



# ADHD Across the Life Cycle: An Overview

**Joseph Biederman, MD**

Professor of Psychiatry

Harvard Medical School

Chief, Clinical and Research Programs in

Pediatric Psychopharmacology and Adult ADHD

Director, Bressler Program for Autism Spectrum Disorders

Trustees Endowed Chair in Pediatric Psychopharmacology

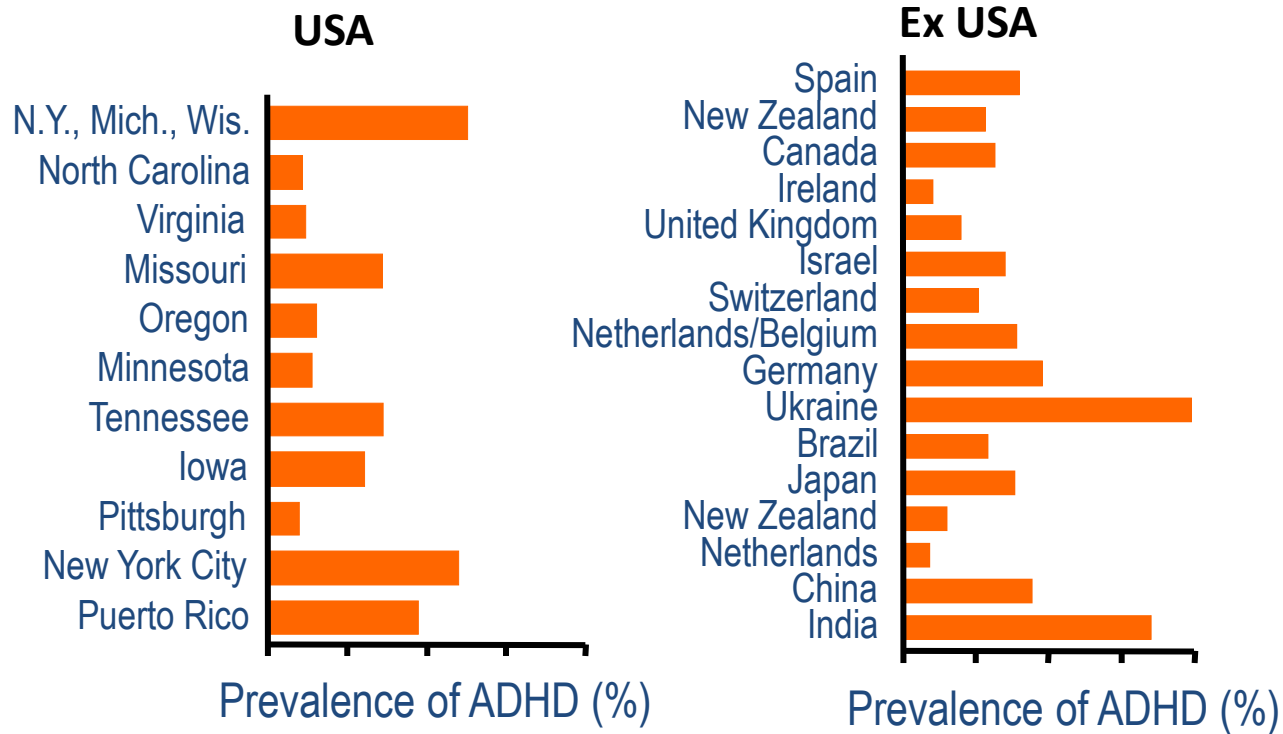
Massachusetts General Hospital

# 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

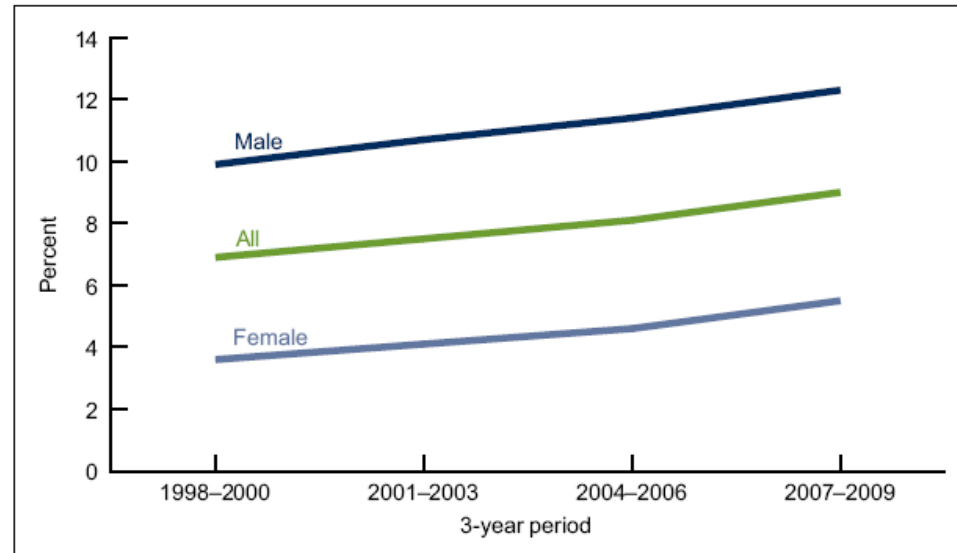
## Key findings

### 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](http://www.cdc.gov/nchs/data/databriefs/db70_tables.pdf#1).  
SOURCES: CDC/NCHS, Health Data Interactive and National Health Interview Survey.



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 the prevalence of ADHD in samples or subsamples of Black people, and were conducted in countries with Black minority populations. All studies were assessed and passed quality evaluation.

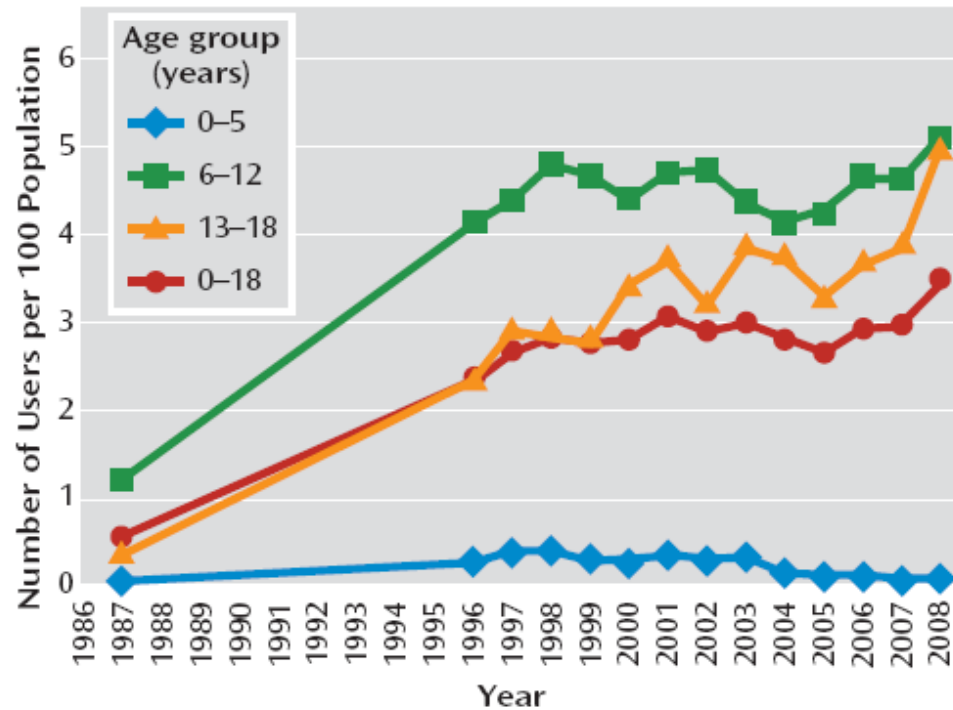
considered a minority population group (eg. in Northern America and Europe) are

**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 highlight the importance of establishing accurate diagnoses and culturally appropriate care.

1):21-28.

2020.2788

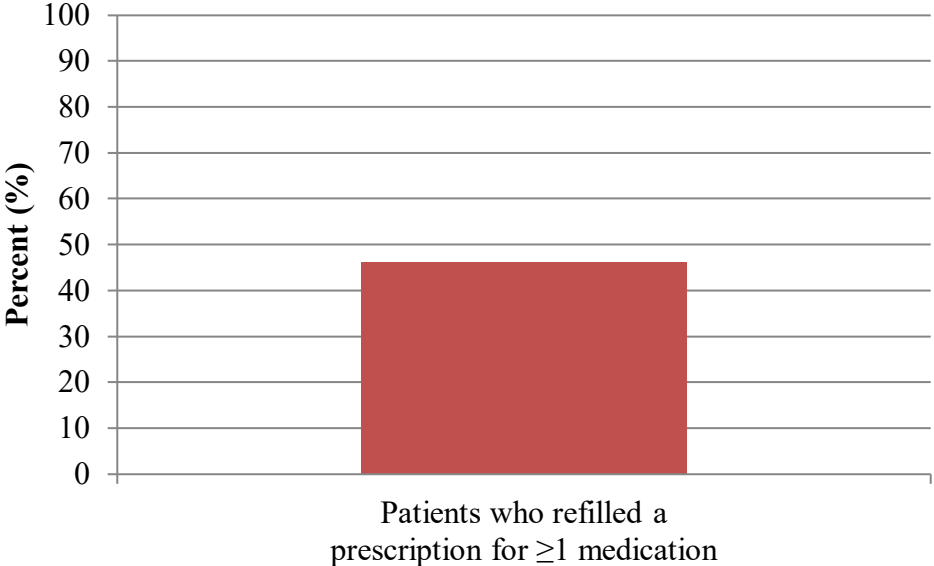
**FIGURE 1. Trends in Prevalence of Stimulant Use in the U.S. Population Age 18 and Younger, 1987–2008<sup>a</sup>**



<sup>a</sup> Based on the Medical Expenditure Panel Survey (1996–2008) and the National Medical Expenditure Survey (1987).

# 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 $\geq 1$ medication	% of patients who refilled
2,206	1,023	46%



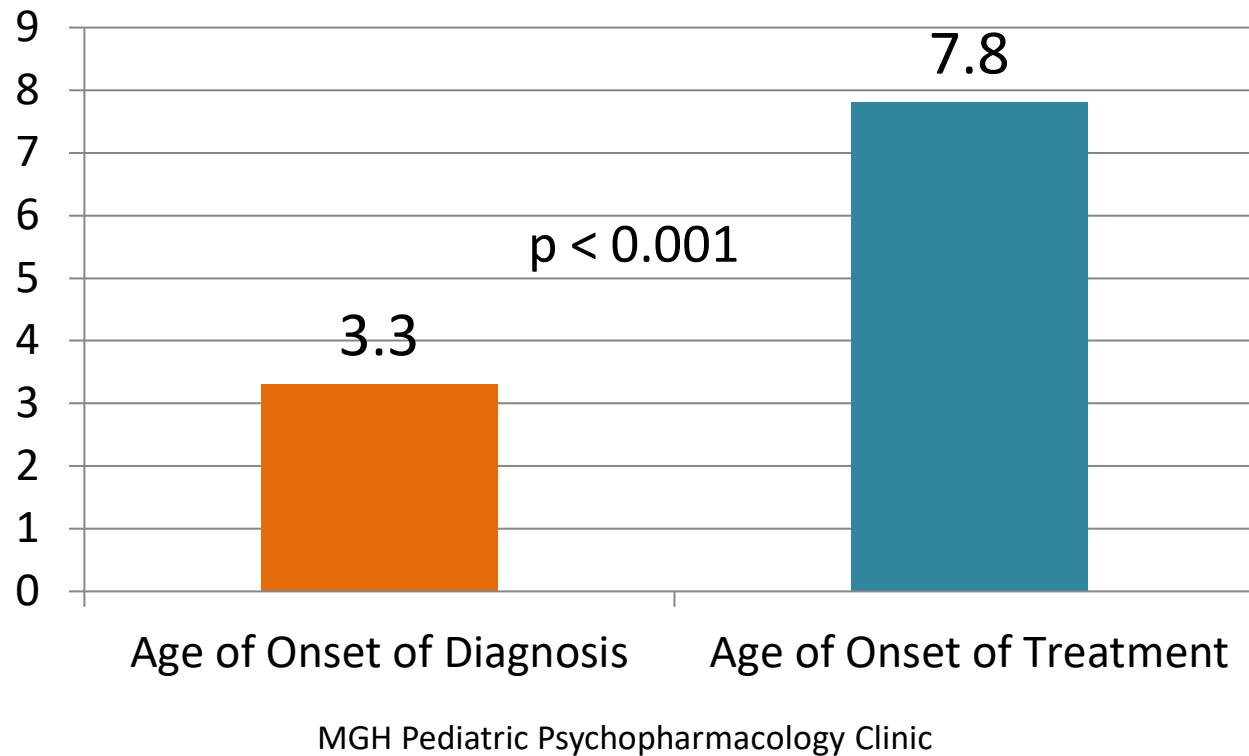
Biederman et al. *Psychiatric Services* 2019;70:874-880

# Poor Adherence to Treatment in ADHD

- Poor adherence occurs despite the well documented morbidity of ADHD, the marked efficacy and safety of stimulants as well as the fact that ADHD symptoms return rapidly when the medication is not taken



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



# 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

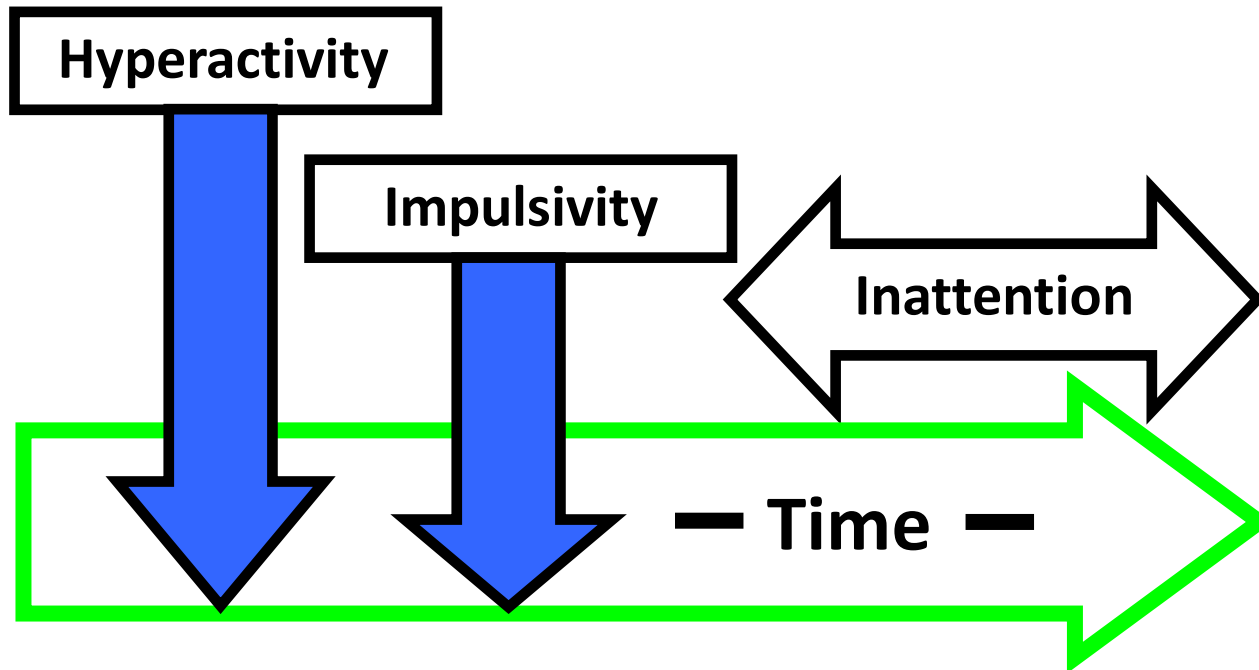
# ADHD: Core Symptom Areas

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**Inattention**

**Impulsivity/Hyperactivity**

# ADHD: Course of the Disorder



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

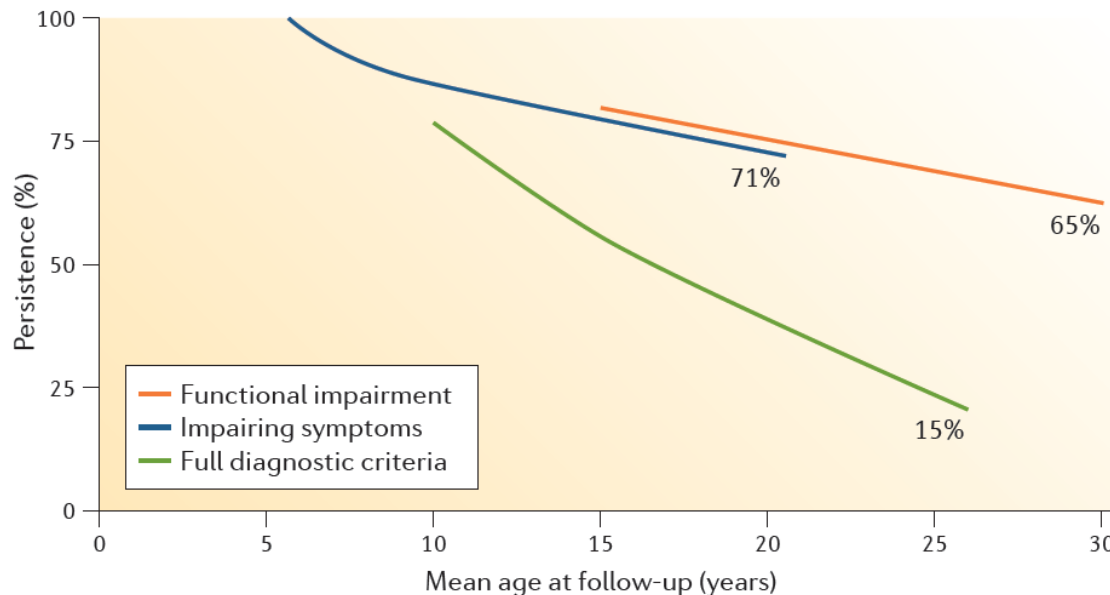


Figure 2 | **The age-dependent decline and persistence of attention-deficit/hyperactivity disorder throughout the lifetime.** Follow-up studies have assessed children with attention-deficit/hyperactivity disorder (ADHD) at multiple time points after their initial diagnosis. Although they document an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

Faraone et al. *Nature Reviews Disease Primers* 2015

## 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

Manos Adamou, consultant psychiatrist, Service for adults with ADHD, Mangates 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, Maudsley 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.<sup>1</sup> 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.<sup>2</sup>

ADHD is a clinical syndrome defined in the *Diagnostic and Statistical Manual of Mental Dis-*

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

*orders*, 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.<sup>3</sup>

### 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.<sup>4,5</sup>

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,<sup>6</sup> and overlapping genetic influences between ADHD and neurodevelopmental disorders such as autism and specific reading difficulties.<sup>7,8</sup> Disorders that commonly, but not invariably, occur in adults with ADHD include antisocial personality, substance misuse, and depression.<sup>4</sup>

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

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

# Changes in DSM-5 ADHD

- “Neurodevelopmental” - not “disruptive”
- $\geq 6/9$  inattentive or  $\geq 6/9$  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 as a Brain Disorder: Neuroimaging Findings





# PRIMER

## Attention-deficit/hyperactivity disorder

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

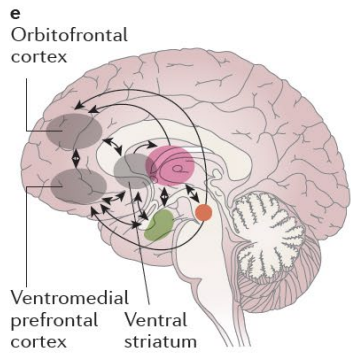
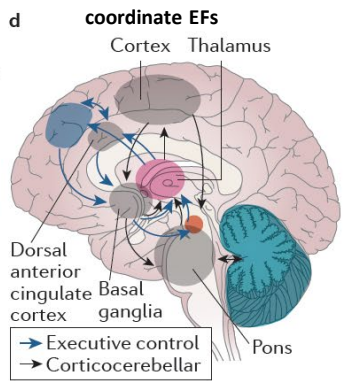
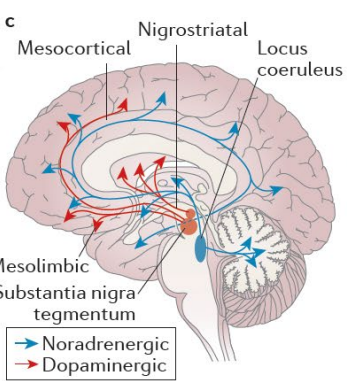
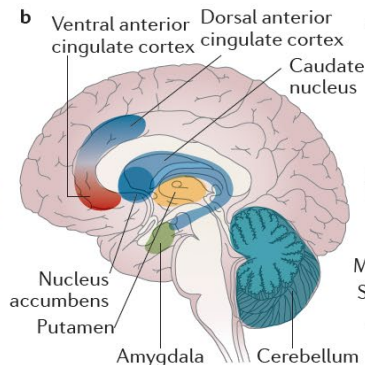
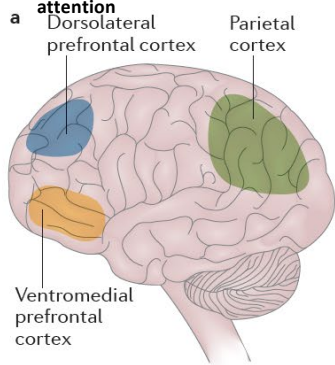
Abstract | Attention-deficit/hyperactivity disorder (ADHD) is a persistent neurodevelopmental disorder that affects 5% of children and adolescents and 2.5% of adults worldwide. Throughout an individual's lifetime, ADHD can increase the risk of other psychiatric disorders, educational and occupational 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/l6jiw>

Faraone et al. *Nature Reviews Disease Primers* 2015

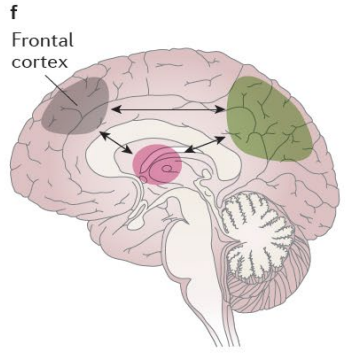
The DLPC is linked to WM, the VMPFC to complex decision making and strategic planning, and the parietal cortex to attention

# Brain Mechanisms in ADHD

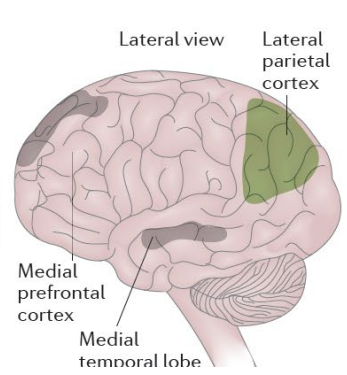
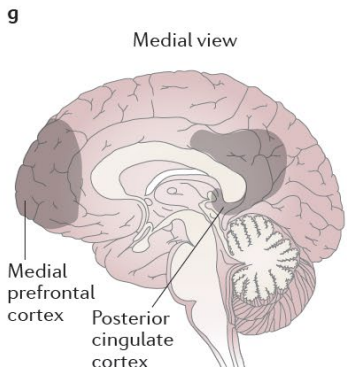
The executive control and cortico-cerebellar networks coordinate EFs



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

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



# ADHD as a Neurobiological Disorder: Catecholamine Dysregulation

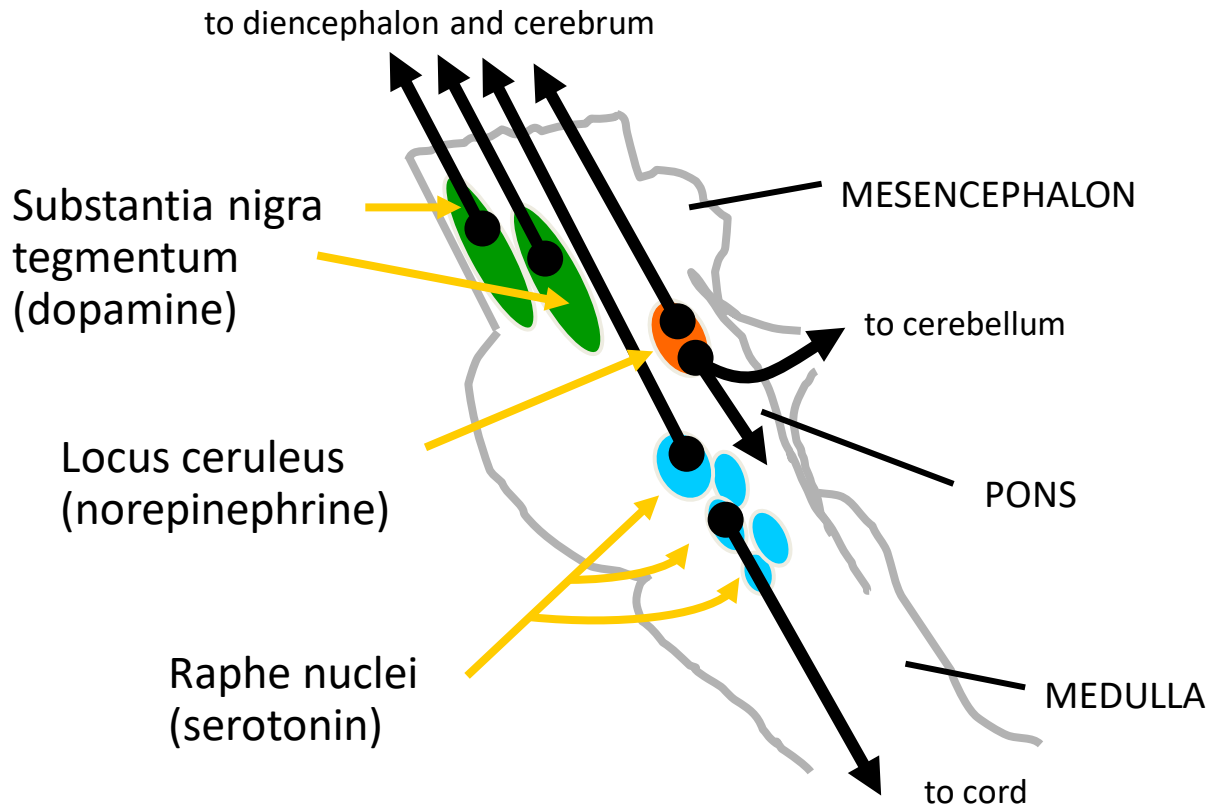
# Frontosubcortical Networks and Catecholamines

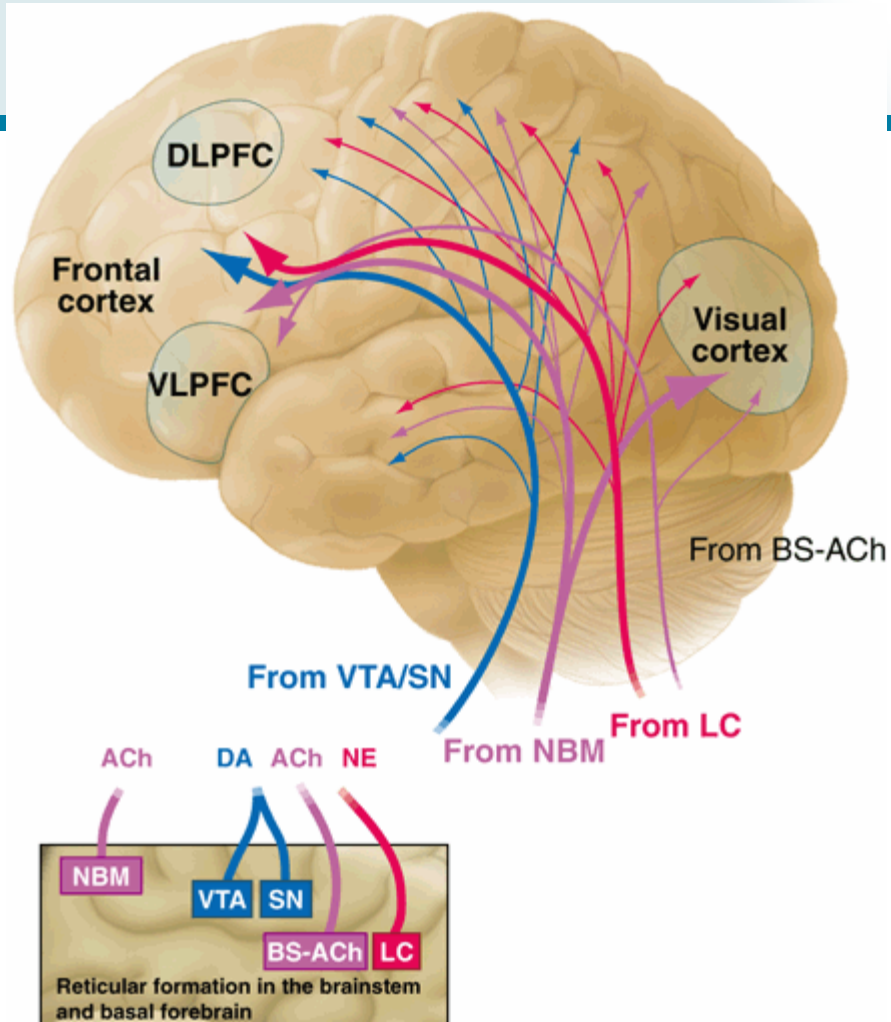
- Dopaminergic and noradrenergic dysregulation abnormalities in fronto subcortical pathways
- Medications that are effective in ADHD are either dopaminergic or noradrenergic

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

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

# Brain Stem





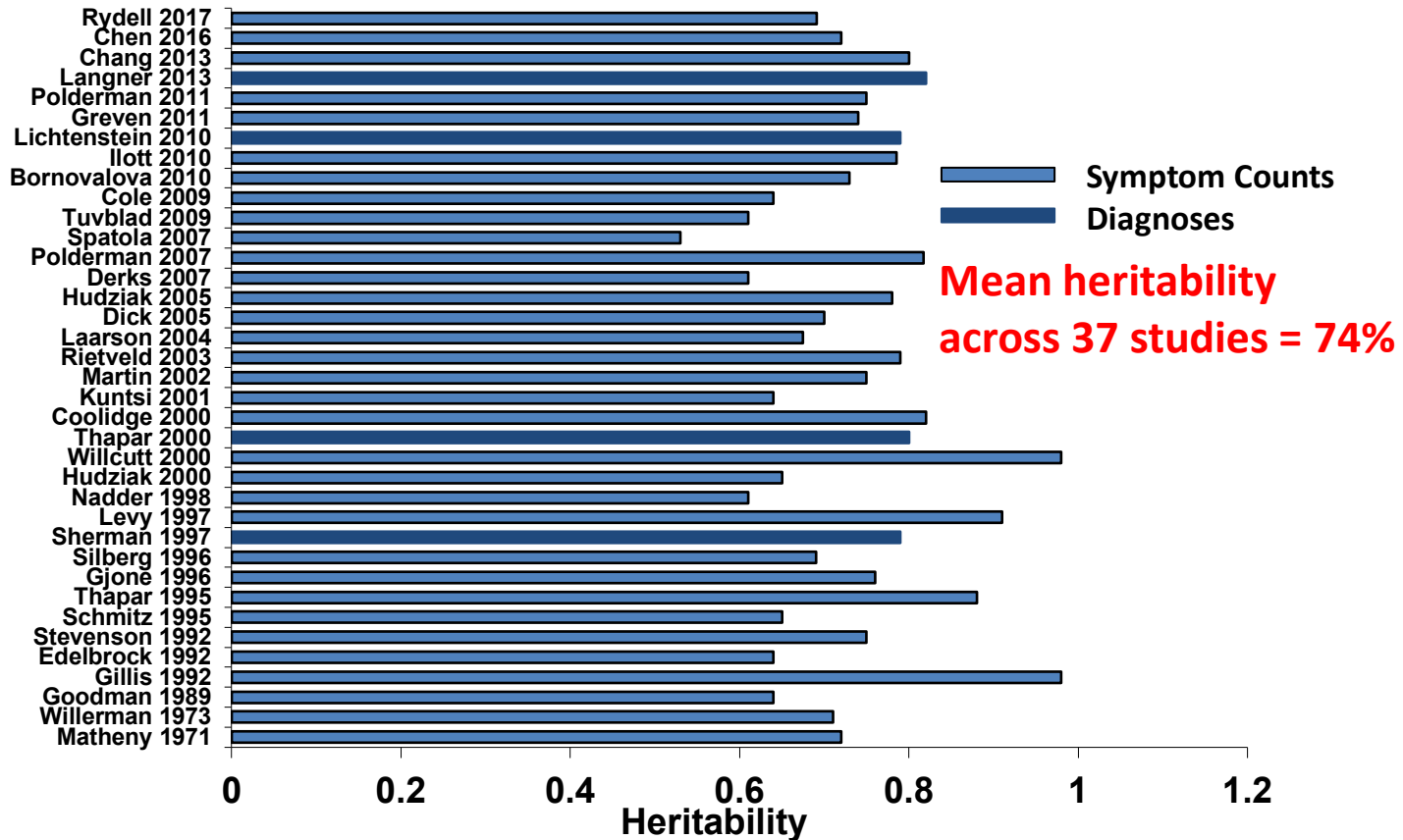


# ADHD as a Neurobiological Disorder: Genetic Findings

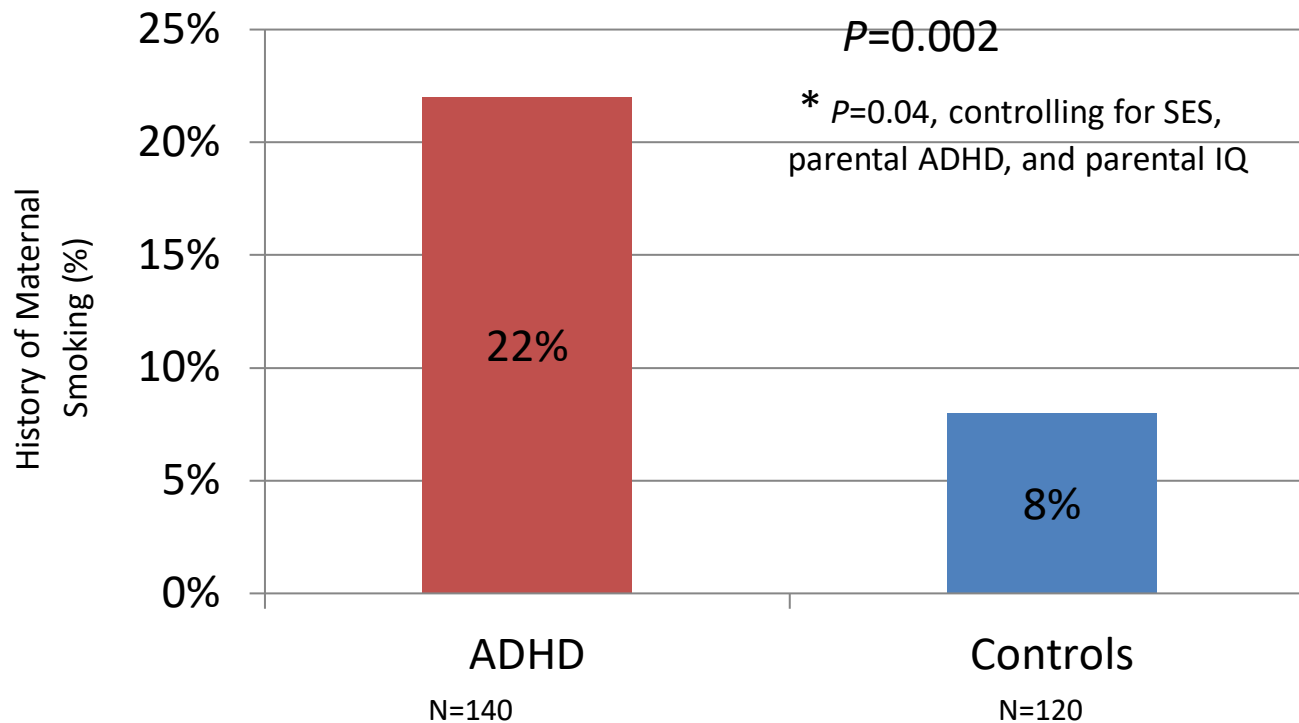


# Twin Studies of ADHD

(Faraone & Larsson, Molecular Psychiatry, 2018)



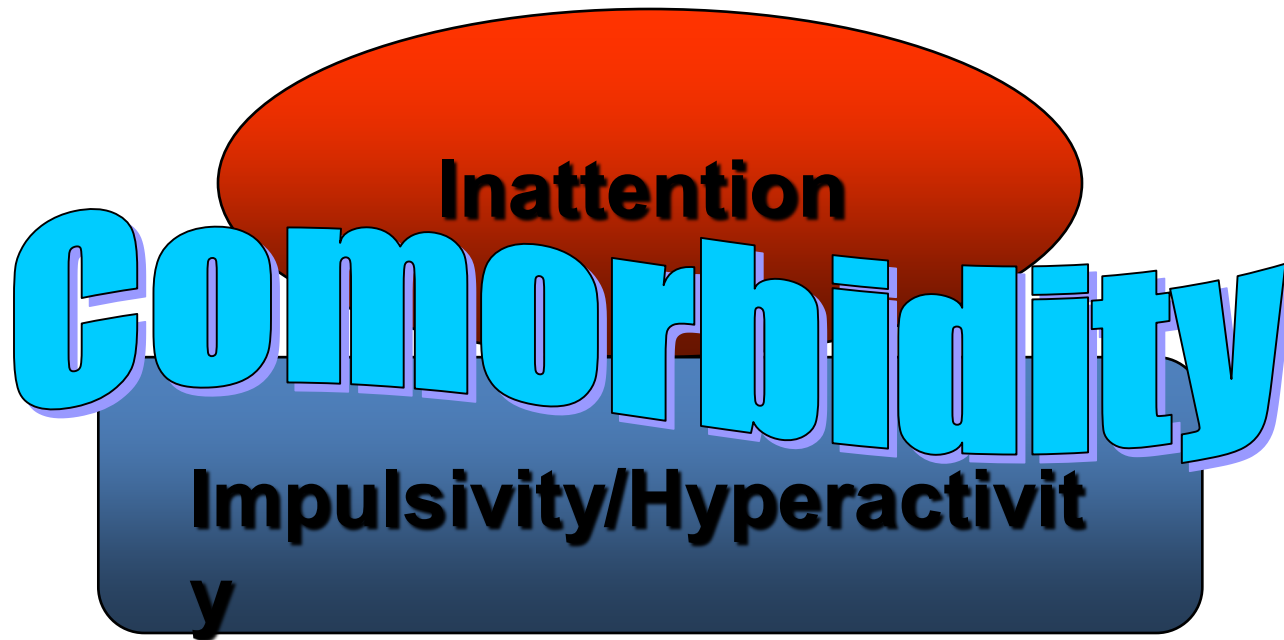
# Maternal Smoking During Pregnancy: Results in Children



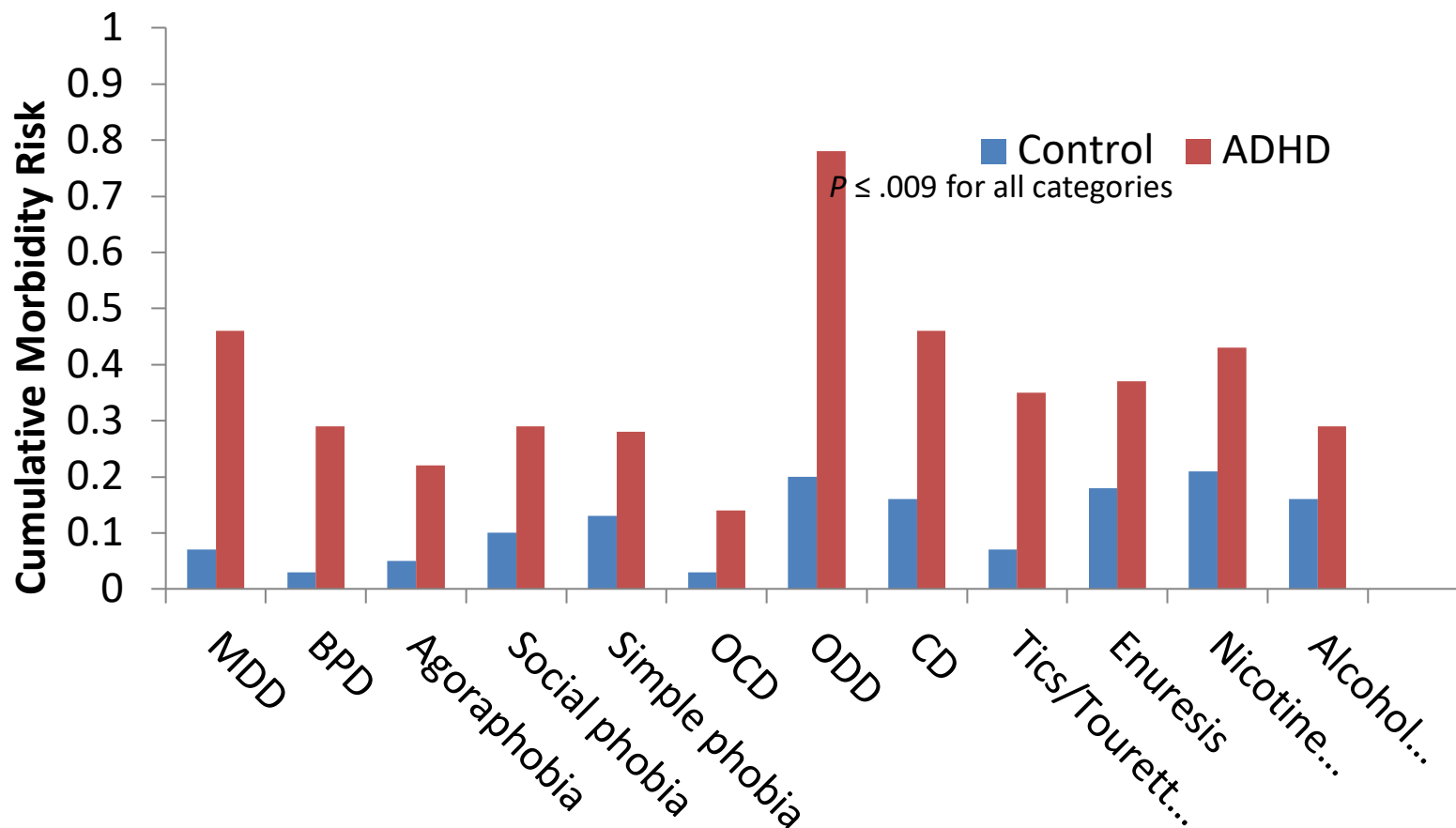
Milberger et al. Am J Psychiatry 1996;153:1138.

# ADHD Diagnostic Considerations

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



# THE AMERICAN JOURNAL OF PSYCHIATRY



Teaching Trainees to Negotiate  
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◀ Adult Psychiatric Outcomes of Girls  
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(PAARTNERS): Evidence for  
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Neurocognitive Functioning in  
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Monica E. Calkins, Ph.D., et al. 459

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Official Journal of the  
AMERICAN PSYCHIATRIC ASSOCIATION

[ajp.psychiatryonline.org](http://ajp.psychiatryonline.org)

Biederman et al.  
*AJP*, April 2010

# 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)

## Do Stimulants Protect Against Psychiatric Disorders in Youth With ADHD? A 10-Year Follow-up Study

### abstract

**OBJECTIVE:** Little is known about the effect of stimulant treatment in youth with attention-deficit/hyperactivity disorder (ADHD) on the subsequent development of comorbid psychiatric disorders. We tested the association between stimulant treatment and the subsequent development of psychiatric comorbidity in a longitudinal sample of patients

**CONCLUSIONS:** We found evidence that stimulant treatment decreases the risk for subsequent comorbid psychiatric disorders and academic failure in youth with ADHD. *Pediatrics* 2009;124:71–78

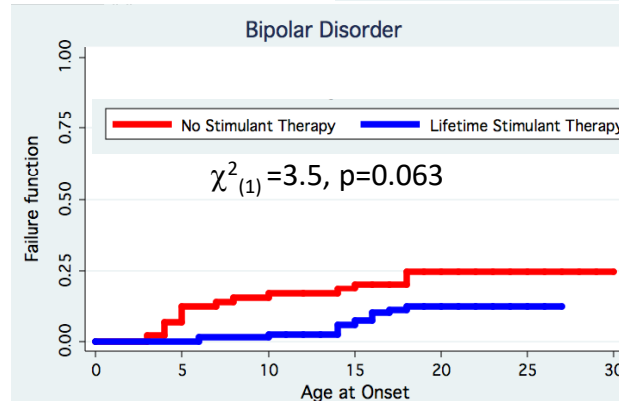
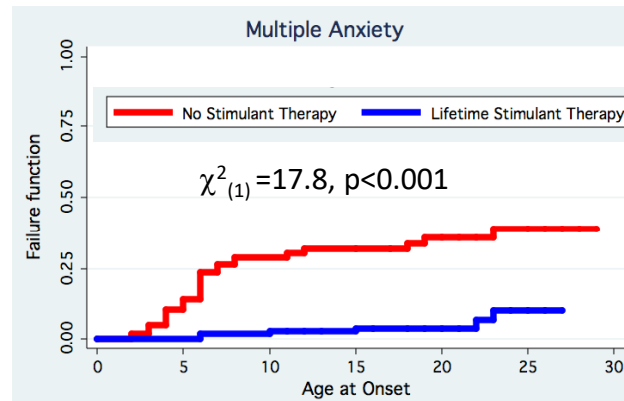
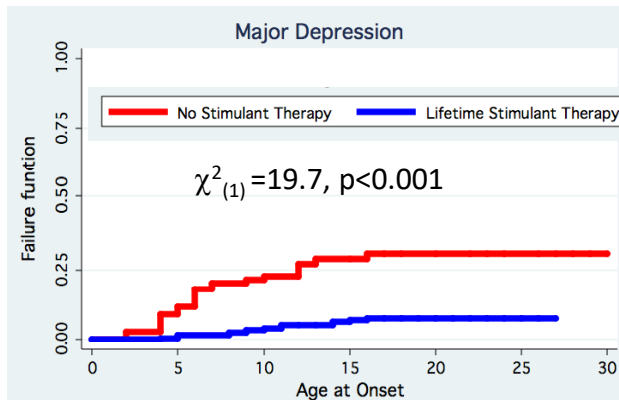
112 (80%) and 105 (88%) of the children in the ADHD and control groups, respectively, were reassessed (mean age: 22 years). We examined the association between stimulant treatment in childhood and adolescence and subsequent comorbid disorders and grade retention by using proportional hazards survival models.

**RESULTS:** Of the 112 participants with ADHD, 82 (73%) were previously treated with stimulants. Participants with ADHD who were treated with stimulants were significantly less likely to subsequently develop depressive and anxiety disorders and disruptive behavior and less likely to repeat a grade compared with participants with ADHD who were not treated.

**CONCLUSIONS:** We found evidence that stimulant treatment decreases the risk for subsequent comorbid psychiatric disorders and academic failure in youth with ADHD. *Pediatrics* 2009;124:71–78

Biederman et al.  
*Pediatrics* 2009  
Jul;124(1):71-8.

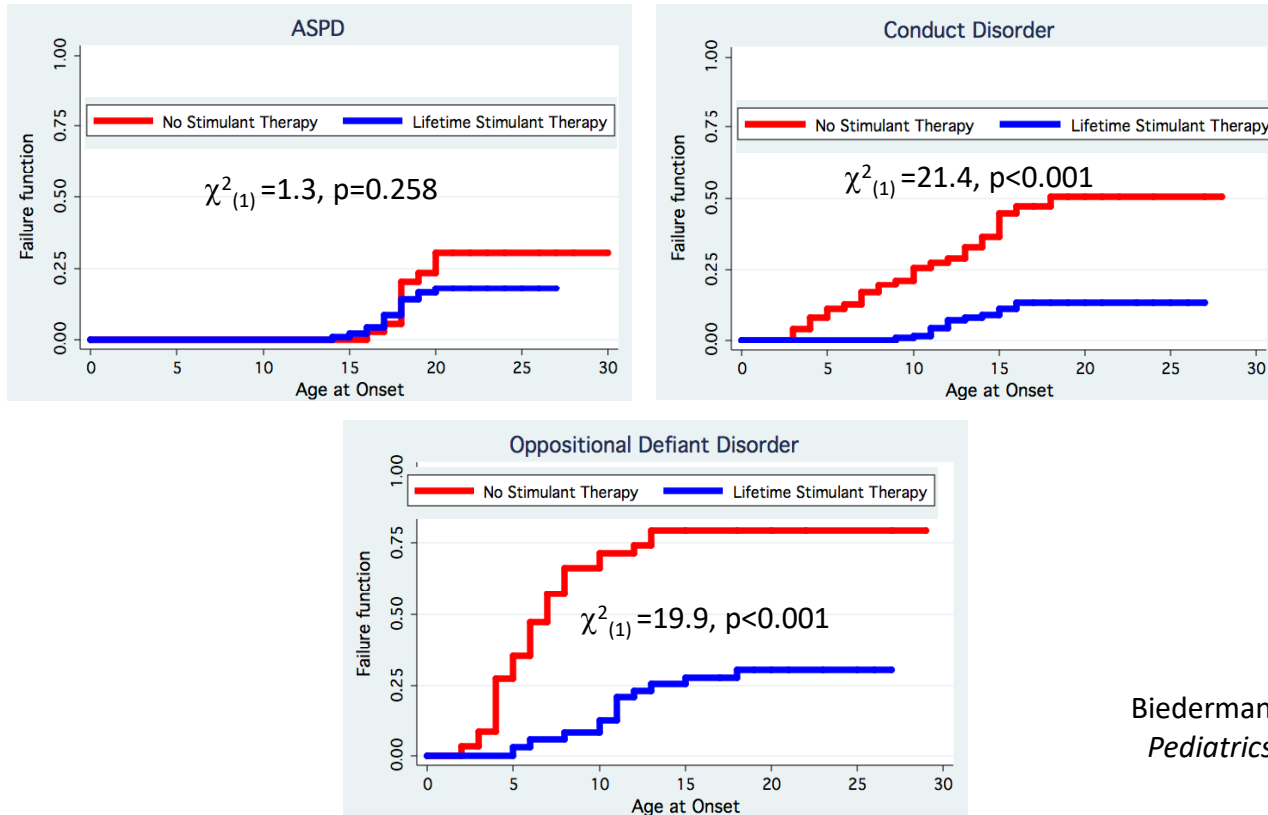
# Protective Effect of Stimulants on Comorbidity



Biederman et al.  
*Pediatrics* 2009

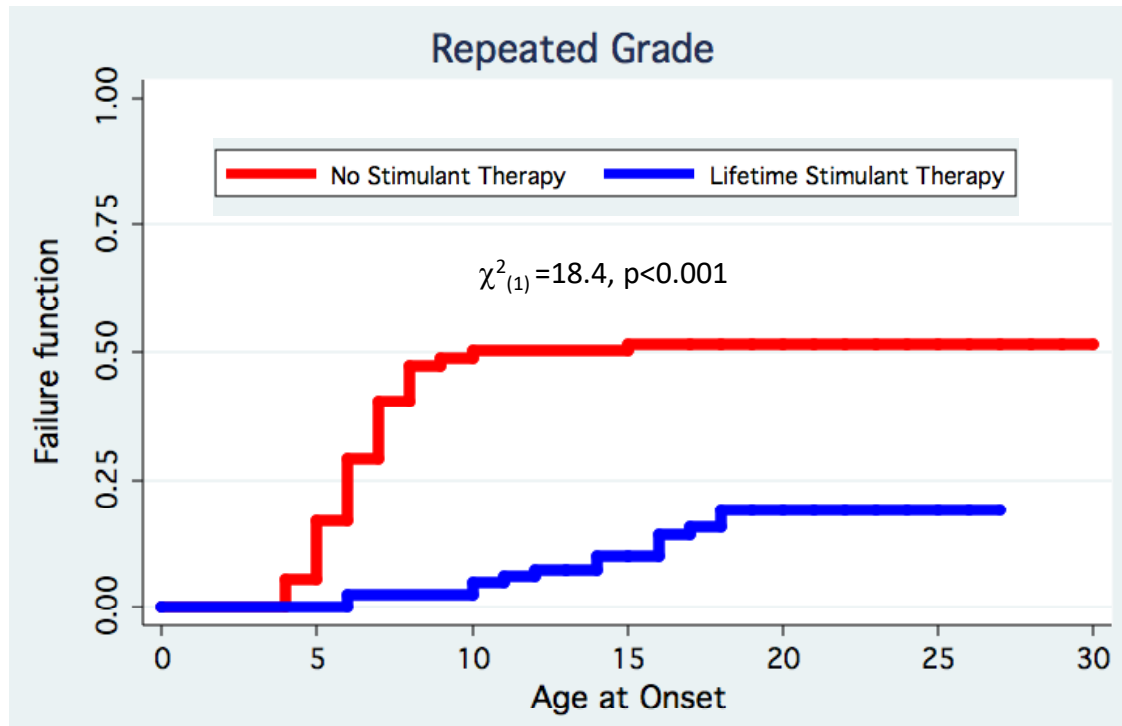


# Protective Effect of Stimulants on Comorbidity



Biederman et al.  
*Pediatrics* 2009

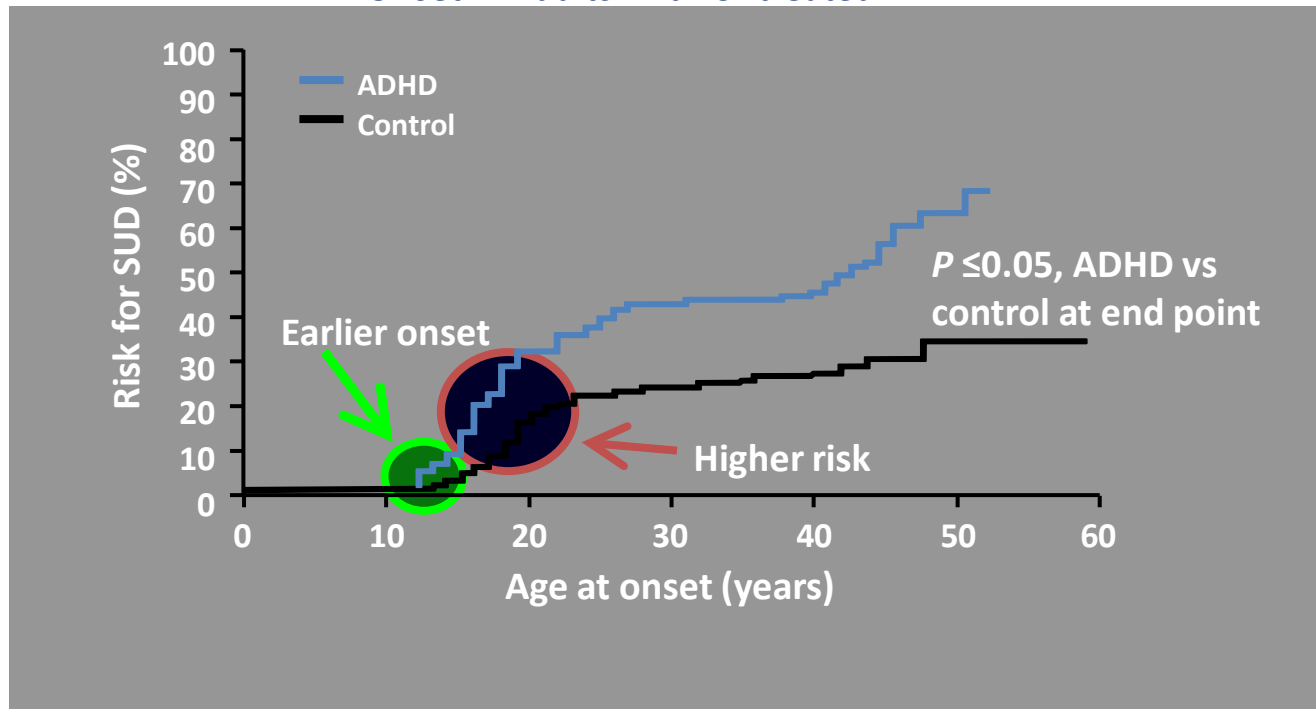
# Protective Effect of Stimulants



Biederman et al. *Pediatrics* 2009

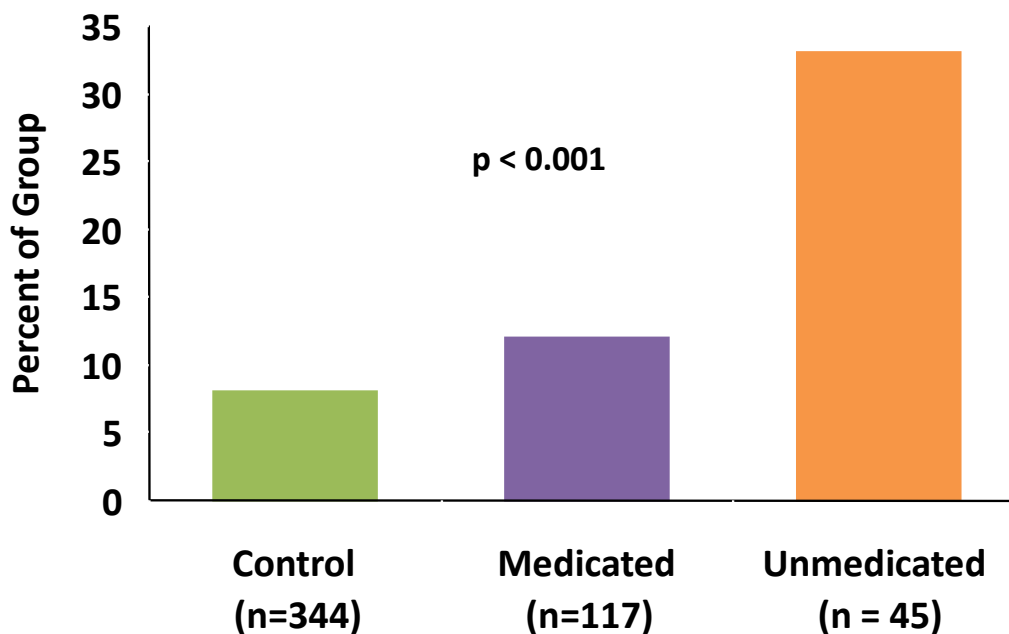
# ADHD and SUDs

Risk for Substance Use Disorder (SUD)  
Onset in Adults With Untreated ADHD



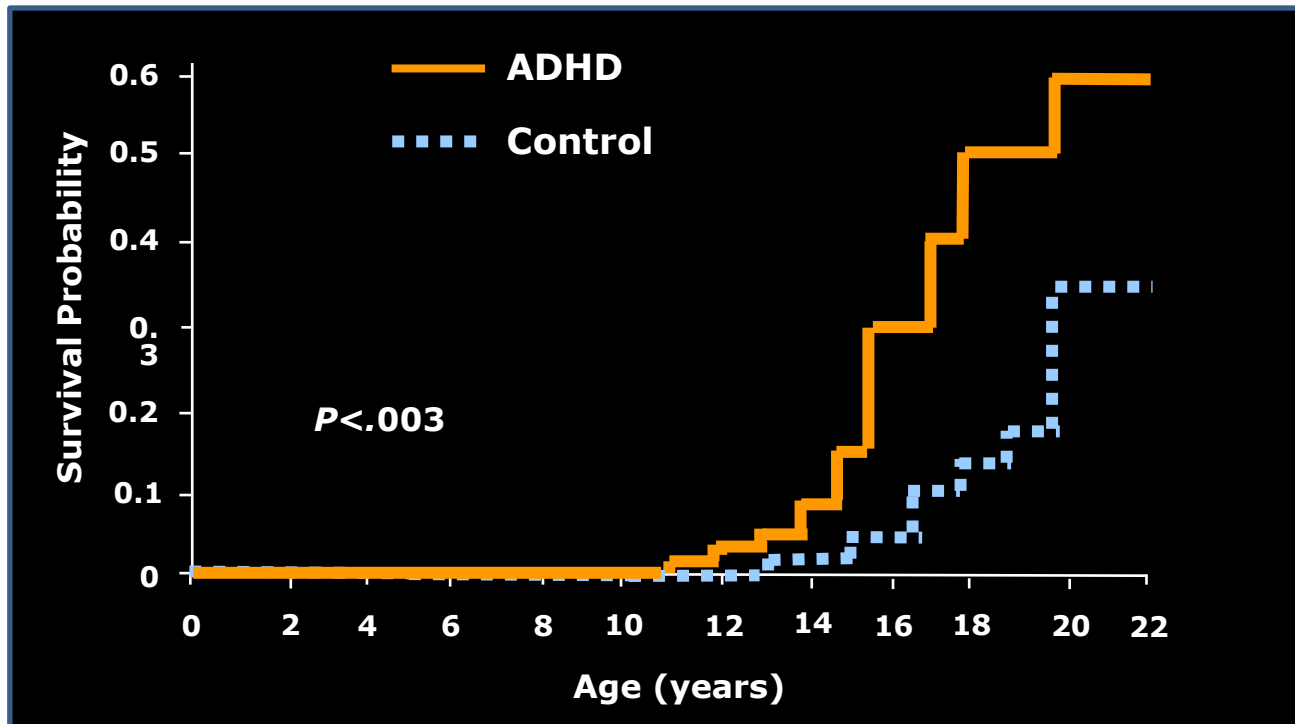
Wilens et al. *J Nerv Ment Dis.* 1997;185(8): 475-482.

# SUD in ADHD Youth Growing Up: Overall Rate of Substance Use Disorder



Biederman, Wilens, Mick et al., Pediatric 1999

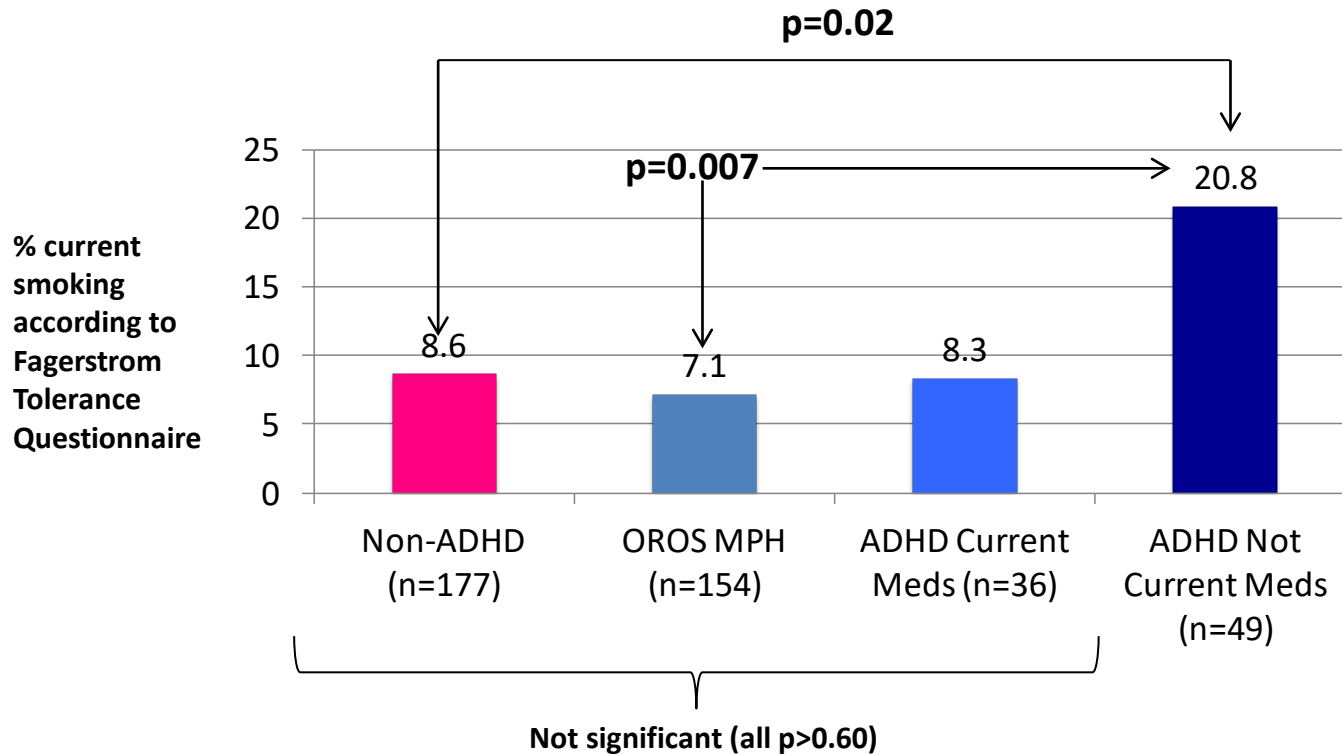
# Onset of **Nicotine Use** in Children and Adolescents with ADHD



Milberger S, et al. *J Am Acad Child Adolesc Psychiatry*. 1997;36:37-44.

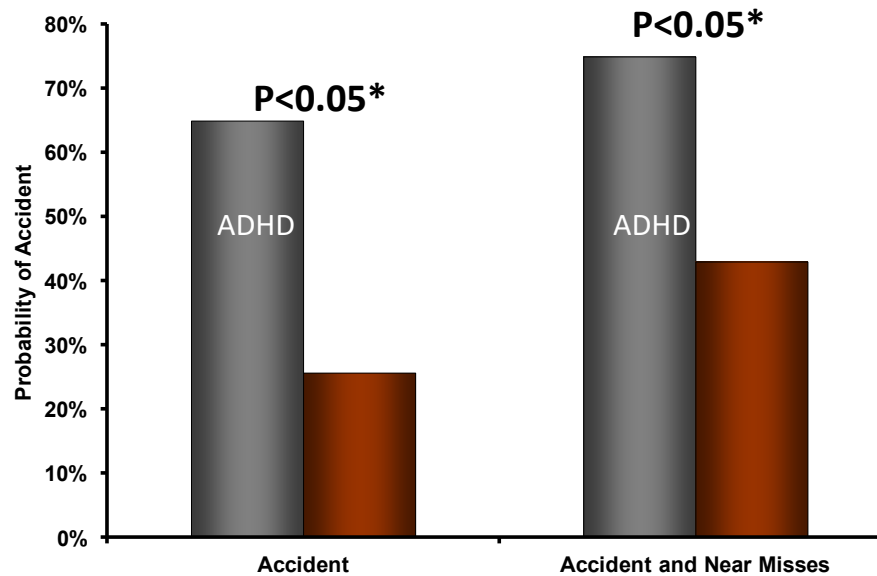
# Prospective Study of OROS MPH vs. non-ADHD and ADHD

Omnibus test, chi-squared(1)=8.44, p=0.04



Hammerness and Biederman, Journal of Pediatrics 2012

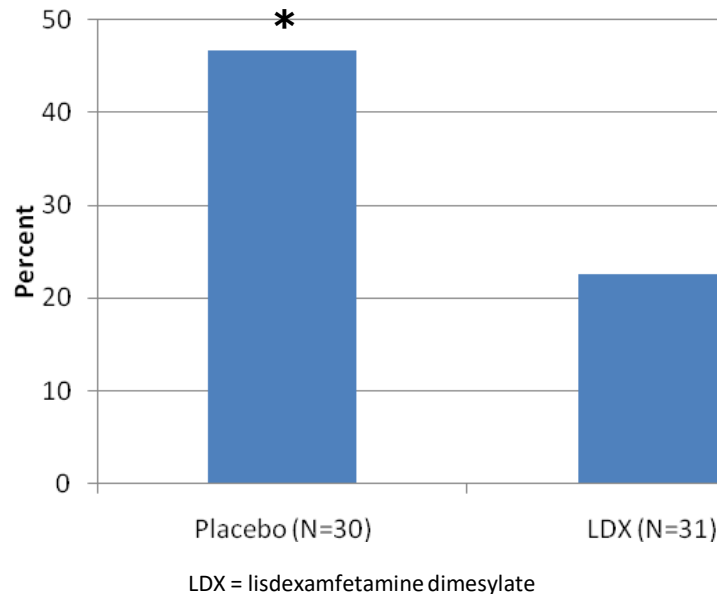
# Accidents and Near Misses



\*Indicates  $P < 0.05$  after controlling for gender, age, time of day and the age\*ADHD interaction

*(Reimer et al., 2016)*

# Percent of Subjects Involved in Collisions During Surprise Events



- During the five surprise events, drivers in the medication group were 67% less likely to have a collision than drivers in the placebo group

Biederman et al. 2012





# 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

# Nonpharmacologic Treatments for Attention-Deficit/Hyperactivity Disorder: A Systematic Review

**RESULTS:** We identified 54 studies of nonpharmacologic treatments, including neurofeedback, avis, PhD,<sup>e</sup>

**LIMITATIONS:** Studies often did not reflect the primary care setting and had short follow-up periods, small sample sizes, variations in outcomes, and inconsistent reporting of comparative statistical analyses. ski, PhD,<sup>b</sup>

**CONCLUSIONS:** Despite wide use, there are significant gaps in knowledge regarding the effectiveness of ADHD nonpharmacologic treatments.

mean difference  $-0.08$ ; 95% confidence interval  $-0.47$  to  $0.32$ ;  $I^2 = 0.0\%$ ;  $P = .56$ ).

**CONTEXT:** No  
encompass  
complete

**OBJECTIVES:**

ADHD among individuals 17 years of age and younger.

**DATA SOURCES:** PubMed, Embase, PsycINFO, and Cochrane Database of Systematic Reviews for relevant English-language studies published from January 1, 2009 through November 7, 2016.

**STUDY SELECTION:** We included studies that compared any ADHD nonpharmacologic treatment strategy with placebo, pharmacologic, or another nonpharmacologic treatment.

**DATA EXTRACTION:** Study design, patient characteristics, intervention approaches, follow-up times, and outcomes were abstracted. For comparisons with at least 3 similar studies, random-effects meta-analysis was used to generate pooled estimates.

abstract

# 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