



The outcome of ADHD: Forewarned is Forearmed

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Conflicts of interest for the last 5 years

Has worked as a consultant or clinical expert for

- The Danish Health and Medicines Authority, in *The Danish national clinical guidelines for assessment and treatment of children and adolescents with ADHD, 2013-14*
- The Institute for Rational Pharmacotherapy, Danish Health and Medicines Authority, Review of evidence for lisdexamfetamindimesylat in ADHD-treatment, 2013
- *The Danish Psychiatric Association, member of the working group suggesting clinical guidelines for assessment and treatment of adults with ADHD, December 2011-2012*
- The Danish Association for Child and Adolescent Psychiatry, on *Clinical Guidelines for Assessment and Treatment of Children and Adolescents with ADHD, 2011-2012*
- The Ministry of the Interior and Social Affairs, *Screening for ADHD among socially disadvantaged people: Homeless, drug abusers, and prostitutes, 2009-2011*
- No other conflicts of interest

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Forewarned is Forearmed, why this title?

- Oxford dictionary:
Prior knowledge of possible dangers or problems gives one a tactical advantage
- Worries about the prognosis can cause panic in parents
 - A panicking parent does not help his/her child with ADHD
- Not knowing the evidence or discarding it, does not help
- So, we need to know - to be prepared
 - Even if it's scary

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ADHD – as a lifelong disorder

- The majority of children with ADHD continue to have significant impairment in adulthood, due to ADHD¹
- Despite fewer ADHD core symptoms, many often experience higher impairment as adults²
- Still, many adults with ADHD are not diagnosed or treated³⁻⁵

1. Mannuzza & Klein. Long-term prognosis in attention-deficit/hyperactivity disorder. *Child Adolesc Psychiatry Clin Nam.* 2000; 9(3): 711-26.
 2. Klein, et al. Clinical and functional outcome of childhood attention-deficit/hyperactivity disorder 33 years later. *Arch Gen Psychiatry.* 2012; 69(12): 1295-303.
 3. Kessler, et al. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry.* 2005; 62(6): 593-602.
 4. Kessler, et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. *A J Psychiatry.* 2005; 163(4): 716-23.
 5. Fayyad, et al. Cross-national prevalence and correlates of adult attention-deficit hyperactivity disorder. *Br J Psychiatry.* 2007; 190: 402-9.
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ADHD and the outcome

- ADHD increases the risk of hospital contacts,¹ injuries,² substance abuse,³ criminality,⁴ and the development of more severe psychiatric disorders, including psychosis^{5,6}
- Comorbid oppositional defiant disorder or conduct disorder (ODD/CD) are strong predictors of negatives outcomes^{3,7}

1. Dalsgaard et al. Consequences of ADHD medication use for children's outcomes. *J Health Econ.* 2014; **37**: 137-51.
2. Dalsgaard, et al. Effect of Medication On the Risk of Injuries in Children with Attention-Deficit/Hyperactivity Disorder - A Prospective Cohort Study. 2015 (in press *Lancet Psychiatry*).
3. Dalsgaard, et al. ADHD, stimulant treatment in childhood and subsequent substance abuse in adulthood - a naturalistic long-term follow-up study. *Addict Behav* 2014;**39**:325-8
4. Dalsgaard, et al. Long-term criminal outcome of children with attention deficit hyperactivity disorder. *Criminal behaviour and mental health : CBMH* 2013;**23**:86-98
5. Dalsgaard, et al. Association between Attention-Deficit Hyperactivity Disorder in childhood and schizophrenia later in adulthood. *Eur Psychiatry* 2014;**29**:259-63.
6. Maling, et al. Risk of schizophrenia increases after all child and adolescent psychiatric disorders – a nationwide study. *Schizophr Bull.* 2014; Sept 5.
7. Dalsgaard, et al. Conduct problems, gender and adult psychiatric outcome of children with attention-deficit hyperactivity disorder. *Br J Psychiatry.* 2002; **181**: 416-21.

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Evidence for effects of medications in ADHD

- Core symptoms of inattention, hyperactivity and impulsivity
 - Very large positive effects in children and adolescents^{1,2}
 - Moderate positive effects in adults^{1,3}
- Comorbid symptoms of ODD/CD
 - Moderate to large positive effects in children¹

1. National Institute for Health and Clinical Excellence: NICE clinical guideline 72: Attention deficit hyperactivity disorder: Diagnosis and management of ADHD in children, young people and adults. London: National Institute for Health and Clinical Excellence, NICE; 2006.
2. Sundhedsstyrelsen: National klinisk retningslinje for udredning og behandling af ADHD hos børn og unge; 2014.
3. Sundhedsstyrelsen: National klinisk retningslinje for udredning og behandling af ADHD hos voksne med forstyrrelse af aktivitet og opmærksomhed samt opmærksomhedsforstyrrelse uden hyperaktivitet; 2015.

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Other possible effects of ADHD-medications

- Could ADHD-medication reduce the risk of some negative outcomes associated with the disorder?
- Outcomes such as substance use disorder (SUD), criminality, accidents, and injuries?

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How to study the effects of medication?

- A randomized controlled trial (RCT) is the gold standard for examining effects of medication
- However, in measuring effects on long-term outcomes RCTs are often inconvenient or impossible
- Observational follow-up studies in Denmark and Sweden using register-data offers alternative methods in examining this
- However, as participants in an observational study are not randomized, *confounding by indication* can be a problem

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Methods to reduce confounding by indication

- Use each individual as his/her own control
 - Comparing treated to non-treated periods in the statistical analyses
 - Comparing two groups of individuals (treated and non-treated) at two time-points (before and after treatment)
- "Natural experiment", a method often used in economics
 - Changes in legal regulations over time
 - Geographical differences in prescription practices
 - In Denmark large regional differences in prevalence of ADHD-medication

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Criminality and juvenile delinquency

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Consequences of ADHD medication use for children's outcomes 

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ADHD, criminality and effects of medication

- A Danish collaborative study
 - In adolescents with ADHD, treatment with medication reduced the risk of police-contacts before age 15 **by 17%**¹
- A Swedish study in NEJM by Lichtenstein et al. (2012)
 - In adults with ADHD medication reduces the risk of criminal behaviour **by 30-40%**²

1. Dalsgaard S, Nielsen HS, Simonsen M. Consequences of ADHD medication use for children's outcomes. J Health Econ. 2014; 37: 137-51.
2. Lichtenstein P, Halldner L, Zetterqvist J, et al. Medication for attention deficit-hyperactivity disorder and criminality. N Engl J Med. 2012; 367(21): 2006-14.

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ADHD and injuries

- ADHD is associated with an increased risk of
 - Sustaining an injury and having more visits to the emergency ward¹
 - Bone fractures and head injuries
 - Traffic accidents
- Probably due to the core symptoms of ADHD
 - Move too fast, trip and fall
 - Follows sudden impulses, seem unpredictable to others
 - Have fewer strategies to assess potential dangers
- May also be more likely to “seek” danger
- May also be due to comorbid conditions

1. Dalsgaard S, Leckman JF, Mortensen PB, Nielsen HS, Simonsen M: Effect of drugs on the risk of injuries in children with attention deficit hyperactivity disorder: a prospective cohort study. Lancet Psychiatry 2015, 2(8):702-709.

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Effect of drugs on the risk of injuries in children with attention deficit hyperactivity disorder: a prospective cohort study



Søren Dalsgaard, James F Leckman, Preben Bo Mortensen, Helena Skyt Nielsen, Marianne Simonsen

The Lancet Psychiatry 2015, 2(8):702-709.

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How did we reduce confounding by indication?

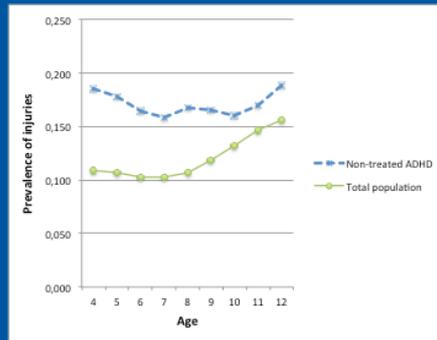
- Difference-in-difference design (often used in studies of health service use)
- Included children who were diagnosed with ADHD after the age of 5 and before the age of 10
- Some of these children received treatment
- We estimated the prevalence of injuries at age 4 and at age 10 in both group
- We then examined the *change in prevalence of injuries* from age 4 to 10, comparing the two groups (treated and non-treated)

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ADHD, injuries and effects of medication

- Prevalence of injuries in children



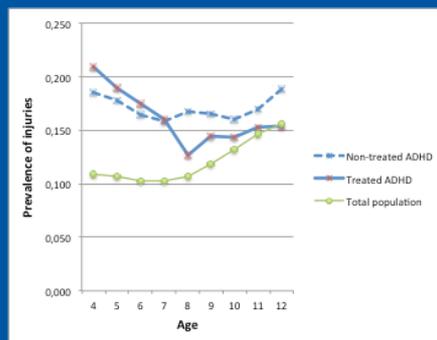
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ADHD, injuries and effects of medication

- Prevalence of injuries in children



1. Dalsgaard, et al. Effect of Medication on the risk of Injuries in Children with ADHD - A Prospective Cohort Study. 2015 Lancet Psychiatry.

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	Difference-in-difference			Adjusted linear mixed model*		
	β †	p value	DID % change in treated (95% CI)‡	β †	OR (95% CI)	p value
Injuries						
Overall estimate§	-0.063	<0.0001	-31.5% (-43.3 to -19.7)	-0.035	0.82 (0.74 to 0.89)	<0.0001
At age 10 years	-0.045	0.008	-31.5% (-54.8 to -8.2)	-0.031	0.84 (0.74 to 0.95)	0.003
At age 11 years	-0.051	0.005	-33.6% (-56.8 to -10.3)	-0.036	0.85 (0.74 to 0.95)	0.005
At age 12 years	-0.067	0.001	-43.5% (-69.0 to -18.1)	-0.053	0.76 (0.65 to 0.88)	<0.0001
Emergency ward visits						
Overall estimate§	-0.052	<0.0001	-28.4% (-40.2 to -16.6)	-0.029	0.86 (0.79 to 0.93)	0.0003
At age 10 years	-0.048	0.012	-28.2% (-50.1 to -6.3)	-0.032	0.87 (0.76 to 0.97)	0.009
At age 11 years	-0.050	0.009	-27.6% (-48.2 to -7.1)	-0.025	0.89 (0.79 to 0.99)	0.030
At age 12 years	-0.081	<0.0001	-45.7% (-65.7 to -25.8)	-0.056	0.76 (0.65 to 0.87)	<0.0001

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Accidents in adults with ADHD

Research

Original Investigation

Serious Transport Accidents in Adults With Attention-Deficit/Hyperactivity Disorder and the Effect of Medication

A Population-Based Study

Zheng Chang, PhD, Paul Lichtenstein, PhD, Brian M. D'Onofrio, PhD, Arvid Sjölander, PhD, Henrik Larsson, PhD

Supplemental content at jamapsychiatry.com

IMPORTANCE Studies have shown that attention-deficit/hyperactivity disorder (ADHD) is

1. Chang Z, Lichtenstein P, D'Onofrio BM, Sjölander A, Larsson H: Serious transport accidents in adults with attention-deficit/hyperactivity disorder and the effect of medication: a population-based study. JAMA Psychiatry 2014, 71(3):319-326.

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A Swedish study of adults with ADHD

Table 3. Rate of Serious Transport Accident During Medication Periods Compared With Nonmedication Periods Among Swedish Adult Patients With ADHD

Characteristic	Person-years at Risk	No. of Accidents	HR (95% CI)	
			Between Individual	Within Individual
Men				
Medicated	8377	144	0.71 (0.57-0.89)	0.42 (0.23-0.75)
Nonmedicated	33 416	753	1 [Reference]	1 [Reference]
Women				
Medicated	6195	67	0.92 (0.78-1.23)	2.35 (0.83-6.64)
Nonmedicated	21 204	263	1 [Reference]	1 [Reference]

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Medication reduces the risk of traffic accidents

- In males with ADHD, medication was associated with a 58% risk reduction (hazard ratio, 0.42; 95%CI, 0.23-0.75), but there was
- No statistically significant association in females.
- Estimates of the populationattributable fractions suggested that 41%to 49% of the accidents in males with ADHD could have been avoided if they had been receiving treatment during the entire follow-up.
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Injuries and accidents

- Injuries and accidents can be fatal
- Is ADHD associated with premature death due to accidents?
- No previous prospective study have examined this

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<http://www.thelancet.com>

Articles

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



Søren Dalsgaard, Søren Dinesen Østergaard, James F. Luskman, Preben Bo Mortensen, Marianne Gøtz Pedersen

Lancet 2015, 385(9983):2190-2196

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All-cause mortality in ADHD

- Followed a cohort of all children born in Denmark 1981-2011 (1.9 mill)
- Within cohort identified 32,061 with ADHD (8,478 females and 23,583 males)
 - Mean age at ADHD diagnosis was 12.3 years
- During follow-up 110 individuals with ADHD died
- I.e., the absolute mortality rate was very low
- All-cause mortality rate per 10,000 person-years:
- Individuals without ADHD = 2.21 as compared to
- Individuals *with* ADHD = 5.85

1. Dalsgaard S, Østergaard SD, Leckman JF, Mortensen PB, Pedersen MG: Mortality in children, adolescents, and adults with attention deficit hyperactivity disorder: a nationwide cohort study. *Lancet* 2015, 385(9983):2190-2196.

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Mortality in ADHD, adjusted analyses

- Mortality rate ratios (MRR), 3 models, adjusted for
 - Model 1: Calendar year, age, and sex
 - Model 2: Plus family history of psychiatric disorders, maternal and paternal age
 - Model 3: Plus parental educational and employment status
- Fully adjusted MRR in ADHD = 2.07 (95% CI 1.70 - 2.50)
- Stratified on gender
 - In females with ADHD: MRR = 3.01 (1.87 - 4.55)
 - In males with ADHD: MRR = 1.93 (1.55 - 2.38)
 - Clinically relevant gender difference, not statistically sign ($p=0.091$)
 -

1. Dalsgaard S, Østergaard SD, Leckman JF, Mortensen PB, Pedersen MG: Mortality in children, adolescents, and adults with attention deficit hyperactivity disorder: a nationwide cohort study. *Lancet*. 2015; published online Feb 26.

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Mortality in ADHD

- Age at diagnosis of ADHD had a significant effect on MRR ($p < 0.0001$)

Age at first ADHD-diagnosis (years)	Number of deaths	Person-years	Mortality rate per 10 000 person-years	Crude model MRR (95% CI)*	Partly adjusted model MRR (95% CI)†	Fully adjusted model MRR (95% CI)‡
1-5	10	29 944	3.34	2.23 (1.11-3.91)	1.97 (0.99-3.46)	1.86 (0.93-3.27)
6-17	59	136 048	4.34	1.83 (1.40-2.35)	1.63 (1.25-2.09)	1.58 (1.21-2.03)
>17	38	17 057	22.28	5.24 (3.73-7.12)	4.46 (3.18-6.07)	4.25 (3.03-5.78)
No ADHD	5473	247 245 10	2.21	1.00 (reference)	1.00 (reference)	1.00 (reference)
p values§	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$
Overall cohort	5580	24 907 560	2.24

Cohort consisted of 1.92 million children born in 1981-2011. MRR=mortality rate ratio. ADHD=attention deficit hyperactivity disorder. ..=not applicable. *Crude model adjusted for age, calendar year, and sex. †Partly adjusted model adjusted for age, calendar year, sex, parental history of psychiatric disorders, and maternal and paternal age at time of delivery. ‡Fully adjusted model adjusted for age, calendar year, sex, parental history of psychiatric disorders, maternal and paternal age at time of delivery, parental educational, and parental employment status. §p value measures the overall effect of being diagnosed with ADHD at different ages, compared with individuals without ADHD.

Table 2: MRR according to age at first diagnosis of ADHD, compared with those without ADHD at same age

1. Dalsgaard S, Østergaard SD, Leckman JF, Mortensen PB, Pedersen MG. Mortality in children, adolescents, and adults with attention deficit hyperactivity disorder: a nationwide cohort study. *Lancet*. 2015; published online Feb 26.

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Mortality: Time since ADHD diagnosis

- First year after ADHD: MRR = 2.68 (1.54 - 4.28)
- 1 - 2 years after ADHD: MRR = 2.45 (1.58 - 3.59)
- 3 - 4 years after ADHD: MRR = 3.75 (2.48 - 5.39)
- 5 - 9 years after ADHD: MRR = 2.01 (1.30 - 2.93)
- 10+ years after ADHD: MRR = 1.90 (1.17 - 2.90)

(for time trend $p = 0.162$)

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MRRs, stratified on causes of death

- Natural causes
 - Females: MRR = 3.33 (1.51 - 6.24)
 - Males: MRR = 1.38 (0.82 - 2.16)
- Unnatural causes
 - Females: MRR = 3.51 (1.50 - 6.85)
 - Males: MRR = 2.29 (1.69 - 3.04)
- Accidents was the most common cause of death

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Effects of comorbidity on mortality rates in ADHD

We then examined the effect of comorbid oppositional defiant disorder/
conduct disorder (ODD/CD) and substance use disorder (SUD)

- | | |
|--------------------------|-------------------------------|
| • ADHD | adj MRR = 1.50 (1.11 - 1.98) |
| • ADHD + ODD/CD | adj MRR = 2.17 (1.33 - 3.31) |
| • ADHD + SUD | adj MRR = 5.63 (3.69 - 8.16) |
| • ADHD + ODD/CD + SUD | adj MRR = 8.29 (4.85 - 13.09) |
| • No ADHD, ODD/CD or SUD | MRR = 1 (reference) |

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Interpretation of findings

- ADHD doubled mortality rates, highest in females with ADHD
- Comorbid ODD/CD and SUD further increased mortality
- Even without these comorbidities, ADHD had an MRR of 1.5
- Those diagnosed in adulthood carried the highest risk
- Accidents was the most common cause of death

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Some gender differences in outcomes of ADHD

- Females with ADHD have a higher relative risk of some negative outcomes than males with ADHD
 - Premature death
 - Developing other psychiatric disorders in adulthood
- Probably because ADHD in girls/women is underdiagnosed
- So those actually diagnosed have more severe ADHD
- Also, fewer girls than boys are treated with medication

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Predictors of negative outcomes

- In children with ADHD comorbid ODD/CD is one of the most important and strong predictors of many outcomes, such as
 - Developing other psychiatric disorders, including psychosis
 - Criminality
 - Substance use disorder
 - Premature death
- Treatment of ODD/CD should therefore be of highest priority

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Relative risks versus absolute risks

- Although ADHD is associated with an increased relative risk of several problems, the absolute risk is often low
- For instance, looking at a very rare outcome, such as death:
 - Mortality rate of 0.3% in individuals with ADHD
 - compared to 0.15% in individuals without ADHD
- Reflects an increased *relative* and *absolute* risk
- However, it is still a *very* rare event

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Forwarned is Forarmed

- Knowledge on potential negative outcomes is important – although unpleasant
- ODD/CD and SUD and gender predict negative outcomes
- We need more knowledge on predictors of outcome – both environmental and genetic predictors and their interaction
- Need more studies on effects of treatment – pharmacological and non-pharmacological

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In conclusion: ADHD is a real disorder

- It causes impairment throughout the lifespan, and early identification is important
- Risk of negative outcomes should not startle us or parents, but should make us more aware and prepared
- Treatment has positive effects on
 - core and comorbid symptoms, criminality, injuries and traffic accidents
- We need more research on factors that can improve life expectancy in this vulnerable group of patients

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Thank you for your attention

Questions?

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