

Faktorer av betydelse för utfall vid ADHD (neuropsykiatriska tillstånd)

Henrik Larsson

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Conflict of interest: Served as a speaker for Eli-Lilly and Shire and has received research grants from Shire; all outside the submitted work.

Depression

**Psychotic
disorders**

**Substance use
disorders**



Suicidality

Depression

Psychotic disorders

Substance use disorders

ADHD??

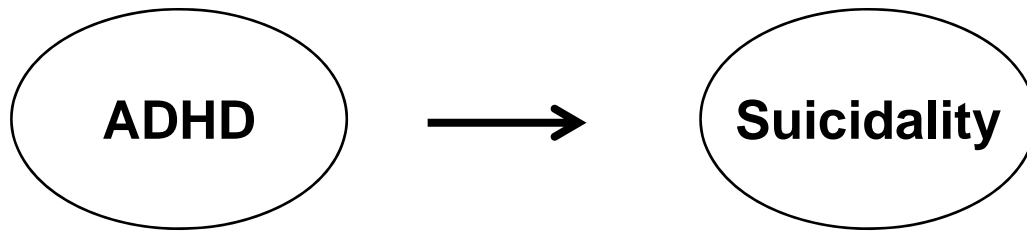


Suicidality

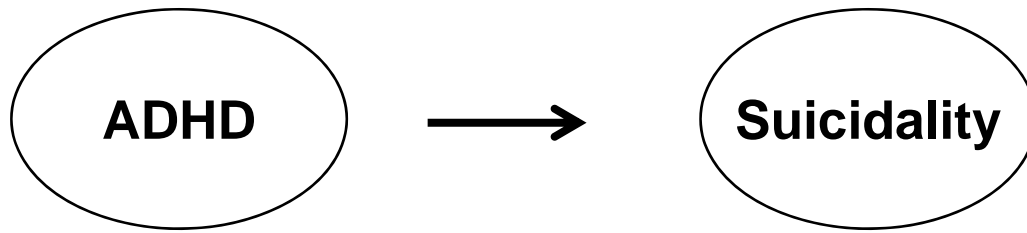
ADHD



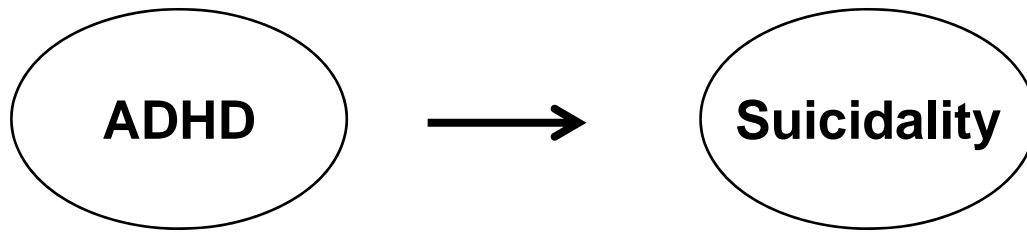
Suicidality



- A study based on the Finnish 1981 Birth Cohort found that ADHD was associated with increased risk of severe suicide attempts Sourander et al (2009) Arch Gen Psychiatry



- An review reported a threefold risk increase of completed suicide in individuals with ADHD *James et al. (2004) Acta Psychiatr Scand*



- General population-data from the Youth Gazel cohort found that ADHD symptoms were associated with adolescent suicide attempts
Galéra et al 2008 Acta Psychiatr Scand

Why are individuals with ADHD at increased risk for suicidal behavior?

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1. Comorbidity

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1. Comorbidity

2 Shared familial factors

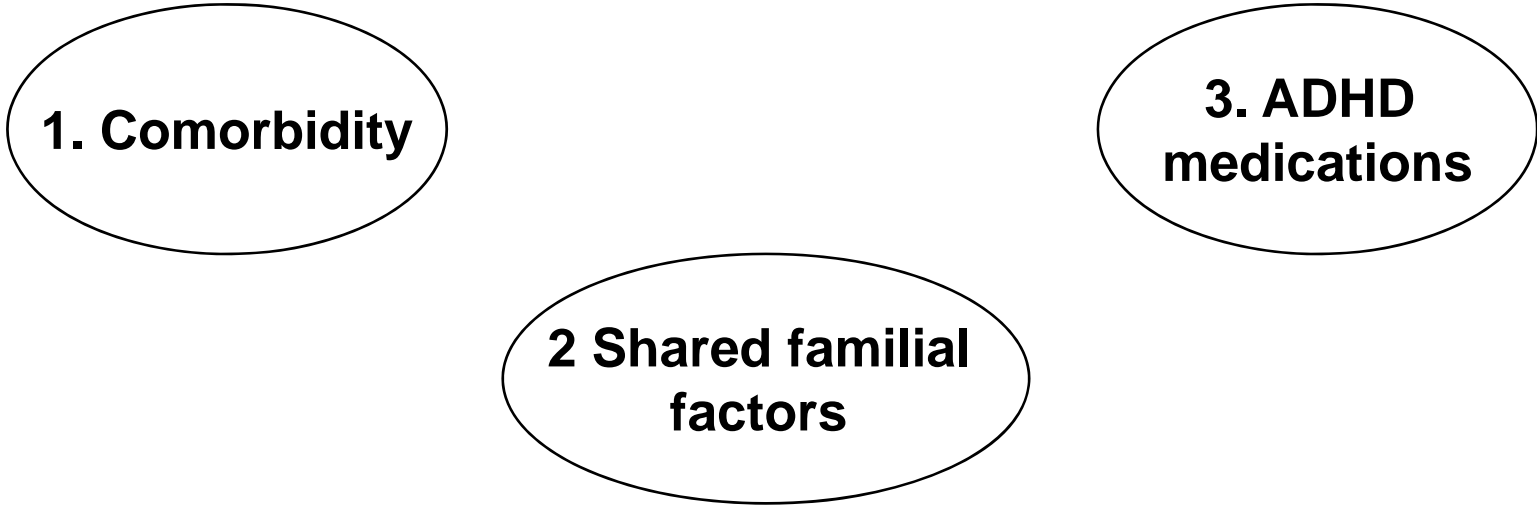
Why are individuals with ADHD at increased risk for suicidal behavior?

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2 Shared familial factors

3. ADHD medications

Why are individuals with ADHD at increased risk for suicidal behavior?



Swedish register-data have recently been used to address these alternative explanations

1) Comorbidity

Common Etiological Factors of Attention-Deficit/ Hyperactivity Disorder and Suicidal Behavior A Population-Based Study in Sweden

Therese Ljung, PhD; Qi Chen, MSc; Paul Lichtenstein, PhD; Henrik Larsson, PhD

JAMA Psychiatry. 2014;71(8):958-964.

1) Comorbidity

Cases	Patient Register Prescribed Drug Register	51 707 with ADHD diagnosis
Control participants	Matched 1:5 on sex and birth year	258 535
Outcome	Patient Register Cause of Death Register	Suicide attempts or completed suicides

1) Comorbidity

ADHD and risk for attempted and completed suicide

Variable	No.		OR (95% CI)		
	Probands With ADHD	Control Participants	Crude	Adjusted for SES	Adjusted for Psychiatric Comorbidities ^a
Attempted suicide					
All	51 707	258 535	8.46 (8.07-8.87)	8.26 (7.87-8.66)	3.62 (3.29-3.98)
Male	36 102	180 510	7.12 (6.68-7.59)	6.88 (6.45-7.34)	2.93 (2.60-3.29)
Female	15 605	78 025	10.39 (9.67-11.15)	10.22 (9.51-10.98)	5.41 (4.60-6.36)
Completed suicide					
All	51 707	258 535	12.22 (8.67-17.22)	12.33 (8.73-17.42)	5.91 (2.45-14.27)
Male	36 102	180 510	10.32 (7.04-15.12)	10.37 (7.05-15.25)	3.70 (1.38-9.95)
Female	15 605	78 025	22.76 (10.06-51.50)	23.23 (10.22-52.78)	NA

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JAMA Psychiatry. 2014;71(8):958-964.

2) Shared familial factors

- The Swedish Multi-Generation Register allowed us to identify first-degree and second-degree relative of both cases and controls

2) Shared familial factors

ADHD and risk for attempted and completed suicide in relatives

	Attempted suicide		Completed Suicide	
	OR	95% CI	OR	95% CI
First-degree relatives				
Parents	2.4	2.3-2.5	2.2	2.1-2.4
Full siblings	2.3	2.2-2.4	2.2	1.8-2.7

Increased risk in relatives
– familial effect

2) Shared familial factors

ADHD and risk for attempted and completed suicide in relatives

	Attempted suicide		Completed Suicide	
	OR	95% CI	OR	95% CI
First-degree relatives				
Parents	2.4	2.3-2.5	2.2	2.1-2.4
Full siblings	2.3	2.2-2.4	2.2	1.8-2.7
Second-degree relatives				
Maternal half-siblings	1.6	1.5-1.7	1.5	1.1-2.1
Paternal half-siblings	1.6	1.5-1.7	2.0	1.5-2.8
Third-degree relatives				
Cousins				1.4-1.7

Similar risks in maternal and paternal half-siblings
– familial effect probably genetic

Why are individuals with ADHD at increased risk for suicidal behavior?

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3) ADHD medications

Drug treatment for attention-deficit/hyperactivity disorder and suicidal behaviour: register based study

Qi Chen *PhD student*¹, Arvid Sjölander *associate professor*¹, Bo Runeson *professor*², Brian M D'Onofrio *associate professor*³, Paul Lichtenstein *professor*¹, Henrik Larsson *associate professor*¹

BMJ 2014;348:g3769 doi: 10.1136/bmj.g3769 (

3) ADHD medications

- Results from a **meta-analysis of clinical trials** have suggested that the increased risk of suicidal behavior in individuals with ADHD may be explained by ADHD medications

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 - Suicide related events were very rare

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- Results from a **meta-analysis of clinical trials** have suggested that the increased risk of suicidal behavior in individuals with ADHD may be explained by ADHD medications
- Limitations
 - Suicide related events were very rare
 - Suggested **only** a significant association between atomoxetine and suicidal ideation
 - No effect on suicidal behavior was observed
 - The effect of stimulant medication on suicidal behavior was not explored

3) ADHD medications

Sample	Patient Register	37,936 with ADHD diagnosis
Exposure	Prescribed Drug Register	ADHD medication
Outcome	Patient Register Cause of Death Register	Suicide related event (suicide attempts or completed suicides)

3) ADHD medications

Association between ADHD medication and suicide related events

	Between-individual		Within-individual	
	Hazard ratio	95% Confidence interval	Hazard ratio	95% Confidence interval
Males and females	1.31	1.19-1.44	0.89	0.79-1.00

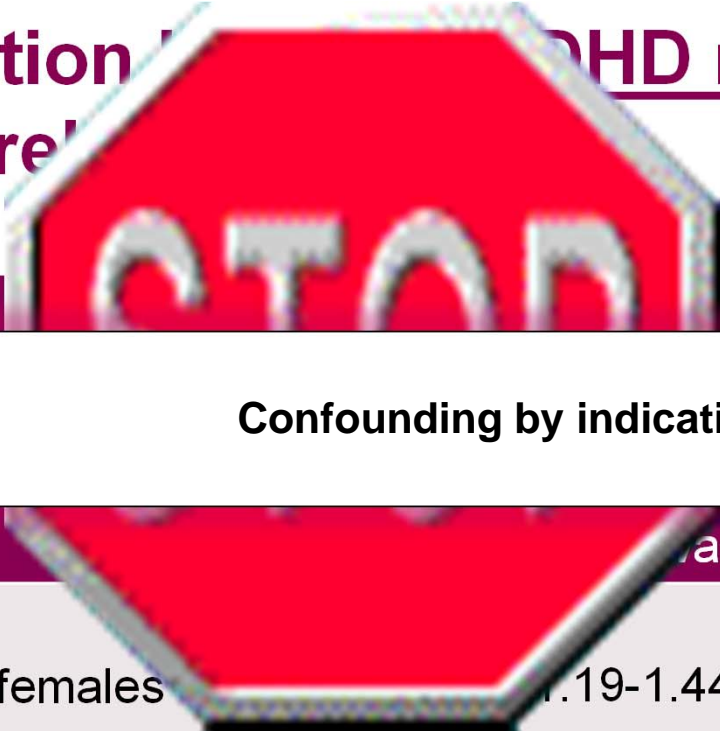
3) ADHD medications

Association between ADHD medication and suicide related events

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	Hazard ratio	95% Confidence interval	Hazard ratio	95% Confidence interval
Males and females	1.31	1.19-1.44	0.89	0.79-1.00

3) ADHD medications

Association of ADHD medication and suicide risk



Confounding by indication

	Overall	Within individual	95% confidence interval
Males and females	1.19-1.44	0.89	0.79-1.00

3) ADHD medications

Association between ADHD medication and suicide related events

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3) ADHD medications

Association between ADHD medication and suicide related events

	Between-individual	Within-individual
	Explore the rate of the outcome in the same individual during medication versus non-medication periods	
Males and females	Adjusts for factors that are constant within individuals, such as genetic factors and all environmental factors before enrollment	

3) ADHD medications

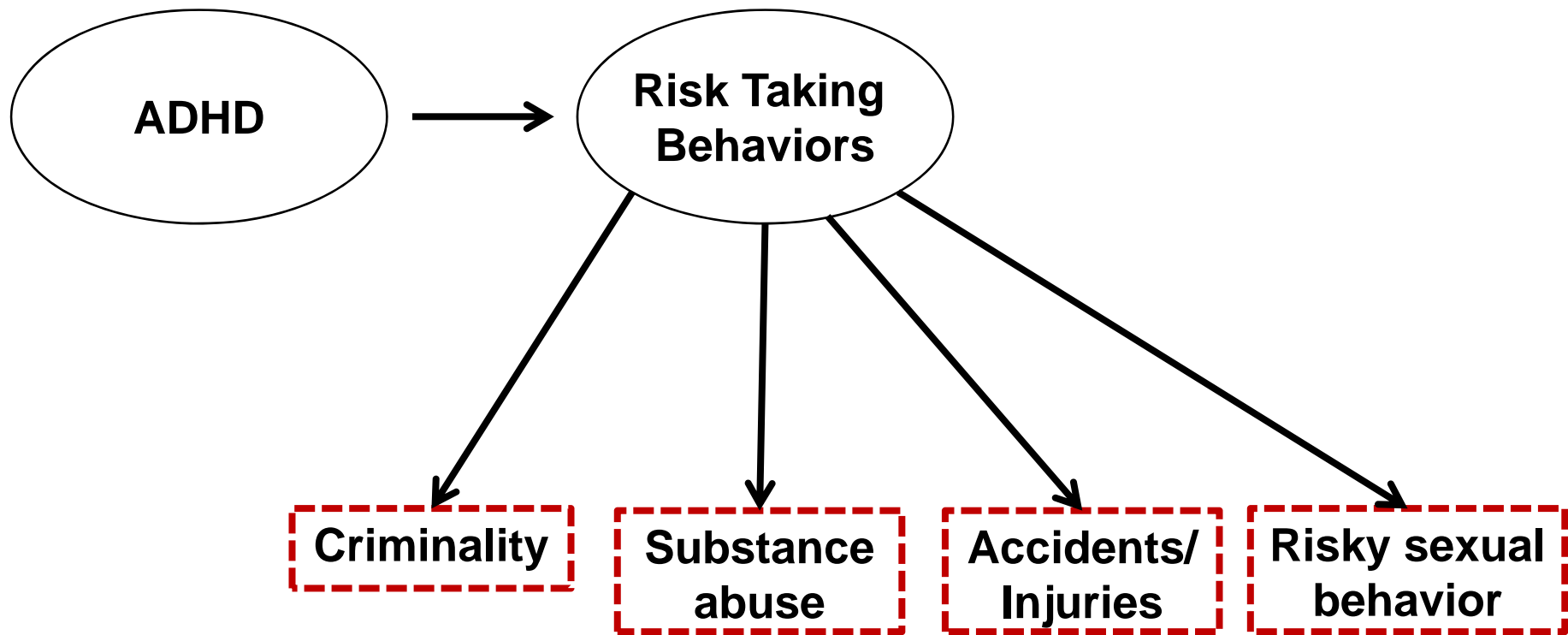
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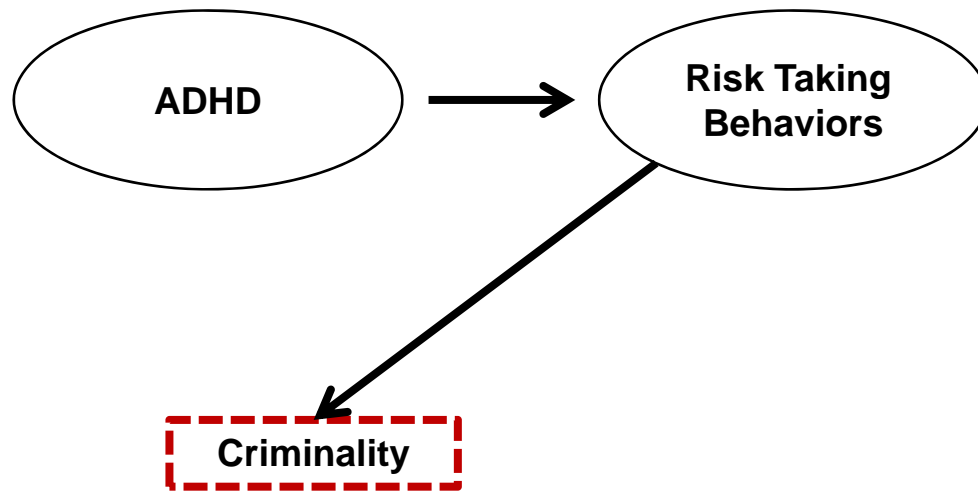
	Between-individual		Within-individual	
	Hazard ratio	95% Confidence interval	Hazard ratio	95% Confidence interval
Males and females	1.31	1.19-1.44	0.89	0.79-1.00

The within-individual analysis provided no support for an increased rate of suicide related events

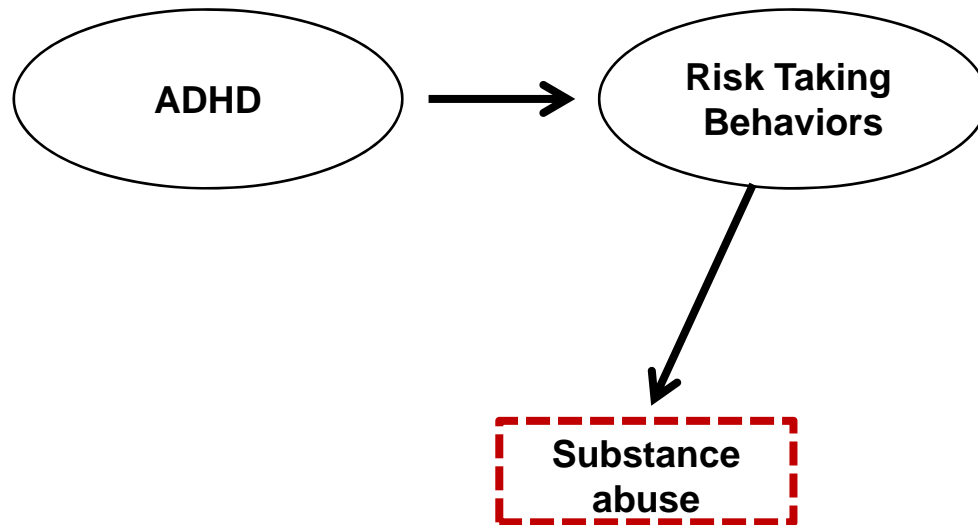
Interpretations and Implications: Suicidality

- Comorbidity
 - Detection and treatment of comorbid conditions probably help reduce risk of suicidal behavior in ADHD
- Shared familial factors
 - Pleiotropic effects, reflecting genetic variants associated with impulsivity
- ADHD medications
 - Highlight the importance of using within-individual designs to control for confounding in future pharmaco-epidemiological studies



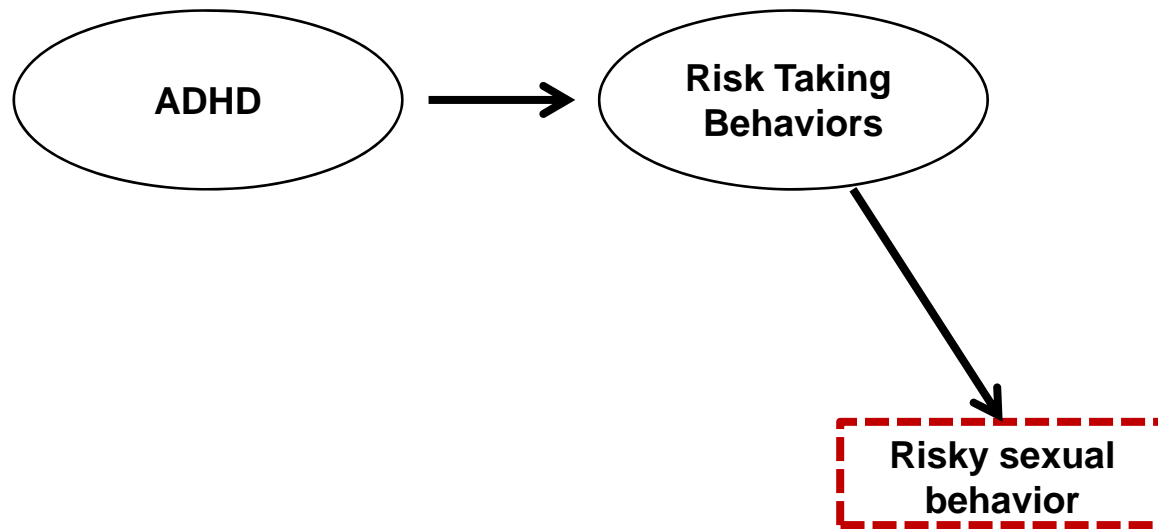


- A Danish register-study found that childhood ADHD was associated with a fivefold increased risk of criminal convictions in adulthood Dalsgaard et al (2013) Criminal Behaviour and Mental health

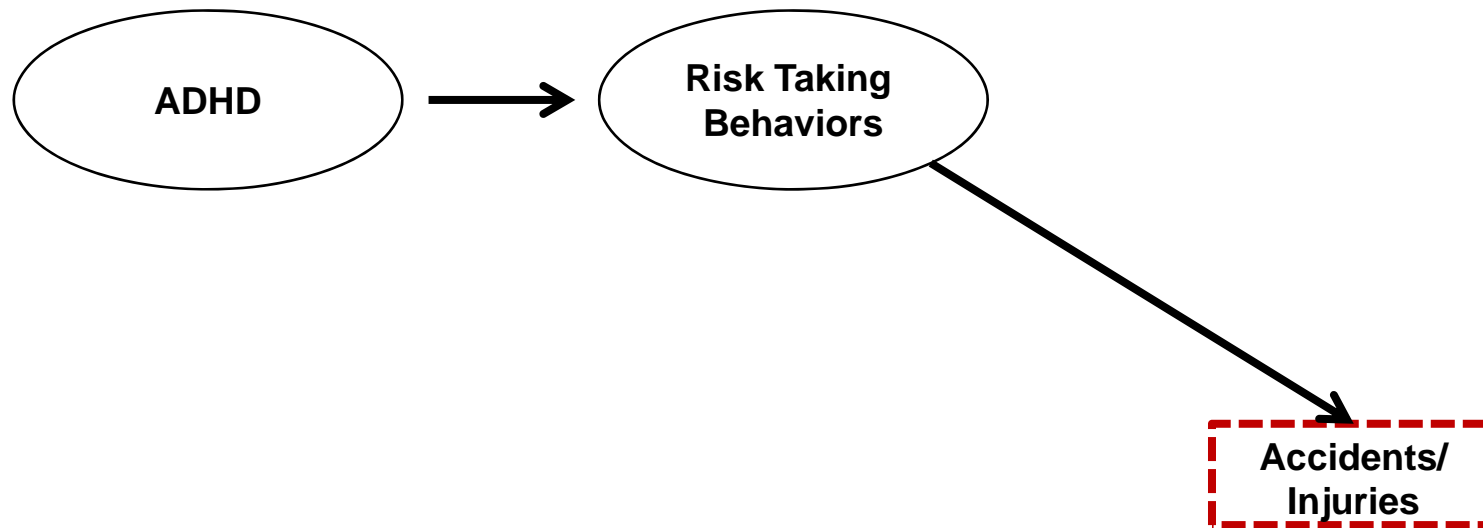


- One meta-analysis suggest prospective associations of ADHD with future substance use disorders, with a doubling of risk for substance use disorders. Lee et al (2011) Clinical Psychology Review

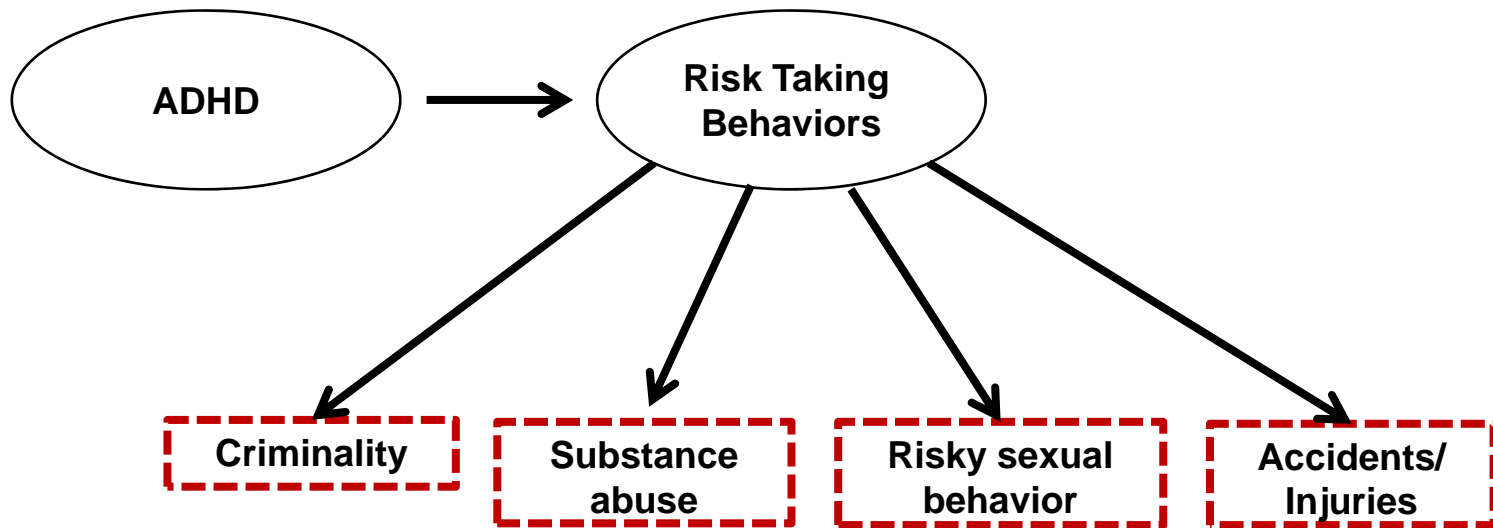
→ Largely consistent with a recent Danish register-based study Ottosen et al (2016) J Am Acad Child Adolesc Psychiatry

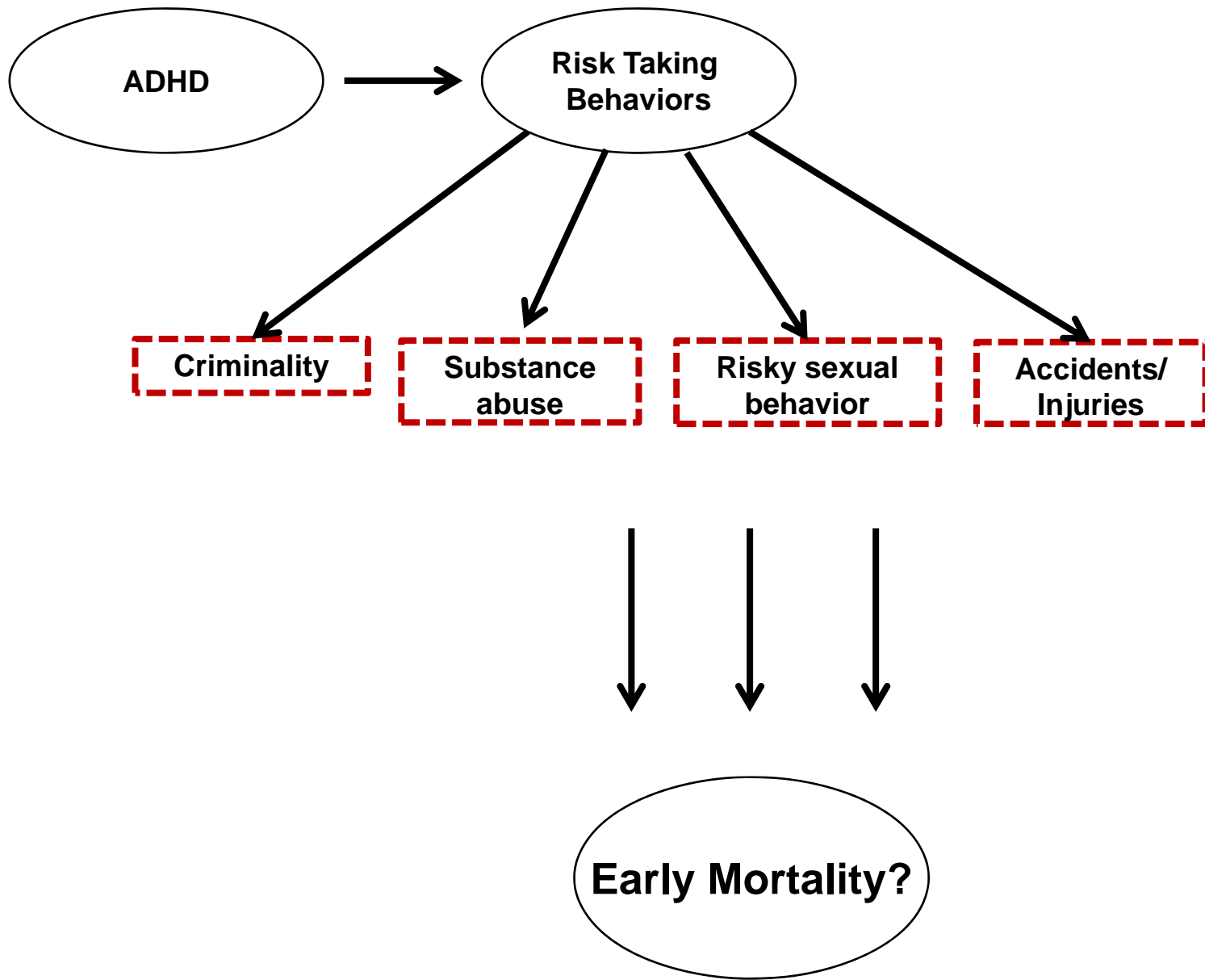


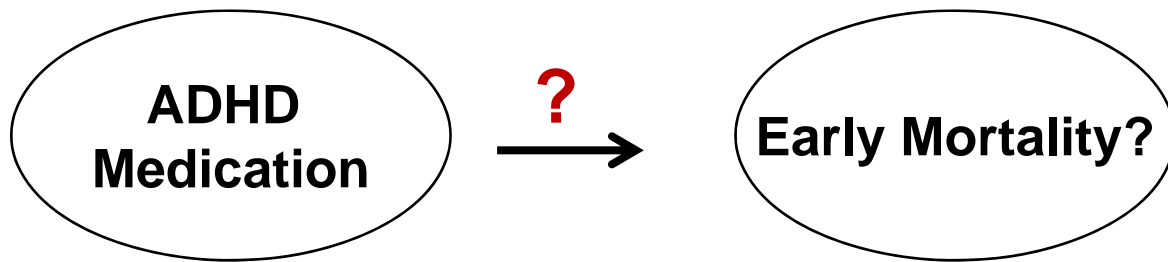
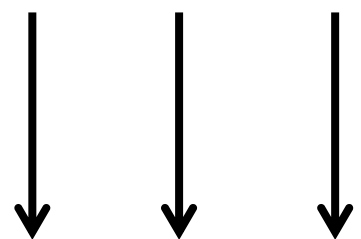
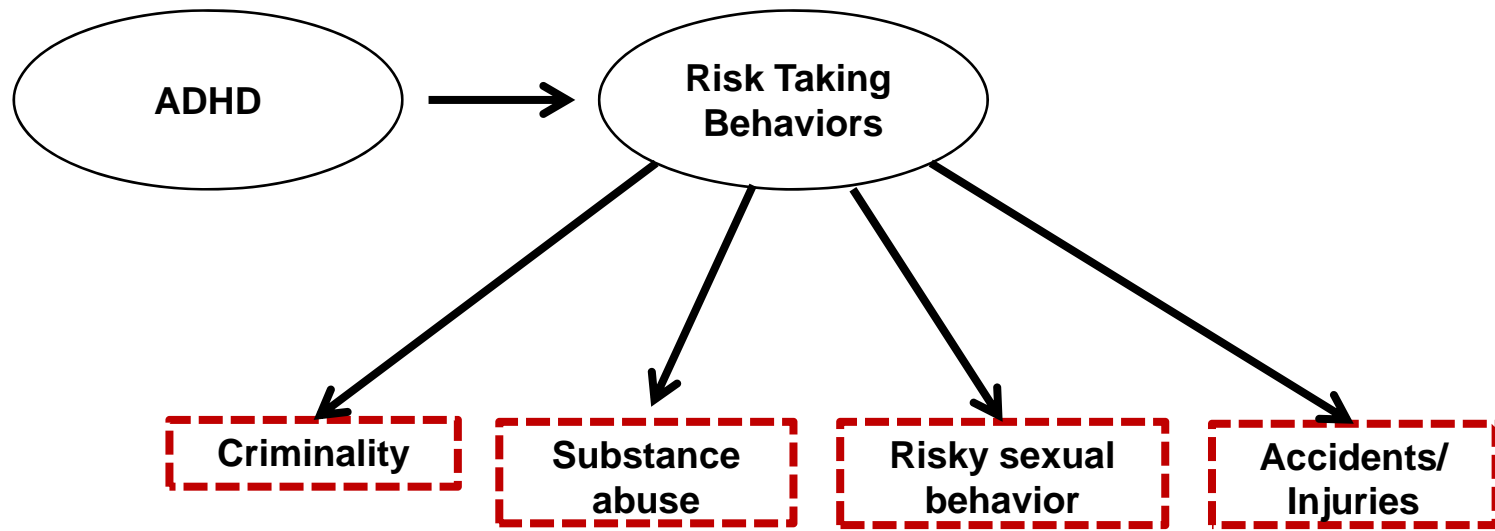
- Findings from a longitudinal study of children with ADHD suggest a fourfold increased risk of sexually transmitted disease *Barkley et al (2006) J Am Acad Child Adolesc Psychiatry*



- A Swedish register-based study found that individuals with ADHD had a 45% to 47% increased rate of serious transport accidents compared with individuals without ADHD, in both men and women *Chang et al (2014) JAMA Psychiatry*







Early mortality

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

Søren Dalsgaard, Søren Dinesen Østergaard, James F Leckman, Preben Bo Mortensen, Marianne Giørtz Pedersen

www.thelancet.com Published online February 26, 2015

Early mortality

Cohort	1.92 million children born in 1981–2011	
Exposure	The Danish Psychiatric Central Research Register and the National Patient Register	32 061 patients with diagnosis of ADHD
Outcome	Danish Cause of Death Register	Date and causes of death

Early mortality

	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)‡
Age at first ADHD-diagnosis (years)						
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	24 734 510	2.21	1.00 (reference)	1.00 (reference)	1.00 (reference)
<p>Two-fold increased risk of mortality in people with ADHD</p>						
Overall cohort	5580	24 907 560	2.24

Early mortality

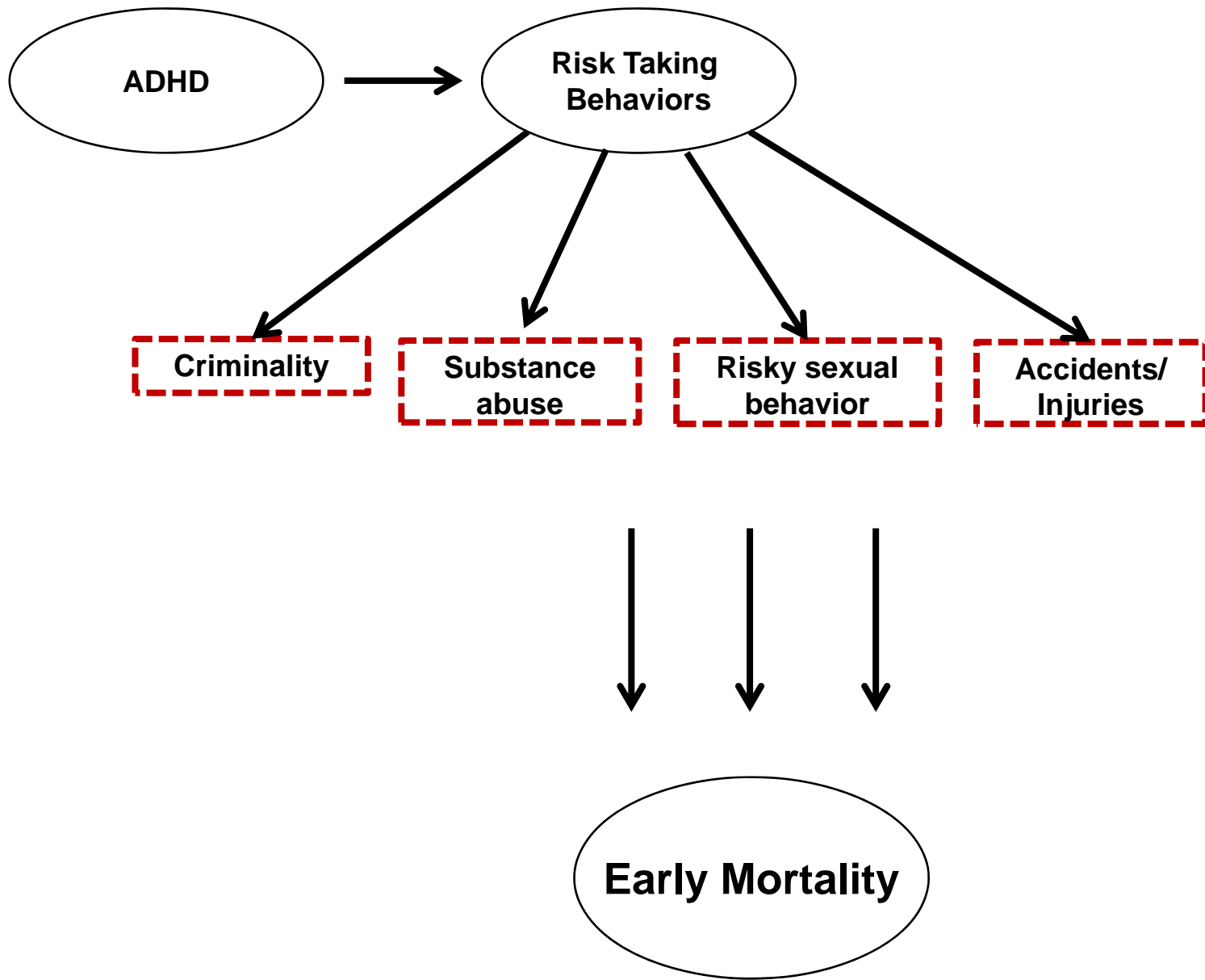
	Number of deaths	Person-years	Mortality rate, per 10 000 person-years	Crude model MRR (95% CI)*	Partly adjusted model, MRR (95% CI)†	Fully adjusted model, MRR (95% CI)‡
Diagnosed with ADHD	47	138198	3.40	1.70 (1.26-2.24)	1.55 (1.14-2.04)	1.50 (1.11-1.98)
Diagnosed with ADHD and oppositional defiant disorder or conduct disorder	19	31177	6.09	2.56 (1.57-3.90)	2.26 (1.39-3.44)	2.17 (1.33-3.31)
Diagnosed with ADHD and substance use disorder	25	9722	25.71	7.01 (4.59-10.16)	5.91 (3.87-8.57)	5.63 (3.69-8.16)
Diagnosed with ADHD, oppositional defiant disorder or conduct disorder, and substance use disorder	16	3953	40.48	10.37 (6.07-16.36)	8.74 (5.12-13.80)	8.29 (4.85-13.09)
Diagnosed with oppositional defiant disorder, conduct disorder or substance use disorder	472	330192	14.29	4.00 (3.62-4.41)	3.65 (3.30-4.02)	3.55 (3.21-3.92)
No diagnosis of ADHD, oppositional defiant disorder or conduct disorder	5001	24 204 219	2.05	1.00 (reference)	1.00 (reference)	1.00 (reference)
Overall cohort	5580	24 907 560	2.24

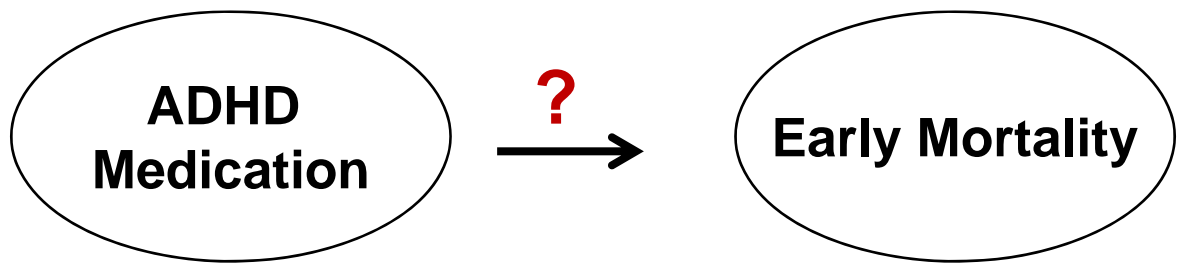
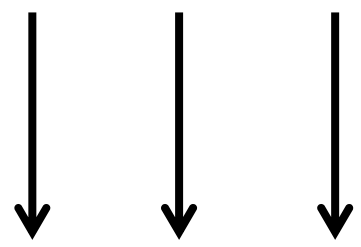
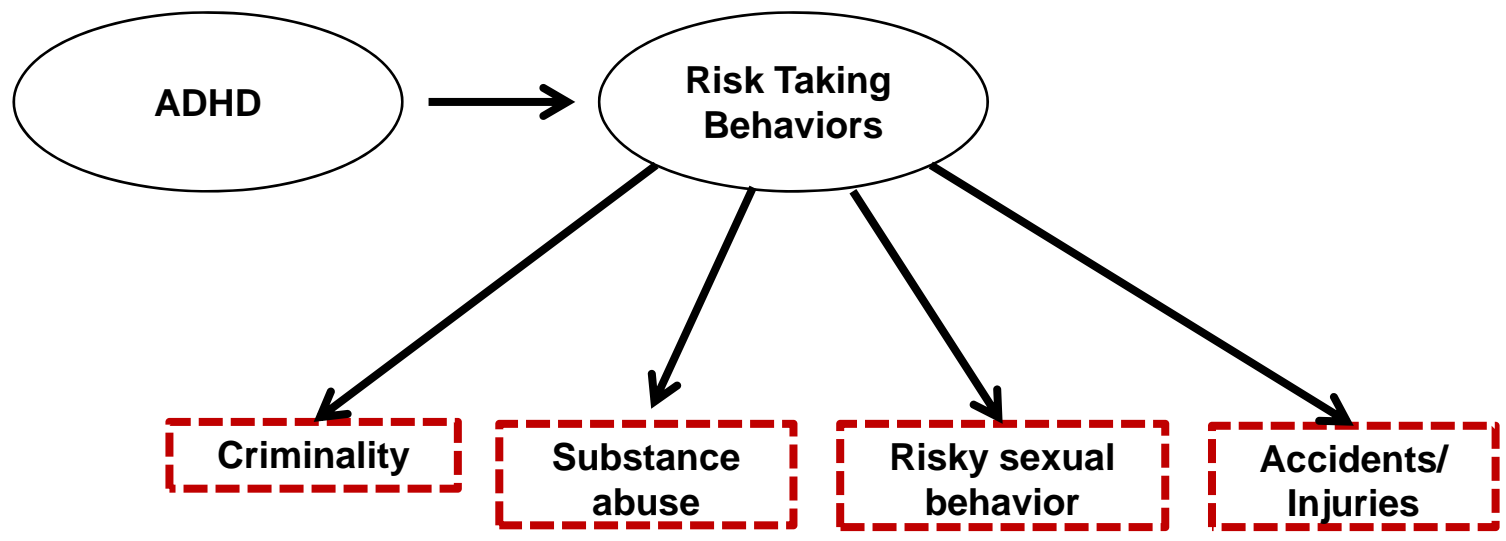
ODD, CD, and SUD increased mortality in a dose-response manner

Early mortality


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Diagnosed with oppositional defiant disorder, conduct disorder or substance use disorder	472	330 192	14.29	4.00 (3.02-4.41)	3.05 (2.30-4.02)	3.55 (2.71-3.92)
No diagnosis of ADHD, oppositional defiant disorder or conduct disorder, or substance use disorder	5001	24 394 318	2.05	1.00 (reference)	1.00 (reference)	1.00 (reference)
p value§	p<0.0001	p<0.0001	p<0.0001
Overall cohort	5580	24 907 560	2.24

The increased mortality risk in ADHD was mainly driven by deaths from unnatural causes, especially accidents





ADHD Medication



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

JAMA Psychiatry. 2014;71(3):319-325.

ADHD Medication

Sample	Patient Register	17,338 with ADHD diagnosis
Exposure	Prescribed Drug Register	ADHD medication
Outcome	Patient Register Cause of Death Register	Emergency hospital care or death due to transport accidents

ADHD Medication

Association between ADHD medication and transport accident among men with ADHD

	Crude		Within-individual	
	Hazard ratio	95% Confidence interval	Hazard ratio	95% Confidence interval
Men	0.71	0.57-0.89	0.42	0.23-0.75

ADHD Medication

Association between ADHD medication and transport accident among men with ADHD

	Crude		Within-individual	
	Hazard ratio	95% Confidence interval	Hazard ratio	95% Confidence interval
Men	0.71	0.57-0.89	0.42	0.23-0.75

Both crude (29%) and the adjusted within-individual (58%) analysis suggest that ADHD medication reduces the rate of accidents

ADHD Medication: Similar results have been observed in three independent studies

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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

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Methylphenidate and the Risk of Trauma

Kenneth K.C. Man, MPH^a, Esther W. Chan, PhD^a, David Coghill, MD^b, Ian Douglas, PhD^c, Patrick Ip, MBBS, MPH^d, Ling-pong Leung, MBBS^e, Matthew S.H. Tsui, MBBS^e, Wilfred H.S. Wong, MMedSc^d, Ian C.K. Wong, PhD^a

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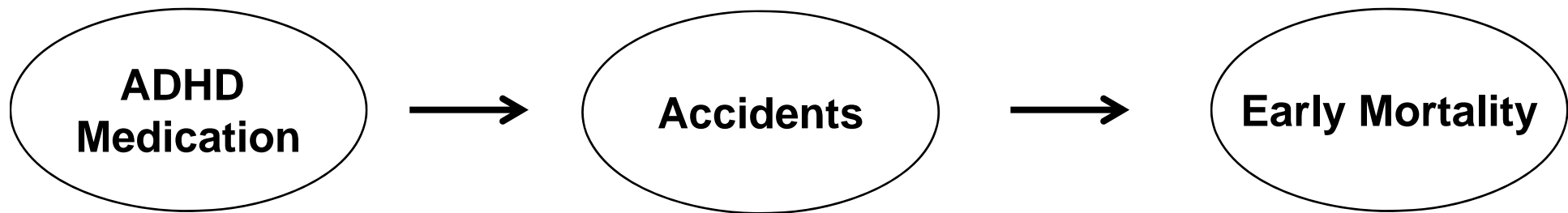
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Methylphenidate and the Risk of Trauma

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**Injury Prevention by Medication Among Children With Attention-Deficit/Hyperactivity Disorder
A Case-Only Study**

Rafael Mikolajczyk, MD, PhD; Johannes Horn, Dipl Biomath; Niklas Schmedt, MA; Ingo Langner, PhD; Christina Lindemann, MSc; Edeltraut Garbe, MD, PhD



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

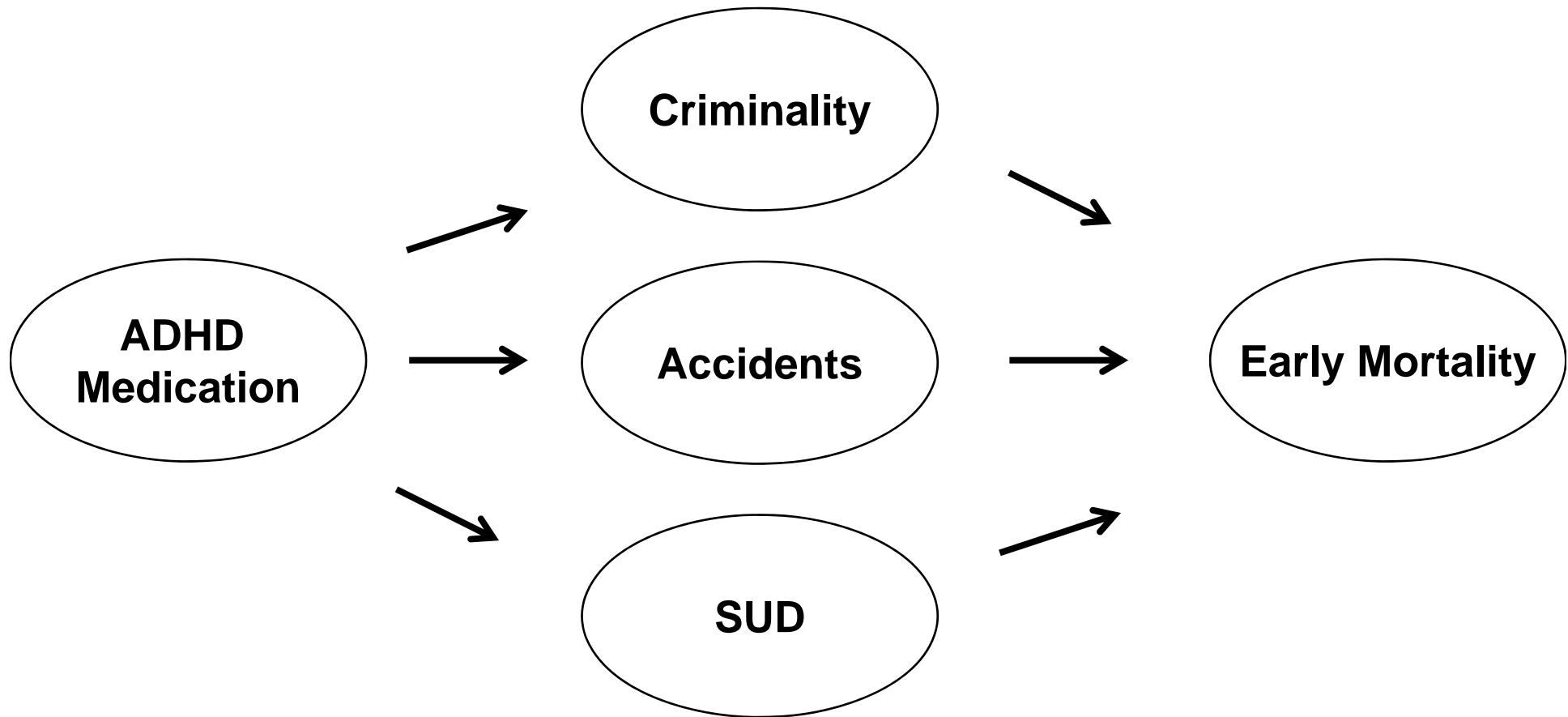
Medication for Attention Deficit– Hyperactivity Disorder and Criminality

Paul Lichtenstein, Ph.D., Linda Halldner, M.D., Ph.D., Johan Zetterqvist, M. Ed.,
Arvid Sjölander, Ph.D., Eva Serlachius, M.D., Ph.D.,
Seena Fazel, M.B., Ch.B., F.R.C.Psych., M.D.,
Niklas Långström, M.D., Ph.D., and Henrik Larsson, M.D., Ph.D.

Stimulant ADHD medication and risk for substance abuse

Zheng Chang,¹ Paul Lichtenstein,¹ Linda Halldner,^{1,2} Brian D'Onofrio,³ Eva Serlachius,⁴
Seena Fazel,⁵ Niklas Långström,¹ and Henrik Larsson¹

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Conclusions

- ADHD associated with suicidal and risk taking behaviors
- Comorbidity and genetic factors play a role
- ADHD medication most likely help reduce the increased risk

General implications

- ADHD is a disorder that can be associated with serious outcomes including suicide and accidents
 - But remember: THE ABSOLUTE RISK IS LOW
- The findings highlight the potential public health relevance of diagnosing ADHD and treating ADHD early

Acknowledgements

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- Laura Ghirardi
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- Shihua Sun
- Andrea Johansson Capusan
- Therese Ljung
- Paul Lichtenstein
- Arvid Sjölander
- Brian D'Onofrio



CoCA research programme on ADHD

