ADHD: Shifting the paradigm to improve function and modify the natural history

Daryl Efron

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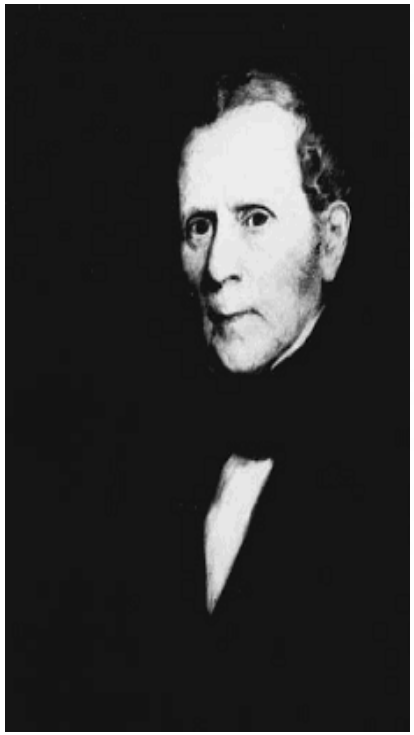
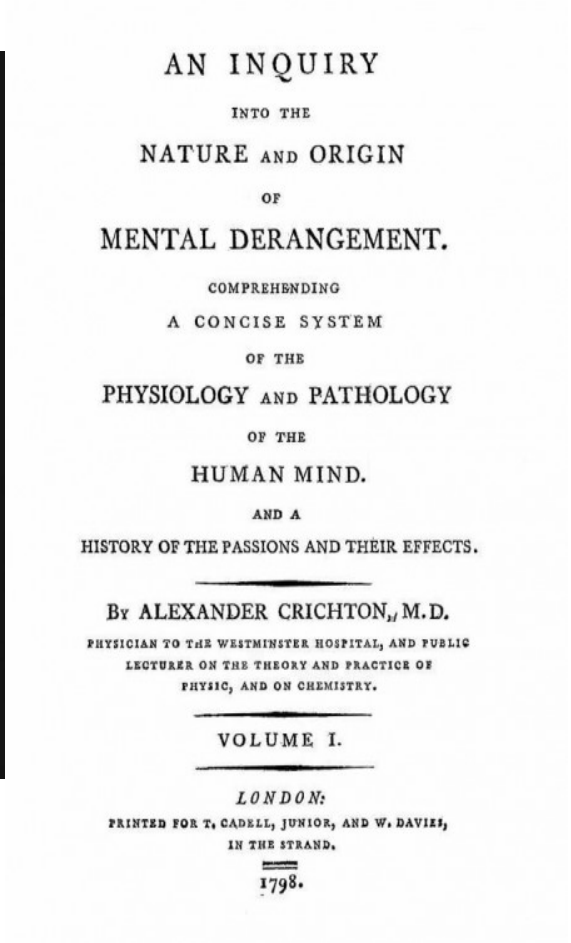
1798 Sir Alexander Crichton





AN INQUIRY

INTO THE

NATURE AND ORIGIN

OF

MENTAL DERANGEMENT.

COMPREHENDING

A CONCISE SYSTEM

OF THE

PHYSIOLOGY AND PATHOLOGY

OF THE

HUMAN MIND.

AND A

HISTORY OF THE PASSIONS AND THEIR EFFECTS.

By ALEXANDER CRICHTON, M.D.

PHYSICIAN TO THE WESTMINSTER HOSPITAL, AND PUBLIC LECTURER ON THE THEORY AND PRACTICE OF PHYSIC, AND ON CHEMISTRY.

VOLUME I.

LONDON:

PRINTED FOR T. CADELL, JUNIOR, AND W. DAVIES, IN THE STRAND.

1798.

Mental restlessness:

- Deficits in attention
- Occurring across situations (e.g. home & school)
- Begins early in life
- Causes impairment in learning

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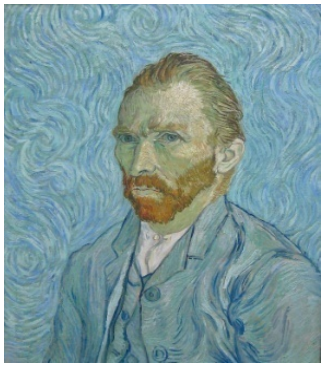
What we know

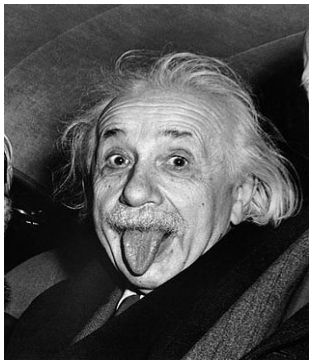
- Kids with ADHD are at increased risk broad range negative outcomes in adolescence and adult life
  - MH, educational / occupational, social, substance abuse
- Meds can really help with symptoms and daily functioning
  - Core symptoms: stimulants, (ATX, clonidine, TCAs)
  - Comorbidities: eg. anxiety – SSRIs; sleep - melatonin
- Behavioural interventions can help too
  - Aggression, internalising symptoms, parent-child relationships, reading (MTA)

People with ADHD can succeed

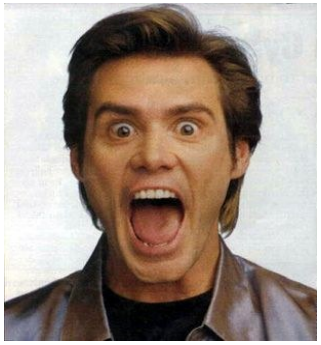
Vincent Van Gogh



Albert Einstein



Jim Carrey



Michael Phelps

Stevie Wonder

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What we don't know

- What are the *key impairments* at different developmental stages ?
- How do *girls* do?
- What's the additional burden of *ASD symptoms*?
- How many, which kids / families access *services*?
- Which kids get *meds*?

- Who will *remit* and who will persist?

- Which kids will do well and which will do poorly in the long run?
  - What are the *modifiable* predictors of better or worse outcomes?
- What (if anything) can make a difference to *long-term outcomes*?
  - What can parents do? Schools? Psychologists? Doctors? Others?
  - Optimal timing? Intensity?

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The Children's Attention Project (CAP)

A longitudinal study of children with and without ADHD

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What is CAP?

- First Australian longitudinal cohort study of children with and without ADHD
- Overcomes limitations of previous cohort studies
  - Community-based sample (rather than clinical)
  - Includes all subtypes, comorbidities, girls and boys
  - Tight age range – developmentally sensitive
- Funded by 2 NHMRC grants: 1008522 (2011-2015); 1065895 (2014-2018)

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Aims

1. Document the natural history and impact of ADHD
   - Children: mental health, quality of life, social & academic functioning
   - Parents: mental health and family functioning.
2. Identify risk & protective factors associated with poor versus better outcomes

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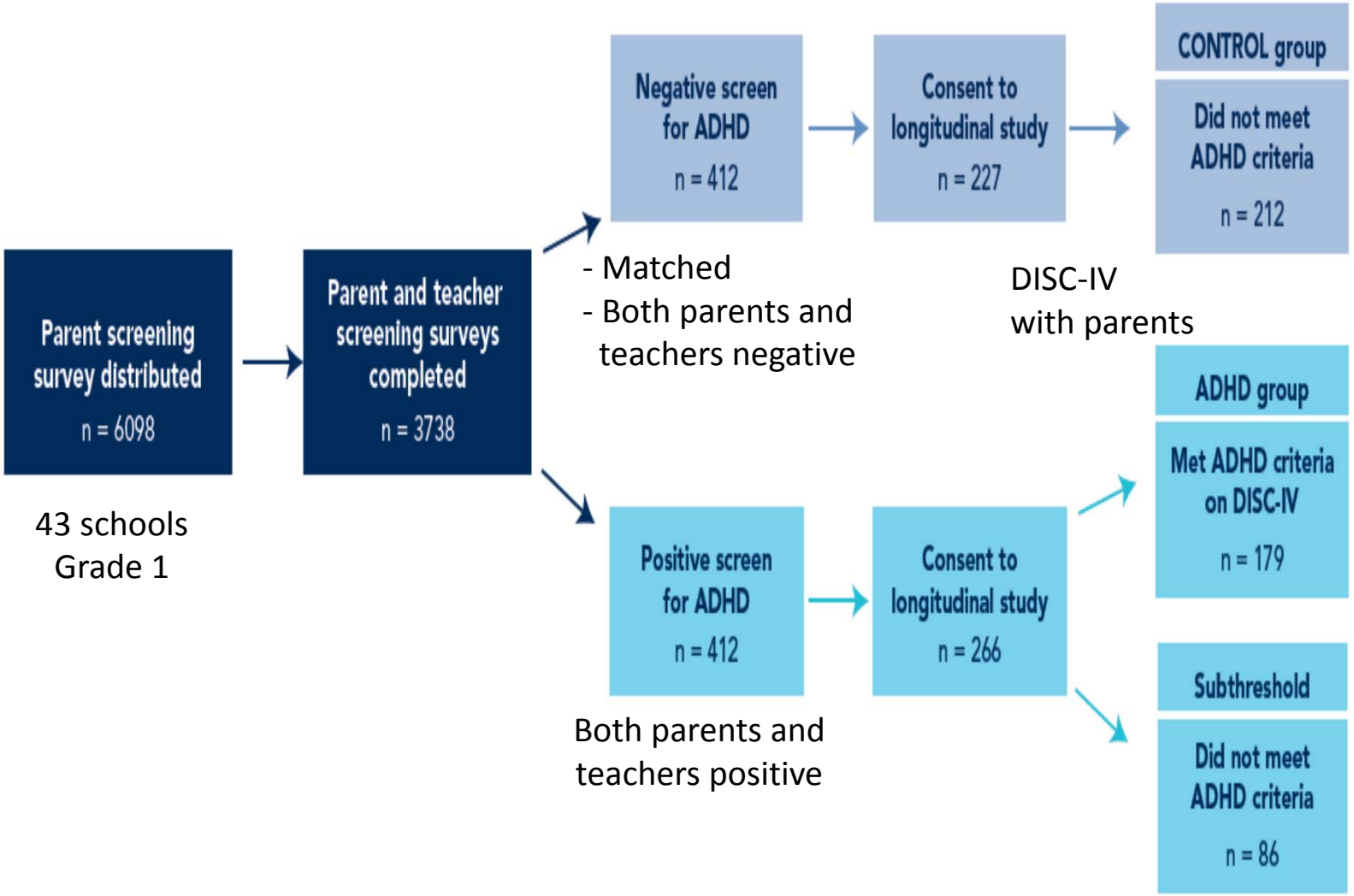
Recruitment flowchart



43 schools
Grade 1

- Matched
- Both parents and teachers negative

DISC-IV with parents

Both parents and teachers positive

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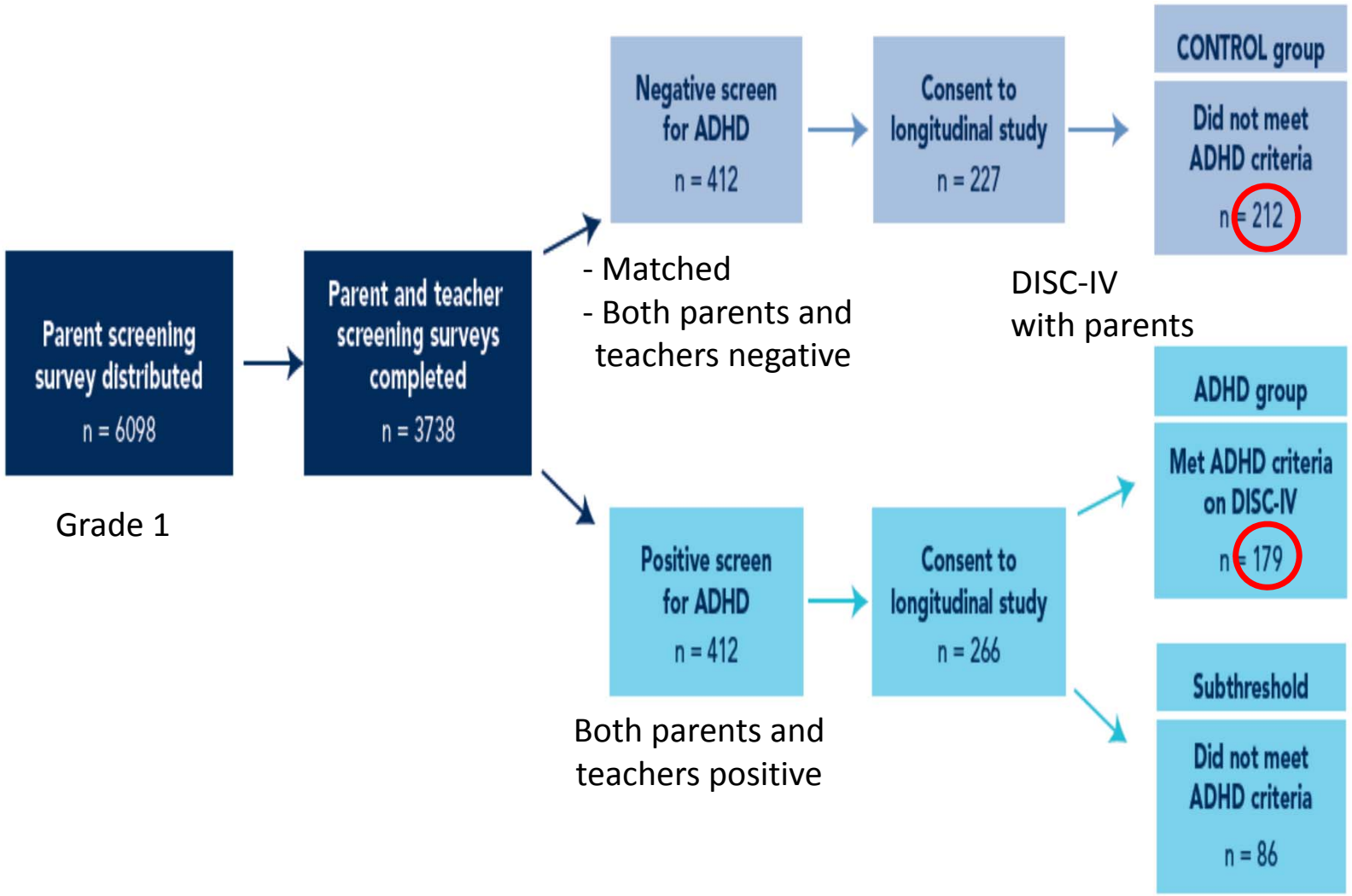
Recruitment flowchart



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Measures on CAP

	Wave 1	Wave 2	Wave 3	Wave 4
Grade (year)	Grade 1 (2011-12)	Grades 3-4 (2013-14)	Grades 5-6 (2015)	Grades 6-7 (2016-2017)
Child assessment	✓		✓	✓(NICAP)
Parent interview (DISC-IV)	✓		✓	
Surveys				
Parent	✓	✓	✓	✓
Teacher	✓	✓	✓	
Child			✓	✓

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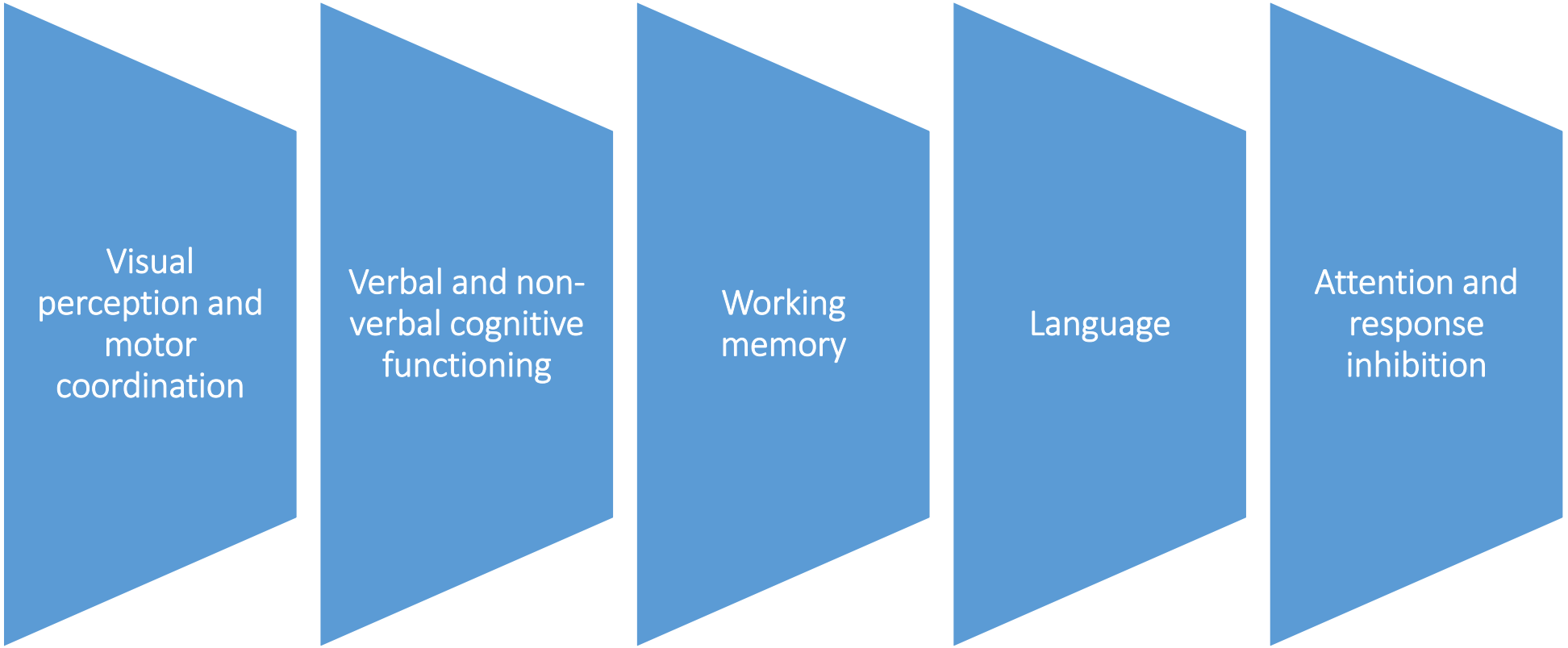
Child assessment measures



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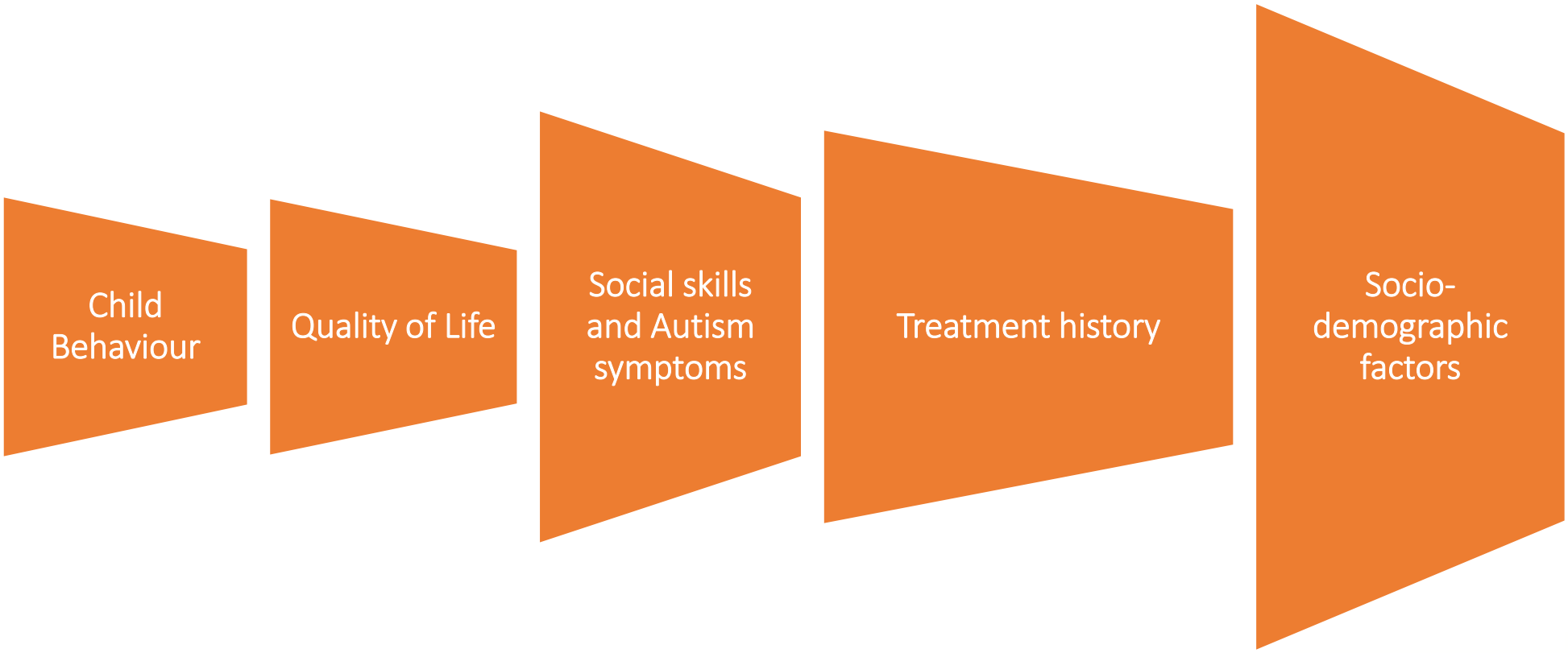
Parent surveys



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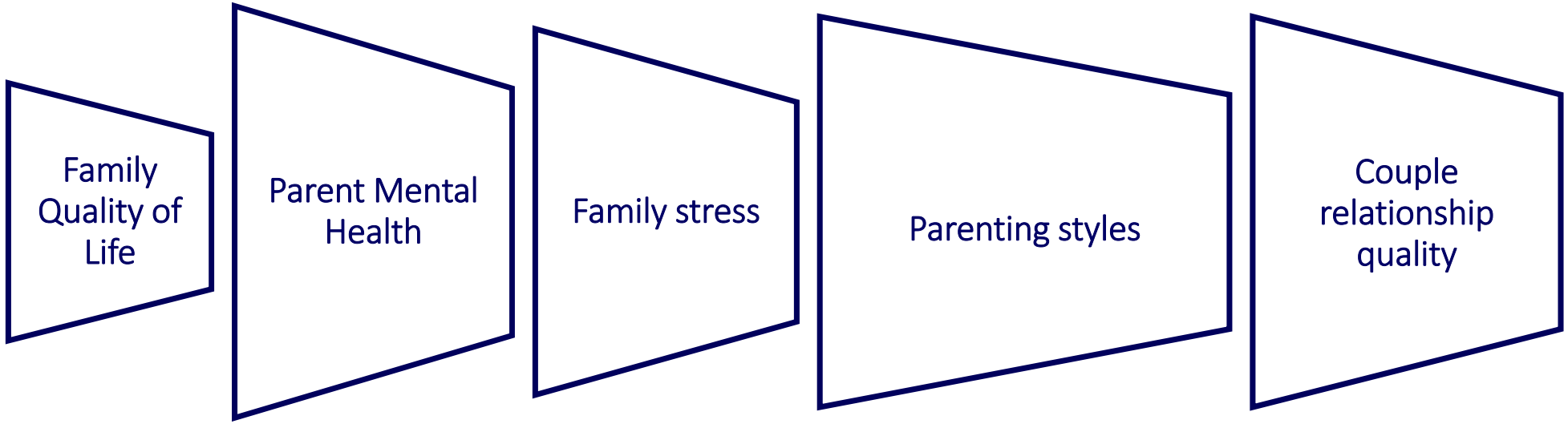
Parent surveys



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Teacher surveys

Child Behaviour

Student-Teacher Relationship

School service use

Social skills & Autism Symptoms

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Response rates

	Wave 1 (n=498)	Wave 2 (n=493)	Wave 3 (n=481)	Wave 4 (n=204)
Grade (year)	Grade 1 (2011-12)	Grades 3-4 (2013-14)	Grades 5-6 (2015)	Grades 6-7 (2016-2017) Current*
Child assessment	99%		77%	68%
Parent interview	99%		75%	-
Surveys				
Parent	94%	80%	74%	68%
Teacher	99%	91%	69%	-
Child			74%	61%

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FINDINGS

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Baseline data

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Sample characteristics

	ADHD (n=179) *	Controls (n=212)	p value
Age, mean (SD)	7.3 (0.4)	7.3 (0.4)	.41
Male, n (%)	124 (69)	135 (64)	.24
Estimated FSIQ, mean (SD)	92 (12)	101 (14)	<.001
Primary caregiver did not complete high school, n (%)	63 (38)	39 (19)	<.001
Previous ADHD diagnosis , n (%)	31 (17)	0	<.001
ASD diagnosis, n (%)	33 (18)	3 (1)	<.001
ADHD medication, n (%)	23 (13)	0	<.001

* Combined 93 (52%), Inattentive 64 (36%), Hyperactive-Impulsive 22 (12%)

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*Combined type (24%), Inattentive (9%) and Hyperactive-Impulsive (14%)

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Co-existing difficulties are common (age 7)

	ADHD (n=179)	Controls (n=212)	P value
Externalising disorder	54%	8%	<.001
Internalising disorder	26%	5%	<.001
Elevated Autism symptoms	21%	3%	<.001
Sleep problems	28%	6%	<.01
Trauma exposure	27%	16%	<.01

- Efron et al., 2014, *Pediatrics*
- Sciberras et al., 2014, *Pediatrics*
- Green et al., 2016, *Eur Child Adolesc Psychiatry*
- Schilpzand et al., *Under review*

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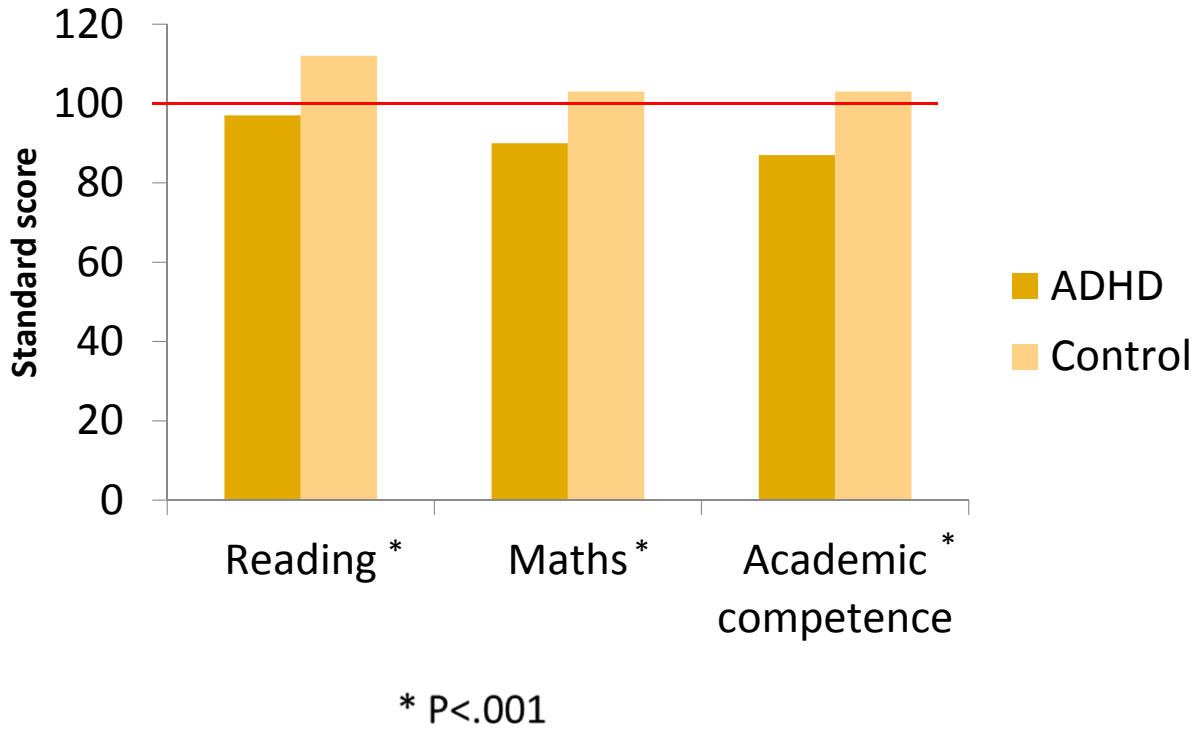
Academic functioning (*WRAT-IV)*



Efron et al., 2014, *Pediatrics*

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Language Problems *(CELF-4, screener)*

			Odds ratio (95% CI)			
	ADHD *n=178*	Control *n=212*	Unadjusted	p	Adjusted	p
Language problem, n (%)	72 (40)	37 (17)	3.2 (2.0, 5.1)	<.001	2.8 (1.5, 5.1)	.001

Sciberras et al., 2014, *Pediatrics*

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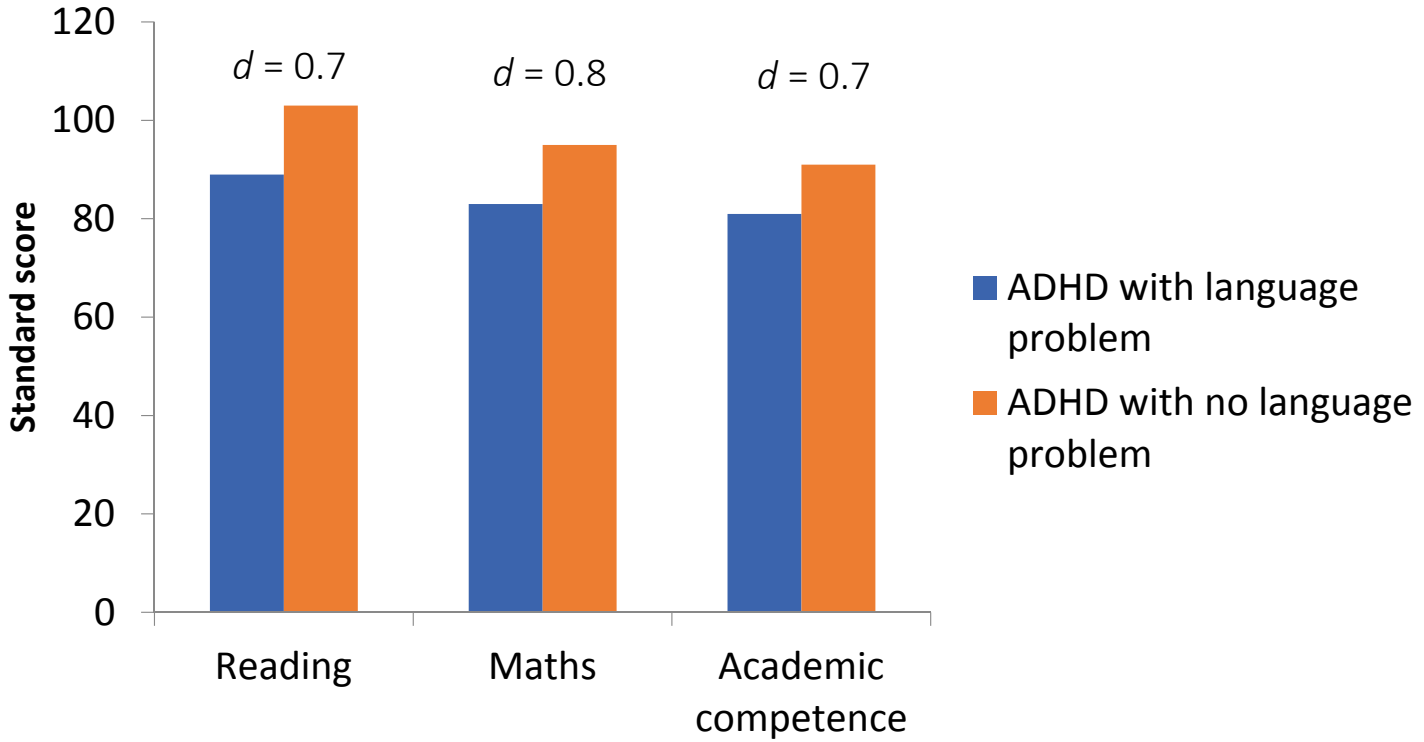
Relationship between Language Problems & Academic Functioning



Adjusted findings

Sciberras et al., 2014, *Pediatrics*

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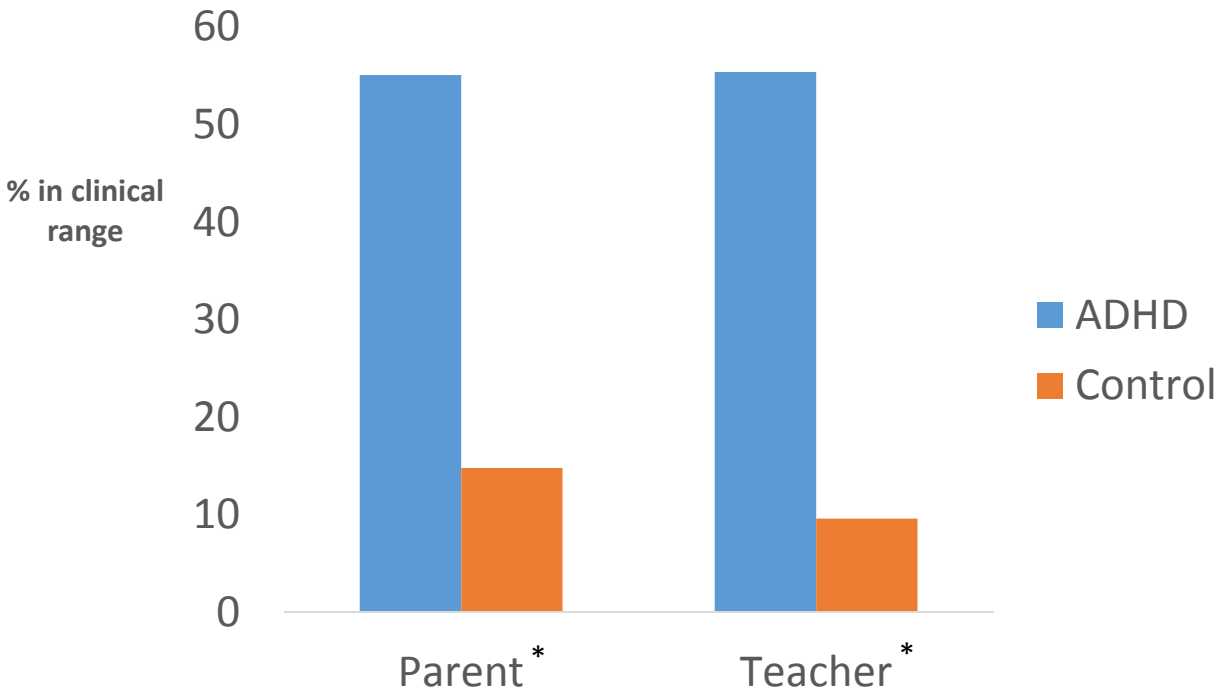
Social functioning *(SDQ: Peer problems)*



* P<.001

Efron et al., 2014, *Pediatrics*

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Girls with ADHD (compared to boys with ADHD)

- Similar profile of difficulties:
  - **Internalising disorders** (adjusted OR, 1.1; 95% CI, 0.5 to 2.4)
  - **Externalising disorders** (adjusted OR, 0.8; 95% CI, 0.3 to 1.7)
  - **Word reading** (adjusted mean difference [AMD] 1.2; 95% CI, 24.6 to 7.0)
  - **Math computation** (AMD, 4.0; 95% CI, 20.8 to 8.8)
  - **Language problems** (42% vs 40%)
- Less **parent-reported peer problems** (AMD, 0.7; 95% CI, 0.03 to 1.4; P = .04)
  - No difference by teacher report (AMD, 0.1; 95% CI, 20.16 to 0.8; P = .82).
- Less likely to be **diagnosed:**

	Overall	Boys	Girls	OR	95% CI	p
Baseline (age 7)	31/179 (17%)	28/124 **(22%)**	3/55 **(5%)**	5.2	1.6-17.5	.007
3 years (age 10)	49/130 (38%)	41/91 **(45%)**	8/39 **(21%)**	3.3	1.3-8.4	.01

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Autism Spectrum Disorders

- Children with ADHD had more ASD symptoms than controls (AMD = 4.0, 95% CI 2.8; 5.3, $p < 0.001$)
- Greater ADHD symptom severity assoc with greater ASD symptom severity (regression co-efficient = 1.6, 95% CI 1.2; 2.0, $p < 0.001$).
- Boys with ADHD had greater ASD symptom severity than girls with ADHD (AMD = 2.9, 95% CI 0.8; 5.2, $p = 0.01$)
- No differences by ADHD subtype.
- ASD symptoms associated with increased internalising (OR 1.8) , externalising (OR 1.5), & sleep problems (OR 1.5), and decreased QoL

Green et al *Arch Dis Child* 2016

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Service use

- *Have you sought professional help for concerns about your child's learning, behaviour or emotions in last 12 months?*
    - GP
    - Paediatrician
    - Psychologist
    - Psychiatrist
    - Speech path,
    - OT
    - educational specialist

- child & family **predictors**
    - univariate and multivariate logistic regression

Efron et al *Arch Dis Child* 2016

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Service use

- 37% had **not** received professional services in past 12 months
- Services used
  - Paediatrician 35%
  - Psychologist 26%
  - GP 22%
  - Speech path 21%
  - OT 11%
- Predictors
  - Age
  - Impact of behaviour on family
  - (academic failure – fell out in adjusted analyses)

Efron et al *Arch Dis Child* 2016

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3 year data

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Comorbidities, academic function

	Age 7		p	Age 10		p
	ADHD	Control		ADHD	Control	
Externalising disorder	54%	8%	<.001	51%	9%	<.001
Internalising disorder	26%	5%	<.001	26%	7%	<.001
<25th percentile reading or maths	53%	17%	<.001	69%	28%	<.001

Outcomes did not differ by medication status or gender

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ADHD persistence

- 67% of children with ADHD met full ADHD criteria 3 years later.
  - Boys more likely to persist than girls (74% vs 50%; OR: 3.4; 95% CI 1.3, 8.4, p=0.01)
  - Persistent ADHD more likely to have (cf remitted):
    - Externalising disorder (57% vs 33%; p=0.008)
    - Mood disorder (8% vs 0%; p=0.04)
    - Better word reading (MD 5.5; 95% CI 0.2, 10.8; p=0.04)

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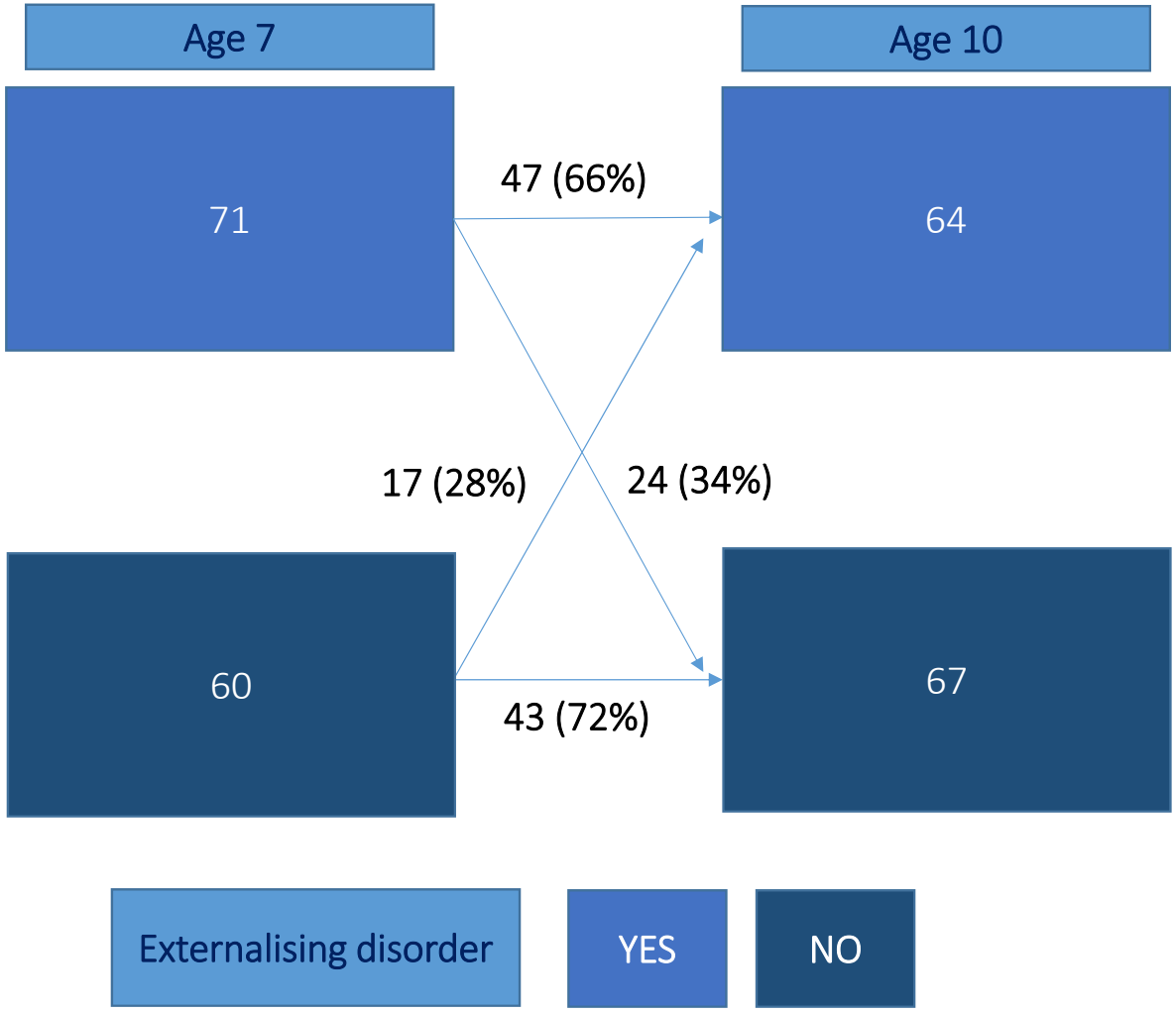
Development of externalising disorders in ADHD (n=131)



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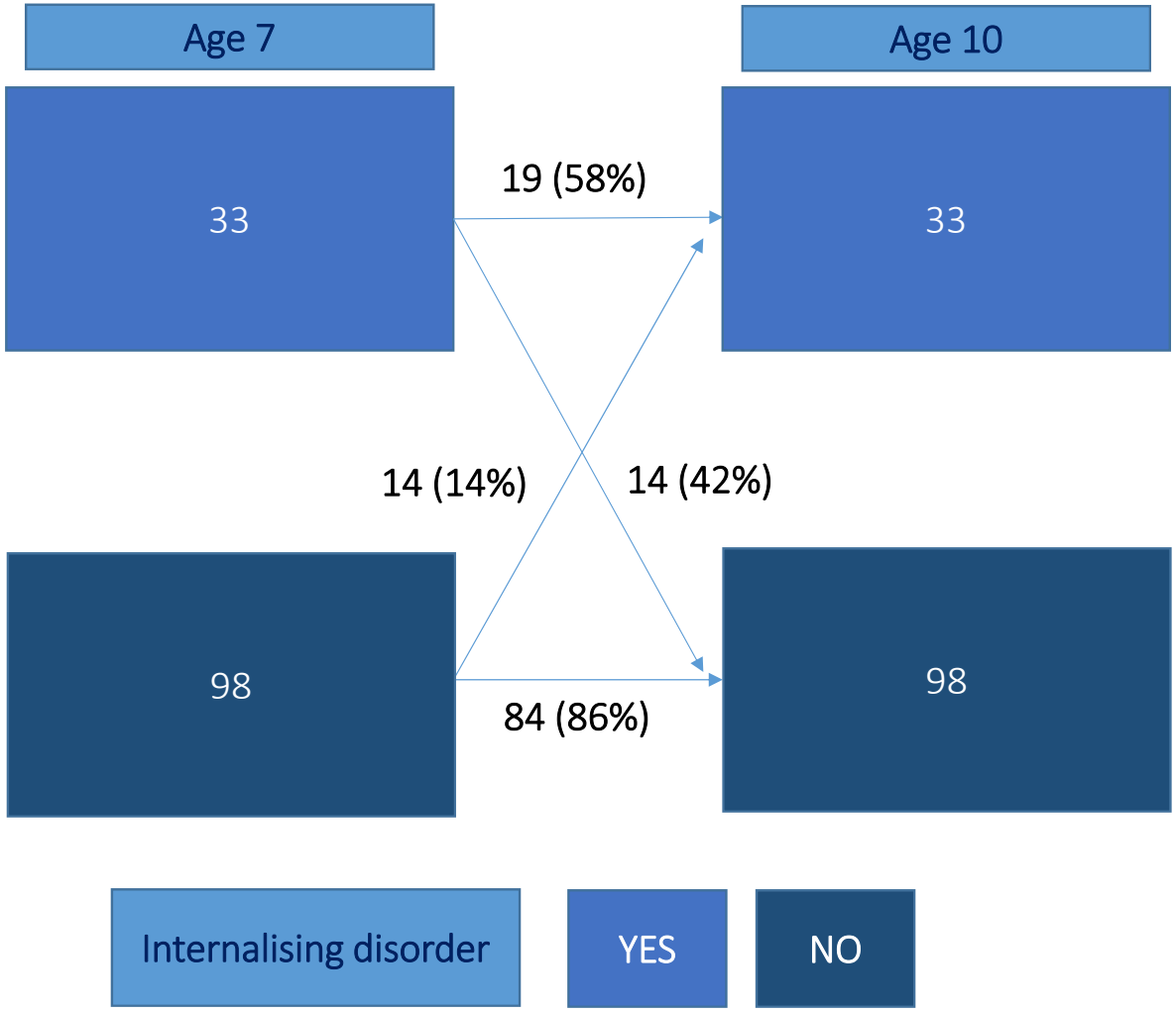
Development of internalising disorders in ADHD (n=131)



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Predictors of medication use

	Clinical diagnosis	ADHD med prescribed
Baseline (age 7)	31/179 (17%)	21/179 (13%)
3 years (age 10)	49/144 (38%)	35/144 (26%)

Predictors (adjusted analyses):

- ADHD symptom severity *(Conners ADHD Index, parent report)*
  - Baseline (OR 1.25, 95%CI 1.06-1.47, **p=.01**)
  - 3 yrs (OR 1.17, 95%CI 1.05-1.30, **p=.004**)
- Socio-economic status *(SEIFA)*
  - Baseline (OR 0.51, 95%CI 0.30-0.85, **p=.01**)
  - 3 yrs (OR 0.65, 95%CI .37-1.12, p=.12)

Not academic performance, gender, comorbidities, social problems, maternal MH

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Other CAP work

- Anxiety
- Health problems (obesity, injuries, sleep problems)
- Disruptive Mood Dysregulation Disorder
- Parenting (relation to child function)
- Maternal ADHD symptoms (relation to child function)
- Peer victimization
- Global self-worth
- Influence of age at school entry on rate of ADHD medication use
- Chronic tics / Tourette
- Quality of Life

- Mulraney et al 2015, *Eur Child Adolesc Psychiatry*
- Sciberras et al 2016, *Child Care Health Dev*.
- Mulraney et al., 2016, *J Atten Disord*
- Bhide et al., 2017, *J Atten Disord*
- Sciberras et al 2017, *MJA* (letter)
- Efron et al, *under review*
- Wijaya et al, *under review*

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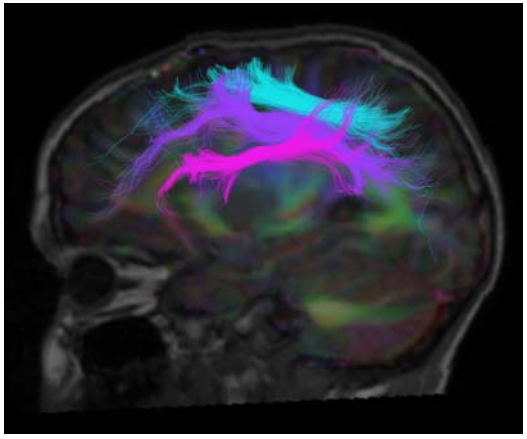
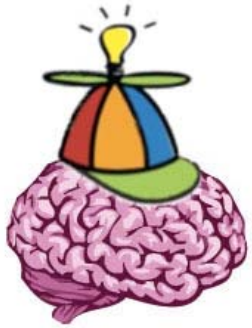
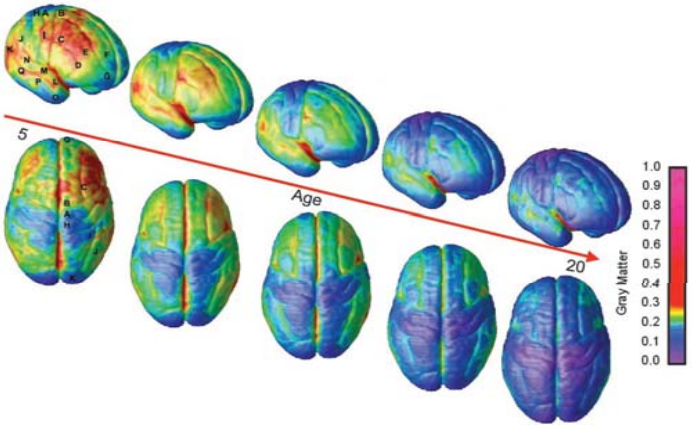
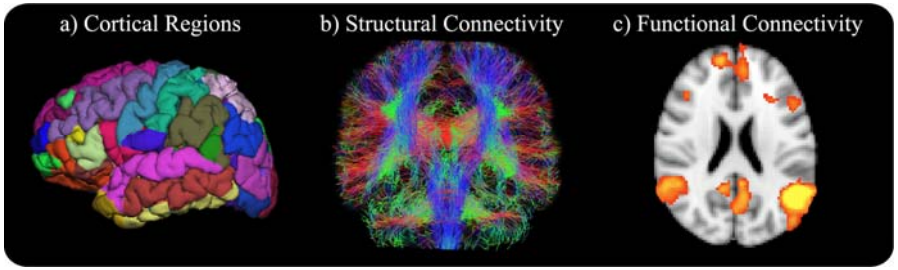
Neuroimaging of the Children's Attention Project (NICAP) Dr Tim Silk









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NICAP

- Aim: To investigate trajectories in brain structure and function for children with and without ADHD
  - associations with academic, cognitive, social and mental health outcomes

- Longitudinal multi-modal MRI
  - ages 11, 12.5, 14

- Scans completed
  - Wave 1: 180 of 206 (87%)
  - Wave 2: 146 of 160 (90%) *to date*

Silk et al, 2016, *BMC Psychiatry*

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Summary

- CAP will help us understand the natural history of ADHD and the factors influencing outcomes
  - important information for health and education professionals, families and policy makers

We wouldn't be able to do this research without the support of families, schools and teachers

Murdoch Childrens Research Institute

CAP Staff

Investigator Team

Dr Emma Sciberras MCRI, RCH
Dr Daryl Efron RCH, MCRI
Prof Jan Nicholson La Trobe, MCRI
Prof Vicki Anderson MCRI, RCH
Dr Tim Silk MCRI
Prof Philip Hazell SSWAHS, USYD
Dr Brad Jongeling CDS, UWA
Dr Obioha Ukoumunne PenCLAHRC
Ms Karen Underwood DEECD

Current Project Team

Alisha Gulenc Project Coordinator
Lilli Nonneman Research Assistant
Charles Malpas Post-Doctorate
Helena Brace Intern

Current Students

Sampada Bhide MPSYCH/PhD
Hannah Korrel MPSYCH/PhD
Sila Genc PhD
Kate Stephens PhD
Howard Chiu MPSYCH
Phoebe Thomson Honours
William Poh Scholarly selective

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Australian paediatric practice: Assessment

- Multi-site audit paediatric practice
  - 24 paediatricians: Vic and WA, private and public
  - 137 patients, 77% male, mean age 8.1 yrs
- **Questionnaire** use: Parent 88%, teacher 85%
- **Comorbidities** identified:

Efron et al *J Paed Child Health* 2016

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Australian paediatric practice: Assessment

- Multi-site audit paediatric practice
  - 24 paediatricians: Vic and WA, private and public
  - 137 patients, 77% male, mean age 8.1 yrs
- **Questionnaire** use: Parent 88%, teacher 85%
- **Comorbidities** identified:

	Internalising (%)	Externalising (%)	Sleep problems (%)
Paediatrician	18	15	4
Parent (SDQ)	51	66	39

Efron et al *J Paed Child Health*2016

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Children Attending Paediatricians Study (CAPS)

- 2-week audit
  - Nov 2013
- N=185
- 7514 consultations

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Research Institute

5151249322

1. PATIENT INFORMATION - PLEASE PRINT IN CAPITAL LETTERS

Paediatrician ID: ☐☐☐☐

a. Date of visit ☐☐/☐☐/2013 **b. Gender** ○ M ○ F

c. Start Time (pls circle) ☐☐:☐☐ **AM / PM**

d. FAMILY Postcode: ☐☐☐☐

e. PAED postcode THIS session: ☐☐☐☐

f. Where seen?
- ○ Public Outpatients
- ○ Private Room
- ○ Community Heath Centre

g. Is English main language spoken at home?
○ Y ○ N → **which language?** _____

Need interpreter? ○ Y ○ N

h. Mark those that apply
- ○ HCC / Carer's Allowance
- ○ ATSI

i. Child's Date of Birth ☐☐/☐☐/☐☐☐☐

j. Parent overall rating of child's health
poor fair good v.good excellent

k. Parent overall rating of own health
poor fair good v.good excellent

l. Pls mark if parent refused (j)+(k): ○

m. Child's Ht if possible ☐☐☐ cm

n. Child's Wt if possible ☐☐☐.☐ kg

2. PROVIDER'S DIAGNOSIS FOR THIS VISIT

Current diagnoses/problem list at this visit - please refer to code list on opposite page and mark whether new or continuing. If **no code**, please specify the diagnosis.

	CODE	OR PLEASE PRINT Dx	New	Cont
(1)	☐☐	_____	○	○
(2)	☐☐	_____	○	○
(3)	☐☐	_____	○	○
(4)	☐☐	_____	○	○

3. MEDICATIONS

○ NONE

Include Rx & OTC drugs, immunizations, allergy shots, chemotherapy & dietary supplements that were ordered, supplied, administered or continued during visit.

		New	Cont
(1)	_____	○	○
(2)	_____	○	○
(3)	_____	○	○
(4)	_____	○	○

4. MEDICARE ITEMS

Medicare Item Nos: (Pls mark if applicable)

○ New	1 1 0
○ R/V	1 1 6
○ New long	1 3 2
○ R/V long	1 3 3
○ Autism	1 3 5
○ Other	☐☐☐

5. IMAGING

Mark all imaging sites at this visit:

	Abdo	Chest	CNS	Limb	Renal	Other	
X-ray:	○	○	○	○	○	○	_____
CT:	○	○	○	○	○	○	_____
MRI:	○	○	○	○	○	○	_____
U/sound:	○	○	○	○	○	○	_____

Other: _____

6. OTHER Ix & Mx

Mark all tests ordered/requested at this visit:

Blood:
- ○ Haem ○ Biochem
- ○ Endocrine ○ Genetic

Other:
- ○ Urine ○ Stool
- ○ Diagnostic/Screening qstre
- ○ Written management plan
- ○ Other, please specify

_____

7. REFERRALS

Mark all referrals made at this visit:
- ○ Psychology
- ○ Speech Pathology
- ○ Audiology
- ○ Subspecialist
- ○ Multidisciplinary Team
- ○ Other Allied Health
- ○ Other, please specify

_____

8. VISIT DISPOSITIONS

a. Please mark one:
- ○ No further follow-up by me
- ○ Follow-up by me
- ○ Admission

b. Finish time (pls circle) ☐☐:☐☐ **AM / PM**

c. Extra time required after visit (eg phone, letters): ☐☐☐ mins

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CAPS 2013: Medications prescribed

Medication group	Proportion of consultations in which medication prescribed (%)
Psychotropic	27
Laxatives	5
Asthma medications	4
Melatonin	4
Acid-suppressing agents	3
Eczema medications	2
Antihistamine	1
Enuresis medications	1
Specialised infant formula	0.5
Other	12

Efron et al *J Paed Child Health* In Press

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CAPS 2013: Psychotropics

Medication group	Proportion of consultations in which medication prescribed (%)
Psychotropic any	27
Stimulants	17
SSRI/SNRI	4
Antipsychotics	3
Clonidine	2
Atomoxetine	1
Tricyclics	0.5
Anti-epileptic drugs	4

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