
University of Colorado **Boulder**

**Institute for Behavioral Genetics**

# Genomic Structural Equation Modeling: A Brief Introduction

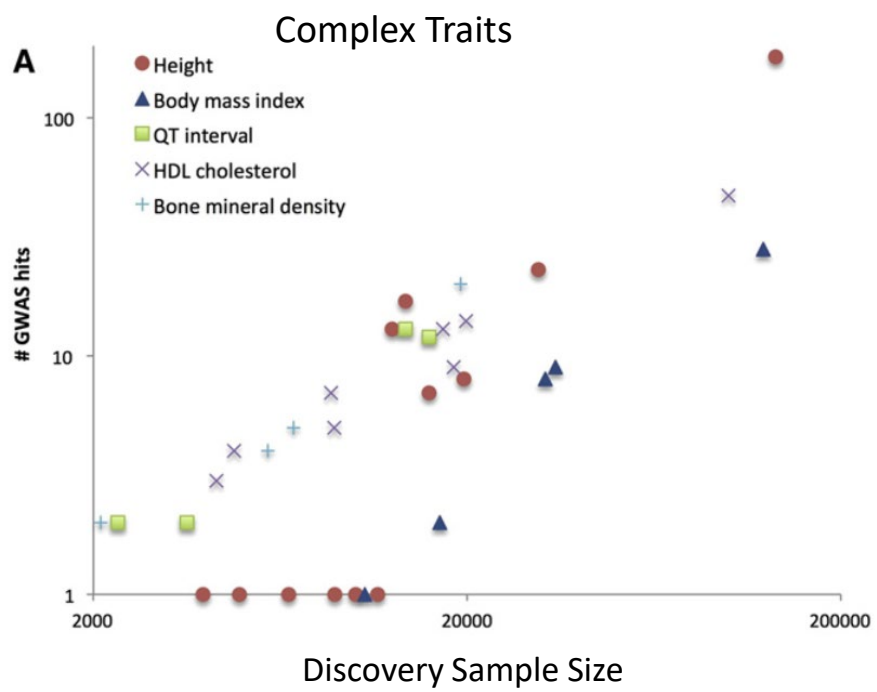
Andrew Grotzinger

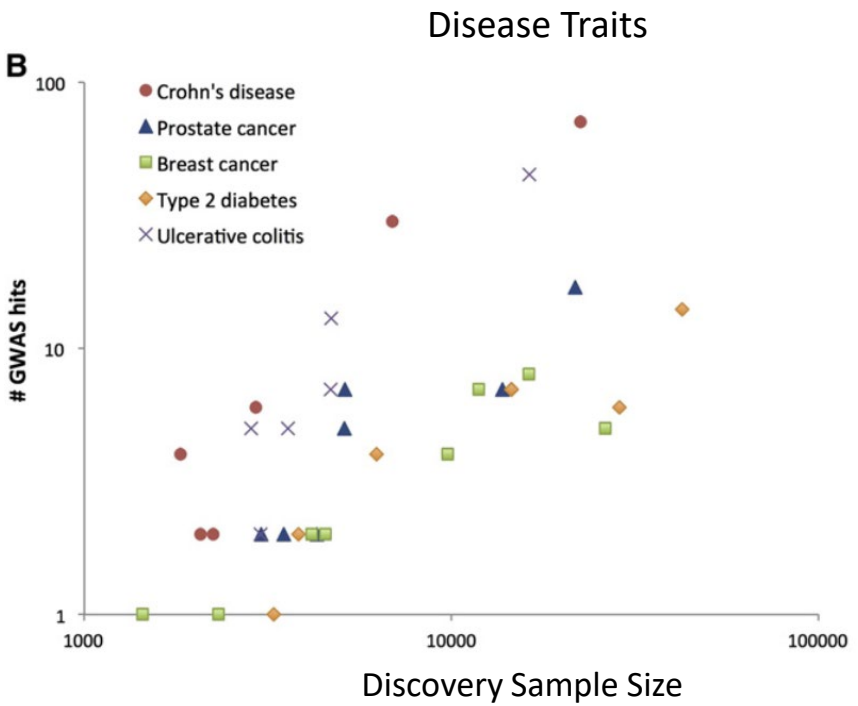
IBG Workshop 2021

Paper: Grotzinger, A. D., Rhemtulla, M., de Vlaming, R., Ritchie, S. J., Mallard, T. T., Hill, W. D, Ip, H. F., McIntosh, A. M., Deary, I. J., Koellinger, P. D., Harden, K. P., **Nivard, M. G**., & **Tucker-Drob, E. M.** (in press). **Genomic SEM provides insights into the multivariate genetic architecture of complex traits.** *Nature Human Behaviour.*

*Link to paper:* rdcu.be/bvn7t

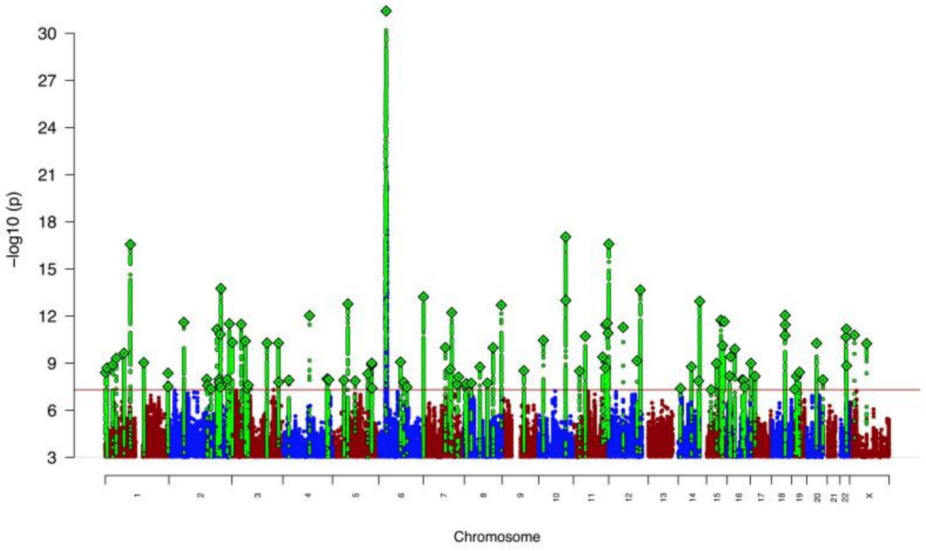
# The gradual realization that human complex traits are associated with *many* genes



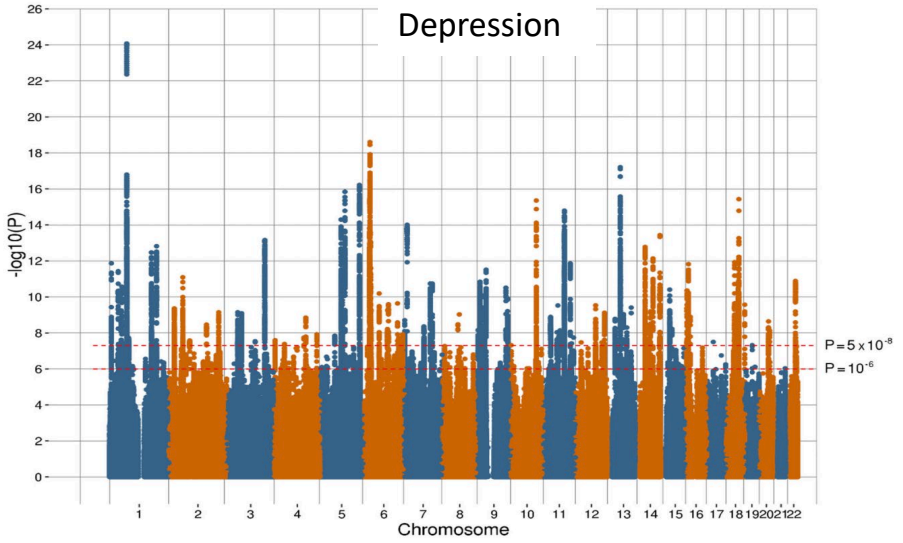




Kendler et al., 2012

Schizophrenia




Depression




Traits are highly polygenic, so not simply a matter of identifying ~5 overlapping genes

# An atlas of genetic correlations across human diseases and traits

Brendan Bulik-Sullivan, Hilary K Finucane, Verneri Anttila, Alexander Gusev, Felix R Day, Po-Ru Loh, ReproGen Consortium, Psychiatric Genomics Consortium, Genetic Consortium for Anorexia Nervosa of the Wellcome Trust Case Control Consortium 3, Laramie Duncan, John R B Perry, Nick Patterson, Elise B Robinson, Mark J Daly, Alkes L Price & Benjamin M Neale

*Nature Genetics* **47**, 1236–1241 (2015) | Download Citation

**Estimates genetic correlations between samples with varying degrees of sample overlap using publicly available data**

# Pervasive (Statistical) Pleiotropy Necessitates Methods for Analyzing Joint Genetic Architecture

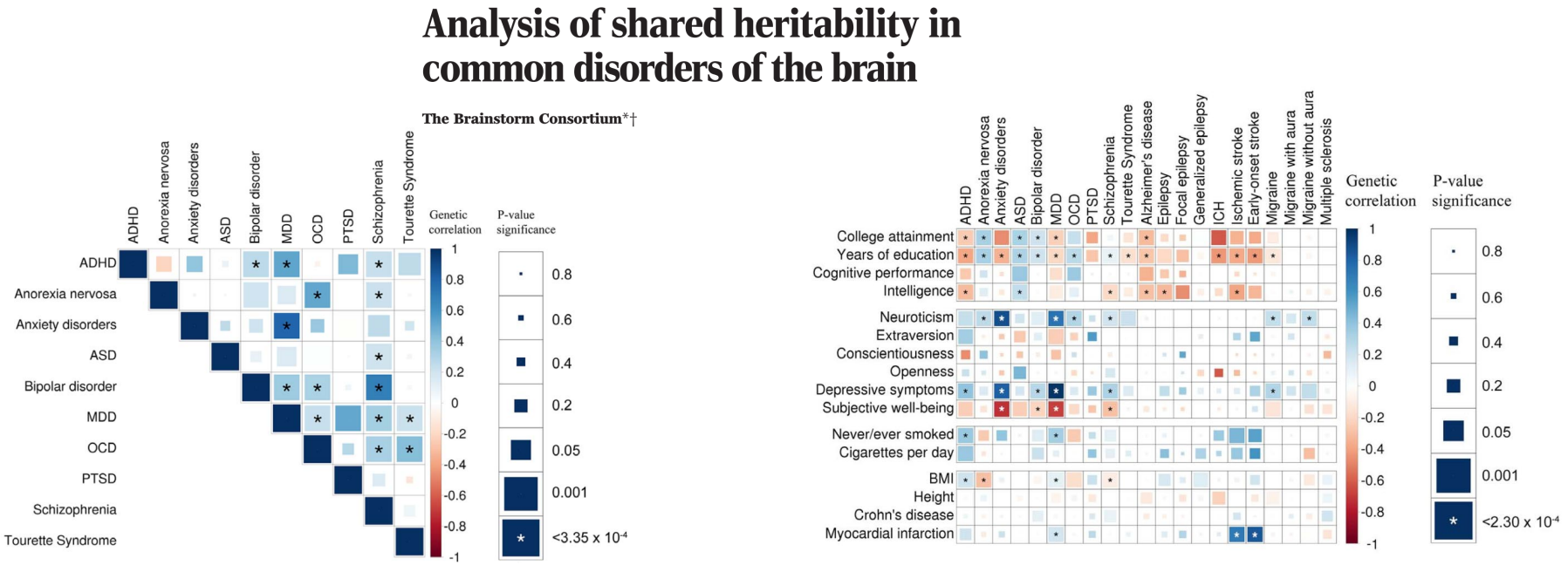



**Fig. 1. Genetic correlations across psychiatric phenotypes.** The color of each box indicates the magnitude of the correlation, and the size of the box indicates its significance (LDSC), with significant correlations filling each square completely. Asterisks indicate genetic correlations that are significantly different from zero after Bonferroni correction.

**Fig. 4. Genetic correlations across brain disorders and behavioral-cognitive phenotypes.** The color of each box indicates the magnitude of the correlation, and the size of the box indicates its significance (LDSC), with significant correlations filling each square completely. Asterisks indicate genetic correlations that are significantly different from zero after Bonferroni correction.

The Brainstorm Consortium, *Science* **360**, 1313 (2018) 22 June 2018

# Background

- Genome-wide methods are clearly suggestive of both high polygenicity and pervasive pleiotropy

- **Genetic correlations as data to be modeled, not simply results by themselves**
  - What data-generating process gave rise to the correlations?

# Genomic SEM

nature human behaviour

ARTICLES

https://doi.org/10.1038/s41562-019-0566-x

## Genomic structural equation modelling provides insights into the multivariate genetic architecture of complex traits

Andrew D. Grotzinger[1*], Mijke Rhemtulla[2], Ronald de Vlaming[3,4], Stuart J. Ritchie[5,6], Travis T. Mallard[1], W. David Hill[5,6], Hill F. Ip[7], Riccardo E. Marioni[5,8], Andrew M. McIntosh[5,9], Ian J. Deary[5,6], Philipp D. Koellinger[3,4], K. Paige Harden[1,10], Michel G. Nivard[7,11] and Elliot M. Tucker-Drob[1,10,11]

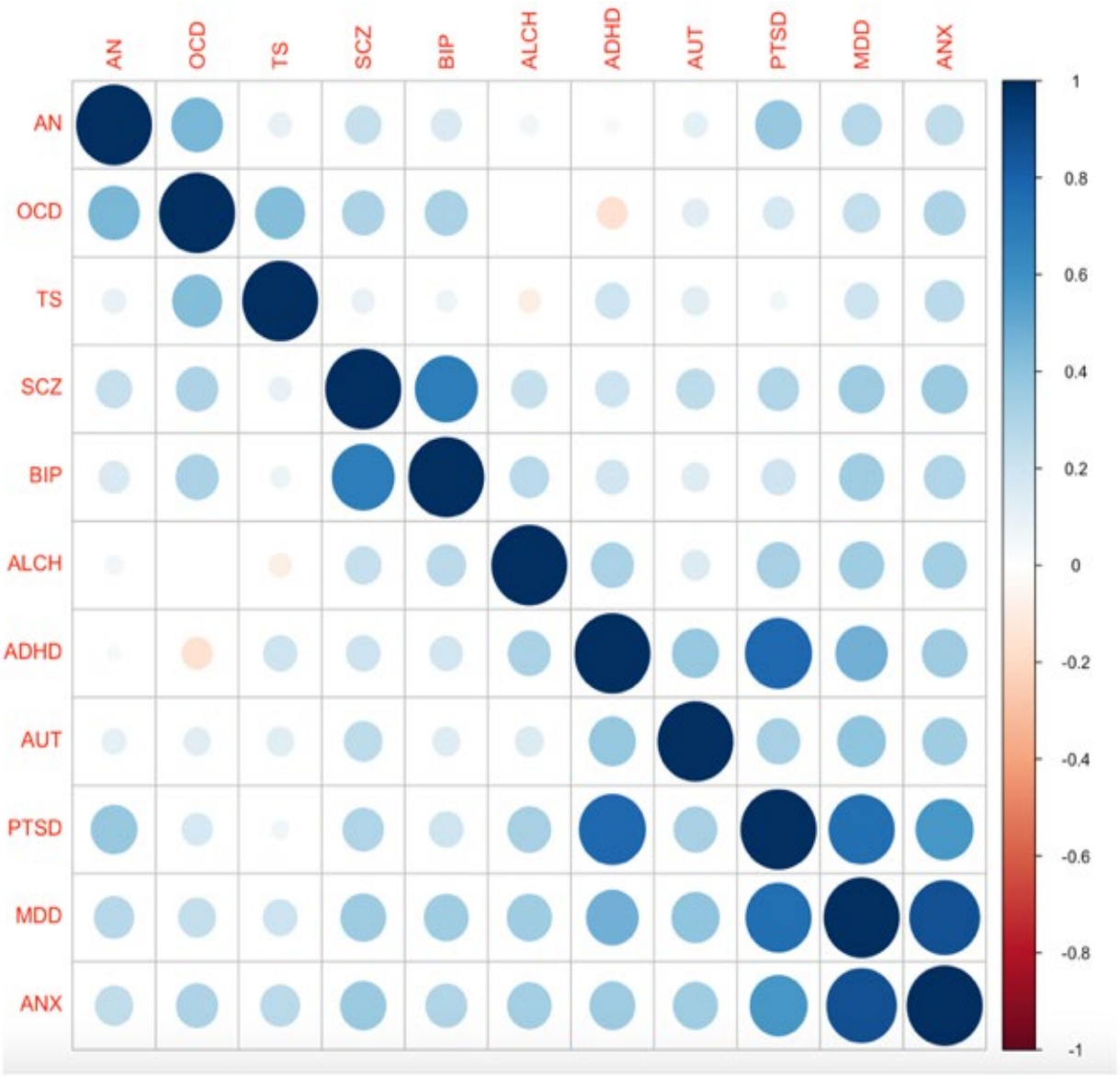
Nivard

Tucker-Drob

# Our solution: GenomicSEM

- Apply structural equation model to estimated genetic covariance matrices
  - Allows user to examine traits that could not be measured in the same sample

- Genomic SEM provides flexible framework for estimating limitless models using GWAS summary statistics
  - Can be applied to GWAS “sumstats” with varying and unknown degrees of overlap

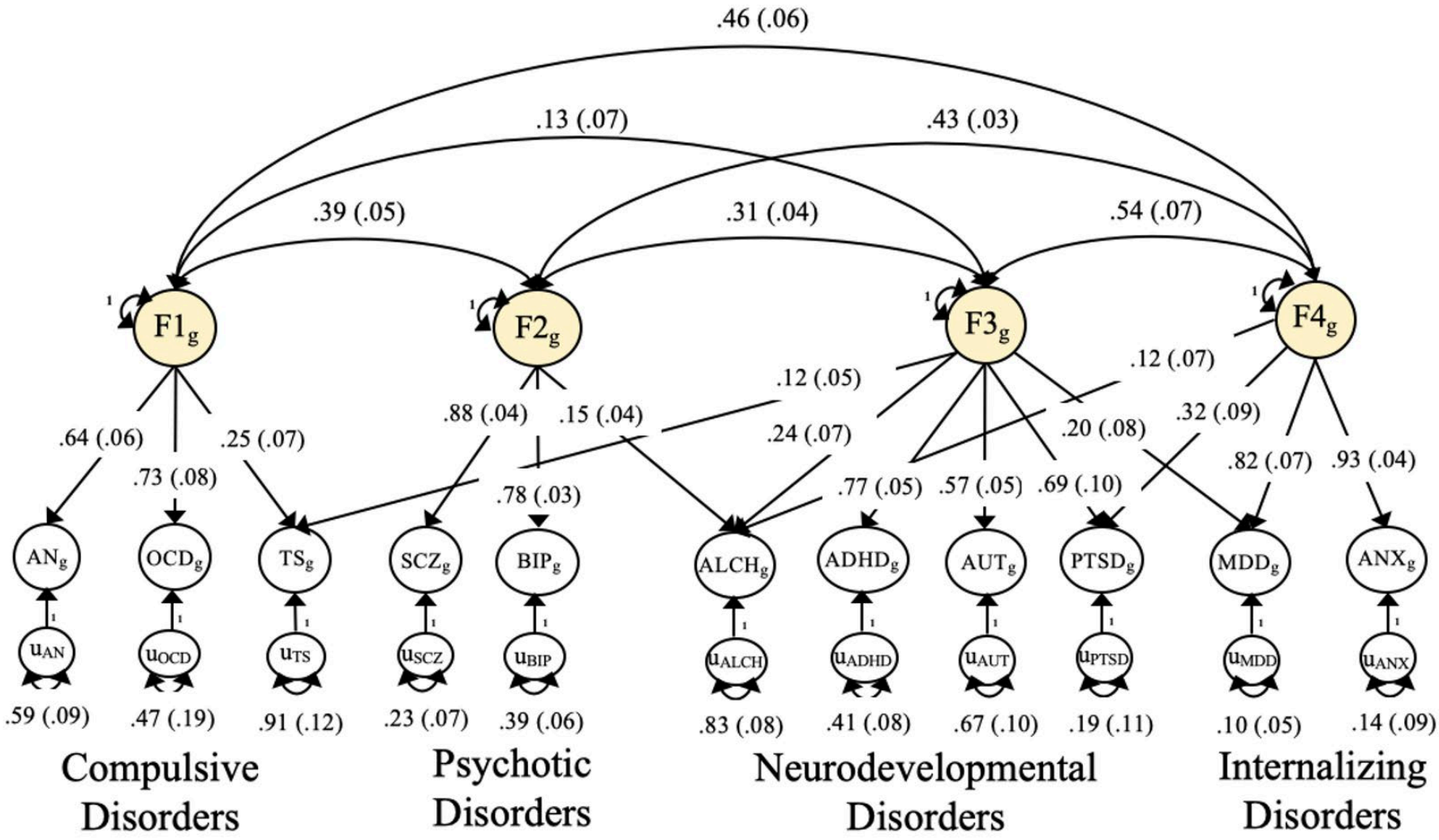



Genetic “heatmap” across 11 Major Psychiatric Disorders

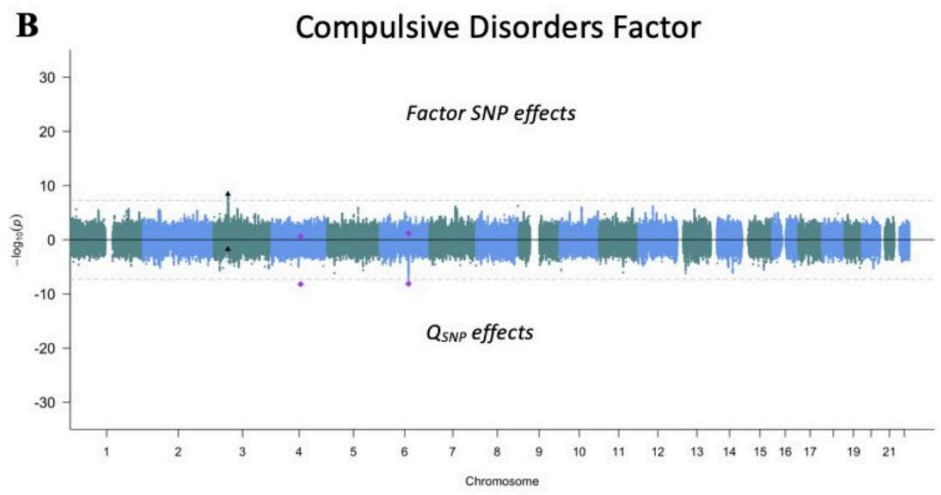
Many of these disorders could not be measured in the same sample

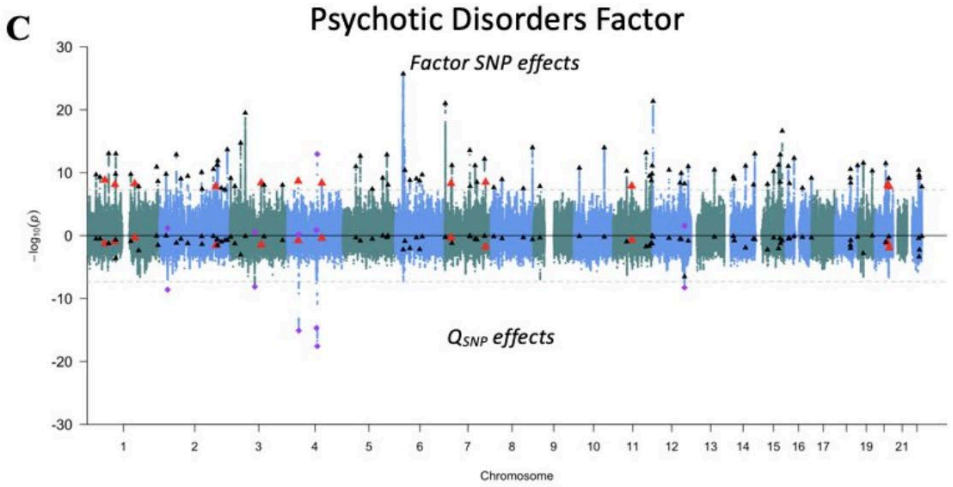
Genomic SEM offers unique opportunity to model system of relationships across rare and mutually exclusive clinical presentations

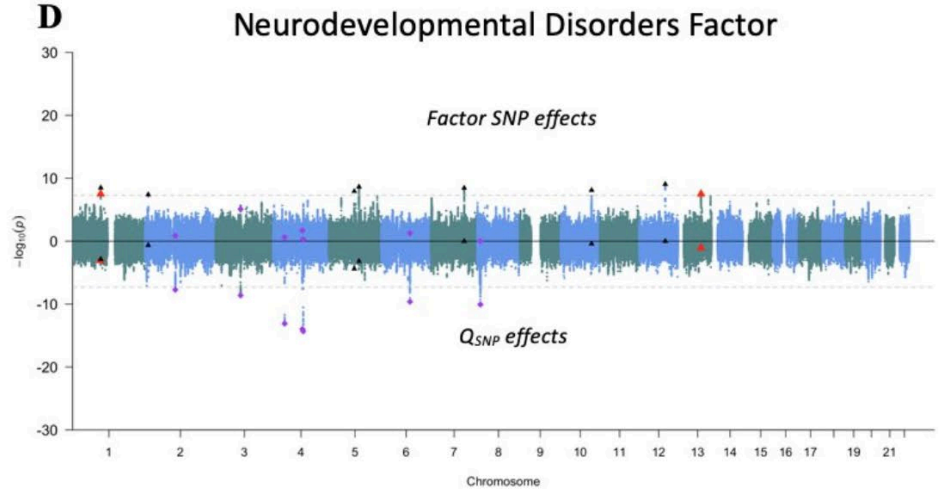
# Genetic Relationships Across Eleven Major Psychiatric disorders

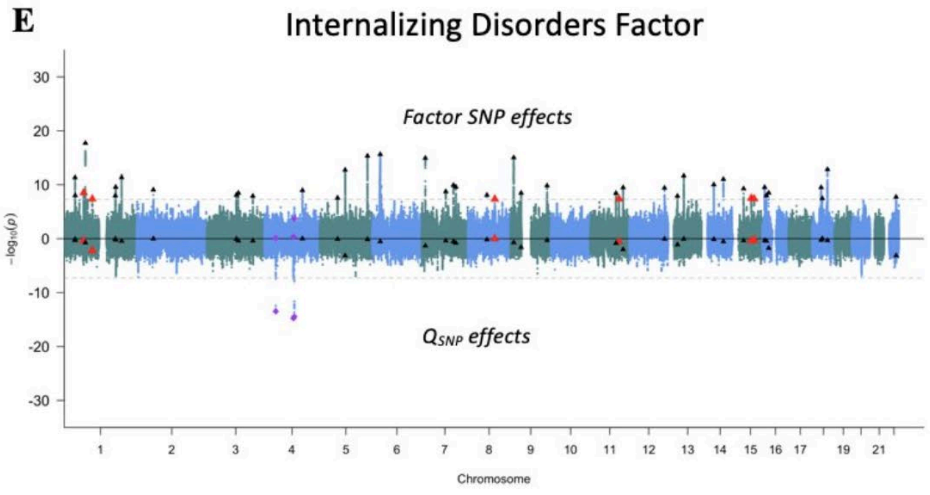


# Genetic Relationships Across Eleven Major Psychiatric disorders



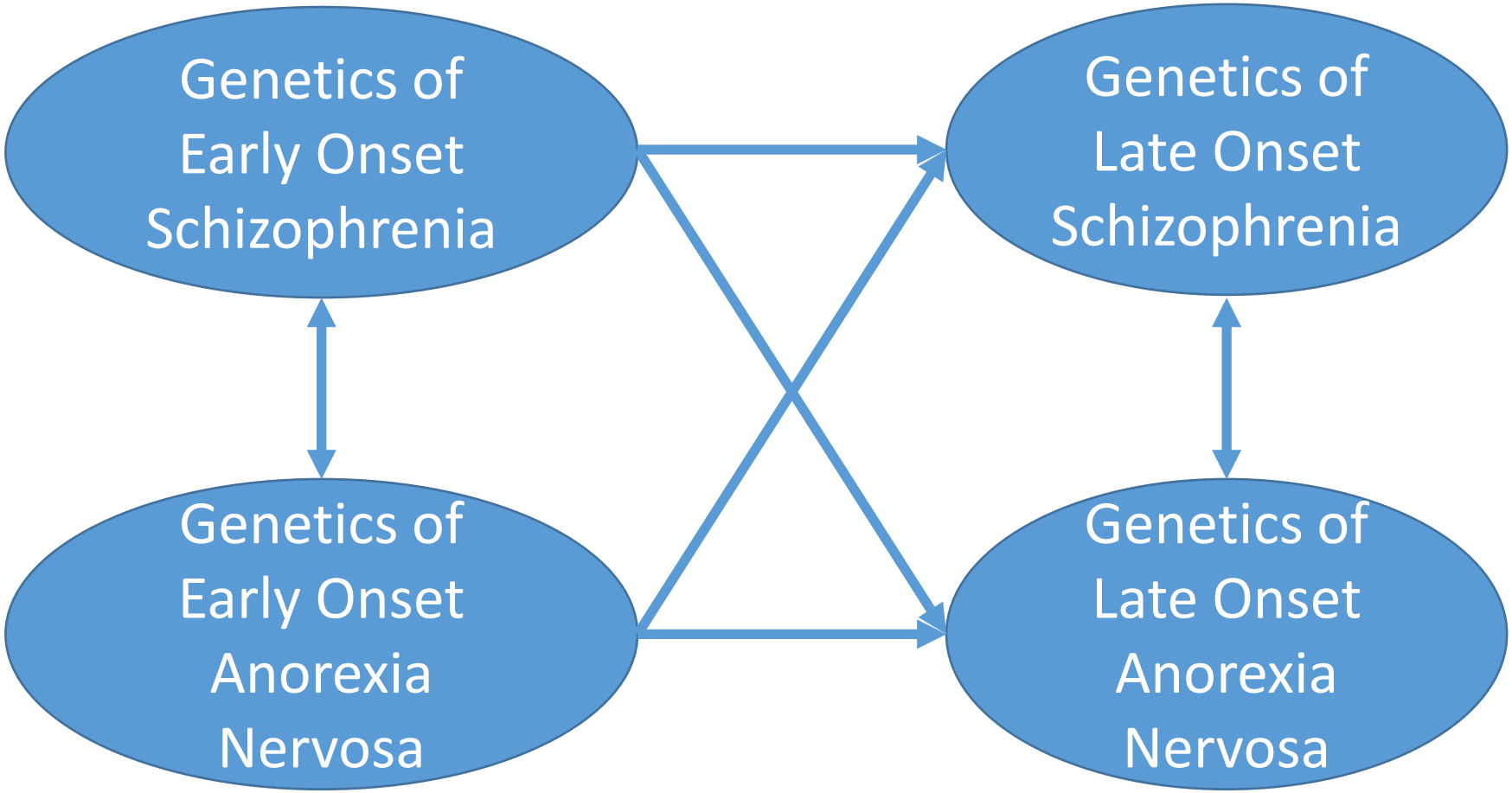



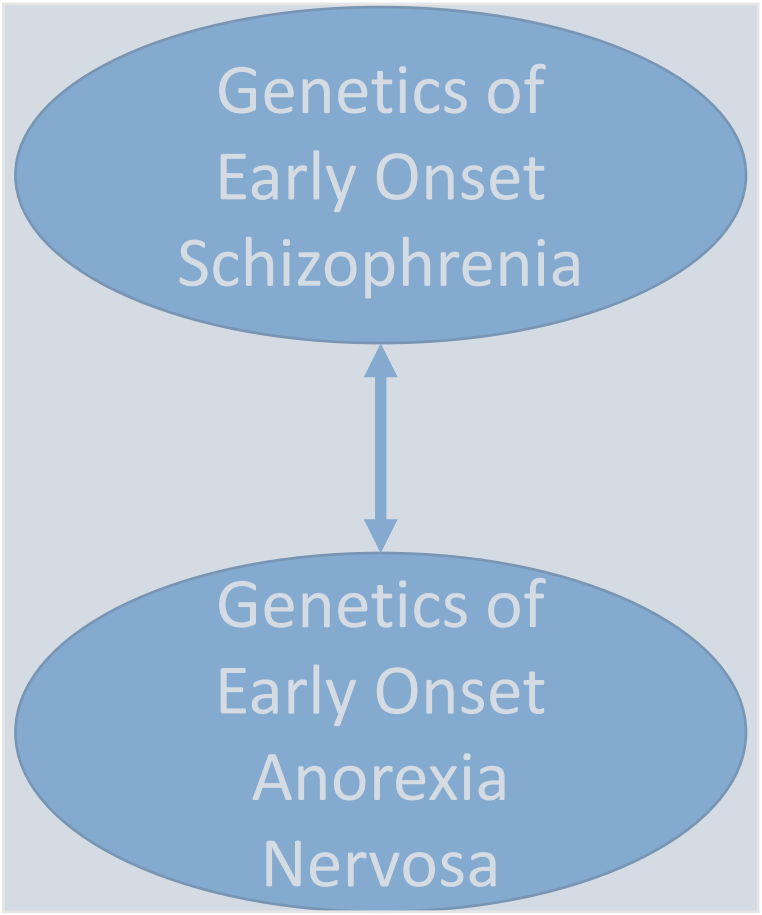



***Even if you are not interested in genetics:***

Can now examine systems of relationships between a wide array of (rare) traits

***that could not be measured in the same sample***


Genetics of Early Onset Schizophrenia
Genetics of Late Onset Schizophrenia
Genetics of Early Onset Anorexia Nervosa
Genetics of Late Onset Anorexia Nervosa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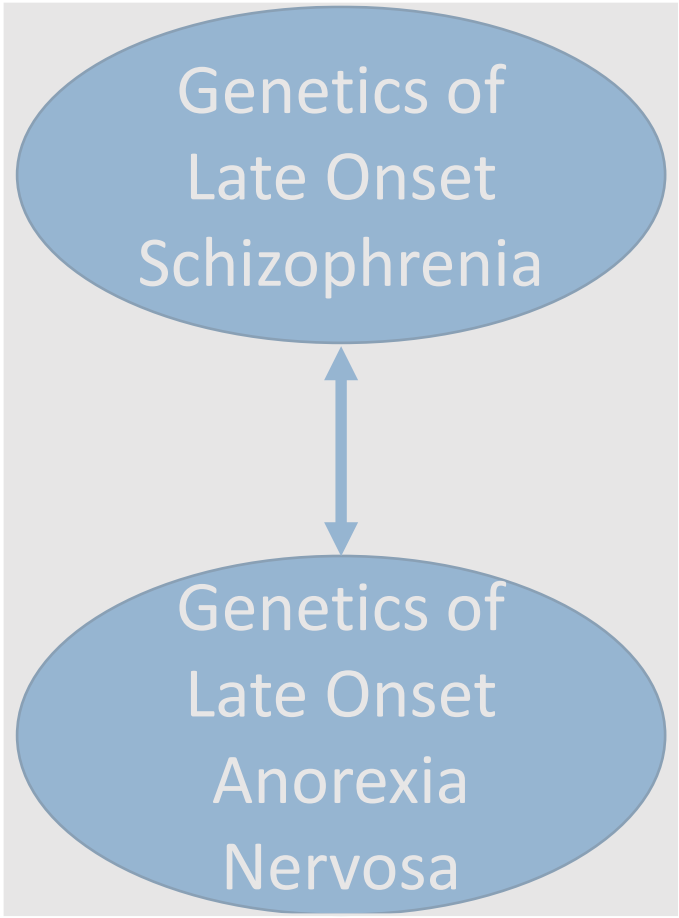
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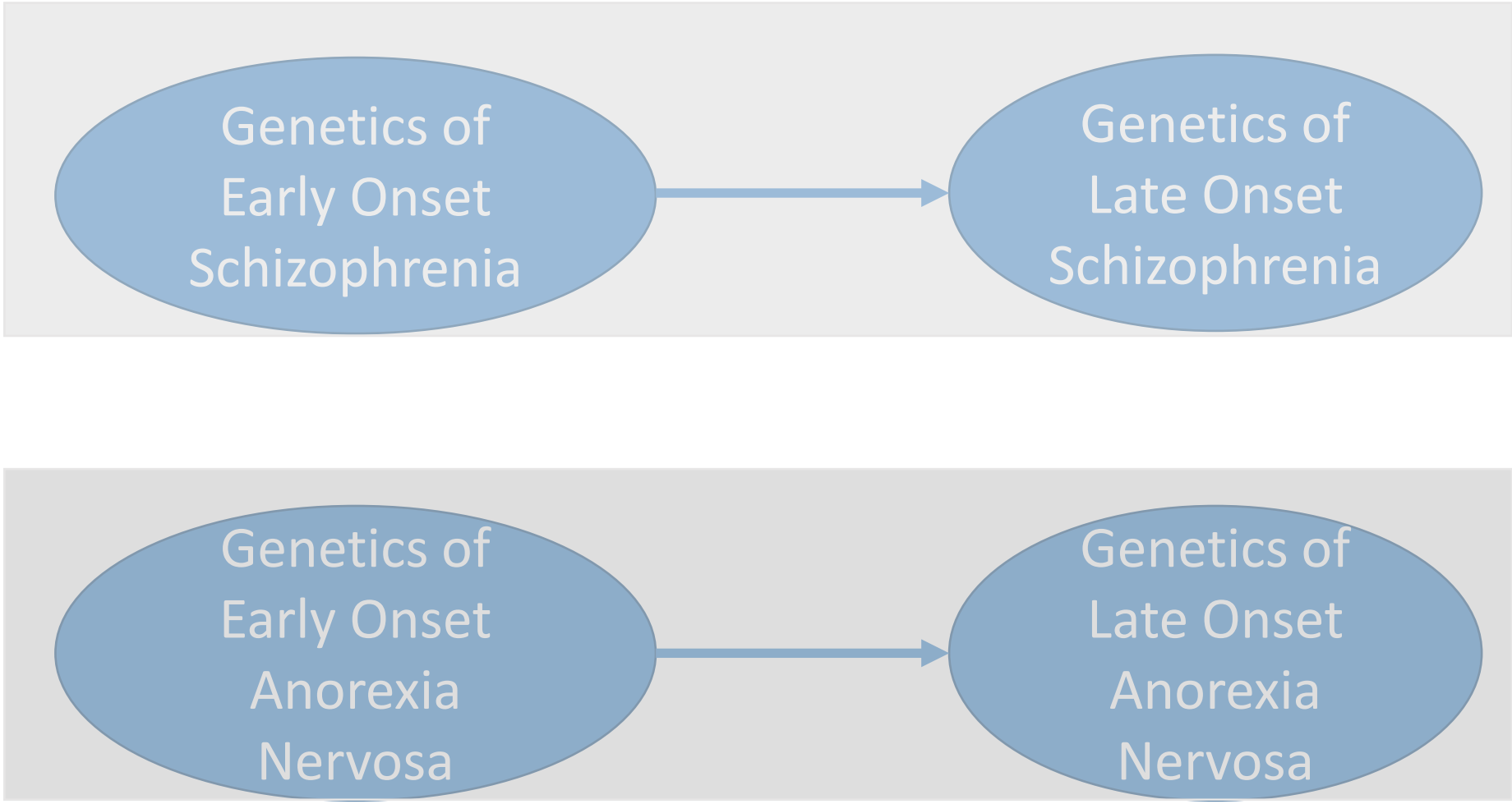
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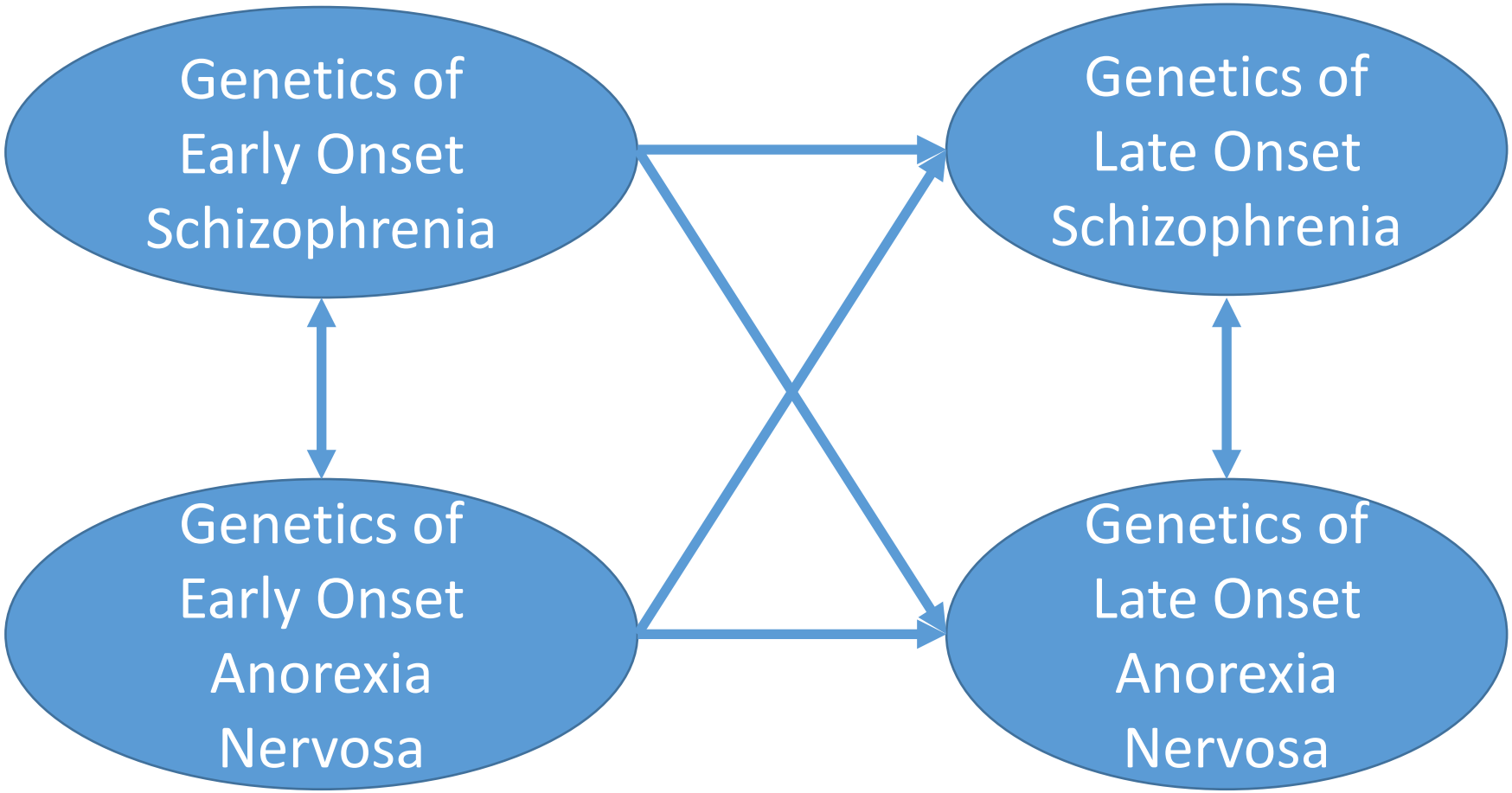
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Genetics of Early Onset Anorexia Nervosa
Genetics of Late Onset Anorexia Nervosa

Psychological Medicine

# Genetic heterogeneity in self-reported depressive symptoms identified through genetic analyses of the PHQ-9

Jackson G. Thorp (a1), Andries T. Marees (a1) (a2), Jue-Sheng Ong (a3), Jiyuan An (a3) ...

DOI: https://doi.org/10.1017/S0033291719002526

Published online by Cambridge University Press: 18 September 2019

Molecular Psychiatry

# Genomic prediction of cognitive traits in childhood and adolescence

A. G. Allegrini, S. Selzam, K. Rimfeld, S. von Stumm, J. B. Pingault & R. Plomin

*Molecular Psychiatry* **24**, 819–827 (2019) | Download Citation

nature genetics

ARTICLES

https://doi.org/10.1038/s41588-020-00754-2

Check for updates

# Investigating the genetic architecture of noncognitive skills using GWAS-by-subtraction

Perline A. Demange[1,2,3,20], Margherita Malanchini[4,5,6,20], Travis T. Mallard[6], Pietro Biroli[7], Simon R. Cox[8], Andrew D. Grotzinger[6], Elliot M. Tucker-Drob[6,9], Abdel Abdellaoui[1,10], Louise Arseneault[5], Elsje van Bergen[1,3], Dorret I. Boomsma[1], Avshalom Caspi[5,11,12,13], David L. Corcoran[12], Benjamin W. Domingue[14], Kathleen Mullan Harris[15], Hill F. Ip[1], Colter Mitchell[16], Terrie E. Moffitt[5,11,12,13], Richie Poulton[17], Joseph A. Prinz[12], Karen Sugden[11], Jasmin Wertz[11], Benjamin S. Williams[11], Eveline L. de Zeeuw[1,3], Daniel W. Belsky[18,19,21], K. Paige Harden[6,21] and Michel G. Nivard[1,21]

Cell

Volume 179, Issue 7, 12 December 2019, Pages 1469-1482.e11

CellPress

Article

# Genomic Relationships, Novel Loci, and Pleiotropic Mechanisms across Eight Psychiatric Disorders

Cross-Disorder Group of the Psychiatric Genomics Consortium [1]

# Genetic stratification of depression by neuroticism: revisiting a diagnostic tradition

*Psychological Medicine*

Mark J. Adams[1], David M. Howard[1,2], Michelle Luciano[3,4], Toni-Kim Clarke[1], Gail Davies[3,4], W. David Hill[3,4], 23andMe Research Team[5], Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium†, Daniel Smith[6], Ian J. Deary[3,4], David J. Porteous[7] and Andrew M. McIntosh[1,3]

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Revised: 1 August 2019
Accepted: 5 September 2019

Article | Published: 07 September 2020

# A general dimension of genetic sharing across diverse cognitive traits inferred from molecular data

Javier de la Fuente, Gail Davies, Andrew D. Grotzinger, Elliot M. Tucker-Drob & Ian J. Deary

*Nature Human Behaviour* **5**, 49–58(2021) | Cite this article

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