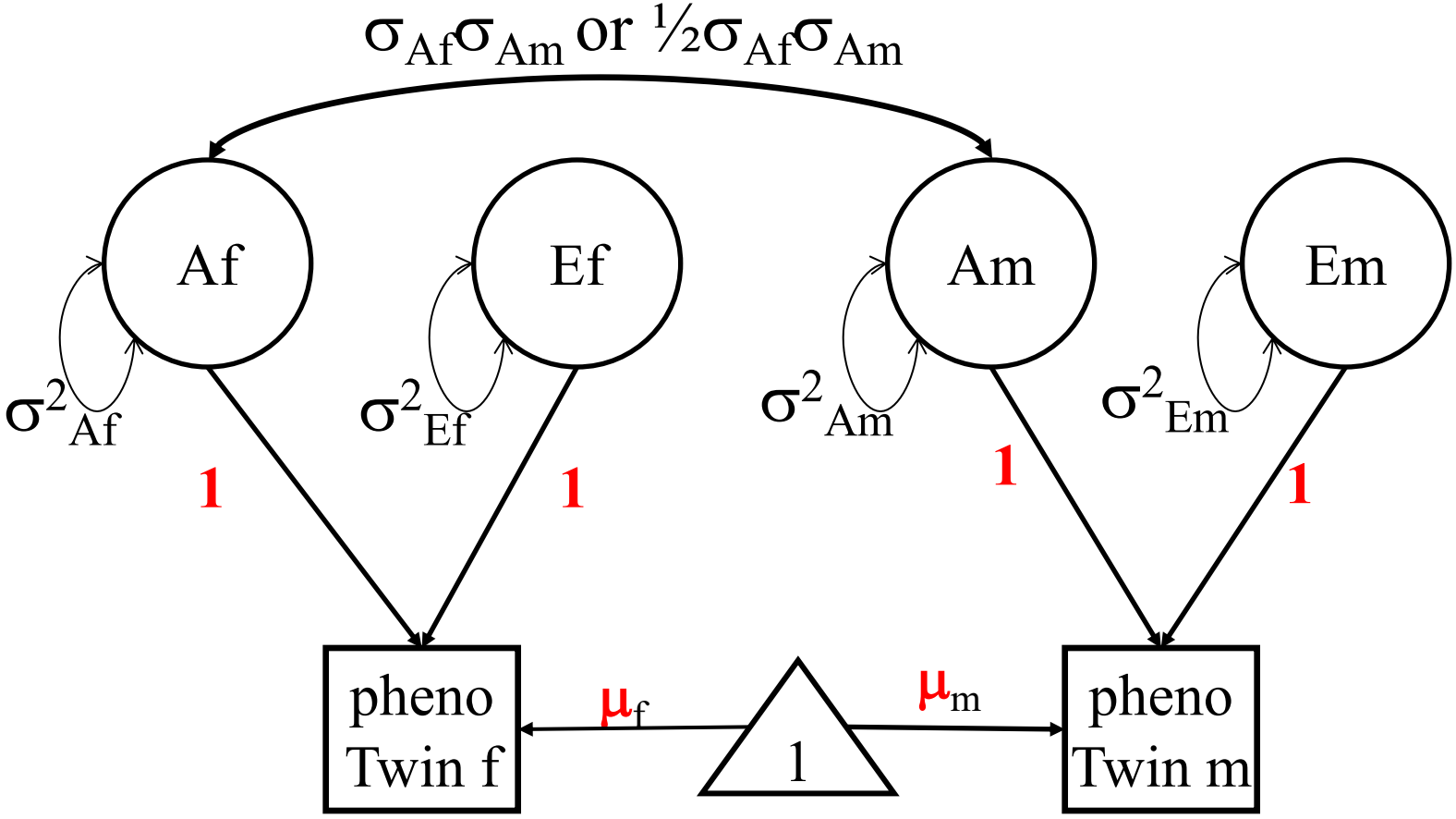
Females twins

$\mu_f = \mu_m$? sex differences in main effects

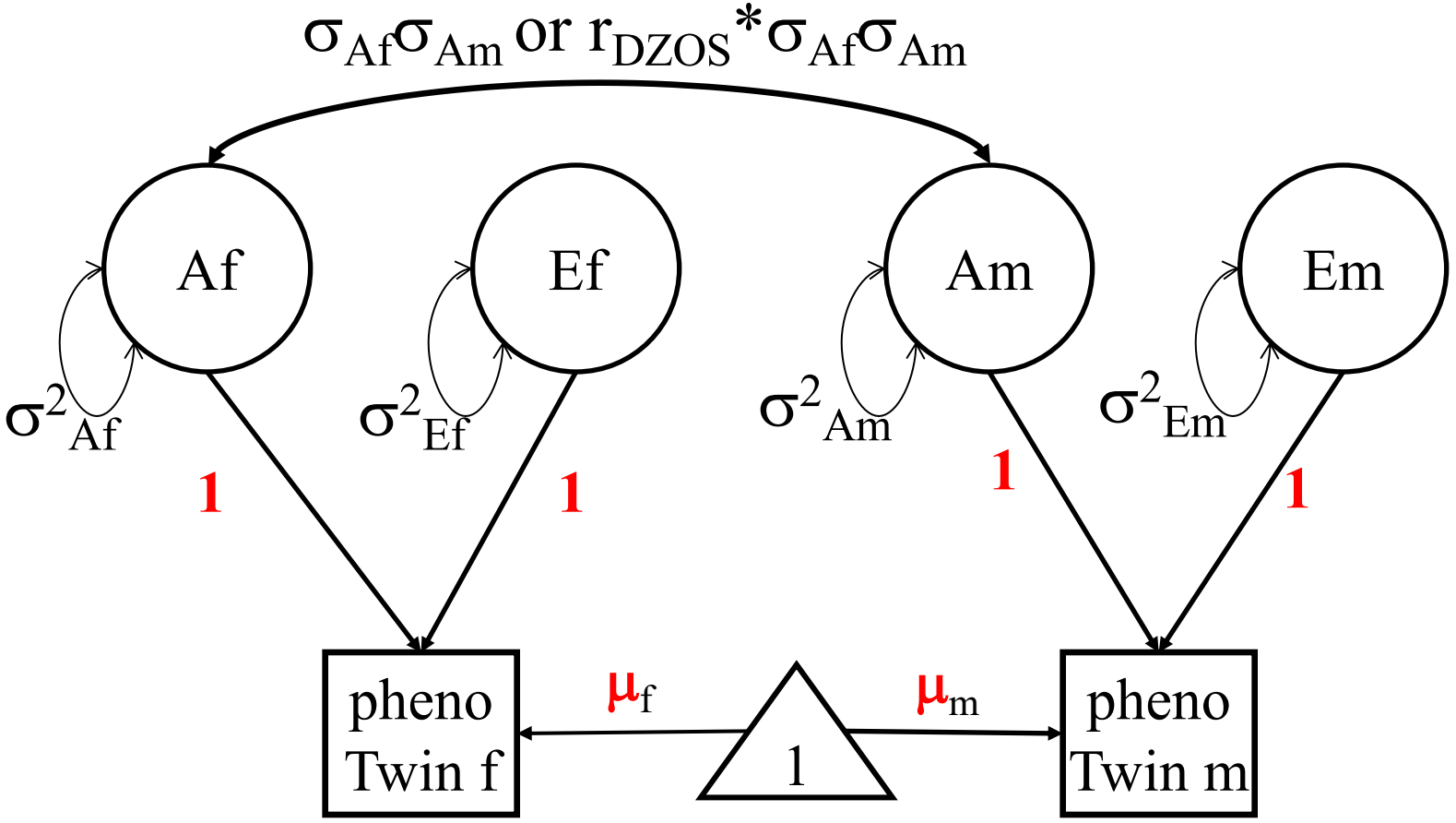
$s^2_{Af} = s^2_{Am}$? sex differences in A variance

$s^2_{Ef} = s^2_{Em}$? sex differences in E variance

(add $s^2_{Df} = s^2_{Dm}$ or $s^2_{Cf} = s^2_{Cm}$)



DZOS (f,m) twins



DZOS twins

$r_{DZOS}*\sigma_{Af}\sigma_{Am}$ note: r_{DZOS} is not necessarily ½

$r_{DZOS} = ½$ or $r_{DZOS} < ½$?

Models (ACE) (Stat or Subst)

total homogeneity (Subst)

$\mu_f = \mu_m$ (main effect absent)

$\sigma^2_{Am}=\sigma^2_{Af}$ & $\sigma^2_{Cm}=\sigma^2_{Cf}$ & $\sigma^2_{Ef}=\sigma^2_{Ef}$

$r_{DZOS} = ½$

total variance homogeneity (Stat)

$\mu_f \neq \mu_m$ (main effect present)

$\sigma^2_{Am}=\sigma^2_{Af}$ $\sigma^2_{Cm}=\sigma^2_{Cf}$ & $\sigma^2_{Ef}=\sigma^2_{Ef}$

$r_{DZOS} = ½$

$\mu_f \neq \mu_m$ (main effect present)

scalar sex limitation $r_{DZOS} = ½$ (Stat)

$\sigma^2_{Am} \neq \sigma^2_{Af}$ & $\sigma^2_{Cm} \neq \sigma^2_{Cf}$ & $\sigma^2_{Ef} \neq \sigma^2_{Ef}$

$\sigma^2_{Am} = k*\sigma^2_{Af}$ & $\sigma^2_{Cm} = k*\sigma^2_{Cf}$ & $\sigma^2_{Ef} = k*\sigma^2_{Ef}$

k is nonzero positive constant (to be estimated)

raw variances differ, but standardized variances are equal

$\sigma^2_{Af}/(\sigma^2_{Af}+\sigma^2_{Cf}+\sigma^2_{Ef}) = k*\sigma^2_{Af}/(k*\sigma^2_{Af}+k*\sigma^2_{Cf}+k*\sigma^2_{Ef})$

$= k*\sigma^2_{Af}/\ k*(\sigma^2_{Af}+\sigma^2_{Cf}+\sigma^2_{Ef}) = \sigma^2_{Af}/(\sigma^2_{Af}+\sigma^2_{Cf}+\sigma^2_{Ef})$

parsimonious model for sex differences in variance,
but quite restrictive (and not Subst!)

$\mu_f \neq \mu_m$ (main effect present)

non-scalar quantitative sex limitation

$r_{DZOS} = ½$ (Subst)

$\sigma^2_{Am} \neq \sigma^2_{Af}$ &/or $\sigma^2_{Cm} \neq \sigma^2_{Cf}$ &/or $\sigma^2_{Ef} \neq \sigma^2_{Ef}$

$\sigma^2_{Am} \neq \sigma^2_{Af}$ &genetic effects are different, but $r_{DZOS} = ½$ implies same genes in males and females.

So: sex moderates genetic effects (e.g., gene expression).

$\mu_f \neq \mu_m$ (main effect present)

non-scalar qualitative sex limitation

$r_{DZOS} \neq ½$ (Subst)

$\sigma^2_{Am} \neq \sigma^2_{Af}$ &/or $\sigma^2_{Cm} \neq \sigma^2_{Cf}$ &/or $\sigma^2_{Ef} \neq \sigma^2_{Ef}$

$\sigma^2_{Am} \neq \sigma^2_{Af}$ genetic effects are different, and $r_{DZOS} \neq ½$ implies (*at least in part* different genes).

Nesting ACE model (cov structure, discarding the means)

non-scalar qualitative
7 parameters: σ^2_{Am} σ^2_{Af} σ^2_{Cm} σ^2_{Cf} σ^2_{Ef} σ^2_{Ef} r_{DZOS})

fix r_{DZOS} = ½ (1 df): **non-scalar quantative** (omnibus: 3 differences)
6 parameters: σ^2_{Am} σ^2_{Af} σ^2_{Cm} σ^2_{Cf} σ^2_{Em} σ^2_{Ef}

proportionality constraint (2df): **scalar**
4 parameters: σ^2_{Cf} σ^2_{Ef} σ^2_{Ef} k

set k=1 (1 df): **homogeneity**
3 parameters σ^2_{Cf} σ^2_{Ef} σ^2_{Ef}

Alternate Parameterization for Scalar and Non-scalar Sex-limitation Models in Mx

Sarah E. Medland[1, 2]

Twin Research Volume 7 Number 3 pp. 299–308

Caveat: Tests of moderation (interaction) are scale dependent.

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.

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

Memory & Cognition
1978, Vol. 6 (3), 312-319

On interpretation of interactions

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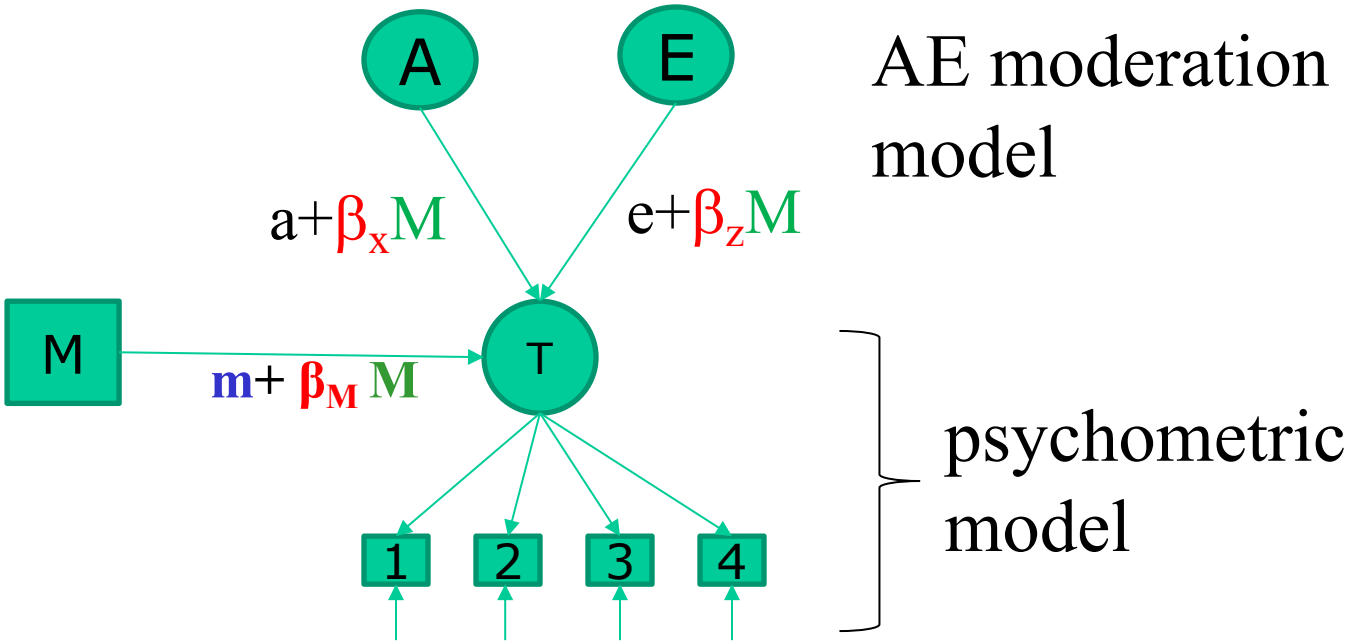
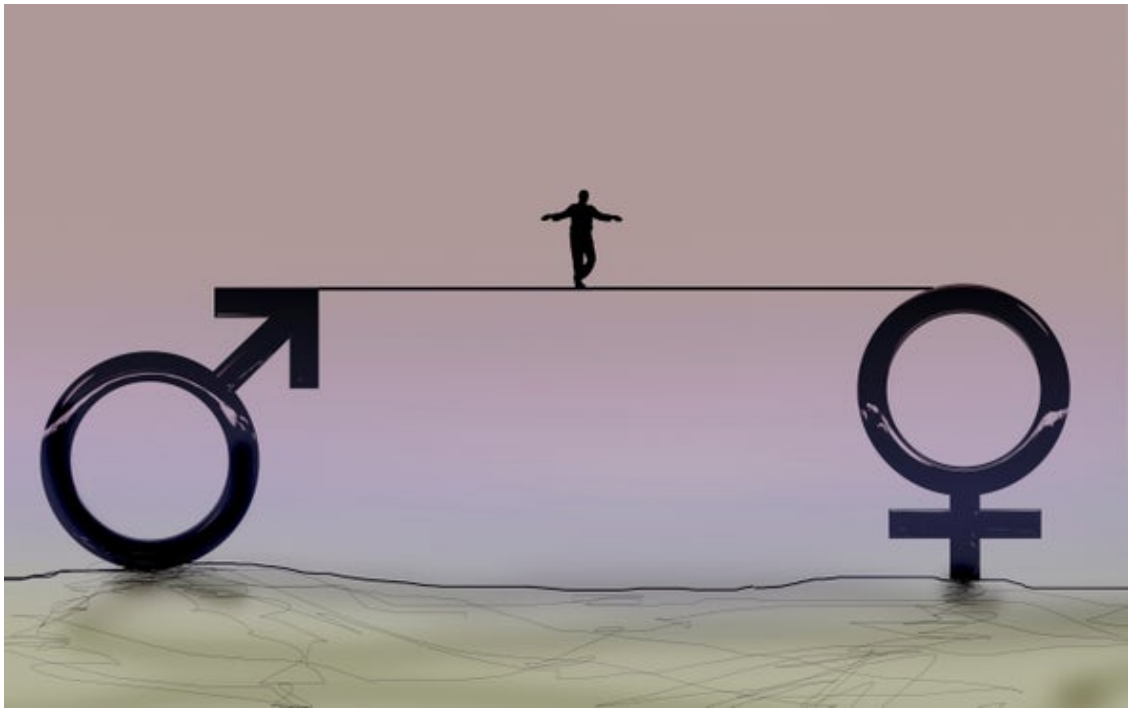
Solution???: Common pathway model with appropriate psychometric model (IRT model or a common factor model) & Define moderation at the level of the latent phenotype (Nathan Friday)





How would you revise the sex limitations model if you had a dimensional measure of sex?