



Lessons from Three Decades Investigating ADHD Genetics

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Financial Disclosures (Past 2 Years)

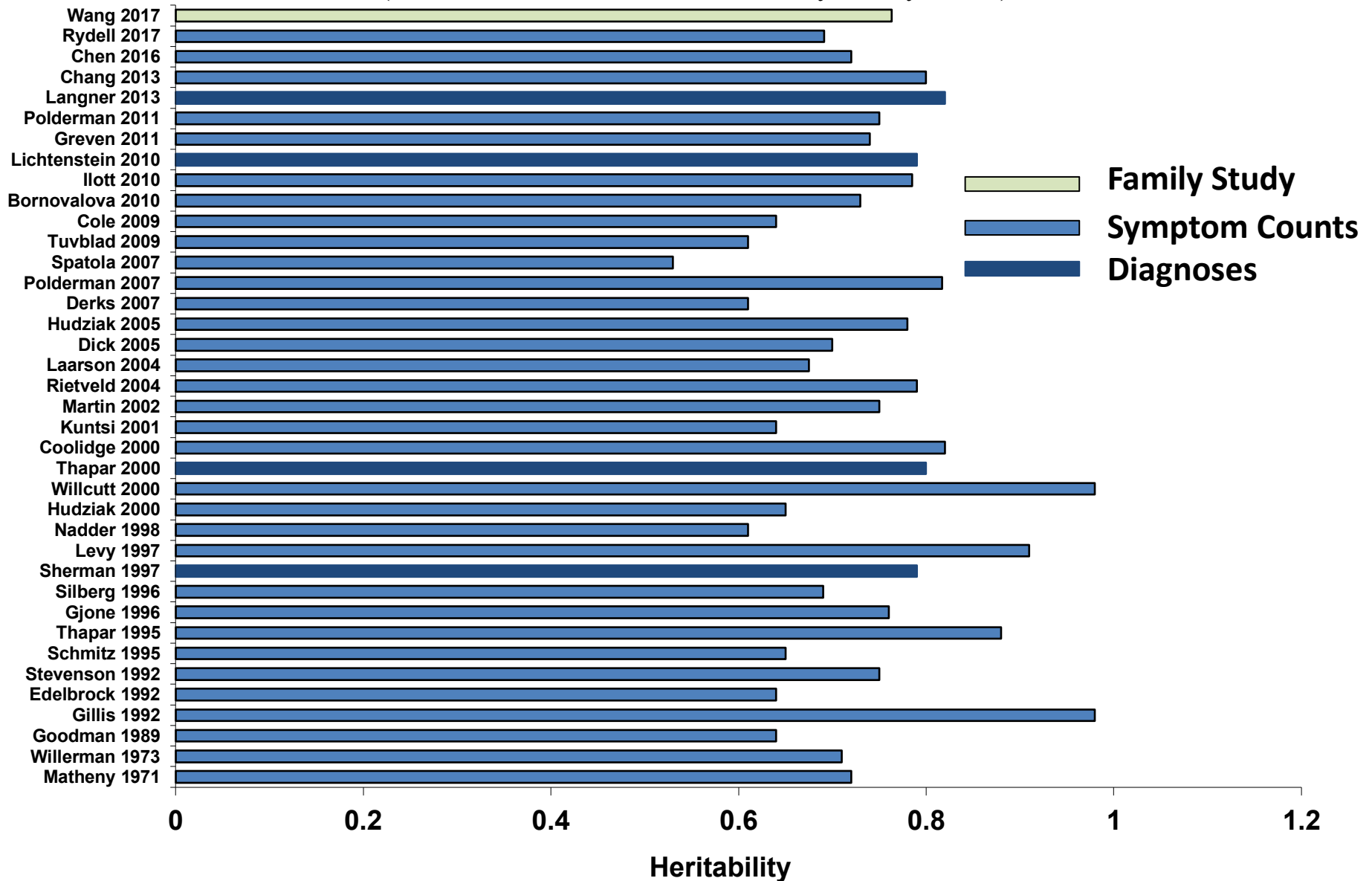
Source	Research or CME Funding	Consult Fees	Speakers Bureau	Royalties or IP	In Kind Services	Stock / Equity	Honorarium or expenses for this meeting
NHE Inhibitor Patent				X			
Shire/Takeda	X				X		
Rhodes		X					
Akili		X				X	
Vallon		X					
Tris		X					
Otsuka	X						
IronShore		X			X	X	
Supernus		X					
Sunovion	X	X					
Genomind		X			X	X	
Arbor	X				X		
OnDosis		X					

Lesson 1:

Much of ADHD's Etiology is Coded in the Genome

Heritability of ADHD

(Faraone & Larsson, Molecular Psychiatry, 2018)



Mean heritability across 38 studies = 74%

Lesson 2:

ADHD & Most Common Forms of Psychopathology are Polygenic

Polygenicity and Genetic Correlations

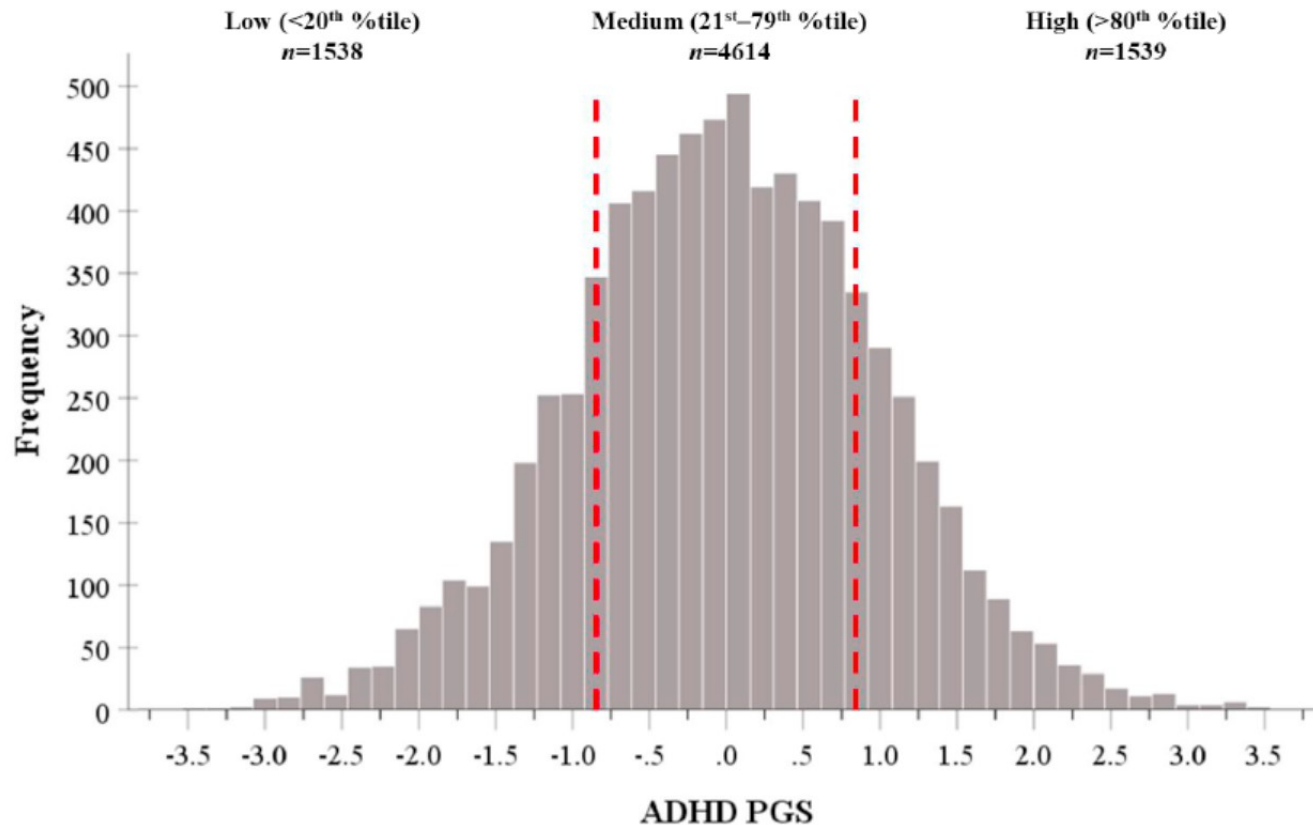
(Smoller et al., Molecular Psychiatry, 2018)

- Given GWAS data from an individual, we can compute their polygenic risk score for many psychiatric and non-psychiatric disorders.
- These scores can be correlated with one another to compute a genetic correlation.
- The genetic correlation tells us the degree to which two disorders share common DNA variants

ADHD Polygenic Risk in 7,000 Adolescents

(Li, BioRxiv; <http://dx.doi.org/10.1101/611897>)

- A polygenic risk score indexes the number of ADHD risk alleles carried by an individual.



Genetic Correlation with ADHD Symptoms in the Population

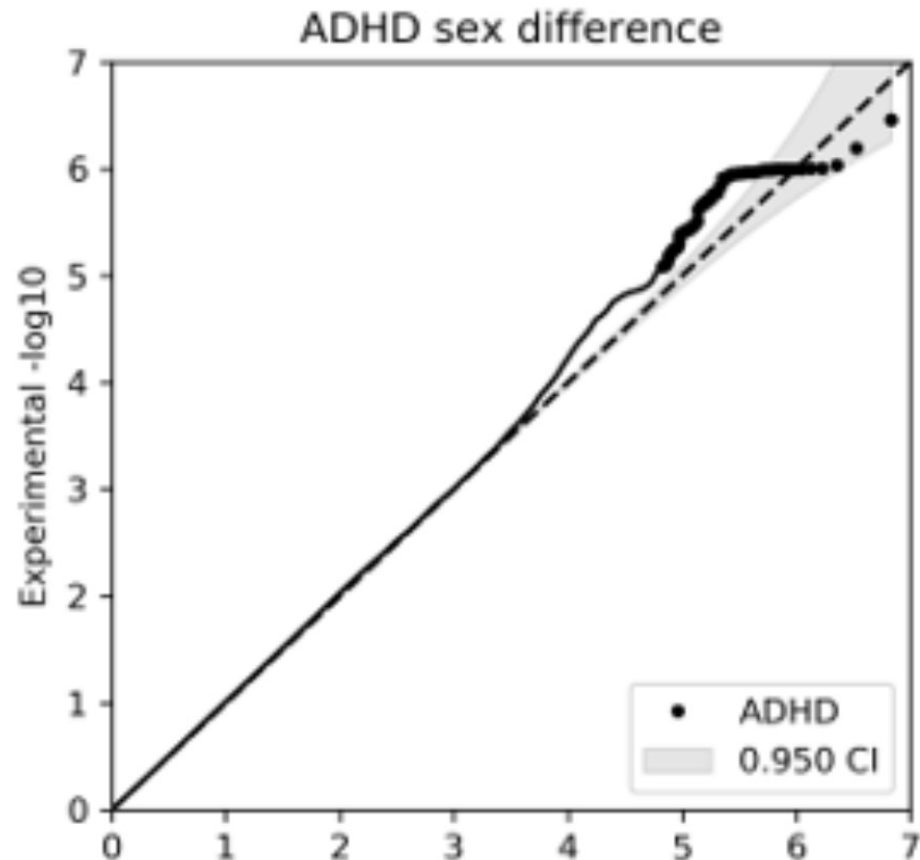
- The EAGLE/QIMR data comprises ADHD parental rating scale scores from 20,464 children and adolescents from the general population.
- Correlation of polygenic score for diagnosis of ADHD and symptoms in the population: $r_g = 0.97$, $SE = 0.2$

Sex Differences in Common Genetic Variants

(Martin et al., Biol. Psychiatry, 2018)

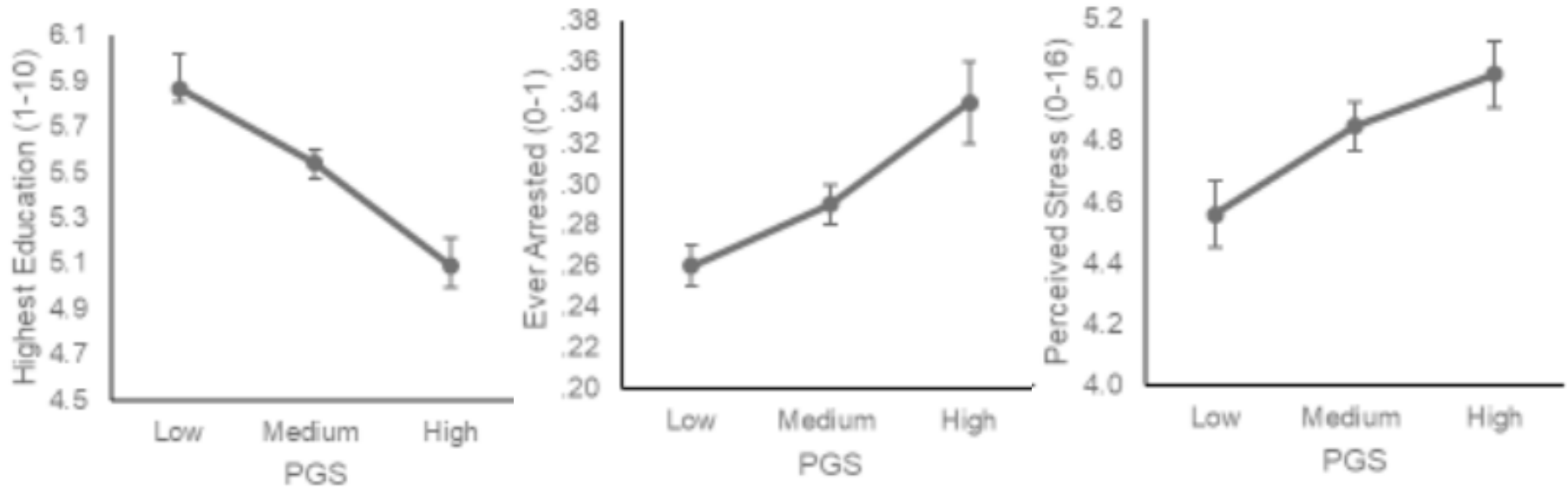
Genetic Correlation
between Males and
Females:

$R_g = 1.2, p < 0.000000001$



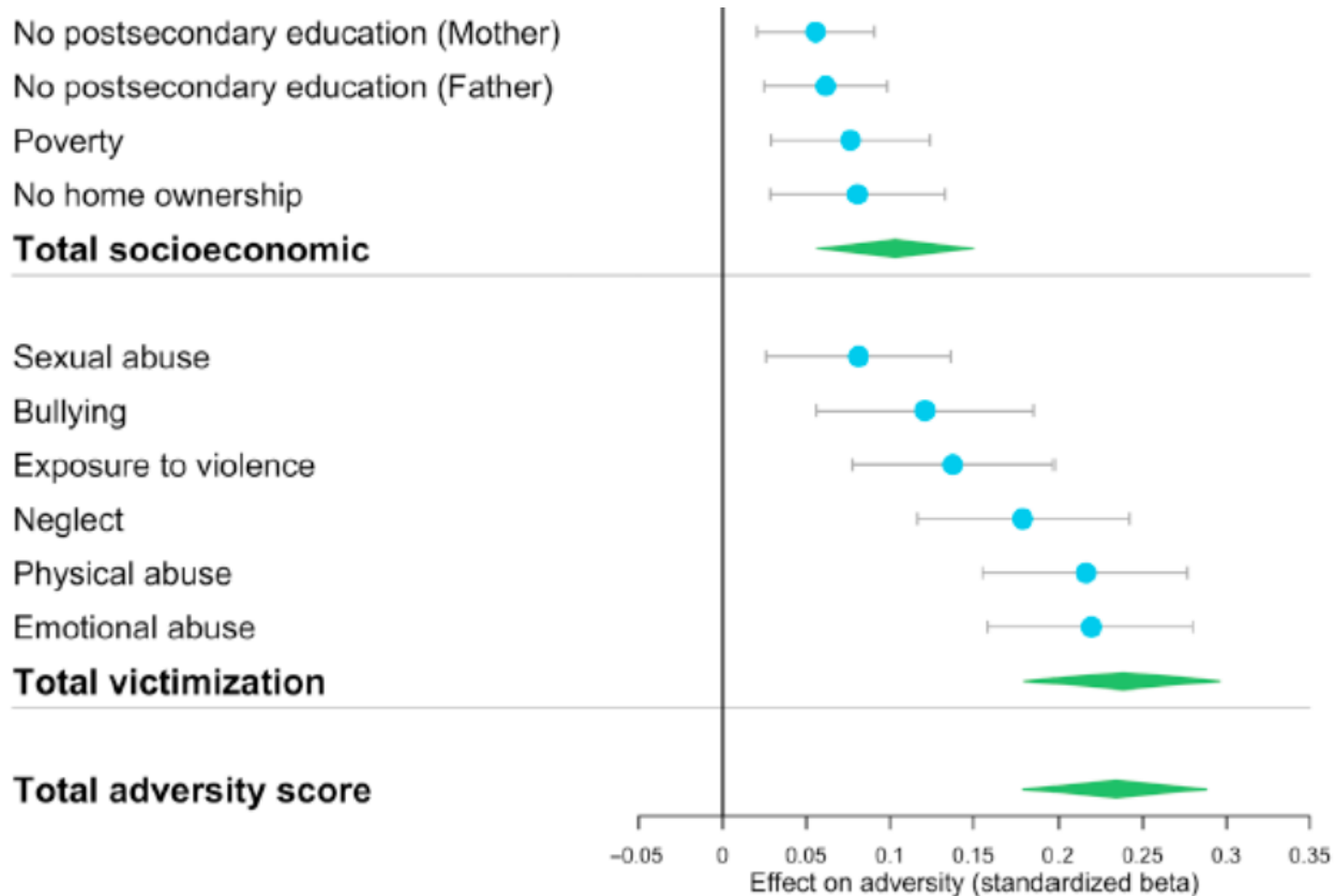
ADHD Polygenic Risk and Functional Outcomes in 7,000 Adolescents

(Li, BioRxiv; <http://dx.doi.org/10.1101/611897>)



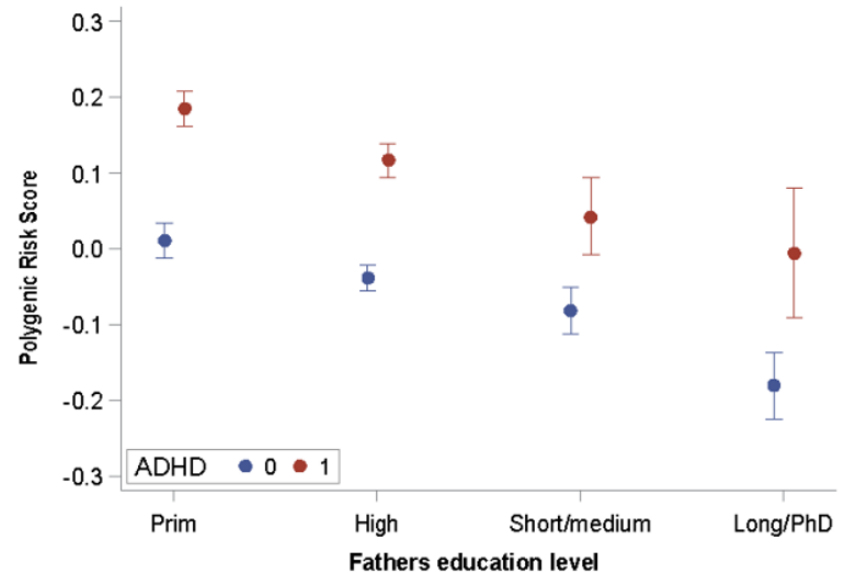
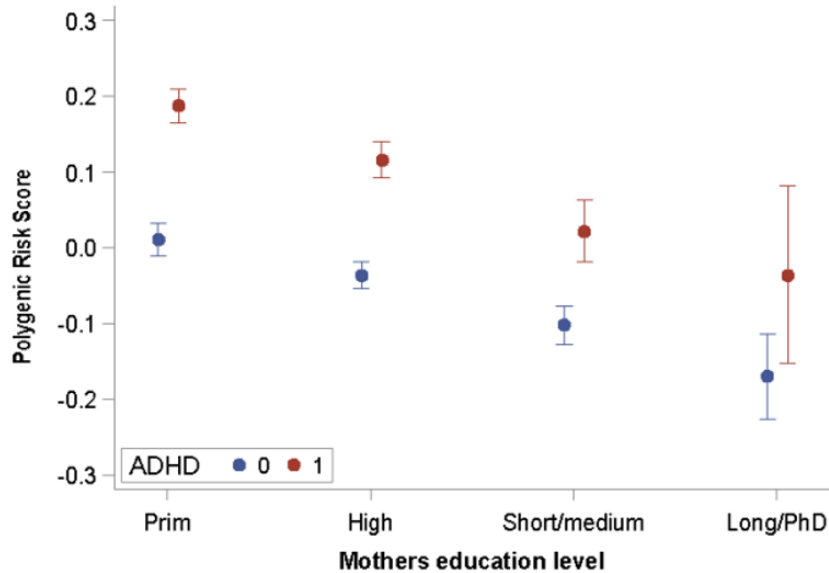
ADHD Polygenic Risk Correlates with Adversity

(Zwicker et al., JCPP, 2019)



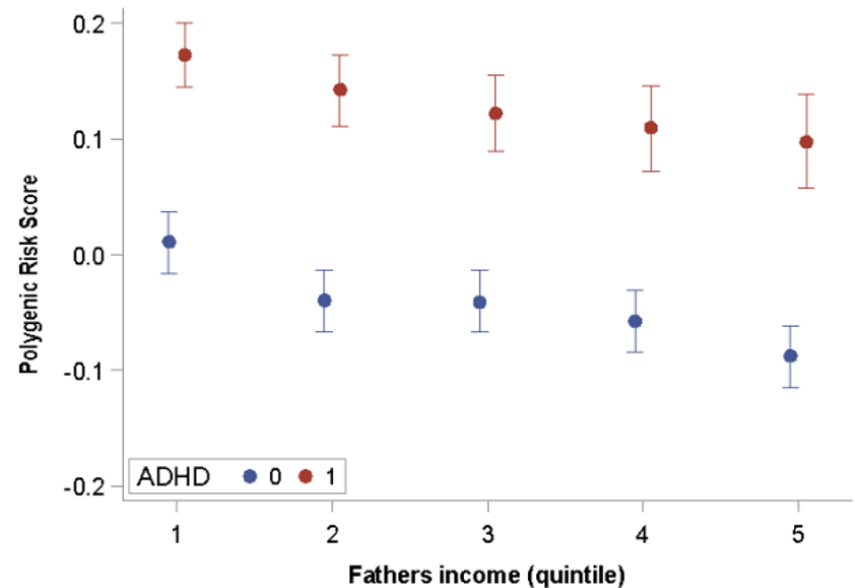
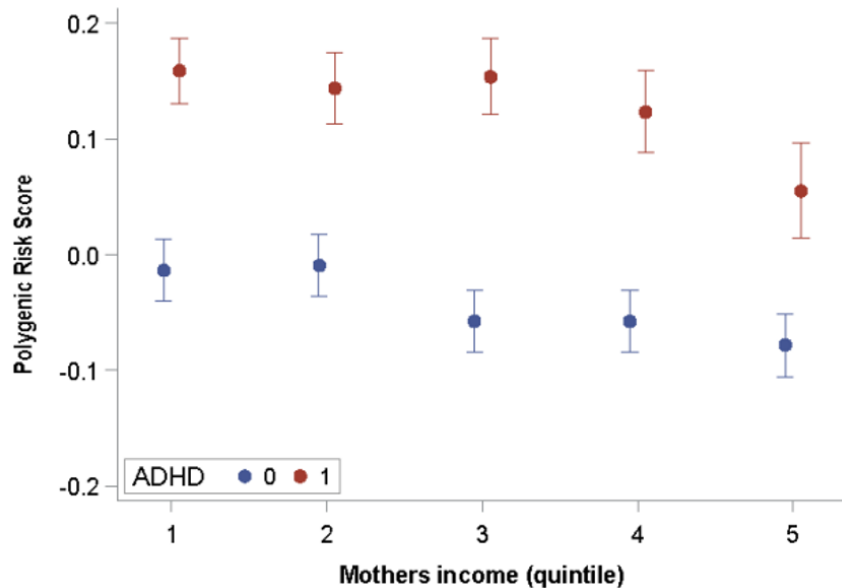
Parental Education Correlates with but does not Moderate ADHD Polygenic Risk

(Ostergaard et al., Transl. Psychiat., 2020)



Parental Income Correlates with but does not Moderate ADHD Polygenic

(Ostergaard et al., Transl. Psychiat., 2020)

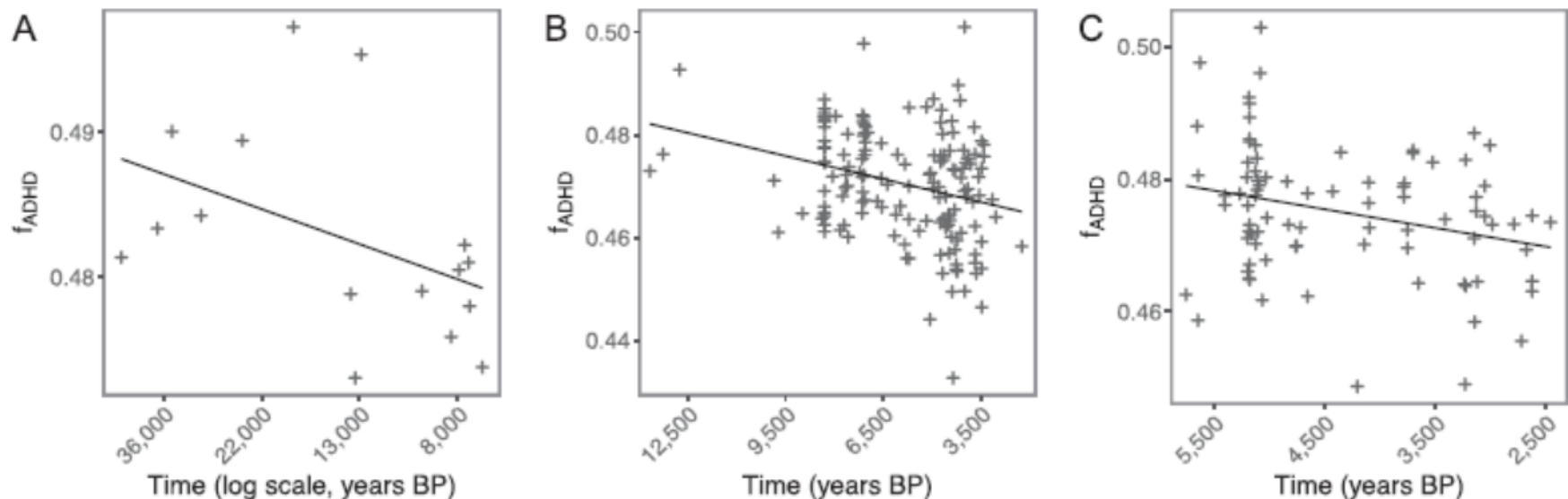


Genomic analysis of the natural history of attention-deficit/hyperactivity disorder using Neanderthal and ancient *Homo sapiens* samples

www.nature.com/scientificreports

Paula Esteller-Cucala^{1,2,11}, Iago Maceda^{1,2}, Anders D. Børglum^{3,4,5}, Ditte Demontis^{3,4,5}, Stephen V. Faraone⁶, Bru Cormand^{7,8,9,10,12} & Oscar Lao^{1,2,12}

- The frequency of genetic variants associated with ADHD has steadily decreased since Paleolithic times.
- These findings indicate long-standing selective pressures acting against ADHD risk variants.

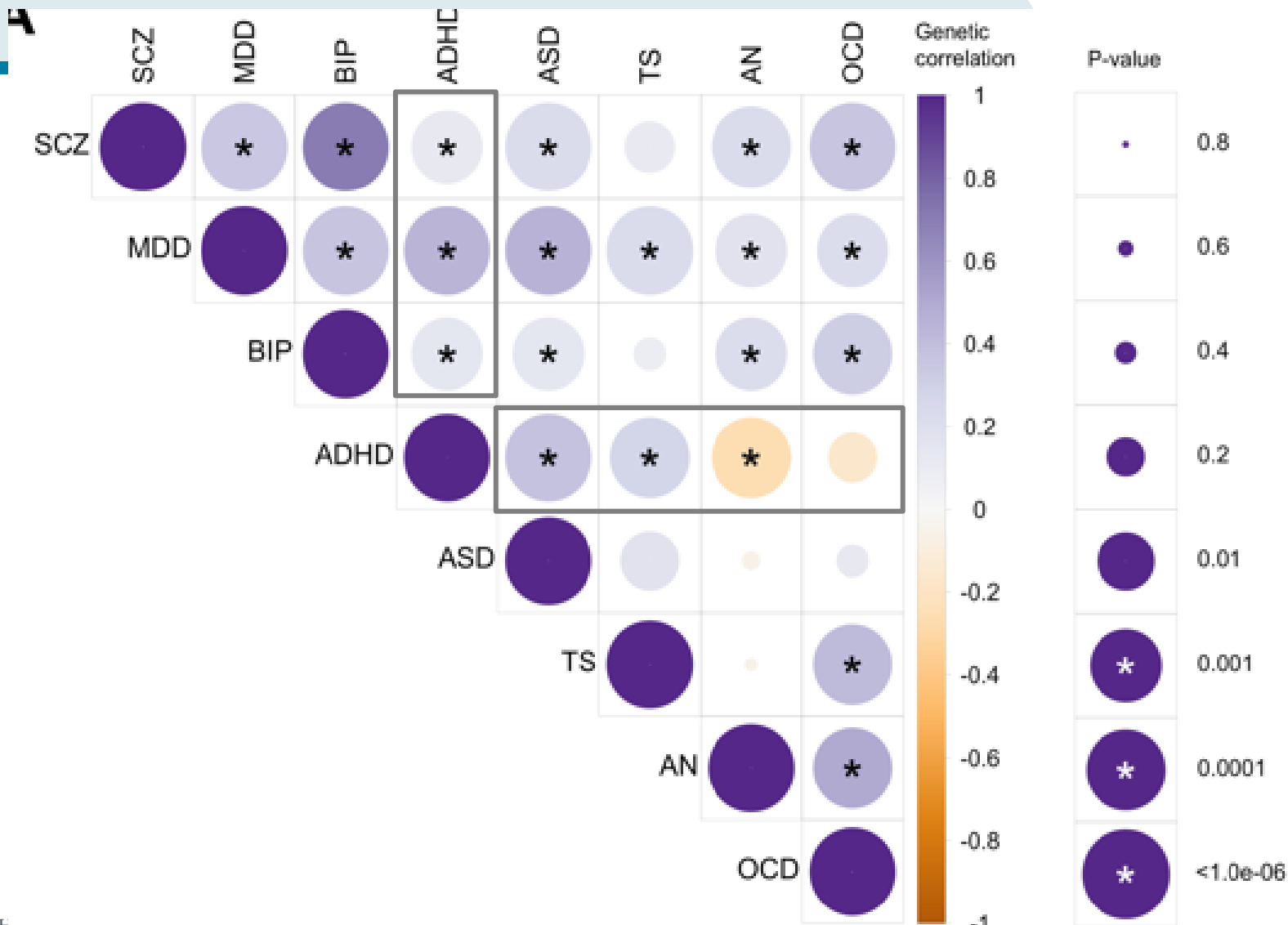


Lesson 3:

ADHD Shares its Genetic Etiology with other Psychiatric Disorders

Genetic Correlations among Psychiatric Disorders

(PGC Cross Disorder Group, Cell, 2019)



Genetic Correlations for ADHD & Substance Use Disorders

(Vilar-Ribo et al., 2020, AJMG-B)

Mendelian Randomization Analyses

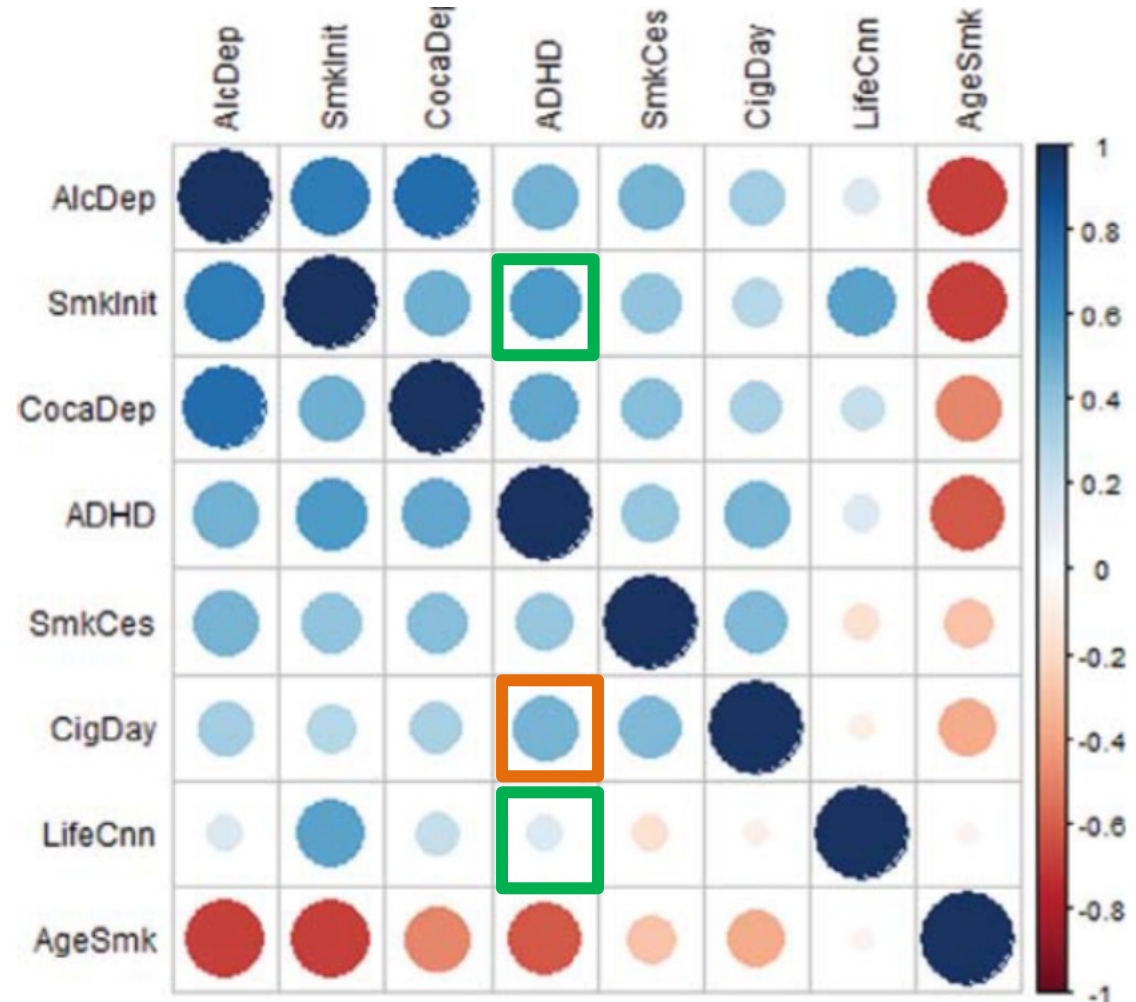


Bi-directional causality



ADHD causes SUD Phenotype

Note: Other causal effects not tested



Causal Modeling of ADHD and Depression

(Riglin et al., Psych Medicine, 2020)

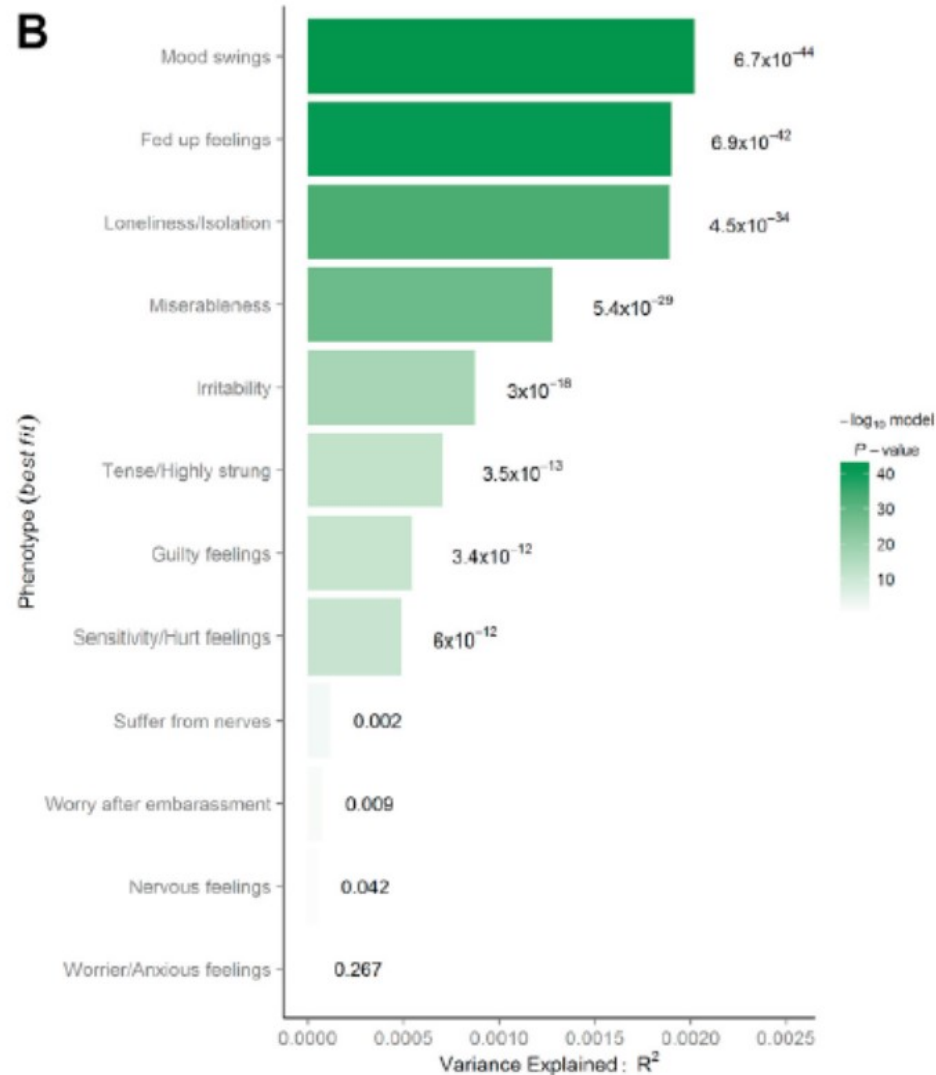
- Used ALSPAC longitudinal, population cohort (N = 8310)
- Childhood ADHD predicted depression in young adulthood
- Mendelian Randomization:
 - Causal effect of ADHD on depression
 - Causal effect of depression on ADHD was only significant for broad definition of depression

Lesson 4:

ADHD Shares Polygenes with Psychological Traits and Medical Conditions

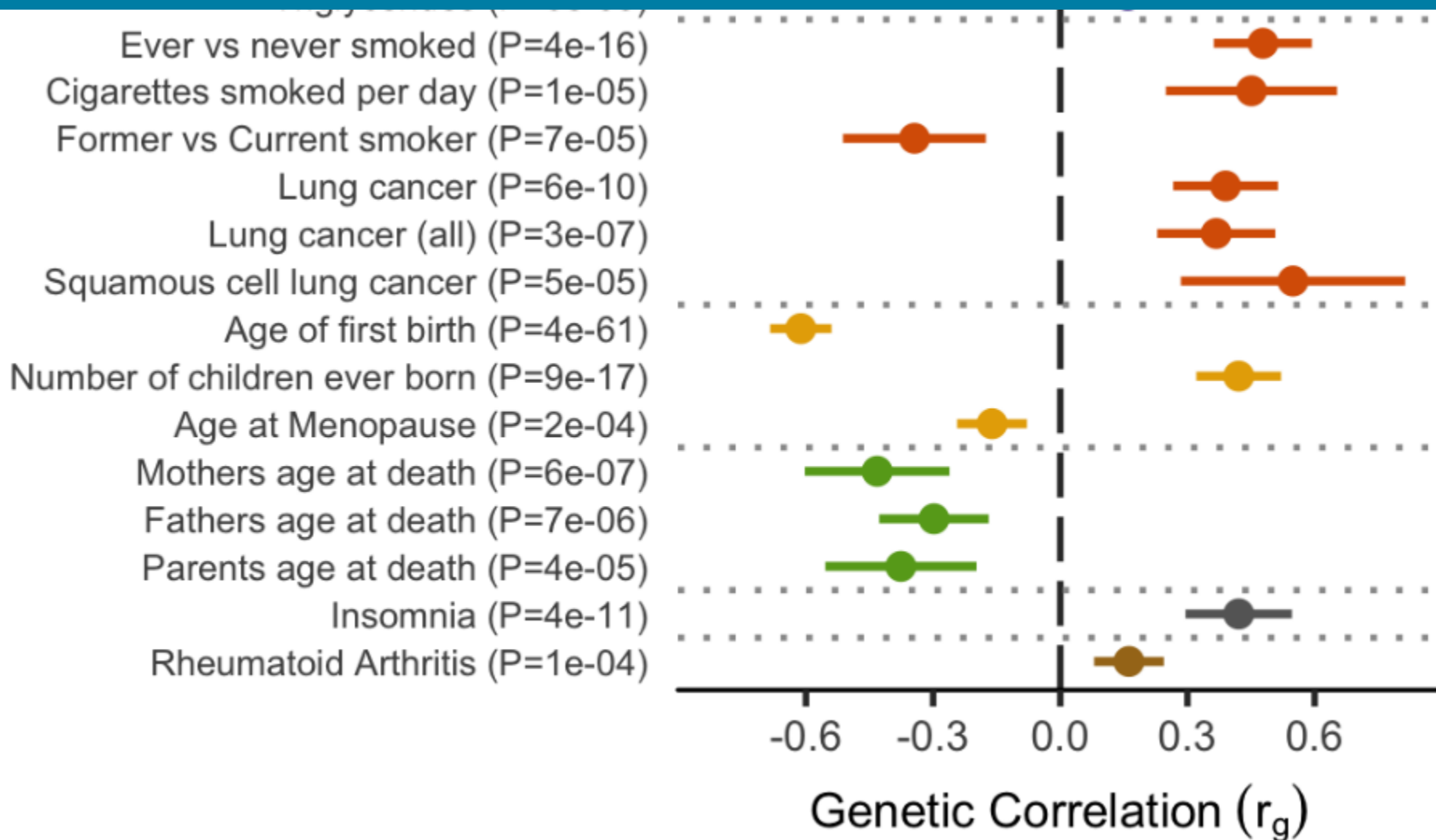
Genetic Correlations with Neuroticism Traits

(Du Rietz et al., Bio Psychiat CNNI, 2017)



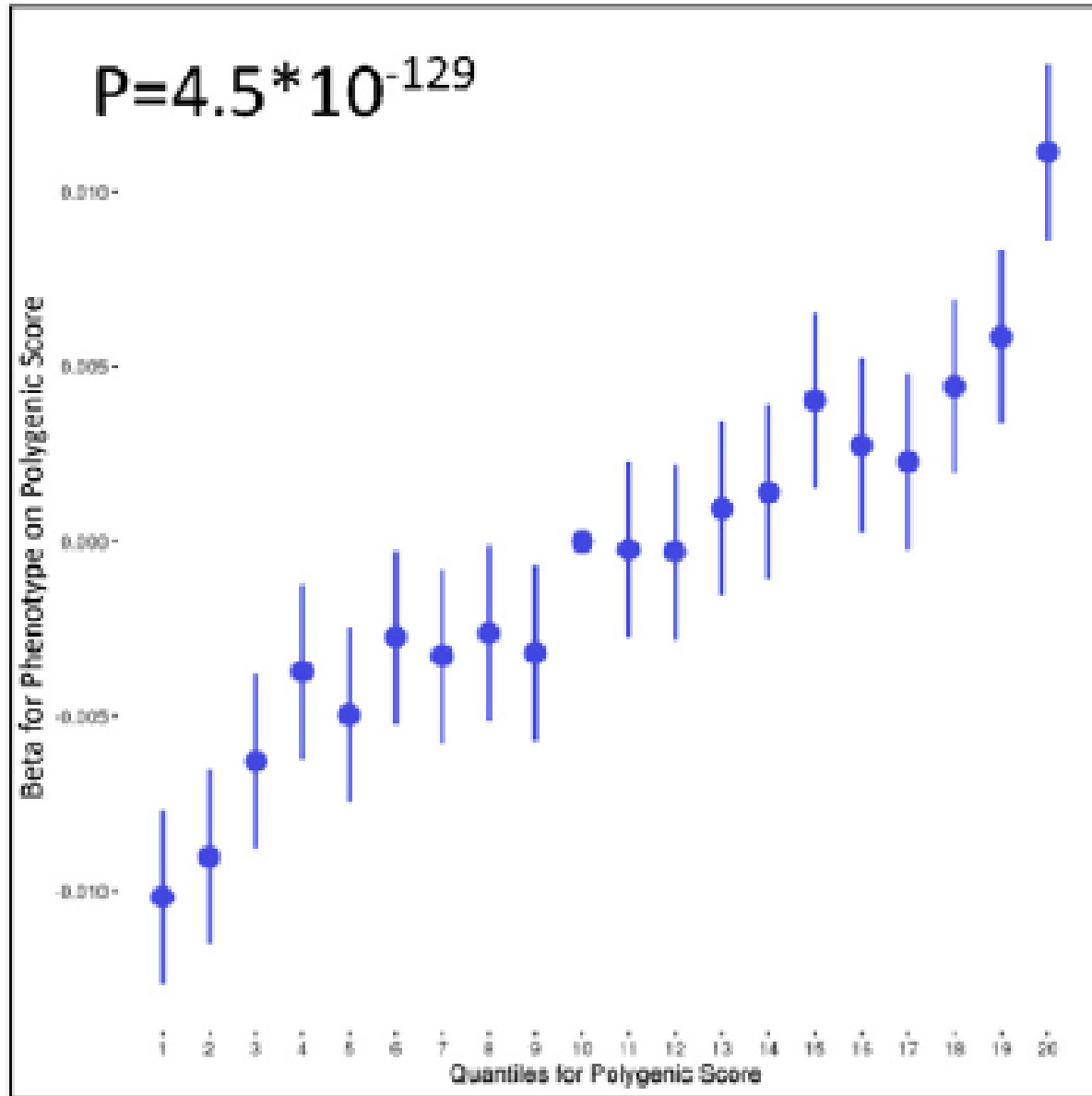
Genetic Correlations: Other Traits

(Demontis et al., Nature Genetics, 2018)



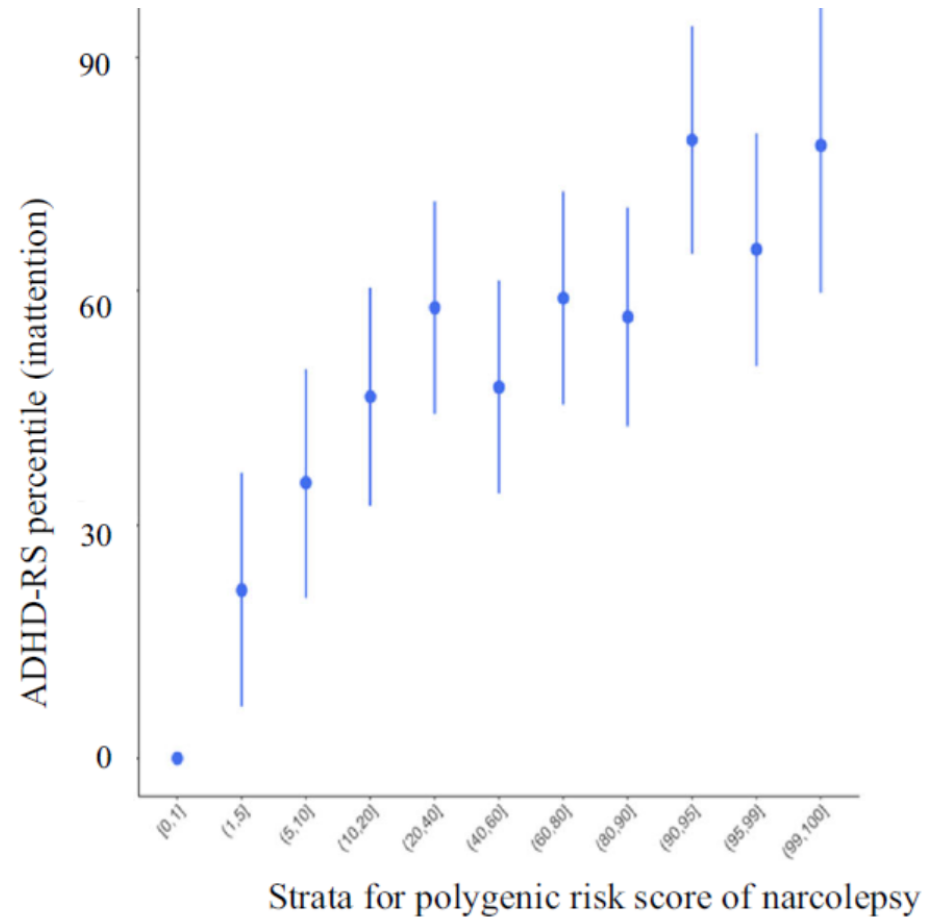
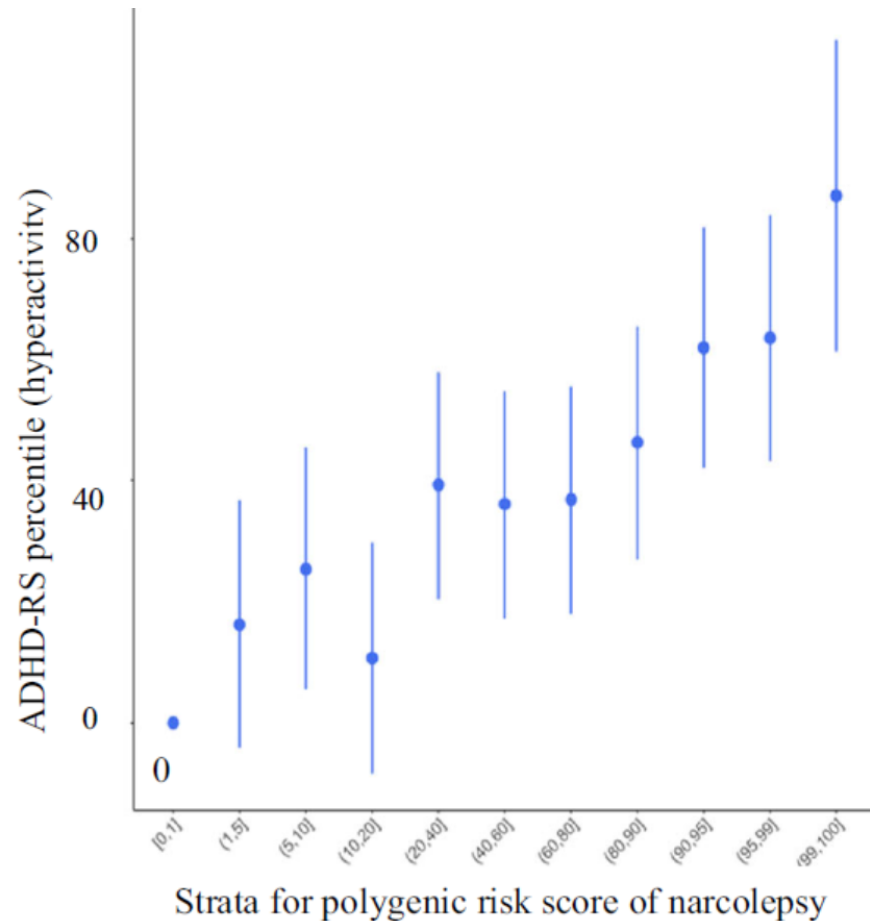
Association of Polygenic Risk and BMI

(Du Rietz et al., Bio Psychiat CNI, 2017)



Narcolepsy PRS Predict ADHD Symptoms in Youth from the General Population

(Takahashi, Transl. Psychiat., 2020)

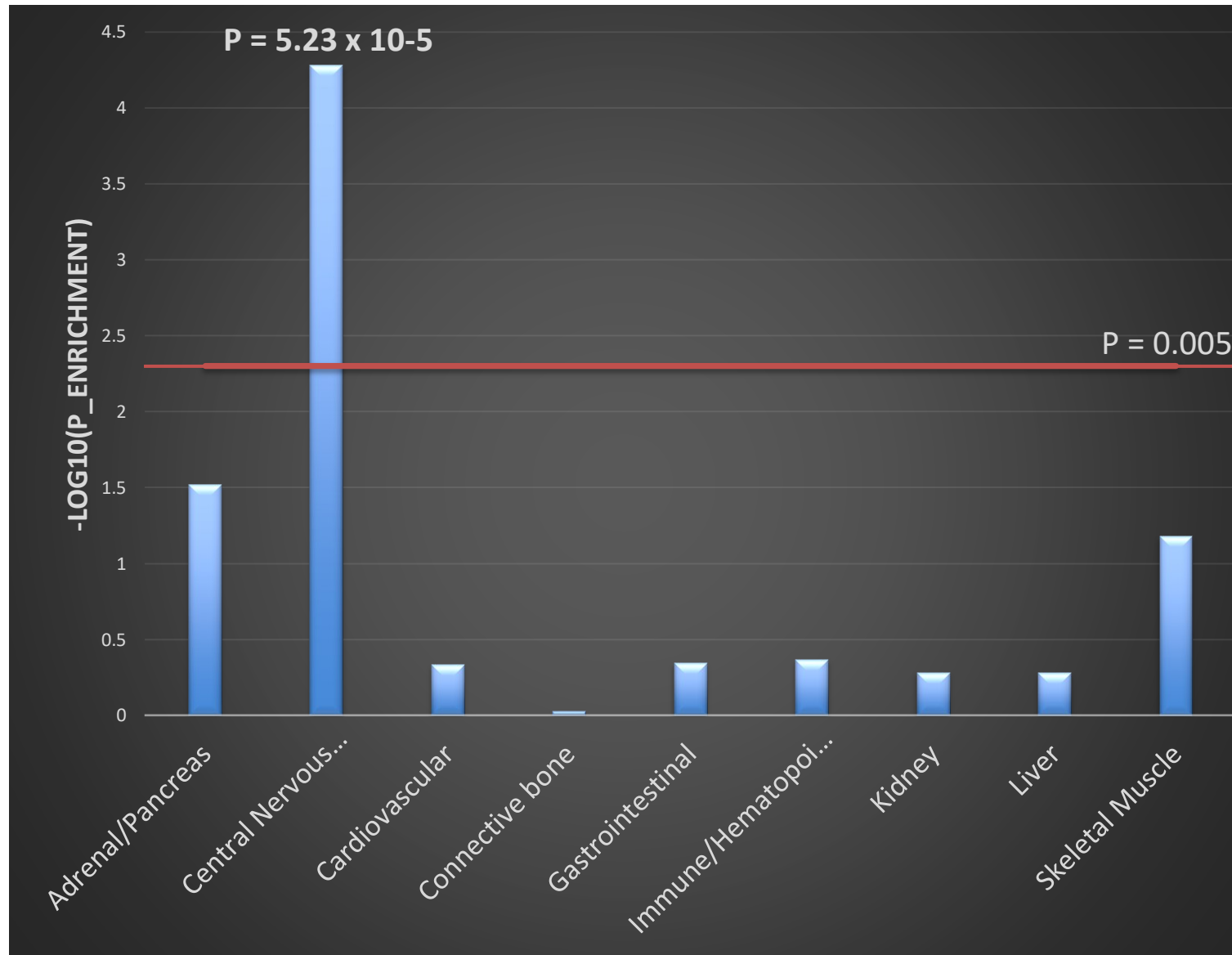




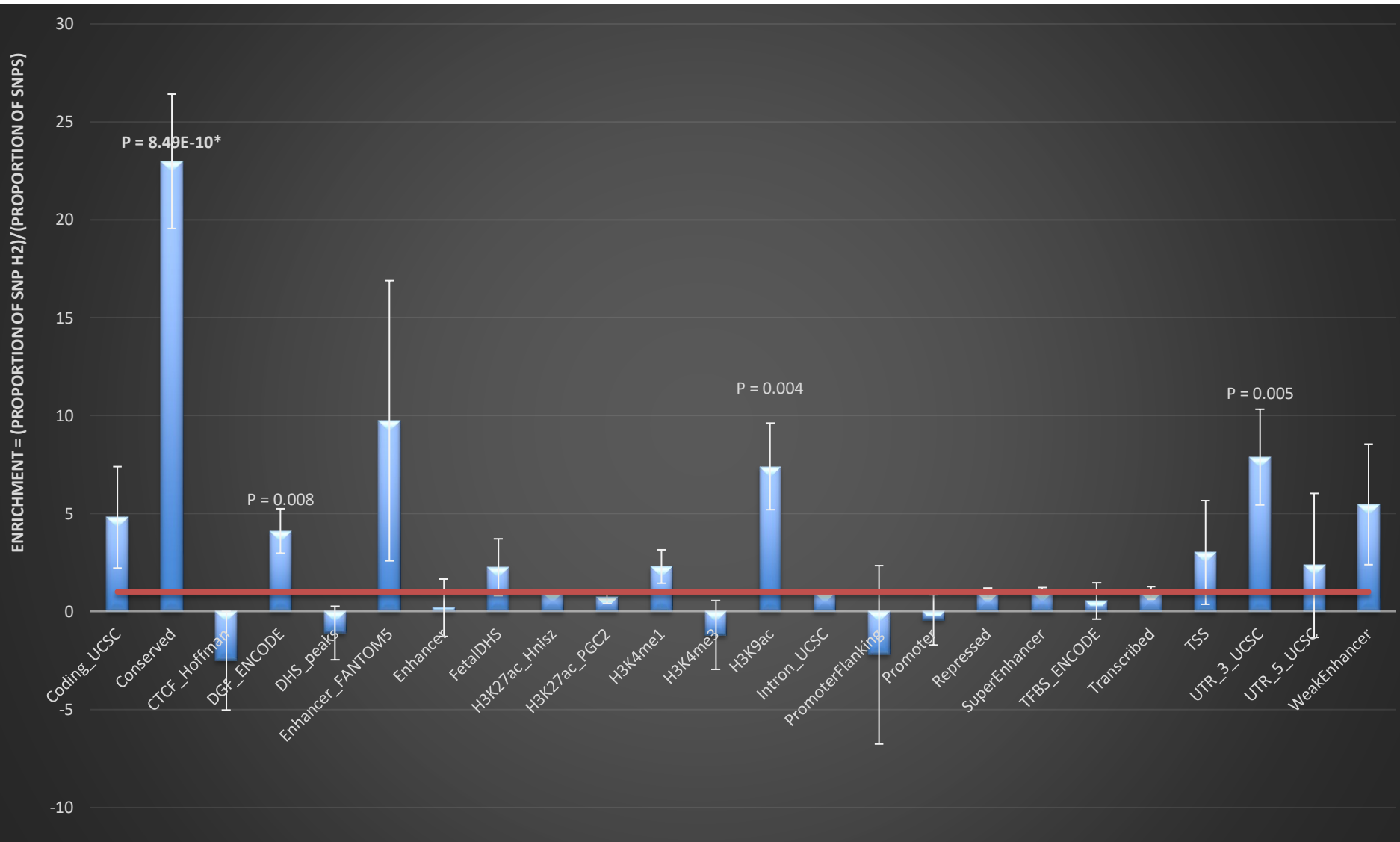
Lesson 5:

Genomewide Significant Findings Implicate Genes and Regulatory Elements Expressed in Brain

Partitioning Polygenic Risk by Tissue Group Annotations



Functional Annotations Implicates Epigenetic Effects



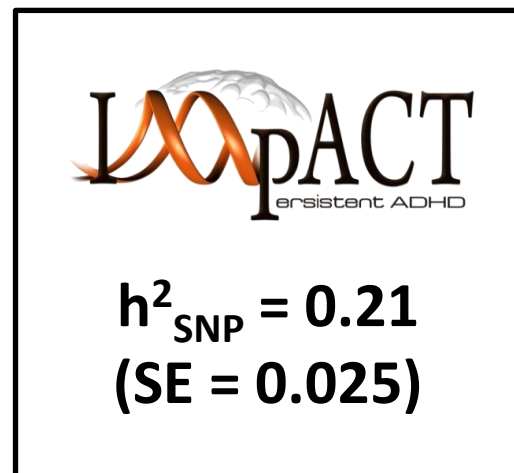
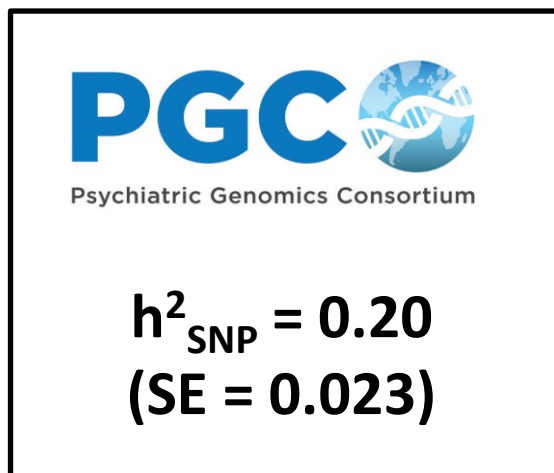


Lesson 6:

ADHD in Childhood and ADHD in Adulthood Share Many Polygenes

Common Genetic Variants Mostly the Same for Childhood and Adult ADHD

(Rovira et al., Neuropsychopharm, 2020)



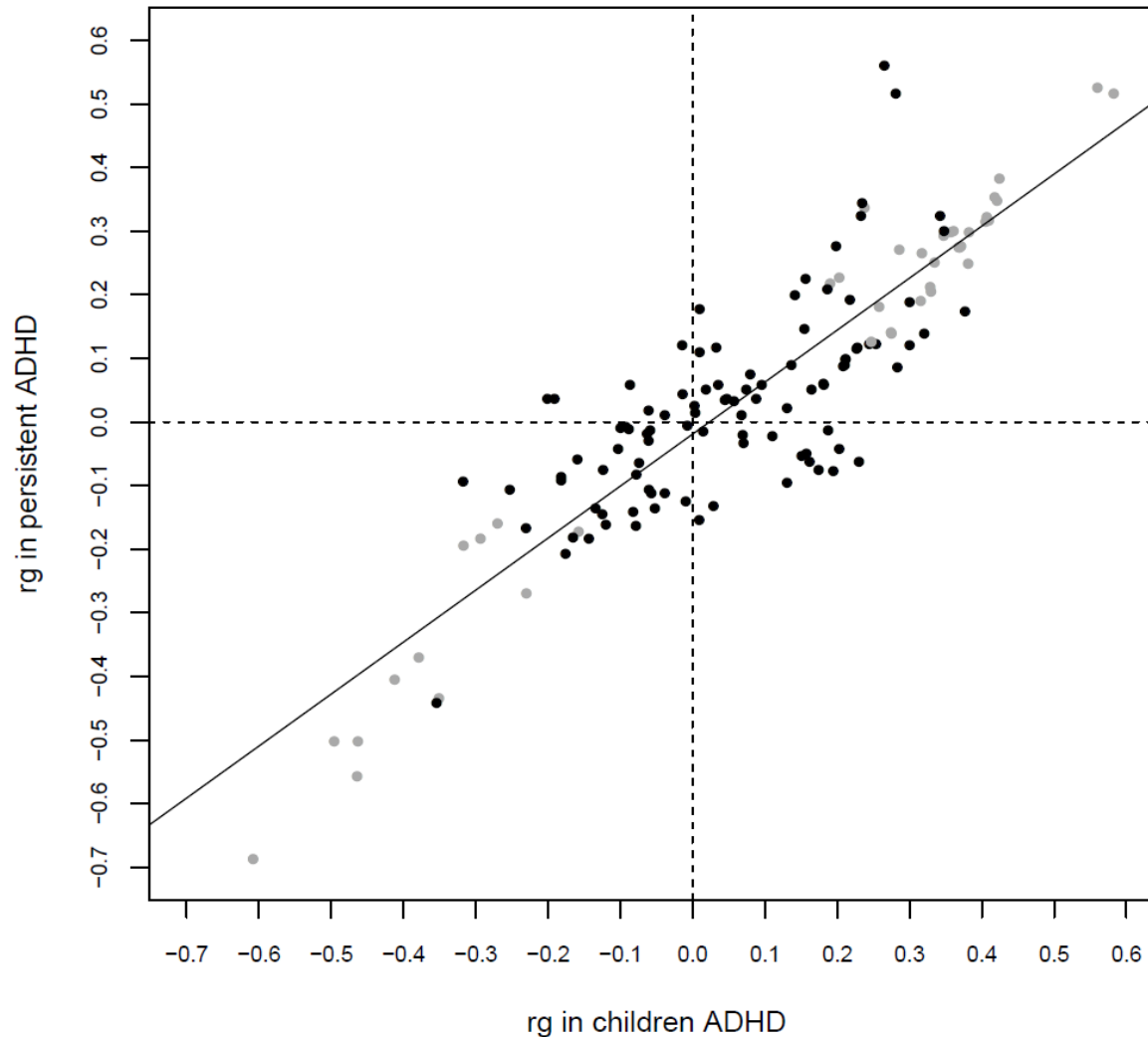
Genetic Correlation

$$R_g = 0.81 (0.08)$$

$$P\text{-Value} = 5.1235e-21$$

Genetic Correlations with Other Traits the Same for Childhood and Adult ADHD

(Rovira et al. submitted)



Lesson 7:

What is the Pathway Towards Actionable Genomic Information?

Can We Use DNA to Make Psychiatric Diagnoses?

- No
- Current polygenic risk scores are not sufficiently accurate for use in the clinic
- Accuracy may improve as samples get larger, more sophisticated algorithms are applied and other data sources (transcriptome, epigenome imaging) are combined

How Should we Think about Psychiatric Comorbidity in ADHD?

- The new molecular genetic data will, hopefully, put an end to debates about psychiatric comorbidity.
- We now know that most psychiatric disorders are correlated with one another at the level of DNA.
- Diagnosticicians should expect “pervasive comorbidity”
 - ADHD can co-occur with many disorders
 - Multiple comorbidities are to be expected in some patients

What About Drug Development?

- Theoretically, genetic studies might identify new targets for drugs with novel mechanisms of action.
- These targets, however, may be most important early in development and would be relevant for prevention, not treatment.
- We have many targets to choose from, which suggests that multi-target therapies may be needed.

Summary: Lessons From ADHD Genetics

ADHD has a strong genetic component

Most forms of ADHD have a polygenic etiology

ADHD shares DNA risk variants with other disorders

Genetic risk for ADHD predicts psychological traits and medical outcomes.

The genetic risk for ADHD is expressed in the brain

ADHD in childhood and adulthood share polygenic risk

Diagnostic practice should incorporate comorbidity assessments

Thanks for Listening!

Free CME: www.adhdinadults.com

MyADHD Blogs: www.linkedin.com/in/stephenfaraone

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8th World Congress on ADHD

From Child to Adult Disorder

6 – 9 May 2021