Familial and socio-economic influences on foetal growth across three generations

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London School of Hygiene and Tropical Medicine
and *University of Stockholm

LSHTM, 23 February 2011
Outline

1 Background
2 The UBCoS Multigen Study
3 Preliminary results
4 Genetic biometrical model
5 Results
6 Potential biases
7 Summary
Outline

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7 Summary
Intergenerational studies: strong correlations in size at birth between parents and offspring (0.20-0.25 for mothers, less for fathers).

Two mechanisms:

1. **Genetic**:
   - father-offspring: can only be explained via *foetal genes*
   - mother-offspring: could also be attributed to *maternal genes* that influence fetal growth

2. **External environment**:
   - *maternal lifestyle* influences in utero environment (e.g. smoking and diet) and is correlated across generations.

However:

- incorrect *paternity* attribution may inflate difference between mother-offspring and father-offspring correlations
- **limited evidence** of impact of earlier generations socio-economic factors on size at birth correlations
- little *data* on more than 2 generations.
Intergenerational correlations in size at birth

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A) whether correlations in size at birth across three generations are consistent with those found across two generations

B) the extent to which these correlations could be explained by socio-demographic continuities across generations.

Using the unique and rich data available in **UBCoS Multigen**
Uppsala Birth Cohort Multigenerational Study (UBCoS Multigen)
Prospective study of men and women born in Uppsala, Sweden (1915-1929) and their descendants (currently linking to 4th & 5th generation)

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Three generations

**Original cohort** (Leon et al. 1998)

- **Generation 1 (G1):** all Uppsala births in 1915-29 (∼14,000),
  **Source:** Uppsala Academic Hospital (UAH) birth records

**descendants traced via the Swedish Multigenerational Registry** (Koupil, 2007):

- **Generation 2 (G2):** their children (∼20,000),
- **Generation 3 (G3):** their grandchildren (∼33,000)
- great-grand-children (G4), great-great-grand-children (G5) . . .
  **Source:** several

- 8,550 UBCoS G1 grandparents with 33,693 grandchildren
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Data sources

- **Birth data**: UAH, Swedish Birth Registry (1972-)
- **SEP, demographic vars**: Censuses (1960, 1970, 1980), linked longitudinal studies, etc
- **Others**: Conscripts Register, School records, ...

**Linkage depends on calendar year ⇒ no birth data for G2**

![Graph showing birth weight and gestation across generations](image)
Main variables and data for these analyses

- **standardized size at birth** (birth weight and length)
- **SEP and demographic variables**

  - Mat age
  - Mat marital Status
  - Occupation
  - Occupation
  - Education
  - Mat age
  - Maternal smoking
  - Parental education
  - Parental income

- **inclusions**, for each generation: singletons, not adoptees
- **restrictions**: to G3 with birth data ⇒ 7,657 G1 and 25,141 G3
Data complexities

Four types of grandparents:

<table>
<thead>
<tr>
<th>GP type</th>
<th>G1</th>
<th>G1-G3</th>
</tr>
</thead>
<tbody>
<tr>
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<td>2,340</td>
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* Some grandparents contribute to maternal and paternal entries
† Some grandchildren have more than one grandparent

Analytical complexity:

(a) Clustered data
- ~ 3 G3 per G1

(b) Prospective design
- Incomplete pedigrees

(c) Missing data
- Mat Gmothers least complete
**Data complexities**

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A) are correlations maintained across 3 generations?

Correlation coefficients for standardized BW ($N_{pairs} = 28,152$)

<table>
<thead>
<tr>
<th>G1</th>
<th>4 groups Coef. (95% CI)</th>
<th>2 groups Coef. (95% CI)</th>
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<tr>
<td>Mat gm</td>
<td>0.124 (0.095, 0.153)</td>
<td>0.125 (0.105, 0.145)</td>
</tr>
<tr>
<td>Mat gf</td>
<td>0.126 (0.099, 0.153)</td>
<td></td>
</tr>
<tr>
<td>Pat gm</td>
<td>0.093 (0.065, 0.121)</td>
<td>0.096 (0.077, 0.115)</td>
</tr>
<tr>
<td>Pat gf</td>
<td>0.099 (0.073, 0.126)</td>
<td></td>
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Estimates based on a RE model with GP as clusters; adj for G1 & G3 parity and year of birth

- **Correlations maintained across generations**
- Stronger associations for maternal grandparents
- Model with 2 groups equally good fit → maternal/paternal lineage as the main discriminant ($p=0.02$)
Including SEP variables as potential mediators:

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<td>0.091  (0.065, 0.117)</td>
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GP: grandparent

- Minimally: adjusted (for G0 & G2 parity and G1 & G3 year of birth)
- Fully: additionally adjusted for G2 smoking, G2 income, G1 and G2 education, G0 and G2 mat age, G0 and G1 SEP, G0 mat marital status
- analysis carried out on a subset because of missing values: $N_{pairs}=14,382$

No evidence of mediation  (or effect modification)
Critique

Results might be affected by bias because:

- likely measurement/missclassification error affecting the socio-economic variables
- missing data

They also do not exploit the family structure of the data.

Alternative approach:

**Genetic biometrical model**

Partition total variance of size at birth into: foetal genes, maternal genes, shared environmental factors, unshared environmental factors.
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Partitioning the variance of size at birth of the G1 and G3 study members, under certain assumptions, may lead to a model such as this:

Ass: rand mating, genotypic parent-child: 0.5; no interactions, constant effects
Twin design:

- Data on $Y$: phenotype of interest
- measured in pairs of monozygotic (MZ) and dizygotic (DZ) twins
- Exploit: MZ twins share all their genes while DZ share half

**ACE Model**

Widely used to separate genetic from environmental sources of variation in a phenotype $Y$.

Specific assumptions:

- genes have additive effects
- twins in a set experience the same environment (at least in childhood)

Gielen et al, Behav Genet (2008) 38:4454
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ACE Model

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The ACE model for one member of the twins set

The phenotype is a weighted sum of three components:

\[ Y = aA + cC + eE \]

- **genetic** factors: represented by the latent variable \( A \)
- **shared** environmental factors: represented by \( C \)
- **unshared** environmental factors: represented by \( E \)

All latent factors: independent \( N(0,1) \); \( a, c, \) and \( e \): *path coefficients*.
The ACE model for the twins set

\[ Y_{ij} : \text{phenotype for twin } i \text{ in set } j \]

Covariance between \( A_{1j} \) and \( A_{2j} \) is 1 for MZ and \( \frac{1}{2} \) for DZ
Heritability and identification

\[ Y_{ij} = aA_{ij} + cC_j + eE_{ij} \]

This model implies:

- \( \text{Var}(Y_{ij}) = a^2 + c^2 + e^2 \)
- \( \text{Cov}(Y_{1j}, Y_{2j}) = a^2 + c^2 \) for MZ twins
- \( \text{Cov}(Y_{1j}, Y_{2j}) = \frac{a^2}{2} + c^2 \) for DZ twins

**Useful:**

To estimate heritability (\( h \)):

\[ h = \frac{a^2}{a^2 + c^2 + e^2} \]

**Identification:**

The model has 3 parameters with three sufficient statistics.
Heritability and identification

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**Useful:**

to estimate heritability (h) = \( \frac{a^2}{a^2 + c^2 + e^2} \)

**Identification:**

The model has 3 parameters with three sufficient statistics
Partition the variance of standardised BW into components from:

- **foetal** genes: represented by $F$; **maternal** genes: $M$
- **shared** environm factors: $C$; **unshared** environmental factors: $E$

\[ \text{Ass: rand mating, genotypic parent-child: 0.5; no interactions, constant effects} \]

Covariance btwn $F_{1j}$ and $F_{3j}$ is $\frac{1}{4}$ for all, covariance btwn $M_{1j}$ and $M_{3j}$ is $\frac{1}{4}$ for Mat Grandparents, 0 otherwise.
Genetic biometrical model

Identification

Y_{ij}: phenotype for member i in family j

\[ Y_{ij} = fF_{ij} + mM_{ij} + cC_j + eE_{ij} \]

This model implies:

- \( \text{Var}(Y_{ij}) = f^2 + m^2 + c^2 + e^2 \)
- \( \text{Cov}(Y_{1j}, Y_{3j}) = \frac{1}{4} f^2 + \frac{1}{4} m^2 + c^2 \) for Maternal GParents
- \( \text{Cov}(Y_{1j}, Y_{3j}) = \frac{1}{4} f^2 + c^2 \) for Paternal GParents

Since the model has 4 parameters, it is not identified.
However, it can be identified if we specify C in terms of some observables
The full genetic biometrical model for G1-G3 pairs
Genetic biometrical model
 Contributions to the variances and covariances

The model implies:
- \( \text{Var}(Y_{ij}) = f^2 + m^2 + c^2 + e^2 \)
- \( \text{Cov}(Y_{1j}, Y_{3j}) = \frac{1}{4} f^2 + \frac{1}{4} m^2 + c^2 \) for Maternal GP\(\hat{a}rents \)
- \( \text{Cov}(Y_{1j}, Y_{3j}) = \frac{1}{4} f^2 + c^2 \) for Paternal GP\(\hat{a}rents \)

Contributions to the variance:
- \( \text{Foetal} = \frac{f^2}{f^2 + m^2 + c^2 + e^2} \)
- \( \text{Maternal} = \frac{m^2}{f^2 + m^2 + c^2 + e^2} \)
- \( \text{Shared environment} = \frac{c^2}{f^2 + m^2 + c^2 + e^2} \)

Contribution to the covariances:
- \( \Rightarrow \text{Environm contribution of Maternal \(\hat{a}rrents\):} \frac{c^2}{f^2/4 + m^2/4 + c^2} \)
- \( \Rightarrow \text{Environm contribution of Paternal \(\hat{a}rrents\):} \frac{c^2}{f^2/4 + c^2} \)

When \( Y \) is standardized, these are contributions to the correlations

BL De Stavola/Foetal growth across generations
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Factor loadings for C

- G0 Maternal age
  - G0 manual occ
  - G1 Education
  - G1 manual occ
  - G2 Education
  - G2 Maternal Age
  - G2 Mat high income
  - G2 Pat high income
  - G2 Maternal Smoking Status

Higher socio-demographic status ⇒ positive C
Path coefficients

- **Good fit**: Observed predicted correlations: Mat GP: 0.114 \ 0.113; Pat GP: 0.093 \ 0.090
- Estimates conditional on G0 and G2 parity and G1 and G3 year of birth
- robust SE to account for clustering: N_{adj} = 14,382
### Contributions to the correlations

<table>
<thead>
<tr>
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<tr>
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<td>Estimate</td>
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<td>11.6</td>
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- Estimates of fetal, maternal and shared environment contributions to the variance: $\sim 30\%$ ; $\sim 10\%$; $\sim 1\%$. 

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Linkage leads to systematic missingness

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</tr>
<tr>
<td>Maternal age</td>
<td>0%</td>
</tr>
<tr>
<td>Parity</td>
<td>0%</td>
</tr>
<tr>
<td>Maternal smoking</td>
<td>46%</td>
</tr>
<tr>
<td>G1 Education, SEP</td>
<td>0-2%</td>
</tr>
<tr>
<td>Parity</td>
<td>3%</td>
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<td>Maternal age</td>
<td>0%</td>
</tr>
<tr>
<td>All</td>
<td>49%</td>
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Mat grandmother most affected by missingness
Sources of missingness

- Due to Linkage:
  missing maternal smoking status because born before 1980 (when smoking status started to be recorded)
  ⇒ G3 Year of birth ‘causes’ missingness

- G3 year of birth is completely observed: ⇒ MAR

- G3 year of birth is already included in the model: ⇒ Missing mechanism is ignorable if using ML+EM
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Updated contributions to the correlations

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Evidence of contribution of shared environment
Revisiting the regression models

Replacing the multiple environmental indicators with estimated $C$:

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<td>Cor.</td>
<td>Cor.</td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td>(95% CI)</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>Mat GP</td>
<td>0.122</td>
<td>0.121</td>
<td>0.116</td>
</tr>
<tr>
<td></td>
<td>(0.095, 0.150)</td>
<td>(0.093, 0.148)</td>
<td>(0.089, 0.144)</td>
</tr>
<tr>
<td>Pat GP</td>
<td>0.091</td>
<td>0.092</td>
<td>0.087</td>
</tr>
<tr>
<td></td>
<td>(0.065, 0.117)</td>
<td>(0.066, 0.117)</td>
<td>(0.061, 0.113)</td>
</tr>
</tbody>
</table>

GP: grandparent

Some effect is now explained by the environmental factors.
Outline

1. Background
2. The UBCoS Multigen Study
3. Preliminary results
4. Genetic biometrical model
5. Results
6. Potential biases
7. Summary
Do continuity in size at birth depend on social disadvantage?

- shared environment  13-19% of the intergenerational correlations in standardized size at birth

On which basis?

- Assuming a specific genetic model, in particular a specific maternal genetic influence
- Assuming missingness was MAR, estimates were slightly inflated
- Results robust when some of the assumptions were relaxed

Why are results different from those from standard regression?

- addressing measurement error in SEP/demographic indicators recuperated part of the effect of shared environment not identified by standard regression
Separating biological and social pathways involves assuming and measuring specific pathways.

When these cannot be properly measured an alternative approach is to separate components of ‘correlations’ into biological and environmental pathways.

Explicitly assessing the interplay of biology and environment would require access to genetic data (and several other assumptions).

Final results are very much dependent on the quality of the data.
### Variance components

<table>
<thead>
<tr>
<th></th>
<th>Stand Birth weight</th>
<th>Stand Birth length</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate 95% CI</td>
<td>Estimate 95% CI</td>
</tr>
<tr>
<td>Foetal genetic</td>
<td>32.5 21.4,43.5</td>
<td>26.6 16.6, 36.6</td>
</tr>
<tr>
<td>Maternal genetic</td>
<td>7.5  -9.6,24.5</td>
<td>3.7  -11.9,19.2</td>
</tr>
<tr>
<td>Environment</td>
<td>1.3  0.8, 1.9</td>
<td>1.1  0.1, 1.6</td>
</tr>
</tbody>
</table>

- Weaker results for head circumference
- Similar results for birth weight and birth length, adjusted for gest age and sex
- Reassuring that estimates of genetic and maternal heritability similar to those published by Lunde (2007)
The 3 generations genetic model

P: phenotype
M: maternal gene
G: foetal gene

P: phenotype
M: maternal gene
G: foetal gene
Potential biases
Misclassification

What if paternity is erroneously attributed?