Biometrical modeling of twin and family data

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Outline

- Genetic variance components model: ACDE
- Liability model for binary traits
- Models for twin designs
  - Assumptions and two parameterizations (P1, P2) as mixed/multilevel models
  - Continuous adult height: P1 ACE, P2 ACE
  - Continuous neuroticism: P2 ADE
  - Binary hay-fever status: P2 ADE & AE
- Models for nuclear family designs
  - Continuous birth weight data

Genetic variance components models: ACDE

- y_{ij} is continuous trait or phenotype for member i of family j

$$y_{ij} \;=\; \mathbf{x}_{ij}'\boldsymbol{\beta} + A_{ij} + D_{ij} + C_{ij} + \epsilon_{ij}$$

- Error components
  - $A_{ij} \sim N(0, \sigma_A^2)$: Additive genetic, potentially correlated
  - $D_{ij} \sim N(0, \sigma_D^2)$: Dominance genetic, potentially correlated
  - $C_{ij} \sim N(0, \sigma_C^2)$: Common environment, potentially correlated
  - $\epsilon_{ij} \sim N(0, \sigma_E^2)$: Unique environment, independent
  - A_{ij}, D_{ij}, C_{ij}, ϵ_{ij} mutually independent
- Nature (A_{ij} and D_{ij}) versus nurture (C_{ij} and ϵ_{ij})
  - **Heritability** is percentage of variance in trait that is due to genes

$$h^2 \;=\; \frac{\sigma_A^2(+\sigma_D^2)}{\sigma_A^2 + \sigma_D^2 + \sigma_C^2 + \sigma_E^2}$$

Liability model for binary traits

- Continuous ‘liability’ (propensity)

$$y^*_{ij} \;=\; \mathbf{x}'_{ij}\boldsymbol{\beta} + A_{ij} + D_{ij} + C_{ij} + \epsilon_{ij}, \qquad \epsilon_{ij} \sim N(0,1)$$

- Binary trait

$$y_{ij} \;=\; \begin{cases} 1 & \text{if } y^*_{ij} > 0 \\ 0 & \text{otherwise} \end{cases}$$

- Probit model

$$\text{Pr}(y_{ij} = 1 | \mathbf{x}_{ij}, A_{ij}, D_{ij}, C_{ij}) \;=\; \Phi(\mathbf{x}'_{ij}\boldsymbol{\beta} + A_{ij} + D_{ij} + C_{ij})$$

  - $\Phi(\cdot)$ is standard normal CDF (inverse probit link)

- Heritability

$$h^2 \;=\; \frac{\sigma^2_A(+\sigma^2_D)}{\sigma^2_A + \sigma^2_D + \sigma^2_C + \underbrace{1}_{\sigma^2_E}}$$

Assumptions for models considered here

- Hardy-Weinberg equilibrium
- No epistasis (interactions between alleles at different loci)
- No gene-environment interactions
- Random (non-assortative) mating
- Correlations among error components
  - For A_{ij} and D_{ij} this follows from Mendelian genetics, under assumptions above, and from type of kinship
  - For C_{ij} make additional assumptions

Model formulation

- Usually biometrical models for twin and family data expressed as a multi-group structural equation models (SEMs) and fitted in Mx, Mplus, or other SEM software
- Can formulate models as mixed/multilevel models [Rabe-Hesketh, Gjessing & Skrondal, 2008] and fit them in Stata
  - `xtmixed`: Continuous phenotypes and models that do not require equality constraints for variances at different levels
  - `gllamm`: Continuous, binary (or ordinal) phenotypes
- Models with the fewest random effects are easiest to estimate for binary (or ordinal) phenotypes

Models for twin designs

- Monozygotic (MZ) or ‘identical’ twins share all genes by descent
- Dizygotic (DZ) or ‘fraternal’ twins share half their genes by descent
- Equal environment assumption: MZ and DZ twins have same degree of similarity in their environments, so that excess similarity between MZ twins can be attributed to the greater proportion of shared genes

Models for twin designs (cont'd)

- Consider two twin pairs: (MZ1, MZ2), (DZ1, DZ2):

$$\text{Cov}(\mathbf{A}) \;=\; \sigma_A^2 \begin{bmatrix} 1 & 1 & 0 & 0 \\ 1 & 1 & 0 & 0 \\ 0 & 0 & 1 & 1/2 \\ 0 & 0 & 1/2 & 1 \end{bmatrix} \qquad \text{Cov}(\mathbf{D}) \;=\; \sigma_D^2 \begin{bmatrix} 1 & 1 & 0 & 0 \\ 1 & 1 & 0 & 0 \\ 0 & 0 & 1 & 1/4 \\ 0 & 0 & 1/4 & 1 \end{bmatrix}$$

$$\text{Cov}(\mathbf{C}) \;=\; \sigma_C^2 \begin{bmatrix} 1 & 1 & 0 & 0 \\ 1 & 1 & 0 & 0 \\ 0 & 0 & 1 & 1 \\ 0 & 0 & 1 & 1 \end{bmatrix} \qquad \text{Cov}(\mathbf{E}) \;=\; \sigma_E^2 \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}$$

- ACDE model not identified here; consider ACE and ADE (as well as AE, CE)

Twin datasets

- All data: `M` is dummy for MZ; `pair` is twin-pair j; `member` is i
- Continuous adult heights `twin_bmi.dta` [Posthuma & Boomsma, 2005]
  - Variables `height` (in cm) and `male`
  - 304 twin pairs (13% with height missing for one member)
    307 DZ members (40% male). 262 MZ members (43% male)
- Continuous neuroticism `twin_neur.dta` [Sham, 1998]
  - Variable `neurot` (Eysenck personality questionnaire)
  - 794 female twin pairs (no missing data)
    272 DZ pairs. 522 MZ pairs
- Binary hay fever status `twin_hay.dta` [Hopper et al., 1990]
  - Variables h, `male`, pair-level frequency weights `freq`
  - 3,807 twin pairs (no missing data)
    2,009 DZ pairs (18% male, 45% mix). 1,798 MZ pairs (31% male)

Parameterization 1 (P1) of ACE as mixed model

- Three-level data
  - Level 3: Twin-pair j
  - Level 2: Member i (same as level 1)

```
. use twin_bmi, clear
. list pair M member male height if s==1, sepby(pair) noobs

  +------------------------------------------+
  | pair   M   member   male   height |
  |------------------------------------------|
  |    2   1        1      1      190 |
  |    2   1        2      1    190.7 |
  |------------------------------------------|
  |   16   1        2      1      178 |
  |------------------------------------------|
  |  269   0        1      1      183 |
  |  269   0        2      0    158.5 |
  +------------------------------------------+
```

- Use twin-pair level (level-3) random effect $c_j^{(3)}$ with variance σ_C^2 for shared environment
- Use member level (level-1) residual ϵ_{ij} with variance σ_E^2 for unique environment

Parameterization 1 (P1) of ACE as mixed model (cont'd)

- Problem: Additive genetic component completely shared (correlation 1) for MZ twins and partially shared (correlation 0.5) for DZ twins
- Solution:
  - Shared component $a_j^{(3)}$ with variance σ_A^2 contributes only half as much variance to DZ twins as to MZ twins

    $$a_j^{(3)}[M_j + \sqrt{\frac{1}{2}}\overline{M}_j]$$

    - M_j is dummy for MZ
    - $\overline{M}_j = 1 - M_j$ is dummy for DZ
  - Remaining variance for DZ twins comes from unshared component $a_{ij}^{(2)}$ with variance σ_A^2

    $$a_{ij}^{(2)}\sqrt{\frac{1}{2}}\overline{M}_j$$

Continuous adult height: P1 ACE

- Cannot estimate in `xtmixed` because of equality constraint for variances at different levels
- In `gllamm`:

```
generate var3 = M + sqrt(1/2)*(1-M)
generate var2 = sqrt(1/2)*(1-M)
eq var3: var3
eq var2: var2
generate one = 1
eq cons: one

cons def 1 [mem1_1]var2 = [pai2_1]var3
gllamm height male, i(member pair) nrf(1 2)
    eqs(var2 var3 cons) nocor constr(1) adapt
```

Continuous adult height: P1 ACE (cont'd)

```
log likelihood = -1727.820312522015

 ( 1)  [mem1_1]var2 - [pai2_1]var3 = 0
------------------------------------------------------------------------------
      height |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        male |   12.99536   .6166593    21.07   0.000     11.78673    14.20398
       _cons |   167.9549    .438026   383.44   0.000     167.0963    168.8134
------------------------------------------------------------------------------

Variance at level 1
------------------------------------------------------------------------------

  2.392252 (.30445676)

Variances and covariances of random effects
------------------------------------------------------------------------------

***level 2 (member)

    var(1): 40.342974 (5.1760754)

***level 3 (pair)

    var(1): 40.342974 (5.1760754)
    cov(2,1): fixed at 0

    var(2): 1.8175006 (5.2567317)
------------------------------------------------------------------------------

. disp 40.342974/(40.342974+1.8175006+ 2.392252 )
.90551078
```

Parameterization 2 (P2) of ACE as mixed model

- Three-level model
  - Level 3: Twin-pair j
  - Level 2: Hybrid k, $\quad k = \begin{cases} \text{pair } j & \text{for MZ twins} \\ \text{member } i & \text{for DZ twins} \end{cases}$
  - Level 1: Member i
- ϵ_{ij} with variance σ_E^2 for unique environment as before
- $u_{kj}^{(2)}$ with variance $\sigma_A^2/2$ for half the additive genetic variance that is shared for MZ and unique for DZ
- $u_j^{(3)}$ with variance $\sigma_A^2/2 + \sigma_C^2$ for the other half of additive genetic variance that is shared for everyone and for common environment
- **Note:** Only two random effects instead of three

Continuous adult height: P2 ACE

```
generate k = pair if M==1
replace k = member if M==0
xtmixed height male || pair: || k:, mle variance
```

```
                                                Wald chi2(1)       =    446.47
Log likelihood = -1727.8203                     Prob > chi2        =    0.0000

------------------------------------------------------------------------------
      height |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        male |   12.99535   .6150212    21.13   0.000     11.78993    14.20077
       _cons |   167.9549   .4379076   383.54   0.000     167.0966    168.8131
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
pair: Identity               |
                  var(_cons) |   21.98932   3.482324      16.12173    29.99244
-----------------------------+------------------------------------------------
k: Identity                  |
                  var(_cons) |   20.17123   2.588088      15.68621     25.9386
-----------------------------+------------------------------------------------
               var(Residual) |   2.392253   .3044573      1.864131    3.069997
------------------------------------------------------------------------------
```

Continuous adult height: P2 ACE: (cont’d)

- Already have $\widehat{\sigma^2_E}$
- Get $\widehat{\sigma^2_A}$ and $\widehat{\sigma^2_C}$ using `nlcom`

```
. nlcom (var_A: 2*exp(2*[lns2_1_1]_cons))
>     (var_C: exp(2*[lns1_1_1]_cons)-exp(2*[lns2_1_1]_cons))

       var_A:  2*exp(2*[lns2_1_1]_cons)
       var_C:  exp(2*[lns1_1_1]_cons)-exp(2*[lns2_1_1]_cons)

-------------+----------------------------------------------------------------
      height |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       var_A |   40.34246   5.176177     7.79   0.000     30.19734    50.48758
       var_C |   1.818089   5.256801     0.35   0.729    -8.485051    12.12123
------------------------------------------------------------------------------

* Heritability:
. disp 40.34246/(40.34246+1.818089+2.392253)
.90549771
```

- Use `_diparm` with option `ci(probit)` to get confidence interval for heritability; however, requires derivatives
- Would be nice to have `ci(probit)` option in `nlcom`!

Parameterization 2 for ACE, AE, ADE, CE

- **ACE**: $\widehat{\sigma_A^2} = 2\widehat{\text{Var}}(u_{kj}^{(2)})$ and $\widehat{\sigma_C^2} = \widehat{\text{Var}}(u_k^{(3)}) - \widehat{\text{Var}}(u_{kj}^{(2)})$
  - Potential problem: $\widehat{\sigma_C^2}$ can be negative
  - Solution 1: **AE**: constrain σ_C^2 to zero by constraining $\text{Var}(u_j^{(3)}) = \text{Var}(u_{kj}^{(2)})$ (in `gllamm` only; see slide 22)
  - Solution 2: ADE (see below)
- **ADE** (same model as ACE): $\widehat{\sigma_A^2} = 3\widehat{\text{Var}}(u_j^{(3)}) - \widehat{\text{Var}}(u_{kj}^{(2)})$ and $\widehat{\sigma_D^2} = 2[\widehat{\text{Var}}(u_{kj}^{(2)}) - \widehat{\text{Var}}(u_j^{(3)})]$
- **CE**: Set $\text{Var}(u_{kj}^{(2)}) = 0$, giving two-level model
- **Note**: Conventional likelihood ratio tests to compare models are conservative [Dominicus et al., 2006]

Continuous neuroticism: P2 ADE

```
generate k = pair if M==1
replace k = member if M==0
xtmixed neurot || pair: || k:, mle variance
```

```
------------------------------------------------------------------------------
      neurot |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       _cons |   10.23203   .1237788    82.66   0.000     9.989426    10.47463
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
pair: Identity               |
                  var(_cons) |   3.345268   1.034871      1.824351    6.134134
-----------------------------+------------------------------------------------
k: Identity                  |
                  var(_cons) |   5.023933   1.187507      3.161151    7.984402
-----------------------------+------------------------------------------------
               var(Residual) |   9.559881   .5823694      8.483966    10.77224
------------------------------------------------------------------------------
```

Continuous neuroticism: P2 ADE (cont'd)

- Note that $\widehat{\sigma^2_C} = \widehat{\text{Var}}(u_k^{(3)}) - \widehat{\text{Var}}(u_{kj}^{(2)}) < 0$
- For ADE model, get $\widehat{\sigma^2_A}$ and $\widehat{\sigma^2_D}$ using `nlcom`

```
. nlcom (var_A: 3*exp(2*[lns1_1_1]_cons) - exp(2*[lns2_1_1]_cons) )
>     (var_D: 2*(exp(2*[lns2_1_1]_cons) - exp(2*[lns1_1_1]_cons)))

       var_A:  3*exp(2*[lns1_1_1]_cons) - exp(2*[lns2_1_1]_cons)
       var_D:  2*(exp(2*[lns2_1_1]_cons) - exp(2*[lns1_1_1]_cons))

------------------------------------------------------------------------------
      neurot |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       var_A |    5.01187   4.088337     1.23   0.220    -3.001123    13.02486
       var_D |   3.357331   4.180764     0.80   0.422    -4.836817    11.55148
------------------------------------------------------------------------------

* heritability
. disp  (5.01187+3.357331)/(5.01187+3.357331+9.559881)
.46679473
```

Binary hay fever status: P2 ADE

```
generate num3 = freq
gllamm h male, i(k pair) link(probit) fam(binom)
 adapt weight(num)
```

```
log likelihood = -4603.3053

------------------------------------------------------------------------------
           h |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        male |  -.1636205   .0534943    -3.06   0.002    -.2684675   -.0587736
       _cons |  -.6874611    .040749   -16.87   0.000    -.7673276   -.6075945
------------------------------------------------------------------------------

Variances and covariances of random effects
------------------------------------------------------------------------------

***level 2 (k)

    var(1): .89076163 (.16434027)

***level 3 (pair)

    var(1): .65503535 (.10341492)
------------------------------------------------------------------------------
```

- Note: Estimation fast because only 40 rows of data and pair-level frequency weights

Binary hay fever status: P2 ADE (cont’d)

```
. nlcom (var_A: 3*[pair2]_consˆ2 - [k1]_consˆ2)
>       (var_D: 2*([k1]_consˆ2 - [pair2]_consˆ2))

       var_A:  3*[pair2]_consˆ2 - [k1]_consˆ2
       var_D:  2*([k1]_consˆ2 - [pair2]_consˆ2)

-------------------------------------------------------------------------------
             |
           h |      Coef.   Std. Err.       z     P>|z|      [95% Conf. Interval]
-------------+-----------------------------------------------------------------
             |
       var_A |   1.074344   .3679161     2.92   0.003      .3532421    1.795447
       var_D |   .4714526   .4085908     1.15   0.249     -.3293708    1.272276
-------------------------------------------------------------------------------

. *Heritability
. disp (1.074344+.4714526)/(1.074344+.4714526+1)
.60719564
```

Binary hay fever status: P2 AE (cont’d)

```
constr def 1 [pair2]_cons = [k1]_cons
gllamm h male, i(k pair) link(probit) fam(binom) adapt
 weight(num) constr(1)
```

```
log likelihood = -4604.027077892745

 ( 1)  - [k1]_cons + [pair2]_cons = 0
------------------------------------------------------------------------------
             h |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
---------------+--------------------------------------------------------------
          male |  -.1608356   .0523616    -3.07   0.002    -.2634623   -.0582088
         _cons |  -.6758232   .0388389   -17.40   0.000     -.751946   -.5997004
------------------------------------------------------------------------------

Variances and covariances of random effects
------------------------------------------------------------------------------

***level 2 (k)

    var(1): .73240456 (.08174648)

***level 3 (pair)

    var(1): .73240456 (.08174648)
------------------------------------------------------------------------------

. disp .73240456/(.73240456+1)
.42276762
```

ACE for nuclear family designs

- Nuclear family with two children (mother, father, child1, child2)

$$\text{Cov}(\mathbf{A}) \;=\; \sigma^2_A \begin{bmatrix} 1 & 0 & 1/2 & 1/2 \\ 0 & 1 & 1/2 & 1/2 \\ 1/2 & 1/2 & 1 & 1/2 \\ 1/2 & 1/2 & 1/2 & 1 \end{bmatrix} \qquad \text{Cov}(\mathbf{C}) \;=\; \sigma^2_C \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 1 \\ 0 & 0 & 1 & 1 \end{bmatrix}$$

$$\text{Cov}(\mathbf{E}) \;=\; \sigma^2_E \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}$$

Parametrization as mixed model

- Four-level model
  - Level 4: Family k
  - Level 3: Hybrid: Sibling pair j, individual parents i
  - Level 2: Member i (same as level 1)

$$y_{ijk} = \mathbf{x}'_{ik}\boldsymbol{\beta} + a^{(4)}_{1k}[M_i + K_i/2] + a^{(4)}_{2k}[F_i + K_i/2] + a^{(2)}_{ijk}[K_i/\sqrt{2}] + c^{(3)}_{jk} + \epsilon_{ijk}$$

  - M_i is a dummy for mother, F_i for father, K_i for child
- Var$(c^{(3)}_{jk}) = \sigma^2_C$ and Var$(\epsilon_{ijk}) = \sigma^2_E$
- First three terms represent additive genetic component with Var$(a^{(4)}_{1k})$ = Var$(a^{(4)}_{2k})$ = Var$(a^{(2)}_{ijk}) = \sigma^2_A$
  - $a^{(4)}_{1k}$ and $a^{(4)}_{2k}$ induce the required additive genetic covariances between each parent and each child and among the children
  - $a^{(2)}_{ijk}$ provides remaining variance $\sigma^2_A/2$ for children

Continuous birthweight: Nuclear family data

- 1000 Nuclear families from Norwegian birth registry [Magnus et al., 2001]
- One child per family (no level 3, j), model simplifies to two-level model

$$\begin{aligned} y_{ijk} &= \mathbf{x}'_{ik}\boldsymbol{\beta} + a^{(4)}_{1k}[M_i{+}K_i/2] + a^{(4)}_{2k}[F_i{+}K_i/2] + a^{(2)}_{ijk}[K_i/\sqrt{2}] + c^{(3)}_{jk} + \epsilon_{ijk} \\ y_{ik} &= \mathbf{x}'_{ik}\boldsymbol{\beta} + a^{(4)}_{1k}[M_i{+}K_i/2] + a^{(4)}_{2k}[F_i{+}K_i/2] + a^{(4)}_{3k}[K_i/\sqrt{2}] + \epsilon_{ij} \end{aligned}$$

- Model with $c^{(3)}_{jk}$ not identified
- $a^{(2)}_{ijk}[K_i/\sqrt{2}] \equiv a^{(4)}_{3k}[K_i/\sqrt{2}]$ because K_i is non-zero for one member per family
- Level 4 becomes level 2

$$y_{ik} \;=\; \mathbf{x}'_{ik}\boldsymbol{\beta} + a^{(2)}_{1k}[M_i + K_i/2] + a^{(2)}_{2k}[F_i + K_i/2] + a^{(2)}_{3k}[K_i/\sqrt{2}] + \epsilon_{ij}$$

Continuous birthweight: Nuclear family data (cont’d)

- `fam_birthwt.dta` contains `M`, `F`, `K`, `family`, `bwt` and
  - `male`: dummy for being male
  - `first`: dummy for being the first child
  - `midage`: dummy for mother aged 20-35 at time of birth
  - `highage`: dummy for mother’s age above 35 at time of birth
  - `birthyr`: year of birth minus 1967

```
. list family M F K male birthyr bwt if family<3, sepby(family) noobs

  ┌──────────────────────────────────────────────┐
  │ family   M   F   K   male   birthyr     bwt │
  ├──────────────────────────────────────────────┤
  │      1   1   0   0      0         5    3520 │
  │      1   0   1   0      1         6    3940 │
  │      1   0   0   1      0        26    3240 │
  ├──────────────────────────────────────────────┤
  │      2   1   0   0      0         5    3660 │
  │      2   0   1   0      1         2    3990 │
  │      2   0   0   1      1        29    4330 │
  └──────────────────────────────────────────────┘
```

Estimation using `xtmixed`

- Stata commands:

```
generate var1 = M + K/2
generate var2 = F + K/2
generate var3 = K/sqrt(2)

xtmixed bwt male first midage highage birthyr
    || family: var1 var2 var3,
       nocons cov(ident) mle variance
```

- Note: Option `covariance(identity)` enforces variance equality constraint (and independence of error components) within a level

Estimation using `xtmixed`

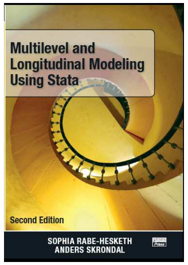
```
. xtmixed bwt male first midage highage birthyr  || family: var1 var2 var3,
>   nocons cov(ident) mle variance

------------------------------------------------------------------------------
         bwt |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        male |   158.4546   17.34853     9.13   0.000     124.4521    192.4571
       first |  -139.3974    18.7415    -7.44   0.000      -176.13   -102.6647
      midage |    57.0553   31.89569     1.79   0.074    -5.459111    119.5697
     highage |   118.8564   54.67221     2.17   0.030     11.70082    226.0119
     birthyr |   3.627799   .6882291     5.27   0.000     2.278894    4.976703
       _cons |   3461.459   34.77956    99.53   0.000     3393.292    3529.625
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
family: Identity             |
           var(var1 var2 var3) |   99263.68   10157.96      81223.99      121310
-----------------------------+------------------------------------------------
               var(Residual) |   133560.1   9069.929      116915.7    152574.2
------------------------------------------------------------------------------
LR test vs. linear regression: chibar2(01) =    97.80 Prob >= chibar2 = 0.0000
```

Concluding remarks

- Advantage of using multilevel models
  - More widely known and available in software than SEM
  - Can handle varying family sizes and missing data easily
  - Can extend to more levels, e.g., random neighborhood environment effects
- Other models considered in [Rabe-Hesketh, Skrondal & Gjessing, 2008]
  - Sibling and cousin data
  - Prameterization 1 for Twin ADE models
- Wishlist for Stata 12
  - Constraints for variance-covariance parameters in `xtmixed`, particularly equality constraints across levels
  - `nlcom` with `ci(probit)` option

References to own work

- Rabe-Hesketh, S., Skrondal, A. and Gjessing, H. K. (2008). Biometrical modeling of twin and family data using standard software for mixed models. *Biometrics* 64, 280-288.

- 

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