

## Risks and Benefits of Attention-Deficit/Hyperactivity Disorder Medication on Behavioral and Neuropsychiatric Outcomes: A Qualitative Review of Pharmacoepidemiology Studies Using Linked Prescription Databases

### *Supplemental Information*

Supplementary Table S1. Included studies on the association between ADHD medication and behavioral or neuropsychiatric outcomes.

Outcome	Study	Data source	Country/ Region	Sample	Age (range or mean)	Exposure	Design	Long-term/short- term effect	Effect size
<b>Injuries and traumas</b>									
	<b>Chen et al., 2017 (1)</b>	Insurance claims database	Taiwan	6201 individuals diagnosed with ADHD	<18	Stimulants	Traditional regression adjustment	Long-term	<i>Treatment duration vs no treatment:</i> 1-180 days: HR= 1.18 (0.98–1.43); >180 days: HR= 0.77 (0.63–0.94). <i>Treatment vs no treatment:</i> HR= 0.774 (0.518-0.986). <i>Treatment duration:</i> HR= 0.914 (0.699-0.950). <i>After vs before treatment:</i> OR=0.82 (0.74-0.89).  <i>Treatment vs no treatment in the 12 months before the event:</i> OR= 0.71 (0.64–0.79). <i>Treatment duration:</i> OR=0.61 (0.51–0.73). <i>Different defined daily dosage (DDD) vs 0 DDD:</i> 0–28 DDDs: HR= 0.88 (0.83–0.92) 28–84 DDDs: HR= 0.76 (0.72–0.80) >84 DDDs: HR= 0.49 (0.47–0.51) <i>Different defined daily dosage (DDD) vs &lt;90 DDD:</i> 90-364 DDD: HR= 1.04 (0.98-1.10) >=365 DDD: HR= 0.93 (0.80-0.99) <i>Periods on treatment vs periods off treatment:</i> Overall: IRR= 0.91 (0.86-0.97); Males: IRR= 0.92 (0.86-0.98); Females IRR= 0.83 (0.68-1.00). <i>Treatment adherence:</i> Medium vs low: HR= 0.97 (p=0.64); High vs low: HR= 0.89 (p=0.07).
	<b>Chien et al., 2017 (2)</b>	Insurance claims database	Taiwan	665 individuals diagnosed with ADHD	>=18	Any ADHD medication	Propensity score matching	Long-term	
	<b>Dalsgaard et al., 2015 (3)</b>	Whole-population register	Denmark	4557 individuals diagnosed with ADHD and 705 563 controls	5 to 26	Any ADHD medication	Within-individual comparison	Short-term	
	<b>Jacob et al., 2017 (4)</b>	Population-based database	Germany	2 894 individuals diagnosed with ADHD	6 to 19	Any ADHD medication	Traditional regression adjustment	Short-term and long-term	
	<b>Liao et al., 2018 (5)</b>	Insurance claims database	Taiwan	124 438 individuals diagnosed with ADHD	<18	Stimulants	Traditional regression adjustment	Long-term	
	<b>Liou et al., 2018 (6)</b>	Insurance claims database	Taiwan	72 181 individuals diagnosed with ADHD	3-29	Any ADHD medication	Traditional regression adjustment	Long-term	
	<b>Man et al., 2015 (7)</b>	Whole-population register	Hong Kong	4934 individuals with a prescription for methylphenidate and a trauma-related ED admission	6 to 19	Stimulants	Within-individual comparison	Short-term	
	<b>Marcus et al., 2008 (8)</b>	Insurance claims database	California	11 770 individuals diagnosed with ADHD	6 to 17	Stimulants	Traditional regression adjustment	Long-term	

Outcome	Study	Data source	Country/ Region	Sample	Age (range or mean)	Exposure	Design	Long-term/short- term effect	Effect size
	<b>Mikolajczyk et al., 2015 (9)</b>	Insurance claims database	Germany	2128 individuals diagnosed with ADHD with one hospitalization of injury	3 to 17	Any ADHD medication	Within-individual comparison	Short-term	<i>Periods on treatment vs periods off treatment:</i> All injuries: IRR= 0.87 (0.74-1.02); Brain injuries: IRR= 0.66 (0.48-0.91).
	<b>Raman et al., 2013 (10)</b>	Population-based database	United Kingdom	328 individuals diagnosed with ADHD, with prescription for stimulants and a previous event	1 to 18	Stimulants	Within-individual comparison	Short-term	<i>Periods on treatment vs periods off treatment:</i> Overall: IRR= 0.68 (0.50 to 0.91); Males: IRR= 0.63 (0.50 to 0.91); Females: IRR= 1.01 (0.46 to 2.21).
	<b>van den Ban et al., 2014 (11)</b>	Population-based database	Netherlands	1289 individuals with ADHD medication	<=18	Stimulants	Traditional regression adjustment	Short-term	<i>Current treatment vs prior treatment:</i> IRR= 0.68 (0.29-1.60).
<b>Motor accidents</b>									
	<b>Chang et al., 2014 (12)</b>	Whole-population register	Sweden	17 408 individuals diagnosed with ADHD	18 to 46	Any ADHD medication	Within-individual comparison	Short-term	<i>Periods on treatment vs periods off treatment:</i> Males: HR= 0.42 (0.23-0.75); Females: HR= 2.35 (0.83-6.64).
	<b>Chang et al., 2017 (13)</b>	Insurance claims database	United States	2 319 450 individuals diagnosed with ADHD or prescribed any ADHD medication	>=18	Any ADHD medication	Within-individual comparison	Short-term and long-term	<i>Periods on treatment vs periods off treatment:</i> Males: OR= 0.62 (0.56-0.67); Females: OR= 0.58 (0.53-0.62). <i>Long-term:</i> Males: OR= 0.66 (0.58-0.76) ; Females: OR= 0.73 (0.64-0.84).
<b>Education</b>									
	<b>Jangmo et al., 2019 (14)</b>	Whole-population register	Sweden	29 128 individuals diagnosed with ADHD; 16 054 individuals treated with ADHD medication	80% 15.5 to 16.5	Any ADHD medication	Traditional regression adjustment	Long-term	<i>Effect of 3 months of treatment:</i> Not eligible for upper secondary school: OR= 0.80 (0.76-0.84) Not completed upper secondary school: OR= 0.89 (0.87-0.91) Grade point sum: $\beta$ = 9.35 (7.88-10.82) Grade point average: $\beta$ = 0.49(0.40-0.58)
	<b>Keilow et al., 2018 (15)</b>	Whole-population register	Denmark	2659 individuals diagnosed with ADHD and treated with ADHD medication	16 (mean age at graduation)	Any ADHD medication	Traditional regression adjustment	Long-term	<i>Discontinuation of treatment vs consistent treatment:</i> Standardized Exam GPA: -0.22 Standardized Teacher Evaluation GPA: -0.18
	<b>Lu et al., 2017 (16)</b>	Whole-population register	Sweden	930 individuals diagnosed with ADHD who had taken the repeated tests during the study follow-up and used medication intermittently	22 (mean age at test in the ADHD group)	Any ADHD medication	Within-individual comparison	Short-term	<i>Mean test score difference between periods on-treatment vs periods off-treatment:</i> Overall: difference= 4.80 (2.26-7.34); Males: difference= 5.69 (2.14-9.23); Females: difference= 3.60 (0.06-7.14).

Outcome	Study	Data source	Country/ Region	Sample	Age (range or mean)	Exposure	Design	Long-term/short- term effect	Effect size
	<b>Marcus et al., 2011 (17)</b>	Insurance claims database	Philadelphia	3543 individuals diagnosed with ADHD or prescribed stimulants and at least one grade in the school records	Elementary (grades 1–4) and middle school (grades 5–8) students	Stimulants	Within-individual comparison	Short-term	<i>Improvement in grade point average for adherence vs non-adherence during marking periods:</i> Overall: difference= 0.108 (p<0.001); Males: 0.106 (p<0.001); Females: 0.111 (p<0.001).
	<b>van der Schans et al., 2017 (18)</b>	Population-based database	Netherlands	441 individuals with data with data on primary school tests (fourth and seventh grade) current and past users of ADHD medication	12 to 13	Stimulants	Traditional regression adjustment	Short-term and long-term	<i>Mean and standard error of test scores:</i> Current users= 532.58 ± .48 Past users= 531.67 ± 1.15 P-value= 0.470  Low dose= 533.16 ± .66 High dose = 532.45 ± .81 P-value= 0.498  Late start= 536.94 ± 1.51 Early start= 532.33 ± .50 P-value= 0.04
	<b>Zoega et al., 2012 (19)</b>	Whole-population register	Iceland	236 individuals starting ADHD medication after 4th grade test	9 and 10	Any ADHD medication	Traditional regression adjustment	Long-term	<i>Decline in mathematics for later of treatment start vs &lt;=12 months after 4<sup>th</sup> grade:</i> 13-24 months: RR= 1.1 (0.77-1.7); 25-36 months: RR= 1.7 (1.2-2.4). <i>Decline in language arts for later of treatment start vs &lt;=12 months after 4<sup>th</sup> grade:</i> 13-24 months: RR= 1.1 (0.71-1.7); 25-36 months: RR=1.1 (0.73-1.8).
<b>Criminality</b>									
	<b>Lichtenstein et al., 2012 (20)</b>	Whole-population register	Sweden	25 656 individuals diagnosed with ADHD	>=15	Any ADHD medication	Within-individual comparison	Short-term and long-term	<i>Periods on treatment vs periods off treatment:</i> Males: HR= 0.68 (0.63-0.73); Females: HR= 0.59 (0.50-0.70). <i>Previous treatment:</i> HR= 0.94 (0.83-1.07).
	<b>Mohr-Jensen, 2019 (21)</b>	Whole-population register	Denmark	4231 individuals with ADHD; 3001 individuals treated with any ADHD medication	>=15	Any ADHD medication	Traditional regression adjustment	Short-term	<i>Periods on treatment vs periods off treatment:</i> Conviction: HR= 0.8 (0.7-0.9) Incarceration: HR= 0.7 (0.6-0.8)
<b>Suicidality</b>									
	<b>Chen et al., 2014 (22)</b>	Whole-population register	Sweden	37 936 individuals diagnosed with ADHD	10 to 46	Any ADHD medication	Within-individual comparison	Short-term	<i>Periods on treatment vs periods off treatment:</i> Overall: HR= 0.89 (0.79-1.00); Males: HR= 0.79 (0.64-0.98); Female: HR= 0.88 (0.76-1.02).

Outcome	Study	Data source	Country/ Region	Sample	Age (range or mean)	Exposure	Design	Long-term/short- term effect	Effect size
	<b>Huang et al., 2018 (23)</b>	Insurance claims database	Taiwan	20 574 individuals diagnosed with ADHD and 61 722 controls	12 to 29	Any ADHD medication	Traditional regression adjustment	Long-term	<p><i>Different cumulative defined daily dosage (cDDD) vs &lt;30 cDDD for stimulants:</i> Overall 30-364cDDD: HR= 1.07 (0.89–1.28); Males 30-364cDDD: HR= 1.04 (0.84–1.30); Females 30-364cDDD: HR= 1.11 (0.79–1.55); Overall &gt;=365cDDD: HR= 1.14 (0.89–1.47); Males &gt;=365cDDD: HR= 1.08 (0.80–1.45); Females &gt;=365cDDD: HR=1.30 (0.82–2.05).</p> <p><i>Different cumulative defined daily dosage (cDDD) vs &lt;30 cDDD for atomoxetine:</i> Overall 30-364cDDD: HR= 1.51 (0.75–3.05); Males 30-364cDDD: HR= 1.44 (0.59–3.49); Females 30-364cDDD: HR= 1.58 (0.50–5.04).</p>
	<b>Liang et al., 2018 (24)</b>	Insurance claims database	Taiwan	84 898 individuals diagnosed with ADHD	<18	Stimulants	Traditional regression adjustment	Long-term	<p><i>Treatment vs no treatment:</i> 1-90 days: HR= 0.86 (0.53-1.41); 91-180 days: HR= 0.41 (0.19-0.90); &gt;180 days: HR= 0.28 (0.17-0.48).</p>
	<b>Linden et al., 2016 (25)</b>	Insurance claims database	United States	297 315 individuals (first-line treatment cohort) and 220 215 individuals (second- line treatment cohort) with a dispensed prescription for stimulants or atomoxetine	5 to 18	Any ADHD medication	Propensity score with inverse probability weighting	Short-term and long-term	<p><i>Current atomoxetine vs current stimulants:</i> First-line treatment cohort: HR= 0.88 (0.50-1.56); Second-line treatment cohort: HR= 0.65 (0.31-1.36).</p> <p><i>Former atomoxetine vs current stimulants:</i> First-line treatment cohort: HR= 0.88 (0.53-1.46); Second-line treatment cohort: HR= 0.67 (0.36-1.24).</p>
	<b>Man et al., 2017 (26)</b>	Whole-population register	Hong Kong	154 individuals with a prescription for methylphenidate and a suicide attempt	6 to 25	Stimulants	Within- individual comparison	Short-term	<p><i>Frist 90 days on treatment vs 90 days preceding treatment initiation:</i> IRR= 0.78 (0.26-2.35).</p>

Outcome	Study	Data source	Country/ Region	Sample	Age (range or mean)	Exposure	Design	Long-term/short- term effect	Effect size
<b>Substance use disorder</b>									
	<b>Chang et al., 2014 (27)</b>	Whole-population register	Sweden	38 753 individuals diagnosed with ADHD	8 to 46	Any ADHD medication	Within-individual comparison	Short-term and long-term	<i>Periods on treatment vs periods off treatment:</i> HR= 0.73(0.68-0.77). <i>Previous treatment:</i> HR= 0.69 (0.57-0.84). <i>Treatment duration:</i> HR= 0.87 (0.80-0.94).
	<b>Quinn et al., 2017 (28)</b>	Insurance claims database	United States	2 993 887 diagnosed with ADHD or prescribed any ADHD medication	>=13	Any ADHD medication	Within-individual comparison	Short-term and long-term	<i>Periods on treatment vs periods off treatment:</i> Males: OR= 0.65 (0.64-0.67); Females: OR= 0.69 (0.67-0.71).  <i>Previous treatment:</i> Males: OR=0.81 (0.78-0.85); Females: OR=0.86 (0.82-0.91). <i>Treatment vs no treatment:</i> HR=0.92(0.74-1.15).
	<b>Steinhausen et al., 2014 (29)</b>	Whole-population register	Denmark	20 742 individuals diagnosed with ADHD	3 to 60	Stimulants	Traditional regression adjustment	Long-term	<i>Periods on treatment vs periods off treatment:</i> HR=0.80(0.70-0.92). <i>Previous treatment:</i> HR=0.58 (0.51-0.67); <i>Treatment duration:</i> HR=0.79 (0.75-0.83).
<b>Depression</b>									
	<b>Chang et al., 2016 (30)</b>	Whole-population register	Sweden	38 752 individuals diagnosed with ADHD	8 to 46	Any ADHD medication	Within-individual comparison	Short-term and long-term	<i>Periods on treatment vs periods off treatment:</i> HR=0.80(0.70-0.92). <i>Previous treatment:</i> HR=0.58 (0.51-0.67); <i>Treatment duration:</i> HR=0.79 (0.75-0.83).
	<b>Lee et al., 2016 (31)</b>	Insurance claims database	Taiwan	71 080 individuals diagnosed with ADHD and 71 080 controls	9 (mean age at diagnosis/recruitment)	Any ADHD medication	Traditional regression adjustment	Long-term	<i>Treatment duration:</i> Stimulants: OR=0.91 (0.88-0.94); Atomoxetine: OR= 0.80 (0.52-1.22).
<b>Bipolar disorder and mania</b>									
	<b>Viktorin et al., 2017 (32)</b>	Whole-population register	Sweden	2 307 individuals diagnosed with bipolar disorder initiating methylphenidate	>=18	Stimulants	Within-individual comparison	Short-term and long-term	<i>After vs before treatment initiation in individuals without mood-stabilizing medication:</i> 0-3 months after: HR= 6.67 (1.98-22.4); 3-6 months after: HR= 9.67 (2.94-31.7). <i>After vs before treatment initiation in individuals with mood-stabilizing medication:</i> 0-3 months: HR= 0.56 (0.36-0.87); 3-6 months: HR= 0.91 (0.50-1.67).

Outcome	Study	Data source	Country/ Region	Sample	Age (range or mean)	Exposure	Design	Long-term/short- term effect	Effect size
	<b>Wang et al., 2016 (33)</b>	Insurance claims database	Taiwan	144 920 individuals diagnosed with ADHD and 144 920 controls	7.7 and 7.8 (mean age at follow-up start for individuals with ADHD and controls, respectively)	Any ADHD medication	Traditional regression adjustment	Long-term	<i>Treatment duration vs no treatment for stimulants:</i> <=365 days: OR= 0.93 (0.85-1.01); >365 days: OR= 0.72 (0.65-0.80). <i>Treatment duration vs no treatment for atomoxetine:</i> <=365 days: OR= 1.08 (0.90-1.30); >365 days: OR= 0.69 (0.37-1.30).
<b>Psychosis</b>									
	<b>Man et al., 2016 (34)</b>	Whole-population register	Hong Kong	103 individuals with a prescription for methylphenidate and a psychotic event	6 to 19	Stimulants	Within-individual comparison	Short-term	<i>Periods on treatment vs periods off treatment:</i> IRR= 0.98 (0.52-1.86).
	<b>Shyu et al., 2015 (35)</b>	Insurance claims database	Taiwan	73 049 individuals diagnosed with ADHD and 73 049 controls	9.4 and 9.6 (mean age at follow-up start for individuals with ADHD and controls, respectively)	Stimulant	Traditional regression adjustment	Long-term	<i>Treatment vs no treatment:</i> Any psychotic disorder: HR= 1.20 (1.04-1.40); Schizophrenia: HR= 1.16 (0.94-1.42).
<b>Seizure</b>									
	<b>Brikell et al., 2019 (36)</b>	Whole-population register	Sweden	21 557 individuals with a seizure history	<19	Any ADHD medication	Within-individual comparison	Short-term	<i>Periods on treatment vs periods off treatment:</i> HR= 0.73 (0.57-0.94)
	<b>Liu et al., 2018 (37)</b>	Insurance claims database	United States	73 083 individuals with epilepsy	3 to 18	Stimulants	Traditional regression adjustment	Short-term and long-term	<i>Current treatment vs no treatment:</i> HR= 0.95 (0.83-1.09). <i>Former treatment vs no treatment:</i> HR= 0.99 (0.86-1.15).
	<b>McAfee et al., 2008 (38)</b>	Insurance claims database	United States	34 727 individuals diagnosed with ADHD	6 to 17	Any ADHD medication	Traditional regression adjustment	Short-term and long-term	<i>Current treatment vs past or no treatment:</i> RR= 1.1 (0.6-2.1). <i>Recent treatment vs past or no treatment:</i> RR= 0.8 (0.0-3.4).
	<b>McAfee et al., 2013 (39)</b>	Insurance claims database	United States	13 398 individuals initiating atomoxetine to 13 322 individuals initiating stimulants	6 to 17	Any ADHD medication	Propensity score matching	Short-term	<i>Naive initiators of atomoxetine vs naive initiators of stimulants:</i> RR= 0.72 (0.37-1.38)

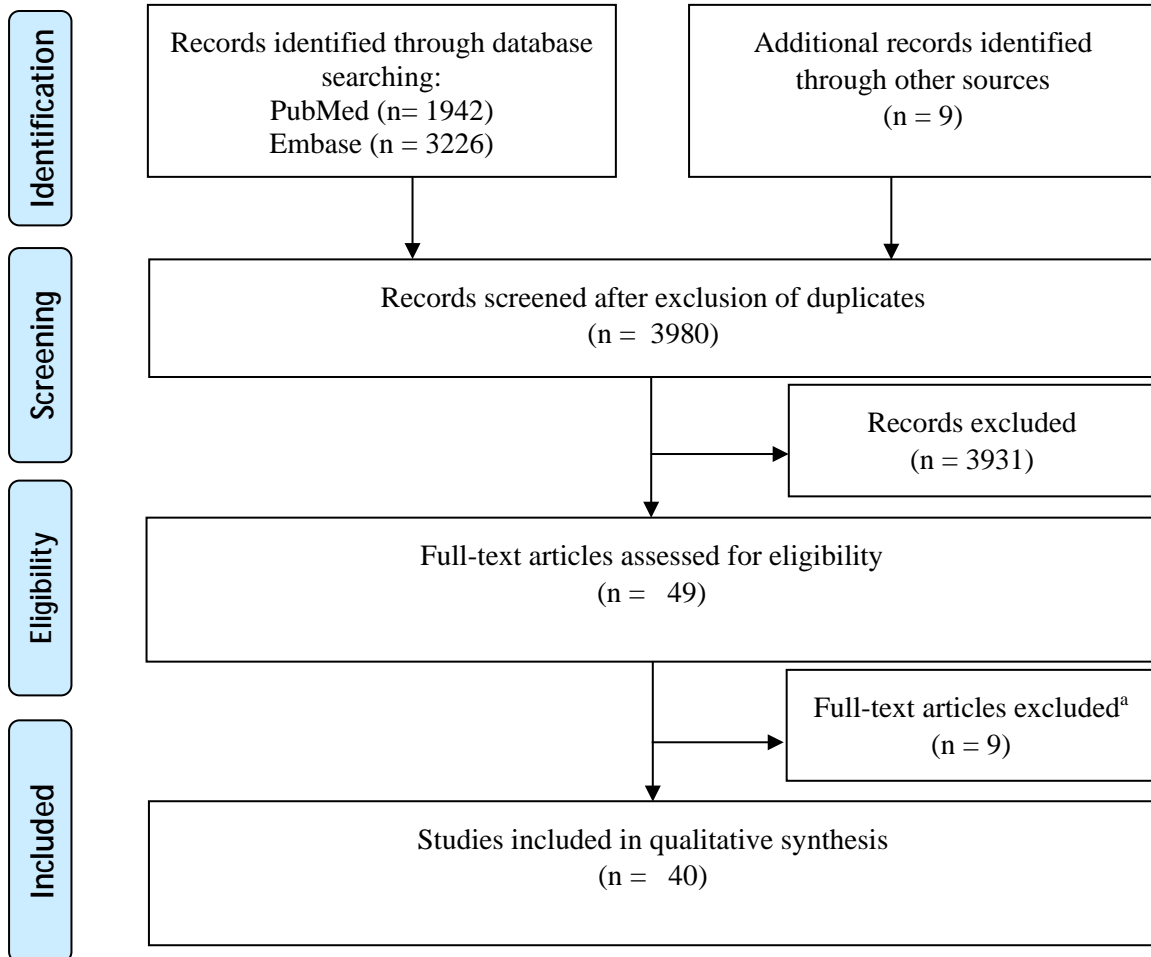
Outcome	Study	Data source	Country/ Region	Sample	Age (range or mean)	Exposure	Design	Long-term/short- term effect	Effect size
	<b>Wiggs et al., 2018 (40)</b>	Insurance claims database	United States	801 838 individuals diagnosed with ADHD or prescribed any ADHD medication	5 to 64	Any ADHD medication	Within- individual comparison	Short-term and long-term	<i>Periods on treatment vs periods off treatment:</i> Prior seizure: OR= 0.71 (0.60-0.85); No prior seizure: OR= 0.51 (0.43-0.62). <i>Treatment duration:</i> Prior seizure: OR= 0.87 (0.59-1.30); No prior seizure: OR= 1.01 (0.80-1.28).

Notes:

“Any ADHD medication” refers to stimulant (for example, methylphenidate and amphetamines) and non-stimulant (for example, atomoxetine, clonidine, guanfacine, and bupropion) medications commonly used for ADHD.

“Within-individual comparison” refers to any type of within-individual comparison, including, for example, difference-in-difference design and self-controlled case series.

“Effect size” when confidence intervals are not reported, p-values are reported.



Supplementary Figure S1. Flow diagram of the systematic review according to PRISMA guidelines.

Notes: <sup>a</sup>Full-text articles excluded: case series (n=1); studies which used data from a single institution (n=2) or from self- or parent-report (n=2) or from a clinical sample (n=1); studies which focused on multimodal interventions (n=1); studies where there was no direct comparison between ADHD medication and unexposed patients/time periods (n=2).



**Supplemental References**

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