Heterogeneity II

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Heterogeneity Questions I

- Standard Univariate Analysis: What are the contributions of additive genetic, dominance/shared environmental and unique environmental factors to the variance?

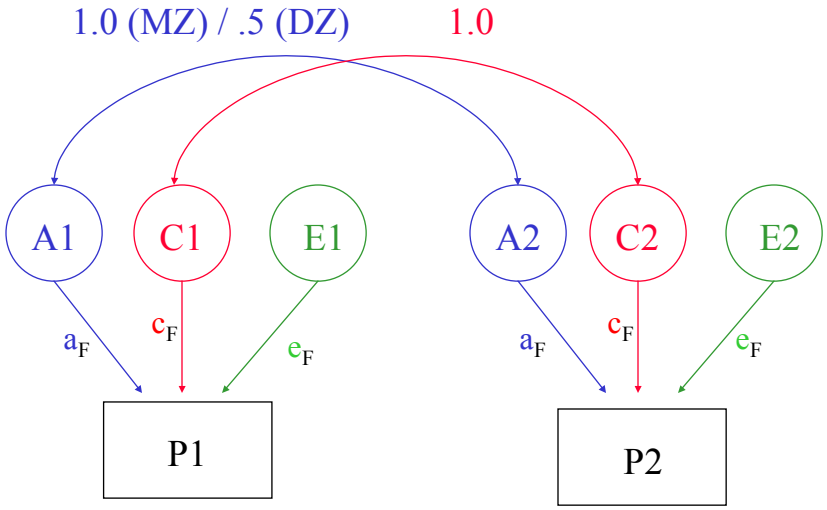
- Heterogeneity: Are the contributions of genetic and environmental factors equal for different groups, such as sex, race, ethnicity, SES, environmental exposure, etc.?

Ways to Model Heterogeneity in Twin Data

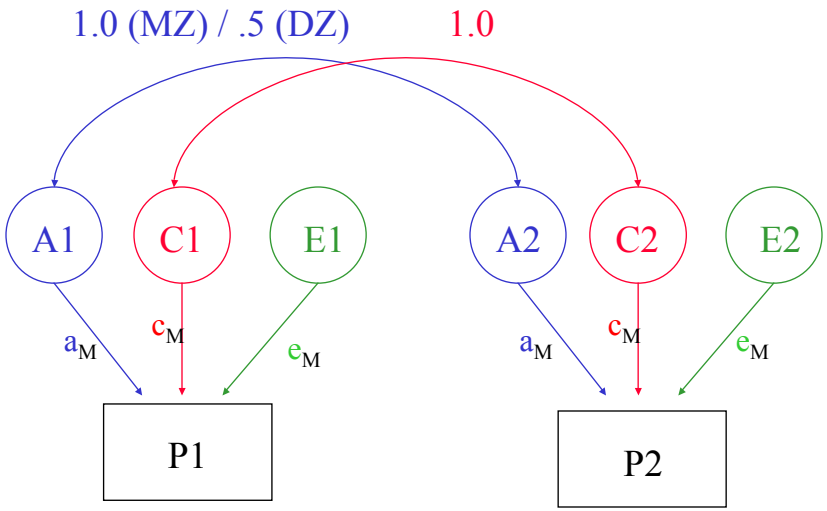
- Multiple Group Models
  - Sex Effects
  - Divorced/Not Divorced
  - Young/Old cohorts
  - Urban/Rural residency
  - Etc…

Sex Effects

Females

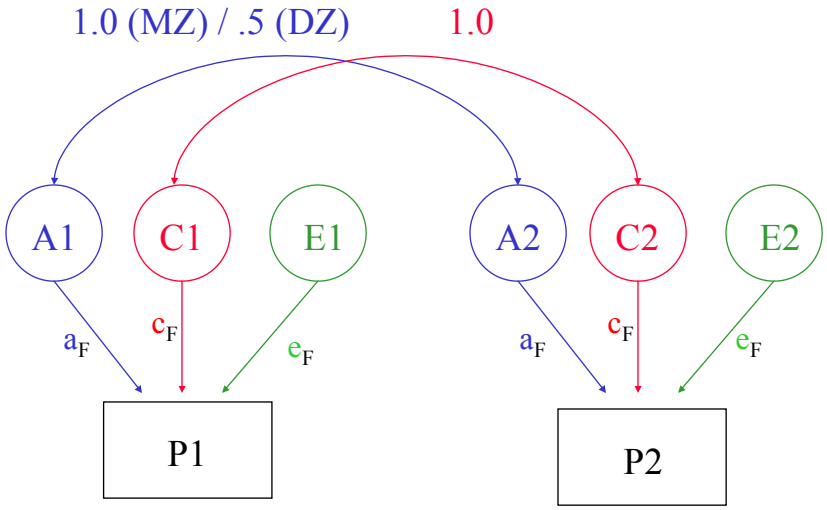


Males

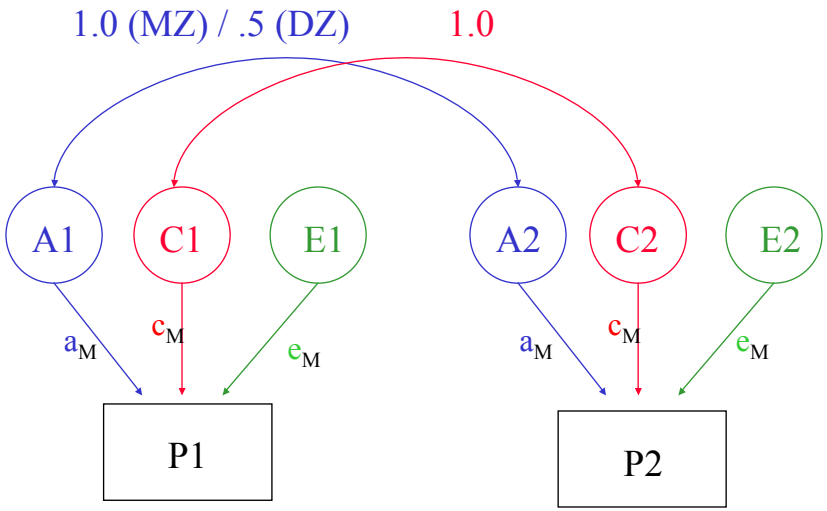


Sex Effects

Females



Males



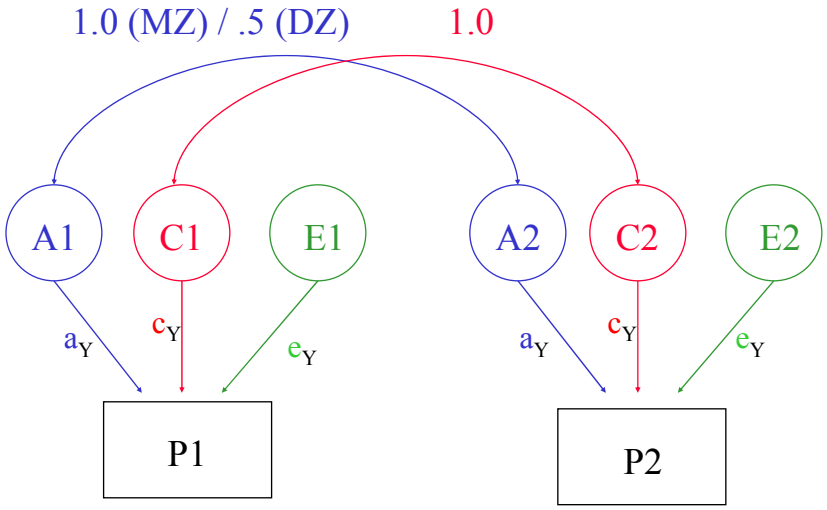
$a_F = a_M$?

$c_F = c_M$?

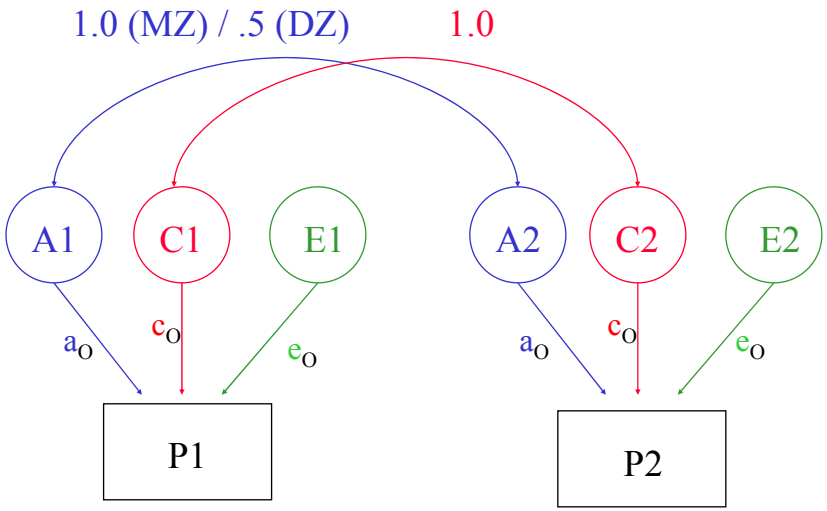
$e_F = e_M$?

Divorce Effects

Divorced



Not Divorced



$a_D = a_{ND}$?

$c_D = c_{ND}$?

$e_D = e_{ND}$?

Problem:

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

    - Grouping these variables into high/low categories may lose information

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

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

Standard model

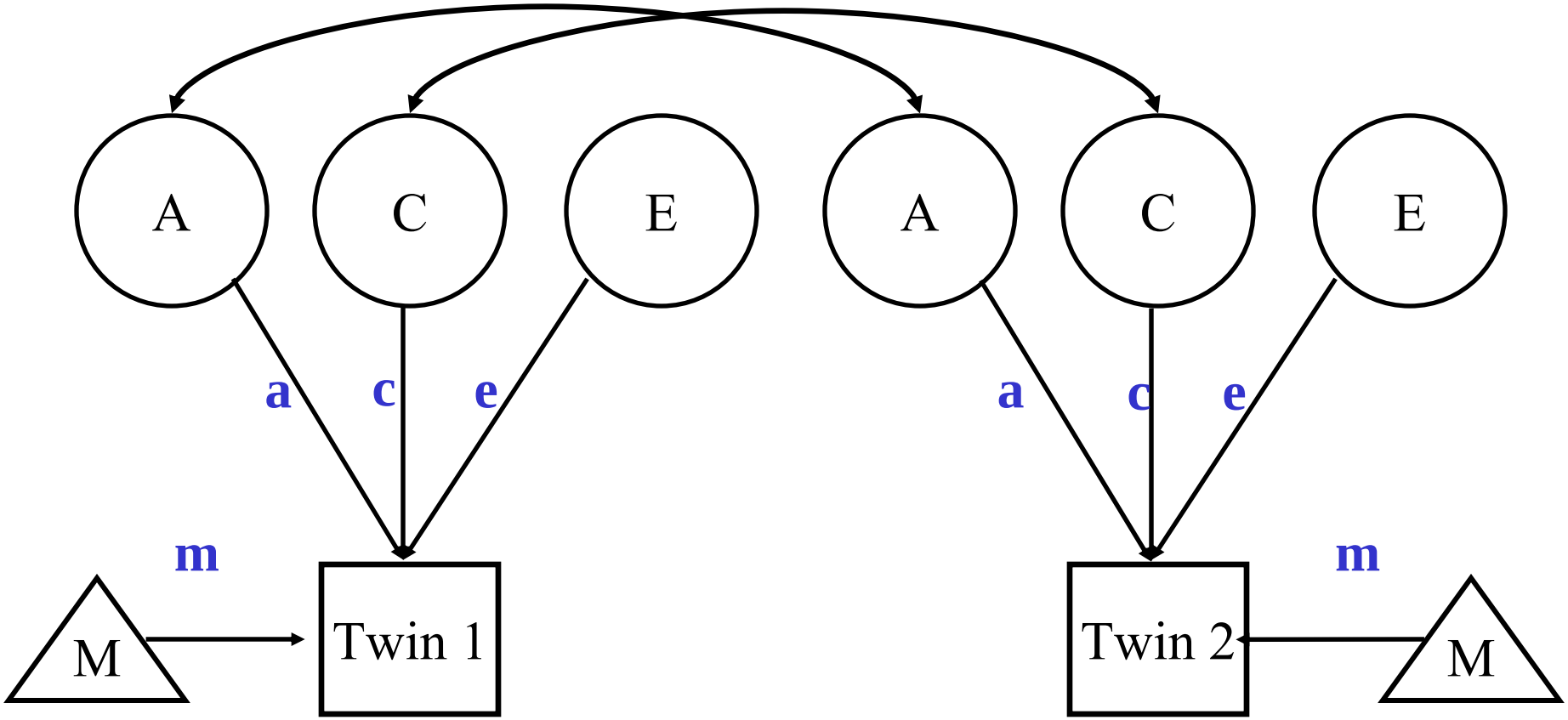
- Means vector

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

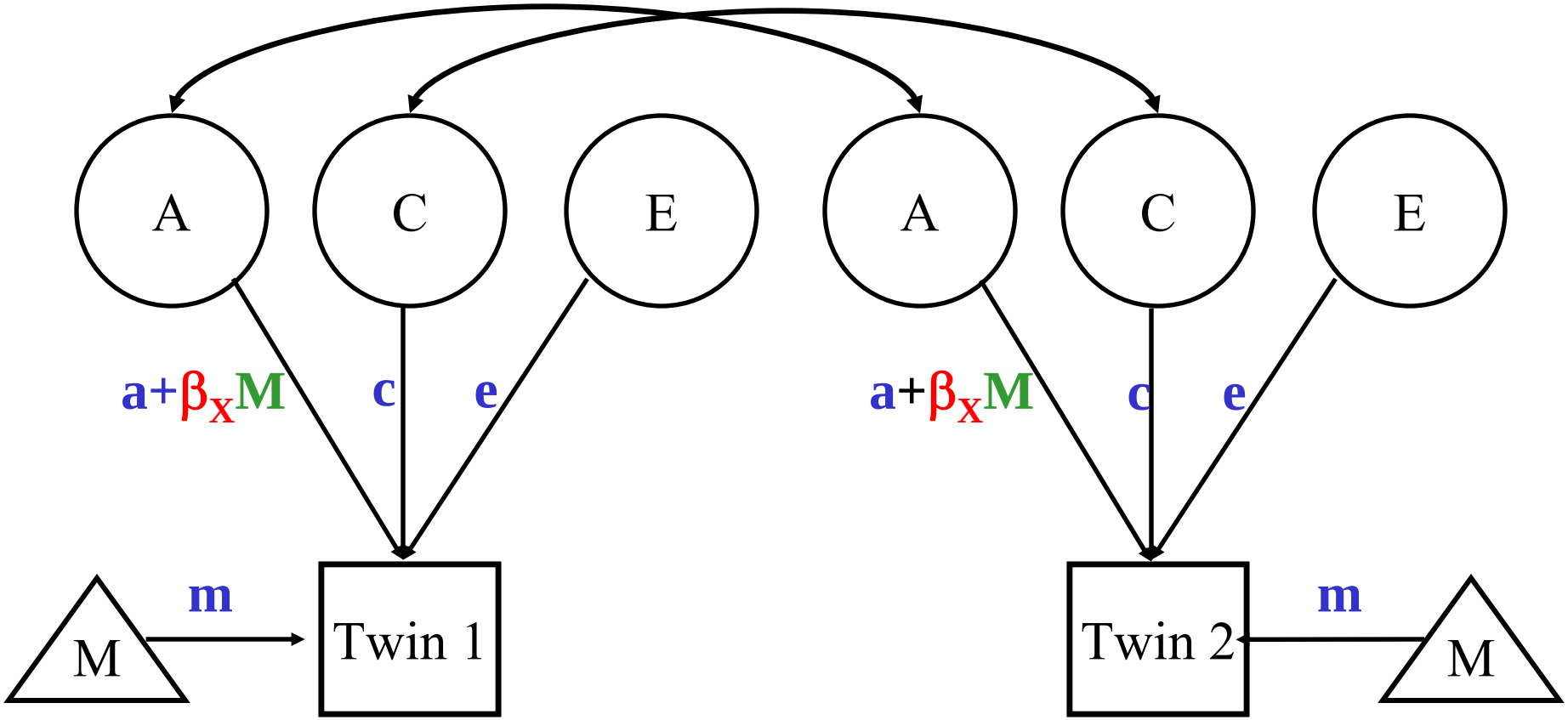
- Covariance matrix

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

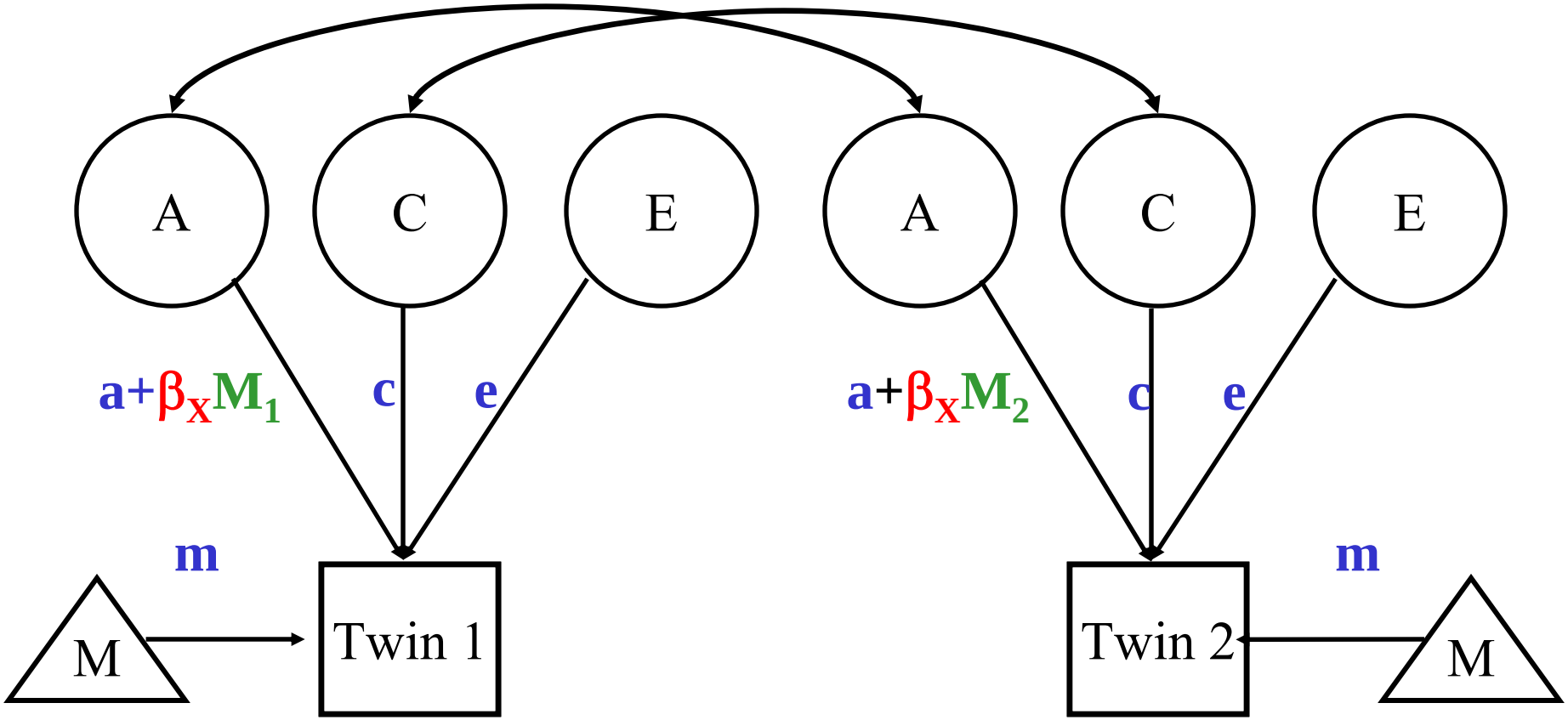
Model-fitting approach to GxE



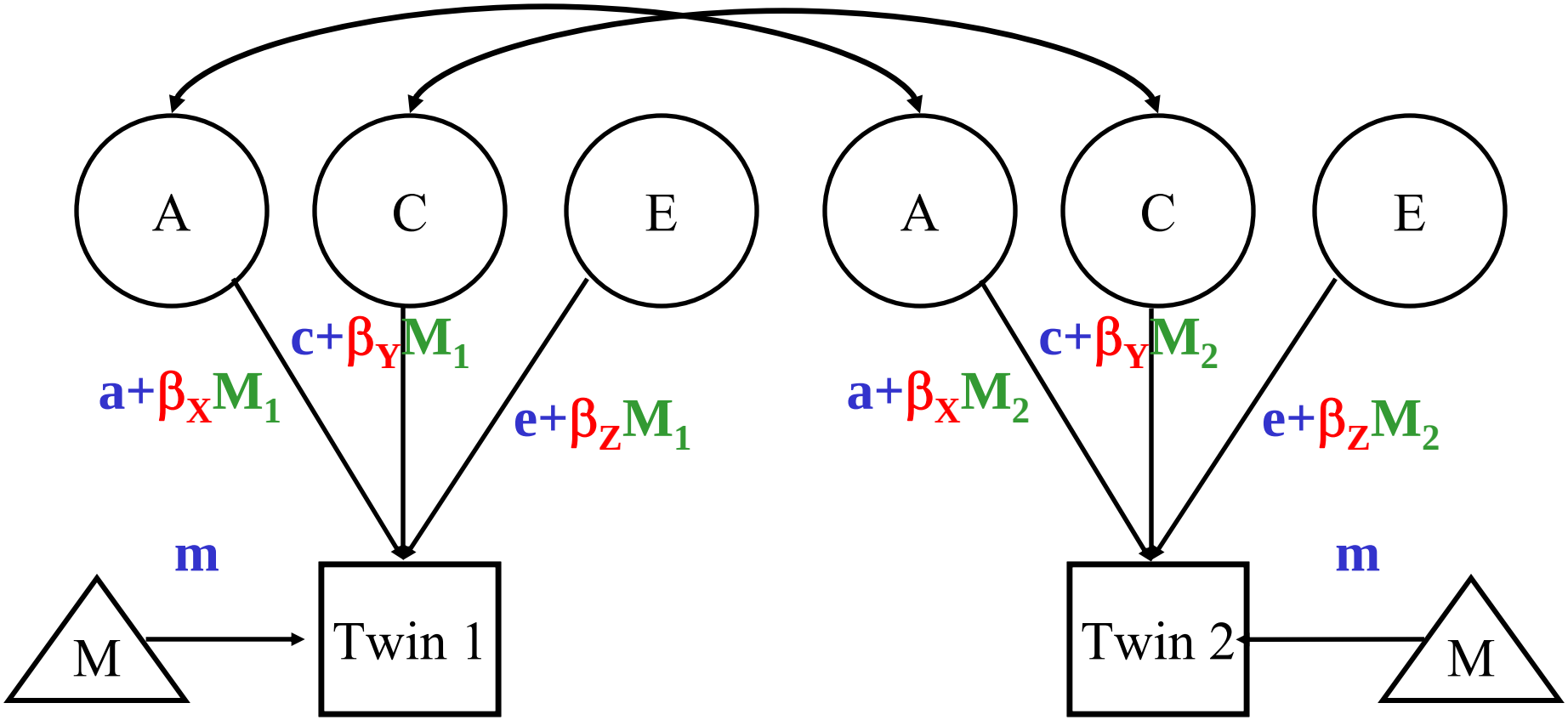
Model-fitting approach to GxE



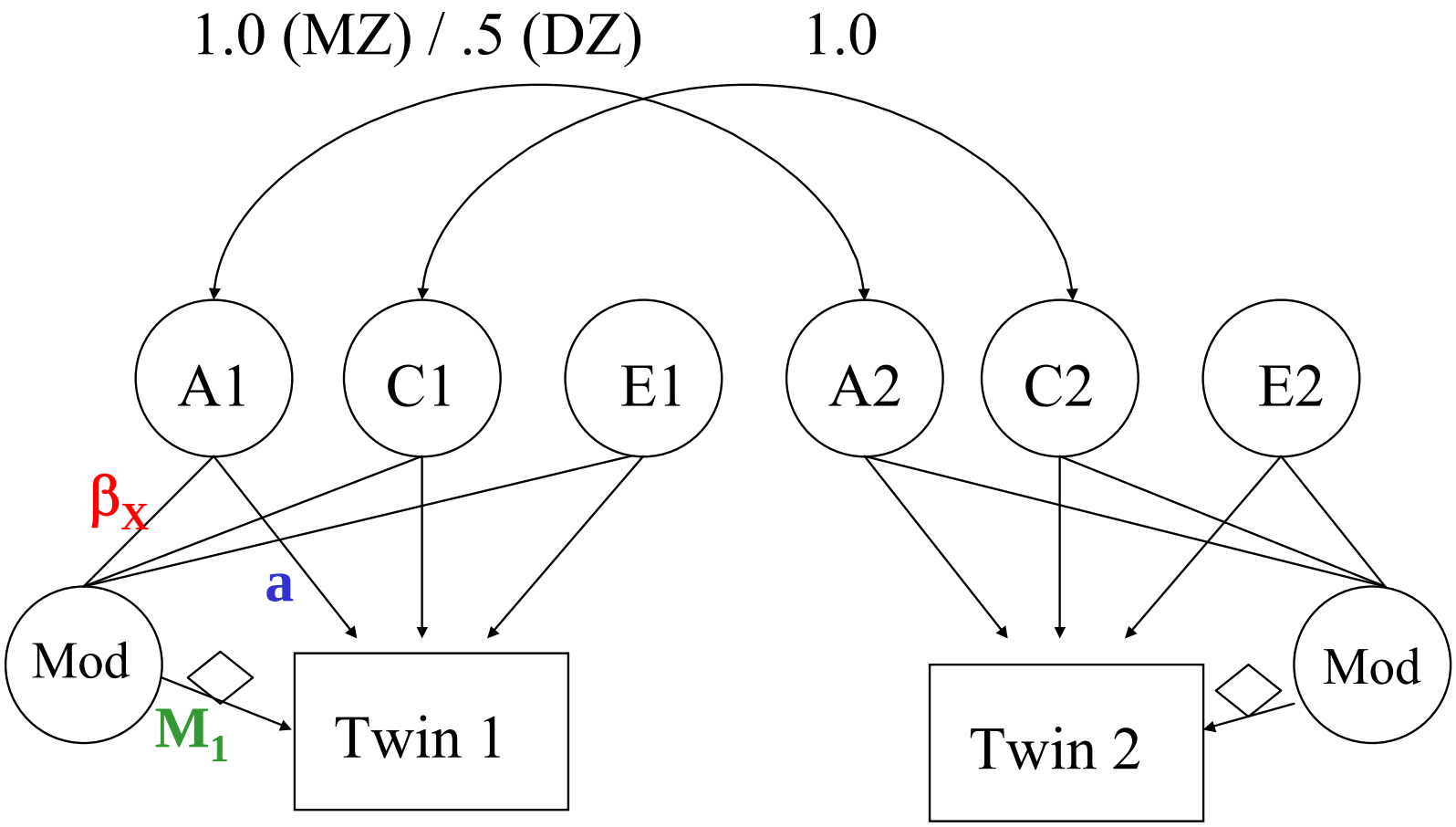
Individual specific moderators



E x E interactions



Definition Variables in Mx

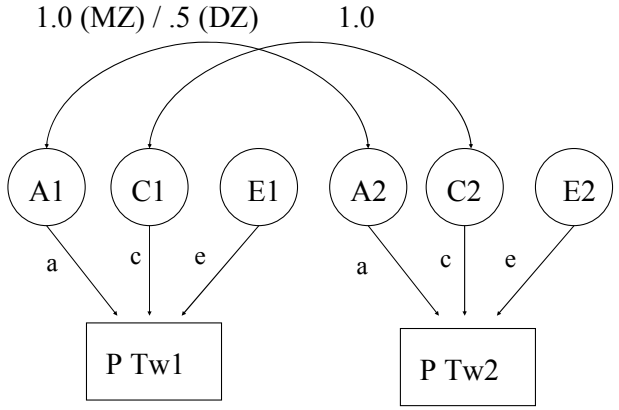


Total genetic variance =

$a+\beta_X M_1$

- Classic Twin Model:

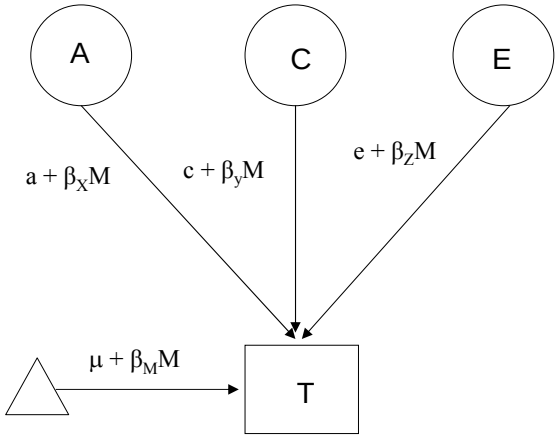
  $\text{Var}(P) = a^2 + c^2 + e^2$



- Moderation Model:

  $\text{Var}(P) =$

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



Purcell 2002,
Twin Research

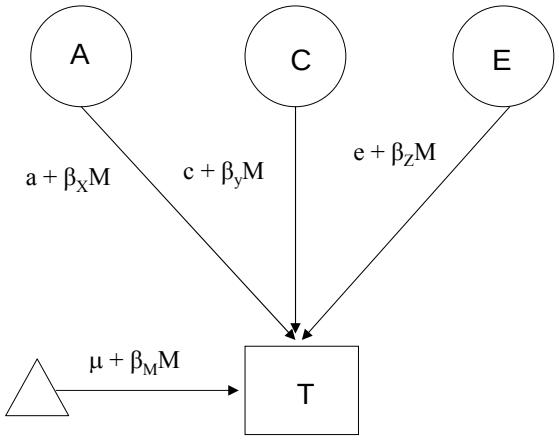
$$\text{Var}(T) = (a + \beta_X M)^2 + (c + \beta_Y M)^2 (e + \beta_Z M)^2$$

Where M is the value of the moderator and

Significance of β_X indicates genetic moderation

Significance of β_Y indicates common environmental moderation

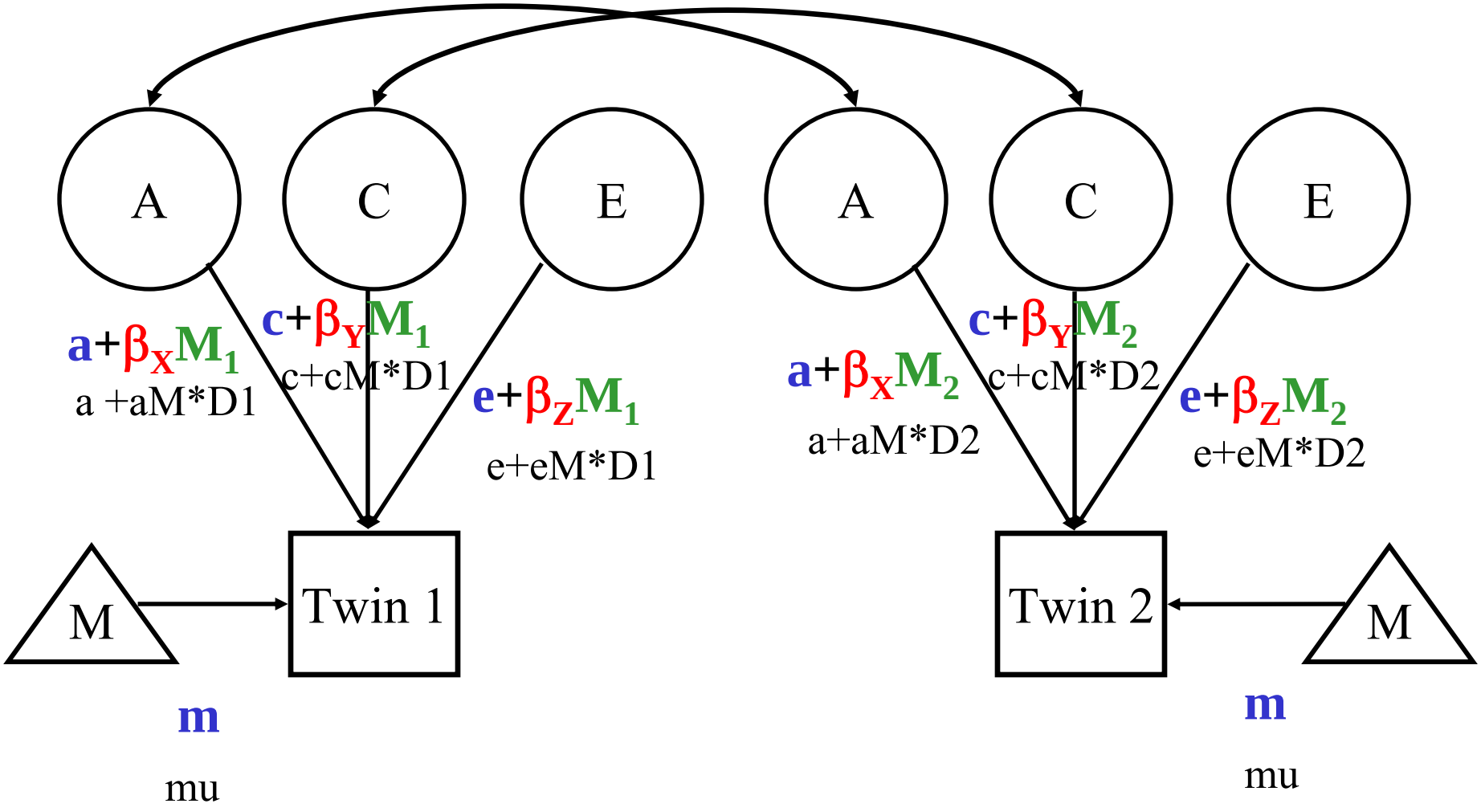
Significance of β_Z indicates unique environmental moderation



Unstandardized versus standardized effects

	GROUP 1		GROUP 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	

Matrix Letters as Specified in Mx Script



‘Definition variables’ in Mx

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- Common uses:

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

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

Definition variables used as covariates

General model with age and sex as covariates:

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

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

Allowing for a main effect of *X*

- Means vector

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

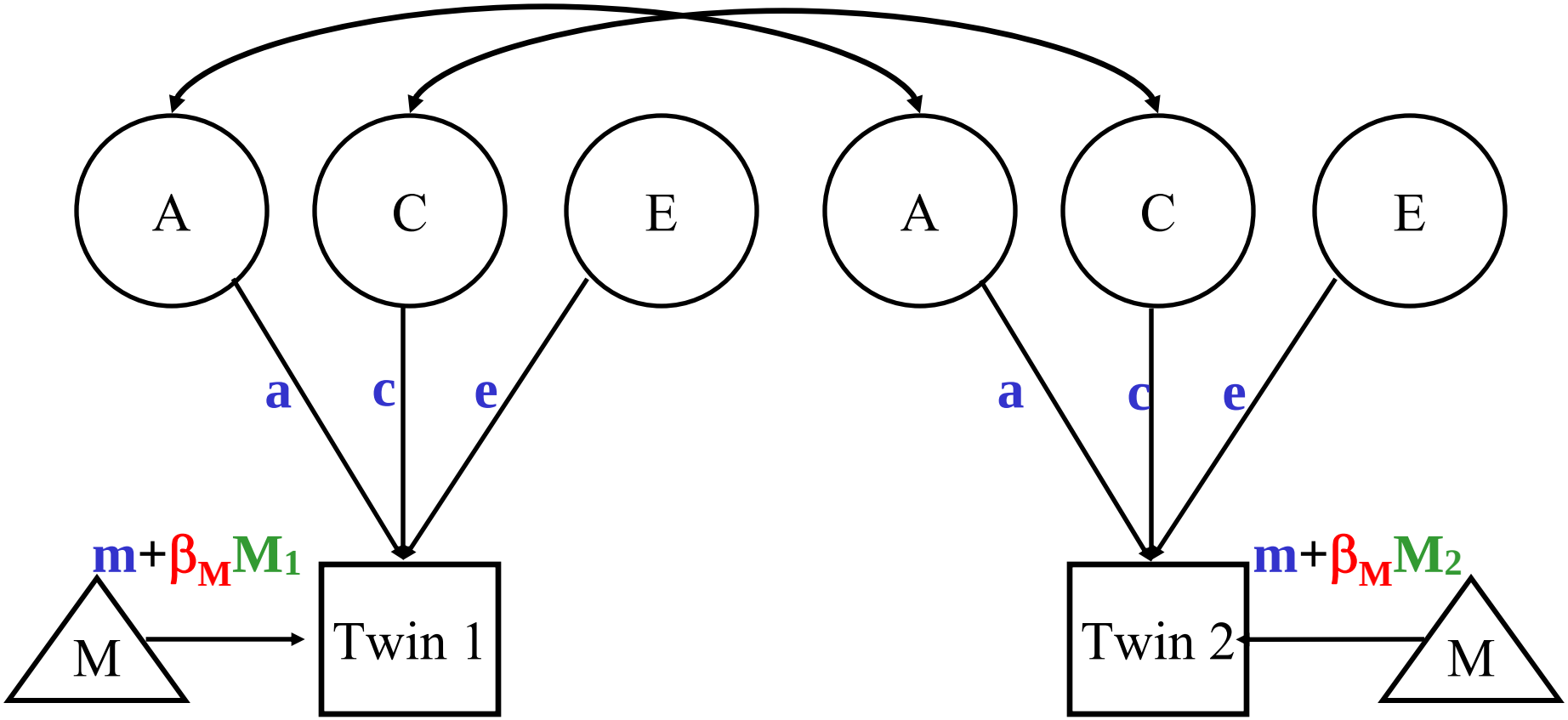
- Covariance matrix

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

Common uses of definition variables in the means model

- Incorporating covariates (sex, age, etc)
- Testing the effect of SNPs (association)
- In the context of GxE, controlling for rGE

Adding Covariates to Means Model



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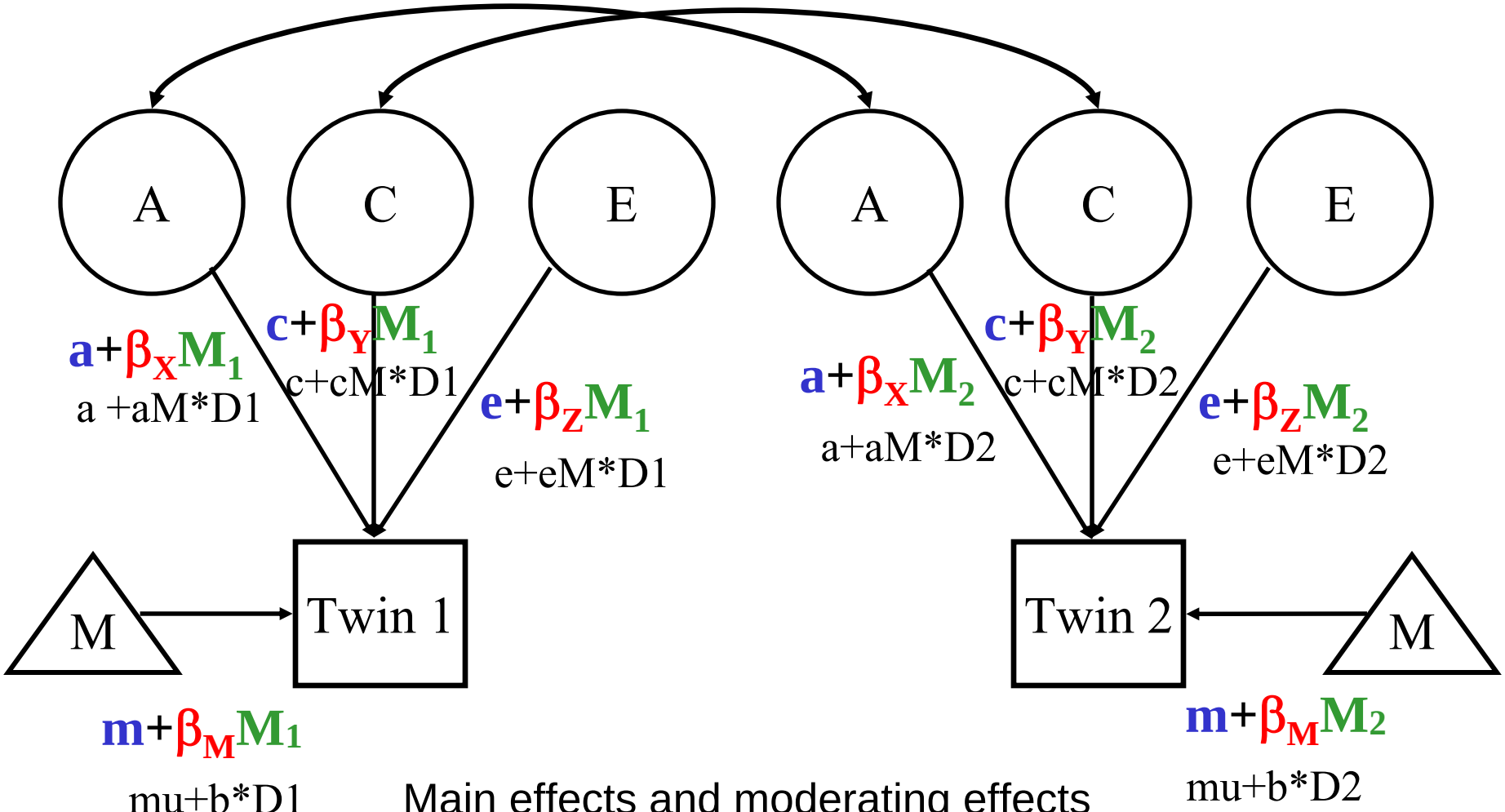

Main effects and moderating effects