Are the effects of methylphenidate really uncertain?

Samuele Cortese, M.D., Ph.D.

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University of Southampton/Solent NHS Trust

Adjunct Associate Professor
New York University (NYU)

Conflicts of interest
(last 5 years)

- 2011-2013: Royalties for online educational activity on ADHD

- No other conflicts of interest

Interpretation of Effect Size (ES)

Description	Value
Small	0.2
Medium	0.5
Large	0.8

Before the 2015 Cochrane review…

Last 15 years:

15 meta-analyses on MPH

Bloch 2009; Charach 2011; Charach 2013; Faraone 2002; Faraone 2006; Faraone 2009; Faraone 2010; Hanwella 2011; Kambeitz 2014; King 2006; Maia 2014; Punja 2013; Reichow 2013; Schachter 2001; Van der Oord 2008

Effect size MPH

ES= 0.79

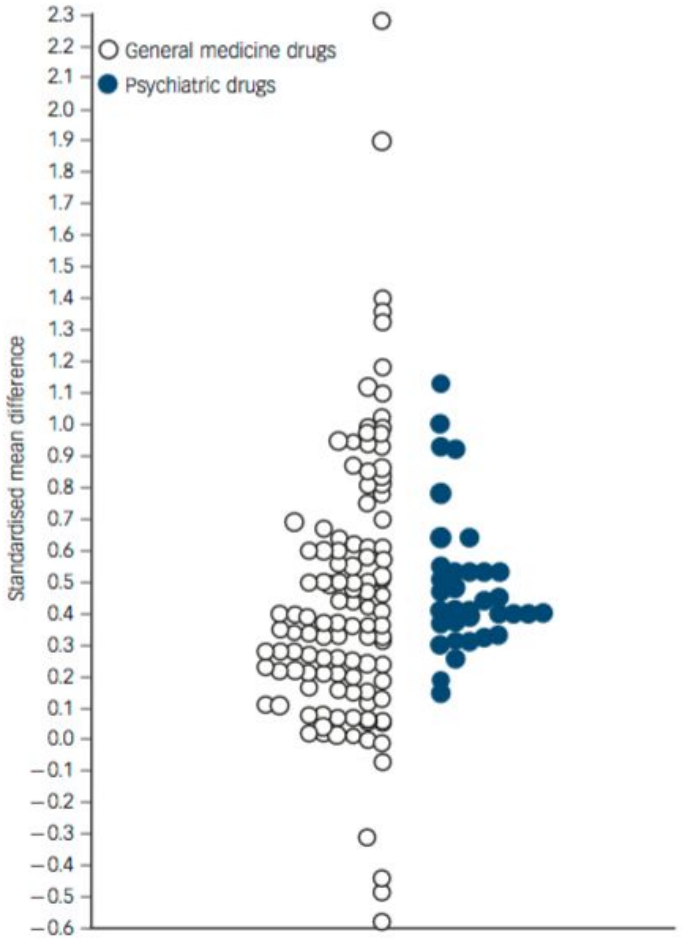
Eur Child Adolesc Psychiatry (2010) 19:353–364
DOI 10.1007/s00787-009-0054-3

ORIGINAL CONTRIBUTION

Comparing the efficacy of stimulants for ADHD in children and adolescents using meta-analysis

Stephen V. Faraone · Jan Buitelaar

MPH vs. other meds



Leucht et al., Br J Psychiatry 2012

NICE 2006:

"The evidence from short-term randomised placebo-controlled trials suggests that methylphenidate is an effective treatment to reduce core symptoms of ADHD in children who continue to take the medication"

2015 Cochrane review

Methylphenidate for children and adolescents with attention deficit hyperactivity disorder (ADHD) (Review)

Storebø OJ, Ramstad E, Krogh HB, Nilausen TD, Skoog M, Holmskov M, Rosendal S, Groth C, Magnusson FL, Moreira-Maia CR, Gillies D, Buch Rasmussen K, Gauci D, Zwi M, Kirubakaran R, Forsbøl B, Simonsen E, Gluud C

38 parallel-group trials (5111 participants)

147 cross-over trials (7134)

ES: 0.77 (0.64-0.90)

Conclusions

"All 185 trials were assessed to be at high risk of bias"

"The quality of the evidence was very low for all outcomes"

Storebø et al., Cochrane Database Syst Rev, 2015

Conclusions (cont'd)

"The low quality of the underpinning evidence means that we cannot be certain of the magnitude of the effects"

"If methylphenidate treatment is considered, clinicians might need to use it for short periods, with careful monitoring of both benefits and harms, and cease its use if no evidence of clear improvement of symptoms is noted, or if harmful effects appear"

Storebø et al., Cochrane Database Syst Rev, 2015

Evidence-Based Mental Health Online First, published on October 6, 2016 as 10.1136/eb-2016-102461

Methylphenidate for ADHD in children and adolescents: throwing the baby out with the bathwater

Tobias Banaschewski,[1] Jan Buitelaar,[2,3] Celine S L Chui,[4] David Coghill,[5] Samuele Cortese,[6,7] Emily Simonoff,[6,8] Ian C K Wong,[4,9] on behalf of the European ADHD Guidelines Group

Eunethydis:

European ADHD Guidelines Group (EAGG)

The devil is in the details…

Study inclusion

- Active control conditions (including MTA)

- Preschoolers

0.77 -> 0.89

Appraisal of study quality

How to GRADE the evidence

Evidence varies from

HIGH	⊕⊕⊕⊕
MODERATE	⊕⊕⊕◯
LOW	⊕⊕◯◯
VERY LOW	⊕◯◯◯

- Randomised controlled trials start as high quality
- Observational studies start as low quality

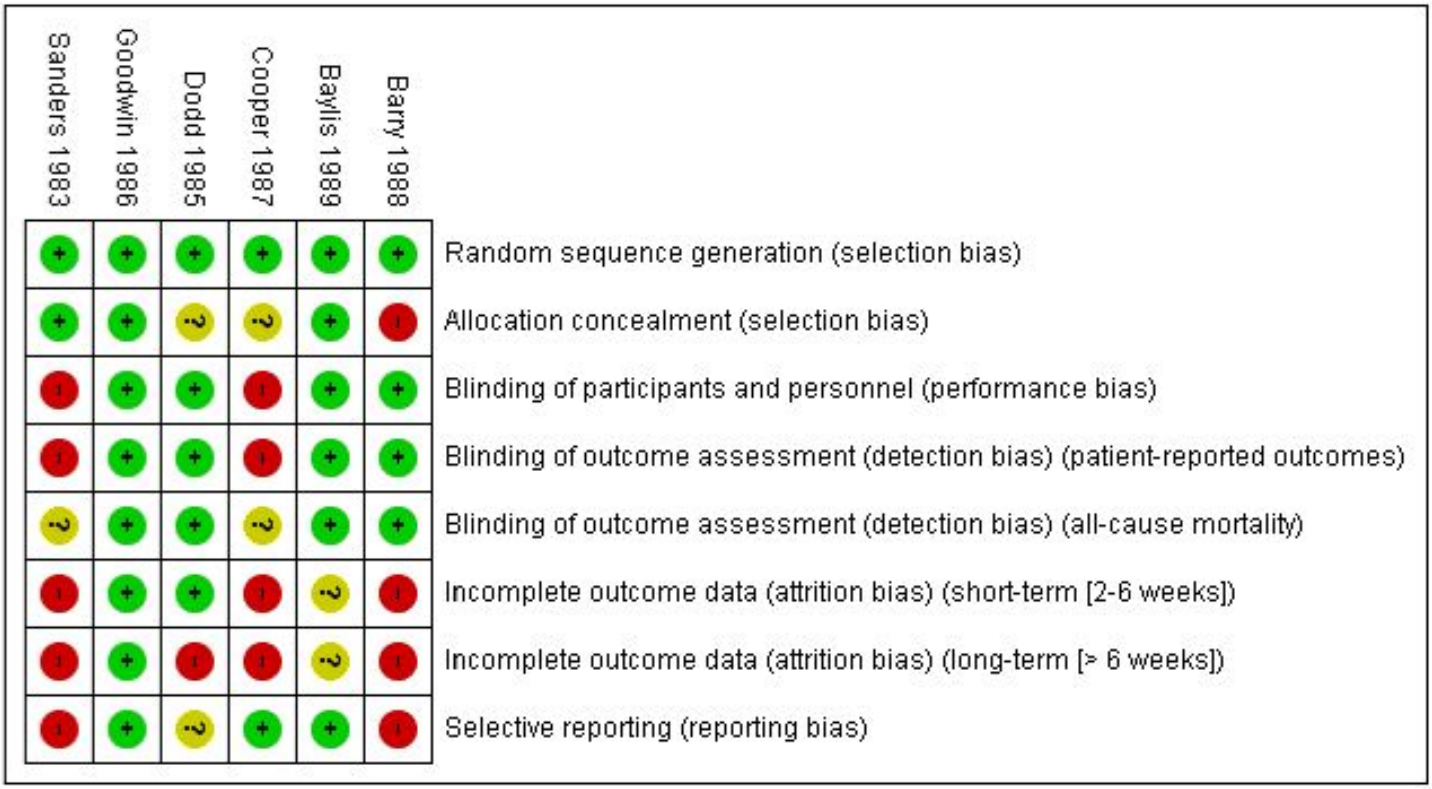
Determinants of quality

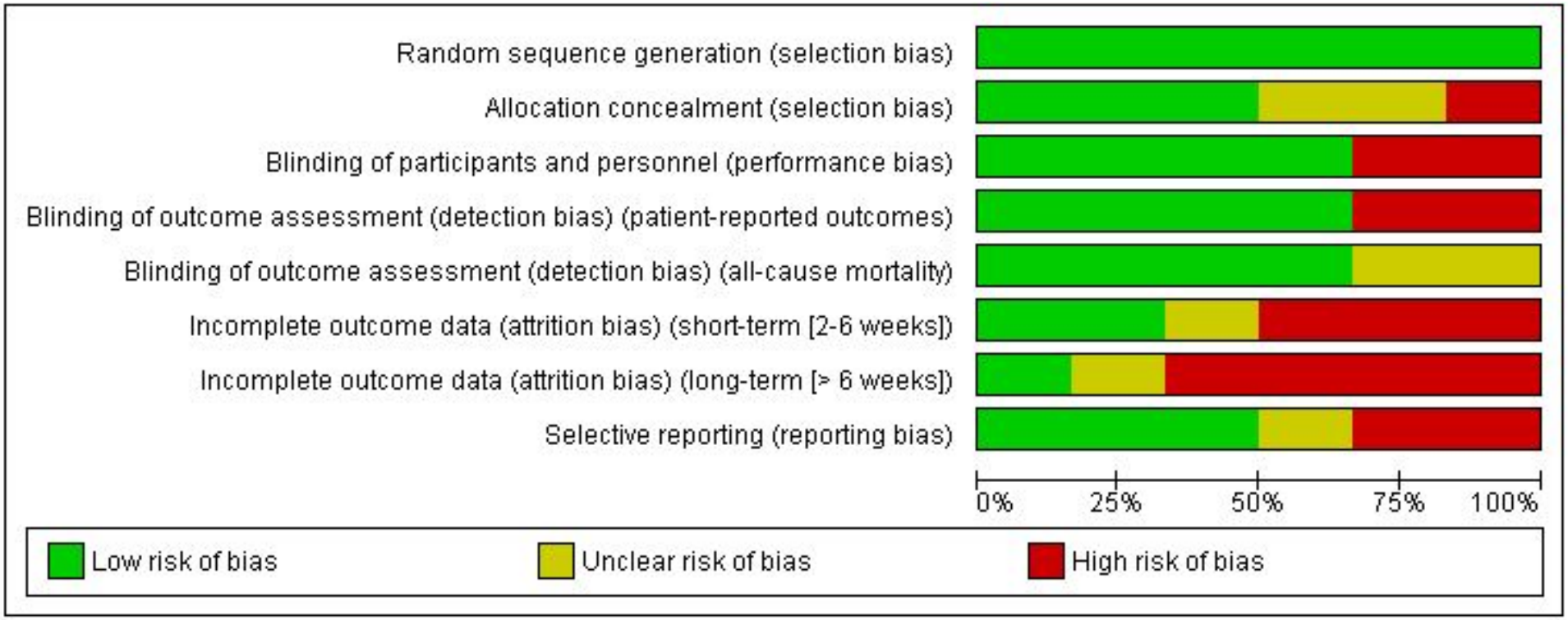
5 factors that can lower quality

1. limitations of detailed design and execution *(risk of bias criteria)*
2. Inconsistency *(or heterogeneity)*
3. Indirectness *(PICO and applicability)*
4. Imprecision *(number of events and confidence intervals)*
5. Publication bias

Risk of bias

- **Selection bias** *(random sequence generation; allocation concealment)*
- **Performance bias** *(blinding participants/personnel)*
- **Detection bias** *(blinding assessor)*
- **Attrition bias** *(incomplete outcome data)*
- **Reporting bias** *(selective reporting)*
- **Other bias**


Sanders 1983
Goodwin 1986
Dodd 1985
Cooper 1987
Baylis 1989
Barry 1988
Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias) (patient-reported outcomes)
Blinding of outcome assessment (detection bias) (all-cause mortality)
Incomplete outcome data (attrition bias) (short-term [2-6 weeks])
Incomplete outcome data (attrition bias) (long-term [> 6 weeks])
Selective reporting (reporting bias)

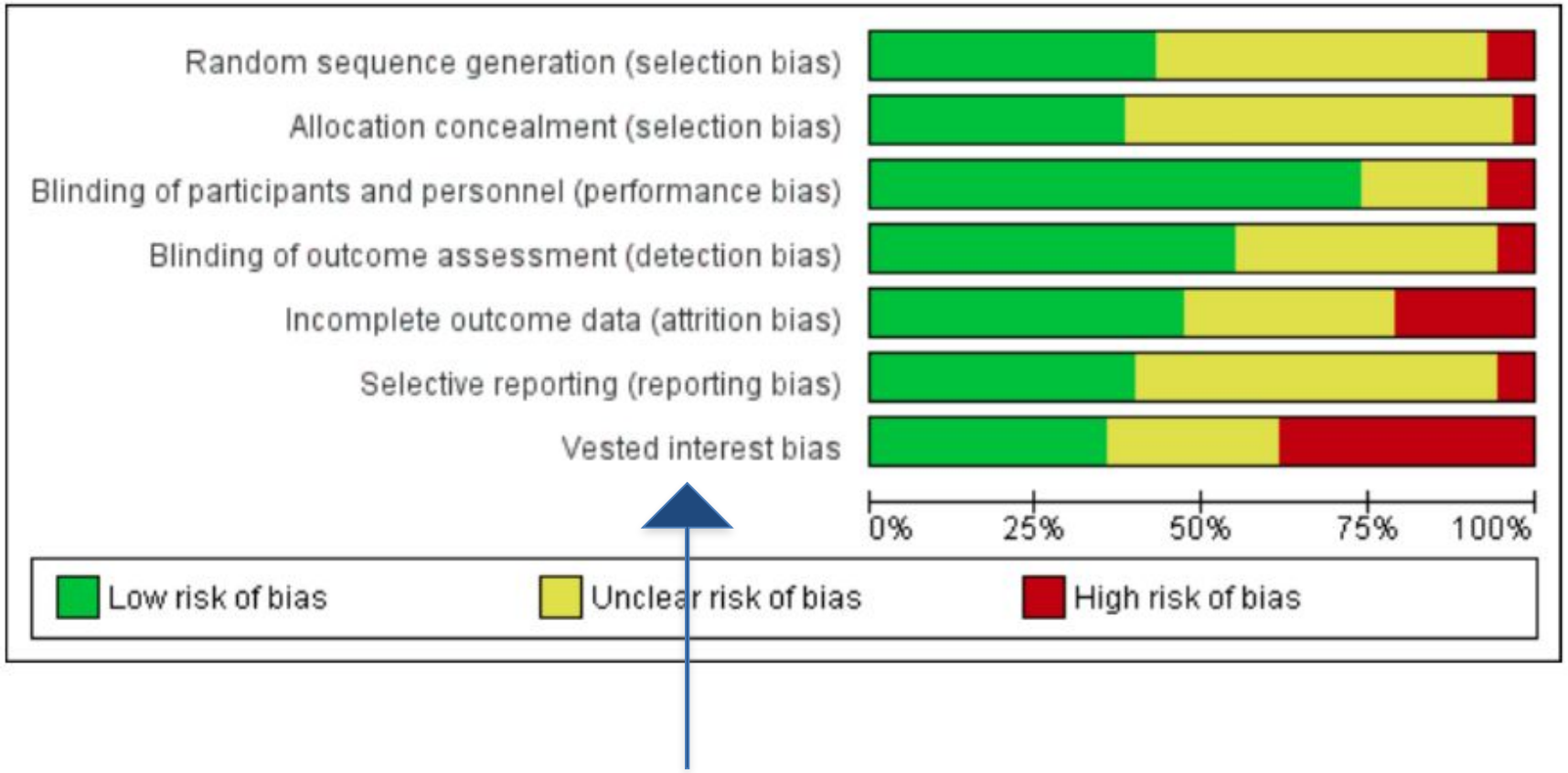

Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias) (patient-reported outcomes)
Blinding of outcome assessment (detection bias) (all-cause mortality)
Incomplete outcome data (attrition bias) (short-term [2-6 weeks])
Incomplete outcome data (attrition bias) (long-term [> 6 weeks])
Selective reporting (reporting bias)
0%
25%
50%
75%
100%
Low risk of bias
Unclear risk of bias
High risk of bias

Storebø et al.,2015

a) Downgraded <u>two</u> levels due to high risk of bias

b) Downgraded <u>one</u> level due to inconsistency: moderate statistical heterogeneity

Storebø et al.,2015



Vested interests ?

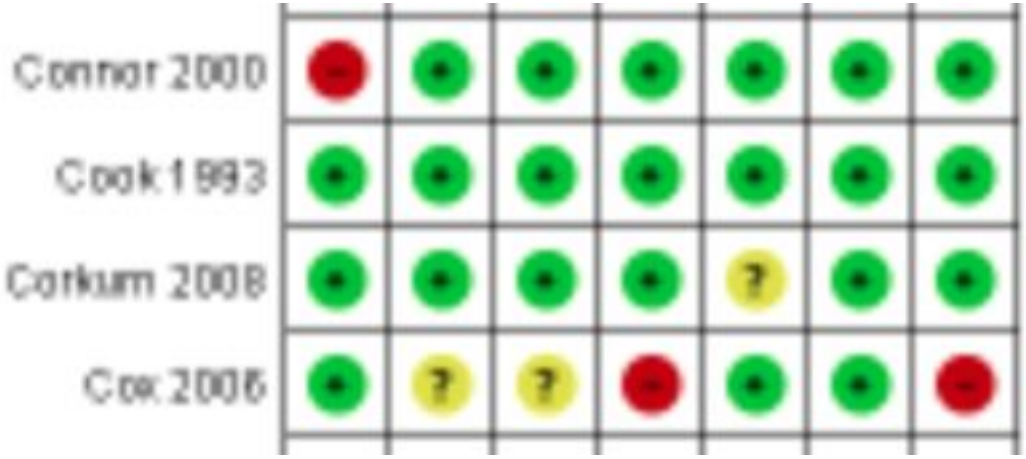
"'Risk of bias' table should be used to assess *specific aspects of methodology* and not vested interests per se "

Sterne JA. Why the Cochrane risk of bias tool should not include funding source as a standard item. Cochrane Database Syst Rev 2013

"We wanted to explore the influence of industry-funded versus publicly-funded sources.. **No between-group differences were found**"

Punja et al., Cochrane Database Syst Rev, 2015

At least 1 unclear/high = HIGH RISK



179 trials: HIGH RISK

The “survivors”

- 6 survived: all green!!

But…….

Risk of deblinding

NOCEBO

Does the risk of bias impact on the ES ??

“No evidence suggested that the intervention effect varied according to risk of bias (low risk of bias versus high risk of bias)”

Storebø et al., Cochrane Database Syst Rev, 2015

Storebø et al.,2015

a) Downgraded <u>two</u> levels due to high risk of bias

b) Downgraded <u>one</u> level due to inconsistency: moderate statistical heterogeneity

Heterogeneity

- Primary outcome: I^2 = **37%**

Cochrane handbook: "Heterogeneity up to 40% 'might not be important"

- Without MTA: I^2 = **25%**

- Punja et al.: I^2 = **50%**

Adverse events

- **No evidence** that methylphenidate was associated with an increase in **serious adverse** events (RR= 0.98, 95% CI 0.44-2.22)

- 60% greater risk for trouble **sleeping/sleep problems** (RR 1.60, 95% CI 1.15-2.23) and 266% greater risk for **decreased appetite** (RR 3.66, 95% CI 2.56-5.23)

THE JOURNAL OF CHILD PSYCHOLOGY AND PSYCHIATRY

ACAMH

Journal of Child Psychology and Psychiatry 54:3 (2013), pp 227–246

doi:10.1111/jcpp.12036

Practitioner Review: Current best practice in the management of adverse events during treatment with ADHD medications in children and adolescents

Samuele Cortese,[1,2,3,*] Martin Holtmann,[4,*] Tobias Banaschewski,[5] Jan Buitelaar,[6] David Coghill,[7] Marina Danckaerts,[8] Ralf W. Dittmann,[5] John Graham,[9] Eric Taylor,[10] Joseph Sergeant,[11] on behalf of the European ADHD Guidelines Group†

Duration of treatment

- 1 to 425 day
- Average: **75 days**

Some reflections on the MTA…

- 14-month RCT; observational follow-up
- Medication lost effectiveness?
- Self selection patients?
- Importance of carefully titrated pharmacological treatment?

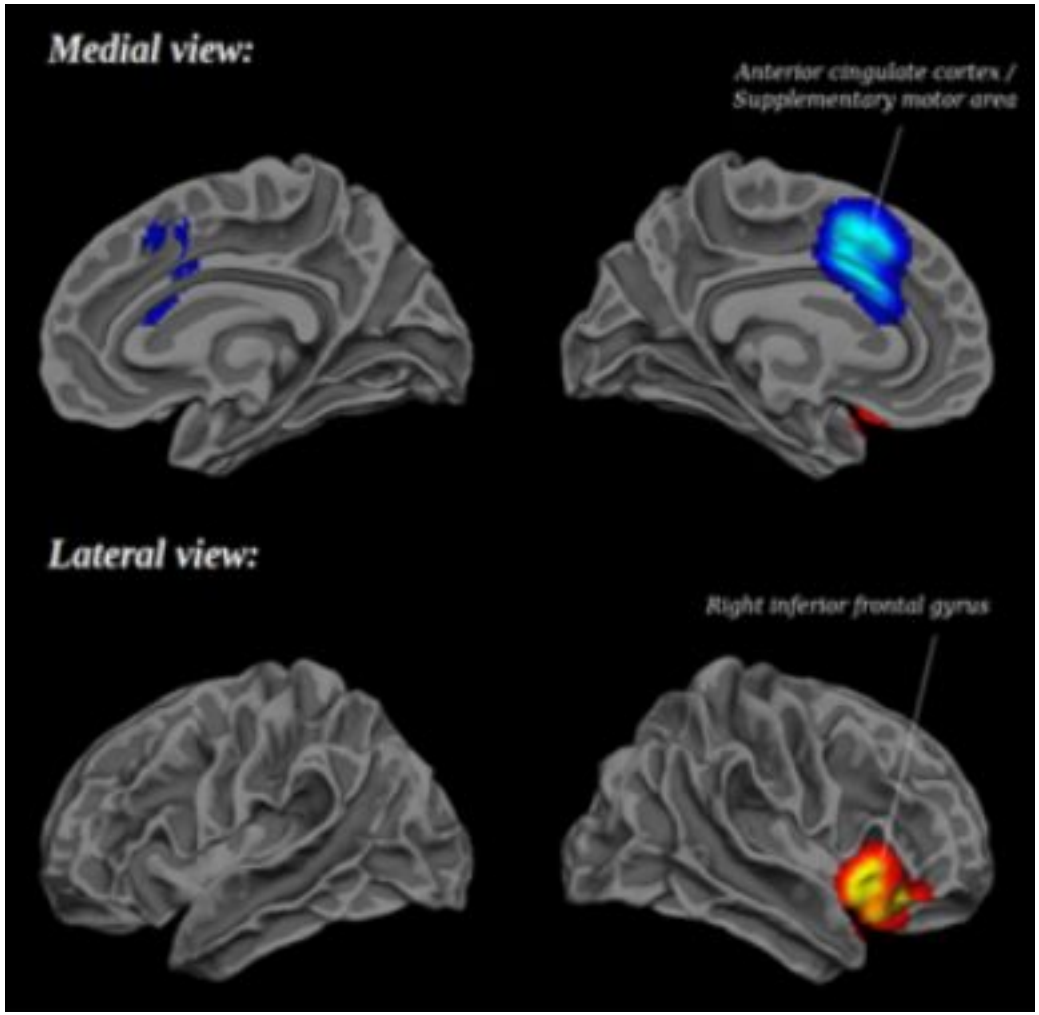
Observational studies

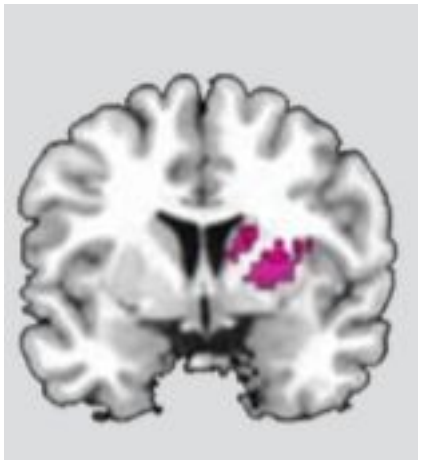
- 25,656 patients with ADHD: significant reduction in **criminality** rates during ADHD pharmacological treatment *(Lichtenstein et al., NEJM, 2012)*

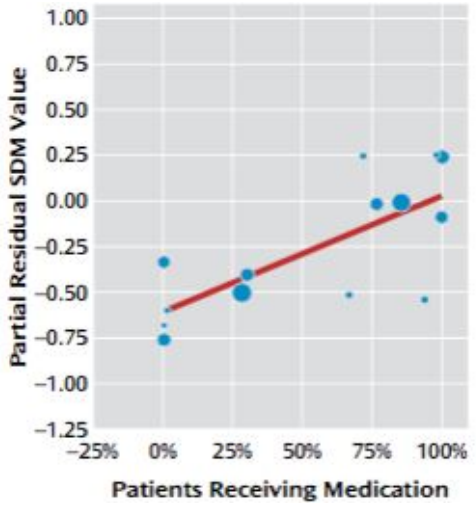
- 806,182 person-years of follow-up: no increased risk of **serious cardiovascular events** *(Habel et al., JAMA 2011)*

- 21,186 patients with ADHD: no association MPH-risk of **cancer** *(Steinhausen et al., JCAP, 2013)*

Brain effects





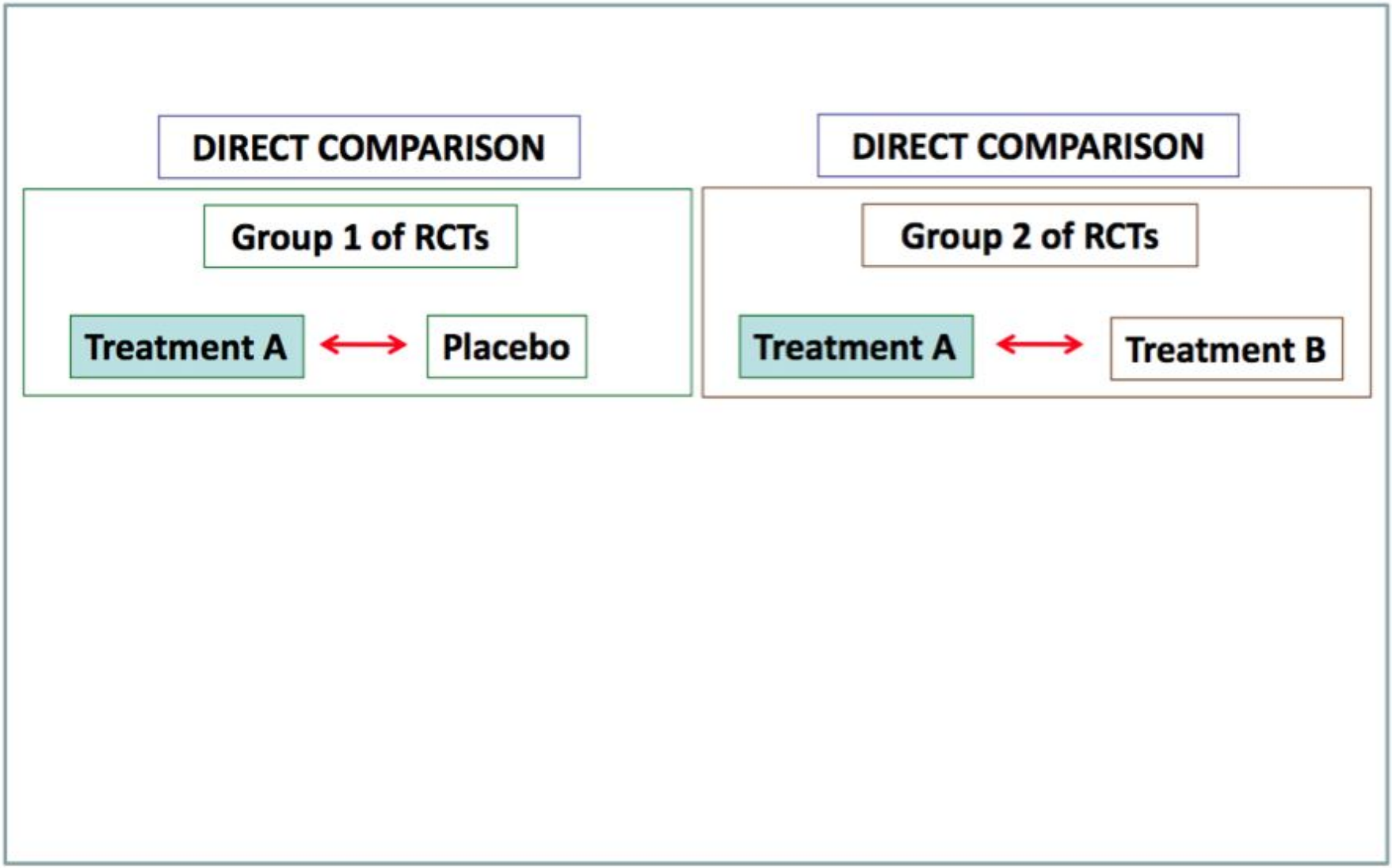


Rubia et al., Biol Psyhciatry, 2014

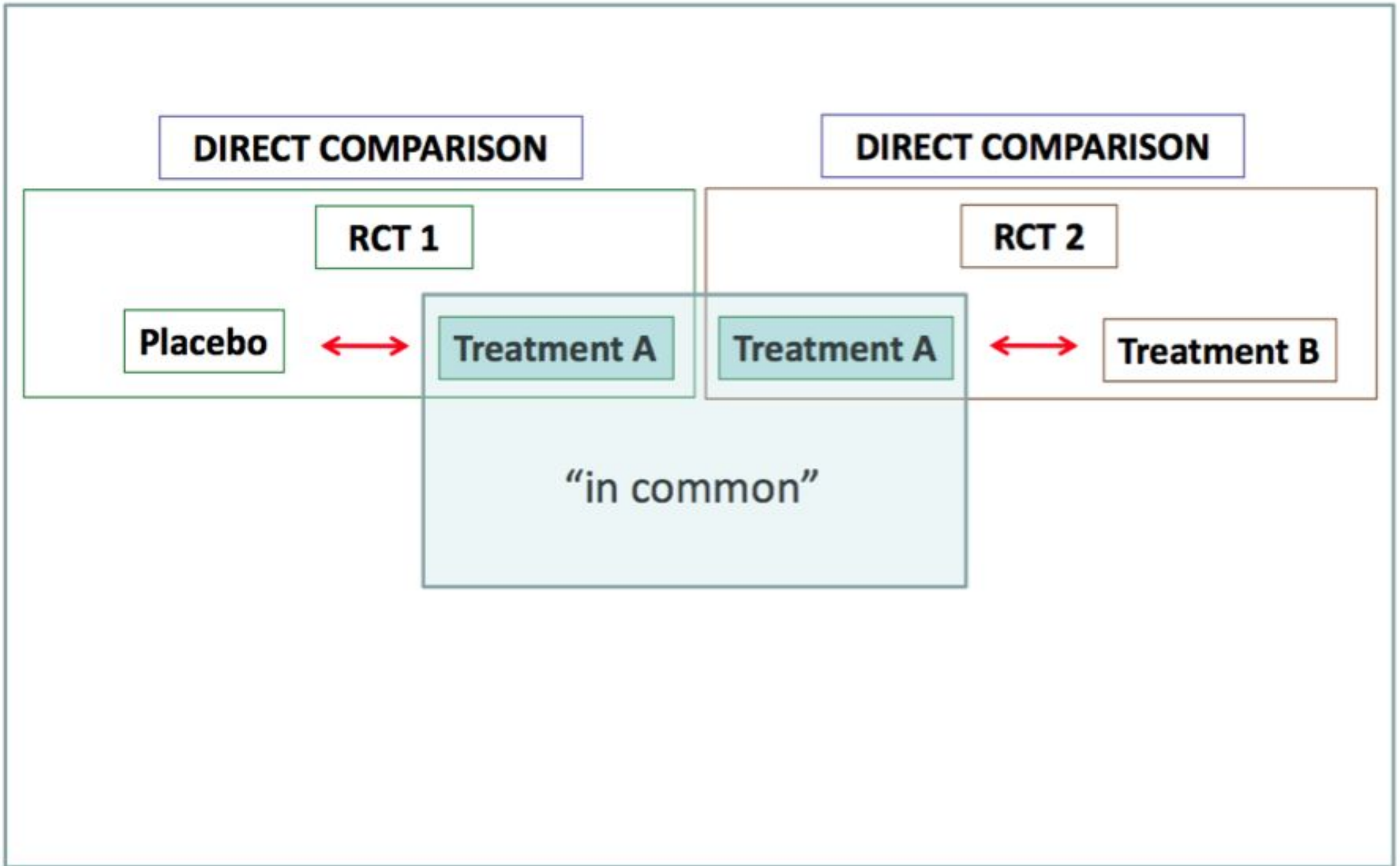
Nakao et al., Am J Psychiatry, 2011

Moving forward….

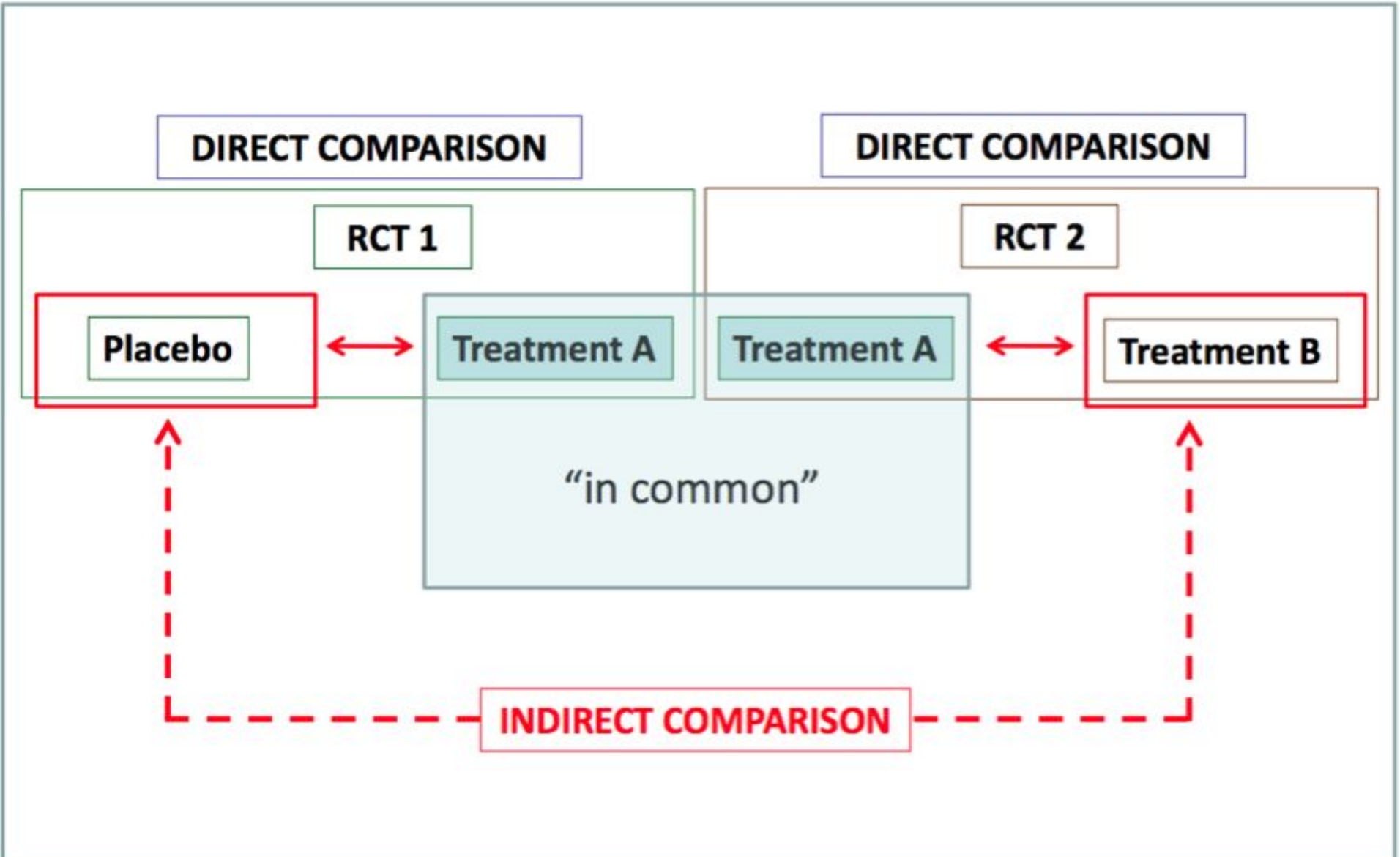
Network meta-analysis…ongoing



INDIRECT COMPARISON

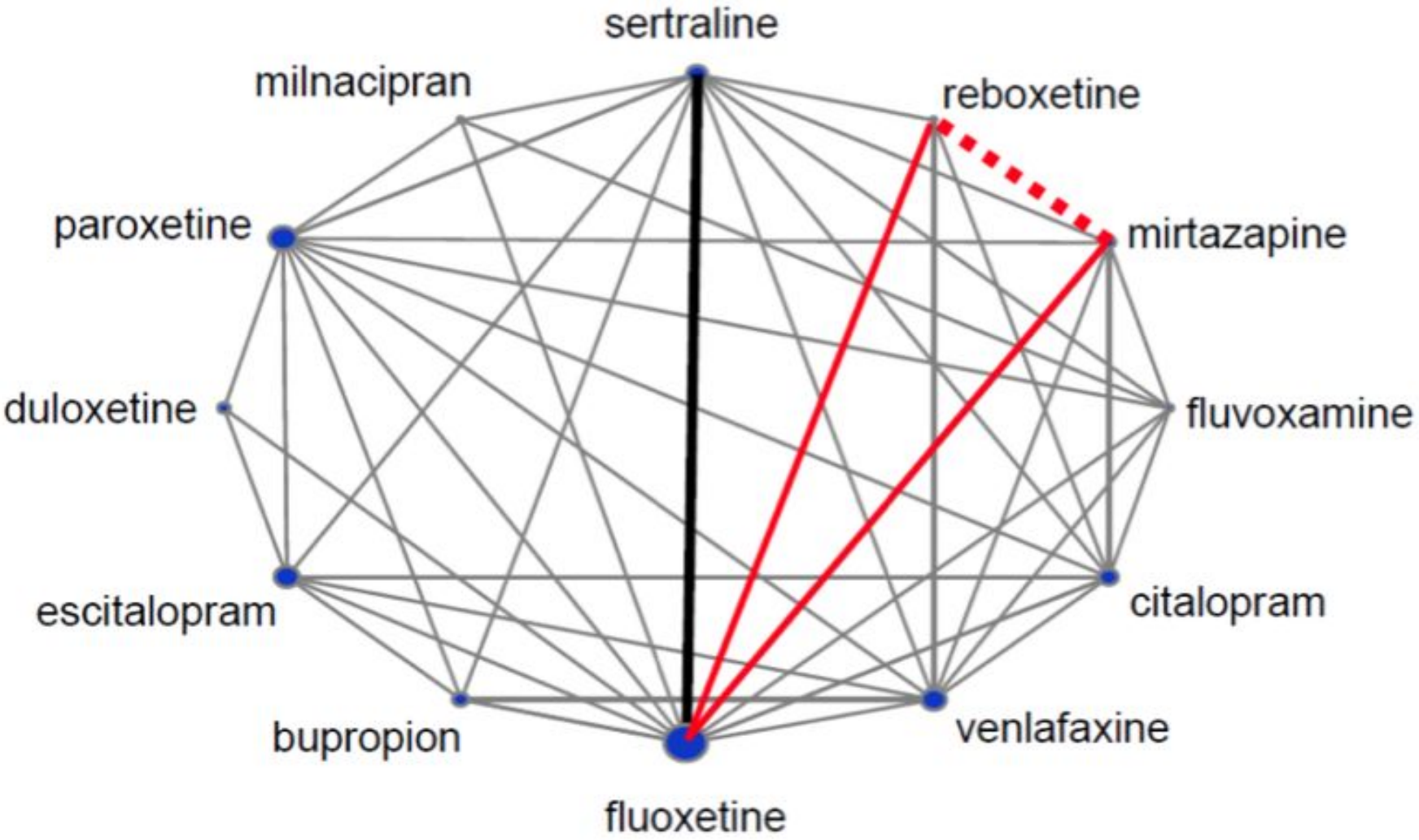


INDIRECT COMPARISON

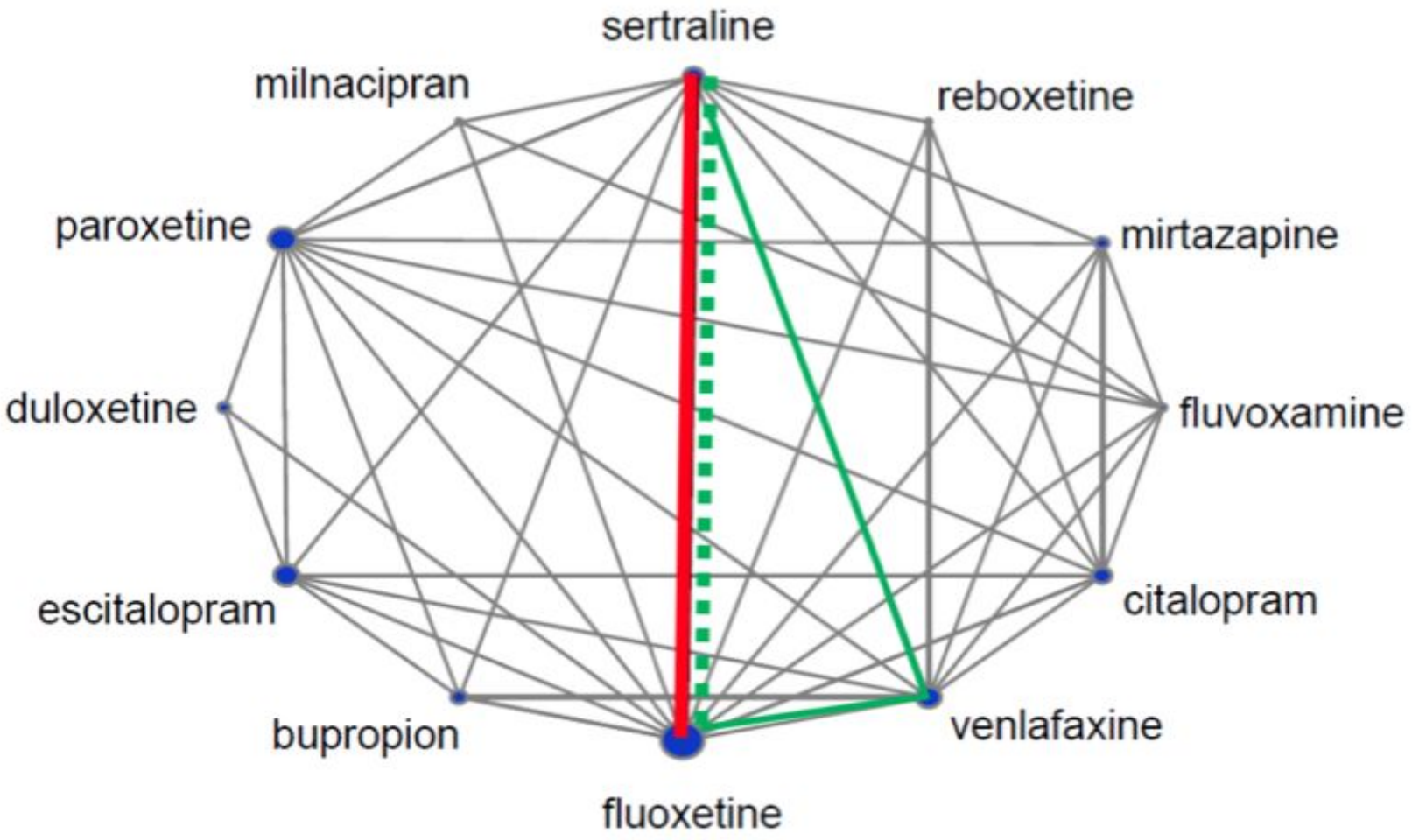


Network of experimental comparisons

NETWORK



NETWORK


Network of experimental comparisons
sertraline
milnacipran
reboxetine
paroxetine
mirtazapine
duloxetine
fluvoxamine
escitalopram
citalopram
bupropion
venlafaxine
fluoxetine

Research priorities

- Long-term effects on cognition, academic functioning, global functioning, quality of life

- Sequencing non pharmacological/pharmacological interventions

ADDITIONAL SLIDES

Inconsistency in bias rating

Examples

Barkley, 1991	**Funding: NIMH Conflicts of interest: no information**	**LOW**
Rapport, 1987	Funding: NIH Conflicts of interest: no information	UNCLEAR

Coghill, 2007	**This work was supported by a local trust through a Tenovus Scotland initiative. Conflicts of interest: Some study authors have affiliations with different pharmaceutical companies**	**UNCLEAR**
Jensen, 1999 (MTA)	This study was supported by several grants from the National Institute of Mental Health, Bethesda, Maryland Conflicts of interest: Several study authors have affiliations with medical companies	LOW

Neuropsychological functions

ARCHIVAL REPORT

Effects of Methylphenidate on Cognitive Functions in Children and Adolescents with Attention-Deficit/ Hyperactivity Disorder: Evidence from a Systematic Review and a Meta-Analysis

David R. Coghill, Sarah Seth, Sara Pedroso, Tatiana Usala, John Currie, and Antonella Gagliano

BIOL PSYCHIATRY 2014;76:603–615

Working memory

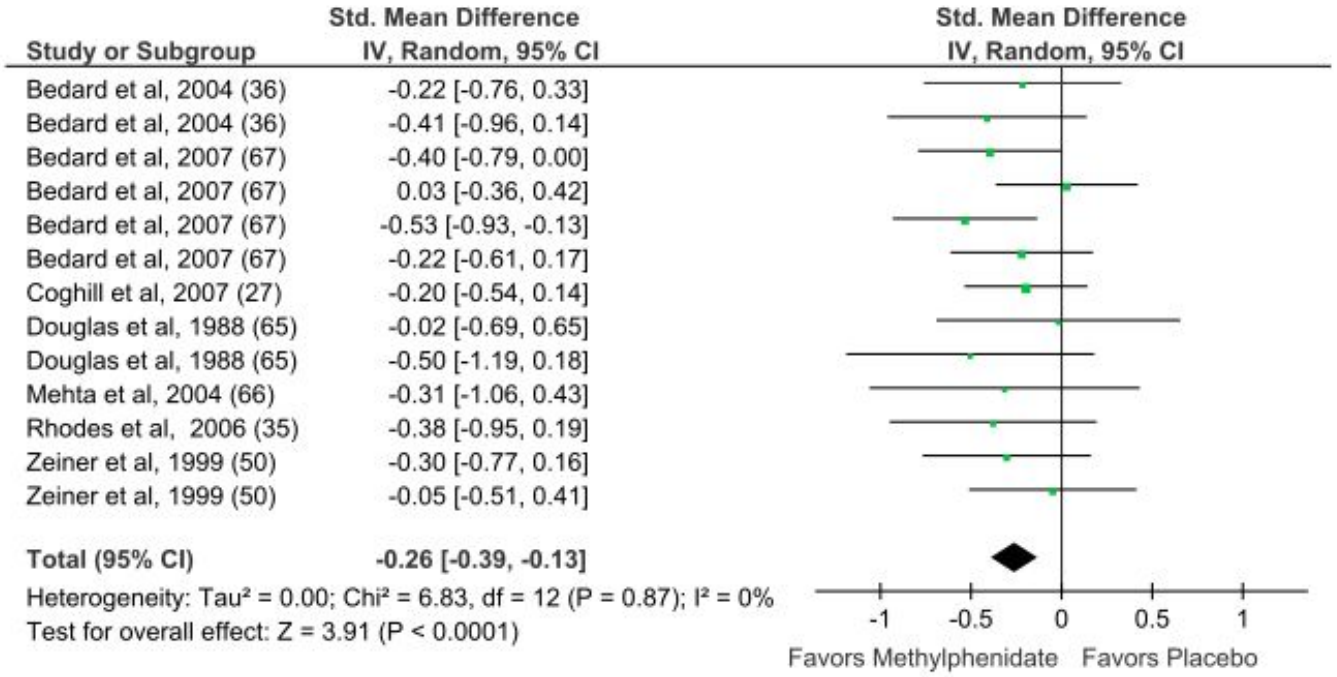


Figure 1. Forest plot with standardized (Std.) mean difference, effect size, and homogeneity statistics for meta-analysis comparing the effects of methylphenidate and placebo on executive aspects of memory. CI, confidence interval.

Reaction time variability

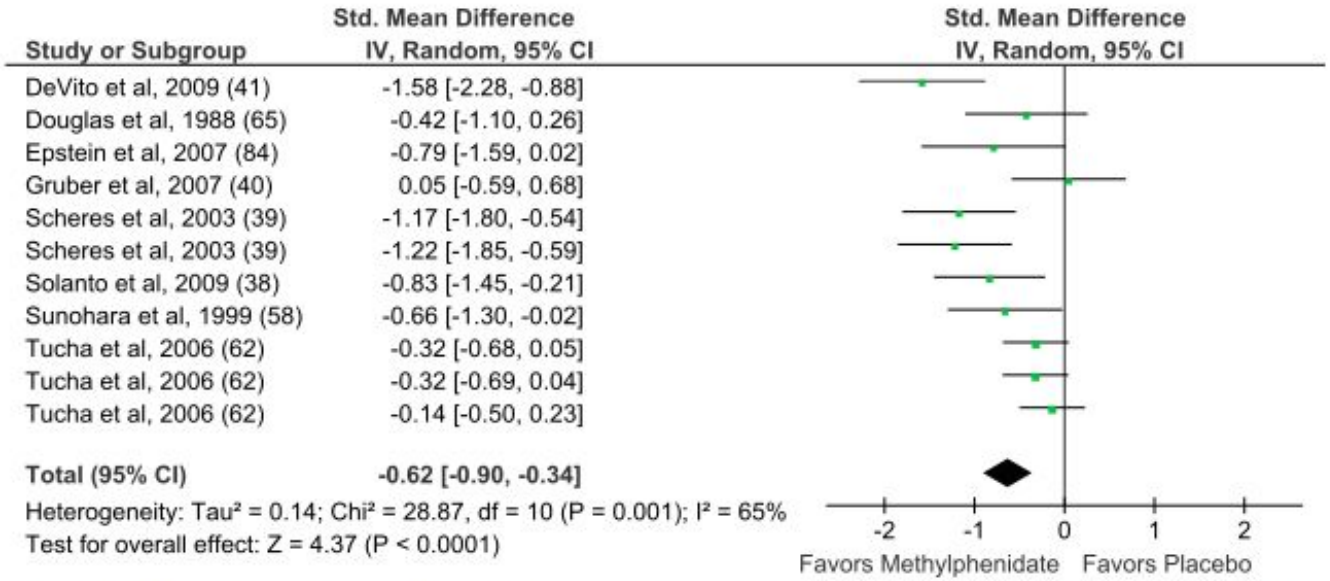


Figure 4. Forest plot with standardized (Std.) mean difference, effect size, and homogeneity statistics for meta-analysis comparing the effects of methylphenidate and placebo on reaction time variability. CI, confidence interval.

Inhibition

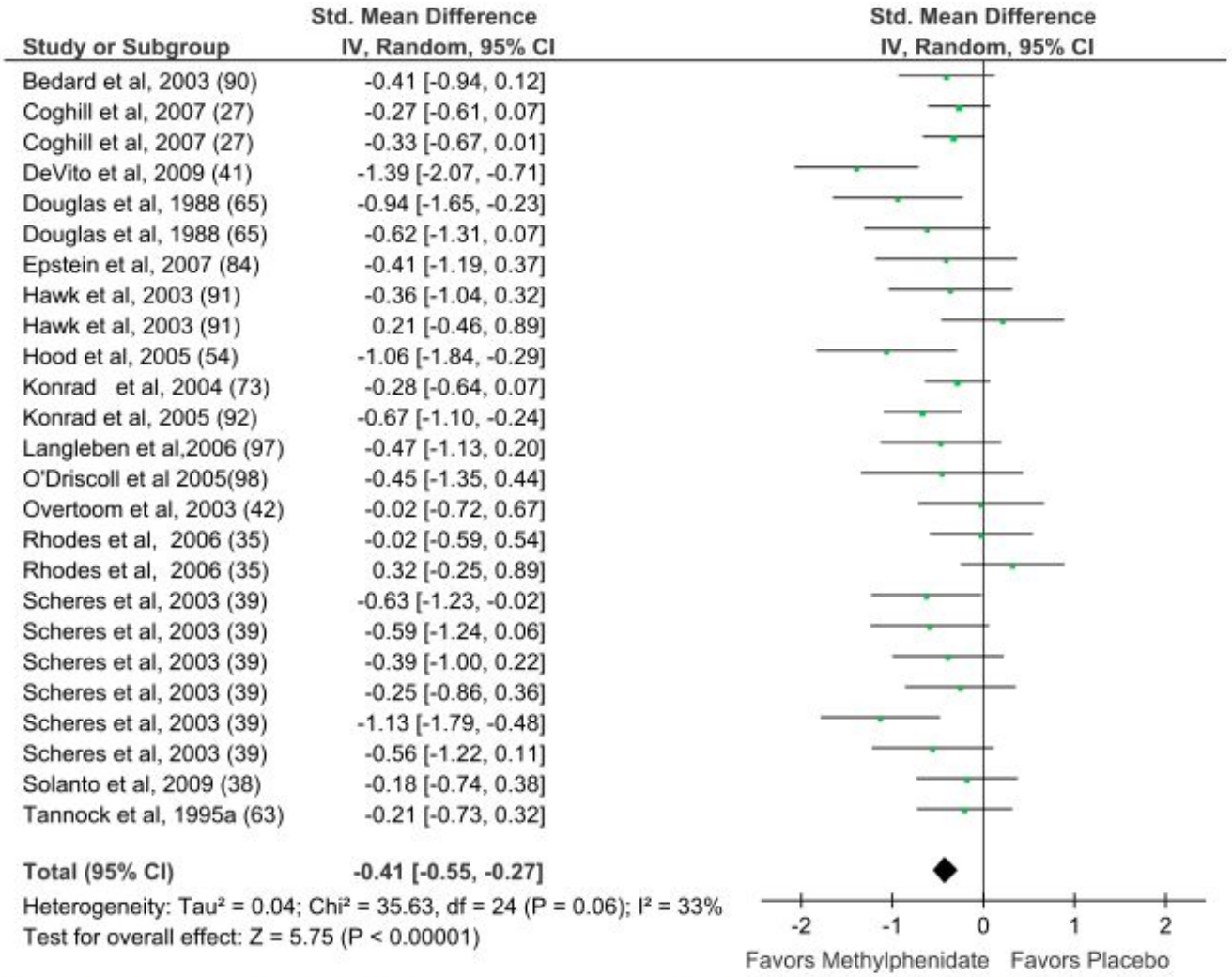
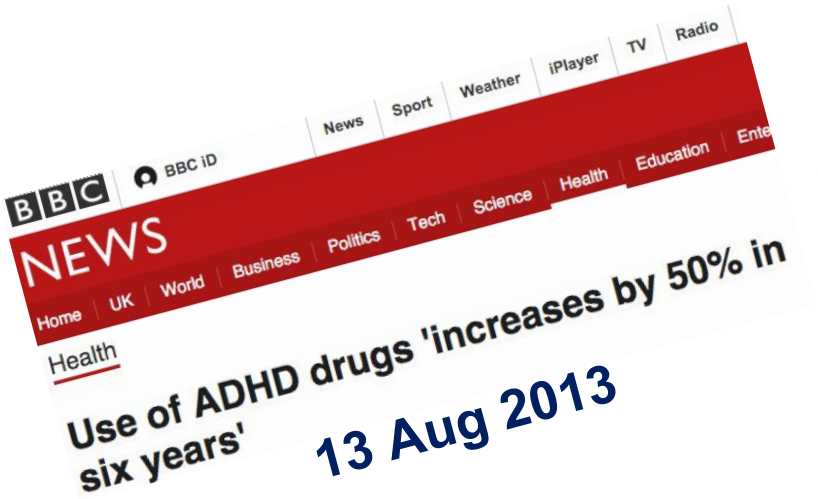


Figure 5. Forest plot with standardized (Std.) mean difference, effect size, and homogeneity statistics for meta-analysis comparing the effects of methylphenidate and placebo on response inhibition. CI, confidence interval.

Popular press



13 Aug 2013

15 Aug 2015

10 Mar 2016

UK estimated prevalence

ADHD (DSM-IV)

- Boys: **3.62%**
- Girls: **0.85%**
- Total: **2.23 %**

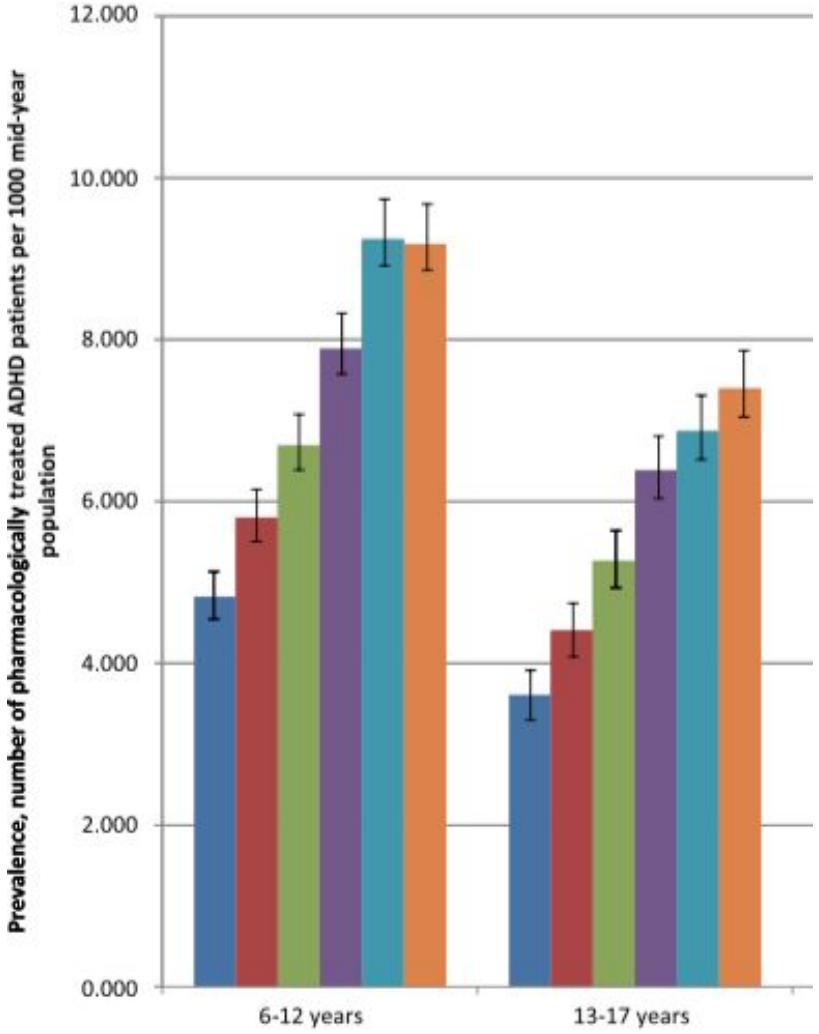
HKD (ICD-10)

- Total: **1.5 %**

Ford et al., JAACAP 2003; Taylor et al., ECAP, 2004

Administrative treatment prevalence

2003-2008



0.9%

McCarthy et al., BMC Pediatrics 2012

Plateau

- **< 16 years**
- General Practice Research Database
- At least one prescription of any ADHD drug
- **0.46 %**

Beau et al., Pharmacoepidemiology and Drug Safety, 2012

Non NHS primary care prescriptions

N items methylphenidate Primary care	N items methylphenidate Privately prescribed
793,749	5,170

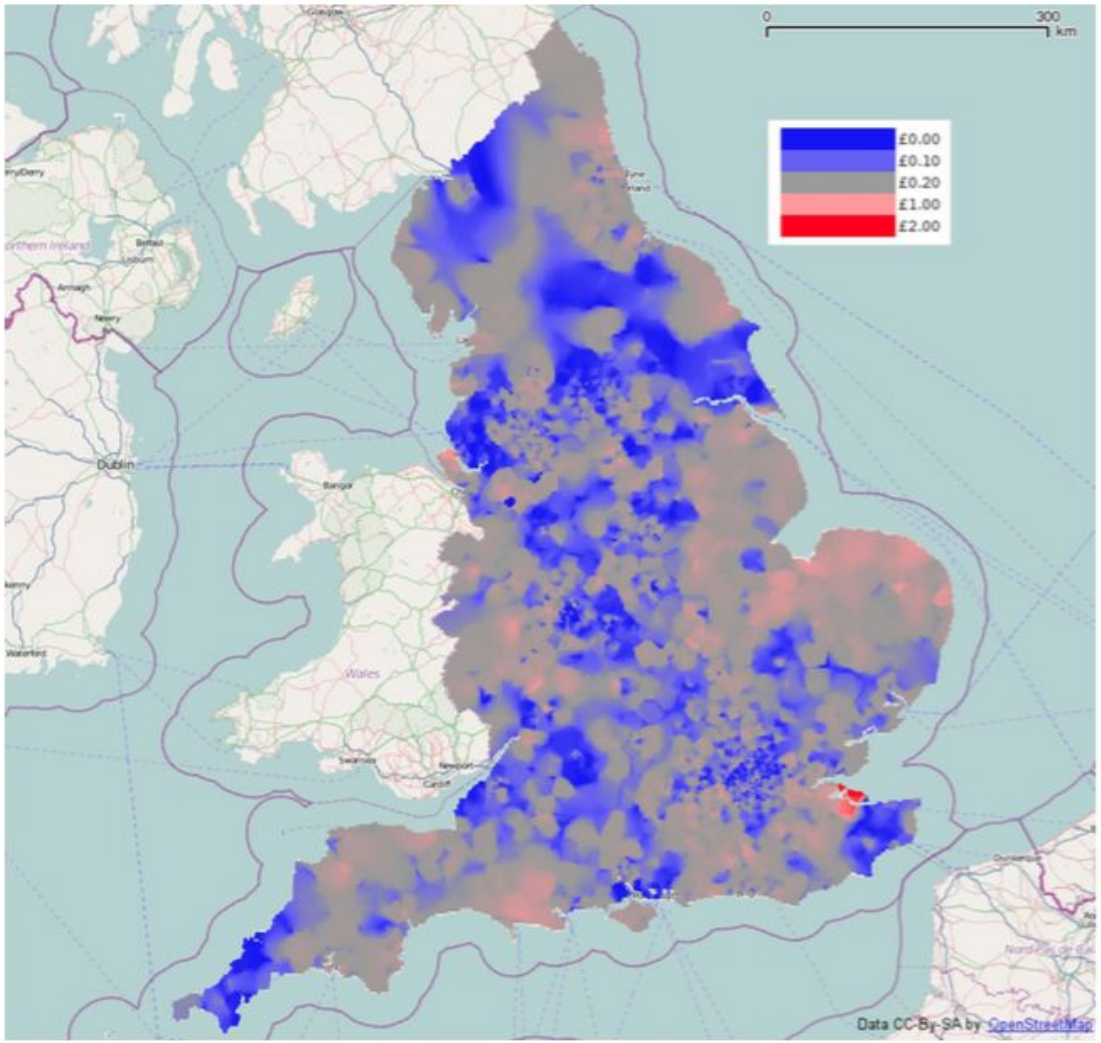
Care Quality Commission, Annual Report 2014

Costs methylphenidate Primary care	Costs methylphenidate FP10HP	Costs methylphenidate Hospital
27,234	5,423	741

Health and Social Care Information Centre, 2014

Geographic variation

Smoothed methylphenidate spending (net ingredient cost per child) 2011



Rowlingson et al., *BMJOpen*, 2013

Geographic variation

- **Scotland: 0.7%**

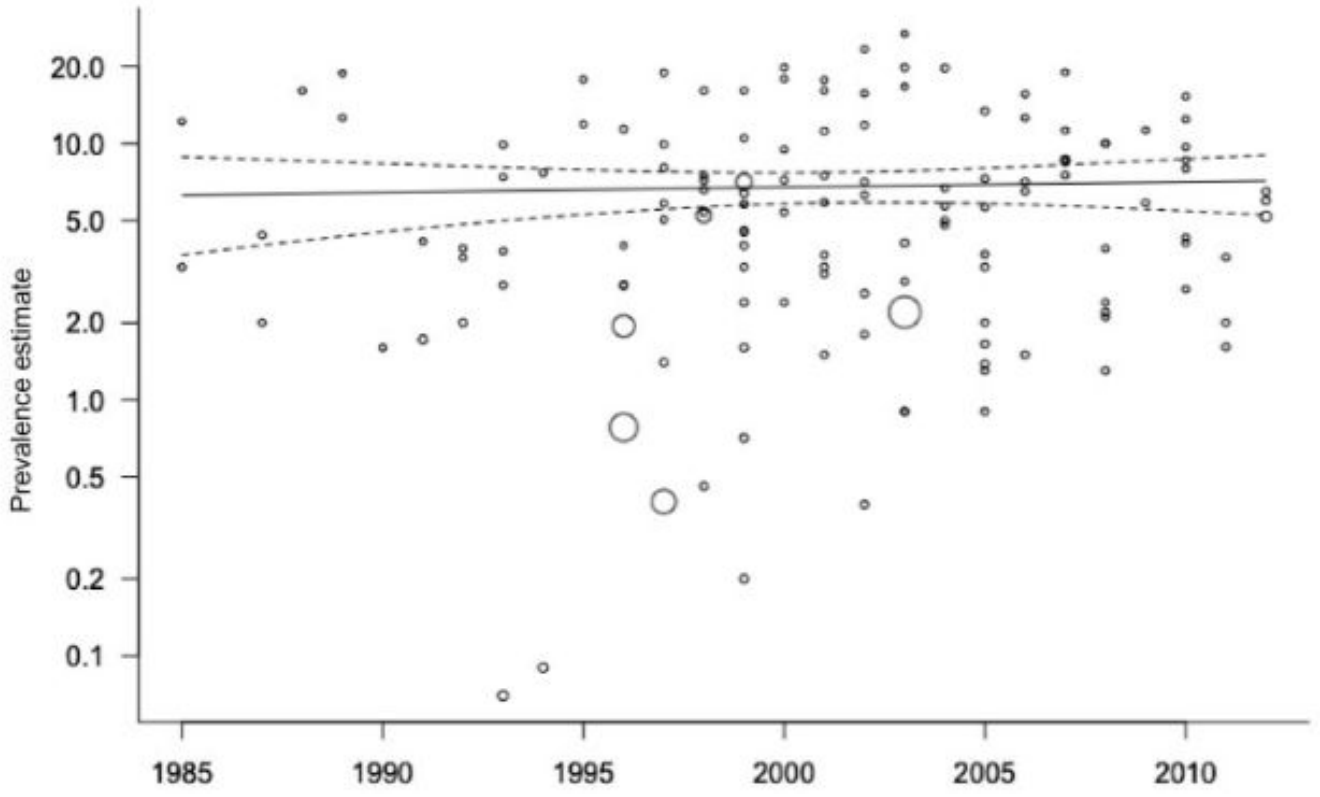
Services Over Scotland (ADHD-SOS) Follow-up Review, 2012

Nation	Adjusted incidence rate ratio (95% CI)
England	1 (ref.)
Scotland	0.97 [0.91, 1.04]
Wales	1.09 [1.02, 1.17]
Northern Ireland	1.26 [1.14, 1.39]

Hire et al, J Att Dis, 2015

Worldwide estimated prevalence

ADHD: **5.29%**



Polanczyk et al., Am J Psychiatry, 2007; Int J Epid, 2014

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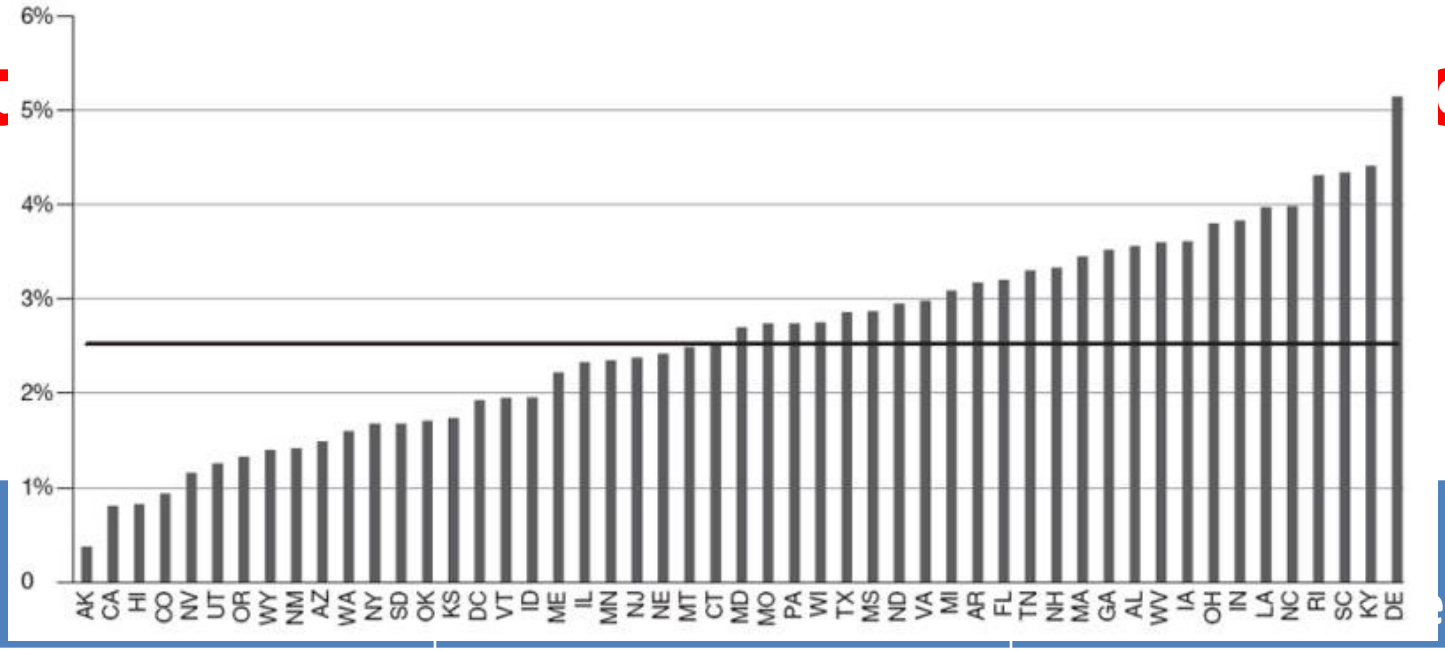


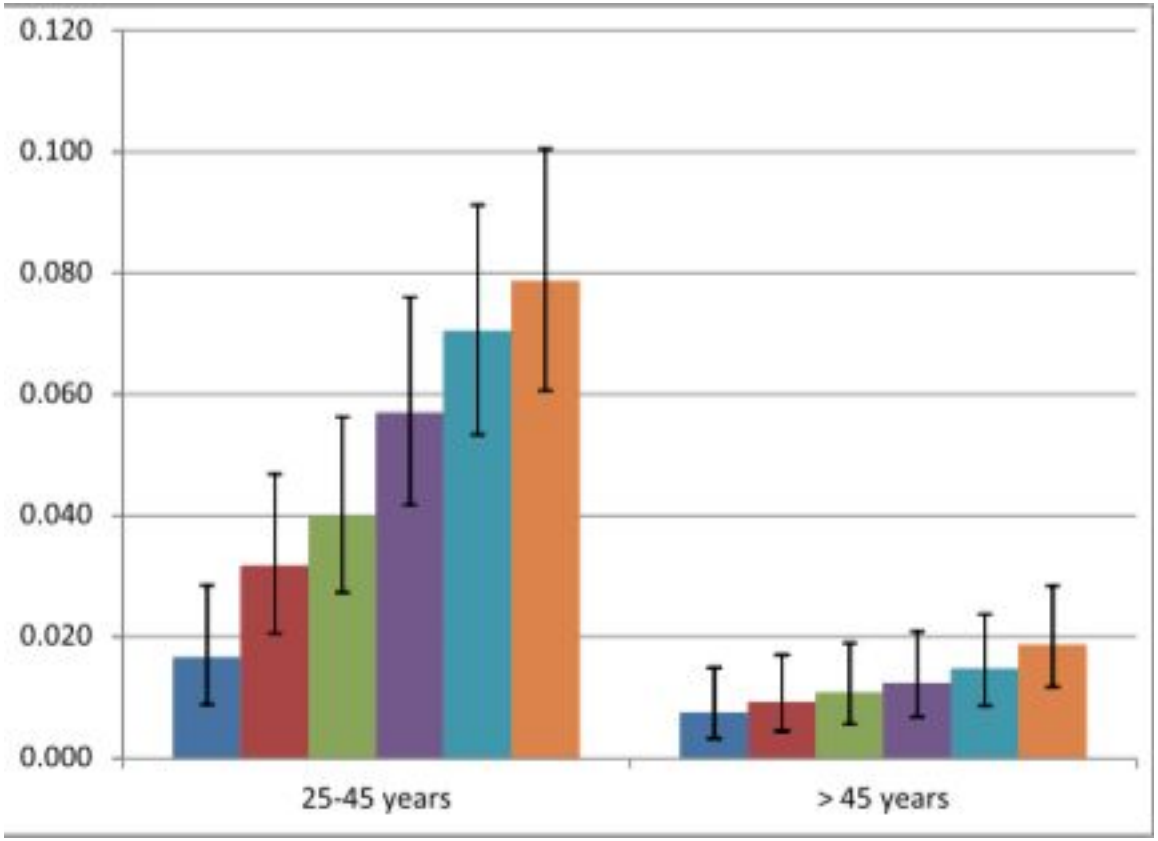
USA	2011	**6.1**
Netherlands	2007	**2.1**
Australia (NSW)	2010	**1.2**
Hong Kong	2013	**1.02**
Germany	2006	**0.9**
Italy	2011	**0.02**

Administrative treatment prevalence 1996-2001

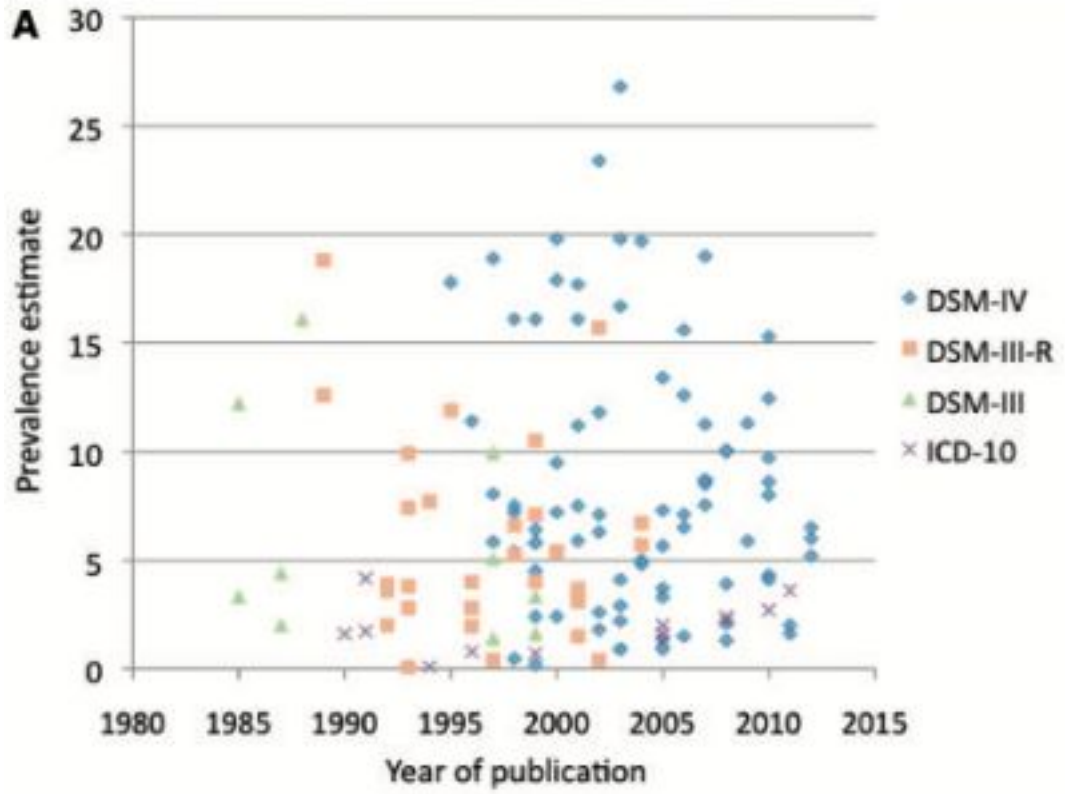
- **5-14 years**
- UK general practice research datalink (GPRD)
- Diagnostic code for “ADHD” and use of MPH
- **0.5%** boys

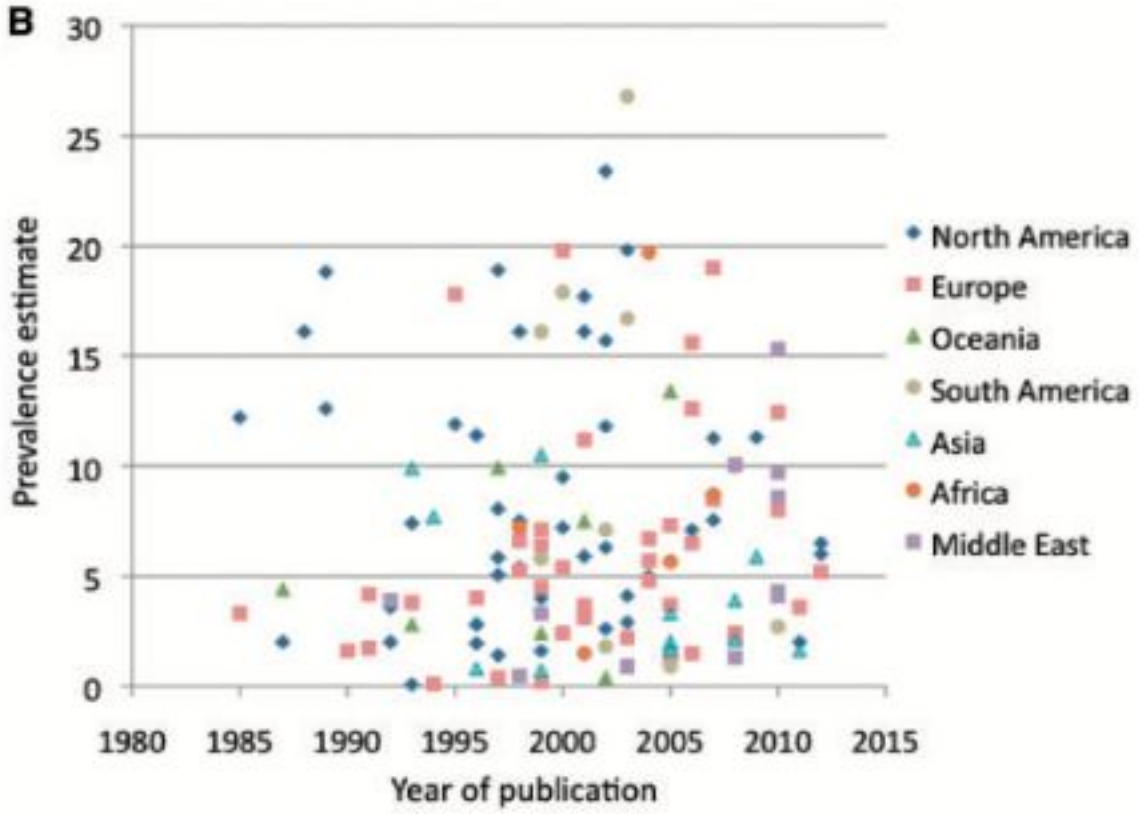
Jick et al., British Journal of General Practice, 2004

Administrative treatment prevalence 2003-2008

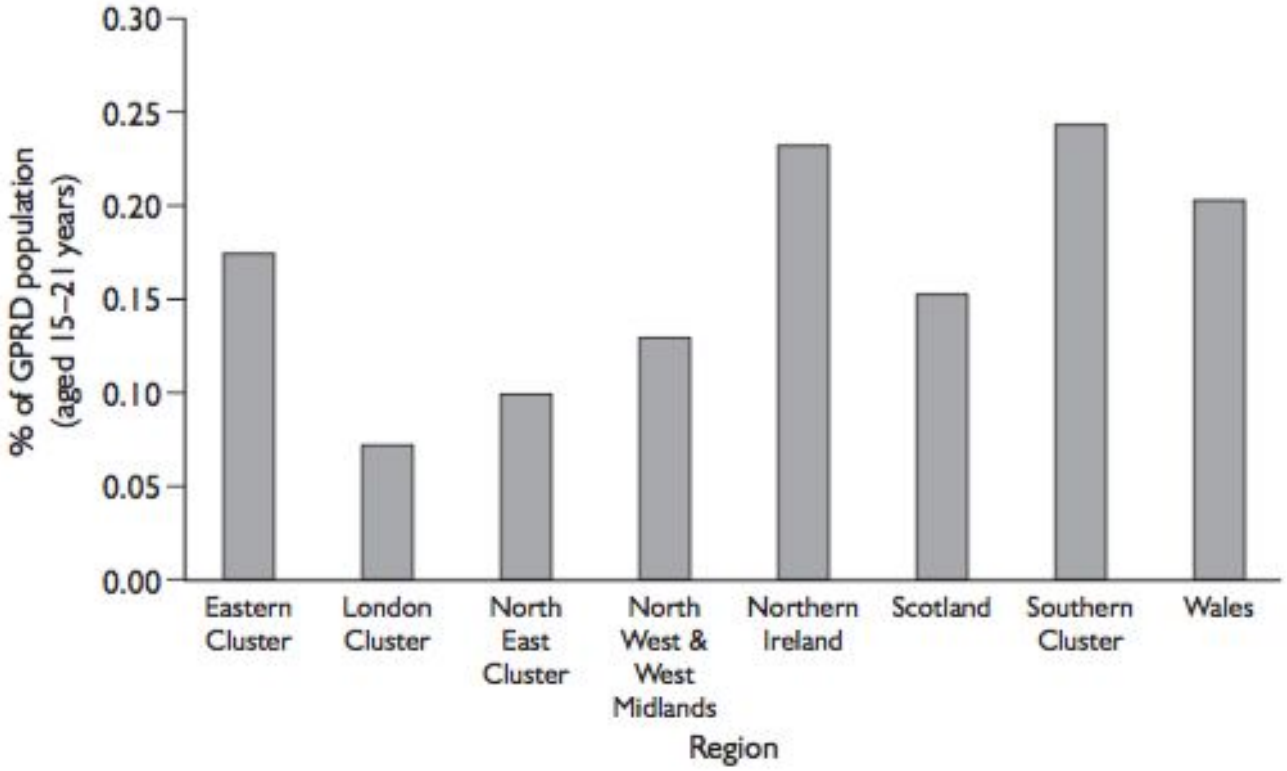


McCarthy et al., BMC Pediatrics 2012


A
30
25
20
15
10
5
0
Prevalence estimate
1980
1985
1990
1995
2000
2005
2010
2015
Year of publication
DSM-IV
DSM-III-R
DSM-III
ICD-10


B
30
25
20
15
10
5
0
Prevalence estimate
1980
1985
1990
1995
2000
2005
2010
2015
Year of publication
North America
Europe
Oceania
South America
Asia
Africa
Middle East

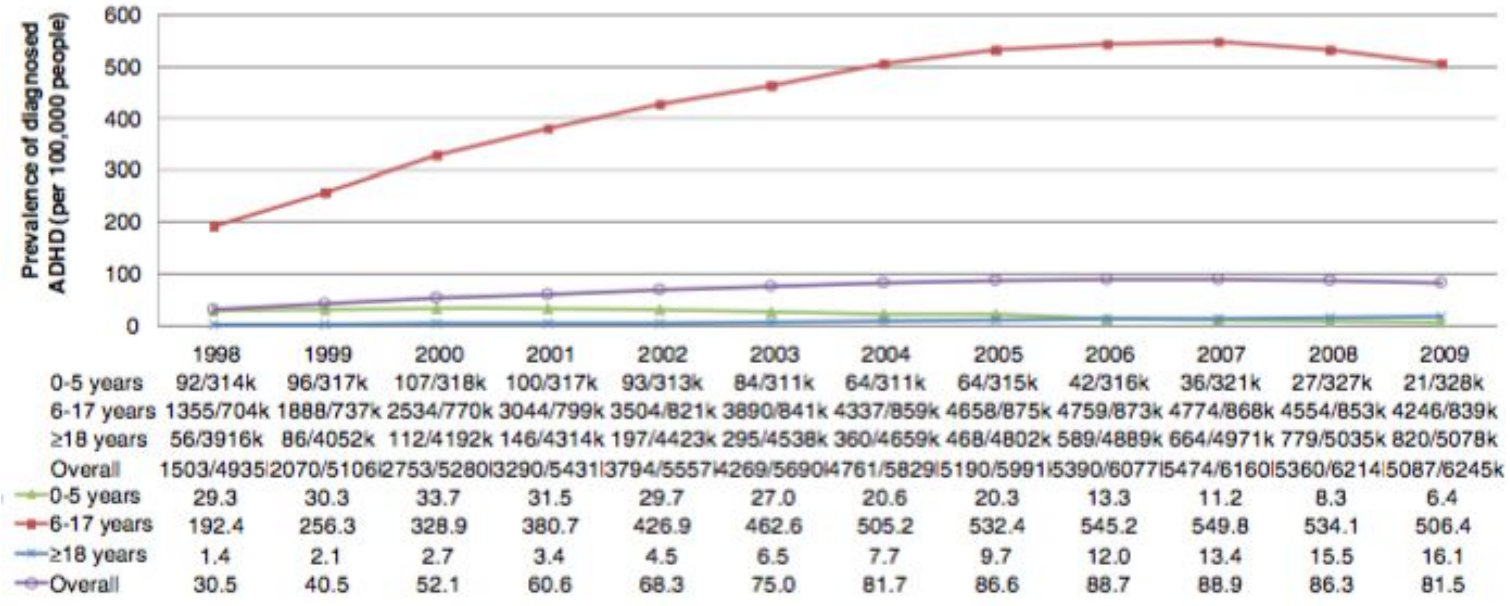
Distribution by region



Wong et al., *Health Technology Assessment*, 2009

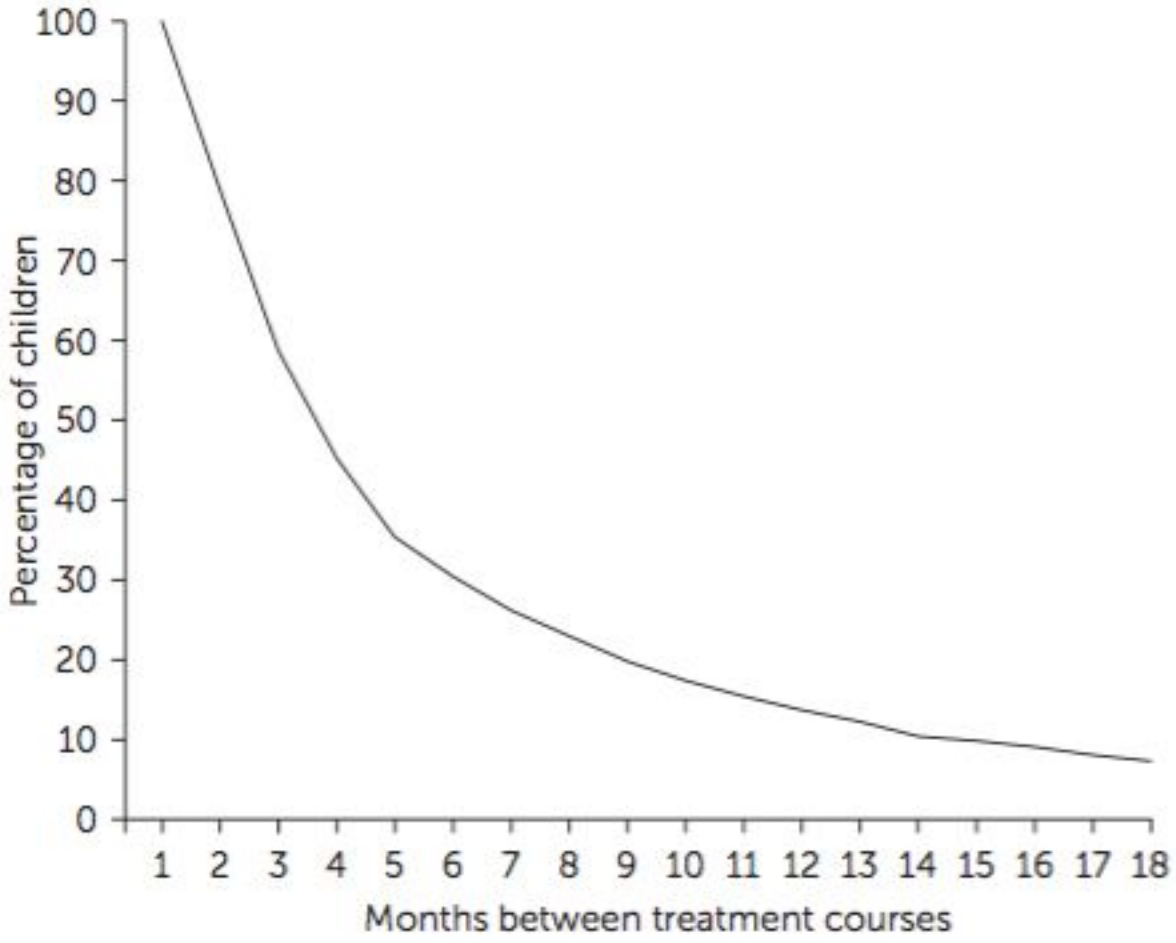
1998-2010

- **CPRD**



	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
0-5 years	92/314k	96/317k	107/318k	100/317k	93/313k	84/311k	64/311k	64/315k	42/316k	36/321k	27/327k	21/328k
6-17 years	1355/704k	1888/737k	2534/770k	3044/799k	3504/821k	3890/841k	4337/859k	4658/875k	4759/873k	4774/868k	4554/853k	4246/839k
≥18 years	56/3916k	86/4052k	112/4192k	146/4314k	197/4423k	295/4538k	360/4659k	468/4802k	589/4889k	664/4971k	779/5035k	820/5078k
Overall	1503/4935	2070/5106	2753/5280	3290/5431	3794/5557	4269/5690	4761/5829	5190/5991	5390/6077	5474/6160	5360/6214	5087/6245k
0-5 years	29.3	30.3	33.7	31.5	29.7	27.0	20.6	20.3	13.3	11.2	8.3	6.4
6-17 years	192.4	256.3	328.9	380.7	426.9	462.6	505.2	532.4	545.2	549.8	534.1	506.4
≥18 years	1.4	2.1	2.7	3.4	4.5	6.5	7.7	9.7	12.0	13.4	15.5	16.1
Overall	30.5	40.5	52.1	60.6	68.3	75.0	81.7	86.6	88.7	88.9	86.3	81.5

Gaps between treatment courses



Raman et al., Psychiatric Services 2015

Databases UK

- General Practice Research Datalink (GPRD)
- IMS Disease Analyzer-Mediplus (Mediplus)
- General Practice Administration System for Scotland (GPASS)
- Medicines Monitoring Unit (MEMO)
- QRESEARCH

1999

- **15 years**
- UK general practice research datalink (GPRD)
- Both a drug prescription and diagnosis of ADHD
- **1.32/1000**

Wong et al., *Health Technology Assessment,* 2009

2006

- **15 years**
- UK general practice research datalink (GPRD)
- Both a drug prescription and diagnosis of ADHD
- **8.31/1000**

Wong et al., *Health Technology Assessment,* 2009

1999

- **21 years**
- UK general practice research datalink (GPRD)
- Both a drug prescription and diagnosis of ADHD
- **0/1000**

Wong et al., *Health Technology Assessment,* 2009

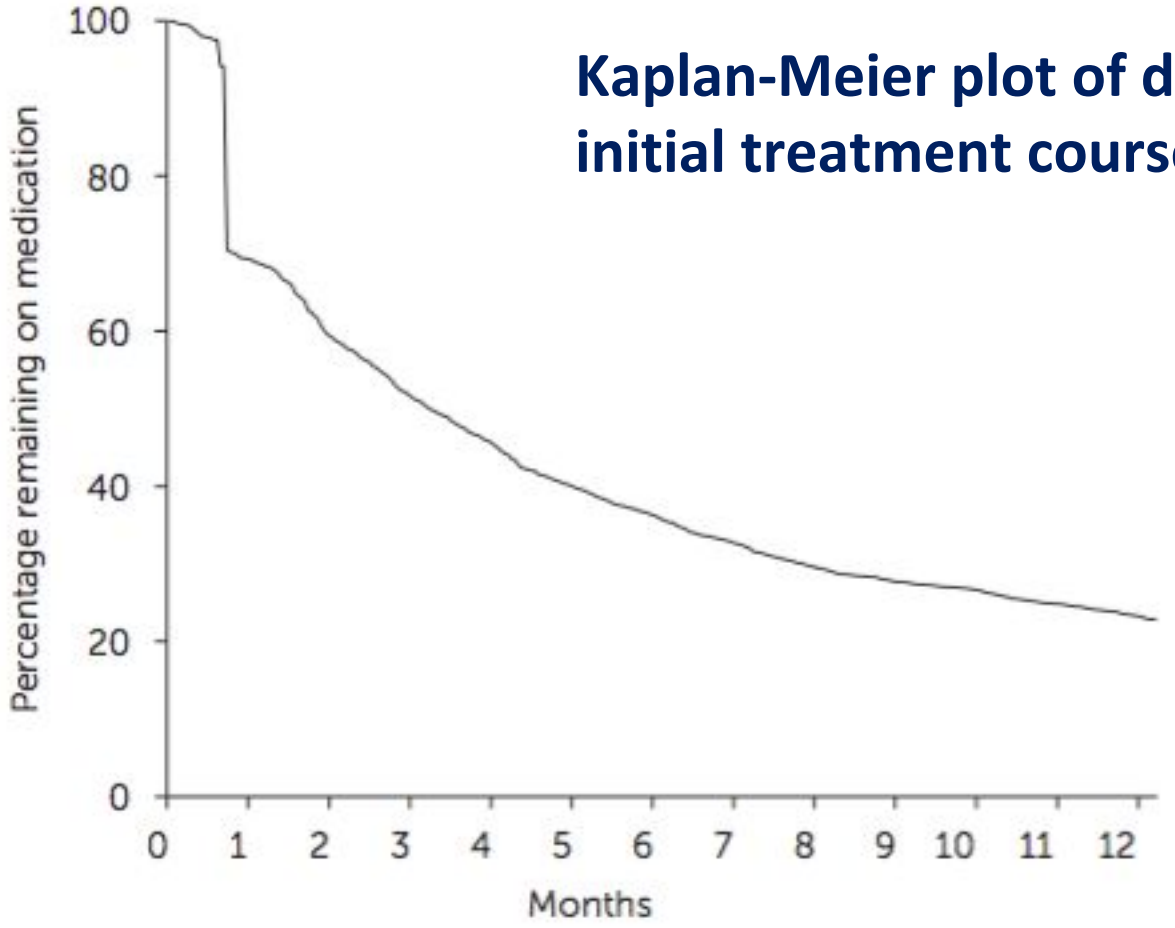
2006

- **21 years**
- UK general practice research datalink (GPRD)
- Both a drug prescription and diagnosis of ADHD
- **0.43/1000**

Wong et al., *Health Technology Assessment,* 2009

2006	354,957
2007	420.421
2008	459,600
2009	492,247
2010	541,516
2012	657,358
2013	725,816
2014	793,749

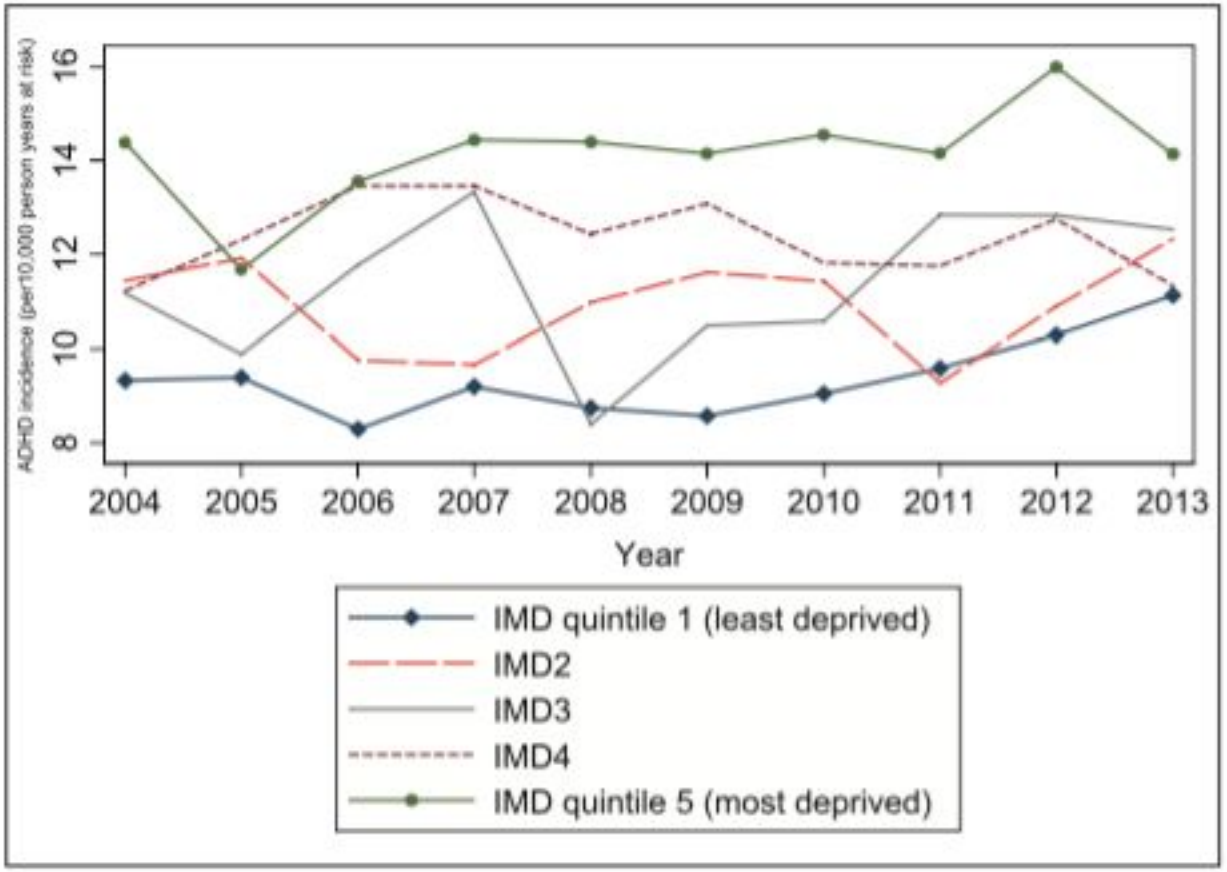
Persistence



Kaplan-Meier plot of duration of initial treatment course

Raman et al., Psychiatric Services 2015

SES and prescription rates



Hire et al., J Att Dis, 2015

Rates HKD

anselmi	2010	2.7
cardo (b)	2011	3.6
deivasigamani'	1990	1.72
dopfner	2008	2.2
esser	1990	1.6
fombonne	1994	0.09
goodman	2005	1.3
hackett	1999	0.71
leung	1996	0.78
malhotra	2002	0.93
mullick	2005	2
schmidt	1991	4.16
skovgaard	2008	2.4
srinath	2005	1.65
taylor	1991	1.72
weyerer	1988	0.3
wong	1992	1.9

Courtesy of Dr Polanczyk, March 2016

Inconsistency in bias rating

Examples

Barkley, 1991	**Funding: NIMH Conflicts of interest: no information**	**LOW**
Rapport, 1987	Funding: NIH Conflicts of interest: no information	UNCLEAR

Coghill, 2007	**This work was supported by a local trust through a Tenovus Scotland initiative. Conflicts of interest: Some study authors have affiliations with different pharmaceutical companies**	**UNCLEAR**
Jensen, 1999 (MTA)	This study was supported by several grants from the National Institute of Mental Health, Bethesda, Maryland Conflicts of interest: Several study authors have affiliations with medical companies	LOW

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Practitioner Review: Current best practice in the management of adverse events during treatment with ADHD medications in children and adolescents

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