MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

# Current Concepts in the Neurobiology and Treatment of ADHD Across the Life Cycle

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**Harvard Medical School**
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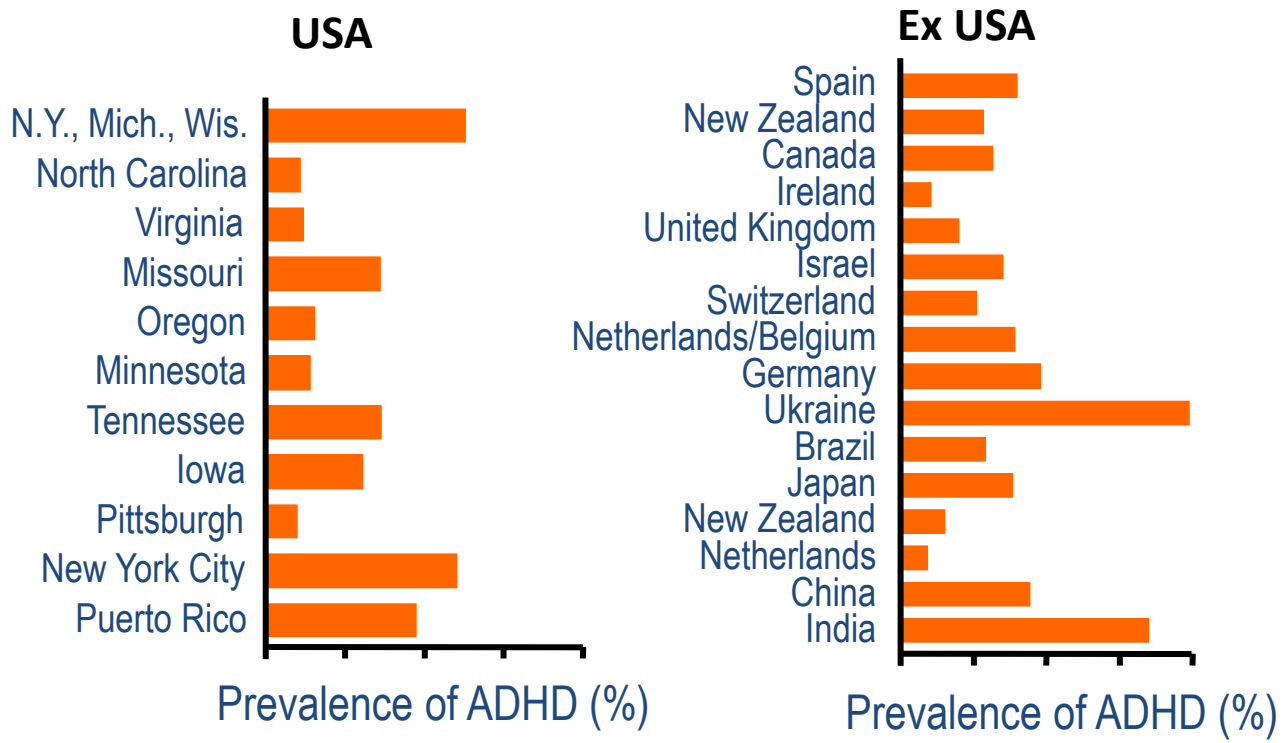
**Director, Bressler Program for Autism Spectrum Disorders**
**Trustees Endowed Chair in Pediatric Psychopharmacology**
**Massachusetts General Hospital**

# Disclosures 2020-2021

My spouse/partner and I have the following relevant financial relationships with commercial interests to disclose:

- *Research support:* Genentech, Headspace Inc., Pfizer Pharmaceuticals, Roche TCRC Inc., Sunovion Pharmaceuticals Inc., Takeda/Shire Pharmaceuticals Inc., and Tris.
- *Consulting fees:* Akili, Avekshan LLC, Jazz Pharma, and Shire/Takeda
- *Honorarium for scientific presentation:* Tris
- *Royalties paid to the Department of Psychiatry at MGH, for a copyrighted ADHD rating scale used for ADHD diagnoses:* Biomarin, Bracket Global, Cogstate, Ingenix, Medavent Prophase, Shire, Sunovion, and Theravance
- Through Partners Healthcare Innovation, I have a partnership with MEMOTEXT to commercialize a digital health intervention to improve adherence in ADHD.

# Worldwide Prevalence of ADHD in Children




Faraone SV et al. (2003), World Psychiatry 2(2):104-113

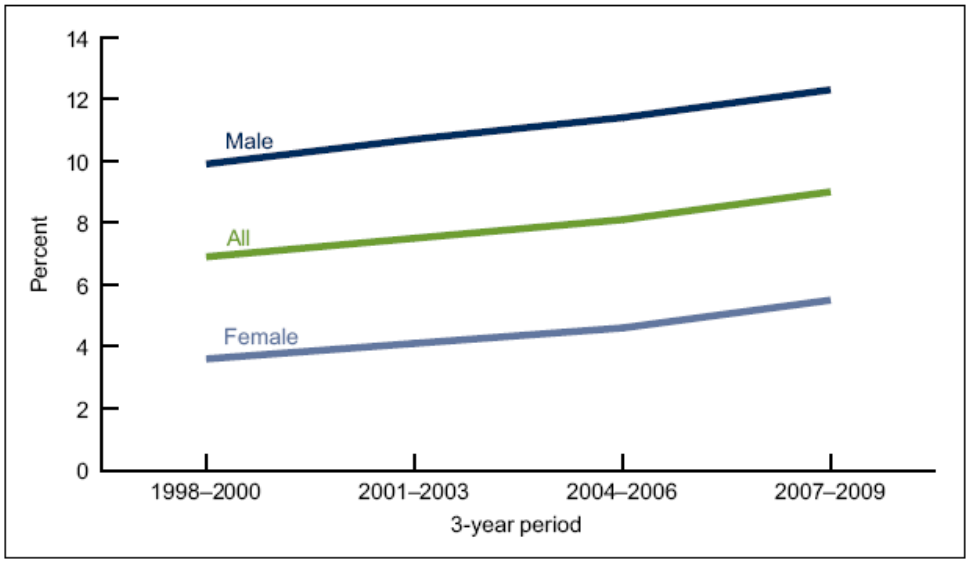
## Key findings

### Data from the National Health Interview Survey, 1998–2009

- The percentage of children ever diagnosed with attention deficit hyperactivity disorder (ADHD) increased from 7% to 9% from 1998–2000 through 2007–2009.
- ADHD prevalence trends varied by race and ethnicity. Differences between groups narrowed from 1998 through 2009; however, Mexican children had consistently lower ADHD prevalence than other racial or ethnic groups.
- From 1998 through 2009, ADHD prevalence increased to 10% for children with family income less than 100% of the poverty level and to 11% for those with family income between 100% and 199% of the poverty level.
- From 1998 through 2009, ADHD prevalence rose to 10% in the Midwest and South regions of the United States.

## The percentage of children ever diagnosed with ADHD increased from 1998 through 2009 among both boys and girls.

Figure 1. Percentage of children aged 5–17 years ever diagnosed with attention deficit hyperactivity disorder, by sex: United States, 1998–2009




NOTE: Access data table for Figure 1 at: http://www.cdc.gov/nchs/data/databriefs/db70_tables.pdf#1.
SOURCES: CDC/NCHS, Health Data Interactive and National Health Interview Survey.

Akinbami et al. *NCHS Data Brief* No. 70, August 2011

Research

JAMA Psychiatry | Original Investigation

# Prevalence and Risk Factors Associated

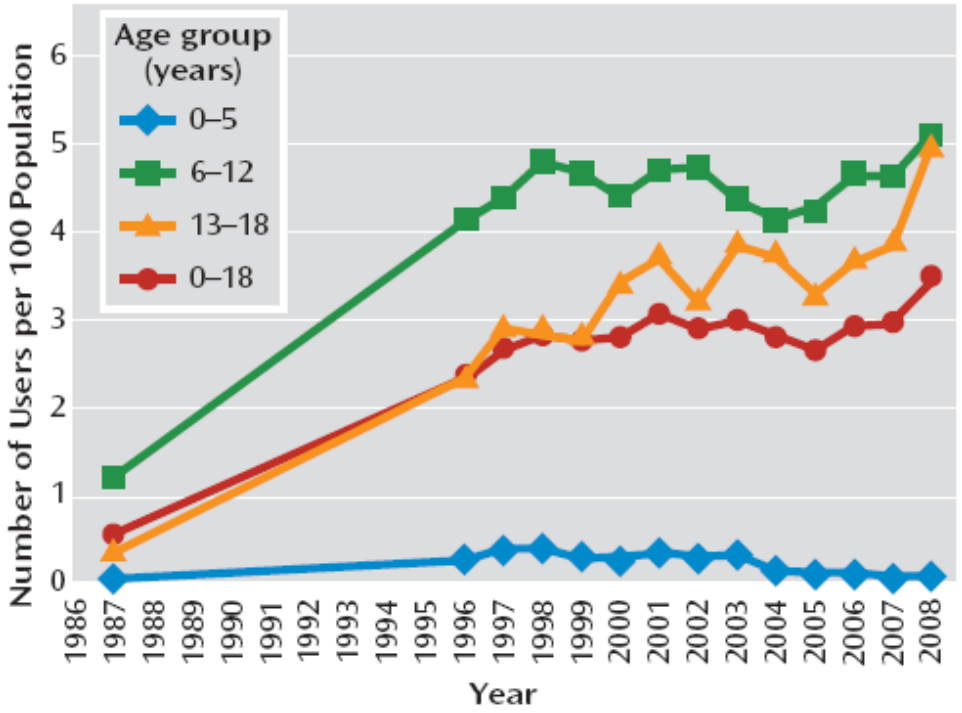
**DATA SOURCES** This systematic review and meta-analysis identified peer-reviewed studies published until October 18, 2019, using the APA PsycInfo, MEDLINE, Embase, Cochrane CENTRAL, CINAHL, ERIC, and Education Source databases.

**STUDY SELECTION** Eligible trials were published in French or English, had empirical data on

**CONCLUSIONS AND RELEVANCE** Contrary to what is stated in the *DSM-5*, the results of this systematic review and meta-analysis suggest that Black individuals are at higher risk for ADHD diagnoses than the general US population. These results highlight a need to increase ADHD assessment and monitoring among Black individuals from different social backgrounds. They also higlight the importance of establishing accurate diagnoses and culturally appropriate care.

Cenat et al. *JAMA Psychiatry*. 2021;78(1):21-28.
doi:10.1001/jamapsychiatry.2020.2788

FIGURE 1. Trends in Prevalence of Stimulant Use in the U.S. Population Age 18 and Younger, 1987–2008[a]

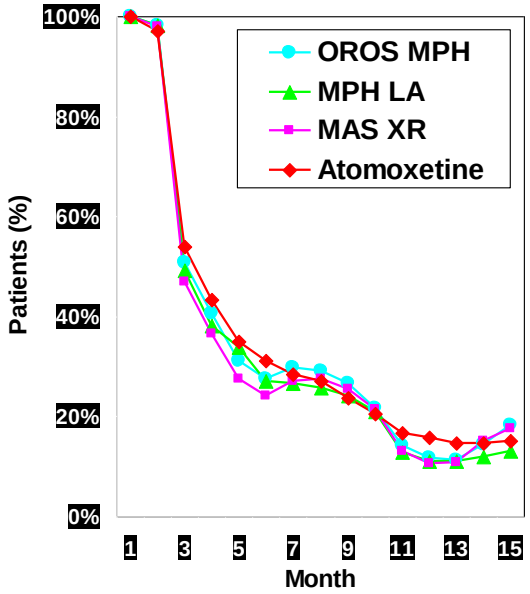



[a] Based on the Medical Expenditure Panel Survey (1996–2008) and the National Medical Expenditure Survey (1987).

Zuvekas al. *Am J Psychiatry* 2012; 169:160-166

# Adherence in ADHD is Dismal

- **Only 13% of patients consistently take their medication one year out**

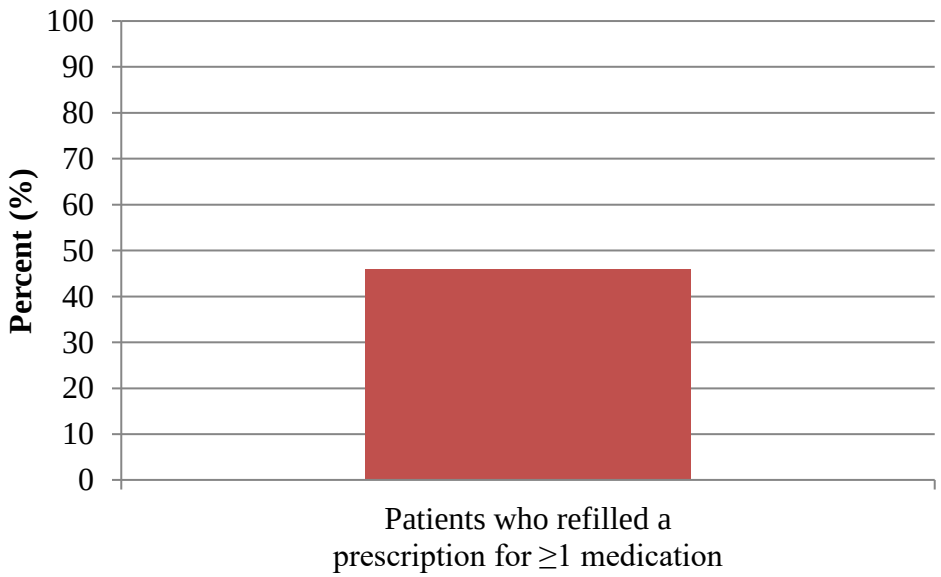



- **Within 2 to 3 months, a majority of patients with ADHD have stopped taking medication consistently**
- **Patients renewed their monthly prescriptions about 2 to 3 times per year**[1]


1. Capone. Presented at CHADD Annual International Conference, Dallas, Texas; October 27, 2005.
2. Perwien et al. *J Manag Care Pharm*. 2004;10(2):122-129.
3. Sanchez et al. *Pharmacotherapy*. 2005;25(7):909-917.

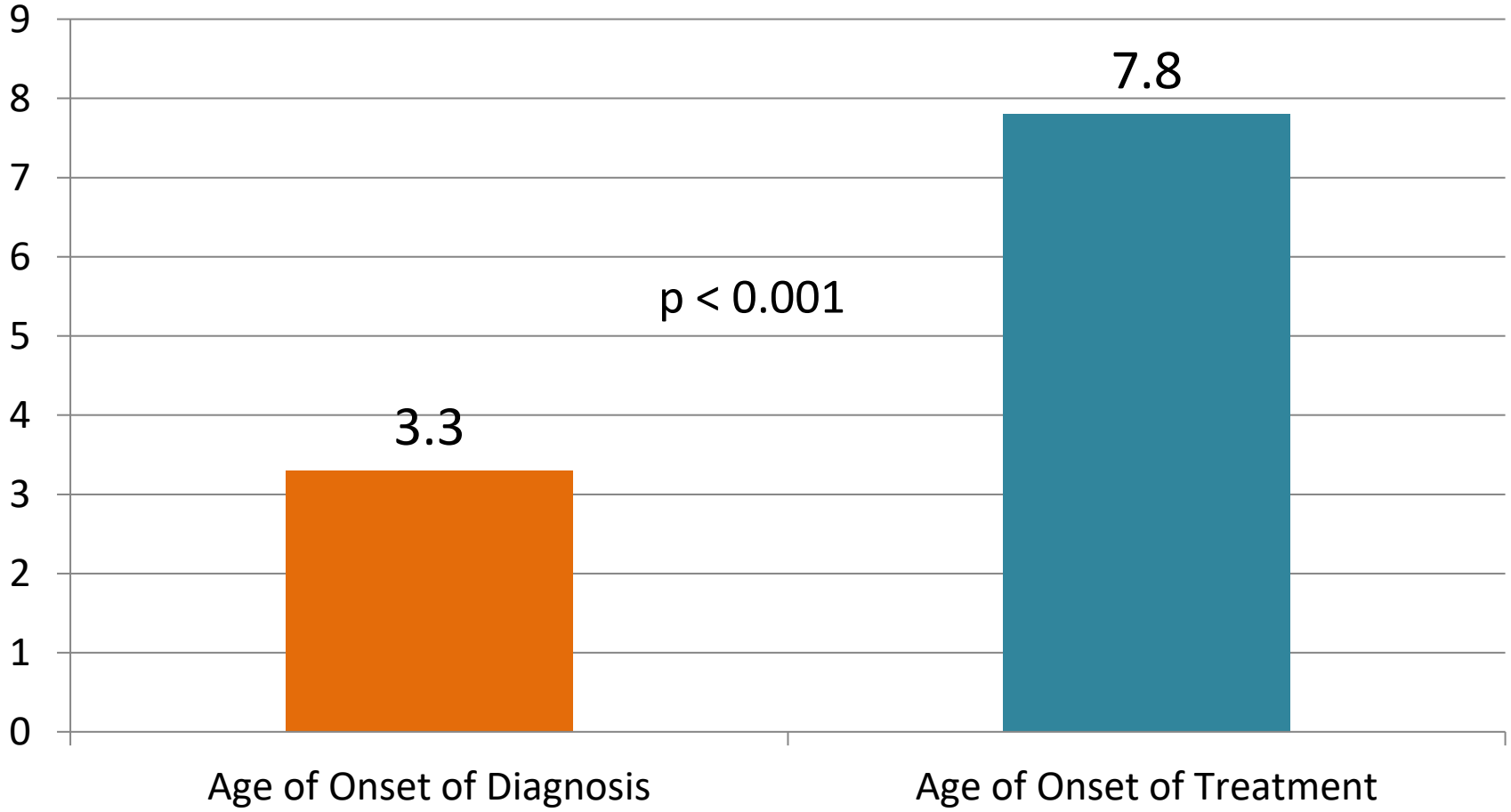
# Percent of Children with ADHD who Renewed their First Stimulant Rx: A Partners Healthcare EMR Review

| # of patients | # of patients who refilled a prescription for ≥1 medication | % of patients who refilled |
|---|---|---|
| 2,206 | 1,023 | 46% |




Biederman et al. *Psychiatric Services* 2019;70:874-880

# Long Delays in the Initiation of Treatment (n=1498)




MGH Pediatric Psychopharmacology Clinic

# Diagnosis of ADHD

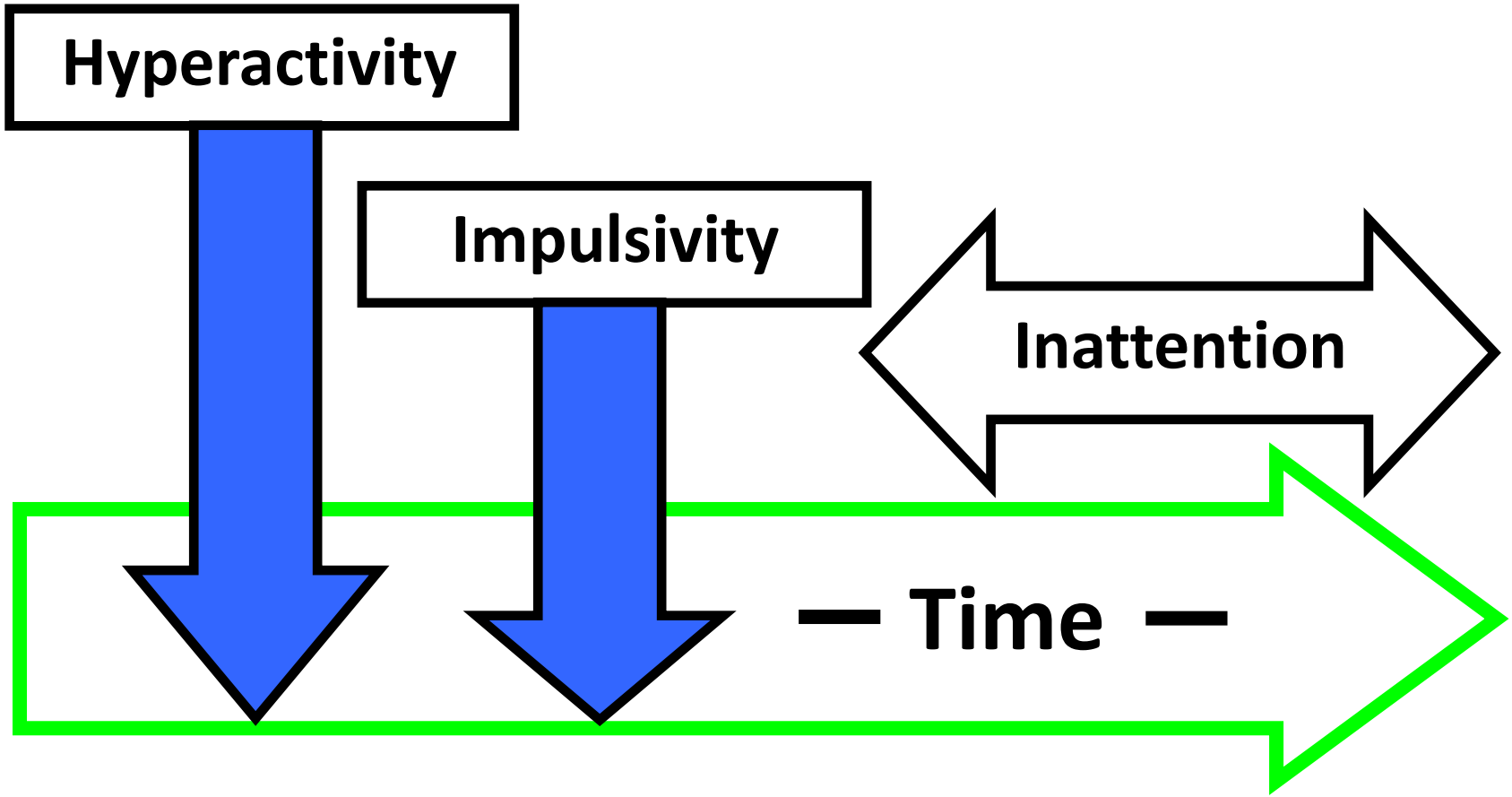
- Diagnosis is based on clinical assessment of symptoms, associated impairment and age of onset
- No test is available
- Symptoms are subjective, as well as developmentally and context sensitive

# ADHD: Core Symptom Areas

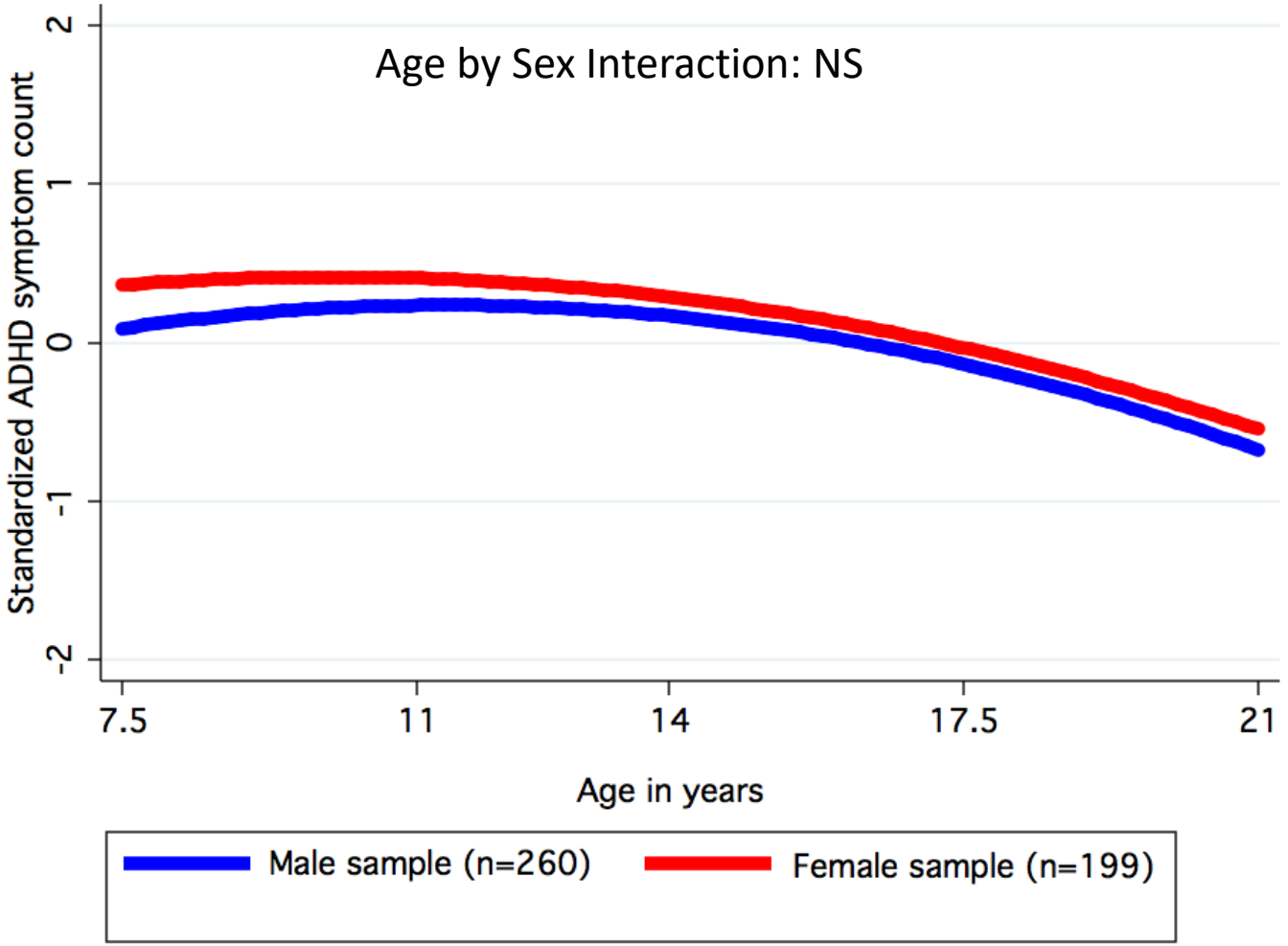

# Changes in DSM-5 ADHD

- "Neurodevelopmental" - not "disruptive"
- ≥ 6/9 inattentive or ≥ 6/9 impulsive/hyperactive symptoms over last six months (>5 for adults)
- Symptoms caused impairment by age 12 (no longer 7)
- ASDs no longer exclusionary
- No more "subtypes"; Inattentive / Hyperactive-impulsive / Combined are now "Presentations"
- Restricted inattentive subtype: In Appendix, worthy of further study

# ADHD: Course of the Disorder



# Course of ADHD Symptoms Over Time by Sex: A Growth Curve Model




Biederman et al. 2009

# Age-Dependent Decline and Persistence of ADHD Throughout the Lifetime

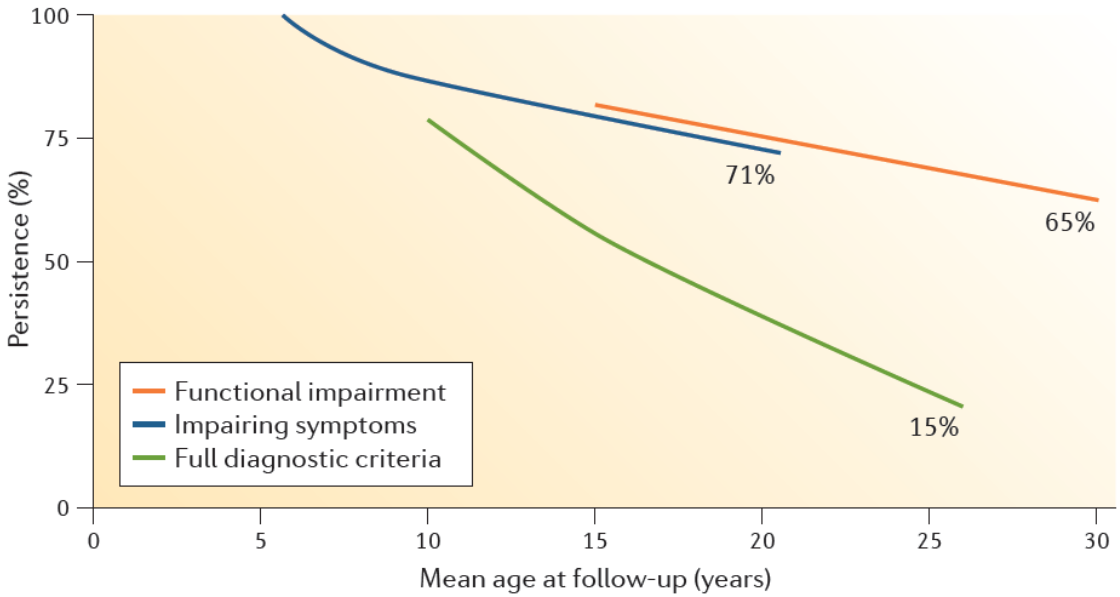



Figure 2 | **The age-dependent decline and persistence of attention-deficit/hyperactivity disorder throughout the lifetime.** Follow-up studies have assessed children with attention-deficit/hyperactivity disorder (ADHD) at multiple time points after their initial diagnosis. Although they document an age-dependent decline in ADHD symptoms, ADHD is also a highly persistent disorder when defined by the persistence of functional impairment[7] or the persistence of subthreshold (three or fewer) impairing symptoms[8]. By contrast, many patients remit full diagnostic criteria[7].

Faraone et al. *Nature Reviews Disease Primers* 2015

Article

# The Prevalence and Correlates of Adult ADHD in the United [illegible]rbidity

Ronald C. Kess
Lenard Adler,
Russell Barkley
Joseph Biederm
C. Keith Conne
Olga Demler, M
Stephen V. Far
Laurence L. Gr
Mary J. Howes

**Results:** The estimated prevalence of current adult ADHD was 4.4%. Significant correlates included being male, previously married, unemployed, and non-Hispanic white. Adult ADHD was highly comorbid with many other DSM-IV disorders assessed in the survey and was associated with substantial role impairment. The majority of cases were untreated, although many individuals had obtained treatment for other comorbid mental and substance-related disorders.

154 respondents,
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DHD.

l prevalence of cur-
4%. Significant cor-
male, previously
and non-Hispanic
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diagnostic interview to assess a wide range of DSM-IV disorders. Blinded clinical follow-up interviews of adult ADHD

mine whether effective treatment would reduce the onset, persistence, and severity of disorders that co-occur with adult ADHD.

*(Am J Psychiatry 2006; 163:716–723)*

# Persistent Controversy BMJ | 3 april 2010 | Vol 340

HEAD TO HEAD

## Is ADHD a valid diagnosis in adults?

**Philip Asherson and colleagues** argue that the concept of ADHD in adults is valid but **Joanna Moncrieff** and **Sami Timimi** believe that it is supported by little more than aggressive marketing

Philip Asherson, professor of molecular psychiatry and honorary consultant psychiatrist, MRC Social Genetic and Developmental Psychiatry, Institute of Psychiatry, King's College London philip.asherson@kcl.ac.uk
Marios Adamou, consultant psychiatrist; Service for adults with ADHD, Manygates Clinic, South West Yorkshire Partnership NHS Foundation Trust, Yorkshire; Blanca Bolea, consultant psychiatrist and honorary lecturer, University of Bristol, Bristol Adult ADHD Clinic, Avon and Wiltshire Partnership Mental Health Trust, Bristol; Ulrich Muller, university lecturer and honorary consultant psychiatrist, Adult ADHD Research Clinic, Department of Psychiatry, University of Cambridge and Peterborough NHS Foundation Trust, Addenbrooke's Hospital, Cambridge; Susan Dunn, Morua founder and chairwoman adult attention deficit disorder UK (AADD-UK), Adult Attention Deficit Disorder UK (AADD-UK), London, and Bristol; Mark Pitts, clinical nurse specialist, Adult ADHD Service, Maudsley Hospital, South London and Maudsley NHS Foundation Trust, London; Johannes Thome, professor of psychiatry, Swansea Medical School, University of Wales, Swansea; Susan Young, senior lecturer in clinical forensic psychology and consultant clinical and forensic psychologist, Department of Forensic Mental Health Science, Institute of Psychiatry, King's College London

**YES** Attention deficit hyperactivity disorder (ADHD) is well established in childhood, with 3.6% of children in the United Kingdom being affected.[1] Most regions have child and adolescent mental health or paediatric services for ADHD. Follow-up studies of children with ADHD find that 15% still have the full diagnosis at 25 years, and a further 50% are in partial remission, with some symptoms associated with clinical and psychosocial impairments persisting.[2]

ADHD is a clinical syndrome defined in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, by high levels of hyperactive, impulsive, and inattentive behaviours in early childhood that persist over time, pervade across situations, and lead to notable impairments. ADHD is thought to result from complex interactions between genetic and environmental factors.[3]

### Proof of validity

Using the Washington University diagnostic criteria, the National Institute for Health and Clinical Excellence (NICE) reviewed the validity of the system used to diagnose ADHD in children and adults.[4,5]

Symptoms of ADHD are reliably identifiable. The symptoms used to define ADHD are found to cluster together in both clinical and population samples. Studies in such samples also separate ADHD symptoms from conduct problems and neurodevelopmental traits. Twin studies show a distinct pattern of genetic and environmental influences on ADHD compared with conduct problems,[6] and overlapping genetic influences between ADHD and neurodevelopmental disorders such as autism and specific reading difficulties.[7,8] Disorders that commonly, but not invariably, occur in adults with ADHD include antisocial personality, substance misuse, and depression.[4]

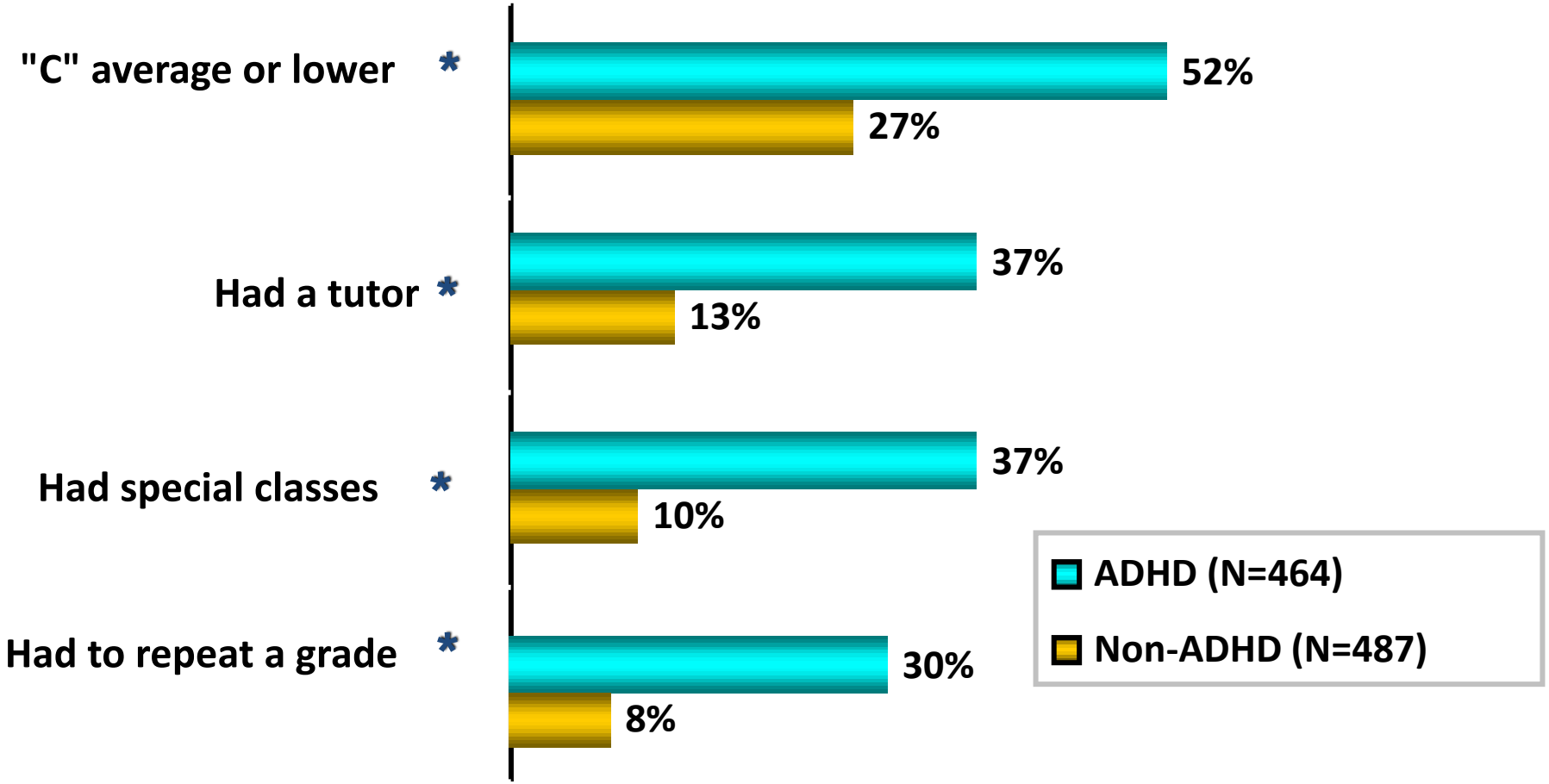
Symptoms of ADHD are continuously distributed throughout the population.[9] As with anxiety and depression, most people have symptoms of ADHD at some time. The disorder is diagnosed by

Joanna Moncrieff senior lecturer and honorary consultant psychiatrist, University College London and North East London Mental Health Trust, UCL Department of Mental Health Sciences, London W1W 7EJ j.moncrieff@ucl.ac.uk
Sami Timimi consultant child and adolescent psychiatrist and

perceptions and variation of diagnosis across sex and class,[3] and serious adverse outcomes being more strongly related to co-occurring problems such as conduct disorder and familial conflict.[4]

# Educational Impairment in High School

## Percentage of Those Who Attended High School

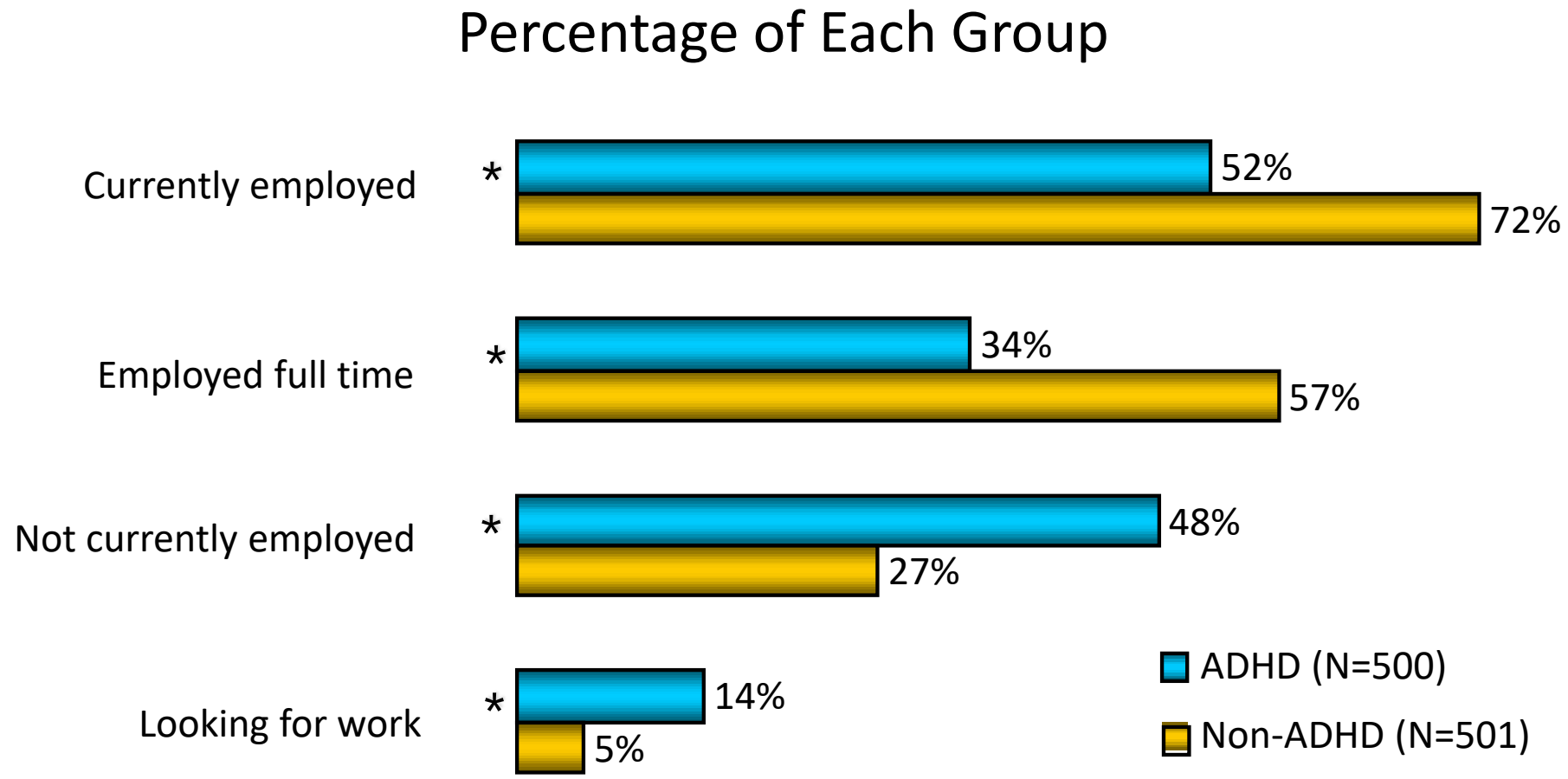



* $p \leq .001$



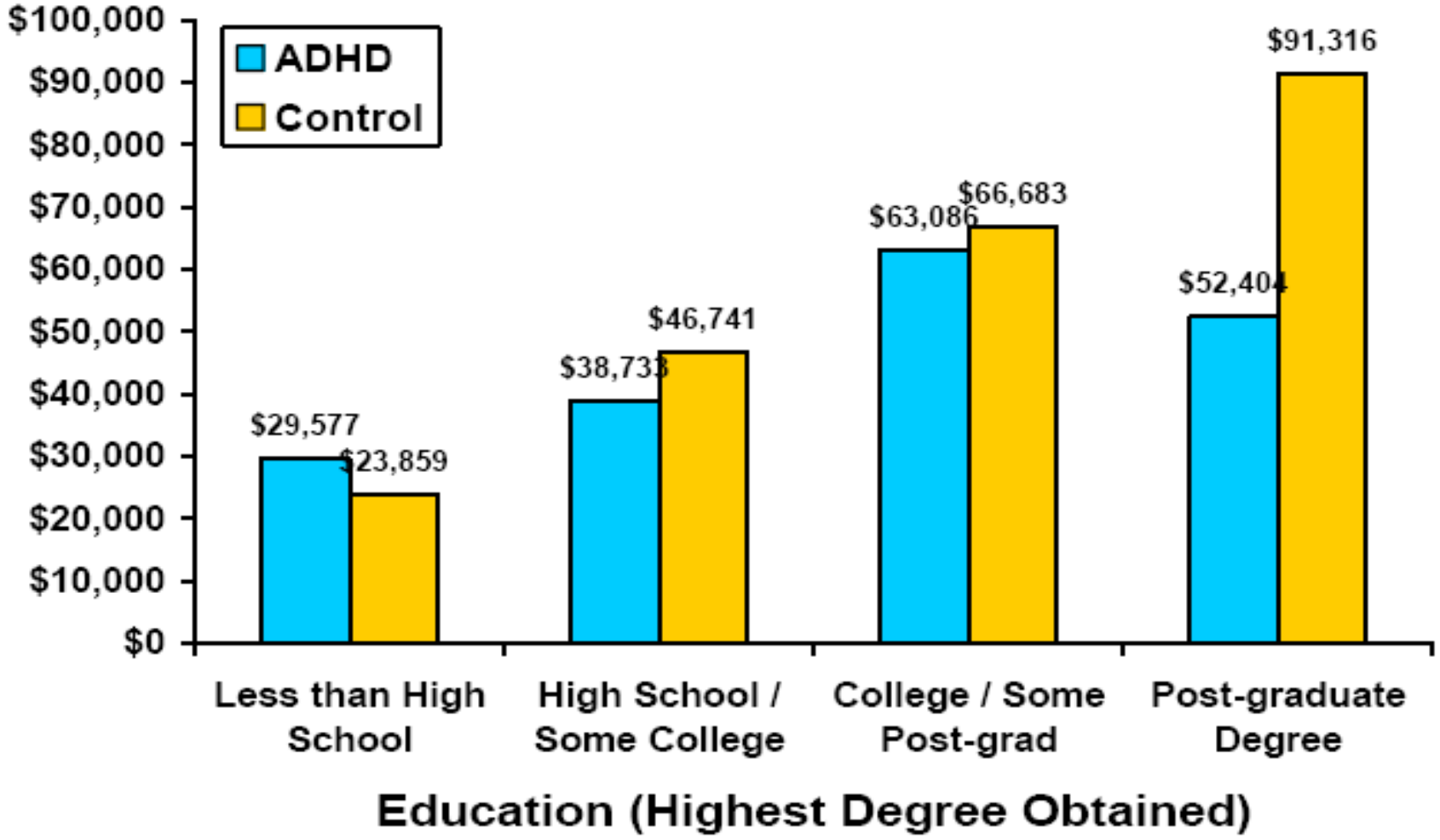
Biederman et al. *J Clin Psychiatry*. 2006 Apr; 67(4):524-40

# Current Employment Status




* $P \leq .001$

# Average Household Income by Education Level Attained



# Mortality in children, adolescents, and adults with attention deficit hyperactivity disorder: a nationwide cohort study

Søren Dalsgaard, Søren Dinesen Østergaard, James F Leckman, Preben Bo Mortensen, Marianne Giørtz Pedersen

## Summary

**Background** Attention deficit hyperactivity disorder (ADHD) is a common mental disorder associated with factors that are likely to increase mortality, such as oppositional defiant disorder or conduct disorder, criminality, accidents, and substance misuse. However, whether ADHD itself is associated with increased mortality remains unknown. We aimed to assess ADHD-related mortality in a large cohort of Danish individuals.

**Methods** By use of the Danish national registers, we followed up 1·92 million individuals, including 32 061 with ADHD, from their first birthday through to 2013. We estimated mortality rate ratios (MRRs), adjusted for calendar year, age, sex, family history of psychiatric disorders, maternal and paternal age, and parental educational and employment status, by Poisson regression, to compare individuals with and without ADHD.

**Findings** During follow-up (24·9 million person-years), 5580 cohort members died. The mortality rate per 10 000 person-years was 5·85 among individuals with ADHD compared with 2·21 in those without (corresponding to a fully adjusted MRR of 2·07, 95% CI 1·70–2·50; p<0·0001). Accidents were the most common cause of death. Compared with individuals without ADHD, the fully adjusted MRR for individuals diagnosed with ADHD at ages younger than 6 years was 1·86 (95% CI 0·93–3·27), and it was 1·58 (1·21–2·03) for those aged 6–17 years, and 4·25 (3·05–5·78) for those aged 18 years or older. After exclusion of individuals with oppositional defiant disorder, conduct disorder, and substance use disorder, ADHD remained associated with increased mortality (fully adjusted MRR 1·50, 1·11–1·98), and was higher in girls and women (2·85, 1·56–4·71) than in boys and men (1·27, 0·89–1·76).

**Interpretation** ADHD was associated with significantly increased mortality rates. People diagnosed with ADHD in adulthood had a higher MRR than did those diagnosed in childhood and adolescence. Comorbid oppositional defiant disorder, conduct disorder, and substance use disorder increased the MRR even further. However, when adjusted for these comorbidities, ADHD remained associated with excess mortality, with higher MRRs in girls and women with ADHD than in boys and men with ADHD. The excess mortality in ADHD was mainly driven by deaths from unnatural causes, especially accidents.

**Funding** This study was supported by a grant from the Lundbeck Foundation.

Dalsgaard, S., Østergaard, S. D., Leckman, J. F., Mortensen, P. B., & Pedersen, M. G. *The Lancet.* 2015; http://dx.doi.org/10.1016/S0140-6736(14)61684-6

# ADHD as a Brain Disorder: Neuroimaging Findings

PRIMER

# Attention-deficit/hyperactivity disorder

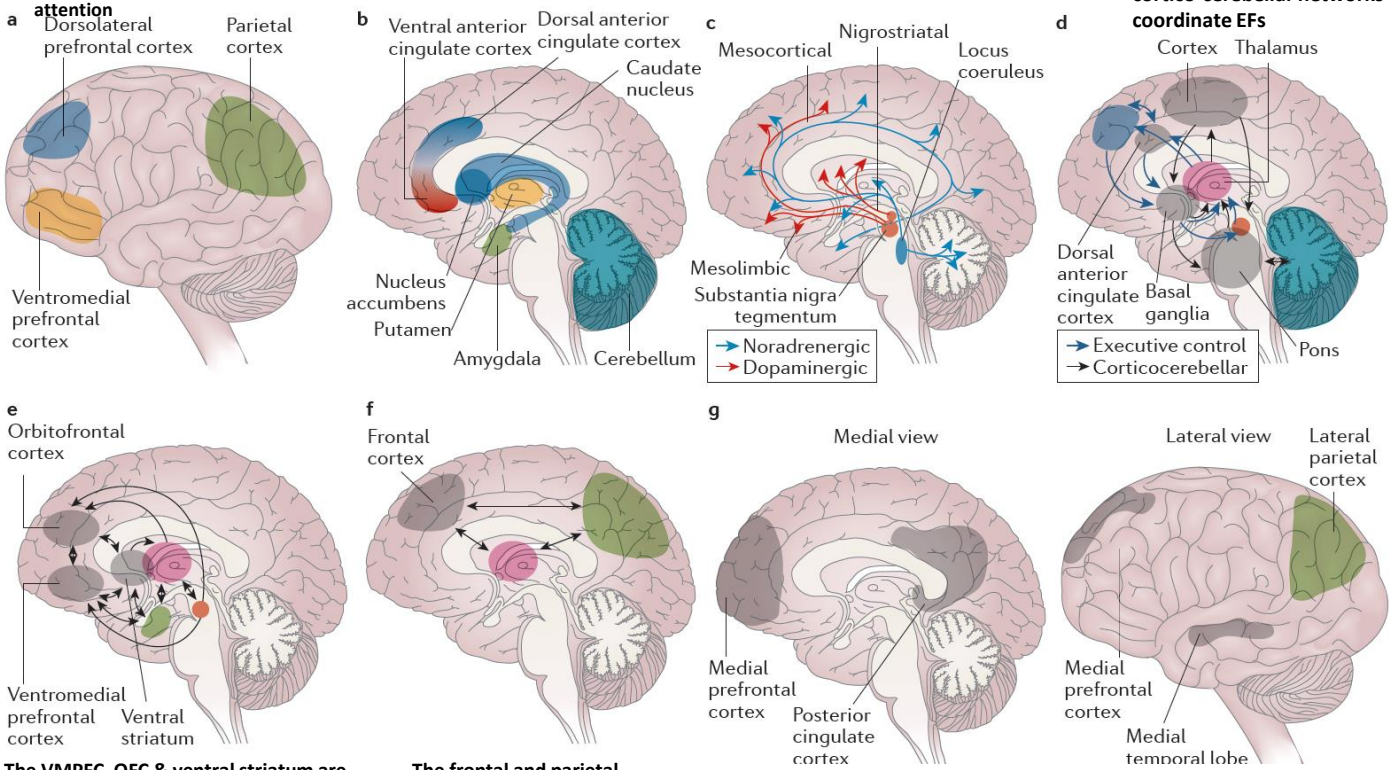
*Stephen V. Faraone[1,2], Philip Asherson[3], Tobias Banaschewski[4], Joseph Biederman[5], Jan K. Buitelaar[6], Josep Antoni Ramos-Quiroga[7–9], Luis Augusto Rohde[10,11], Edmund J. S. Sonuga-Barke[12,13], Rosemary Tannock[14,15] and Barbara Franke[16]*

Abstract | Attention-deficit/hyperactivity disorder (ADHD) is a persistent neurodevelopmental disorder that affects 5% of children and adolescents and 2.5% of adults worldwide. Throughout an individual's lifetime, ADHD can increase the risk of other psychiatric disorders, educational and occupational failure, accidents, criminality, social disability and addictions. No single risk factor is necessary or sufficient to cause ADHD. In most cases ADHD arises from several genetic and environmental risk factors that each have a small individual effect and act together to increase susceptibility. The multifactorial causation of ADHD is consistent with the heterogeneity of the disorder, which is shown by its extensive psychiatric co-morbidity, its multiple domains of neurocognitive impairment and the wide range of structural and functional brain anomalies associated with it. The diagnosis of ADHD is reliable and valid when evaluated with standard criteria for psychiatric disorders. Rating scales and clinical interviews facilitate diagnosis and aid screening. The expression of symptoms varies as a function of patient developmental stage and social and academic contexts. Although there are no curative treatments for ADHD, evidenced-based treatments can markedly reduce its symptoms and associated impairments. For example, medications are efficacious and normally well tolerated, and various non-pharmacological approaches are also valuable. Ongoing clinical and neurobiological research holds the promise of advancing diagnostic and therapeutic approaches to ADHD. For an illustrated summary of this Primer, visit: http://go.nature.com/l6jiwl

Faraone et al. *Nature Reviews Disease Primers* 2015

# Brain Mechanisms in ADHD

**The DLPC is linked to WM, the VMPFC to complex decision making and strategic planning, and the parietal cortex to attention**




**The executive control and cortico-cerebellar networks coordinate EFs**

**The VMPFC, OFC & ventral striatum are the brain network associated with anticipation and reward**

**The frontal and parietal cortices and the thalamus support attentional functioning**

**Negative correlations between the DMN and the frontoparietal control network are weaker in patients with ADHD**



Faraone et al. *Nature Reviews Disease Primers* 2015

# Subcortical brain volume differences in participants with attention deficit hyperactivity disorder in children and adults: a cross-sectional mega-analysis

Martine Hoogman, Janita Bralten, Derrek P Hibar, Maarten Mennes, Marcel P Zwiers, Lizanne S J Schweren, Kimm J E van Hulzen, Sarah E Medland, Elena Shumskaya, Neda Jahanshad, Patrick de Zeeuw, Eszter Szekely, Gustavo Sudre, Thomas Wolfers, Alberdingk M H Onnink, Janneke T Dammers, Jeanette C Mostert, Yolanda Vives-Gilabert, Gregor Kohls, Eileen Oberwelland, Jochen Seitz, Martin Schulte-Rüther, Sara Ambrosino, Alysa E Doyle, Marie F Høvik, Margaretha Dramsdahl, Leanne Tamm, Theo G M van Erp, Anders Dale, Andrew Schork, Annette Conzelmann, Kathrin Zierhut, Ramona Baur, Hazel McCarthy, Yuliya N Yoncheva, Ana Cubillo, Kaylita Chantiluke, Mitul A Mehta, Yannis Paloyelis, Sarah Hohmann, Sarah Baumeister, Ivanei Bramati, Paulo Mattos, Fernanda Tovar-Moll, Pamela Douglas, Tobias Banaschewski, Daniel Brandeis, Jonna Kuntsi, Philip Asherson, Katya Rubia, Clare Kelly, Adriana Di Martino, Michael P Milham, Francisco X Castellanos, Thomas Frodl, Mariam Zentis, Klaus-Peter Lesch, Andreas Reif, Paul Pauli, Terry L Jernigan, Jan Haavik, Kerstin J Plessen, Astri J Lundervold, Kenneth Hugdahl, Larry J Seidman, Joseph Biederman, Nanda Rommelse, Dirk J Heslenfeld, Catharina A Hartman, Pieter J Hoekstra, Jaap Oosterlaan, Georg von Polier, Kerstin Konrad, Oscar Vilarroya, Josep Antoni Ramos-Quiroga, Joan Carles Soliva, Sarah Durston, Jan K Buitelaar, Stephen V Faraone, Philip Shaw, Paul M Thompson, Barbara Franke

**Interpretation** With the largest dataset to date, we add new knowledge about bilateral amygdala, accumbens, and hippocampus reductions in ADHD. We extend the brain maturation delay theory for ADHD to include subcortical structures and refute medication effects on brain volume suggested by earlier meta-analyses. Lifespan analyses suggest that, in the absence of well powered longitudinal studies, the ENIGMA cross-sectional sample across six decades of ages provides a means to generate hypotheses about lifespan trajectories in brain phenotypes.

collaboration, which in the present analysis was frozen at Feb 8, 2015. Individual sites analysed structural T1-weighted MRI brain scans with harmonised protocols of individuals with ADHD compared with those who do not have this diagnosis. Our primary outcome was to assess case-control differences in subcortical structures and intracranial volume through pooling of all individual data from all cohorts in this collaboration. For this analysis, p values were significant at the false discovery rate corrected threshold of p=0·0156.

Department of Human Genetics (M Hoogman PhD, J Bralten PhD, K J E van Hulzen PhD, E Shumskaya PhD, T Wolfers MSc, A M H Onnink PhD, J C Mostert PhD, Prof B Franke PhD), Department

Hoogman at el. (ENIGMA ADHD Working Group) *Lancet Psychiatry* 2017 Feb 16. doi: 10.1016/S2215-0366(17)30049-4.

REVIEW ARTICLE

# Effect of Psychostimulants on Brain Structure and Function in ADHD: A Qualitative Literature Review of Magnetic Resonance Imaging–Based Neuroimaging Studies

*Thomas J. Spencer, MD; Ariel Brown, PhD; Larry J. Seidman, PhD; Eve M. Valera, PhD; Nikos Makris, MD; Alexandra Lomedico, BA; Stephen V. Faraone, PhD; and Joseph Biederman, MD*

# ADHD Imaging Studies Summary

- Neuroimaging studies confirm that brain abnormalities in fronto-subcortical networks are associated with ADHD
- Neuroimaging techniques are not valid tools for ADHD diagnosis; imaging measures are not sensitive or specific enough to be used for diagnostic purposes
- Treatment attenuate neural deficits

Spencer et al. *J Clin Psychiatry* 2013 Sep;74(9):902-17.

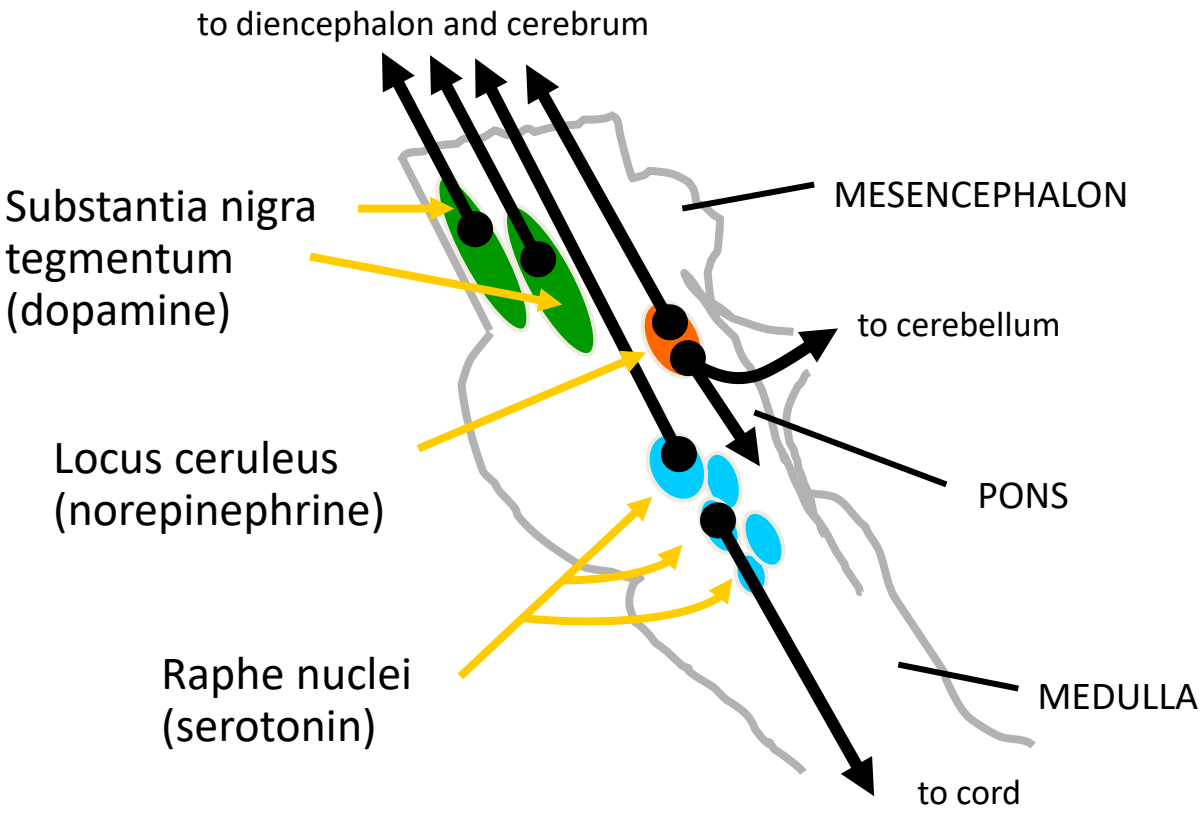
# ADHD as a Neurobiological Disorder: Catecholamine Dysregulation

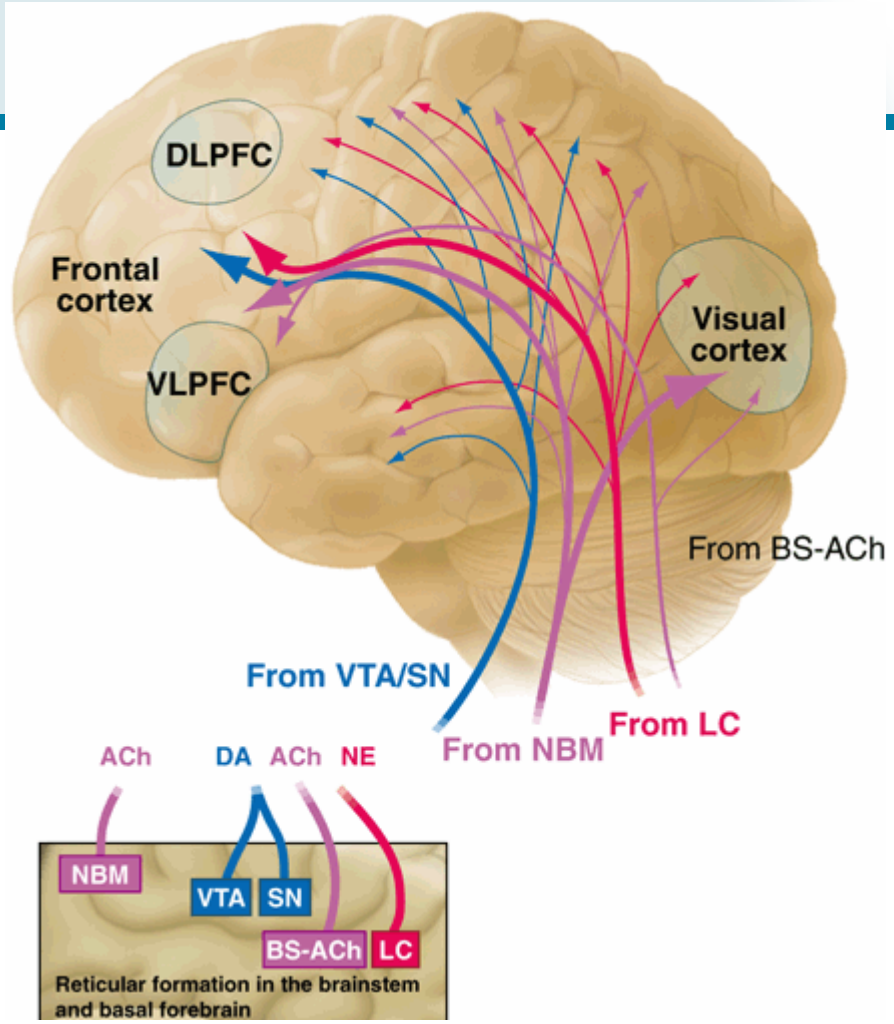
# Frontosubcortical Networks and Catecholamines

- Dopaminergic and noradrenergic dysregulation abnormalities in fronto subcortical pathways
- Medications that are effective in ADHD are either dopaminergic or noradrenergic

Zametkin. *J Am Acad Child Adolesc Psychiatry.* 1987;26(5):676-686

# Brain Stem

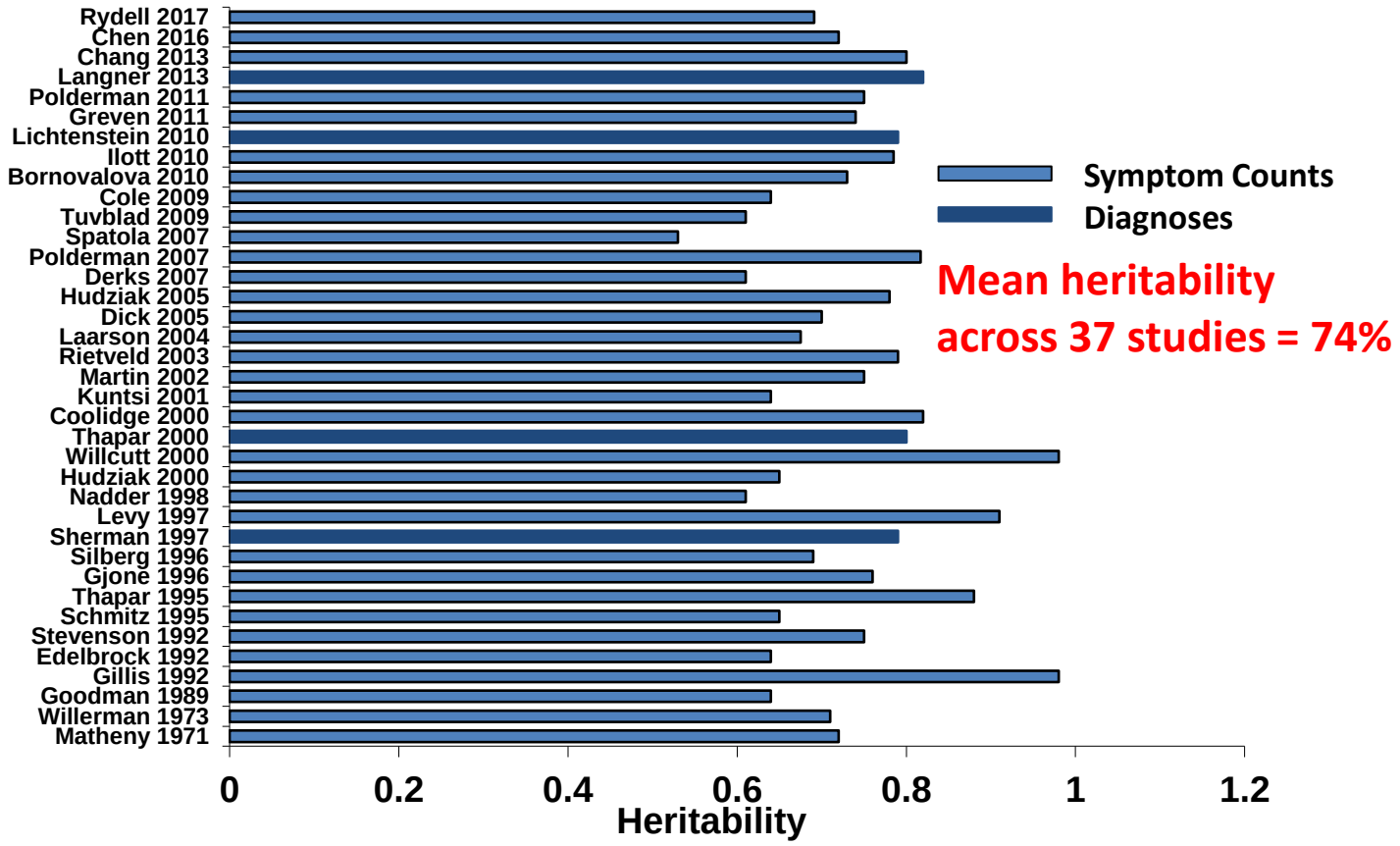

to diencephalon and cerebrum
Substantia nigra tegmentum (dopamine)
MESENCEPHALON
to cerebellum
Locus ceruleus (norepinephrine)
PONS
Raphe nuclei (serotonin)
MEDULLA
to cord


DLPFC
Frontal cortex
VLPFC
Visual cortex
From BS-ACh
From VTA/SN
From NBM
From LC
ACh
DA
ACh
NE
NBM
VTA
SN
BS-ACh
LC
Reticular formation in the brainstem and basal forebrain

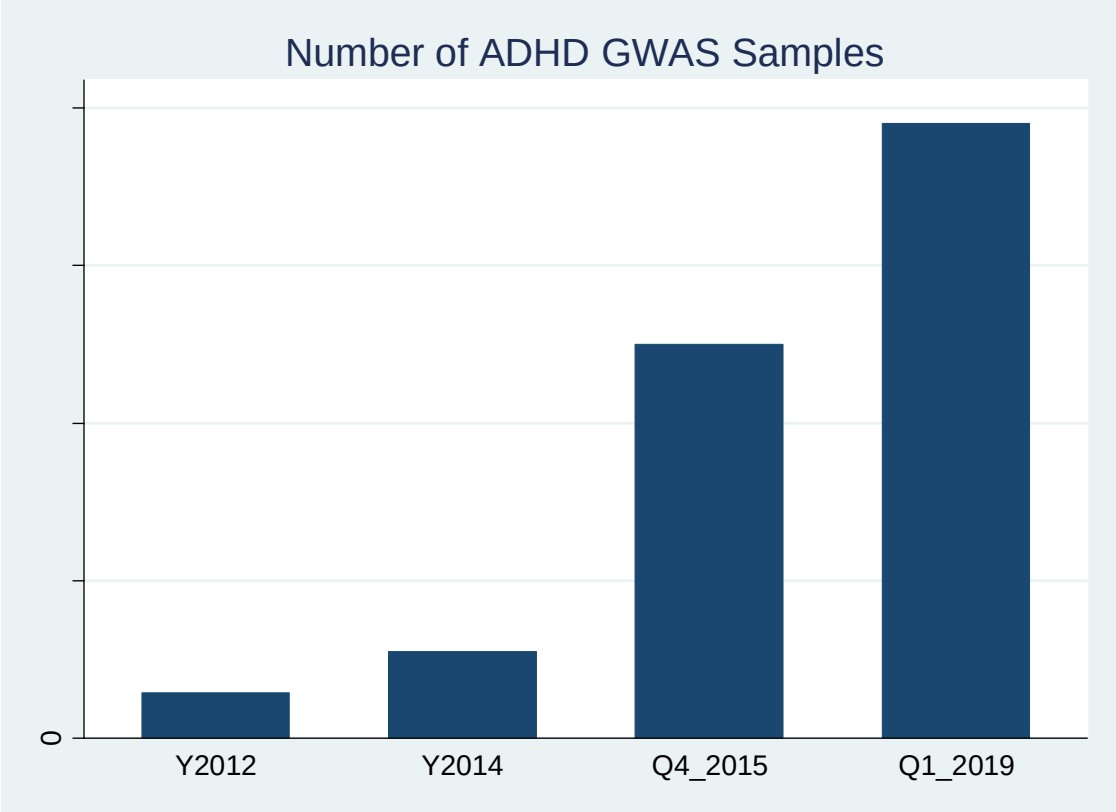
# ADHD as a Neurobiological Disorder: Genetic Findings

# Twin Studies of ADHD

**(Faraone & Larsson, Molecular Psychiatry, 2018)**

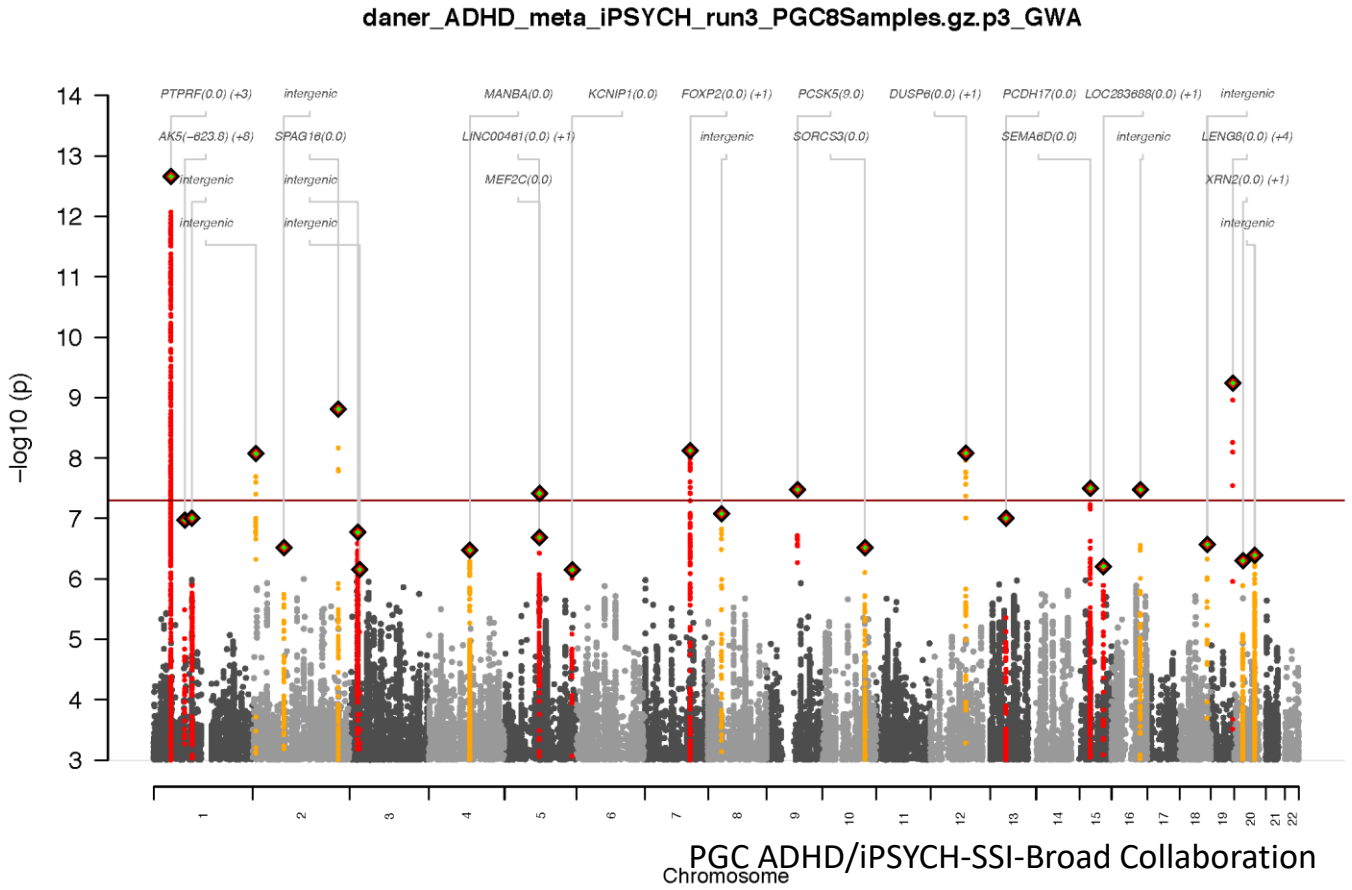


# New Results from Genome-wide Association Studies (GWAS)



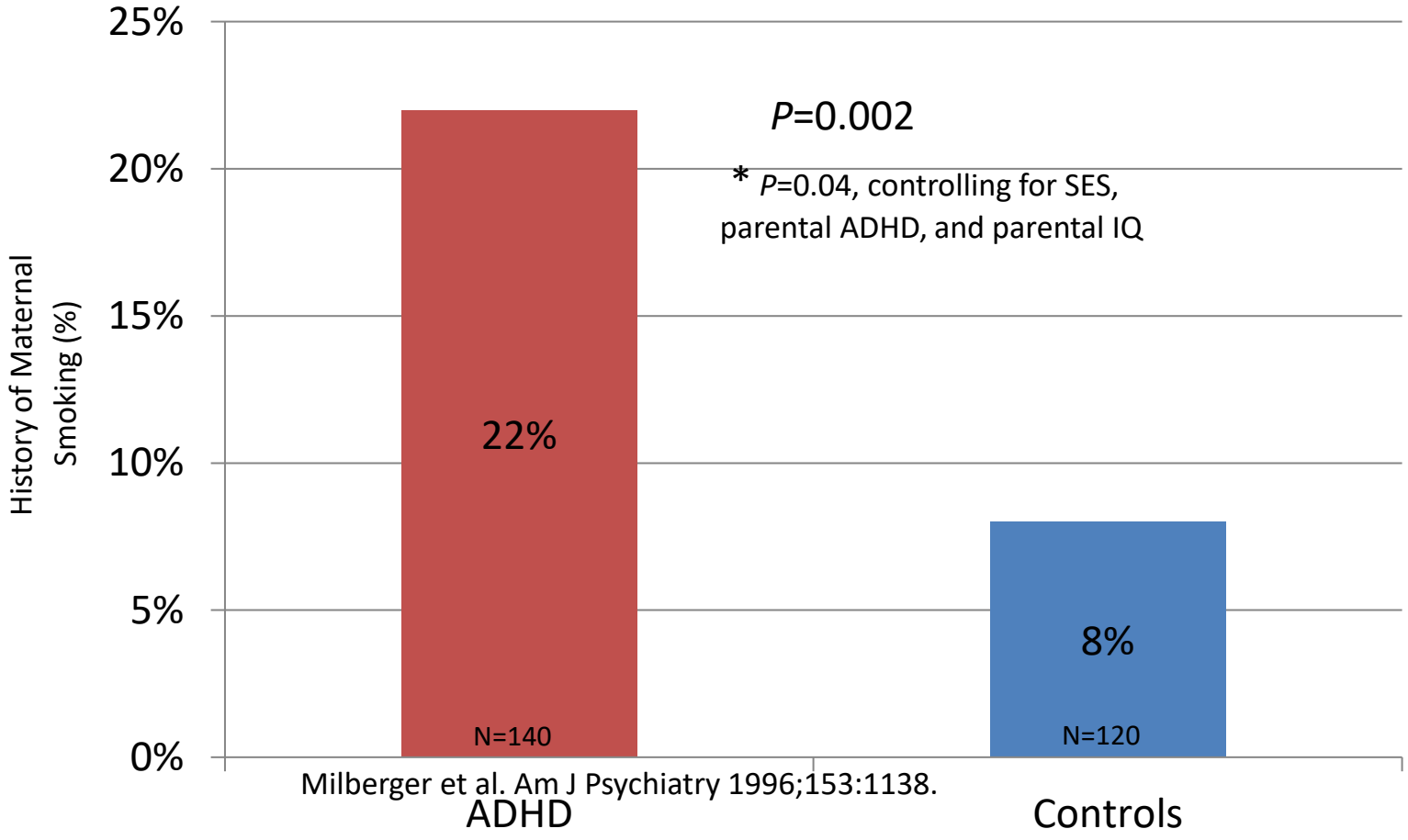

Faraone et al, 2015

# Preliminary ADHD meta-analysis 18,284 cases 33,836 controls



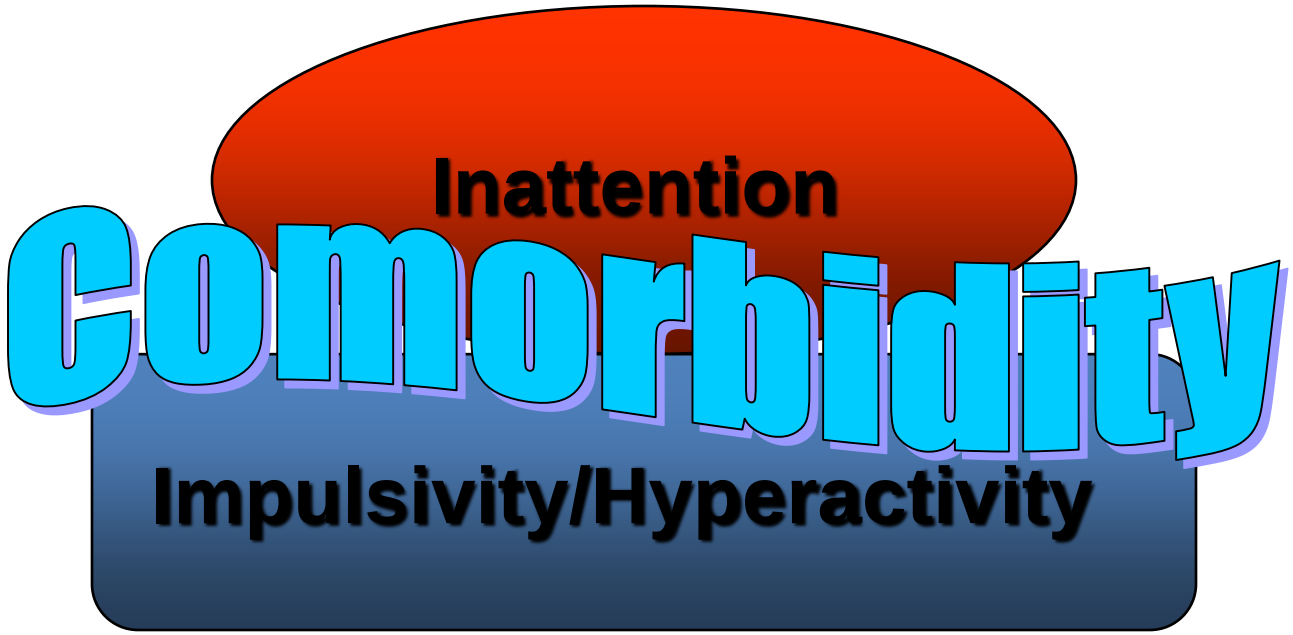

PGC ADHD/iPSYCH-SSI-Broad Collaboration

# Maternal Smoking During Pregnancy: Results in Children

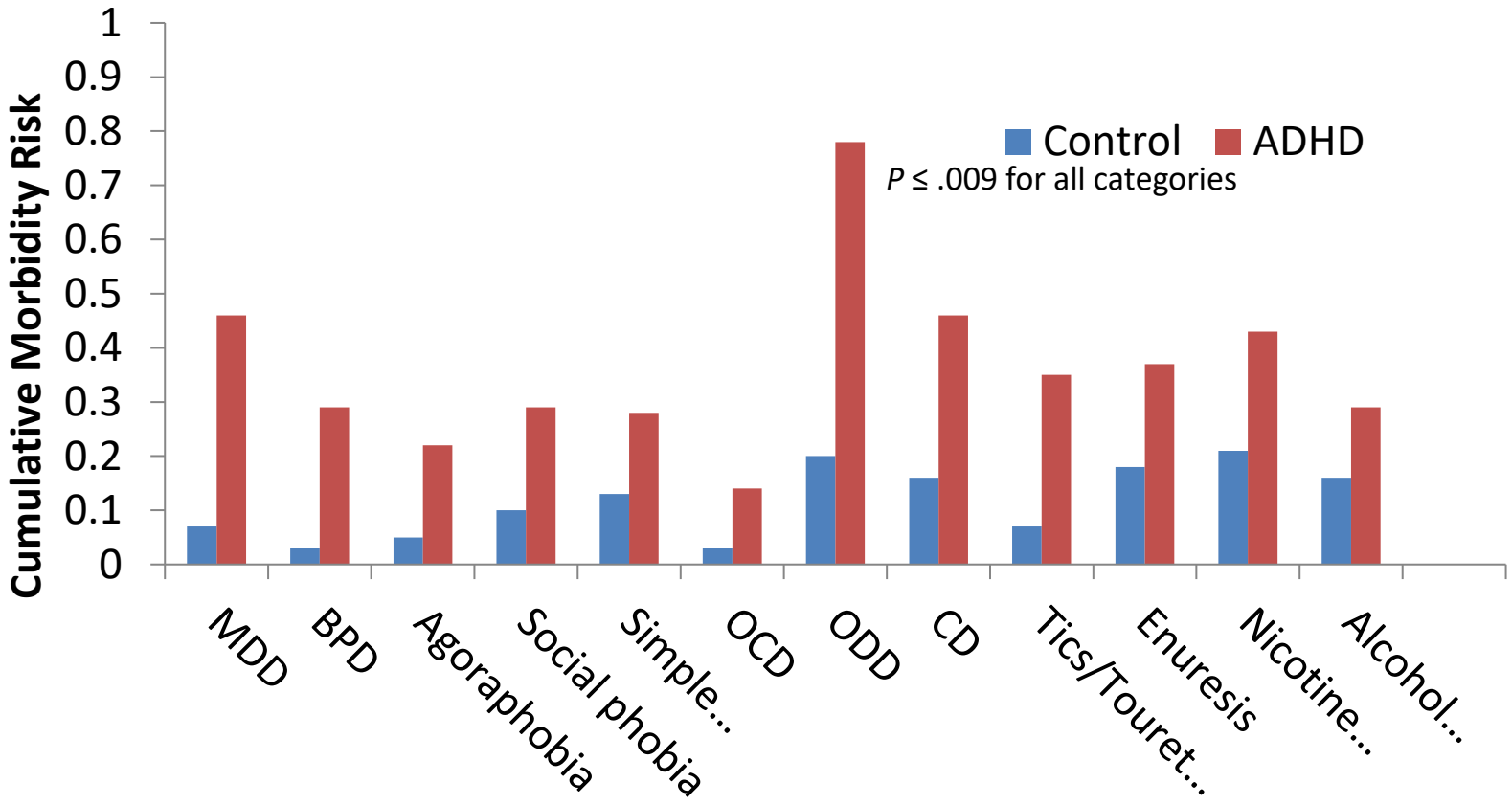



Milberger et al. Am J Psychiatry 1996;153:1138.

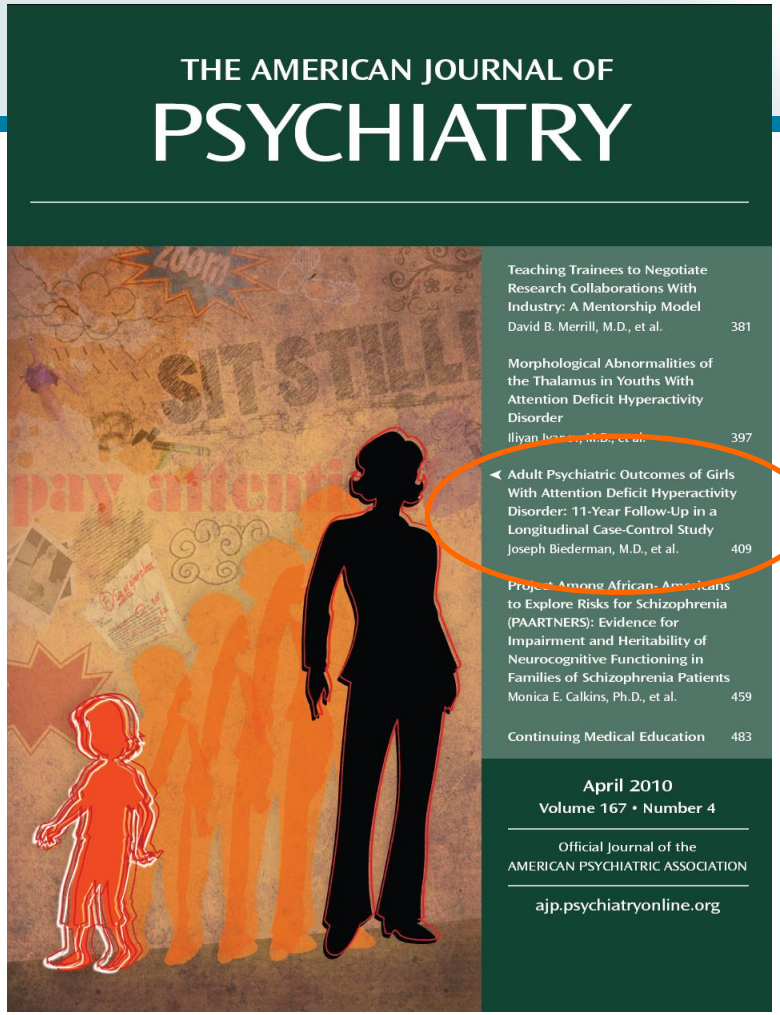
# ADHD Diagnostic Considerations



# Cumulative Morbidity Risks for Psychiatric Disorders in ADHD and Control Probands

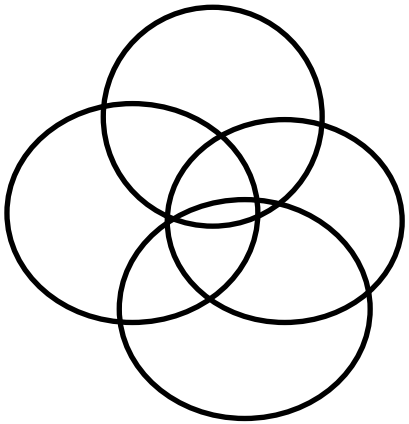



Biederman et al. *Psychological Medicine*, 2006, 36, 167–179.




Biederman et al.
*AJP.* April 2010

# ADHD Comorbidity in Other Psychiatric Disorders



| Disorder | ADHD Rate |
|---|---|
| Major Depression[1] | 20% |
| Bipolar Disorder[2] | 15% |
| Generalized Anxiety Disorders[3] | 20% |
| Substance Abuse[4] | 25% |

Re-evaluate refractory patients for ADHD.


1. Alpert, et al. *Psychiatry Res.* 1996.
2. Nierenberg, et al. Presented at: APA; May 18-23, 2002; Philadelphia, Pa.
3. Fones, et al. *J Affective Dis.* 2000
4. Wilens. *Psych Clin N Am.* 2004.

# ADHD is a Highly Treatable Disorder

- ADHD is among the most treatable of all psychiatric disorders
- Stimulants are among the most effective treatments in medicine with effect sizes of 1
- Studies show that many of ADHD-associated poor outcomes can be mitigated by treatment with stimulants

# Literature Review of Registries and Large Databases Examining the Effects of Stimulants on Functional Outcome

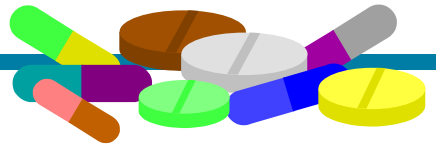
# Summary of Results

- The majority of the N=40 articles identified document a robust protective effect of ADHD medications on **mood disorders, suicidality, criminality, substance use disorders, accidents and injuries, traumatic brain injuries, motor vehicle crashes, and educational outcomes**
- Similarly, the meta-analyses demonstrated an overall protective effect of medication treatment on these functional outcomes

# Pharmacotherapy of ADHD

- ADHD remains the most treatable disorder in Psychiatry
- Stimulants (amphetamines and methylphenidate compounds) remain the mainstay of treatment for ADHD due to their robust (High Effect Size) efficacy and safety
- FDA-approved Non Stimulants (Atomoxetine and Alpha-2 Agonist (guanfacine and clonidine extended release) are generally less effective than the stimulants (moderate effect sizes of 0.4-0.6)

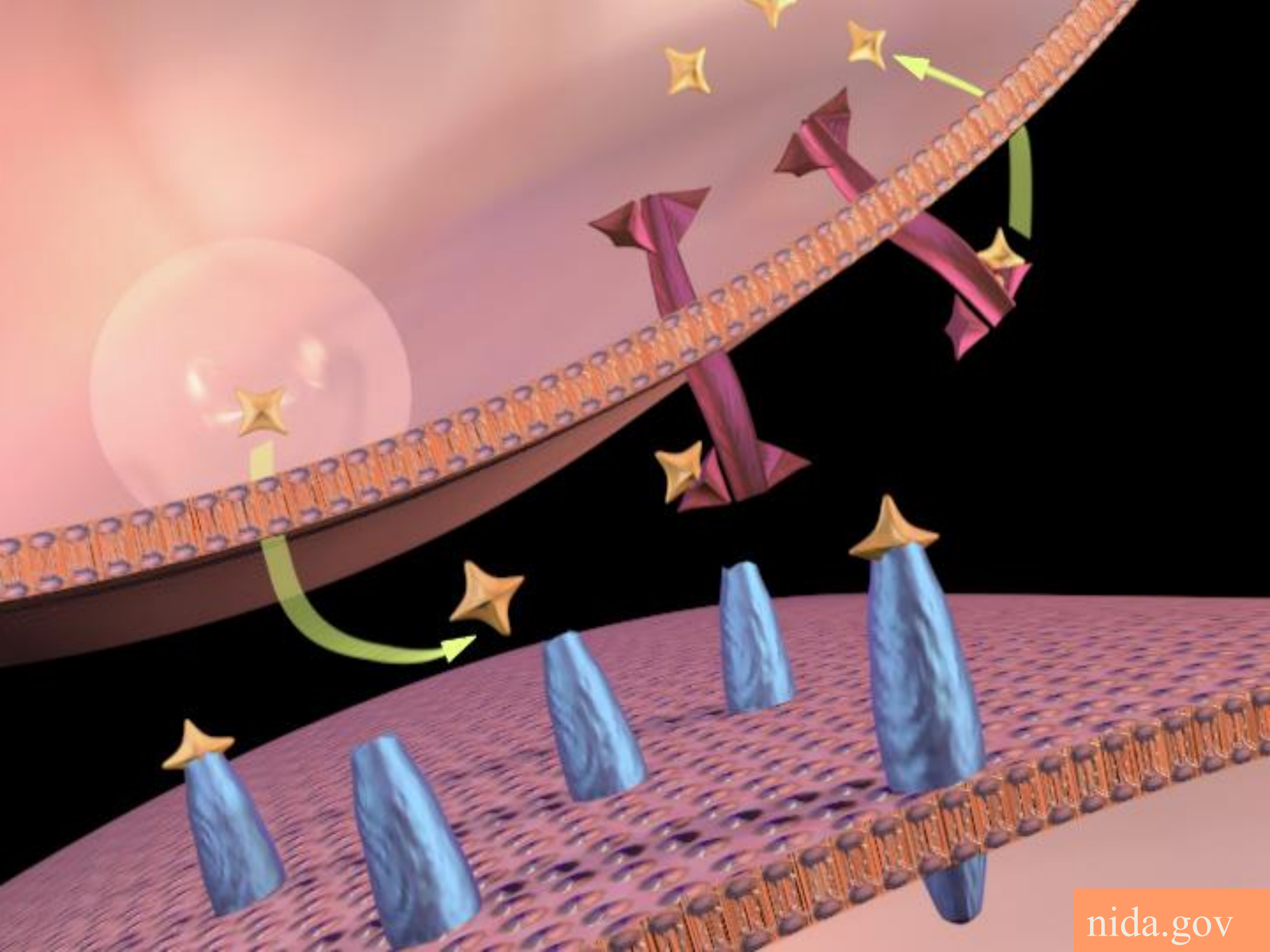
# Pharmacotherapy for ADHD



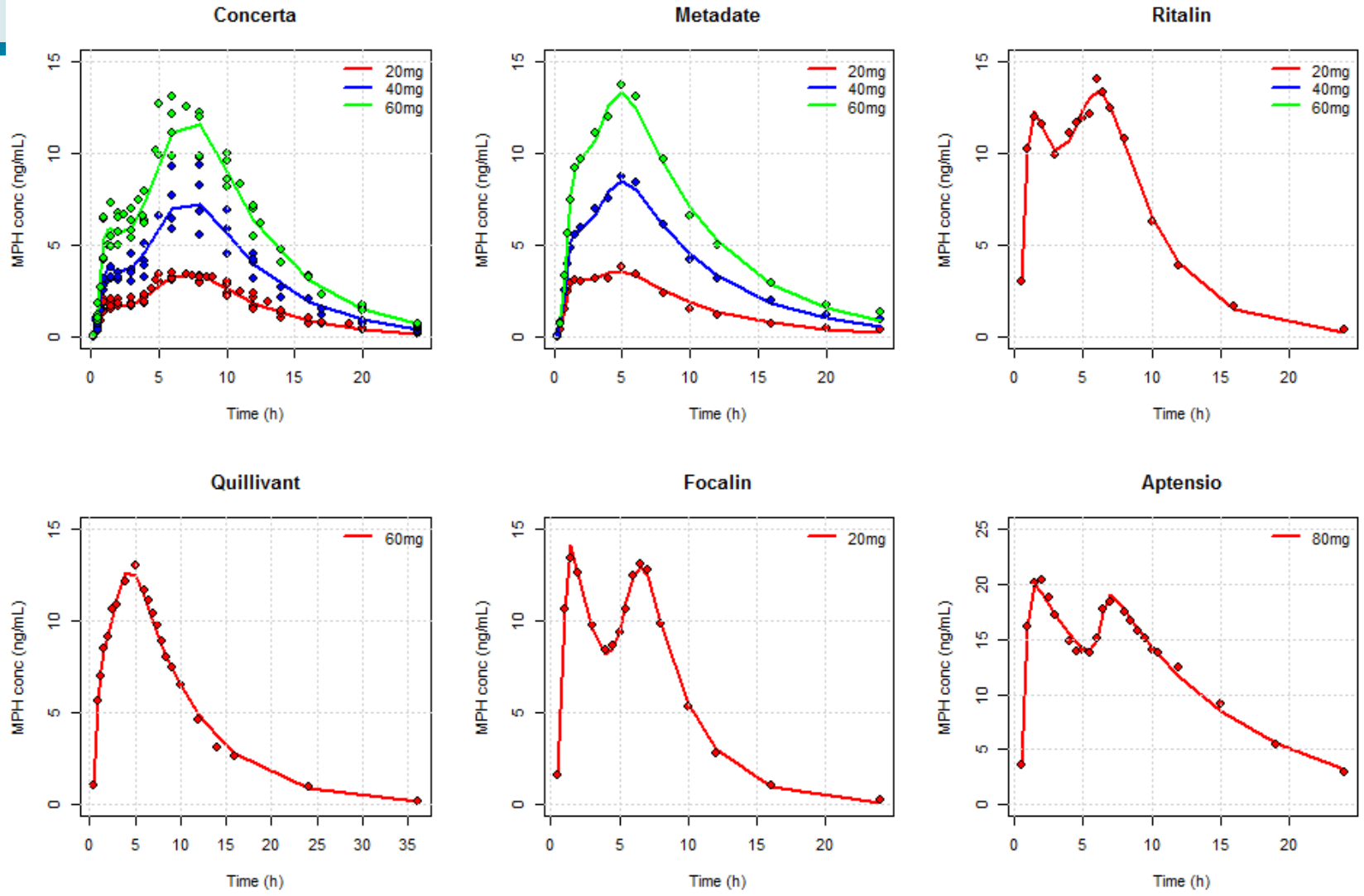
- Stimulants (FDA Approved)
  - Methylphenidate
  - Amphetamine compounds
- Atomoxetine (FDA Approved)
- Alpha Agonists (FDA Approved [peds])
  - Guanfacine (XR)
  - Clonidine (XR)
- Combination Therapy (FDA Approved)

ADHD in Children & Adults. Adler, Spencer, Wilens (eds), Cambridge Press; 2015

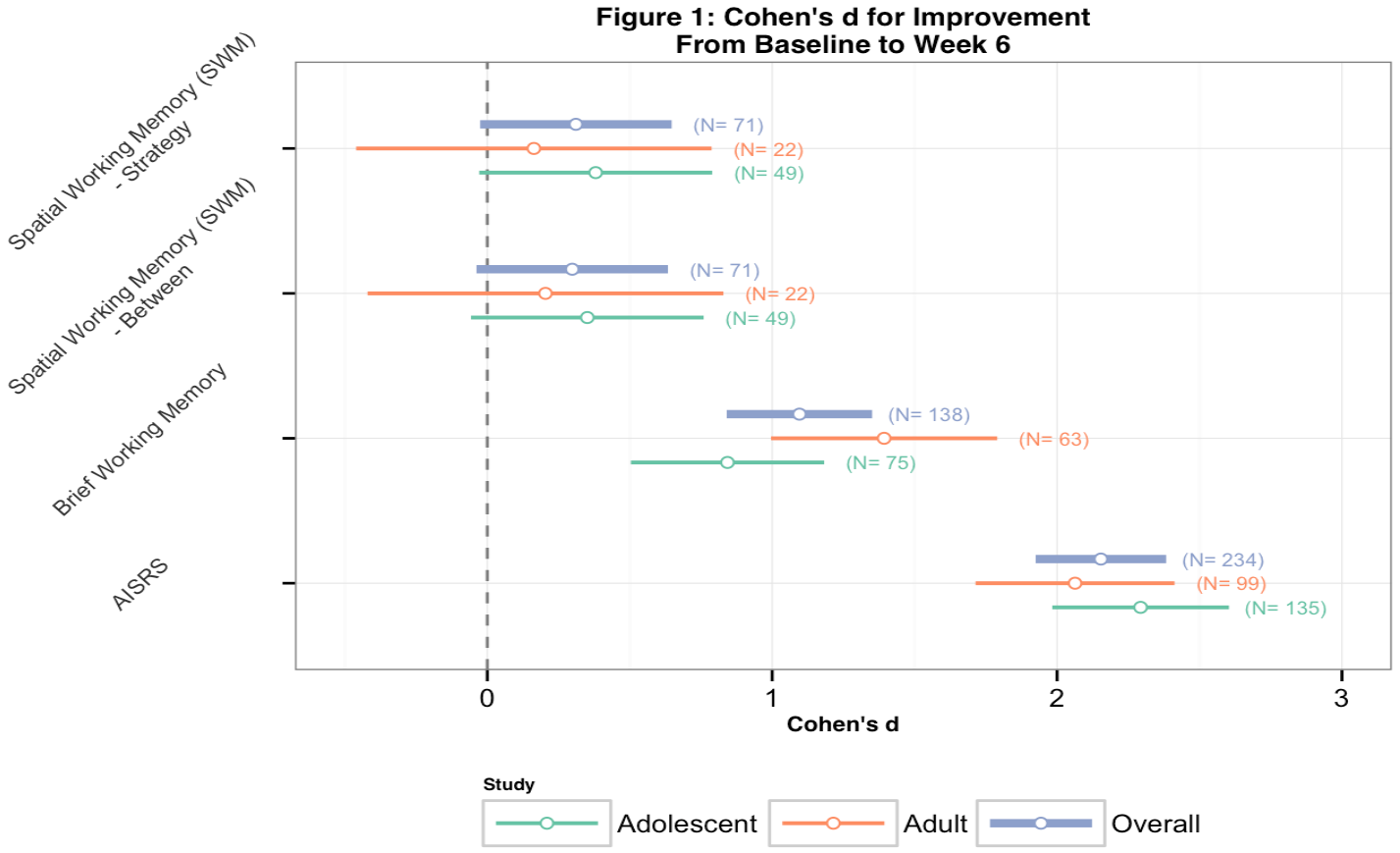
# Stimulants



# Long Acting MPH formulations

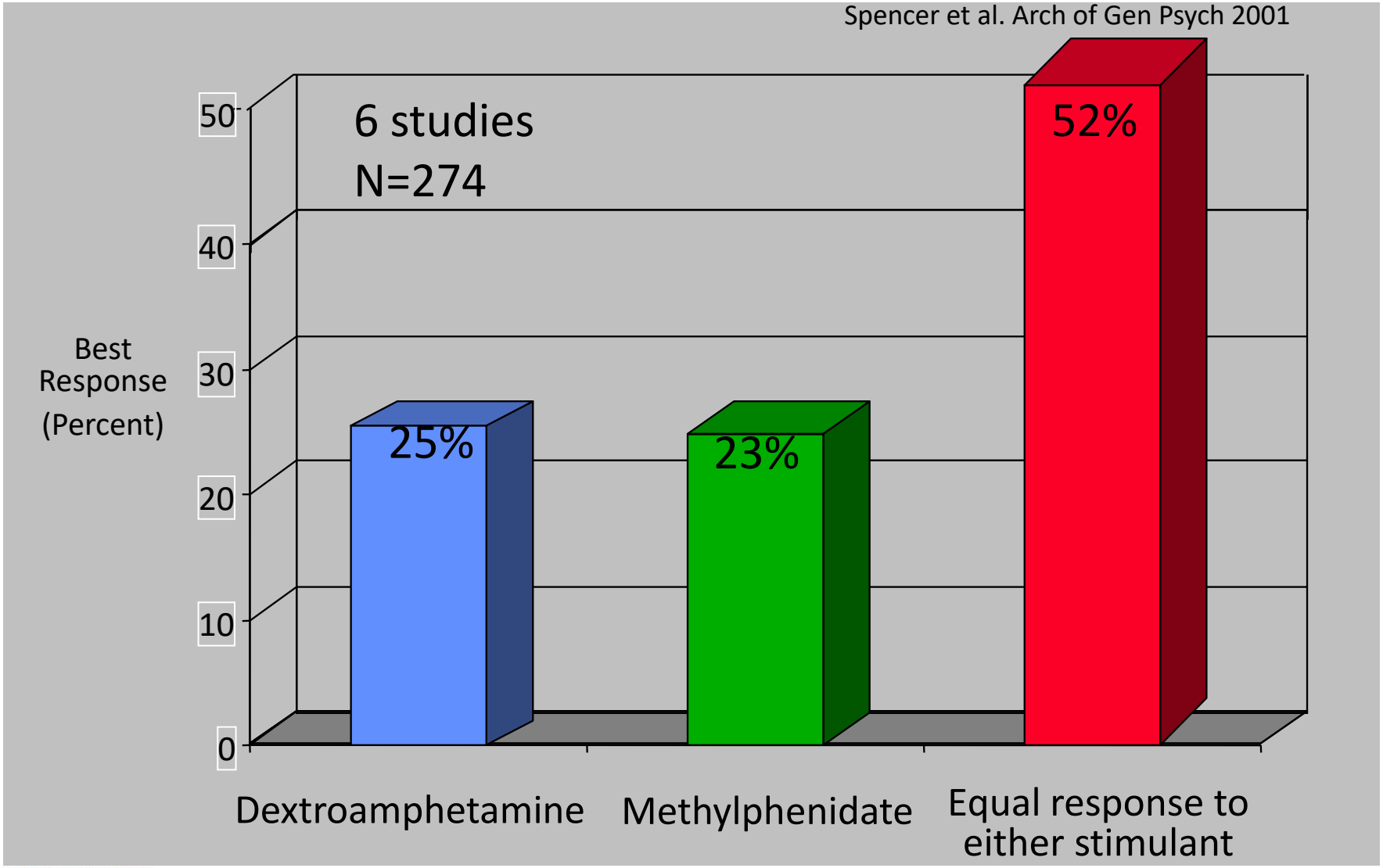


# Pharmacological Dissociation Between The Robust Effects Of Methylphenidate On ADHD Symptoms And Weaker Effects On Working Memory




**Biederman et al. Eur Neuropsychopharmacol 2011**

# Meta-analysis of Within-Subject Comparative Trials Evaluating Response to Stimulant Medications



# Adverse Effects of Stimulants

- Adverse effects (AEs) are similar for all stimulants
  - Decreased appetite
  - Insomnia
  - Headache
  - Stomachache
  - Irritability/rebound phenomena
- Rates of these AEs may be high prior to any medical intervention; thus, baseline levels should always be obtained

ORIGINAL CONTRIBUTION

ONLINE FIRST

# ADHD Medications and Risk of Serious Cardiovascular Events in Young and Middle-aged Adults

Laurel A. Habel, PhD
William O. Cooper, MD, MPH
Colin M. Sox, MD, MS
K. Arnold Chan, MD, ScD
Bruce H. Fireman, MA
Patrick G. Arbogast, PhD

**Context** More than 1.5 million US adults use stimulants and other medications labeled for treatment of attention-deficit/hyperactivity disorder (ADHD). These agents can increase heart rate and blood pressure, raising concerns about their cardiovascular safety.

**Objective** To examine whether current use of medications prescribed primarily to treat ADHD is associated with increased risk of serious cardiovascular events in young and middle-aged adults.

**Design, Setting, and Participants** Retrospective, population-based cohort study

**Results** During 806 182 person-years of follow-up (median, 1.3 years per person), 1357 cases of MI, 296 cases of SCD, and 575 cases of stroke occurred. There were 107 322 person-years of current use (median, 0.33 years), with a crude incidence per 1000 person-

**Conclusions** Among young and middle-aged adults, current or new use of ADHD medications, compared with nonuse or remote use, was not associated with an increased risk of serious cardiovascular events. Apparent protective associations likely represent healthy-user bias.

1.24); for new use vs remote use, the adjusted RR was 1.02 (95% CI, 0.82-1.28); the upper limit of 1.28 corresponds to an additional 0.19 events per 1000 person-years at ages 25-44 years and 0.77 events per 1000 person-years at ages 45-64 years.

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**Conclusions** Among young and middle-aged adults, current or new use of ADHD medications, compared with nonuse or remote use, was not associated with an increased risk of serious cardiovascular events. Apparent protective associations likely represent healthy-user bias.

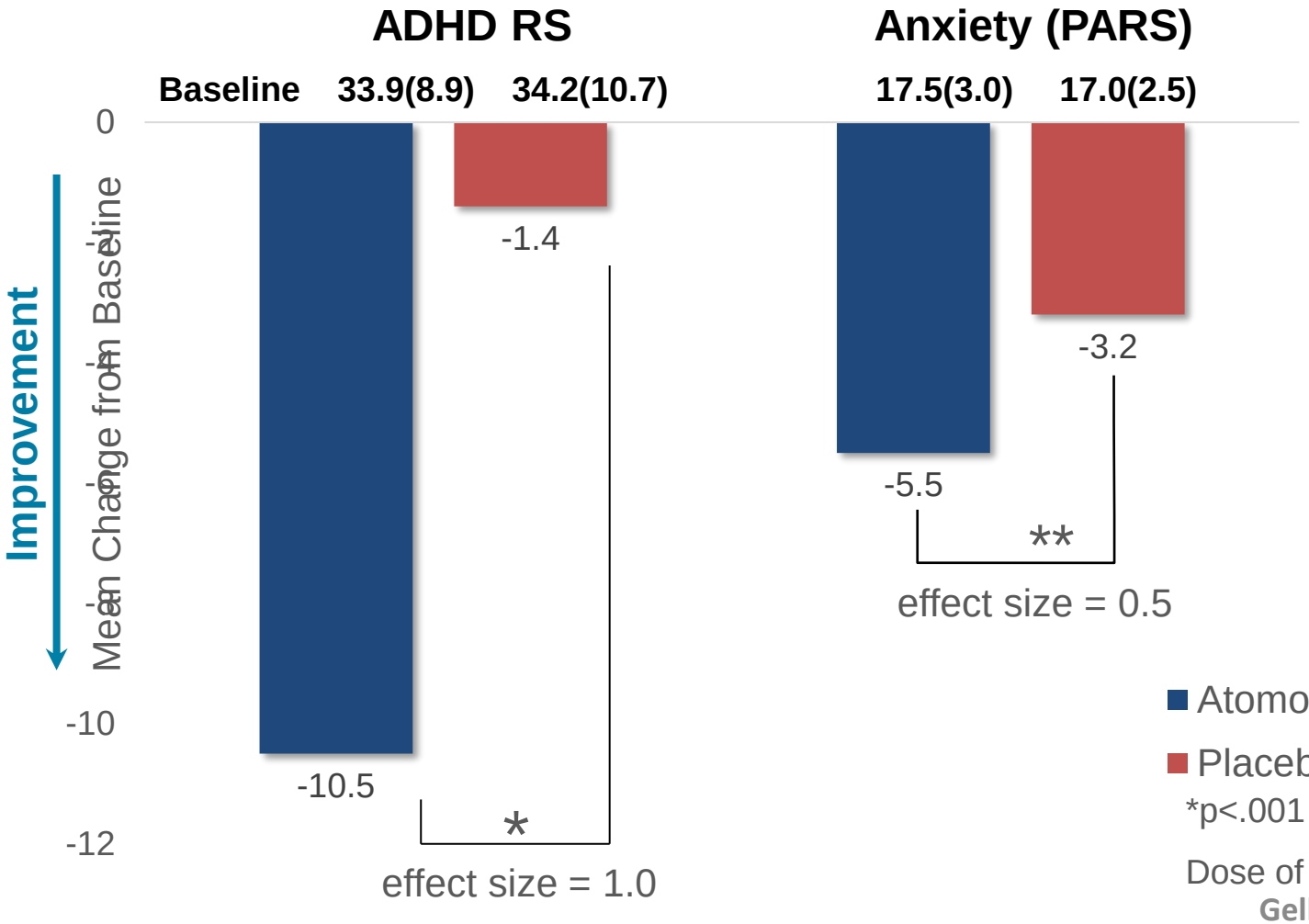
*JAMA. 2011;306(24):doi:10.1001/jama.2011.1830* www.jama.com

# Non-Stimulants

# Atomoxetine

- FDA approval across the lifespan
- Efficacy as monotherapy
- No concerns of diversion
- Comorbid ADHD plus
  - Oppositional disorder
  - Anxiety
  - Tics
  - Substance use disorders

# Atomoxetine Improves Anxiety and ADHD in Youth with ADHD & Anxiety




Atomoxetine (N=55)

Placebo (N=58)

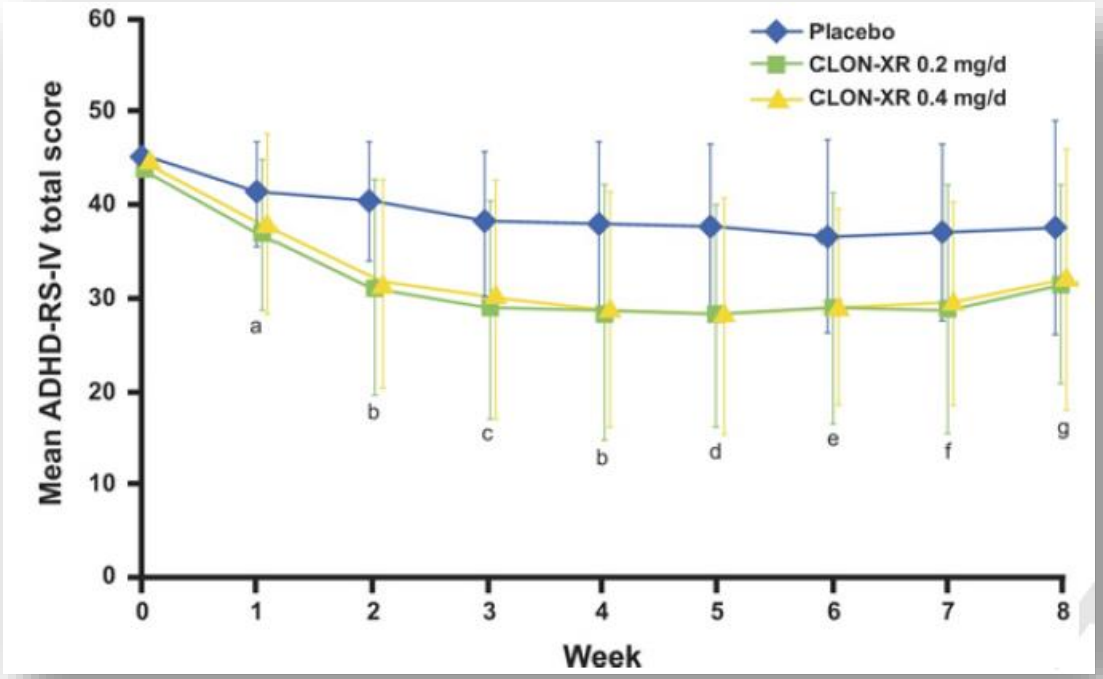
*p<.001 **p=.011

Dose of ATMX = 1.26 mg/kg/day

**Geller et al. JAACAP 2007**

# Extended Release Clonidine for ADHD

**Mean ADHD Rating Scale—IV (ADHD-RS-IV) total score from baseline to Week 5, using a last observation carried forward (LOCF) method:**

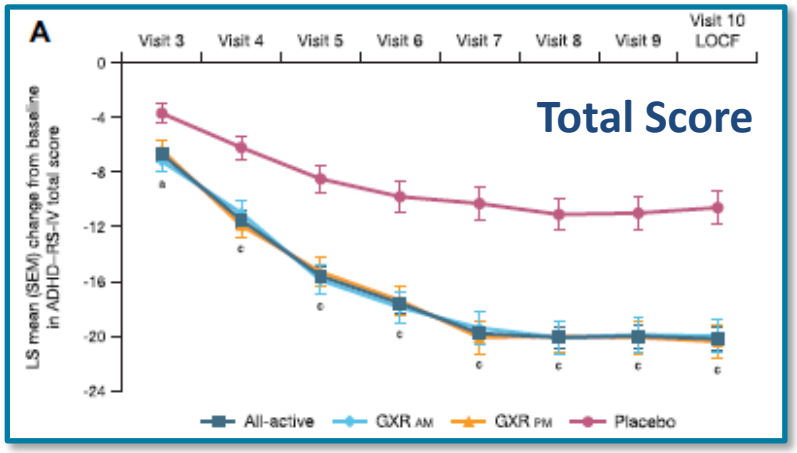


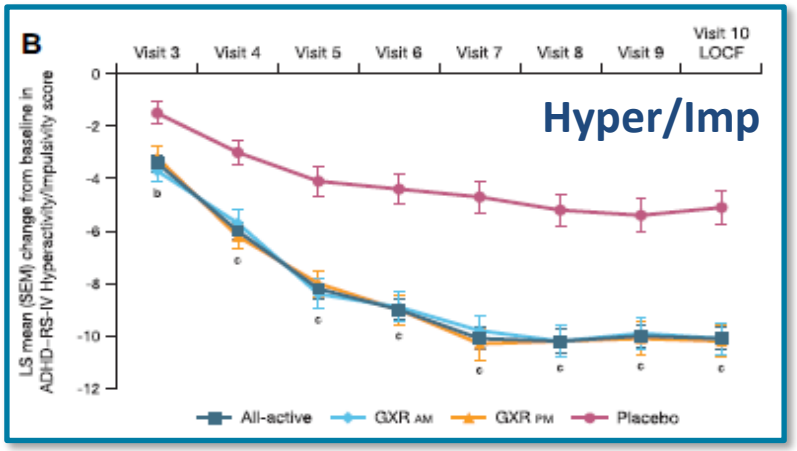

Note: ADHD-RS-IV total score was significantly improved at week 1 for the CLON-XR 0.2-mg/day group. Significant improvement was achieved in both CLON-XR groups beginning at week 2 and continued through study termination. Error bars represent standard deviations. CLON-XR= clonidine hydrochloride extended-release tablets; [a] $p = .0219$ for CLON-XR 0.2 mg/day. [b] $p < .0001$ for both groups. [c] $p < .0003$ for both groups. [d] $p = .0005$ for both groups. [e] $p < .0054$ for both groups. [f] $p < .0074$ for both groups. [g] $p \leq .0288$ for both groups.

N=236; 61% completion rate

Jain et al. JAACAP epub 2011

# Equal Efficacy with Guanfacine XR AM versus PM Administration




**6 to 12 years,**
**dosing 1 to 4 mg/day.**
**GXR AM (n=107),**
**GXR PM (n=114), or**
**placebo (n=112).**

Newcorn JH, et al. *J Am Acad Child Adolesc Psychiatry*. 2013; 52(9):921-930.

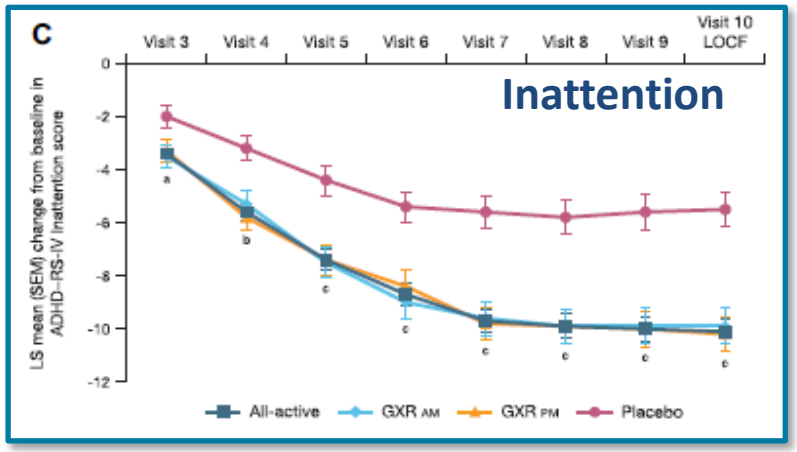



**FIGURE 2** Mean change from baseline in attention-deficit/hyperactivity disorder (ADHD) Rating Scale–IV (ADHD-RS-IV) scores by visit. Note: (A) Total score. (B) Hyperactivity/Impulsivity subscale. (C) Inattention subscale. All *p* values are based on type III sum of squares from an analysis of covariance (ANCOVA) model. GXR = guanfacine extended release; LOCF = last observation carried forward; LS = least squares; SEM = standard error of the mean. [c]$p < .05$ versus placebo based on change from baseline (visit 2). [b]$p < .01$ versus placebo based on change from baseline (visit 2). [c]$p < .001$ versus placebo based on change from baseline (visit 2).

# Summary: Non-Stimulant Pharmacotherapy of ADHD

- A number of non-stimulant medications for ADHD
- Lower effect size than stimulants
- A variety of effective drugs
  - Noradrenergic agents (ATMX) -(FDA Approved)
  - Alpha agonists - FDA approved, used in adol and adults
- Often slow onset-of-action for ADHD
- Useful in comorbidity
- FDA approval on co-administration with stimulants
- Multiple 'pipeline' nonstimulants in development

# Summary

- ADHD is a neurobehavioral disorder with a:
  - Complex etiology
  - Neurobiologic basis
  - Strong genetic component
- ADHD
  - Affects millions of people of both genders
  - Persists through adolescence and adulthood in a high percentage of cases
  - Can have negative impact on multiple areas of functioning
  - ADHD is a highly treatable disorder
  - Adherence to treatment remains very poor