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

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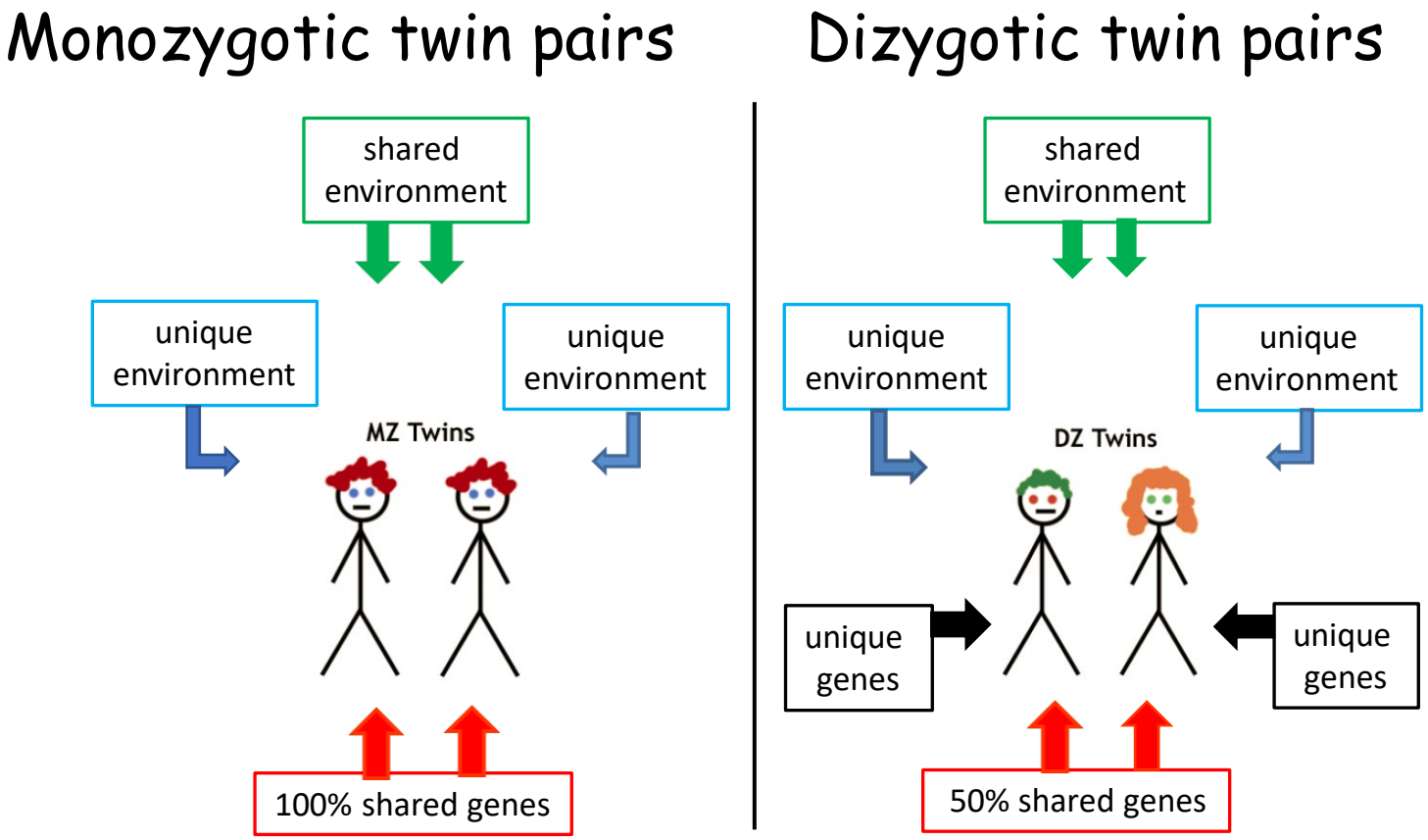
Study Motivation

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.

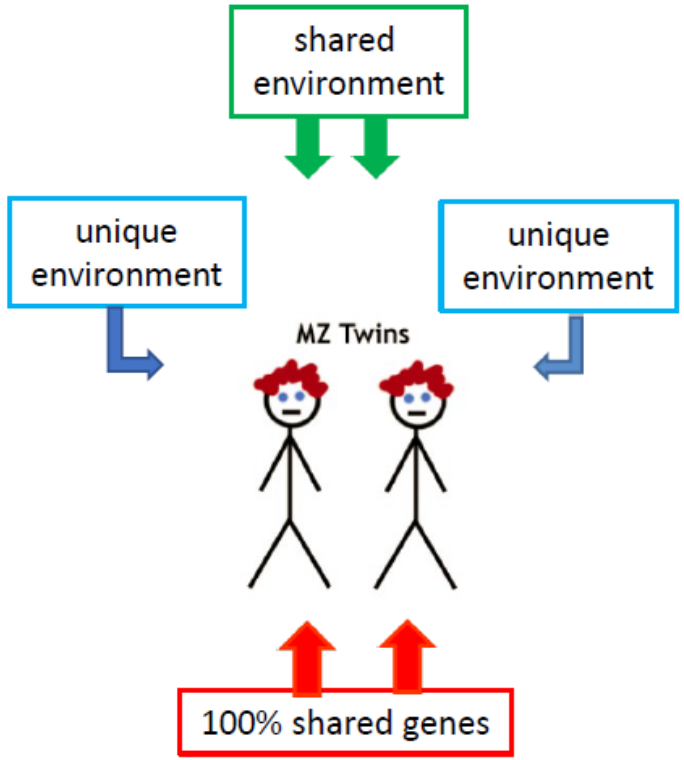
Learning Outcomes

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

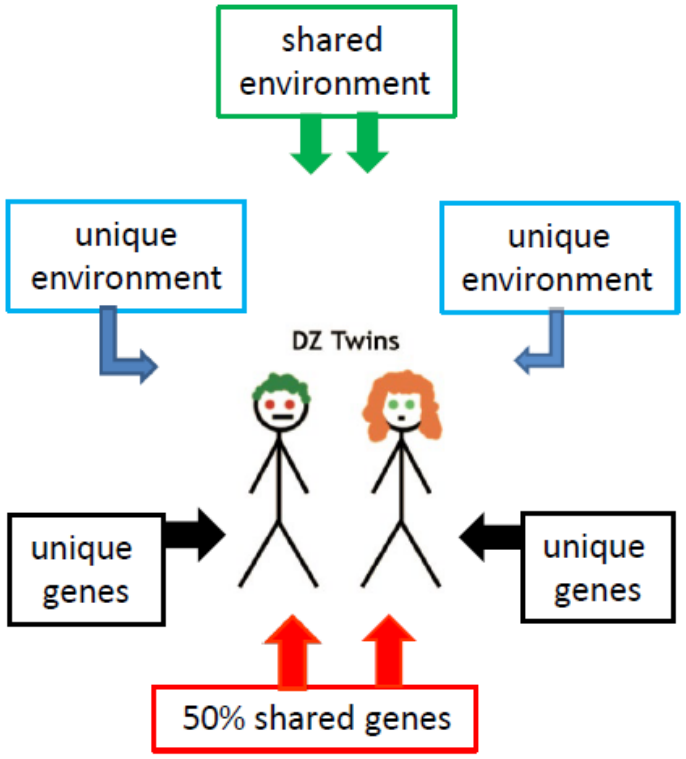
The logic of a co-twin control study



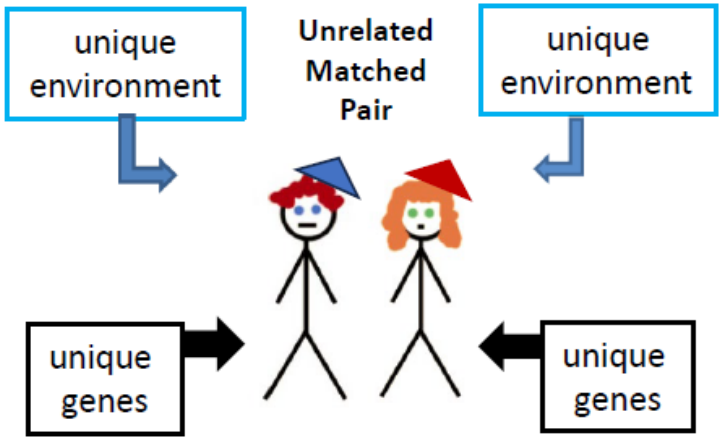
Monozygotic twin pairs



Dizygotic twin pairs



Unrelated pairs



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

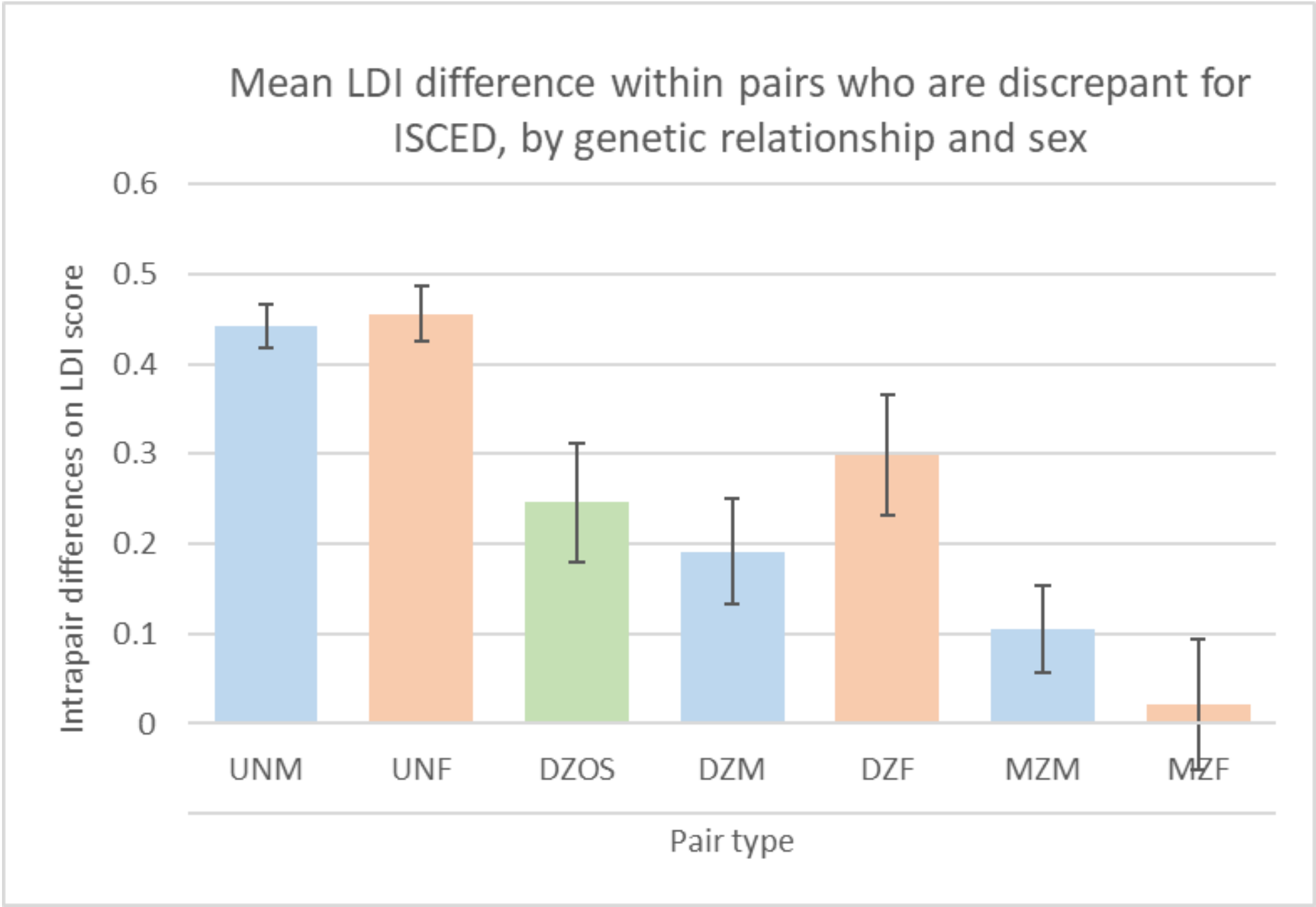
CAATSA
Carolina African American Twin Study of Aging

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
Intrapair differences on LDI score
0.6
0.5
0.4
0.3
0.2
0.1
0
UNM
UNF
DZOS
DZM
DZF
MZM
MZF
Pair type

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.

Turkheimer, E., & Harden, K. P. (2014). Behavior genetic research methods: Testing quasi-causal hypotheses using multivariate twin data.

Results of co-twin control models predicting dementia

	Model 1: Phenotypic	Model 2: Between/ Within	Model 3: Adjusting for Zygosity	Model 4: Adjusting for Sex
-2loglikelihood	321265.6	324298.0	324312.1	325746.1
DF	60018	60017	60015	60010
Fixed Effects	B(se)	B(se)	B(se)	B(se)
intercept	-1.27(.05)*	-0.81(.05)*	-0.80(.06)*	-0.99(.06)*
$Educ_{ij}$ [π] Phenotypic effect	-0.68(.03)*			
$Educ_j$ [π_1] Between families		-0.98(.03)*	-0.98(.03)*	-0.98(.03)*
$Educ_{ij}$ [π_2] Within families		-0.07(.04)	0.13(.09)	0.13(.09)
Zyg_j [π_3]			-0.02(.03)	-0.01(.03)
$Educ_{ij}$*Zyg_j [π_4] Within families X Zygosity			-0.26(.10)*	-0.27(.10)*
$Female_{ij}$ [π_5]				0.33(.03)*
$Female_{ij}$*$Educ_{ij}$ [π_6]				
$Female_{ij}$*Zyg_j [π_7]				
$Female_{ij}$*Zyg_j*$Educ_{ij}$ [π_8]				

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.

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