ADHD and Autism Spectrum Disorder

James Li, Ph.D.

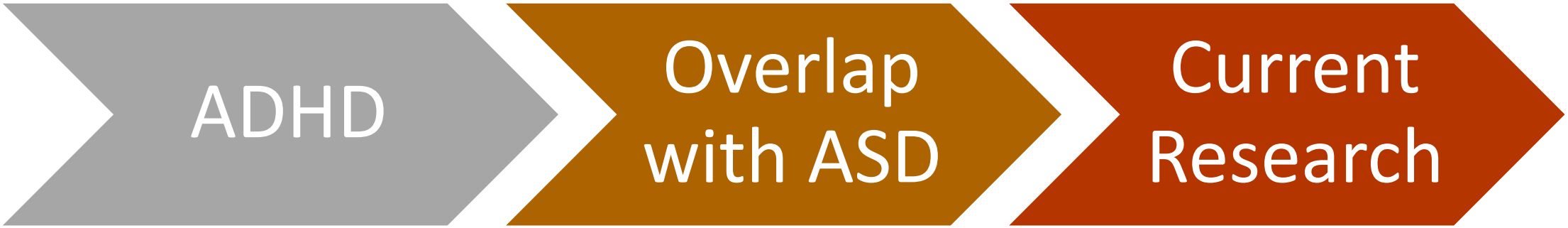
Department of Psychology and the Waisman Center

University of Wisconsin-Madison

Department of Psychology
UNIVERSITY OF WISCONSIN–MADISON

WISCONSIN
UNIVERSITY OF WISCONSIN–MADISON

Roadmap for today's talk



ADHD

Inattention cluster

- **Inattention** cluster – inability to sustain attention, or to stick to tasks or play activities, to remember and follow through on instructions/rules, and to resist distractions

Hyperactivity/impulsivity cluster

- **Hyperactivity/impulsivity cluster** – under control of motor behavior, poor ability to inhibit behavior, and inability to delay a response or defer gratification
  - **Hyperactivity** – relates to the under control of motor behavior (i.e., fidgeting, squirming, running around aimlessly, and being "driven by a motor")
  - **Impulsivity** – relates to the inability to inhibit immediate reactions to stimuli (i.e., blurting out or interrupting others, difficulty waiting for ones turn)

Subtypes

TABLE 8.1 | Diagnostic Criteria for Attention-Deficit/Hyperactivity Disorder (*continued*)

Specify whether:

Combined presentation: If both Criterion A1 (inattention) and Criterion A2 (hyperactivity-impulsivity) are met for the past 6 months.

Predominantly inattentive presentation: If Criterion A1 (inattention) is met but Criterion A2 (hyperactivity–impulsivity) is not met for the past 6 months.

Predominantly hyperactive–impulsive presentation: if Criterion A2 (hyperactivity–impulsivity) is met but Criterion A1 (inattention) is not met for the past 6 months.

Specify if:

In partial remission: When full criteria were previously met, fewer than the full criteria have been met for the past 6 months, and the symptoms still result in impairment in social, academic, or occupational functioning.

Specify current severity:

Mild: Few, if any, symptoms in excess of those required to make the diagnosis are present, and symptoms result in no more than minor impairments in social or occupational functioning.

Moderate: Symptoms or functional impairment between "mild" and "severe" are present.

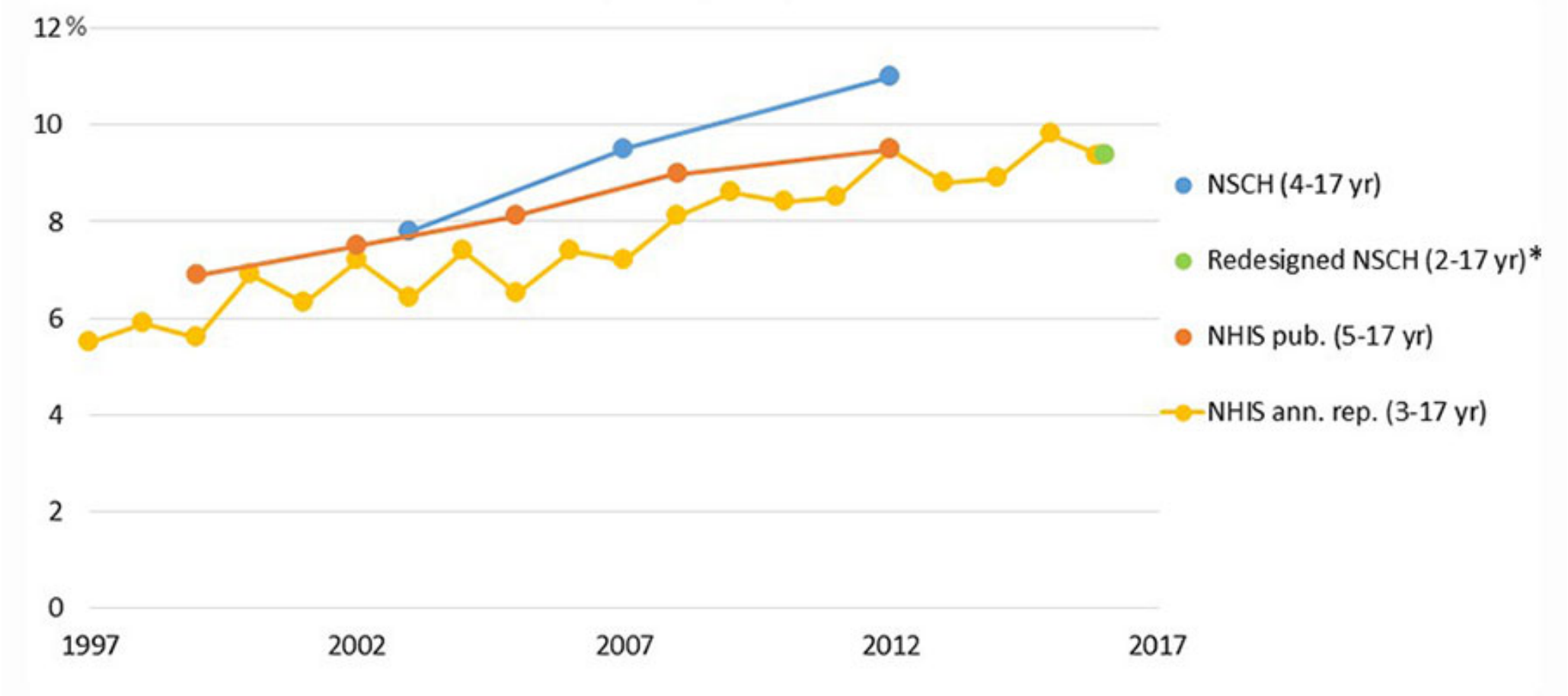
Severe: Many symptoms in excess of those required to make the diagnosis, or several symptoms that are particularly severe, are present, or the symptoms result in marked impairment in social or occupational functioning.

Source: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. American Psychiatric Association.

"When we began our studies in the 1960's no one believed such children existed; while now people find them under every rock."

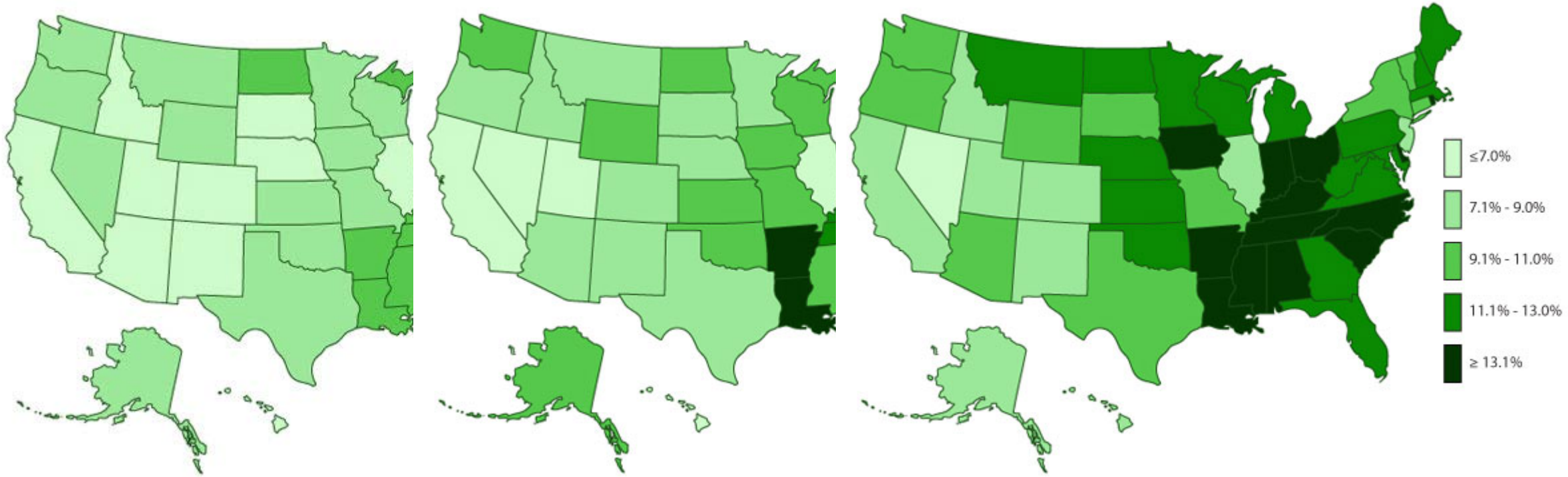
Dr. Leon Eisenberg, child psychiatrist and ADHD pioneer

Increase in U.S. **lifetime prevalence**



https://www.cdc.gov/ncbddd/adhd/timeline.html

Increase in U.S. **lifetime prevalence** rates



2003

2007

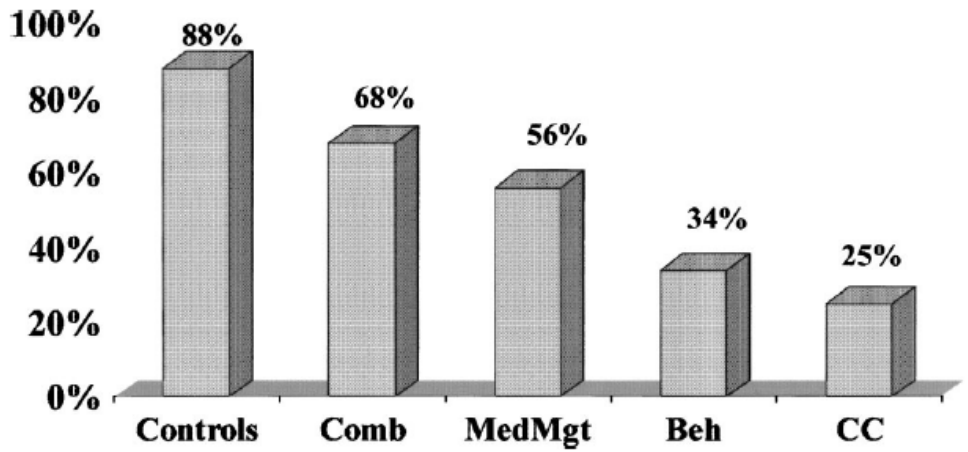
2011

The gold-standard treatment for childhood ADHD…

Table 1. MTA Study Treatment Conditions[a]

	Medication Management Strategy (MedMgt)	Behavioral Treatment Strategy (Beh)	Combined Strategy (Comb)	Community Comparison Group (CC)
Active Treatment	1-month blind titration with methylphenidate for best dose; if unsatisfactory, open titration with d-amphetamine, pemoline, TCA. When effective drug regimen is found, maintain with monthly visits; adjust dose as indicated by monthly monitors and by algorithm.	Intense, multi-component, including 27 group and 8 individual sessions (interspersed with the groups) of parent training, structured 16–20-session teacher/consultation, 8-wk full-time Summer Treatment Program, and 12 wk of half-time paraprofessional aide (PPA), all integrated in complementary fashion, with phone calls between visits.	Integration of all treatment components in first 2 conditions (except bibliotherapy), with **(a)** more extensive data base available from behavioral therapist to assist medication adjustment decisions and **(b)** information from pharmacotherapist to assist in decisions about escalation of behavioral interventions.	*None by MTA Staff.* Assessed-only at same time points as active treatment groups. Families obtain treatment of own choosing in the community. If already has a treatment provider, referred back for treatment; if not, given list of referral agencies, including community MH Center, which can help find community treatment.
Supplementary Treatment	Supplementary general advice and bibliotherapy without systematic behavioral intervention.	Supplementary general advice; no medication.	Supplementary general advice; no bibliotherapy.	None.
Case Manager	Pharmacotherapist is case manager.	Therapist/consultant (TC).	Therapist/consultant, with weekly advice from combined-treatment clinical team.	None.
Emergency Services	ASAP[b] emergency services as needed.	ASAP[b] emergency services as needed.	ASAP[b] emergency services as needed.	None.

MTA, Multimodal Treatment of Attention-Deficit Hyperactivity Disorder.
[a]Subjects in all 4 arms received comprehensive assessments at baseline, 3 months, 9 months, and 14 months.
[b]*ASAP*, Adjunct Services and Attrition Prevention. Each treated subject has a bank of eight "ASAP sessions" that can be used in emergencies, monitored by a cross-site clinical panel.

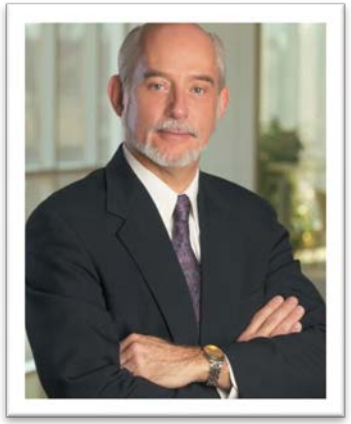


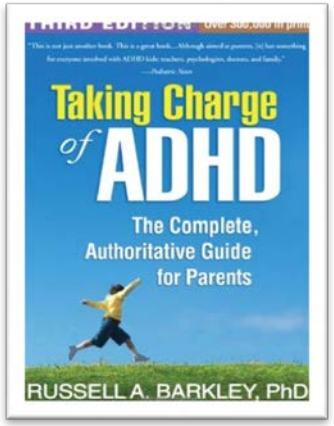
e 6. Percent "normalized" at 14-month endpoint across the four MTA groups. The classroom controls were drawn from the same room cohorts as MTA children were originally, and were age- and gender-matched to assure comparability with MTA subjects. The alization" indicator was based on a composite of parent and teacher ratings, with the overall symptom cutoff required to be indicative of or no" symptoms (Swanson et al, 2001).[15]

Parent management training

- **PMT** – a behavioral intervention that focuses on teaching effective parenting practices and strategies for coping with a child with ADHD. Similar to some components of ABA.

- **Goal:** Through teaching skills to parents, children will increase adaptive behavior and decrease maladaptive problem behaviors.



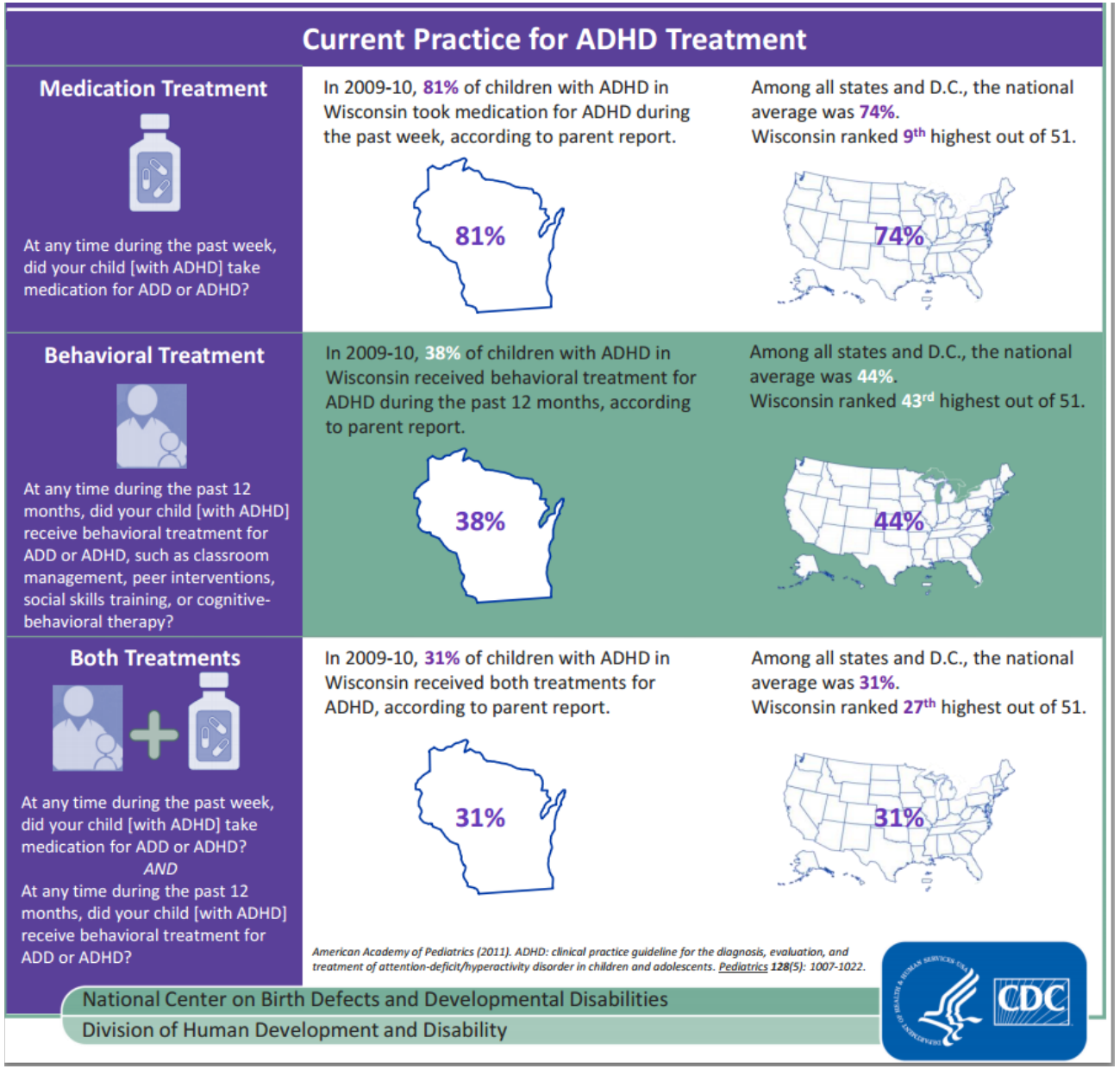


Medications

- Stimulants (increases dopamine *and* norepinephrine in PFC):
  - amphetamines (Adderall)
  - methylphenidates (Ritalin)
  - dextroamphetamine (Vyvanse)

- Nonstimulants (increases norepinephrine in PFC)
  - Atomoxetine (Strattera)

- Released in the CNS over 12-24 hours (longer acting ones are called XR)



Retrieved from http://www.cdc.gov/ncbddd/adhd/prevalence.html

Significance and impact

- National prevalence of 9.4% in the U.S. (2016 survey)
  - 388,000 children aged 2–5 years
  - 4 million children aged 6–11 years
  - 3 million children aged 12–17 years
- Academic and social functioning
- Economic impact
  - $31.6B annual cost for health care, lost productivity, and impact on other family members

https://www.cdc.gov/ncbddd/adhd/research.html#ref1

Overlap with ASD

Can a person have both ADHD and ASD?

- Does it add any value for the child and parents to also diagnose ADHD when ASD is present?

"Only when symptoms cause suffering or lead to impairment in everyday life and, therefore, require ADHD-specific interventions. The holds equally true the other way around." Rommelse, N., Visser, J., & Hartman, C. (2018). Differentiating between ADHD and ASD in childhood: some directions for practitioners.

They are both part of the same cluster in the DSM-5

- **Neurodevelopmental disorders** – impairment of the growth and development of the brain and/or CNS; affect emotion, learning, self-control, and memory.
  - **ADHD**
  - **ASD**
  - Learning disorder
  - Communication disorder
  - Motor disorder
  - Intellectual disability

Red flags in identifying ADHD in a child with ASD

1. ‘Often fails to give close attention to details or makes careless errors in schoolwork, at work or during other activities’
2. ‘Often has difficulty sustaining attention in tasks or activities’, and ‘often unable to play or engage in leisure activities quietly’
3. ‘Often avoids, dislikes or is reluctant to engage in tasks that require sustained mental effort’
4. ‘Often loses things necessary for tasks or activities’
5. ‘Often forgetful in daily activities’

Rommelse, Visser & Hartman, 2018 in *European Child and Adolescent Psychiatry*

Identifying ASD in a child with ADHD

- ‘Deficits in nonverbal communicative behaviors used for social interaction’
- ‘Stereotyped or repetitive motor movements, use of objects, or speech’
- ‘Insistence on sameness, inflexible adherence to routines or ritualized patterns or verbal or nonverbal behavior’
- ‘Highly restricted, fixated interests that are abnormal in intensity or focus’
- ‘Hyper- or hyporeactivity to sensory input or unusual interests in sensory aspects of the environment’

Rommelse, Visser & Hartman, 2018 in *European Child and Adolescent Psychiatry*

How common is the overlap?

- As many as 50% of individuals with ASD present with signs of ADHD; nearly two-thirds of individuals with ADHD similarly present with features of ASD Davis NO, Kollins SH. Treatment for Co-Occurring Attention Deficit/Hyperactivity Disorder and Autism Spectrum Disorder. *Neurotherapeutics* 2012;**9**:518–30.

- Individuals with ASD are **22 times** at higher risk of having ADHD compared with those who did not have ASD Ghirardi L, Brikell I, Kuja-Halkola R, Freitag CM, Franke B, Asherson P, *et al.* The familial co-aggregation of ASD and ADHD: a register-based cohort study. *Molecular Psychiatry* 2018;**23**:257–62.

Treatments?

- Compared to youths with ADHD or ASD alone, youths with both ASD and ADHD are the most likely group to be prescribed psychotropic medications Frazier TW, Shattuck PT, Narendorf SC, Cooper BP, Wagner M, Spitznagel EL. Prevalence and Correlates of Psychotropic Medication Use in Adolescents with an Autism Spectrum Disorder with and without Caregiver-Reported Attention-Deficit/Hyperactivity Disorder. *Journal of Child and Adolescent Psychopharmacology* 2011;**21**:571–9. https://doi.org/10.1089/cap.2011.0057.

- No compelling evidence (i.e., RCTs) that indicate children with ASD and ADHD respond well to these treatments

- Some evidence that they may respond poorly to certain ADHD medications Handen, B.L. et al. (2015). Atomoxetine, Parent Training, and Their Combination in Children with Autism Spectrum Disorder and Attention-Deficit/Hyperactivity Disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, 54(11), 905-915.

Research

What causes the overlap?

Many disorders have a strong genetic basis

	Schizophrenia	Bipolar disorder	MDD	Autism Spectrum	ADHD
h^2	0.81	0.75	0.37	0.80	0.75

Cross disorder group of Psychiatric Genomics Consortium, 2013 in *Nature Genetics*

Genome-wide association study of ASD

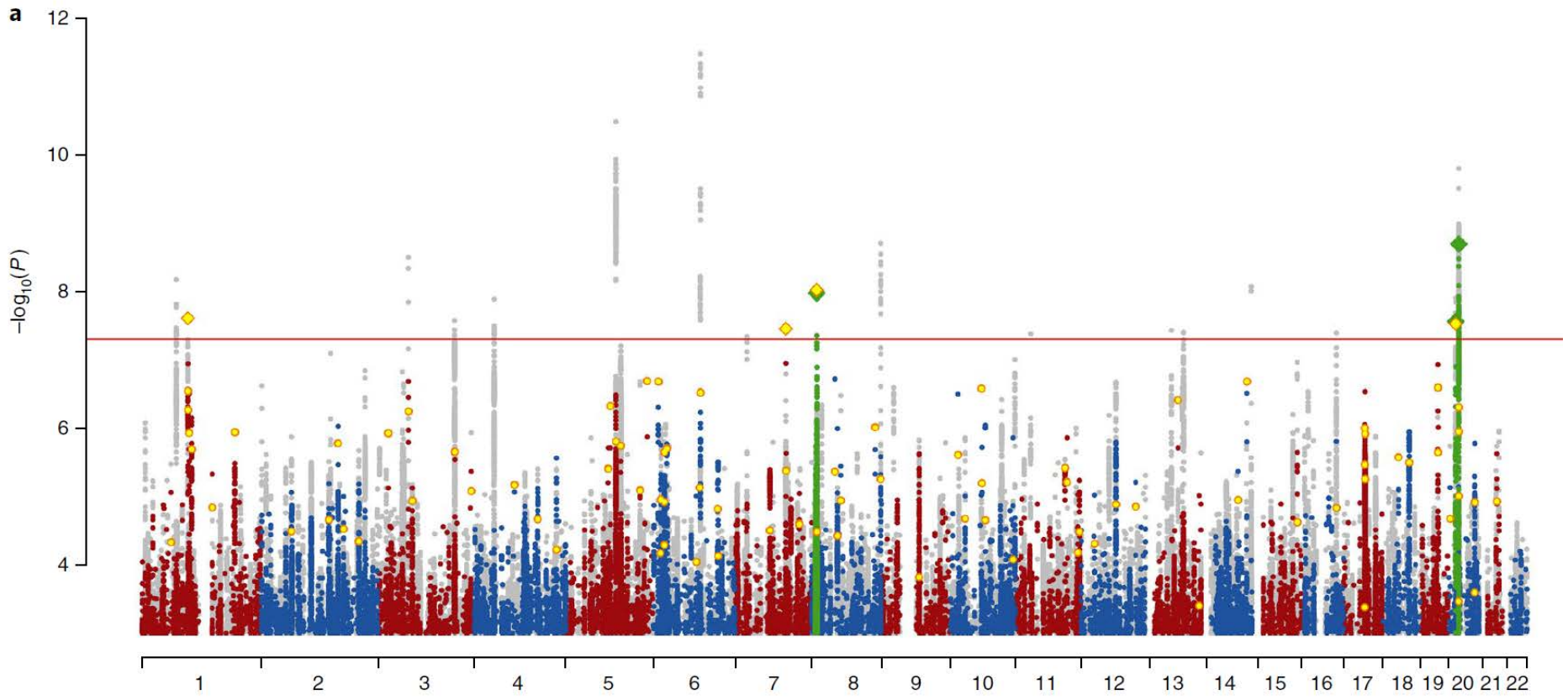
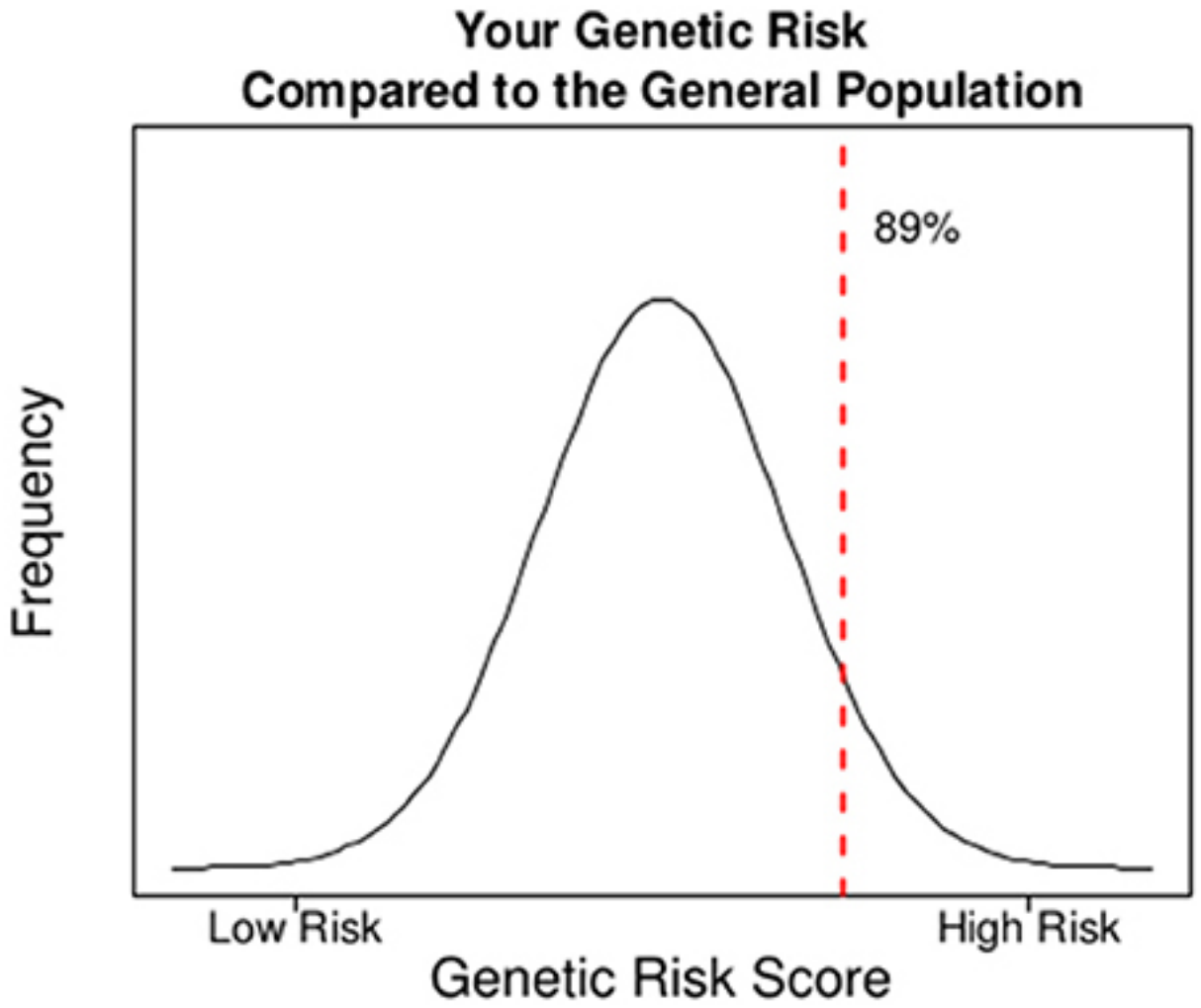


Fig. 1 | Manhattan plots. The *x* axis shows genomic position (chromosomes 1–22), and the *y* axis shows statistical significance as $-\log_{10}(P)$ of *z* statistics. **a**, The main ASD scan (18,381 cases and 27,969 controls), with the results of the combined analysis with the follow-up sample (2,119 cases and 142,379 controls) in yellow in the foreground. Genome-wide-significant clumps are green, and index SNPs are shown as diamonds. **b**–**d**: Manhattan plots for three MTAG scans of ASD together with schizophrenia[15] (34,129 cases and 45,512 controls; **b**), educational attainment[21] ($n = 328,917$; **c**) and major depression[25] (111,902 cases and 312,113 controls; **d**). Full-size plots are shown in Supplementary Figs. 45–48. In all panels, the results of the composite of the five analyses (consisting of the minimal *P* value of the five for each marker) is shown in gray in the background.

Using genomics to predict complex outcomes



Using genetic information to help diagnose ADHD?

Psychological Medicine

cambridge.org/psm

Original Article

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Author for correspondence:
James J. Li, E-mail: james.li@wisc.edu

The positive end of the polygenic score distribution for ADHD: a low risk or a protective factor?

James J. Li

Waisman Center and University of Wisconsin-Madison, Madison, WI, USA

Abstract

Background. Polygenic scores (PGS) are widely used to characterize genetic liability for heritable mental disorders, including attention-deficit/hyperactivity disorder (ADHD). However, little is known about the effects of a low burden of genetic liability for ADHD, including whether this functions as a low risk or protective factor for ADHD and related functional outcomes in later life. The current study examines the association of low ADHD PGS and functional outcomes in adulthood.

Methods. Participants were from Wave IV of the National Longitudinal Study of Adolescent to Adult Health (Add Health) ($N = 7088$; mean age = 29, S.D. = 1.74). ADHD PGS was computed from an existing genome-wide association study, and adult functional outcomes, including cognition, educational attainment, mental health, and physical health were assessed during in-home interviews.

Results. Individuals at the lowest end of the ADHD PGS distribution (i.e. lowest 20th percentile) had the lowest probabilities of ADHD, exhibiting a 17–19% reduction in risk for ADHD relative to the observed 8.3% prevalence rate of ADHD in Add Health. Furthermore, individuals with low ADHD PGS had higher cognitive performance, greater levels of educational attainment, and lower BMI relative to individuals representing the rest of the ADHD PGS distribution, including those who were in the medium and high-PGS groups.

Conclusions. Findings indicate that psychiatric PGS likely capture far more than just the risk and the absence of risk for a psychiatric outcome; where one lies along the PGS distribution may predict diverging functional consequences, for better and for worse.

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder with an estimated prevalence of 8.9% among children (aged 6 to 11) in the United States (Danielson *et al.*, 2018). It is associated with a range of negative functional outcomes in adulthood, including poor cognitive functioning (Boonstra *et al.*, 2005), low-educational attainment (Kuriyan *et al.*, 2013), depression and substance misuse (Lee *et al.*, 2011; Agnew-Blais *et al.*, 2018), involvement in the criminal justice system (Fletcher and Wolfe, 2009), increased stress (Combs *et al.*, 2015), and poor physical health (Brook *et al.*, 2013; Kuriyan *et al.*, 2013). Etiologically, ADHD is among the most heritable of the psychiatric disorders; twin studies have estimated that between 70–75% of the variance in ADHD dimensions can be accounted for by genetic differences in the population (Nikolas and Burt, 2010; Chang *et al.*, 2013; Faraone and Larsson, 2019). Recently, this heritability has been shown to be highly polygenic, reflecting many genes of individually small effects (Franke *et al.*, 2009; Larsson *et al.*, 2014; Zayats *et al.*, 2015; Demontis *et al.*, 2019). As such, studies are increasing using polygenic scores (PGS) (Dudbridge, 2013) to characterize the aggregate genetic liability for ADHD.

PGS are typically computed as the linear composite of alleles one carries across single nucleotide polymorphisms (SNPs) tested in association with a psychiatric trait, with each SNP weighted according to genome-wide association study (GWAS) summary statistics on the trait in question (Anderson *et al.*, 2019). One consistent observation of psychiatric PGS is that they are distributed normally in population-based samples (Krapohl *et al.*, 2016), reflecting the continuum of genetic risk for psychopathology in a population (Plomin *et al.*, 2009). Whereas individuals on the right-tail (e.g. >20th percentile) are often characterized as 'high risk' (Khera *et al.*, 2018; Torkamani *et al.*, 2018), individuals at the left-tail (e.g. <20th percentile) are traditionally considered a 'low risk' group (Torkamani *et al.*, 2018). However, the term 'low risk' for this subgroup is ambiguous and questionable, especially given that few studies have empirically examined the implications of having low PGS. For instance, low risk could equate to the baseline of risk for the disorder observed in the population. Low risk could also indicate a *reduction* of risk for the disorder relative to the population baseline, perhaps reflecting a biologically protective effect of having few risk alleles. In general, few researchers have been 'thinking positively' (Plomin *et al.*, 2009, 875) about PGS, and thus, may have been neglecting potentially important functional consequences of being in the low end of the PGS distribution.

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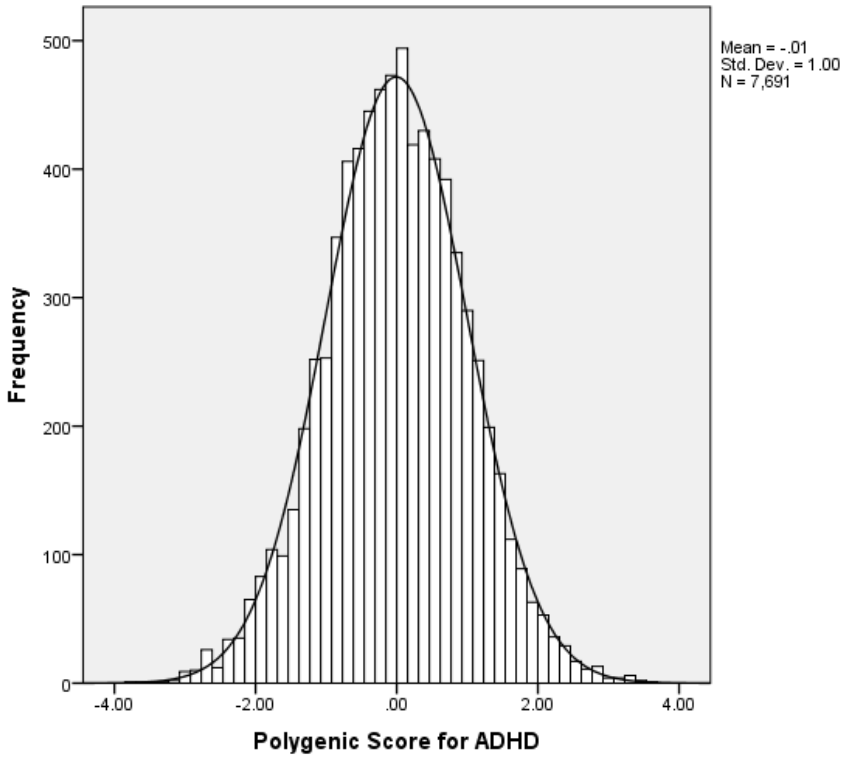


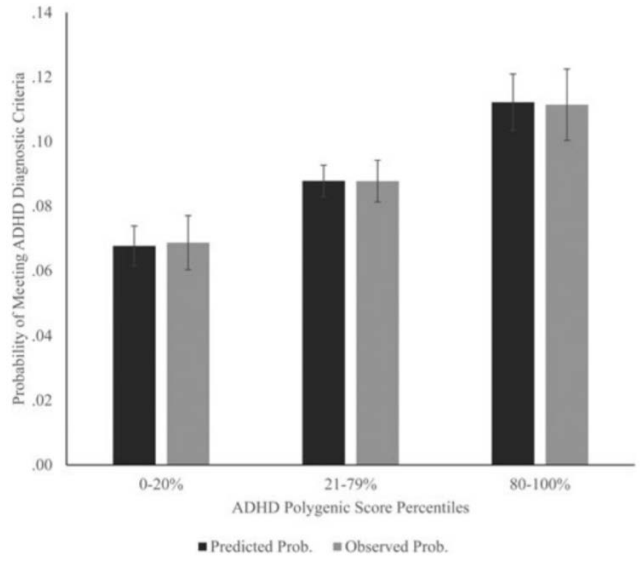


Fig. 2. Predicted and observed probabilities of meeting diagnostic criteria for ADHD in Add Health by ADHD PGS. Figure shows the predicted and observed probabilities of meeting diagnostic criteria for ADHD in Add Health by ADHD PGS groups, according to a binary logistic regression that controlled for age, biological sex and the first 10 principal components of the genetic information (i.e. genetic ancestry). Error bars reflect standard errors.

Li, 2019 in *Psychological Medicine*

But…what if some ADHD genes = ASD genes?

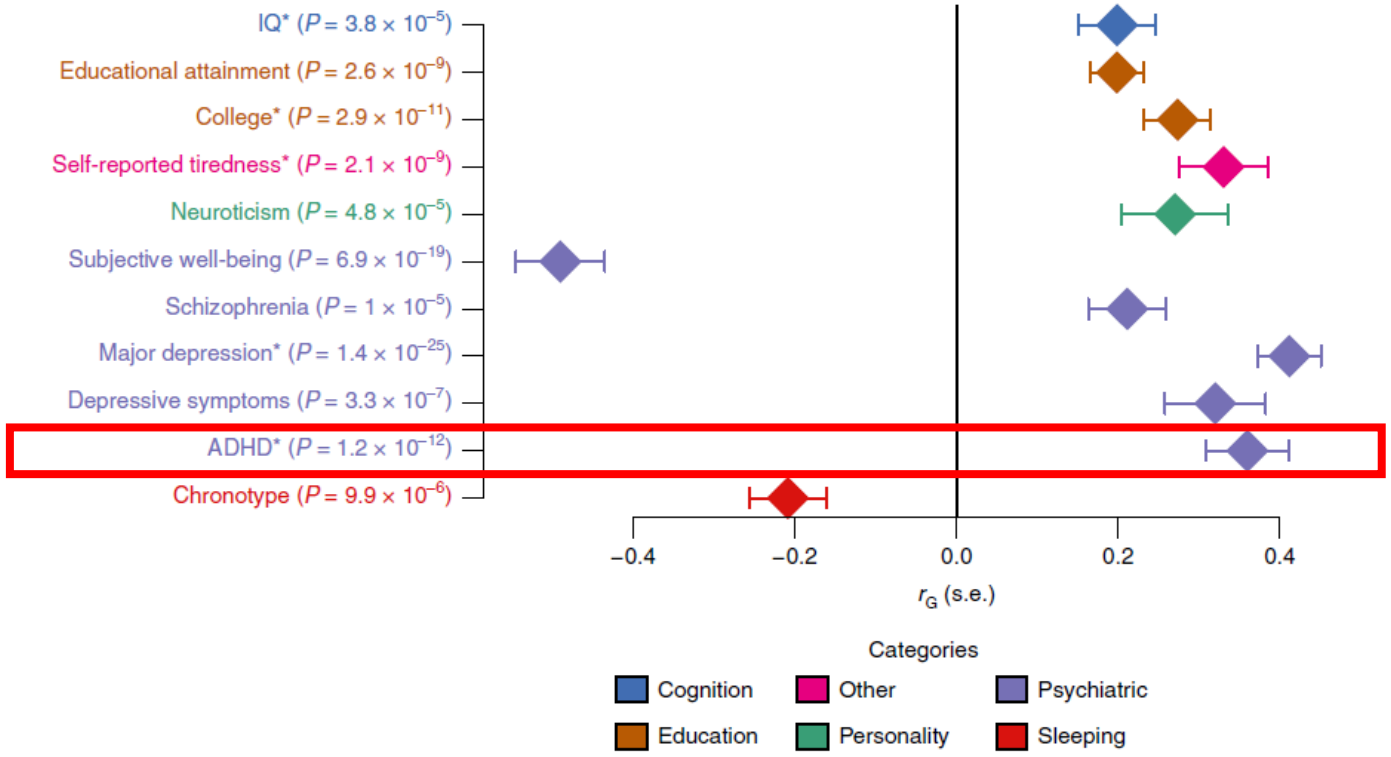
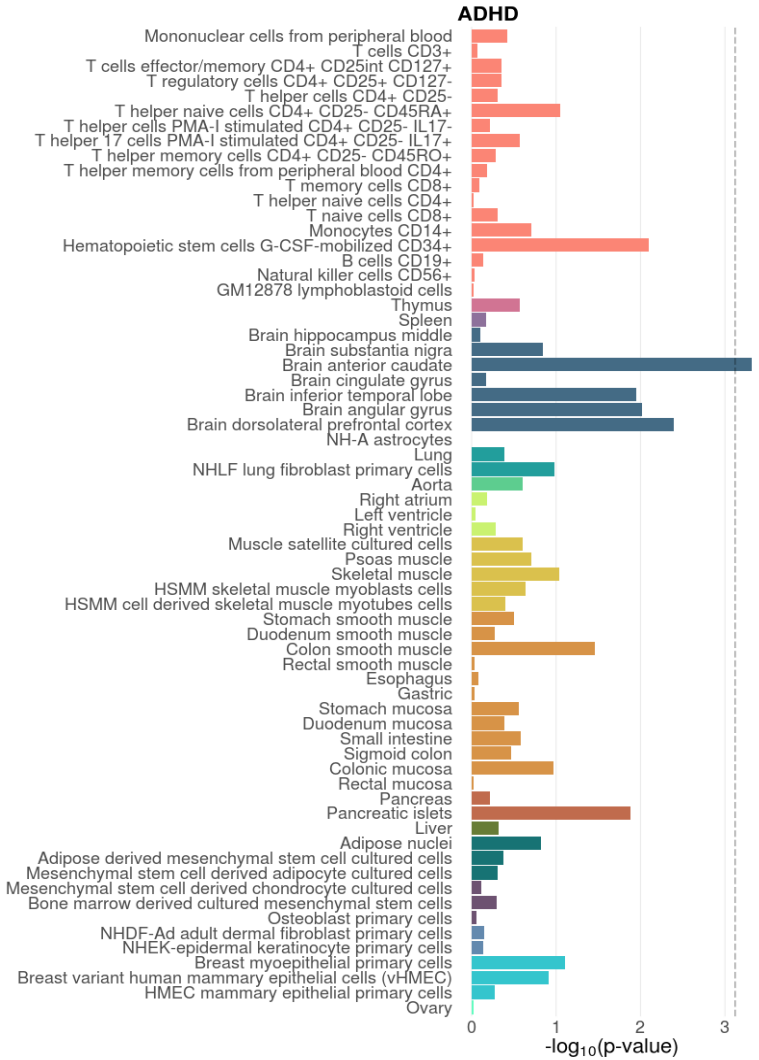


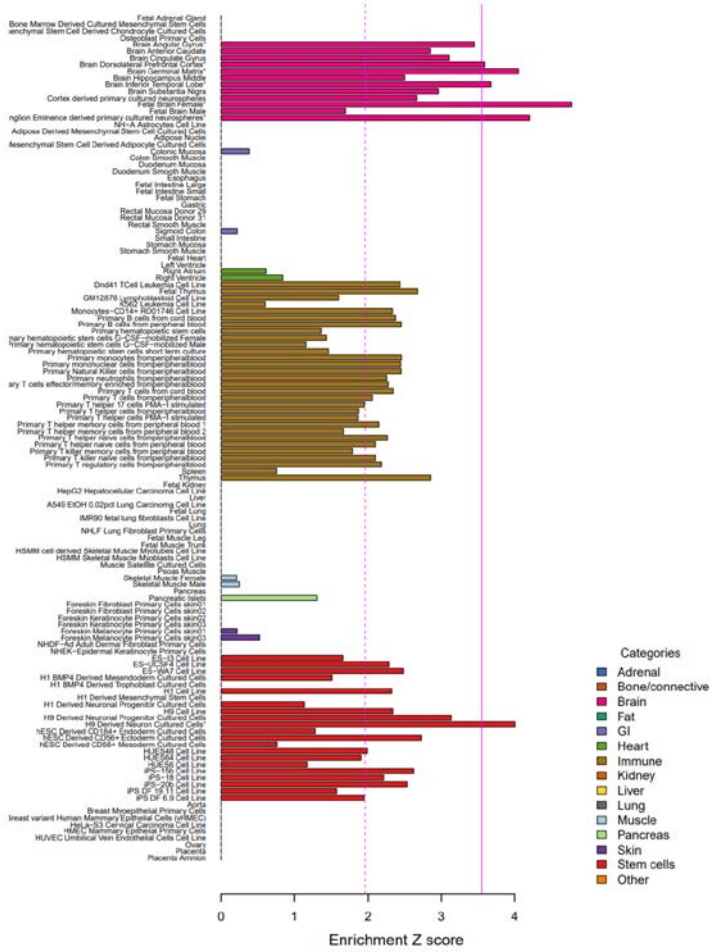
Fig. 2 | Genetic correlation with other traits. Significant genetic correlations between ASD ($n = 46,350$) and other traits after Bonferroni correction for testing a total of 234 traits available at LD Hub with the addition of several new phenotypes. Estimates and tests were performed with LDSC[19]. The results shown correspond to the following GWAS analyses: IQ[41] ($n = 78,308$), educational attainment[21] ($n = 328,917$), college[55] ($n = 111,114$), self-reported tiredness[56] ($n = 108,976$), neuroticism[23] ($n = 170,911$), subjective well-being[23] ($n = 298,420$), schizophrenia[15] ($n = 82,315$), major depression[25] ($n = 480,359$), depressive symptoms[23] ($n = 161,460$), attention deficit/hyperactivity disorder (ADHD)[26] ($n = 53,293$), and chronotype[42] ($n = 128,266$). Supplementary Table 5 shows the full output of this analysis. Asterisks indicate values are from in-house analyses of new summary statistics not yet included in LD Hub.

Grove et al., 2019 in *Nature Genetics*

ASD and ADHD genes are enriched in similar brain regions



Demontis et al., 2018



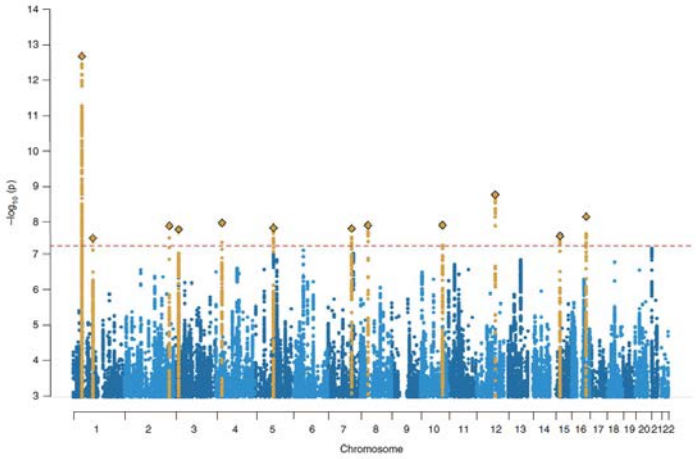
Supplementary Figure 97: Tissue enrichment based on LDSC and roadmap h3k4me1 cell type annotation[59, 60]. The dashed magenta line indicates statistical significance at α-level 0.05 and the solid line significance after Bonferroni correction for the number of tissues tested (significance from z-test). Tissues achieving global statistical significance are marked by an asterisk.

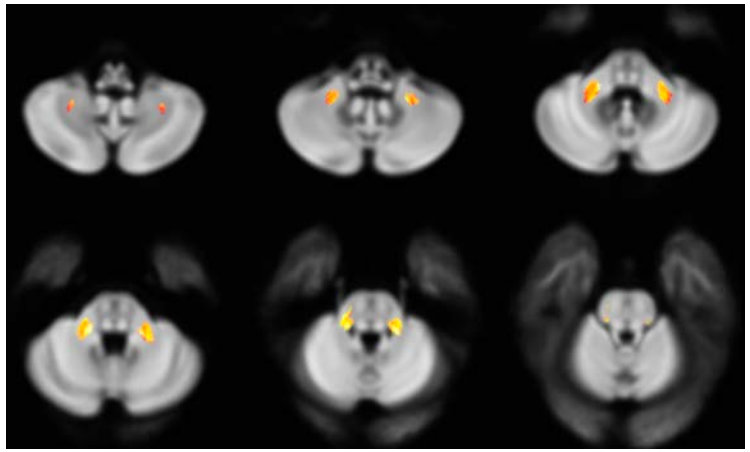
Grove et al., 2019 in *Nature Genetics*

Combining genetics and brain imaging to improve diagnostic precision

SOCIAL AND BEHAVIORAL DEVELOPMENT LAB

THE MOTOR AND BRAIN DEVELOPMENT LAB





- ASD?
- ADHD?
- ASD + ADHD?
- Typical Development?

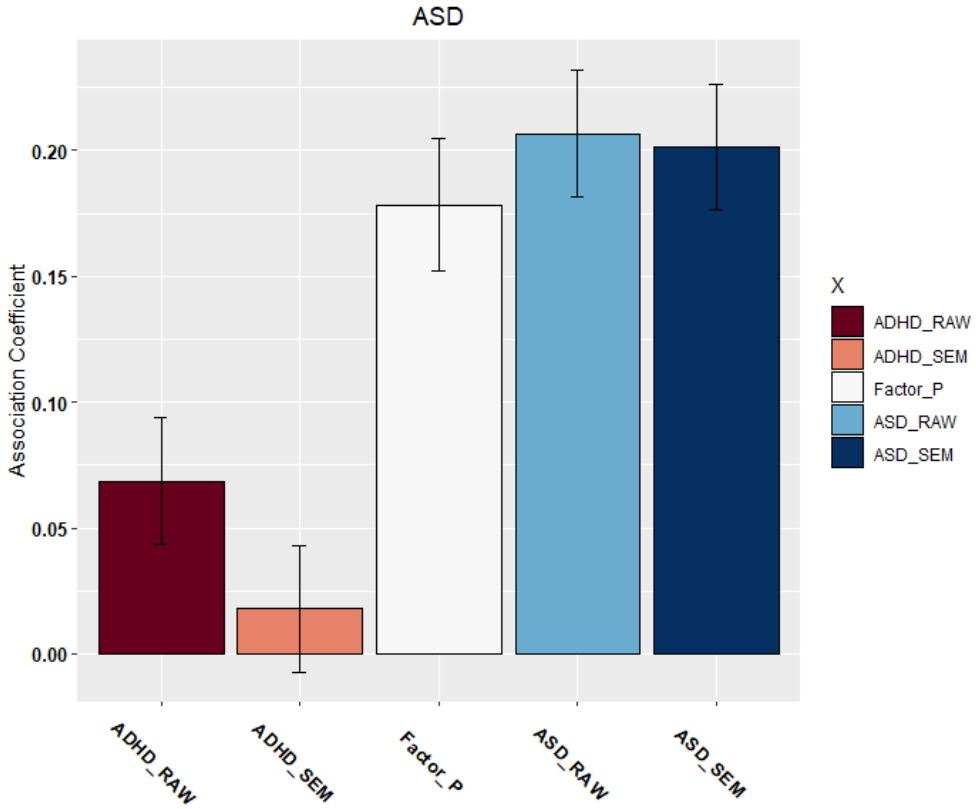
Our guiding research questions

- Can genetic information be used to diagnose ASD, ADHD, and their co-occurrence in early life?

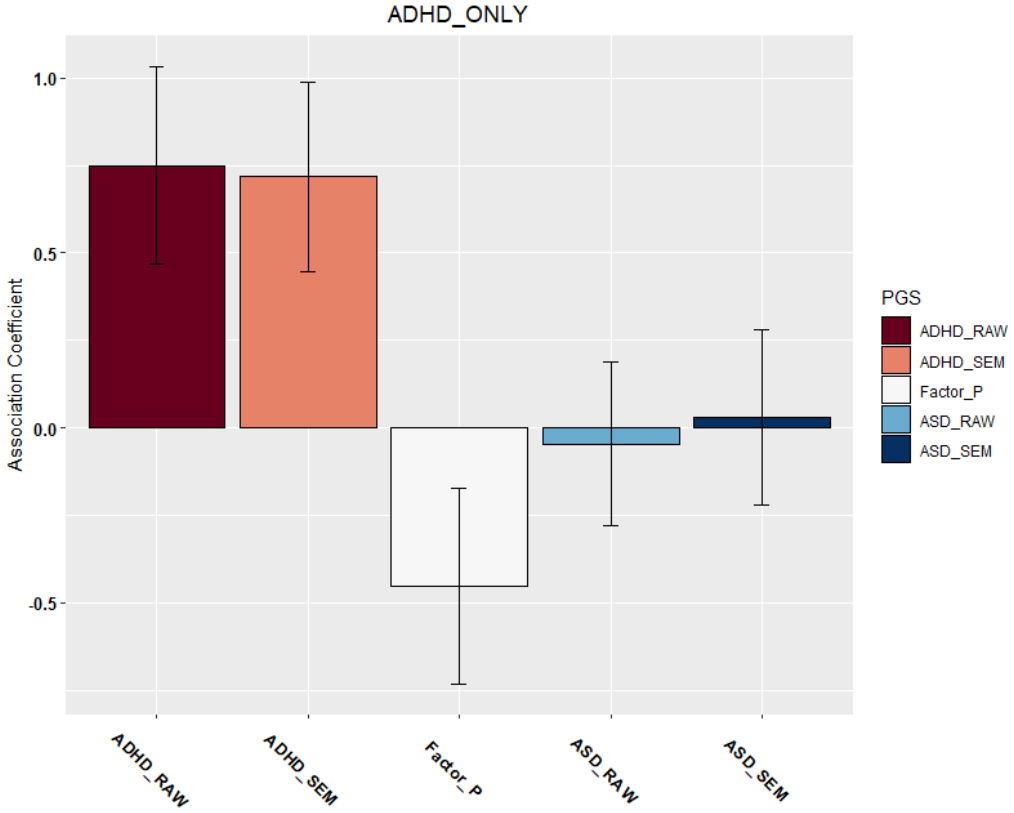
- Can genetic information for ASD, ADHD, and their co-occurrence be traced to brain regions so that we know which areas of the brain to target in the development of new therapeutics?

Preliminary results

Genes for ASD only predict ASD



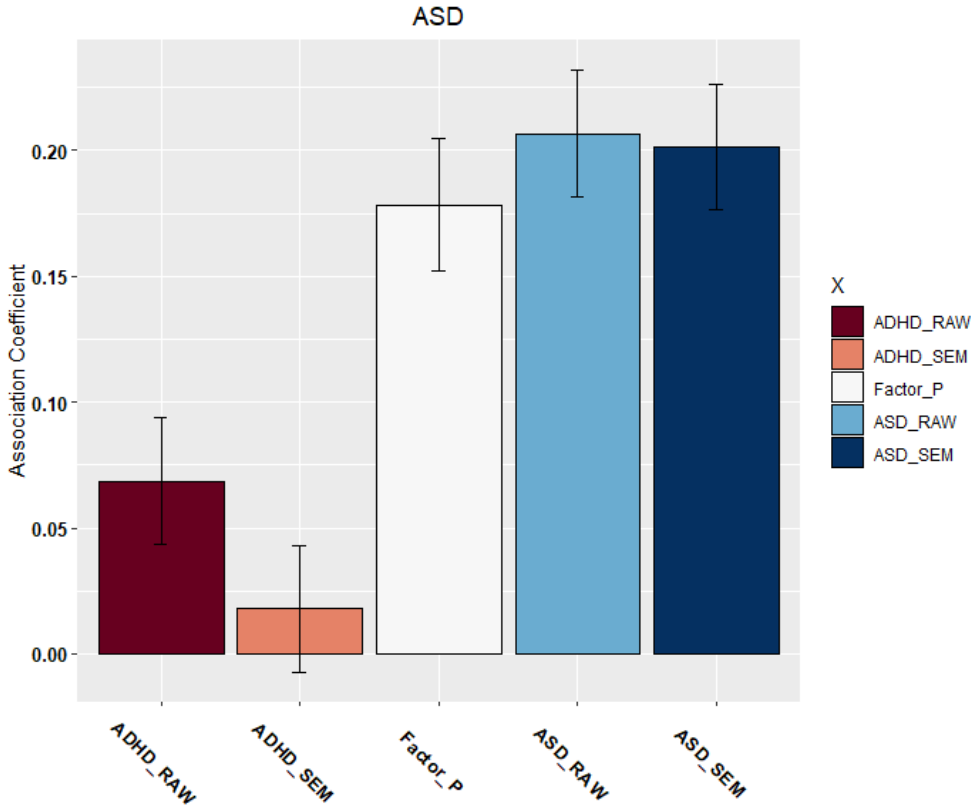
Genes for ADHD only predict ADHD



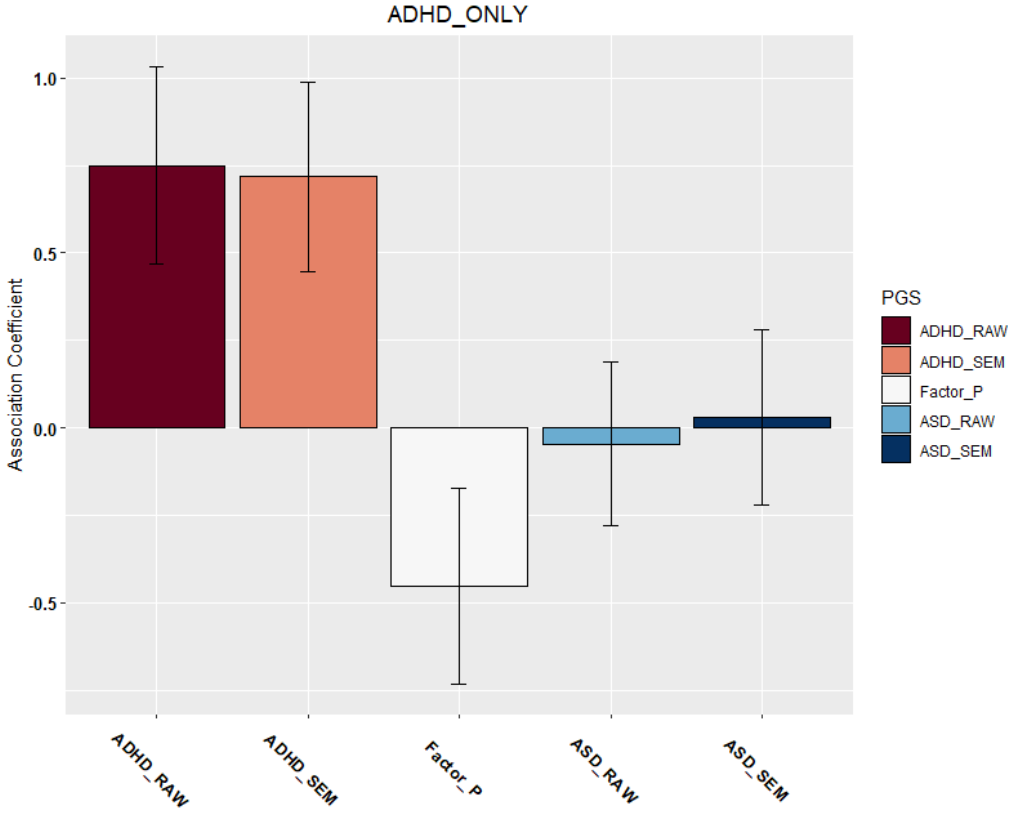
Wang, Li, Travers, and Lu, in prep.

Genetic information used for early diagnosis → early intervention → better outcomes

Genes for ASD only predict ASD



Genes for ADHD only predict ADHD



Wang, Li, Travers, and Lu, in prep.


Jones & Klin, 2013
Infant Later Diagnosed with Autism
is going to go on to develop autism.

Thank you!

- Email: james.li@wisc.edu
- Social and Behavioral Development Lab
- The Motor and Brain Development Lab
- UW Social Genomics group
- All the families and children that participated in our studies