MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

ADHD Across the Life Cycle: An Overview

Joseph Biederman, MD

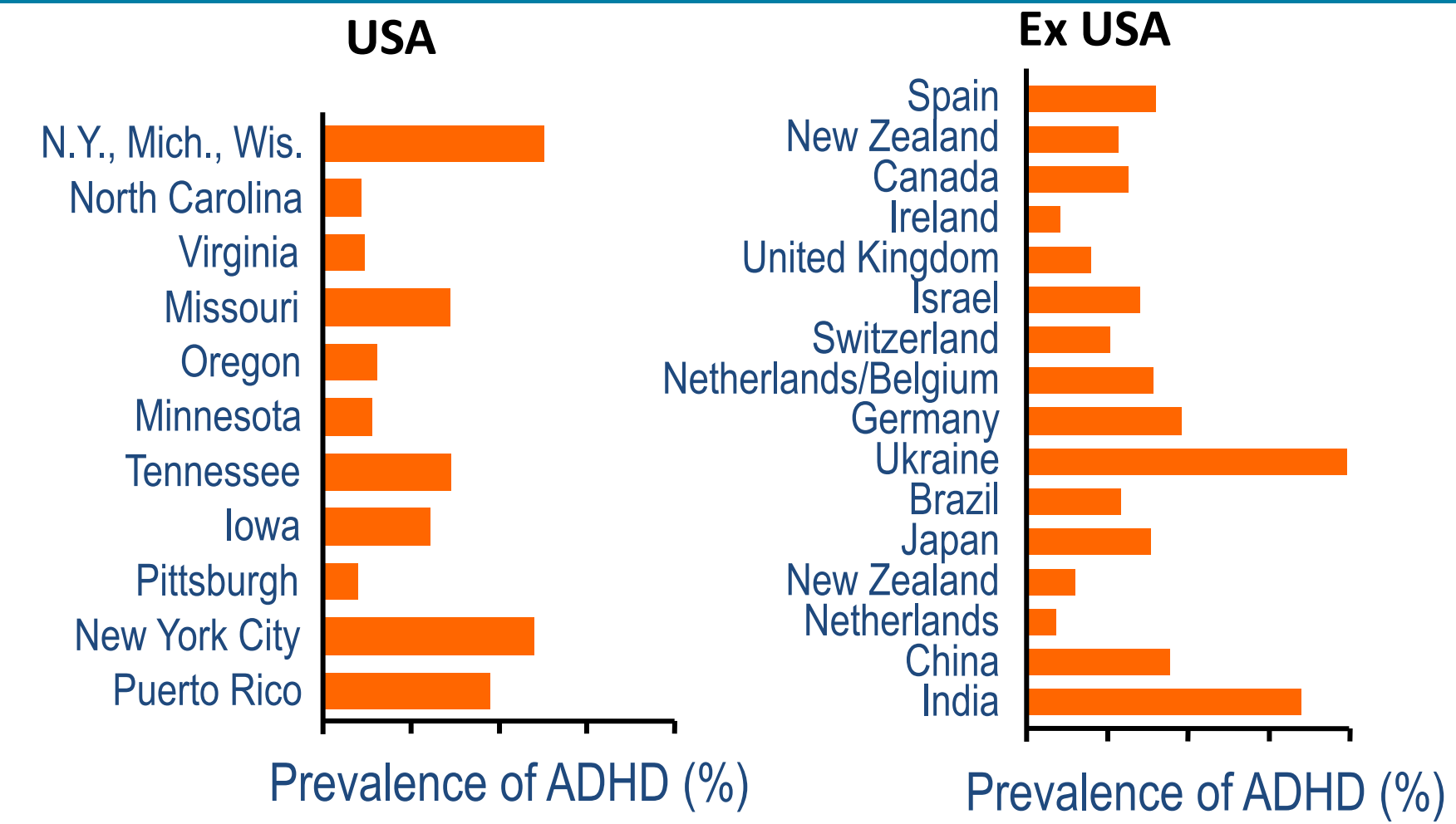
Professor of Psychiatry
Harvard Medical School
Chief, Clinical and Research Programs in
Pediatric Psychopharmacology and Adult ADHD
Director, Bressler Program for Autism Spectrum Disorders
Trustees Endowed Chair in Pediatric Psychopharmacology
Massachusetts General Hospital

Disclosures 2019-2020

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

- *Research support:* Genentech, Headspace Inc., Lundbeck, Neurocentria Inc., Pfizer, Roche TCRC Inc., Shire Pharmaceuticals Inc., Sunovion, and Tris.
- *Consulting fees:* Akili, Avekshan LLC, Jazz Pharma, and Shire/Takeda
- *Scientific Advisory Board through MGH CTNI:* Supernus
- *Royalties paid to the Department of Psychiatry at MGH, for a copyrighted ADHD rating scale used for ADHD diagnoses:* Bracket Global, Ingenix, Prophase, Shire, Sunovion, and Theravance

Worldwide Prevalence of ADHD in Children



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

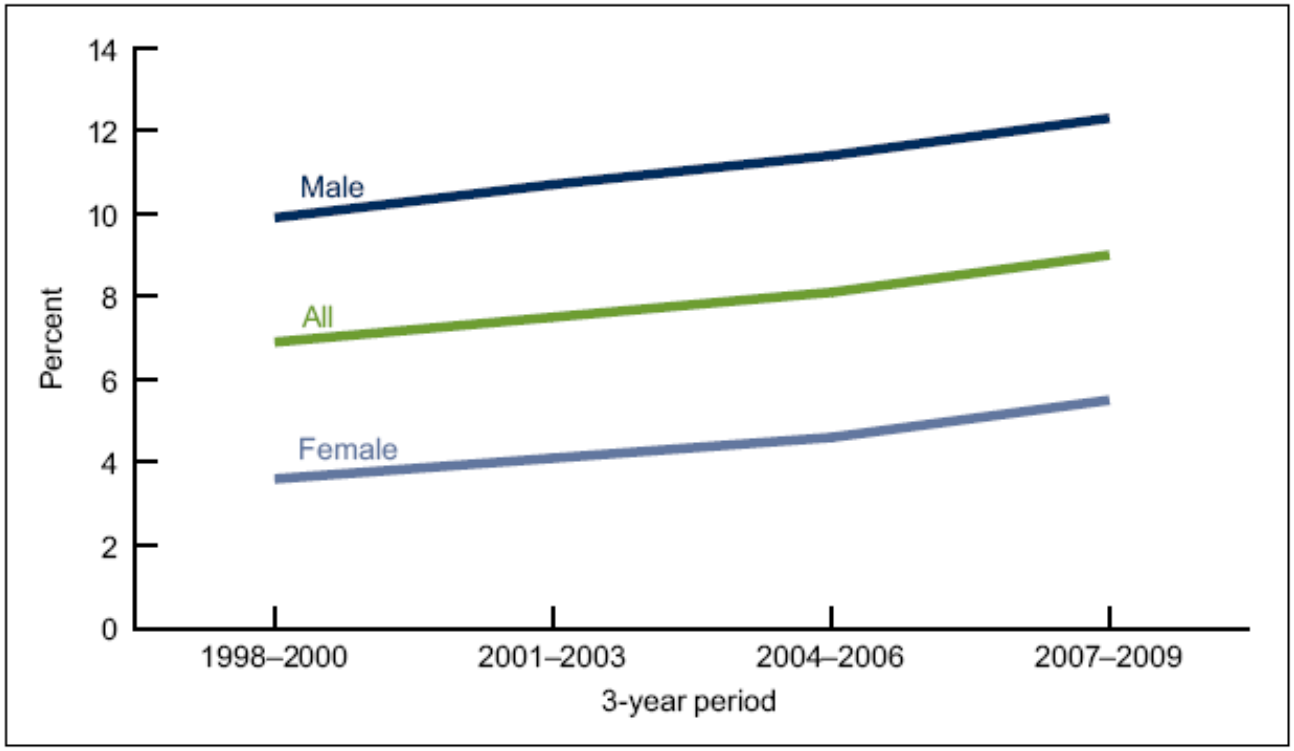
Key findings

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.

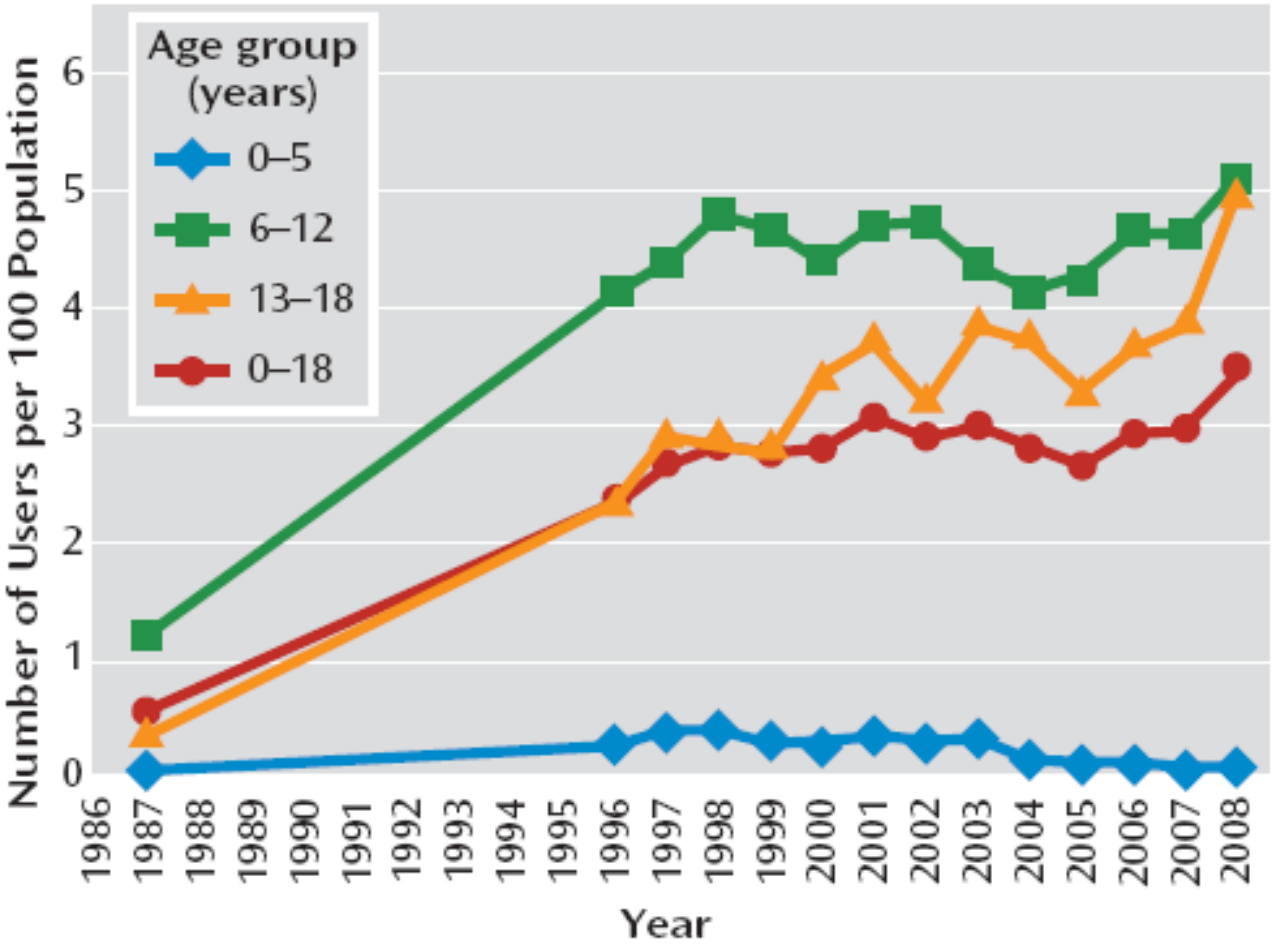
Figure 1. Percentage of children aged 5–17 years ever diagnosed with attention deficit hyperactivity disorder, by sex: United States, 1998–2009



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

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

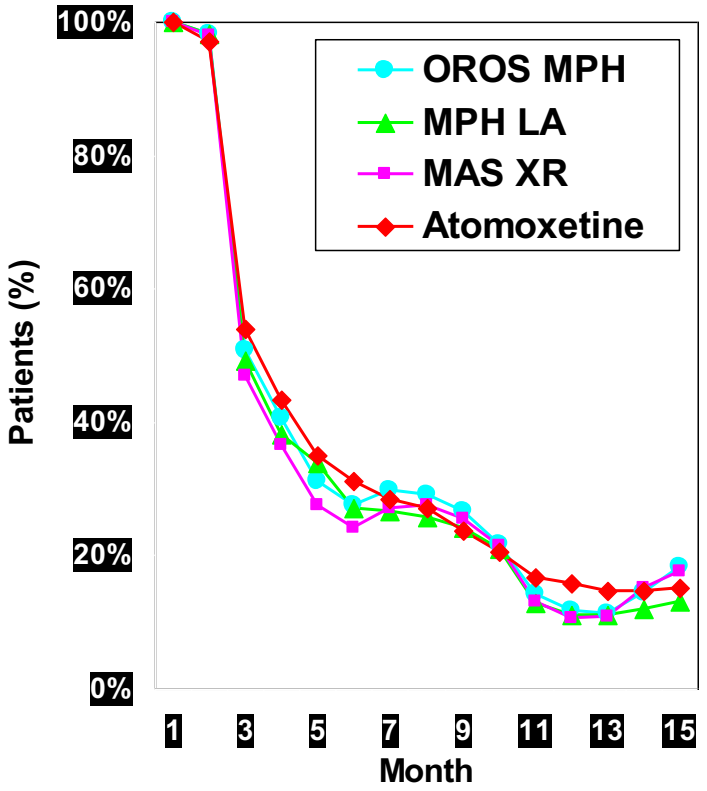


[a] Based on the Medical Expenditure Panel Survey (1996–2008) and the National Medical Expenditure Survey (1987).

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**

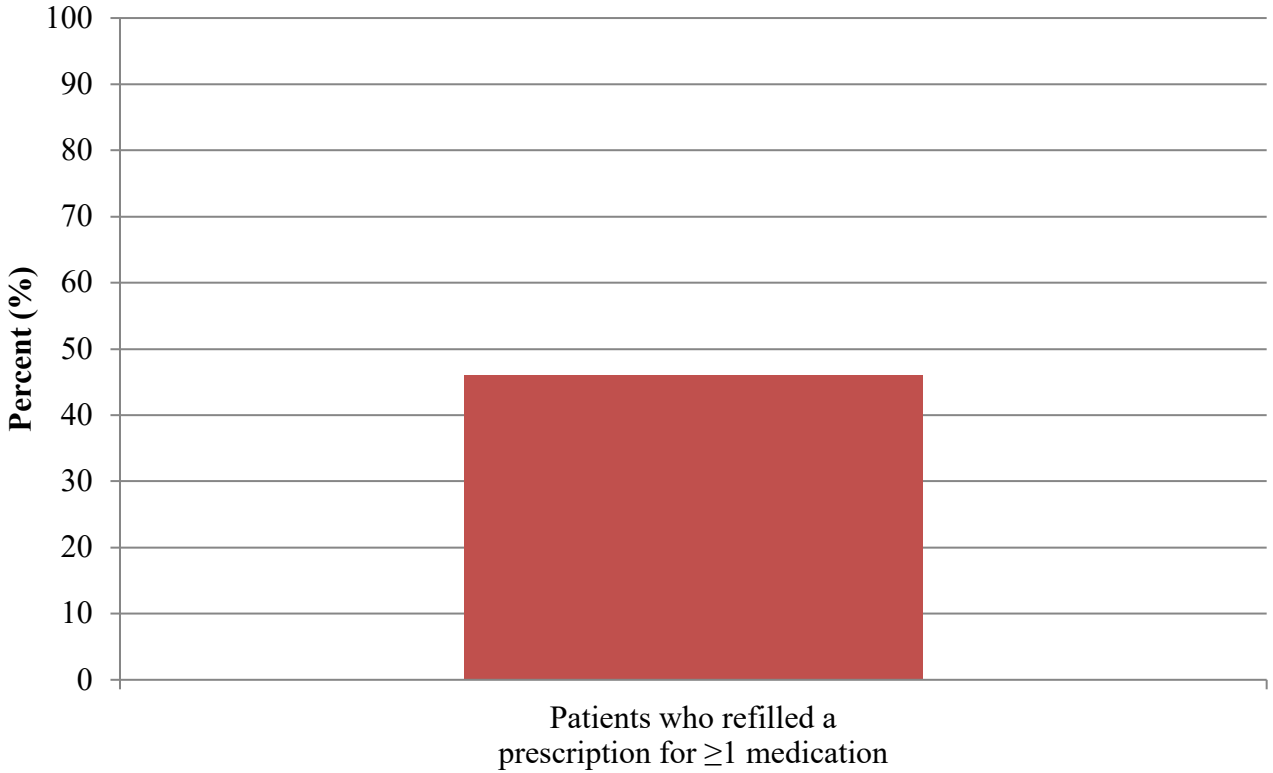


- **Within 2 to 3 months, a majority of patients with ADHD have stopped taking medication consistently**
- **Patients renewed their monthly prescriptions about 2 to 3 times per year**[1]

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%

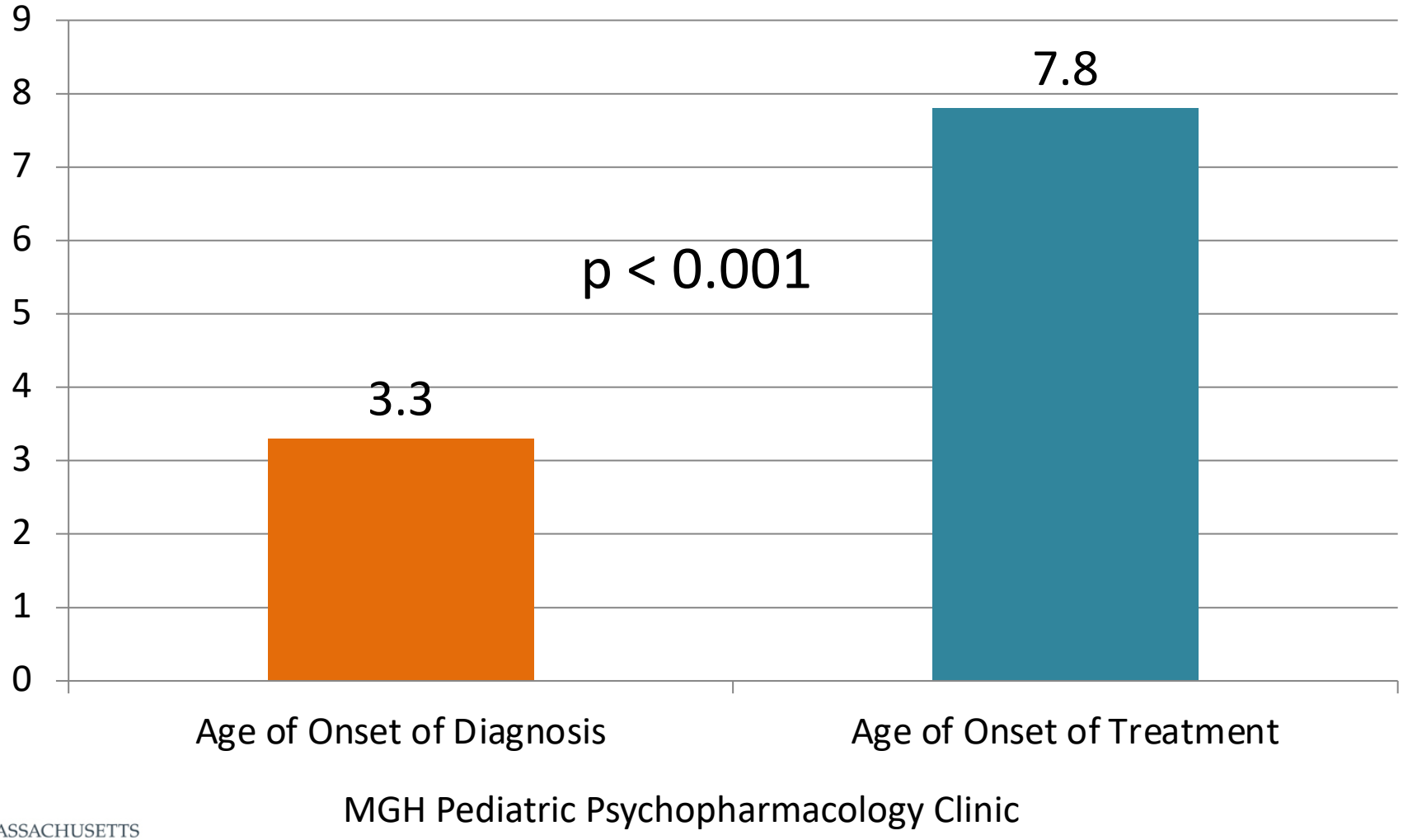


Biederman et al. *Psychiatric Services* 2019;70:874-880

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)



MGH Pediatric Psychopharmacology Clinic

JAMA Network Open

Original Investigation | Psychiatry

Trends in the Prevalence and Incidence

DESIGN, SETTING, AND PARTICIPANTS This cohort study investigated trends in the diagnosis of

EXPOSURES Period of ADHD diagnosis.

CONCLUSIONS AND RELEVANCE This study confirmed the reported increases in rates of ADHD diagnosis among adults, showing substantially lower rates of detection among minority racial/ethnic subgroups in the United States. Higher odds of negative outcomes reflect the economic and personal consequences that substantiate the need to improve assessment and treatment of ADHD in adults.

September 2019.

OBJECTIVE To examine trends, including associated demographic characteristics, psychiatric diagnoses, and negative outcomes, in the prevalence and incidence of adult ADHD diagnosis among 7 racial/ethnic groups during a 10-year period.

Findings In this cohort study of 5 282 877 patients who identified as African American or black, Native

Chung et al. *JAMA Network Open.* 2019;2(11):e1914344.

U.S. Department of Health and Human Services

Office of Inspector General

Many Medicaid-Enrolled Children Who Were Treated for ADHD Did Not Receive Recommended Followup Care

OEI-07-17-00170
August 2019

oig.hhs.gov

Joanne M. Chiedi
Acting Inspector General

School Readiness in Preschoolers With Symptoms of Attention-Deficit/ Hyperactivity Disorder

Hannah T. Perrin, MD, Nicole A. Heller, BA, Irene M. Loe, MD

abstract

OBJECTIVE: To compare school readiness in preschoolers with and without attention-deficit/ hyperactivity disorder (ADHD) symptoms using a comprehensive framework. We hypothesized that preschoolers with ADHD symptoms have higher odds of school readiness impairment.

METHODS: Children ages 4 to 5 years (n = 93) were divided into 2 groups on the basis of presence of ADHD symptoms (ADHD group, n = 45; comparison group, n = 48). School readiness was assessed through 10 component measures, including direct assessments and standardized questionnaires, regarding 5 school readiness domains: physical well-being and motor development, social and emotional development, approaches to learning, language, and

CONCLUSIONS: Preschoolers with ADHD symptoms are likely to have impaired school readiness. We recommend early identification of school readiness impairment by using a comprehensive 5-domain framework in children with ADHD symptoms paired with targeted intervention to improve outcomes.

measures and greater odds of impairment in all domains except for cognition and general knowledge. Overall, 79% of the ADHD group and 13% of the comparison group had school readiness impairment (odds ratio 21, 95% confidence interval 5.67–77.77, $P < .001$).

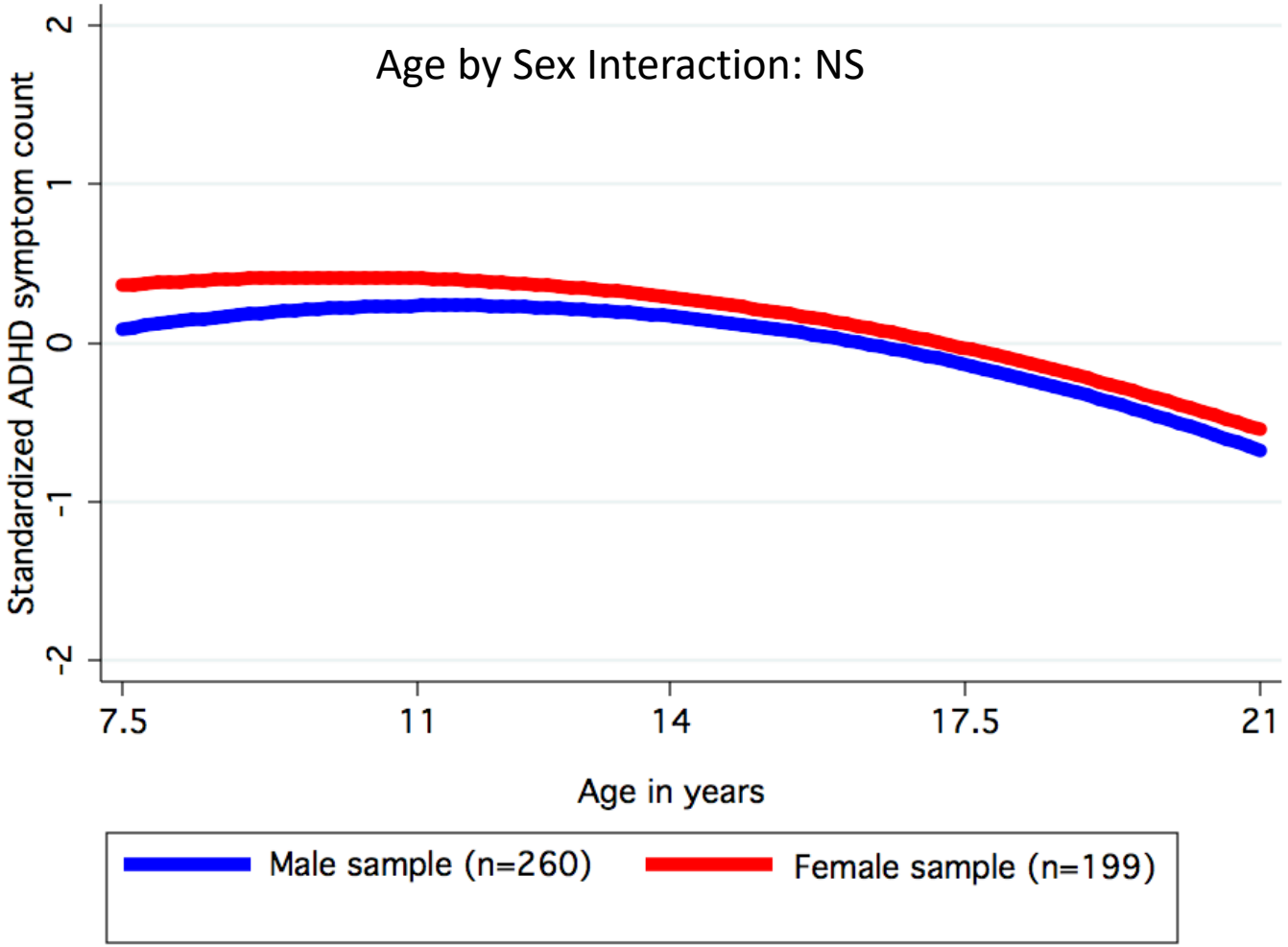
CONCLUSIONS: Preschoolers with ADHD symptoms are likely to have impaired school readiness. We recommend early identification of school readiness impairment by using a comprehensive 5-domain framework in children with ADHD symptoms paired with targeted intervention to improve outcomes.

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

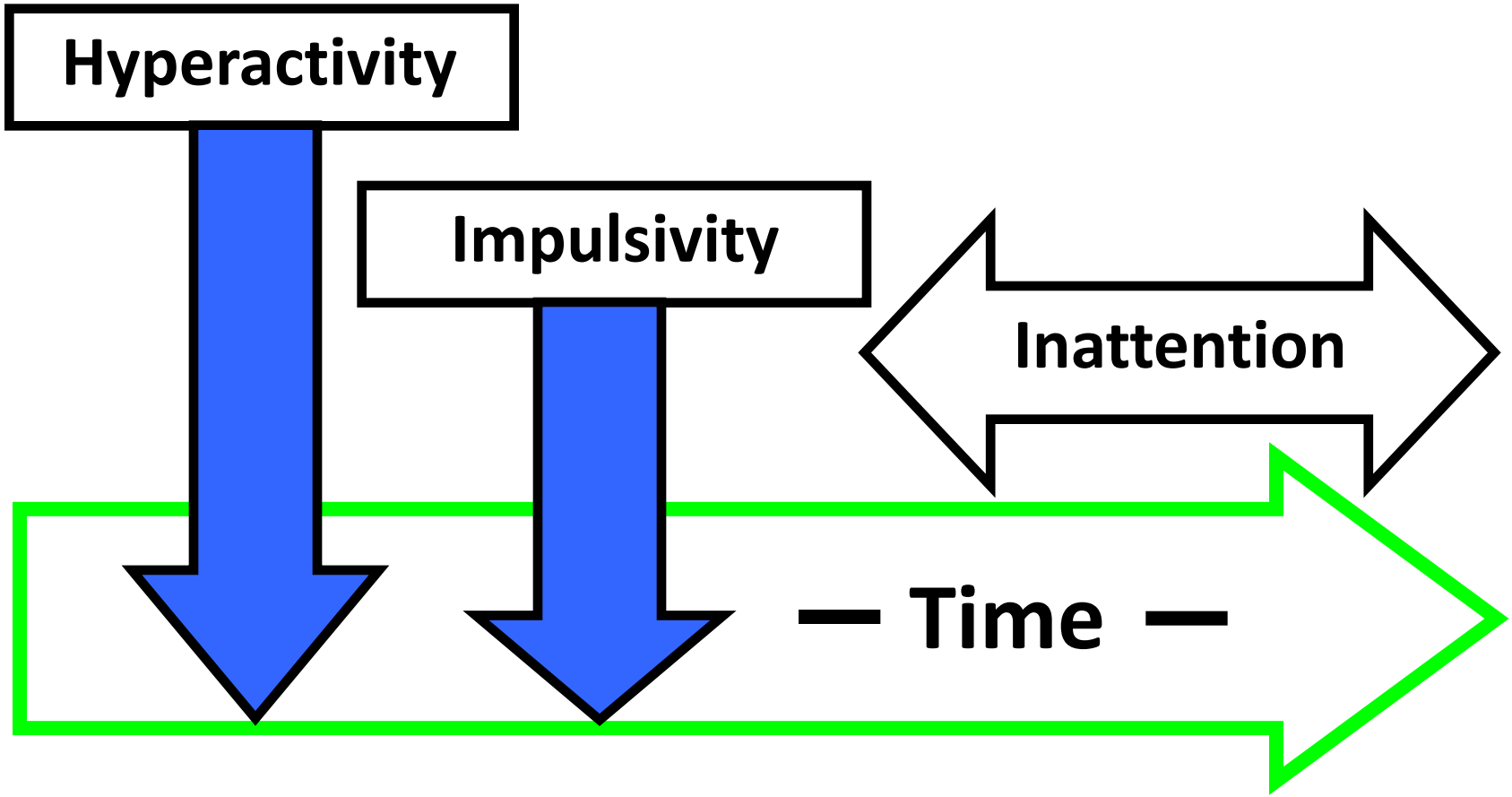
ADHD: Core Symptom Areas

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



Biederman et al. 2009

ADHD: Course of the Disorder



Age-Dependent Decline and Persistence of ADHD Throughout the Lifetime

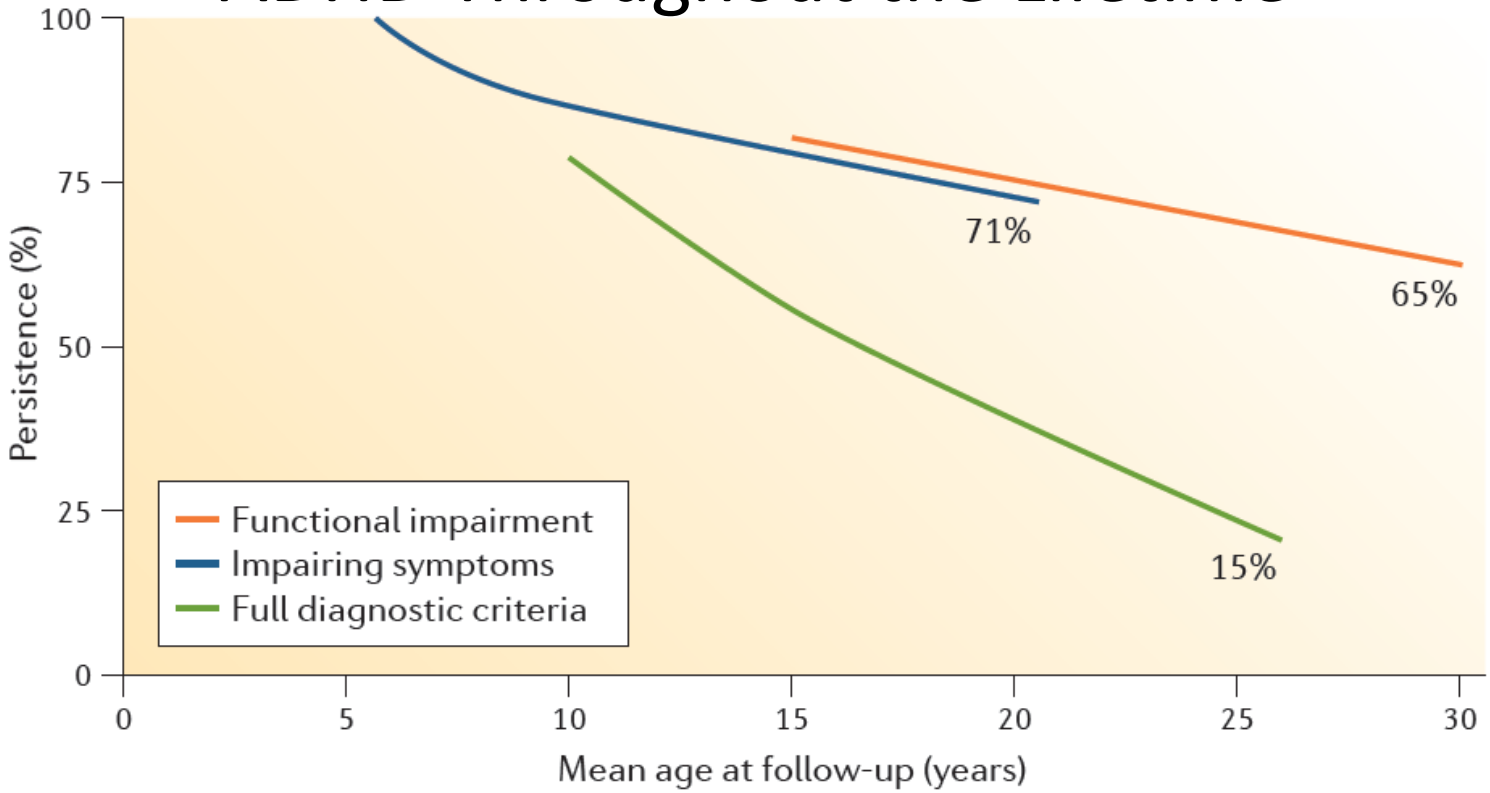


Figure 2 | **The age-dependent decline and persistence of attention-deficit/hyperactivity disorder throughout the lifetime.** Follow-up studies have assessed children with attention-deficit/hyperactivity disorder (ADHD) at multiple time points after their initial diagnosis. Although they document an age-dependent decline in ADHD symptoms, ADHD is also a highly persistent disorder when defined by the persistence of functional impairment[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

American Psychological Association

Journal of Consulting and Clinical Psychology

Results: At age 30, adults with a history of ADHD exhibited substantially wo ey an D. Be yth tha nd su ial de ed de to age 30 were extrapolated using matched census data, male probands were projected to earn $1.27 million less than controls over their working lifetime, reaching retirement with up to 75% lower net worth.

Conclusion: The financial deficit of adults with history of childhood ADHD grows across early adulthood. Projections based on early financial trajectories suggest very large cumulative differences in earnings and savings. With or without persistence of the DSM symptoms, the adult sequela of childhood ADHD can be conceptualized as a chronic condition often requiring consid-erable support from others during adulthood.

Pelham et al. *Journal of Consulting and Clinical Psychology* 2019

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,
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,
ith positive screen
tation was used to
nd correlates of cli-
ADHD.

d prevalence of cur-
.4%. Significant cor-
g male, previously
, and non-Hispanic
s highly comorbid
M-IV disorders as-
nd was associated
npairment. The ma-
ntreated, although
obtained treatment
mental and sub-
s.

are needed to in-
and treatment of
is needed to deter-

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@kd.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]

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

Is ADHD Always a Neurodevelopmental Disorder?:Adult Onset ADHD

- Recent **population studies** raised the intriguing question as to whether adult ADHD is always preceded by childhood onset of symptoms (hence neurodevelopmental) or can develop anew in adult life

Faraone and Biederman JAMA Psychiatry Editorial 2016

Is There an Adult Onset ADHD?

- The age of onset of ADHD by 12 years in DSM-5 is **completely arbitrary** creating the immediate dilemma on how to diagnose patients who have an onset of symptoms >12

Faraone and Biederman JAMA Psychiatry Editorial 2016

Adult Onset ADHD

- A multifactorial etiological view of ADHD suggests that ADHD is a disorder with a continuum of ages of onsets, with some subjects starting their symptoms earlier while others later

Faraone and Biederman JAMA Psychiatry Editorial 2016

EDITORIAL

Can Attention-Deficit/Hyperactivity Disorder Onset Occur in Adulthood?

Stephen V. Faraone, PhD; Joseph Biederman, MD

In this issue of *JAMA Psychiatry*, 2 large, longitudinal, population studies from Brazil[1] and the United Kingdom[2] propose a paradigmatic shift in our understanding of attention-deficit/hyperactivity disorder (ADHD). They conclude, not only that the onset of ADHD can occur in adulthood, but that childhood-onset and adult-onset ADHD may be distinct syndromes.

Prior to these publications, the diagnosis of ADHD in adults had evolved in 2 directions. A meta-analysis[3] of longitudinal studies documented an age-dependent decline in the expression of ADHD symptoms. Two-thirds of youth with ADHD continued to have impairing symptoms of ADHD in young adulthood, despite only 15% meeting full diagnostic criteria for the disorder. The Brazilian and UK studies found the expected rate of persistence to ages 18 to 19 years: 17.2% and 21.9%%, respectively. A longitudinal population study[4] from New Zealand observed a 4.9% persistence rate of ADHD to age 38 years. Practitioners take heed: these low rates of cases meeting full diagnostic criteria ignore the much higher persistence rate of impairing ADHD symptoms, which are relevant in clinical practice.[3]

Related articles

tability for adult ADHD (35%), which could be a sign of substantial measurement error and false-positive diagnoses. Of further concern, another longitudinal study[6] found that current symptoms of ADHD were underreported by adults who had had ADHD in childhood and overreported by adults who did not have ADHD in childhood. Because these concerns suggest that the UK, Brazilian, and New Zealand studies may have underestimated the persistence of ADHD and overestimated the prevalence of adult-onset ADHD, it would be a mistake for practitioners to assume that most adults referred to them with ADHD symptoms will not have a history of ADHD in youth.

These concerns do not argue against the existence of adult-onset ADHD or the idea that it is a clinically relevant syndrome. In fact, as a group, the adult-onset cases showed significant functional impairment. Moreover, one of the studies ruled out the idea that adult-onset ADHD is a misdiagnosis of another disorder. Further support for the validity of adult-onset ADHD comes from a study of referred adults who retrospectively reported childhood symptoms.[7] Based on clinical features and familial transmission, that study concluded that onset of ADHD in late adolescence and early adulthood is valid.[7]

Faraone and Biederman. *JAMA Psychiatry*. 2016 Jul 1;73(7):655-6.

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]

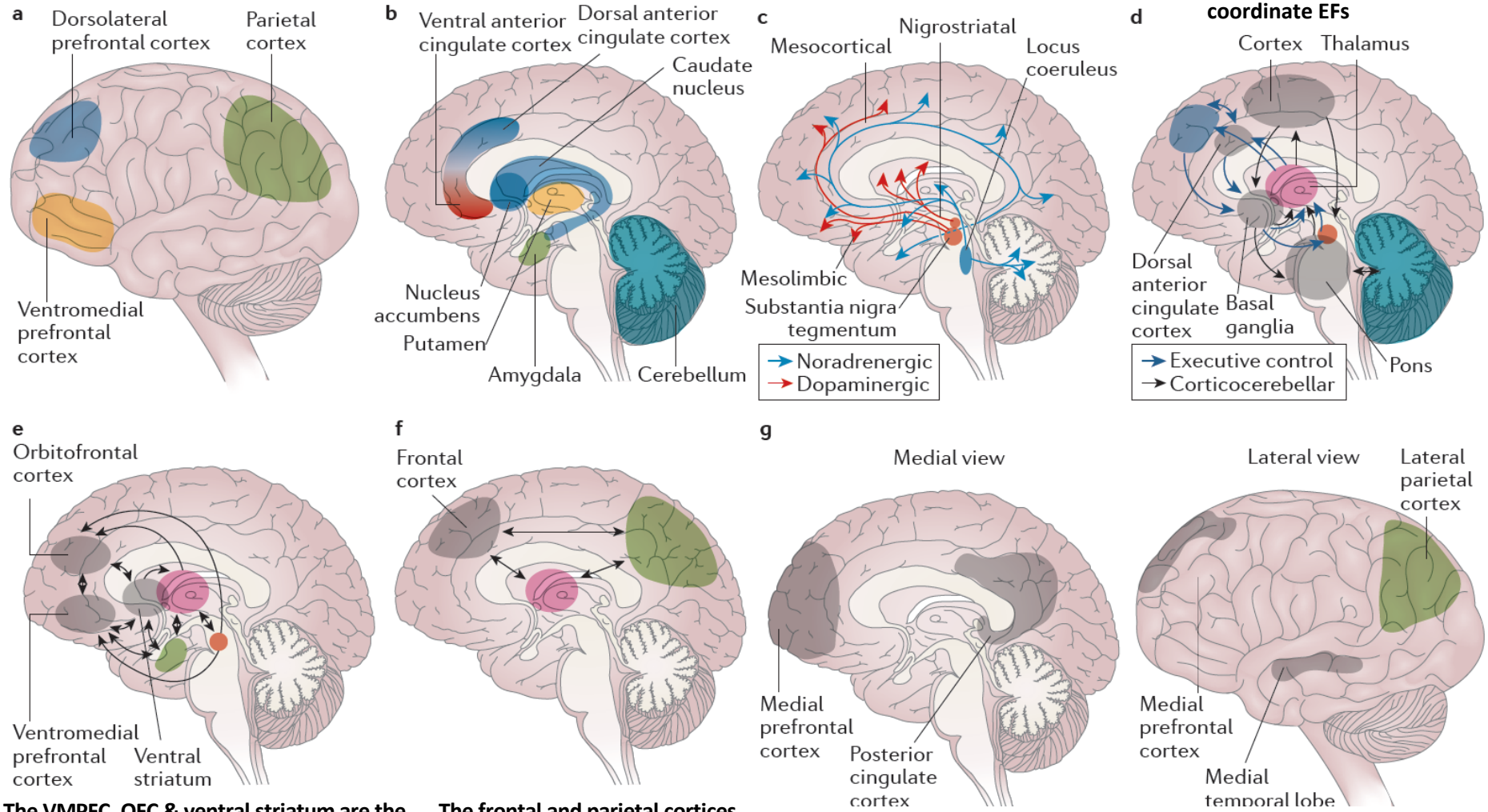
Abstract | Attention-deficit/hyperactivity disorder (ADHD) is a persistent neurodevelopmental disorder that affects 5% of children and adolescents and 2.5% of adults worldwide. Throughout an individual's lifetime, ADHD can increase the risk of other psychiatric disorders, educational and occupational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

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

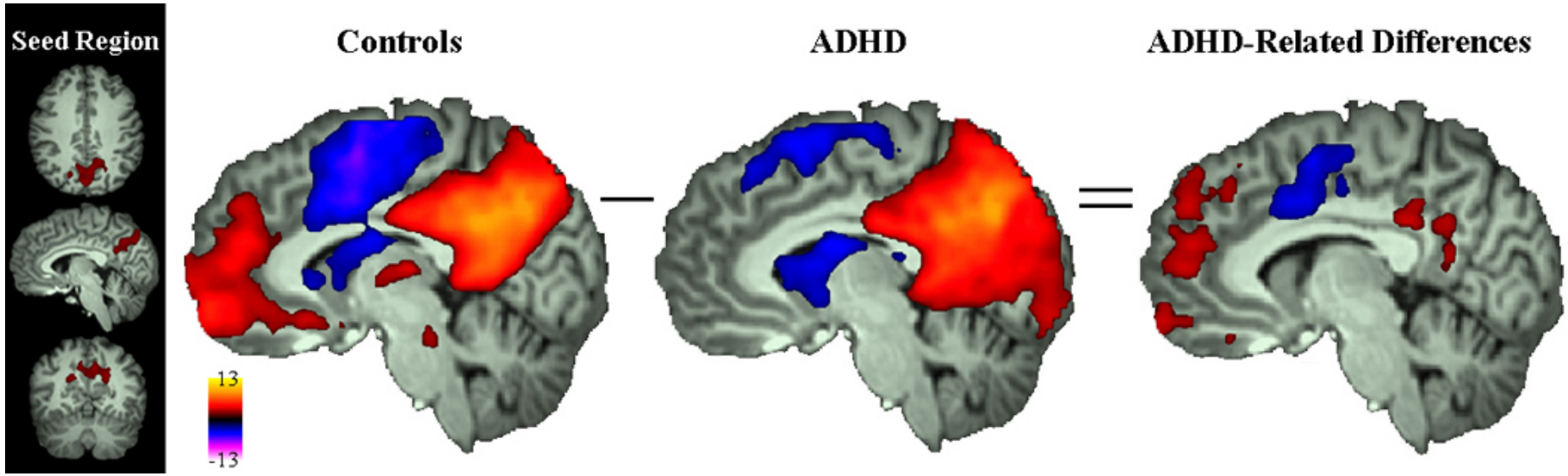
The frontal and parietal cortices and the thalamus support attentional functioning

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

Faraone et al. *Nature Reviews Disease Primers* 2015

Resting-State Functional Connectivity in a Longitudinal Sample of ADHD Children Grown Up

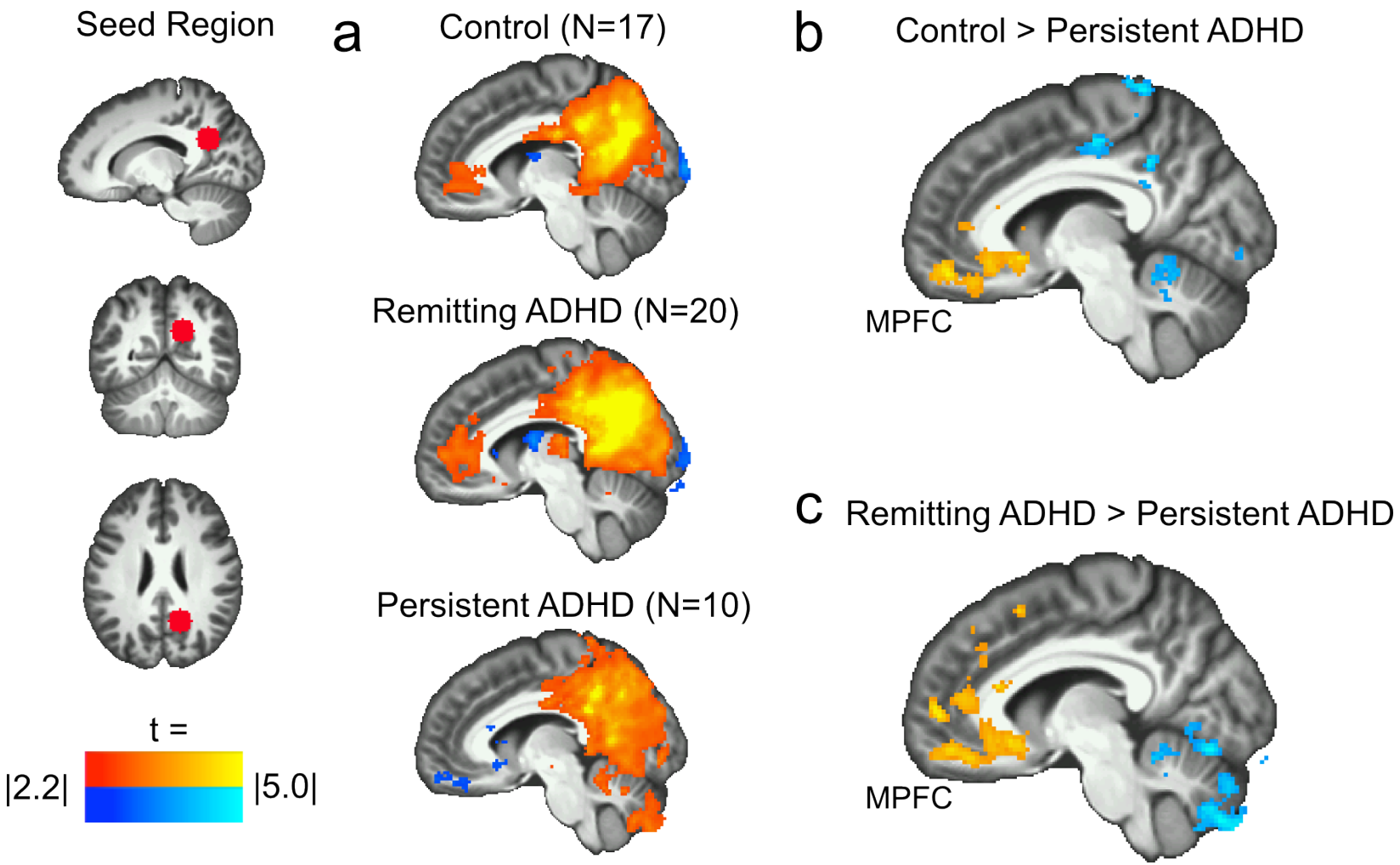
Adult ADHD: Decreased Positive Correlations Between PCC-MPFC



Castellanos et al., 2008

- **20 ADHD participants (mean age = 34.9; 16 male)**
  - **Ascertained retrospectively**
- **20 Controls (mean age = 31.2; 14 male)**

Reduced MPFC-PCC Coupling Reflects Current Diagnostic State of ADHD



Mattfeld et al. *Brain: A Journal of Neurology* 2014, epub: June 10, 2014

Neural Basis of Persistent ADHD

- Persistent ADHD alters intrinsic functional organization of the brain
- Findings supports the idea that adult ADHD diagnosis reflects a true brain difference

Mattfeld et al. *Brain: A Journal of Neurology* 2014, epub: June 10, 2014

Brain Advance Access published June 10, 2014

doi:10.1093/brain/awu137 Brain 2014: Page 1 of 6 | 1

BRAIN
A JOURNAL OF NEUROLOGY

REPORT

Brain differences between persistent and remitted attention deficit hyperactivity disorder

Previous resting state studies examining the brain basis of attention deficit hyperactivity disorder have not distinguished between patients who persist versus those who remit from the diagnosis as adults. To characterize the neurobiological differences and similarities of persistence and remittance, we performed resting state functional magnetic resonance imaging in individuals who had been longitudinally and uniformly characterized as having or not having attention deficit hyperactivity disorder in childhood and again in adulthood (16 years after baseline assessment). Intrinsic functional brain organization was measured in patients who had a persistent diagnosis in childhood and adulthood ($n = 13$), in patients who met diagnosis in childhood but not in adulthood ($n = 22$), and in control participants who never had attention deficit hyperactivity disorder ($n = 17$). A positive functional correlation between posterior cingulate and medial prefrontal cortices, major components of the default-mode network, was reduced only in patients whose diagnosis persisted into adulthood. A negative functional correlation between medial and dorsolateral prefrontal cortices was reduced in both persistent and remitted patients. The neurobiological dissociation between the persistence and remittance of attention deficit hyperactivity disorder may provide a framework for the relation between the clinical diagnosis, which indicates the need for treatment, and additional deficits that are common, such as executive dysfunctions.

who had been longitudinally and uniformly characterized as having or not having attention deficit hyperactivity disorder in childhood and again in adulthood (16 years after baseline assessment). Intrinsic functional brain organization was measured in patients who had a persistent diagnosis in childhood and adulthood ($n = 13$), in patients who met diagnosis in childhood but not in adulthood ($n = 22$), and in control participants who never had attention deficit hyperactivity disorder ($n = 17$). A positive functional correlation between posterior cingulate and medial prefrontal cortices, major components of the default-mode network, was reduced only in patients whose diagnosis persisted into adulthood. A negative functional correlation between medial and dorsolateral prefrontal cortices was reduced in both persistent and remitted patients. The neurobiological dissociation between the persistence and remittance of attention deficit hyperactivity disorder may provide a framework for the relation between the clinical diagnosis, which indicates the need for treatment, and additional deficits that are common, such as executive dysfunctions.

Mattfeld et al. *Brain: A Journal of Neurology* 2014, epub: June 10, 2014

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

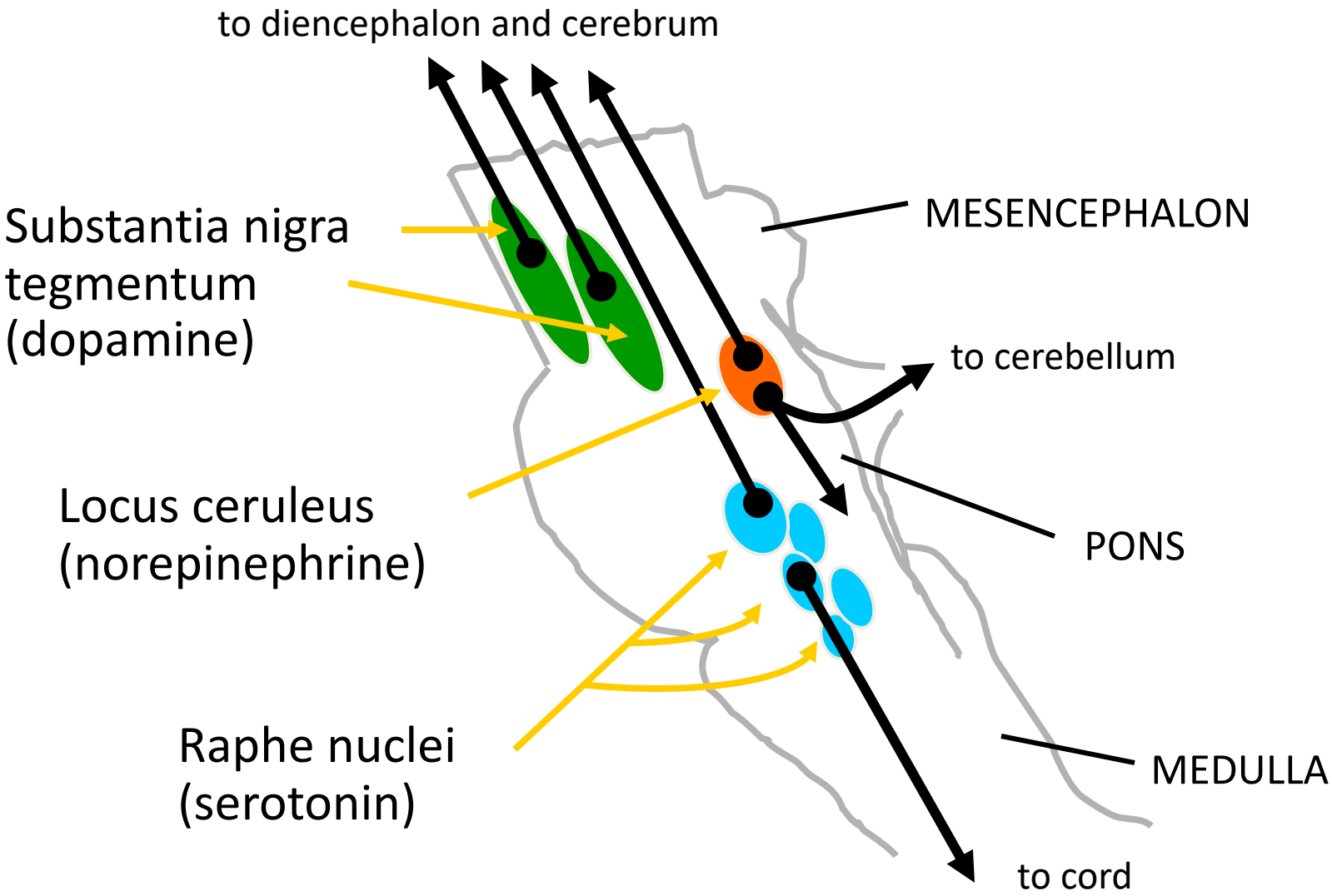
Frontosubcortical Networks and Catecholamines

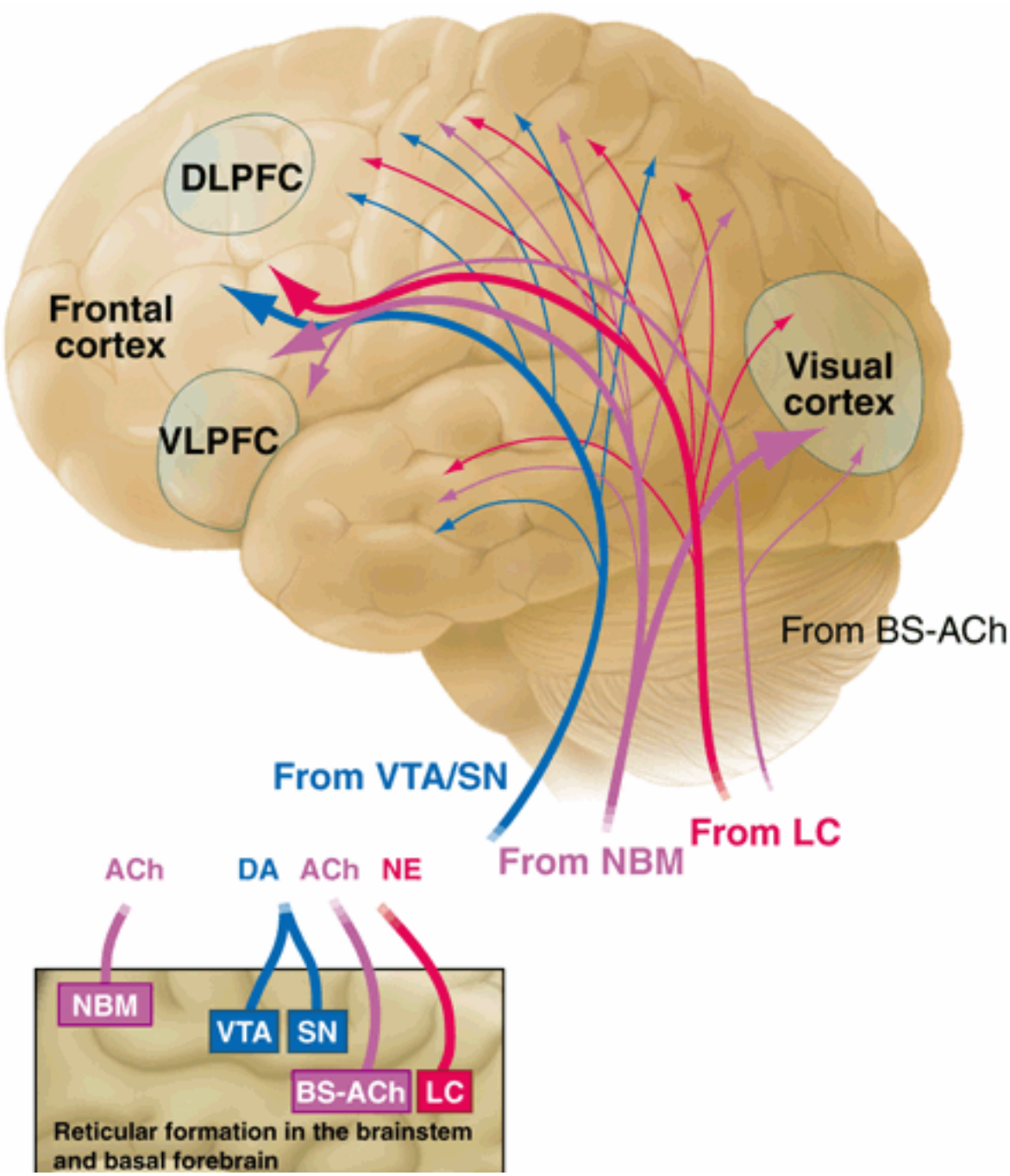
- Dopaminergic and noradrenergic dysregulation abnormalities in fronto subcortical pathways
- Medications that are effective in ADHD are either dopaminergic or noradrenergic

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

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

Brain Stem



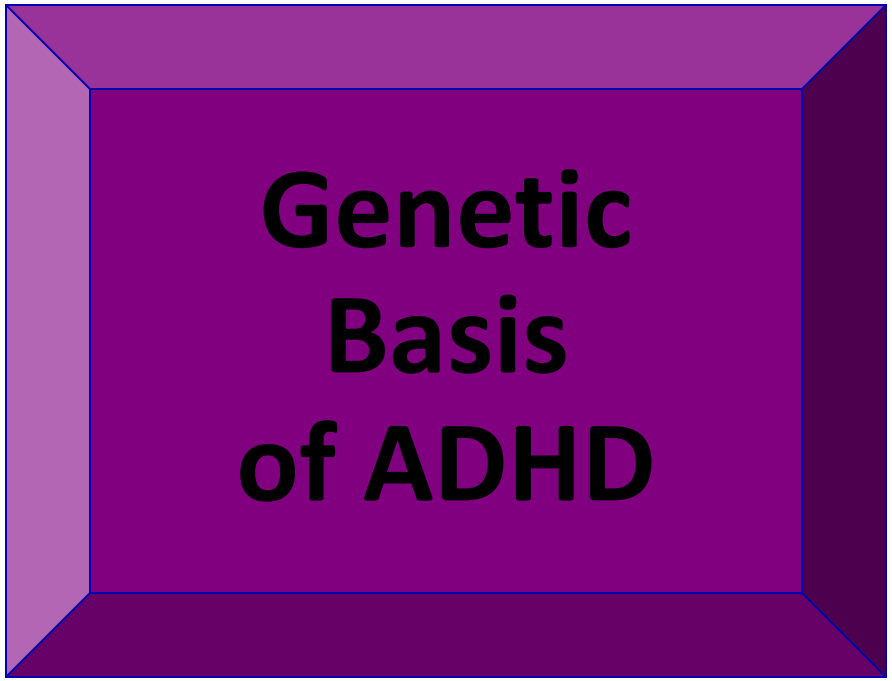

DLPFC
Frontal cortex
VLPFC
Visual cortex
From BS-ACh
From VTA/SN
From NBM
From LC
ACh
DA
ACh
NE
NBM
VTA
SN
BS-ACh
LC
Reticular formation in the brainstem and basal forebrain

ADHD as a Neurobiological Disorder: Genetic Findings

ADHD: Genetics

Twin Studies

Family Studies

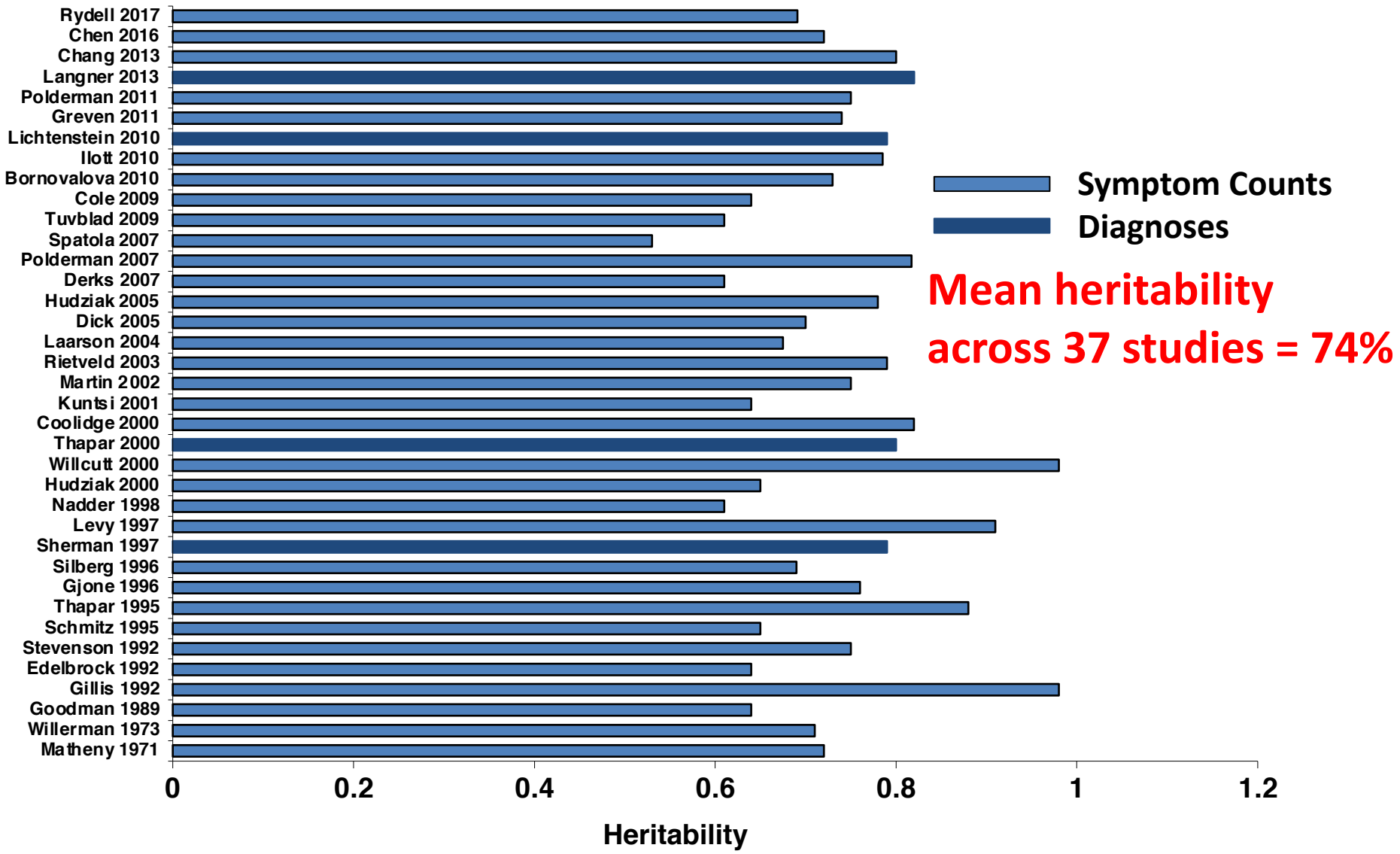


Adoption Studies

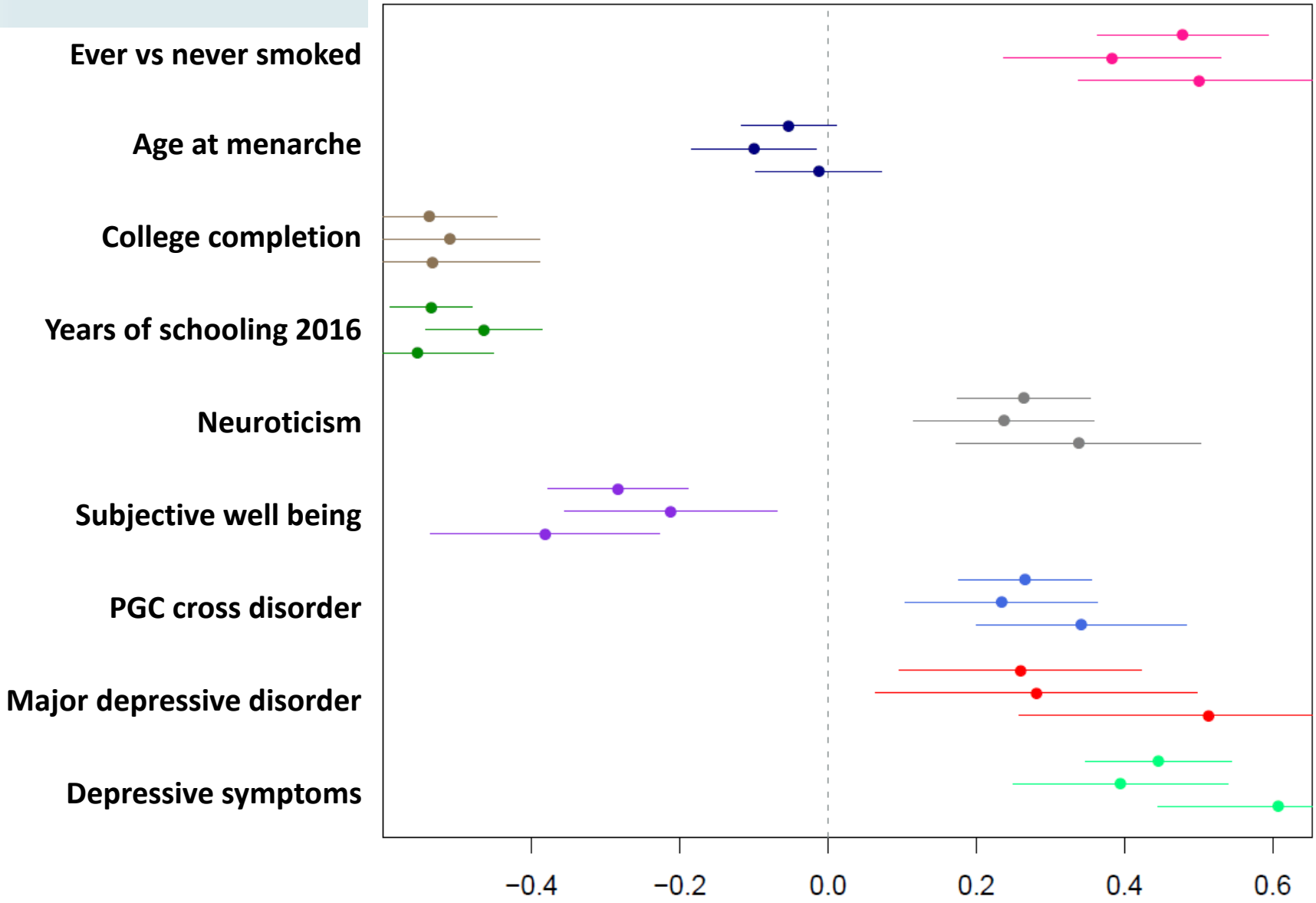
Molecular Genetics

Twin Studies of ADHD

(Faraone & Larsson, Molecular Psychiatry, 2018)

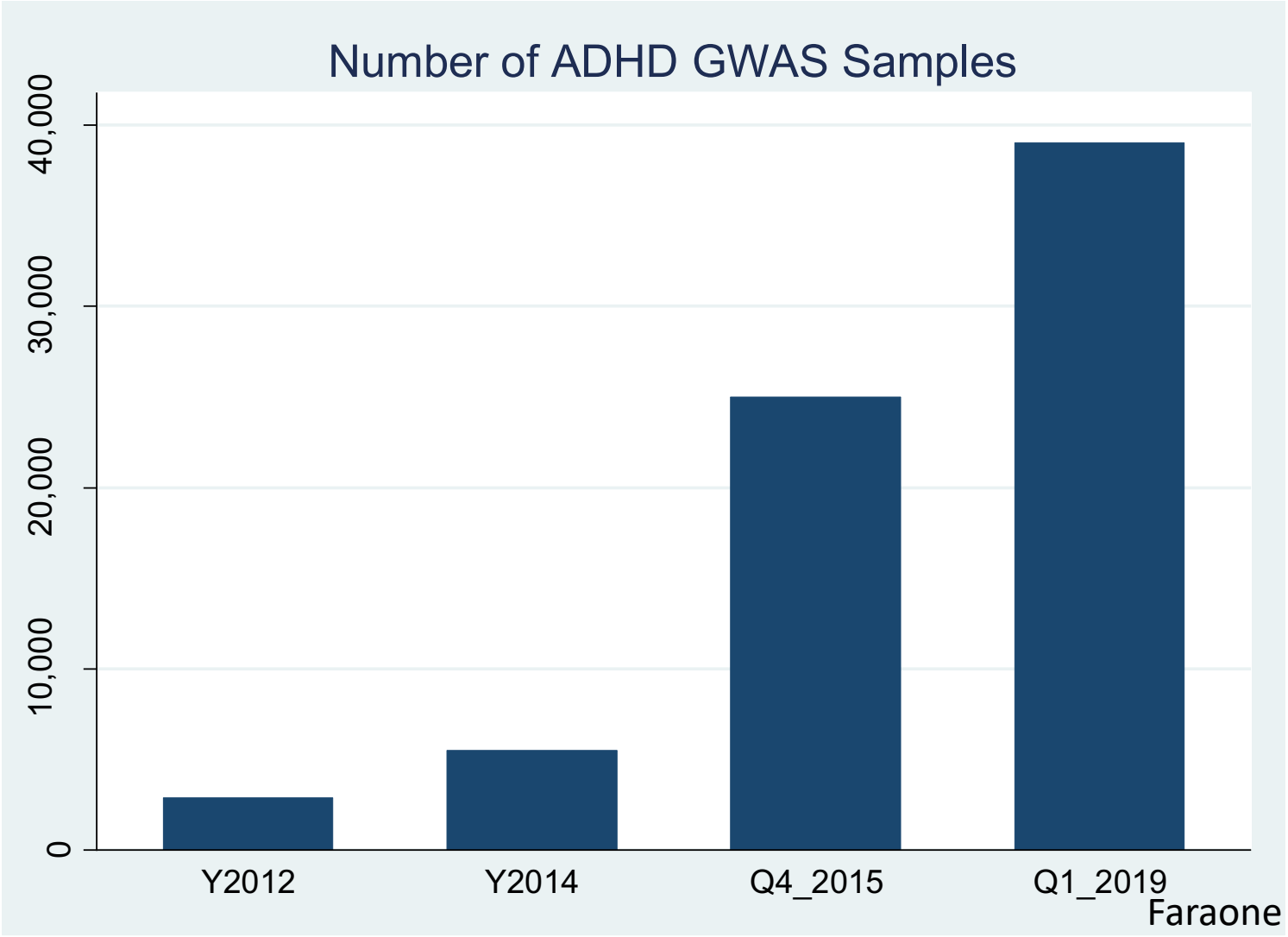


Genetic Correlations with other Traits



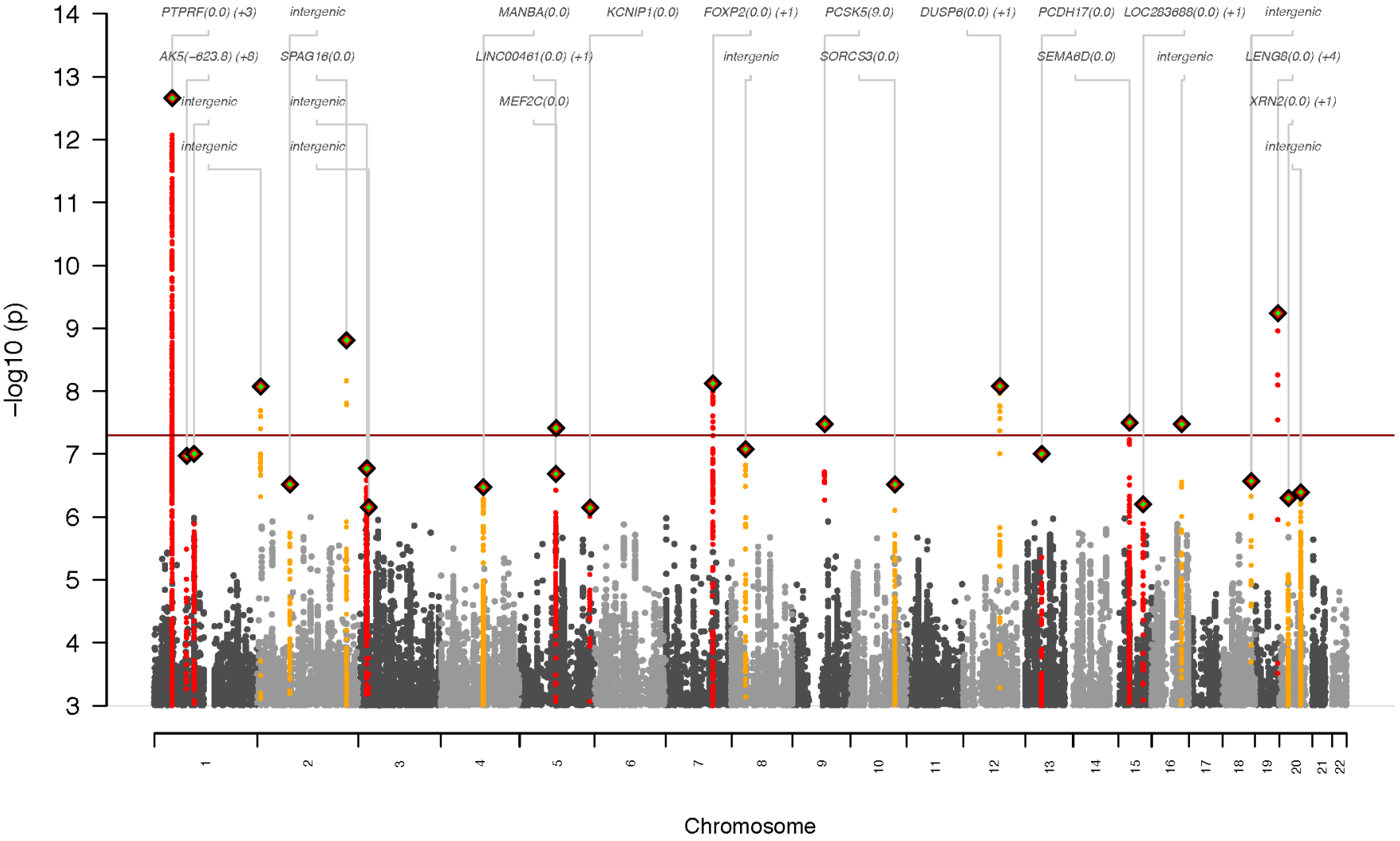
Upper line: ADHD children + adults
Middle line: ADHD children
Lower line: ADHD adults

New Results from Genomewide Association Studies (GWAS)



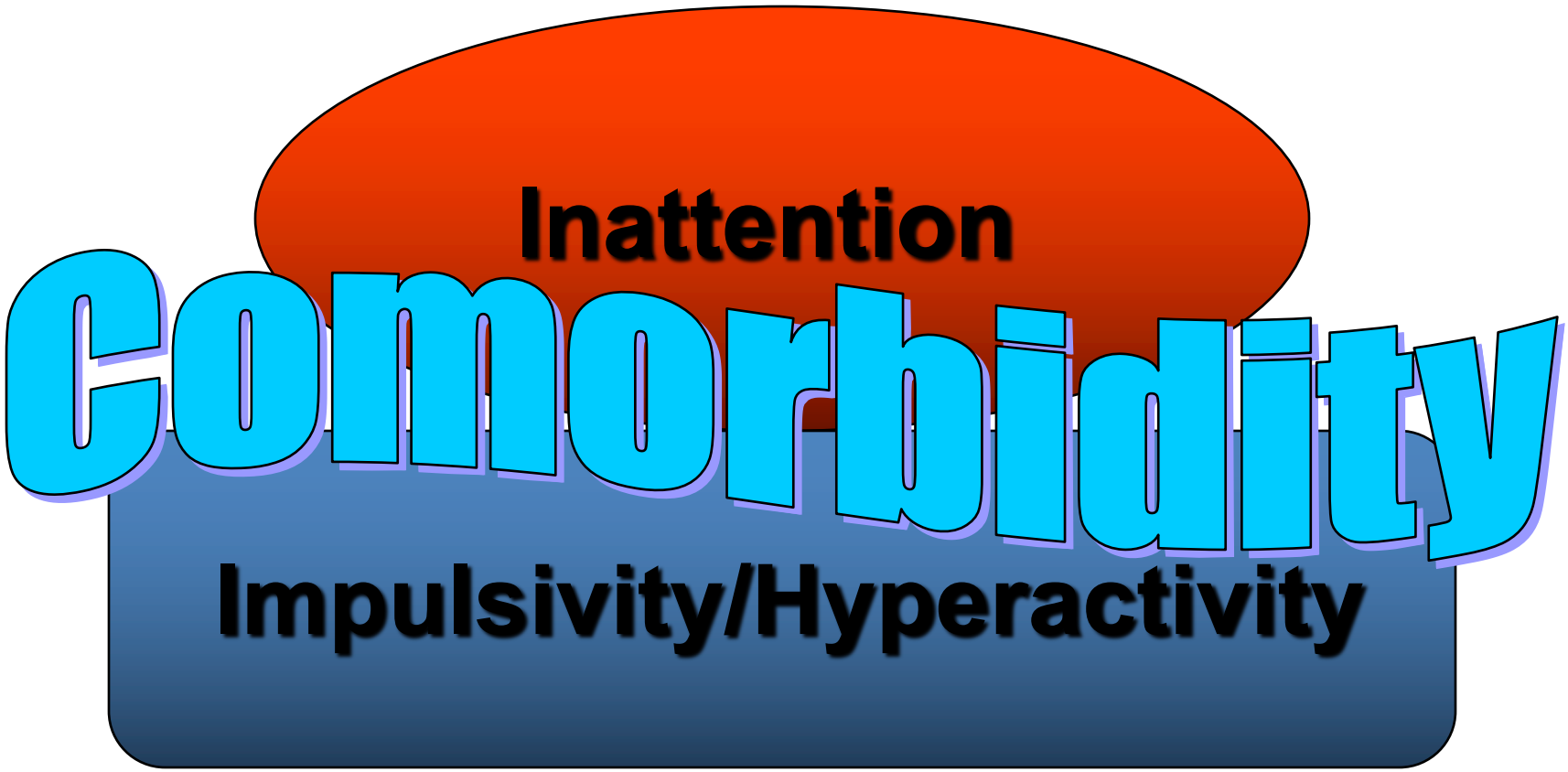
Faraone et al, 2015

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

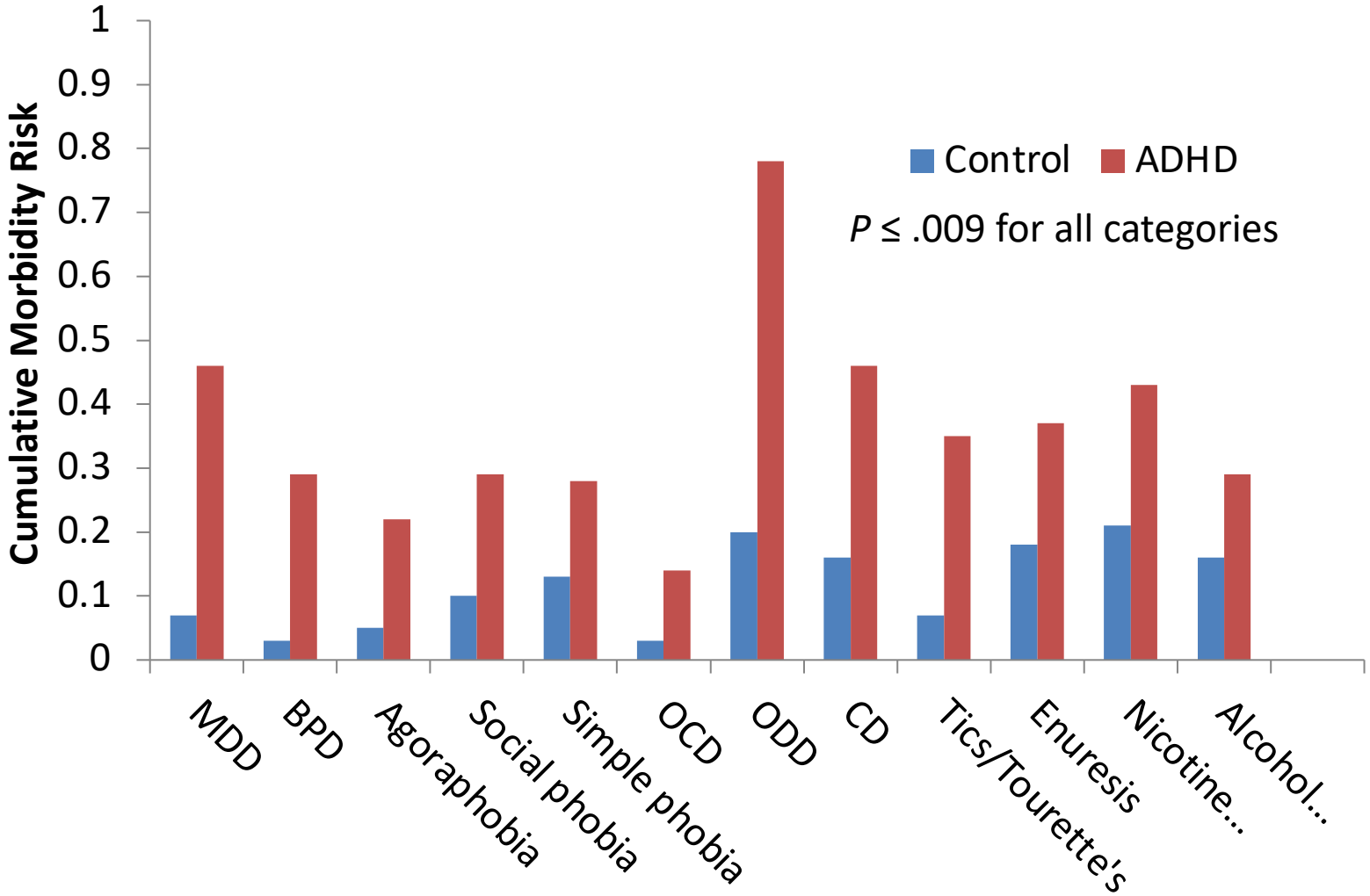


PGC ADHD/iPSYCH-SSI-Broad Collaboration

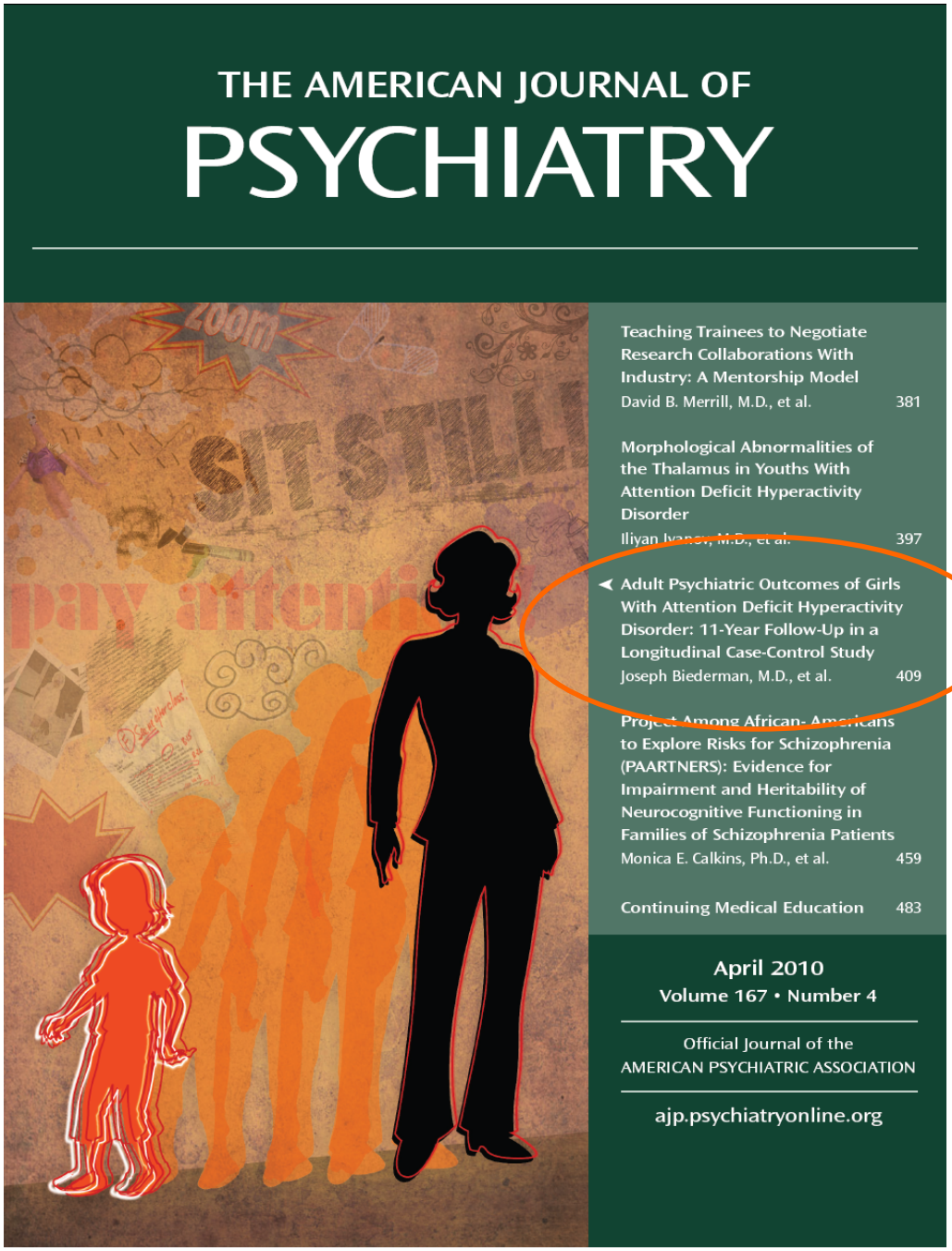
ADHD Diagnostic Considerations



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

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 develop-

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

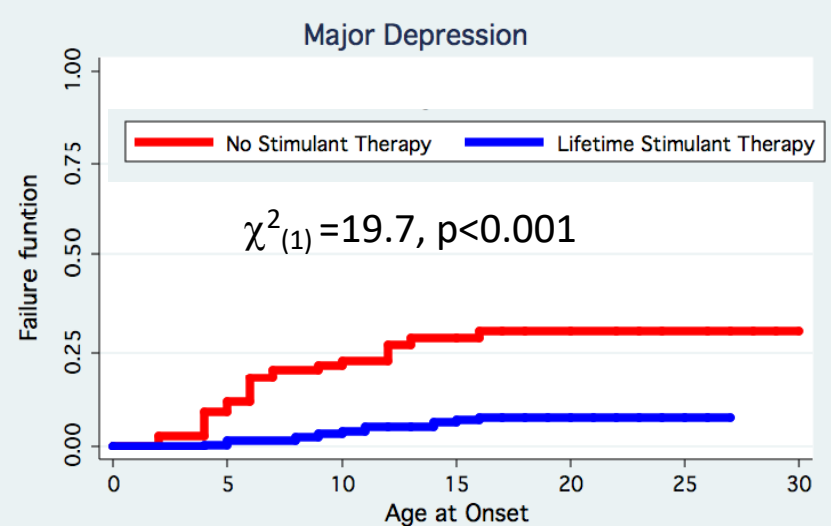
112 (80%) and 105 (88%) of the children in the ADHD and control groups, respectively, were reassessed (mean age: 22 years). We examined the association between stimulant treatment in childhood and adolescence and subsequent comorbid disorders and grade retention by using proportional hazards survival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

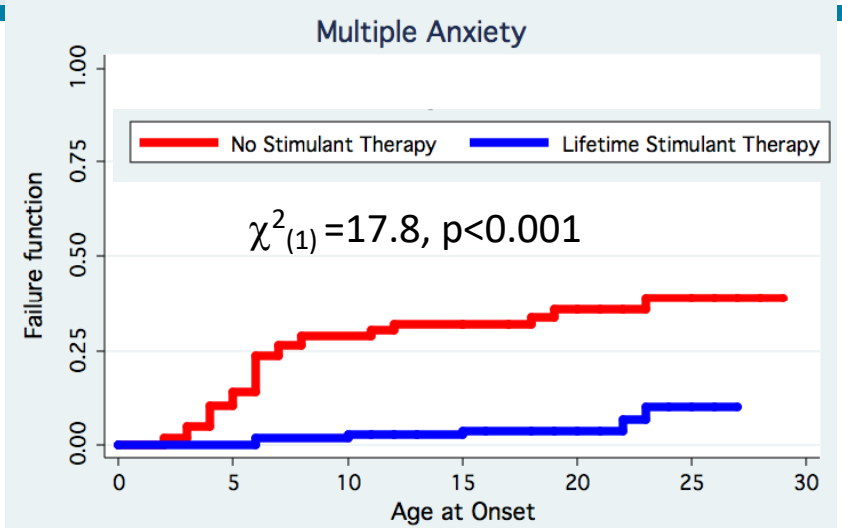
RESULTS: Of the 112 participants with ADHD, 82 (73%) were previously treated with stimulants. Participants with ADHD who were treated with stimulants were significantly less likely to subsequently develop depressive and anxiety disorders and disruptive behavior and less likely to repeat a grade compared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

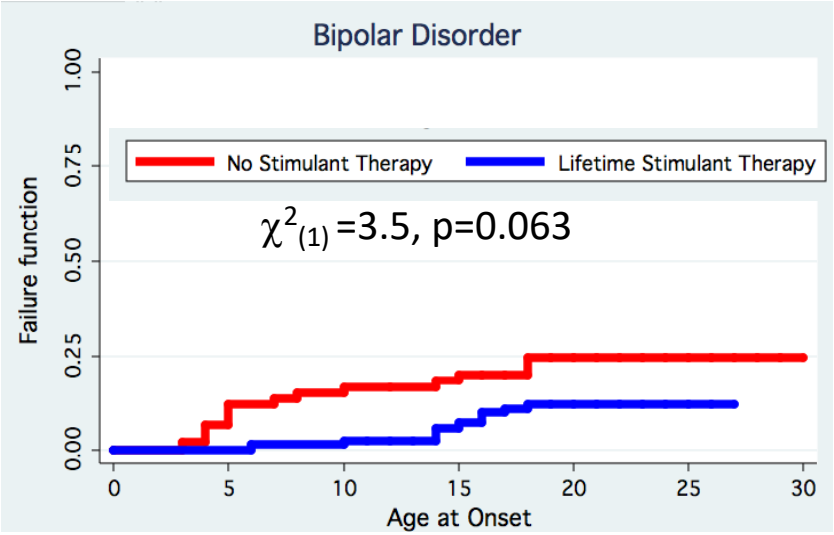
CONCLUSIONS: We found evidence that stimulant treatment decreases the risk for subsequent comorbid psychiatric disorders and academic failure in youth with ADHD. *Pediatrics* 2009;124:71–78

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

Protective Effect of Stimulants on Comorbidity

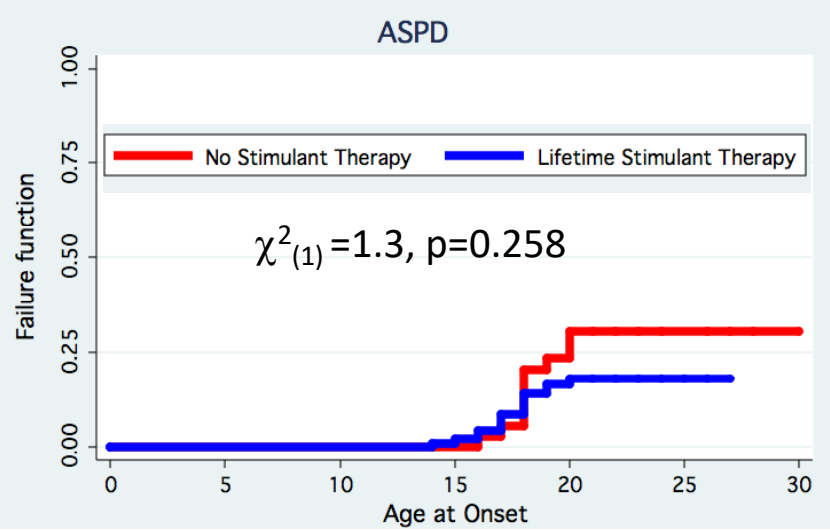


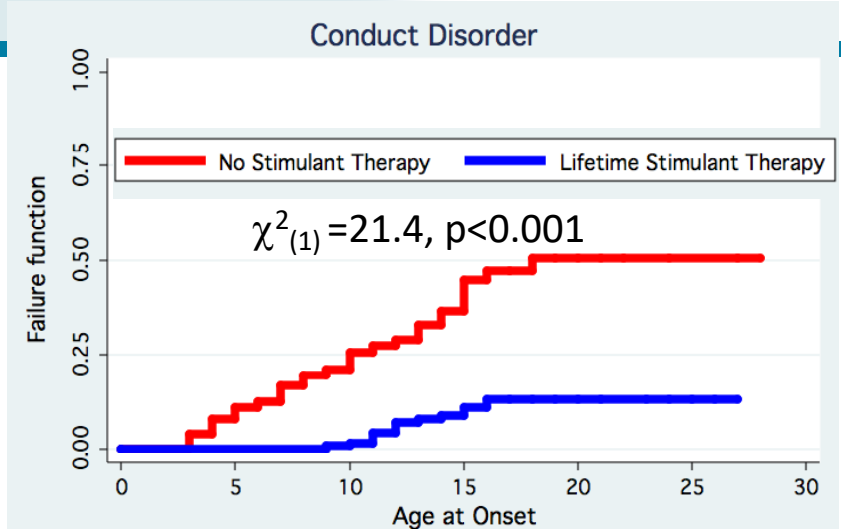


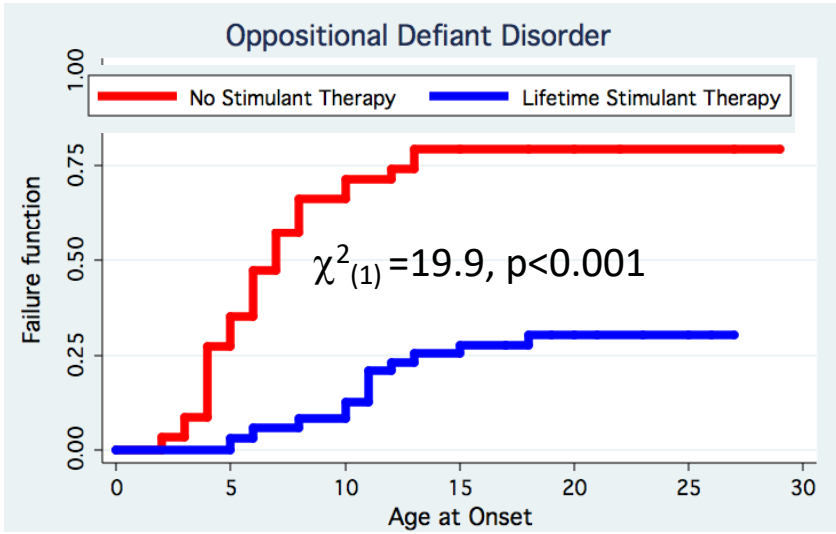


Biederman et al.
Pediatrics 2009

Protective Effect of Stimulants on Comorbidity

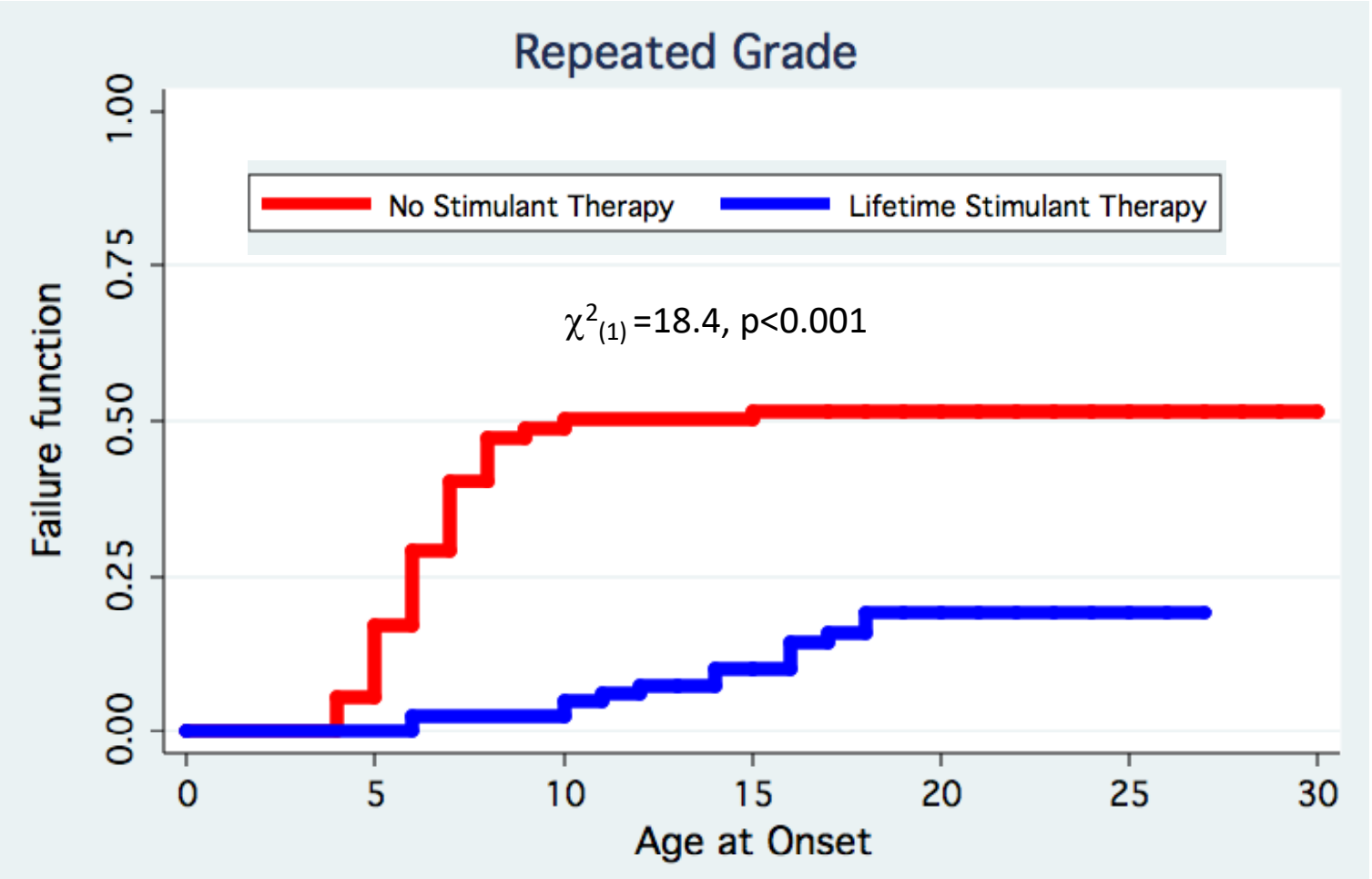






Biederman et al.
Pediatrics 2009

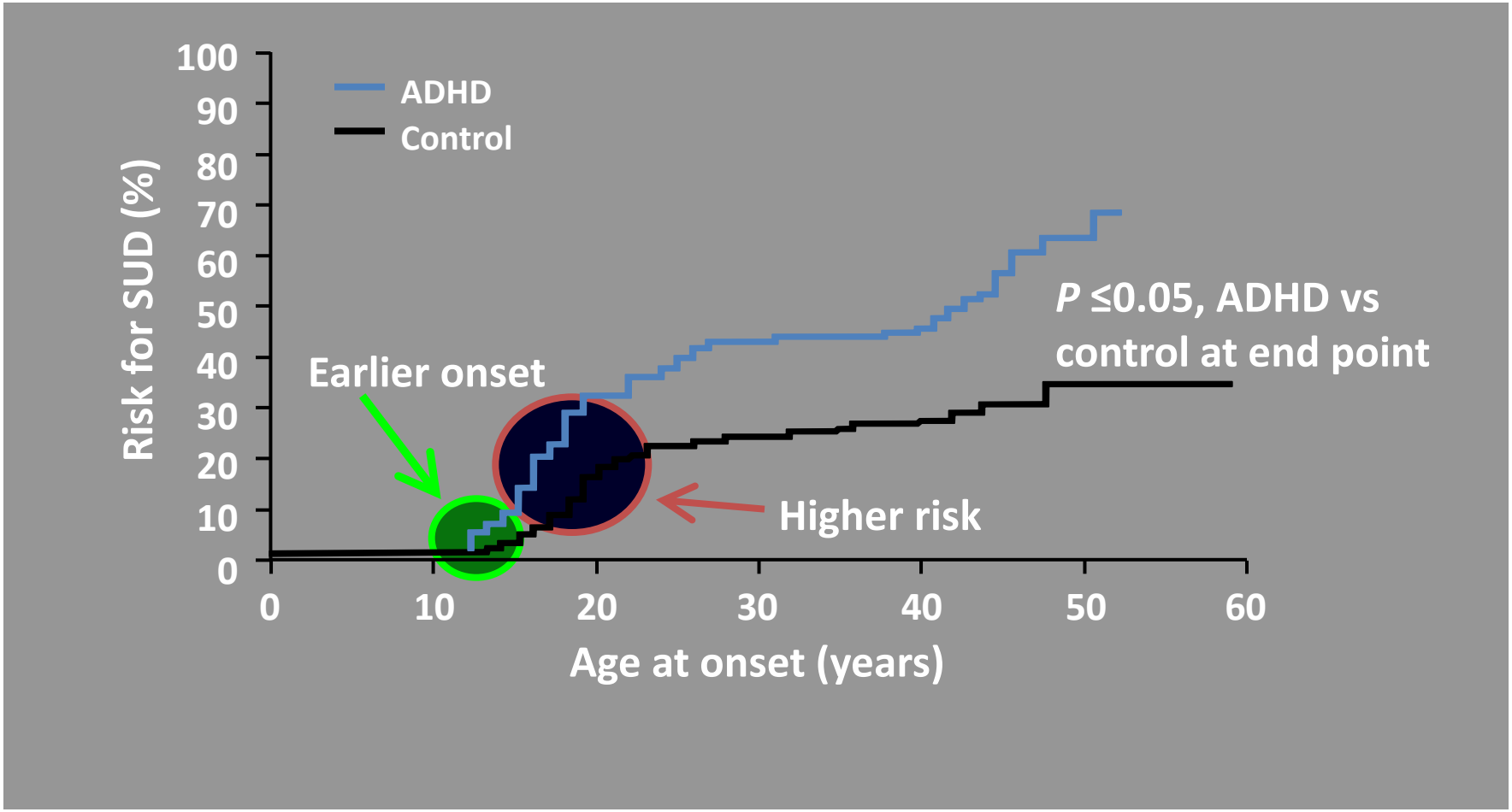
Protective Effect of Stimulants



Biederman et al. *Pediatrics* 2009

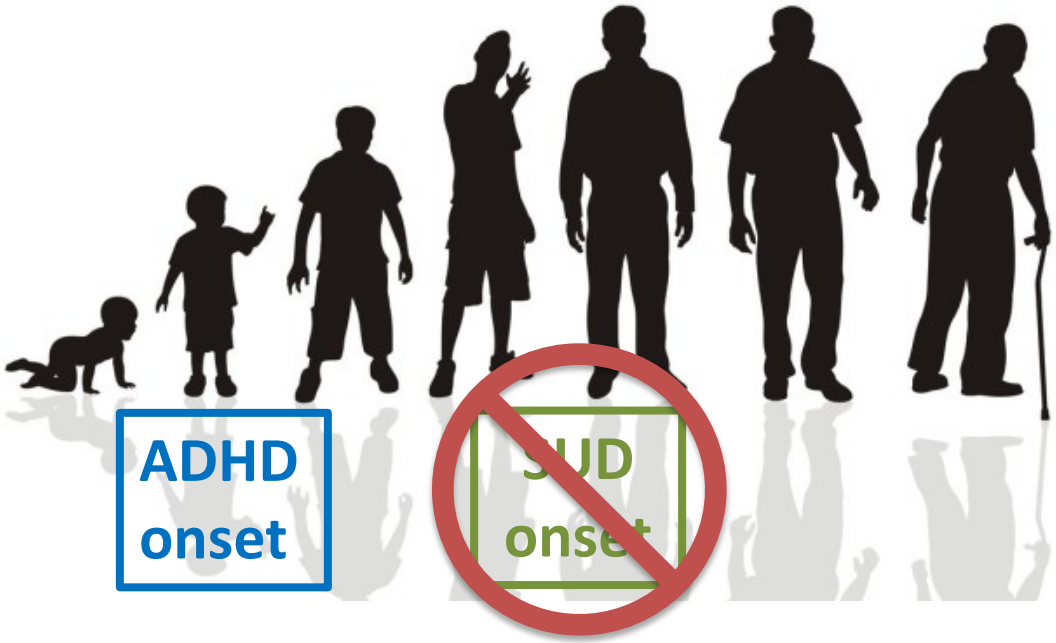
ADHD and Substance Abuse

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



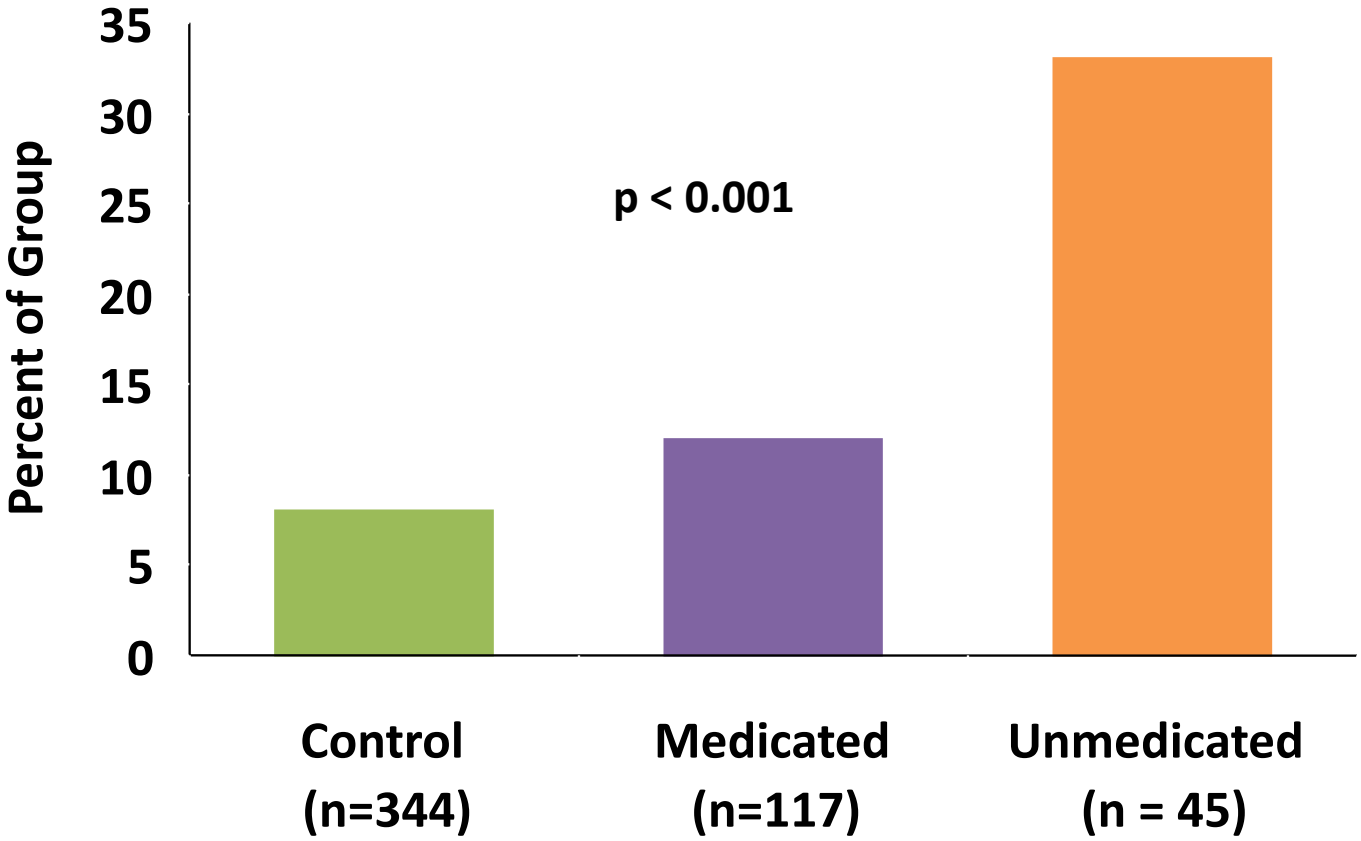
Wilens et al. *J Nerv Ment Dis*. 1997;185(8): 475-482.

Clinical Implications: Potential for Prevention and early intervention



Treating ADHD ↓ risk for SUD in youth with ADHD

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



Biederman, Wilens, Mick et al., Pediatric 1999

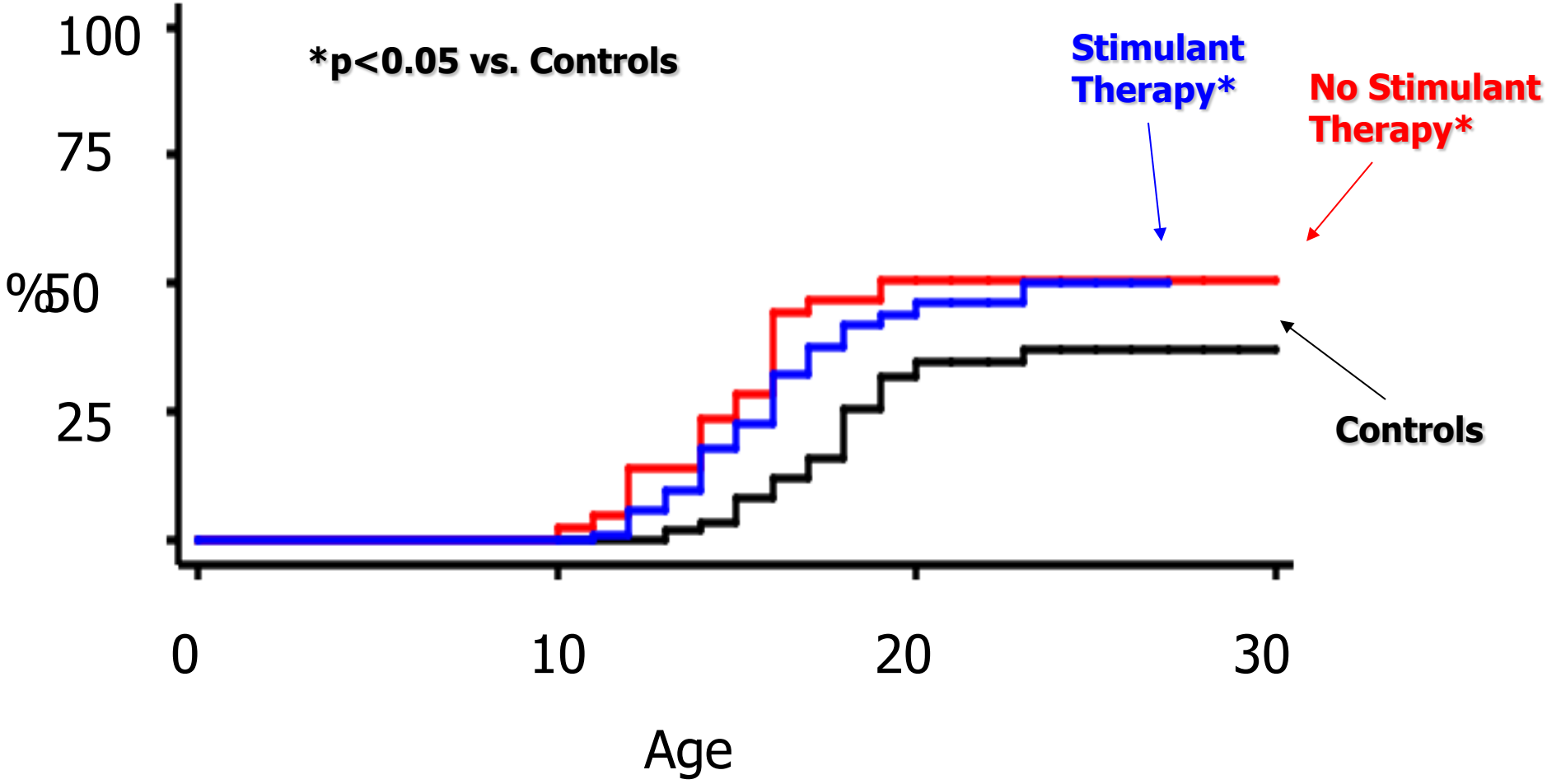
THE AMERICAN JOURNAL OF
PSYCHIATRY

May 2008
Volume 165 • Number 5

Official Journal of the
AMERICAN PSYCHIATRIC ASSOCIATION

ajp.psychiatryonline.org

Stimulant Therapy and Subsequent Risk for Substance Dependence Disorders



Biederman et al. *Am J Psychiatry*. 2008 Mar 3

ONLINE FIRST

Stimulant Medication and Substance Use Outcomes

A Meta-analysis

Kathryn L. Humphreys, MA, EdM; Timothy Eng, BS; Steve S. Lee, PhD

Conclusions: These results provide an important update and suggest that treatment of attention-deficit/hyperactivity disorder with stimulant medication neither protects nor increases the risk of later substance use disorders.

ing childhood and later substance outcomes (ie, lifetime substance use and substance abuse or dependence).

Data Sources: Studies published between January 1980 and February 2012 were identified using review articles, PubMed, and pertinent listservs.

Study Selection: Studies with longitudinal designs in which medication treatment preceded the measurement of substance outcomes.

Data Extraction and Synthesis: Odds ratios were extracted or provided by the study authors. Odds ratios were obtained for lifetime use (ever used) and abuse or de-

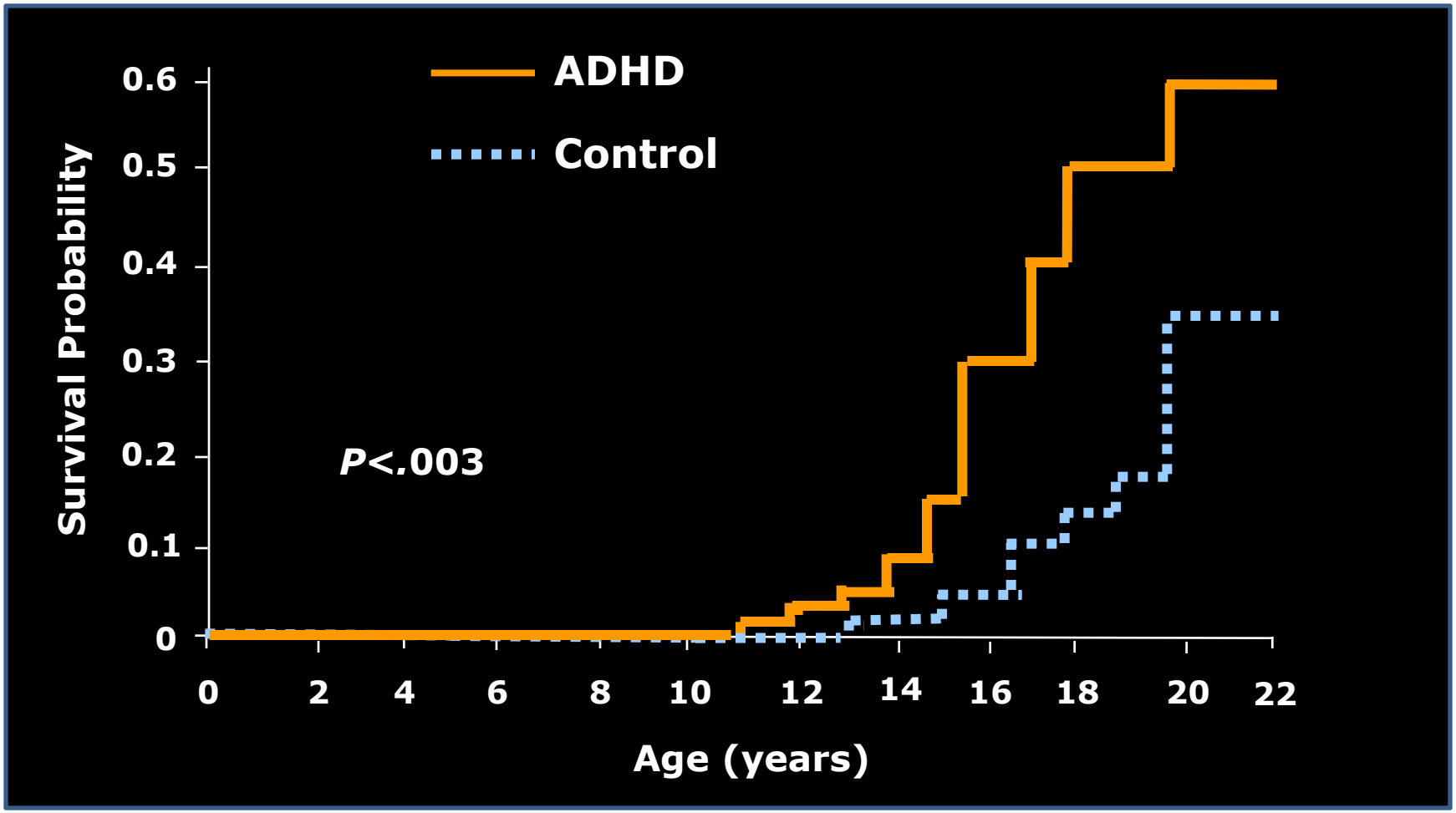
suggested comparable outcomes between children with and without medication treatment history for any substance use and abuse or dependence outcome across all substance types.

Conclusions: These results provide an important update and suggest that treatment of attention-deficit/hyperactivity disorder with stimulant medication neither protects nor increases the risk of later substance use disorders.

JAMA Psychiatry.
Published online May 29, 2013.
doi:10.1001/jamapsychiatry.2013.1273

Humphreys et al. *JAMA Psychiatry* 2013

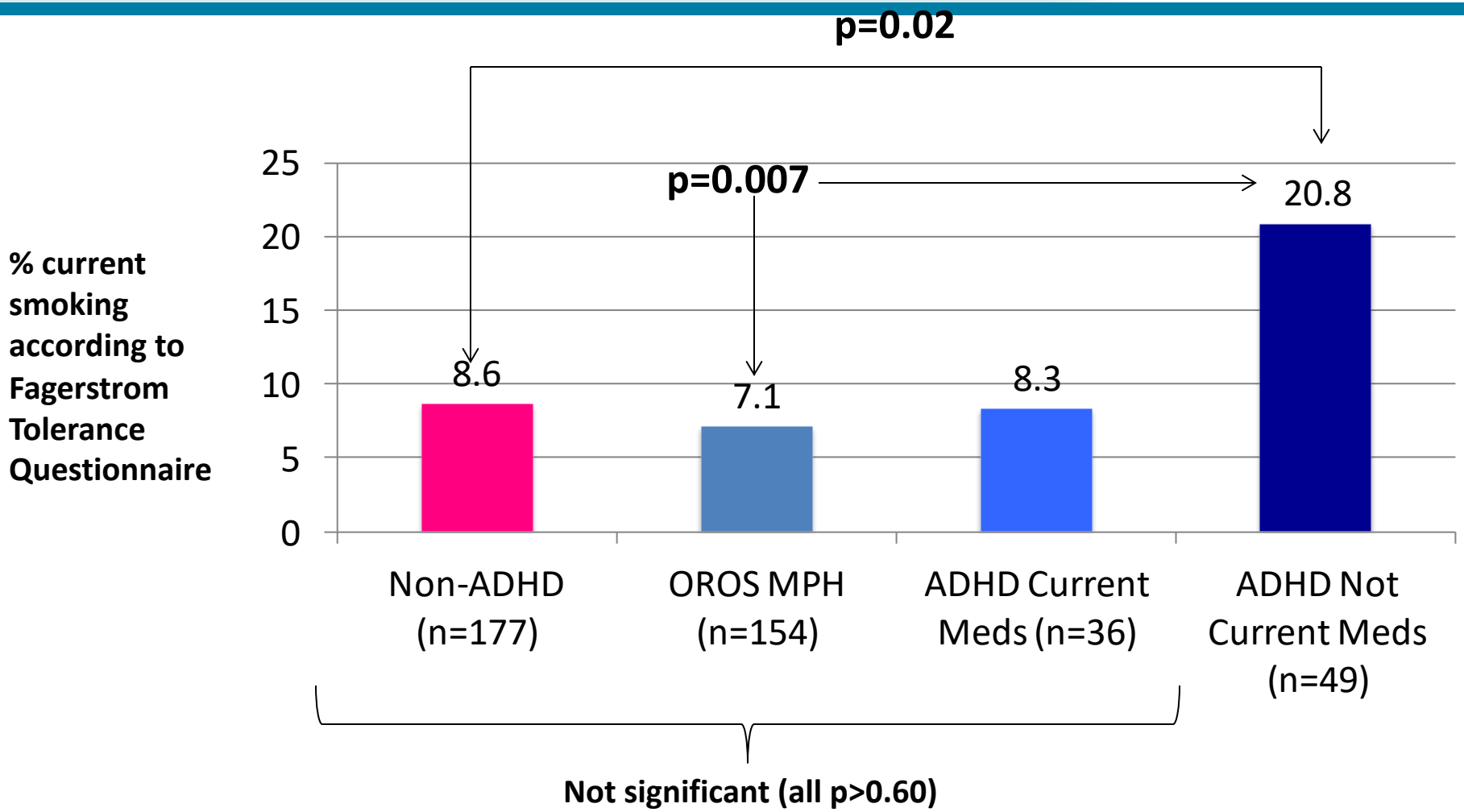
Onset of Nicotine Use in Children and Adolescents with ADHD



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, Jounal of Pediatrics 2012

THE JOURNAL OF PEDIATRICS • www.jpeds.com

Do Stimulants Reduce the Risk for Cigarette Smoking in Youth with Attention-Deficit Hyperactivity Disorder? A Prospective, Long-Term, Open-Label Study of Extended-Release Methylphenidate

Paul Hammerness, MD[1], Gagan Joshi, MD[1], Robert Doyle, MD[1], Anna Georgiopoulos, MD[1], Daniel Geller, MD[1], Thomas Spencer, MD[1], Carter R. Petty, MA[1], Stephen V. Faraone, PhD[2], and Joseph Biederman, MD[1]

Conclusion Although considered preliminary until replicated in future randomized clinical trials, the findings from this single-site, open-label study suggest that stimulant treatment may contribute to a decreased risk for smoking in adolescents with ADHD. If confirmed, this finding would have significant clinical and public health impacts. *(J Pediatr 2012;■:■-■).*

(n = 103) and non-ADHD comparators (n = 188) of similar age and sex assessed with the same assessment battery as that used in subjects participating in the clinical trial.

Results The smoking rate at endpoint (mean, 10 months of methylphenidate treatment) was low in the clinical trial subjects and not significantly different from that in the non-ADHD comparators or the ADHD comparators receiving stimulants naturalistically (7.1% vs 8.0% vs 10.9%; $P > .20$). In contrast, the smoking rate was significantly lower in the clinical trial subjects than in the naturalistic sample of ADHD comparators who were not receiving stimulant treatment (7.1% vs 19.6%; $P = .009$ [not significant], adjusting for comorbid conduct disorder and alcohol and drug abuse).

Conclusion Although considered preliminary until replicated in future randomized clinical trials, the findings from this single-site, open-label study suggest that stimulant treatment may contribute to a decreased risk for smoking in adolescents with ADHD. If confirmed, this finding would have significant clinical and public health impacts. *(J Pediatr 2012;■:■-■).*

Hammerness et al. *J Pediatr* 2012

Cigarette smoking as a risk factor for other substance misuse: 10-year study of individuals with and without attention-deficit hyperactivity disorder

Joseph Biederman, Carter R. Petty, Paul Hammerness, Holly Batchelder and Stephen V. Faraone

Background
We previously documented that cigarette smoking is a risk factor for subsequent alcohol and drug misuse and

Results
Youth with ADHD who smoked cigarettes ($n = 27$) were significantly more likely to subsequently develop drug misuse and dependence compared with youth with ADHD who did not smoke ($n = 138$, $P<0.05$).

Conclusions
These results confirm that cigarette smoking increases the risk for subsequent drug and alcohol use disorders among individuals with ADHD. These findings have important public health implications, and underscore the already pressing need to prevent smoking in children with ADHD.

Conclusions
These results confirm that cigarette smoking increases the risk for subsequent drug and alcohol use disorders among individuals with ADHD. These findings have important public health implications, and underscore the already pressing need to prevent smoking in children with ADHD.

Declaration of interest
J.B. is currently receiving research support from: Elminda, Janssen, McNeil and Shire. He has received: honoraria from the Massachusetts General Hospital (MGH) Psychiatry

Exhibitions, Shire, the Spanish Child Psychiatry Association, The Stanley Foundation, UCB Pharma, Veritas, and Wyeth. In the past 12 months, P.H. has participated in CME activities/writing supported by Shire Pharmaceuticals and, as an investigator/principal investigator, in research funded by: Cephalon, Forest, GlaxoSmithKline, Johnson & Johnson, McNeil, Novartis, Ortho-McNeil Janssen, Shire, Takeda Pharmaceuticals and Elminda. P.H. has also received honoraria from commercial entities supporting the MGH Psychiatry Academy (www.mghcme.org). In the past year, S.V.F. received consulting income and research support from Shire, Otsuka and Alcobra and research support from the National Institutes of Health. He has also received consulting fees or was on advisory boards or participated in CME programmes sponsored by: Shire, McNeil, Janssen, Novartis, Pfizer and Eli Lilly.

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)

Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis

Samuele Cortese, Nicoletta Adamo, Cinzia Del Giovane, Christina Mohr-Jensen, Adrian J Hayes, Sara Carucci, Lauren Z Atkinson, Luca Tessari, Tobias Banaschewski, David Coghill, Chris Hollis, Emily Simonoff, Alessandro Zuddas, Corrado Barbui, Marianna Purgato, Hans-Christoph Steinhausen, Farhad Shokraneh, Jun Xia, Andrea Cipriani

Summary

Background The benefits and safety of medications for attention-deficit hyperactivity disorder (ADHD) remain

Interpretation Our findings represent the most comprehensive available evidence base to inform patients, families, clinicians, guideline developers, and policymakers on the choice of ADHD medications across age groups. Taking into account both efficacy and safety, evidence from this meta-analysis supports methylphenidate in children and adolescents, and amphetamines in adults, as preferred first-choice medications for the short-term treatment of ADHD. New research should be funded urgently to assess long-term effects of these drugs.

clinicians' ratings) and tolerability (proportion of patients who dropped out of studies because of side-effects) at timepoints closest to 12 weeks, 26 weeks, and 52 weeks. We estimated summary odds ratios (ORs) and standardised mean differences (SMDs) using pairwise and network meta-analysis with random effects. We assessed the risk of bias of individual studies with the Cochrane risk of bias tool and confidence of estimates with the Grading of Recommendations Assessment, Development, and Evaluation approach for network meta-analyses. This study is registered with PROSPERO, number CRD42014008976.

Lancet Psychiatry 2018;

Experimental Sciences (CNS and Psychiatry), Faculty of Medicine, University of Southampton, Southampton, UK (S Cortese MD); Solent NHS Trust, Southampton, UK (S Cortese); New York University Child Study Center, New York, NY, USA (S Cortese);

Cortese et al. *Lancet Psychiatry*. 2018 Sep;5(9):727-738.

Original article

Quantifying the Protective Effects of Stimulants on Functional Outcomes in Attention-Deficit/Hyperactivity Disorder: A Focus on Number Needed to Treat Statistic and Sex Effects

Joseph Biederman, M.D. [a,b,*], Maura DiSalvo, M.P.H. [a], Ronna Fried, Ed.D. [a,b], K. Yvonne Woodworth [a], Itai Biederman, M.B.A. [a], and Stephen V. Faraone, Ph.D. [c,d]

[a] *Clinical and Research Programs in Pediatric Psychopharmacology and Adult ADHD, Massachusetts General Hospital, Boston, Massachusetts*
[b] *Department of Psychiatry, Harvard Medical School, Boston, Massachusetts*
[c] *Department of Neuroscience and Physiology, SUNY Upstate Medical University, Syracuse, New York*
[d] *K.G. Jebsen Centre for Psychiatric Disorders, Department of Biomedicine, University of Bergen, Bergen, Norway*

Article history: Received January 22, 2019; Accepted May 23, 2019
Keywords: ADHD; Youth; Gender; Stimulants; Protective effects; Functional outcomes

A B S T R A C T

Purpose: The aim of the study was to help quantify the protective effects of stimulant treatment on important functional outcomes in attention-deficit/hyperactivity disorder (ADHD) using the number needed to treat (NNT) statistic and examine whether these effects are moderated by sex.
Methods: Subjects were derived from three independent samples, two similarly designed case–control, 10-year prospective follow-up studies of boys and girls with and without ADHD grown up and a cross-sectional randomized clinical trial of lisdexamfetamine on driving performance and behavior. For all studies, subjects were evaluated with structured diagnostic interviews. To measure psychopharmacologic treatment in the follow-up studies, we collected information about each subject's stimulant medication use, age at onset, and age at termination of treatment. Subjects in the driving study underwent two driving simulation assessments (premedication and after 6 weeks of treatment on lisdexamfetamine or placebo). For each outcome, we ran a logistic regression model that included an interaction between sex and treatment status. Lifetime rates were used to calculate the NNT statistic. We also calculated adjusted NNT statistics that accounted for sex, age, socioeconomic status, and family intactness.
Results: The NNTs were very low, ranging from 3 to 10. No interaction effects with sex were detected (all $p > .05$). The adjusted NNTs mostly remained the same with the exception of any substance use disorder, which increased after controlling for age.
Conclusions: Stimulants have strong protective effects on functional outcomes in youth with ADHD that are not moderated by sex. These results support the critical importance of early identification and treatment of children with ADHD of both sexes.

IMPLICATIONS AND CONTRIBUTION

Using the number needed to treat statistic to quantify the protective effects of stimulants, this analysis found that stimulant treatment has strong protective effects on important functional outcomes in youth with attention-deficit/hyperactivity disorder supporting the critical importance of early identification and treatment of children with attention-deficit/hyperactivity disorder of both sexes.

IMPLICATIONS AND CONTRIBUTION

Using the number needed to treat statistic to quantify the protective effects of stimulants, this analysis found that stimulant treatment has strong protective effects on important functional outcomes in youth with attention-deficit/hyperactivity disorder supporting the critical importance of early identification and treatment of children with attention-deficit/hyperactivity disorder of both sexes.

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