

# Implicating Causal Brain Endophenotypes in Alzheimer's Disease

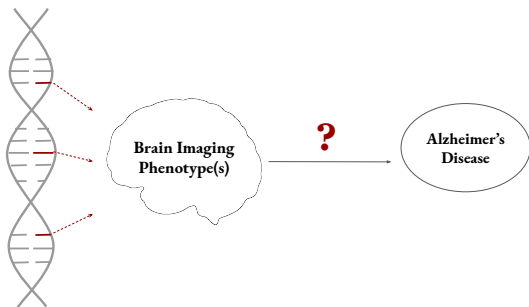
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# MOTIVATION

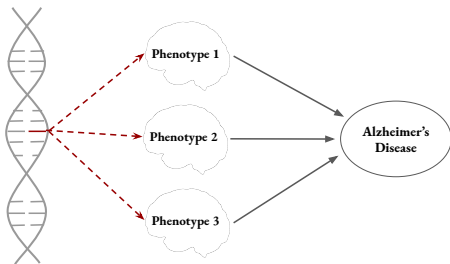
**Goal:** Detect causal genetically-regulated brain imaging phenotypes in Late Onset Alzheimer's Disease



# PROBLEM WITH EXISTING METHODS

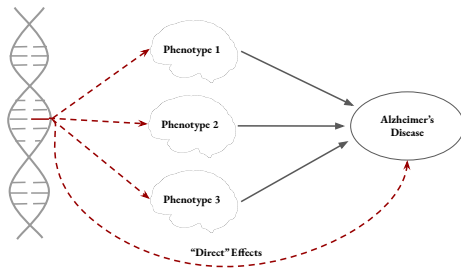
1. Mendelian Randomization (MR)
2. Imaging Wide Association Study (IWAS, Xu et al., 2017)

MR and IWAS effect estimates are inconsistent in the presence of **Genetic Pleiotropy**



# MV-IWAS ACCOUNTS FOR GENETIC PLEIOTROPY

- ▶ **MV-IWAS:** consistent causal estimates by incorporating all intermediate brain phenotypes
- ▶ **MV-IWAS-Egger** accounts for possible unmeasured/unknown pathways



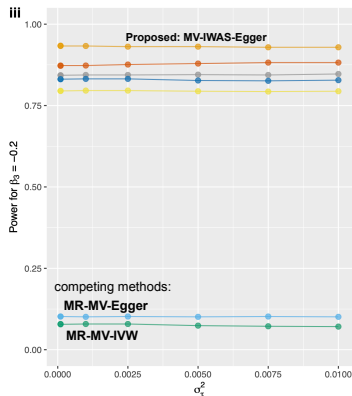
# GWAS SUMMARY STATISTICS BASED APPROACH

Existing IWAS method relies on **individual level** data for large-scale studies

We provide an approach for IWAS and MV-IWAS which only requires publicly available **summary statistics** from Genome-Wide Association Studies (GWAS)

# SIMULATIONS

- ▶ MV-IWAS controls Type-I errors and maintains high power
- ▶ IWAS yields highly inflated Type-I errors
- ▶ MV-IWAS substantially improves power over popular MR methods



# APPLICATION TO 3 POPULAR DATA SOURCES

1. 14 summarized brain ROIs from the **ADNI1** study
  2. GWAS summary statistics on 1,578 **UK Biobank** phenotypes
  3. Replication study using GWAS data for 7 ROIs from **ENIGMA** and UKBB
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- Identified many well-established (hippocampal volume) & biologically plausible causal phenotypes in AD
  - In all applications, IWAS findings suggest many putative false positive discoveries.