SEMs for Genetic Analysis

Session 18, Lecture 14

12/13/06

Basic Genetic Analysis of Twin Samples Using SEMs

- SEMs and variance explained
- Motivating example
- Simple correlation test
- The ‘heritability’ concept
- Structural equation models and genetic analyses
- The equal environments assumption

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The Application of Structural Equation Modeling to Maternal Ratings of Twins' Behavioral and Emotional Problems

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Question: Are childrens' behavioral and emotional problems are result of genetics or environment? (or some of both?)

Motivating Example

- Medical College of Virginia Adolescent Behavioral Development Twin Project
  - Between 1989 and 1990 one parent from a sample of 2,292 white twins residing in the state of Virginia returned a mail questionnaire that included information on the Child Behavior Check List (CBCL)
  - 1,263 completed survey on full twin pairs in which zygosity information was available

Motivating Example

- monozygotic twins: 242 male and 272 female
- dizygotic twins: 255 male and 223 female
- dizygotic twins: 271 opposite-sex pairs

Motivating Example

- Characteristics of interest: externalizing and internalizing behaviors
  - externalizing: e.g. fights, hits others, defiant
  - internalizing: e.g. dependent, feelings easily hurt, fearful, sad
- Do these characteristics reflect genetic influences?

Motivating Example

- Measure: Child Behavior Check List
  - Achenbach, T. M. 1978. "The Child Behavior Profile: I. Boys aged 6-11." *Journal of Consulting and Clinical Psychology* 46:478-488
  - 118 items that reflect the presence of absence of a particular behavior during the previous 6 months
  - Added up subscales and then logged them, to make distribution more normal.

Simple Correlation Test

- Compare correlations between MZ and DZ pairs
  - If inheritance plays a role, then MZ correlation will be higher than DZ correlation
  - This difference forms basis for a rough, simple estimate of heritability estimates

Table 1
Covariances and Correlations Between Twins of a Pair for Externalizing and Internalizing Behaviors

	Externalizing behaviors				Internalizing behaviors			
	Young		Older		Young		Older	
Zygosity group	Twin 1	Twin 2	Twin 1	Twin 2	Twin 1	Twin 2	Twin 1	Twin 2
MZ-M	.781	**.862**	.924	**.833**	.771	**.817**	.665	**.740**
	.696	.835	.766	.914	.606	.714	.473	.614
MZ-F	.886	**.760**	.737	**.800**	.668	**.765**	.740	**.780**
	.659	.849	.621	.816	.538	.740	.593	.782
DZ-M	.534	**.600**	.691	**.692**	.614	**.541**	.763	**.581**
	.373	.724	.494	.738	.320	.569	.422	.691
DZ-F	.662	**.660**	.743	**.629**	.608	**.649**	.663	**.554**
	.482	.807	.542	.998	.400	.625	.371	.678
DZ-O	.853	**.679**	.763	**.721**	.566	**.547**	.802	**.593**
	.542	.746	.563	.800	.318	.599	.473	.792

Note. Boldface type indicates correlations. MZ = monozygotic; M = male; F = female; DZ = dizygotic; O = opposite-sex (twins). For each zygosity group, the first row represents Twin 1 and the second row represents Twin 2.

$$\begin{bmatrix} \sigma_1^2 & \rho_{12} \\ \sigma_{12} & \sigma_2^2 \end{bmatrix}$$

Simple Correlation Test

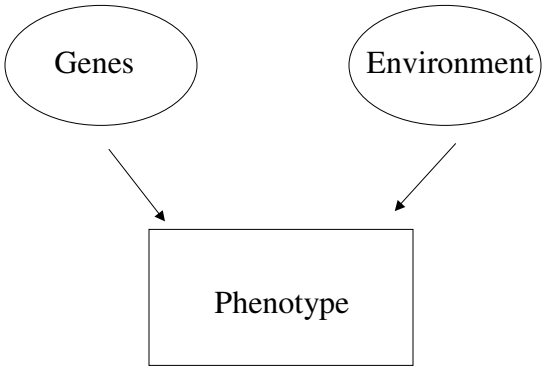
- Compare correlations between MZ and DZ pairs
- If genetic effects are additive then:
  - r_{mz} = Genetic + Shared Environment
  - r_{dz} = .5*Genetic + Shared Environment
  - r_{mz}- r_{dz} = Genetic - .5*Genetic
  - $2(r_{mz} – r_{dz})$ = Genetic Component

The Heritability Concept

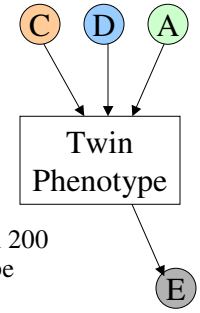
- Four hundred years ago, only rich people ate well; consequently most of the phenotypic variation in height was the result of environmental variation. Today almost everyone eats well; consequently most of the variation in height is now due to genes
  - Heritability can change as a result of environmental influences
  - Heritability depends on sample being studied
  - Recent evidence suggests that genes and the environment interact, a factor difficult to account for in standard genetic SEM models

Structural Equation Models and Genetic Analyses

Genes and Environment are latent variables, phenotype is the observed "manifestation"



Structural Equation Models and Genetic Analyses



- Phenotype = $\beta_a A + \beta_d D + \beta_c C + \beta_e E$
  - Genetic component
    - A additive genetic component
      - E.g. intelligence may be influenced by more than 200 genes, each of which adds a little to the phenotype
    - D non-additive genetic component
      - E.g. eye color, rolling tongue, baldness
  - Environmental component
    - C = shared environmental influence
    - E = non-shared environmental influence/residual

Structural Equation Models and Genetic Analyses

- Phenotype = $\beta_a A + \beta_d D + \beta_c C + \beta_e E$
  - *Assume uncorrelated latent variables*
- Var(P)= $\beta_a^2 var(a) + \beta_d^2 var(d) + \beta_c^2 var(c) + \beta_e^2 var(e)$

(Var(a)=var(d)=var(c)=var(e) = 1)

$Var(P) = \beta_a^2 + \beta_d^2 + \beta_c^2 + \beta_e^2$

Structural Equation Models and Genetic Analyses

- Monozygotic twins share
  - all additive genetic influence
  - all non-additive genetic influence
  - all shared environmental influence

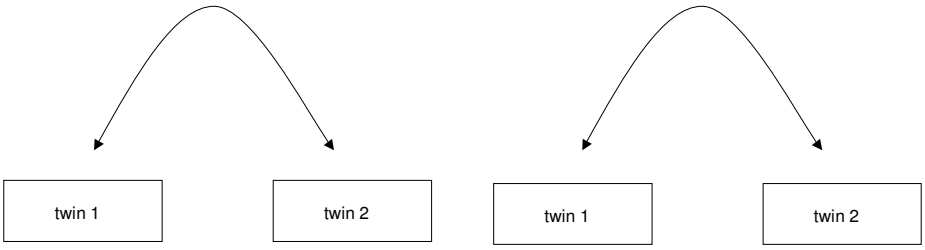
$cov(MZ_{1,2}) = \beta_a^2 + \beta_d^2 + \beta_c^2$

Structural Equation Models and Genetic Analyses

- Dizygotic twins share
  - 50% additive genetic influence
  - 25% additional non-additive genetic influence; sibs have 75% chance of inheriting a dominant gene and only a 25% chance of inheriting the same recessive pair of alleles from parents
  - all shared environmental influence
  - $cov(Dz) = .5\beta_a^2 + .25\beta_d^2 + \beta_c^2$

Structural Equation Models and Genetic Analyses

Observed Model

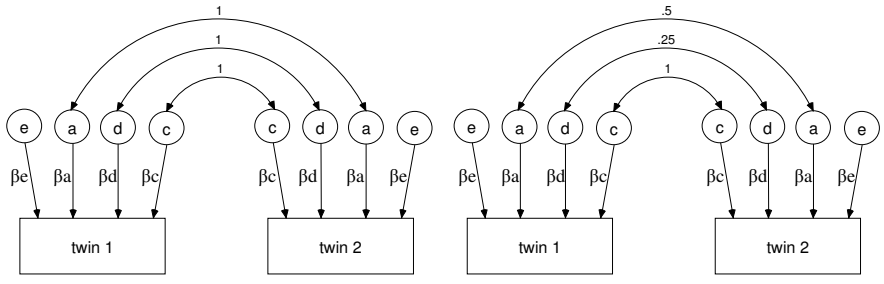


Group 1: Monozygotic

Group 2: Dizygotic

Structural Equation Models and Genetic Analyses

Master Model



Group 1: Monozygotic

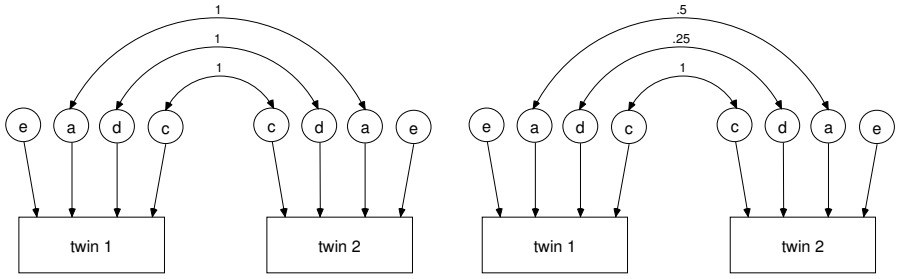
cov(MZ) =

Group 2: Dizygotic

cov(DZ) =

Structural Equation Models and Genetic Analyses

Master Model



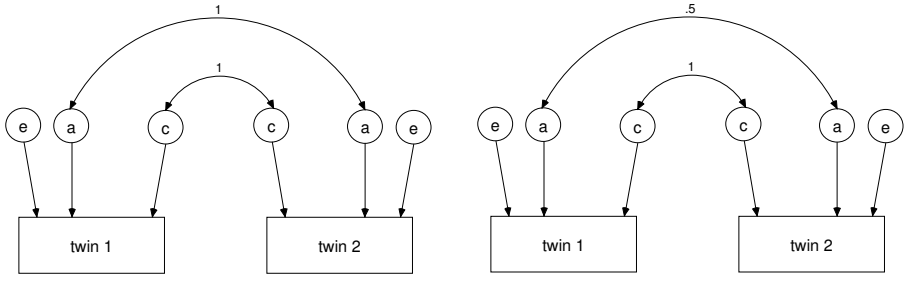
Group 1: Monozygotic

Group 2: Dizygotic

Number of parameters to be estimated:
Number of observed variances and covariances:

Structural Equation Models and Genetic Analyses

ACE Model

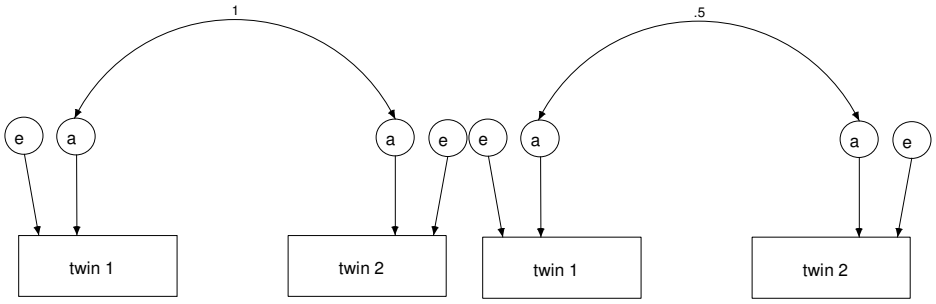


Group 1: Monozygotic

Group 2: Dizygotic

Structural Equation Models and Genetic Analyses

AE Model

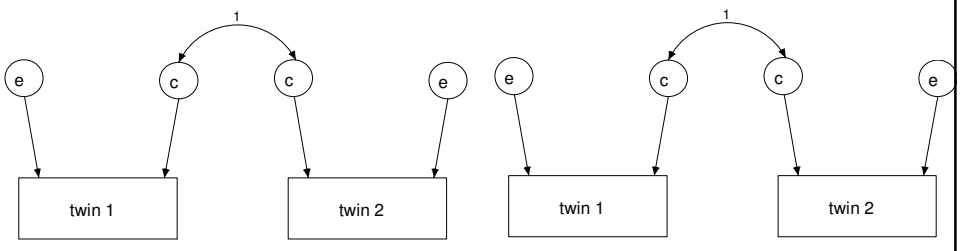


Group 1: Monozygotic

Group 2: Dizygotic

Structural Equation Models and Genetic Analyses

CE Model

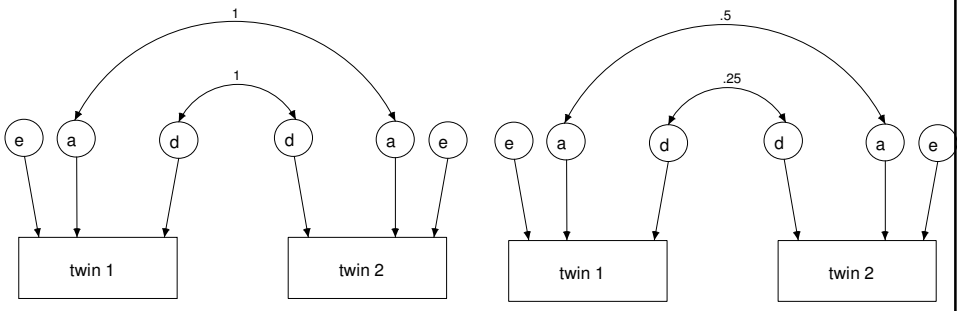


Group 1: Monozygotic

Group 2: Dizygotic

Structural Equation Models and Genetic Analyses

ADE Model



Group 1: Monozygotic

Group 2: Dizygotic

Practical Example

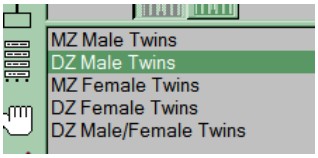
- Among younger twins, do the causes of externalizing behaviors differ between boys and girls.
- How to do this? Fit two models:

  1) constrain boys and girls parameters to be equal

  2) allow boys and girls parameters to vary
- Compare fit of nested models.

Groups/Data Sets

- 5 zygosity groups




```
Male MZ file:
rowtype_,varname_,twin1,twin2
n,xx,116,116
corr,twin1,1
corr,twin2,.862,1
stddev,,.884,.914
```

Twin 1	Twin 2
.781	.862
.696	.835

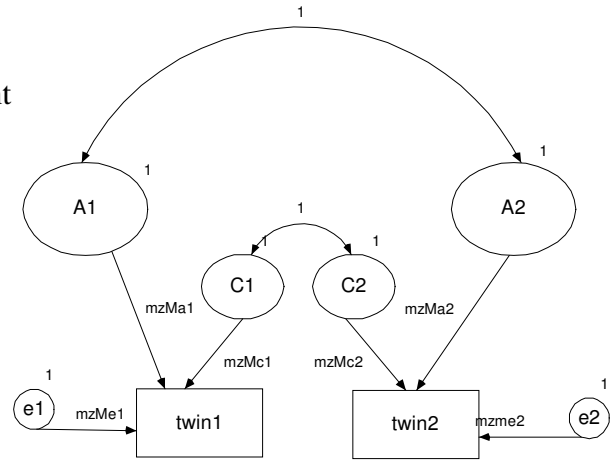
How To Fit These Models

Monozygotic Twins

Fix variances of latent variables to 1

Fix cov(a1,a2) to 1
Fix cov(c1,c2) to 1

MzMa1=MzMa2
MzMc1=MzMc2
mzMe1=mzMe2



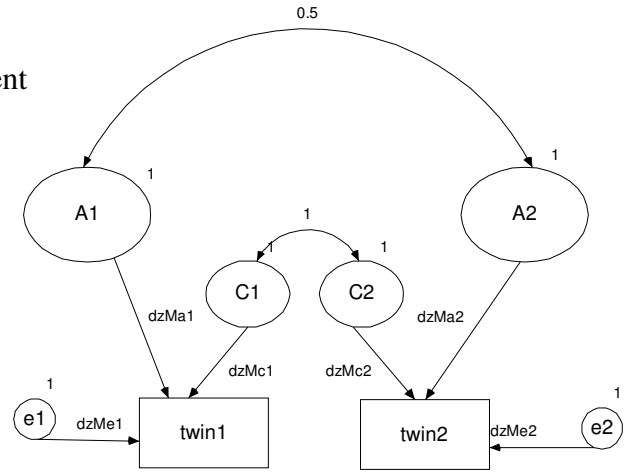
How To Fit These Models

Dizygotic Twins

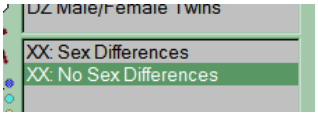
Fix variances of latent variables to 1

Fix cov(a1,a2) to .5
Fix cov(c1,c2) to 1

dzMa1=dzMa2
dzMc1=dzMc2
dzMe1=dzMe2



Models



Sex Differences Model

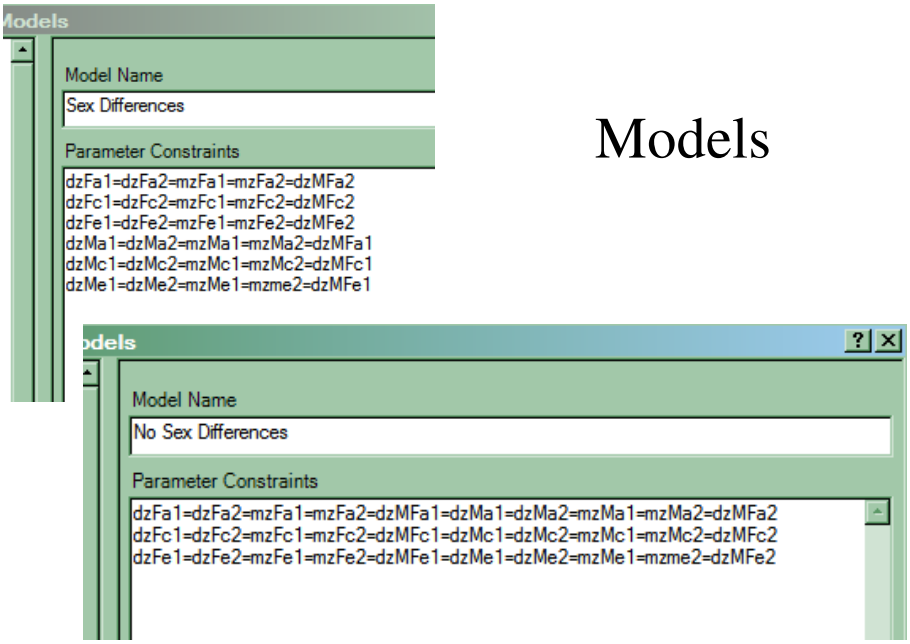
•Constrain male "a" coefficients to be equal
•Constrain all male "c" coefficients to be equal
•Constrain all male "e" coefficients to be equal

•Same for females

No Sex Differences Model

•Constrain all "a" coefficients to be equal
•Constrain all "c" coefficients to be equal
•Constrain all "e" coefficients to be equal

Models



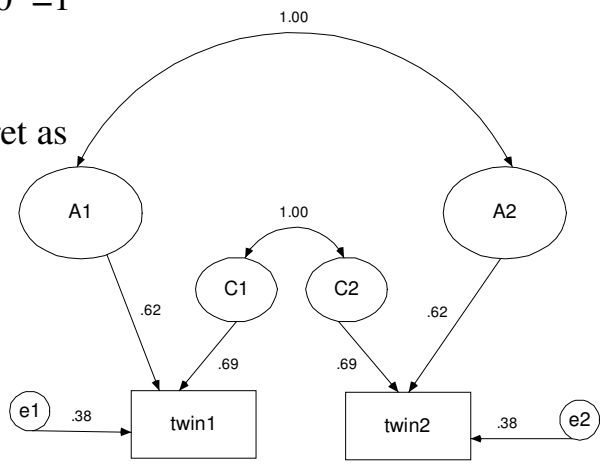
Interpreting Estimates (Male MZ)

$Var(P) = \beta_a^2 + \beta_c^2 + \beta_e^2$

$Var(P) = .62^2 + .68^2 + .40^2 = 1$

With standardized estimates, can interpret as percent variance

A (additive)- 38%
C (common)- 46%
E- 16%



- Sex Differences and No Sex Differences
- What parameters were we estimating?

CMIN

Model	NPAR	CMIN	DF	P	CMIN/DF
Sex Differences	6	12.020	9	.212	1.336
No Sex Differences	3	25.202	12	.014	2.100
Saturated model	15	.000	0		
Independence model	10	482.148	5	.000	96.430

(25.202-12.020)=13.182~ chi2 with 3 d.f. P=.004

Looking at externalizing behaviors in younger children, the degrees To which environment and genetics contribute to phenotype differ Between boys and girls.

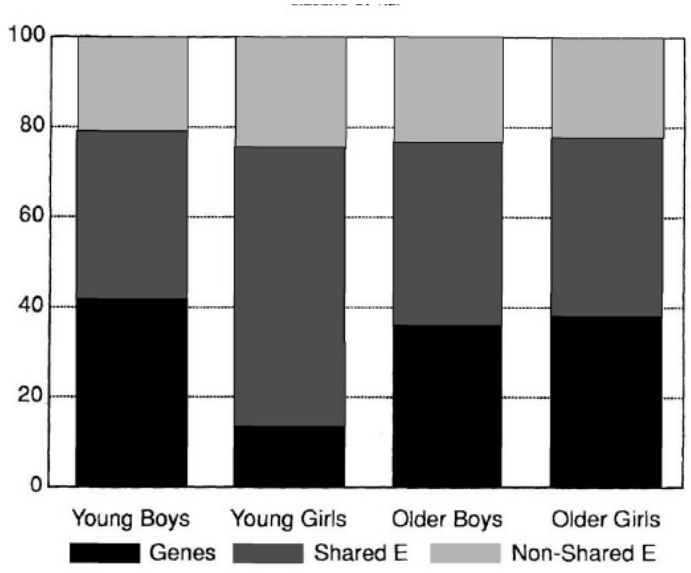


Figure 2. Components of variance for externalizing behaviors. E = environmental effects.

Equal Environments Assumption

- Twin models assume that the degree of environmental similarity is about the same for monozygotic and dyzygotic twins
- If the equal environment assumption is not correct – e.g., if identical twins are treated more similarly than fraternal twins – then a finding of greater phenotypic similarity between identical twins might be due partially to greater environmental similarity

Equal Environments Assumption

- Non-genetic reasons why MZ twin pairs may show more concordance than DZ twin pairs:
  - patterns of social interaction
    - people who spend more time interaction with each other also can become more similar in behavioral and personality traits
  - social networks
    - social networks of MZ twins more similar than that of DZ twins
  - reactions elicited from the environment
    - MZ twins have greater physical resemblance and may have greater chance of receiving similar social reactions