Applying a co-twin control design to clarifying the relationship between education and dementia

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Study Motivation

Low educational attainment is a recognized putatively modifiable risk factor for Alzheimer’s disease and related dementias. However, mechanisms for the association remain unresolved. In this talk, we apply twin methods to data from seven twin samples from Sweden, Denmark, Australia, and the US participating in the IGEMS (Interplay of Genes and Environment in Multiple Studies) consortium.

Learning Outcomes
1. recognize possible mechanisms and confounders in explaining the association between attained education and Alzheimer's disease and related dementias
2. appreciate how a twin design permits distinguishing within family versus between family sources of individual differences
The logic of a co-twin control study

**Monozygotic twin pairs**

- Shared environment
- Unique environment
- 100% shared genes

**Dizygotic twin pairs**

- Shared environment
- Unique environment
- Unique genes
- 50% shared genes
**Monozygotic twin pairs**

- Shared environment
- Unique environment
- MZ Twins
- 100% shared genes

**Dizygotic twin pairs**

- Shared environment
- Unique environment
- DZ Twins
- 50% shared genes

**Unrelated pairs**

- Unique environment
- Unrelated Matched Pair
- Unique genes

- Unique environment
- Unique genes
Study Setup

**Danish Twin Registry**
including both LSADT and MADT

**Swedish Twin Registry**
including SATSA, Gender, OCTO-Twin, and HARMONY

**Older Australian Twins Study**

**US samples**

**MIDUS twins**
Midlife in the United States

**VETSA**
Vietnam Era Twin Study of Aging

**CAATSA**
Carolina African American Twin Study of Aging

**NAS-NRC Twin Registry**
World War II Twins
Measures

• In the Swedish Twin Registry, OATS, and NAS-NRC, individuals were worked up clinically for dementia, and—in Sweden—followed up by linkage to health registries.

• We also constructed a latent dementia index (LDI) for all studies except NAS-NRC. The LDI provides a continuous score representing dementia risk based on cognitive and memory performance and functional ability (i.e., IADL), net of general cognitive ability. For samples without clinical diagnoses, a cutoff score on the LDI designates dementia.

• Education was measured with the International Standard Classification of Education (ISCED).
Results

Mean LDI difference within pairs who are discrepant for ISCED, by genetic relationship and sex
Co-twin control models predicting dementia

In the main analysis, we applied a between-within regression model to test the hypothesis that twins whose education was lower than their co-twins had greater likelihoods of being diagnosed with dementia, statistically adjusting for familial genetic and shared environmental factors.

Specifically, we simultaneously tested whether differences in education between families and intrapair differences on education within families influenced dementia risk.

We then tested the interaction between intrapair differences and zygosity. A significant interaction indicates a significant effect of genetic confounding, while a non-significant interaction indicates confounding due to shared environmental factors.

## Results of co-twin control models predicting dementia

<table>
<thead>
<tr>
<th></th>
<th>Model 1: Phenotypic</th>
<th>Model 2: Between/Within</th>
<th>Model 3: Adjusting for Zygosity</th>
<th>Model 4: Adjusting for Sex</th>
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<tr>
<td>-2loglikelihood</td>
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<td>324312.1</td>
<td>325746.1</td>
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<td>DF</td>
<td>60018</td>
<td>60017</td>
<td>60015</td>
<td>60010</td>
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<tr>
<td>Fixed Effects</td>
<td>B(se)</td>
<td>B(se)</td>
<td>B(se)</td>
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<td>intercept</td>
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<td>-0.81(.05)*</td>
<td>-0.80(.06)*</td>
<td>-0.99(.06)*</td>
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<td>Educij [π] Phenotypic effect</td>
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<td>Educj [π1] Between families</td>
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<td>-0.98(.03)*</td>
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<tr>
<td>Educij [π2] Within families</td>
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<td>-0.07(.04)</td>
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<td>Zygj [π3]</td>
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<td>-0.02(.03)</td>
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<td>-0.26(.10)*</td>
<td>-0.27(.10)*</td>
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<td>Femaleij [π5]</td>
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<td>0.33(.03)*</td>
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<tr>
<td>Femaleij<em>Zygj</em>Educij [π8]</td>
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</table>
Conclusions

• We confirmed that individuals with lower education have greater dementia risk.

• Within a family, the twin with higher educational attainment did not reliably accrue greater protection against developing dementia compared to the less educated twin.

• Differences between families in education were the significant driver of dementia risk. An individual from a family where educational attainment was higher had greater protection than an individual from a family where educational attainment was lower, regardless of the relative amount of education when comparing an individual to their sibling within the same family.