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A literature review and meta-analysis on the effects of ADHD medications on functional outcomes

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ABSTRACT

Objective: To conduct a systematic review and meta-analysis of literature from large databases and registries to assess the effects of ADHD medication on associated functional outcomes.
Study design: A literature search was performed in PubMed, PsycINFO, MEDLINE, and Web of Science for articles published prior to January 2019. Sample size, age range, country of origin, medication type, number of functional events and non-events, odds ratios and hazard ratios, and means and standard deviations were extracted. Random-effects meta-analyses were conducted for 21 studies examining functional outcomes.
Results: 40 articles were included. The majority suggest a robust protective effect of ADHD medication treatment on mood disorders, suicidality, criminality, substance use disorders, accidents and injuries, traumatic brain injuries, motor vehicle crashes, and educational outcomes. Similarly, the meta-analyses demonstrated a protective effect of medication treatment on academic outcomes, accidents and injuries, and mood disorders.
Conclusions: These findings suggest that ADHD medication treatments are associated with decreases in the risks for a wide range of ADHD-associated functional outcomes supporting efforts aimed at early diagnosis and treatment of individuals with ADHD.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a prevalent and morbid neurobiological disorder estimated to affect up to 11% of children (Faraone et al., 2003) and 5% of adults (Polanczyk et al., 2014). It is associated with high rates of many adverse functional outcomes including comorbid psychiatric disorders (Biederman et al., 2006), academic impairments (Barkley et al., 1991), accidents and injuries (Chen et al., 2017), and car accidents (Thompson et al., 2007), among many others.

While treatment with ADHD medications, particularly stimulants, have been shown to improve the core symptoms of ADHD (Faraone et al., 2006), less information is available of their effects on ADHD-associated functional impairments (Faraone and Glatt, 2010). Such information is critical for the careful examination of the risks versus benefits calculus when considering medication treatments for ADHD.

Research on population-based datasets has greatly advanced medical knowledge for a wide range of conditions including pediatric cancer, sickle cell disease, and macular degeneration, among others (Brandl et al., 2019; Rice et al., 2015; Claster et al., 2013). These studies have allowed for the examination of the impact of therapies, regional rates of mortality, and average cost of specific treatments. Such information enables healthcare professionals and organizations to better understand current regional, nationwide and international trends in a wide-range of treatments and healthcare costs. Because these population-based databases are very large and are linked to other health records and registers, they are distinctively poised to provide ecologically informative evidence on the impact of various diseases on the population as well as allowing for the examination of the influence of treatment on these conditions.

Abbreviations: Attention-deficit/hyperactivity disorder, ADHD; Atomoxetine, ATX; Confidence intervals, CI; Emergency Room, ER; Hazard ratios, HR; Odds ratios, OR; Motor Vehicle Crash, MVCs; Standard Mean Difference, SMD; Substance Use Disorders, SUDs; Traumatic Brain Injury, TBIs

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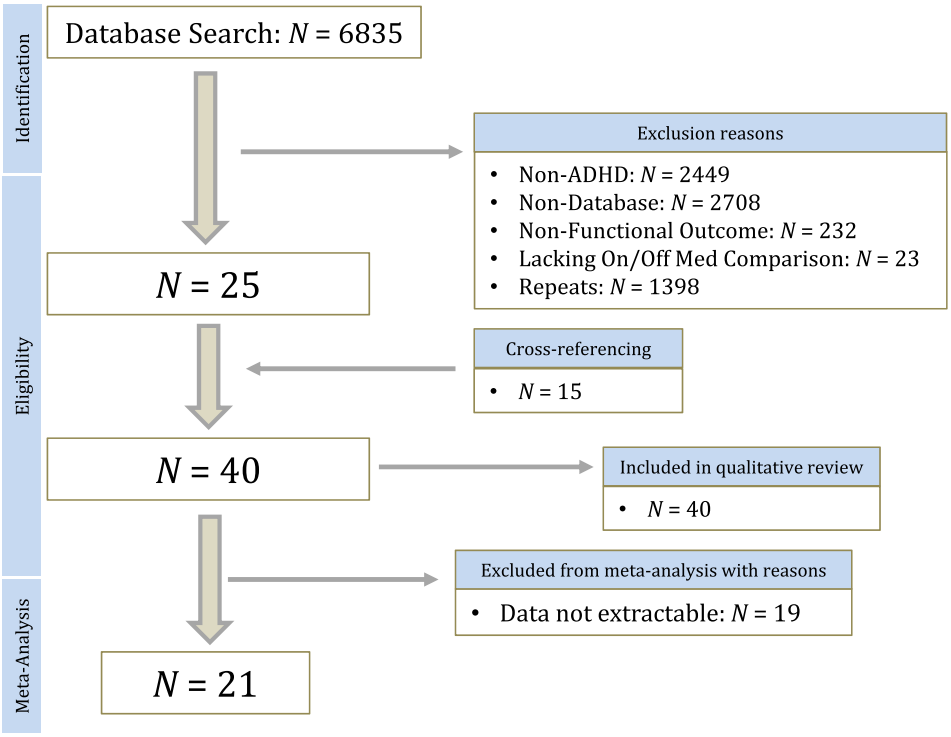

Fig. 1. Prisma diagram.

In recent years, an emergent literature from large databases and registries has examined the effects of medication for ADHD on ADHD-associated functional outcomes, offering a unique opportunity to gain new insights into the impact of these medications on ecologically valid indices of functional impairment. Compared with clinical trials, these studies provide information about the broader benefits of ADHD medications on ADHD-associated functional impairments and outcomes, particularly when they provide information comparing outcomes during medicated and non-medicated time periods within the same individual. They also provide information on the full range of ADHD patients, not only those eligible for clinical trials.

A recent qualitative review (Chang et al., 2019) of studies that investigated the effects of ADHD medication suggested beneficial effects of ADHD medication on injuries, motor vehicle accidents, education, and substance use disorder with estimates of relative risk reduction from 9% to 58% for these outcomes. While highly informative, this review did not subject the findings to meta-analysis.

The main aim of this study was to conduct a systematic review and meta-analysis of the extant literature from large databases to assess the effects of stimulant treatment on ADHD-associated functional outcomes. We hypothesized that this literature would show that ADHD medications improve important ADHD-associated serious and morbid functional outcomes.

2. Methods

2.1. Literature review

A literature search was performed using PubMed, PsycINFO, MEDLINE, and Web of Science. The following algorithm was used: ((ADD) OR (ADHD) OR (attention deficit disorder) OR (attention deficit hyperactivity disorder) OR (hyperkinesis)) AND (medication) AND ((registry) OR (registries) OR (insurance) OR (insurance claims) OR (database)). The search was limited to articles published prior to January 1st, 2019. From the search results, we selected articles using the following criteria: 1) the study's main focus was ADHD; 2) the study relied on population-wide databases or large health insurance claim databases; 3) the main outcomes assessed were functional; 4) data were available comparing individuals taking ADHD medication treatment to those who were not. We excluded articles not published in the English language, review articles, editorials, and commentaries. The lead author and the senior author screened the articles for relevance and eligibility. Articles initially deemed eligible were cross-referenced for other relevant and potentially suitable articles that had been cited in their text. These cited articles were then screened according to the same inclusion and exclusion criteria.

2.2. Data extraction and statistical analysis

The following variables were extracted from each of the studies when available: study sample size, ADHD sample size, age range (or mean age if age range was not reported), country of origin, and medication type. For studies reporting on dichotomous outcomes, we extracted the number of functional events and non-events for each functional outcome of interest or odds ratios (OR) and 95% confidence intervals (CI) if event count was not available. For studies that provided total N and percentages but not number of cases, numbers were calculated based on the percentages provided. We extracted hazard ratios (HR) and 95% CIs for papers reporting on survival analyses. We extracted means and standard deviations for papers reporting on continuous data and calculated standardized mean differences (SMD) as the effect sizes. Only studies that provided sufficient data to make these calculations were included in the meta-analysis. When available, adjusted effect sizes were extracted over crude effect sizes.

We computed meta-analyses for studies examining functional outcomes in medicated ADHD subjects versus unmedicated ADHD subjects. Our meta-analyses used the random effects model of DerSimonian and Laird (1986), which computes a pooled effect size weighted by sample size. We used the I^2 index to assess heterogeneity of effect sizes (Higgins et al., 2003). Its value lies between 0 and 100 and estimates the percentage of variation among effect sizes that can be attributed to heterogeneity. A significant I^2 suggests that the effect sizes analyzed are not estimating the same population effect size. We used the Egger method to assess for publication biases (Egger et al., 1997). The meta-

analyses were weighted by the reciprocal of the variance of effect sizes. All analyses were two-tailed and performed at the 0.05 alpha level using Stata: Version 15.1 (Stata Statistical Software, 2017).

3. Results

3.1. Articles identified

As shown in Fig. 1, our search resulted in 6835 articles. After eliminating repeats, 5437 unique articles were screened according to our inclusion/exclusion criteria. Twenty-five studies meeting these criteria were identified. An additional 15 were deemed eligible through cross-referencing. Thus, the total number of articles included in this review was 40.

Of these 40 articles, ten (25%) were derived from U.S. datasets while the other 30 were derived from non-U.S. sources (eight from Sweden (20%), seven from Taiwan (18%), five from Denmark (13%), three from Germany (8%), two from China (5%), two from the Netherlands (5%), and one from each of the following countries: Iceland (2%), Canada (2%), and United Kingdom (2%)). The sample sizes in these articles ranged from 5718 persons to over 146,000,000. The overwhelming majority of medication treatment consisted of stimulants. Twenty-one studies included data on individuals taking ADHD medication including stimulants and non-stimulants. Seventeen studies provided data on individuals taking only stimulants. Two studies did not specify the types of ADHD medication. No articles provided data on individuals taking only non-stimulants.

Of the 40 articles identified, four examined the effects of ADHD medications on the subsequent development of mood disorders (depression and bipolar disorder), four on substance use disorders (SUD), three on criminality, three on suicidality, two on traumatic brain injury (TBI), two on motor vehicle crash (MVC) rates, 14 on accidents and injuries, and eight on academic outcomes.

Sixteen articles collected data on periods within the same individual when they were adherent to medication compared to time intervals when they were not adherent (Mohr-Jensen et al., 2019; Chang et al., 2017; Lu et al., 2017; Quinn et al., 2017; Man et al., 2015; Mikolajczyk et al., 2015; Chang et al., 2014; Chang et al., 2014b; Dalsgaard et al., 2014; Stein et al., 2014; van den Ban et al., 2014; Raman et al., 2013; Lichtenstein et al., 2012; Marcus and Durkin, 2011; Marcus et al., 2008; Leibson et al., 2006). Adherence to medication in these studies was defined broadly and included definitions such as any exposure to ADHD medication, up to 180 days of receiving medication, and up to five or more years (Chen et al., 2017; Chang et al., 2016; Barbaresi et al., 2007). In this review, we extracted data as reported on those who were deemed medicated versus unmedicated.

3.2. Qualitative review summary

Table 1: Qualitative Review

3.2.1. Psychiatric outcomes

Mood Disorders: Of the four studies that examined mood disorder outcomes, all but one showed that stimulant medication treatment was associated with a **significantly reduced risk** of mood disorders (depression and bipolar disorder) (Chang et al., 2016; Lee et al., 2016; Wang et al., 2016). Only one study (Jerrell et al., 2015) reported that ADHD medication treatment was associated with a significantly increased risk for depression.

Substance Use Disorders (SUDs): SUDs were defined as an emergency room visit insurance claim for a non-tobacco use disorder diagnosis (Quinn et al., 2017), a hospital visit with a linked diagnosis of mental and behavioral disorders due to psychoactive substance use (Chang et al., 2014; Steinhausen and Bisgaard, 2014) including those not involving alcohol (Sundquist et al., 2015), and alcoholism and drug dependence (Steinhausen and Bisgaard, 2014). Of the four studies that examined substance use disorders outcomes, all but one showed that stimulant medication treatment was associated with a **significantly reduced risk** of substance use outcomes (Quinn et al., 2017; Chang et al., 2014; Steinhausen and Bisgaard, 2014). Two of these studies (Quinn et al., 2017; Steinhausen and Bisgaard, 2014) showed that the reduction in substance use outcomes was particularly marked during periods when the same individual was adherent to the medication prescribed when compared to times when the subject was not. One study (Sundquist et al., 2015) found neither increased nor decreased impact of stimulant medication treatment on drug use disorders (a neutral effect).

Criminality: Criminality was defined in these studies broadly, and included crimes such as property offenses, tax offenses, homicides, assaults, interactions with police, threats of harassment, robbery, arson, and drug offenses (Mohr-Jensen et al., 2019; Dalsgaard et al., 2014; Lichtenstein et al., 2012). All three studies that examined ADHD-associated criminality found that ADHD medication treatments, mostly stimulants, were associated with **significantly decreased rates** of criminal activity and contact with the justice system (Mohr-Jensen et al., 2019; Dalsgaard et al., 2014; Lichtenstein et al., 2012). All three studies also documented reduced criminality rates within the same individuals during periods of adherence to ADHD medication compared with period of non-adherence (Mohr-Jensen et al., 2019; Dalsgaard et al., 2014; Lichtenstein et al., 2012).

Suicidality: In all three studies that examined the risk for suicidality, ADHD medications, mostly stimulants, were associated with a **reduced risk** of suicide attempts or repeated suicide attempts (Liang et al., 2018; Man et al., 2017; Chen et al., 2014). Two of these reductions were statistically significant (Liang et al., 2018; Chen et al., 2014), while the third was not (Man et al., 2017). The reductions in suicidal behavior were particularly marked for men and for longer-term stimulant users.

3.2.2. Accidents and Injuries

Traumatic Brain Injury (TBI): The two studies that examined ADHD-associated TBIs reported that stimulant medication treatment was associated with a **significantly reduced risk** of TBIs (Liao et al., 2018; Liou et al., 2018).

Motor Vehicle Crashes (MVCs): The two studies that examined the impact of ADHD medication treatment on MVC rates found a **significantly reduced risk** of MVCs for individuals taking medication compared to periods off medications (Chang et al., 2014b, 2017).

Accident, Injuries, Emergency Room (ER) Visits: Accidents and injuries were defined broadly across the studies, and included bone fractures (forearm, arm, ankle, and other areas of the body), poisoning, foreign body removal, sprains, burns, and others (Chien et al., 2017; Jacob and Kostev, 2017; Raman et al., 2013). Of the 14 studies that examined the impact of ADHD medications, mostly stimulants, on the risk of accidents and injuries, the majority (N = 10) found that treatment was associated with a **reduced risk** of fractures, general injuries, insurance claims, and/or hospital/ER visits (Chen et al., 2017; Chien et al., 2017; Jacob and Kostev, 2017; Merrill et al., 2016; Dalsgaard et al., 2015; Man et al., 2015; Mikolajczyk et al., 2015; Raman et al., 2013; Marcus et al., 2008; Leibson et al., 2006), and of those, eight demonstrated significant reductions (Chen et al., 2017; Chien et al., 2017; Jacob and Kostev, 2017; Dalsgaard et al., 2015; Man et al., 2015; Mikolajczyk et al., 2015; Raman et al., 2013; Leibson et al., 2006) while two showed reductions that were not statistically significant (Merrill et al., 2016; Marcus et al., 2008). Five of these ten studies (Man et al., 2015; Mikolajczyk et al., 2015; Raman et al., 2013; Marcus et al., 2008; Leibson et al., 2006) examined within-individual results. They found that periods of adherence to medication were associated with reductions in risk compared with periods of non-adherence. Four studies found that there was neither a decreased nor increased rate, or a neutral effect, in ADHD associates injuries associated with medication treatment (van den Ban et al., 2014; Lange et al., 2016; Merrill et al., 2009;

Table 1
Qualitative review of articles focusing on functional outcomes of ADHD individuals taking ADHD medication.

First Author, Year	Country of Data	Med Type	Total N	ADHD N	Age	Main Findings and Comments
Psychiatric Outcomes						
Mood Disorders						
Chang et al., 2016	Sweden	Stimulants[a]	Not specified	38,752	Range: 8-46	ADHD medication was associated with a **significantly reduced risk** for depression when compared across individuals.
Lee et al., 2016	Taiwan	Stimulants[a]	150,655	71,080	Avg.: 9.5	ADHD medication was associated with a **significantly reduced risk** of developing a depressive disorder.
Wang et al., 2016	Taiwan	Stimulants[a]	22,800,000	144,920	Range: All ages	ADHD medication was associated with a **significantly reduced risk** of bipolar disorder diagnosis versus non-medicated individuals.
Jerrell et al., 2015	United States	Stimulants[a]	Not specified	22,452	Avg.: 7.8	ADHD medication was associated with a **significantly increased risk** of a subsequent diagnosis of depression.
Substance Use Disorder (SUD)						
Quinn et al., 2017	United States	Stimulants	146,000,000	2,993,887	Range: 15-42	Stimulant medication use was associated with a **significantly lower risk** of substance-related events within the same individuals for periods off medication.
Sundquist et al., 2015	Sweden	Stimulants	551,164	9424	Avg.: 15	Stimulant medication was **not associated with an increased nor decreased risk** for drug use disorder diagnoses when compared to those not taking medication.
Chang et al., 2014	Sweden	Stimulants	Not specified	38,753	Range: 8-46	Stimulant medication was associated with a **significantly reduced risk** of substance abuse outcomes when compared to non-stimulant users.
Steinhausen and Bisgaard, 2014	Denmark	Stimulants	Not specified	20,742	Avg.: 11-20	Stimulant medication was associated with a **significantly reduced risk** for SUD versus non-medicated and within individuals for periods on versus off medication
Criminality						
Mohr-Jensen et al., 2019	Denmark	Stimulants[a]	23,826	4231	Range: 15-34	Stimulant medication was associated with a **significantly lower risk** of criminality versus periods off medication.
Dalsgaard et al., 2014	Sweden	Stimulants[a]	Not specified	25,656	Range: ≥ 15	Stimulant medication was associated with a **significantly lower risk** of criminality versus periods off medication.
Lichtenstein et al., 2012	Denmark	Stimulants and Nonstimulants	Not specified	4556	Avg.: 10	ADHD medication was associated with a **significantly lower risk** for criminality versus periods off medication.
Suicidality						
Liang et al., 2018	Taiwan	Stimulants	Not specified	84,898	Range: 0-18	Stimulant medication treatment **significantly reduced the risk** of suicide attempts among ADHD youths compared to those not taking medication. Within individuals, longer medication use was associated with further reduction of risk.
Man et al., 2017	China	Stimulants	Not specified	25,629	Range: 7-19	Stimulant medication treatment **non-significantly reduced the risk** of suicide risk immediately after initiation of treatment when compared across individuals.
Chen et al., 2014	Sweden	Stimulants[a]	Not specified	37,936	Range: 13-28	Stimulant medication use within individuals was associated with a **significantly lower risk** of suicidal behavior. Non-stimulant treatment had no association with an increased nor decreased rate of suicidal behavior within individuals.
Accidents & Injuries						
Traumatic Brain Injuries (TBIs)						
Liao et al., 2018	Taiwan	Stimulants	Not specified	124,438	Range: 0-18	Stimulant medication was associated with a **significantly reduced risk** for TBI versus individuals not taking medication.
Liou et al., 2018	Taiwan	Stimulants and ATX	Not specified	72,181	Range: 3-29	ADHD medication use was associated with a **significantly lower risk** for TBI.
Motor Vehicle Crashes (MVCs)						
Chang et al., 2017	United States	Simulants and ATX	Not specified	2,319,450	Avg.: 32.5	ADHD medication was associated with a **significantly lower risk** of MVCs versus periods off medication.
Chang et al., 2014b	Sweden	Stimulants and Nonstimulants	Not specified	17,408	Range: 18-46	ADHD medication was associated with a **significantly lower risk** of MVCs versus periods off medications, among males but not among females.

(*continued on next page*)

Table 1 (*continued*)

First Author, Year	Country of Data	Med Type	Total N	ADHD N	Age	Main Findings and Comments
Injuries						
Chen et al., 2017	Taiwan	Stimulants	1,000,000	6201	Range: 0-18	Longer-term stimulant medication use was associated with a **significantly lower risk** for fractures versus those not on stimulant medication or short-term users.
Chien et al., 2017	Taiwan	Stimulants[a]	Not specified	2660	Range: ≥18	Stimulant medication use was associated with a **significantly lower risk** of injury versus those not on stimulant medication.
Jacob and Kostev, 2017	Germany	Stimulants and ATX	1,226,693	36,878	Avg.: 10.3	ADHD medication treatment was associated with a **significantly lower risk** of injury compared to those not taking medication.
Lange et al., 2016	Germany	Not specified	17,641	18,741	Avg.: 10.4	ADHD medication treatment had **no effect** on likelihood of injuries.
Merrill et al., 2016	United States	Stimulants[a]	91,607	17,055	Avg.: 35.5	ADHD treatment **non-significantly reduced the risk** of injury.
Dalsgaard et al., 2015	Denmark	Stimulants[a]	710,120	4557	Range: 10-12	ADHD medication was associated with a **significantly reduced risk** of both injuries and ER visits in children.
Man et al., 2015	China	Stimulants	Not specified	17,381	Range: 6-19	Stimulant medication was associated with a **significantly reduced risk** of trauma-related ER admissions versus periods off medication.
Mikolajczyk et al., 2015	Germany	Stimulants[a]	17,000,000	37,650	Range: 3-17	ADHD medication treatment was associated with a **significantly reduced risk** of brain injuries, but not other injuries, versus periods off medication.
van den Ban et al., 2014	Netherlands	Stimulants and ATX	150,000	8621	Range: 0-18	ADHD medication had a **neutral effect** on rates of hospital admissions for injuries in individuals with ADHD for periods off versus on medication.
Raman et al., 2013	United Kingdom	Stimulants	2,300,000	328	Range: 1-18	Stimulant medication treatment was associated with a **significantly decreased risk** of injury in children treated for ADHD versus non-medicated periods.
Merrill et al., 2009	United States	Stimulants and Non-Stimulants	61,000	2186	Range: 0-64	ADHD medication treatment had a **neutral impact** on injury rates in ADHD patients.
Marcus et al., 2008	United States	Stimulants	Not specified	11,770	Range: 6-17	Stimulant medication treatment had a **non-significantly lower risk** of injury compared to periods off medication.
Leibson et al., 2006	United States	Stimulants	5718	313	Avg.: 7.5	Stimulant medication was associated with a **significantly decreased risk** for ER visits and ER costs versus periods off medication.
Swensen et al., 2004	United States	Not specified	> 100,000	1308	Range: 0-64	ADHD medication treatment **was not associated with a significant difference** in likelihood of an accident claim.
Academic Outcomes						
Jangmo et al., 2019	Sweden	Stimulants	657,720	29,128	Not specified	Stimulant medication was associated with **a significant improvement** in grade point averages (GPAs) and graduation from primary school.
Keilow et al., 2018	Denmark	Stimulants and ATX	577,551	6444	Avg.: 16.1	ADHD medication treatment was associated with **significantly improved GPAs** compared to those not taking medication.
Lu et al., 2017	Sweden	Stimulants[a]	61,640	3718	Avg.: 22	ADHD medication was associated with **significantly higher scores** on education entrance tests compared to periods off medication.
van der Schans et al., 2017	Netherlands	Stimulants	600,000	7736	Range: 12-13	Stimulant medication use was associated with **significantly worse school performance** compared to those not on stimulant medication.
Currie et al., 2014	Canada	Stimulants	Not specified	Not specified	Range: < 16	Stimulant medication was **not associated with an increase nor a decrease in academic outcomes**.
Zoega et al., 2012	Iceland	Stimulants[a]	13,617	1029	Range: 9-12	Later-onset of stimulant medication treatment use was associated with a **decline in academic test scores** versus individuals not receiving stimulant medication.
Marcus and Durkin, 2011	United States	Stimulants	Not specified	3543	Not specified	Stimulant medication adherence was associated with **marginal but significant improvement in grade point averages.**
Barbaresi et al., 2007	United States	Stimulants	5718	370	Avg.: 18.4	Stimulant medication was associated with **significantly improved levels of reading and decreased levels of absent school days** versus those not receiving medication treatment.

ATX: Atomoxetine Hydrochloride.

[a] Data includes non-stimulant users (< 50% of sample).

Swensen et al., 2004).

3.2.3. Academic outcomes

Five of eight studies (Jangmo et al., 2019; Keilow et al., 2018; Lu et al., 2017; Marcus and Durkin, 2011; Barbaresi et al., 2007) found that ADHD medication treatments were associated with **significantly higher scores** on tests, **significant improvements** in grade point averages, **significantly fewer days absent** from school, and **significant improvements** in reading. Two of these five (Lu et al., 2017; Marcus and Durkin, 2011) showed that, within-individuals, adherence to medication was associated with higher scores on education entrance tests and marginal improvement in grade point averages. Two of the eight (van der Schans et al., 2017; Zoega et al., 2012) studies found that treatment was associated with a decline in testing scores and worse school performance, and another (Currie et al., 2014) found no relationship between treatment and academic outcomes. Only one of these three demonstrated a significant decline in academic outcomes (van der Schans et al., 2017).

3.3. Meta-analysis results

Of the 40 articles identified, **21 had *extractable data for meta-analysis of functional outcomes in medicated versus unmedicated ADHD subjects***.

3.3.1. Psychiatric outcomes

Mood Disorders: Consistent with the qualitative review, for the two studies with available OR data for meta-analysis examining the effects of ADHD medication on mood disorders outcomes, the pooled OR was < 1 and statistically significant, indicating **significantly decreased odds** of developing mood disorders in medicated ADHD subjects compared to unmedicated ones (pooled OR = 0.69, 95% CI = 0.64, 0.74; p < 0.001) (Fig. 2C). Overall heterogeneity was low and not significant (I^2 = 28.0%, p = 0.24), suggesting that they were estimating a common OR.

Suicidality: Consistent with the qualitative review, the pooled HR for the two studies with available HR data for meta-analysis examining suicidality showed that although this risk was reduced, it did not attain statistical significance (pooled HR = 0.65, 95% CI = 0.34, 1.27; p = 0.21) (Fig. 3D). Overall heterogeneity was high and significant (I^2 = 88.7%, p = 0.003), suggesting that they were not estimating a common HR.

Substance Use Disorders (SUDs): Consistent with the qualitative review, the pooled HR for the two studies with available HR data for meta-analysis examining SUD outcomes showed that although this risk was reduced, it did not attain statistical significance (pooled HR = 0.79, 95% CI = 0.60, 1.05; p = 0.11) (Fig. 3C). Overall heterogeneity was moderate and not significant (I^2 = 72.9%, p = 0.06), suggesting that they were estimating a common HR.

Criminality: Consistent with the qualitative review, the pooled HR for the two studies with available HR data for meta-analysis examining criminality showed that although this risk was reduced, it did not attain statistical significance (pooled HR = 0.87, 95% CI = 0.74, 1.02; p = 0.08) (Fig. 3B). Overall heterogeneity was moderate and not significant (I^2 = 68.1%, p = 0.08), suggesting that they were estimating a common HR.

3.3.2. Accidents and Injuries

Accidents and Injuries: Consistent with the qualitative review, the six studies with available OR data for meta-analysis examining accidents and injuries showed that the pooled OR for accidents and injuries was < 1 and statistically significant, indicating that medicated ADHD subjects were at **significantly decreased odds** of accidents and injuries compared to unmedicated ones (pooled OR = 0.72, 95% CI = 0.59,

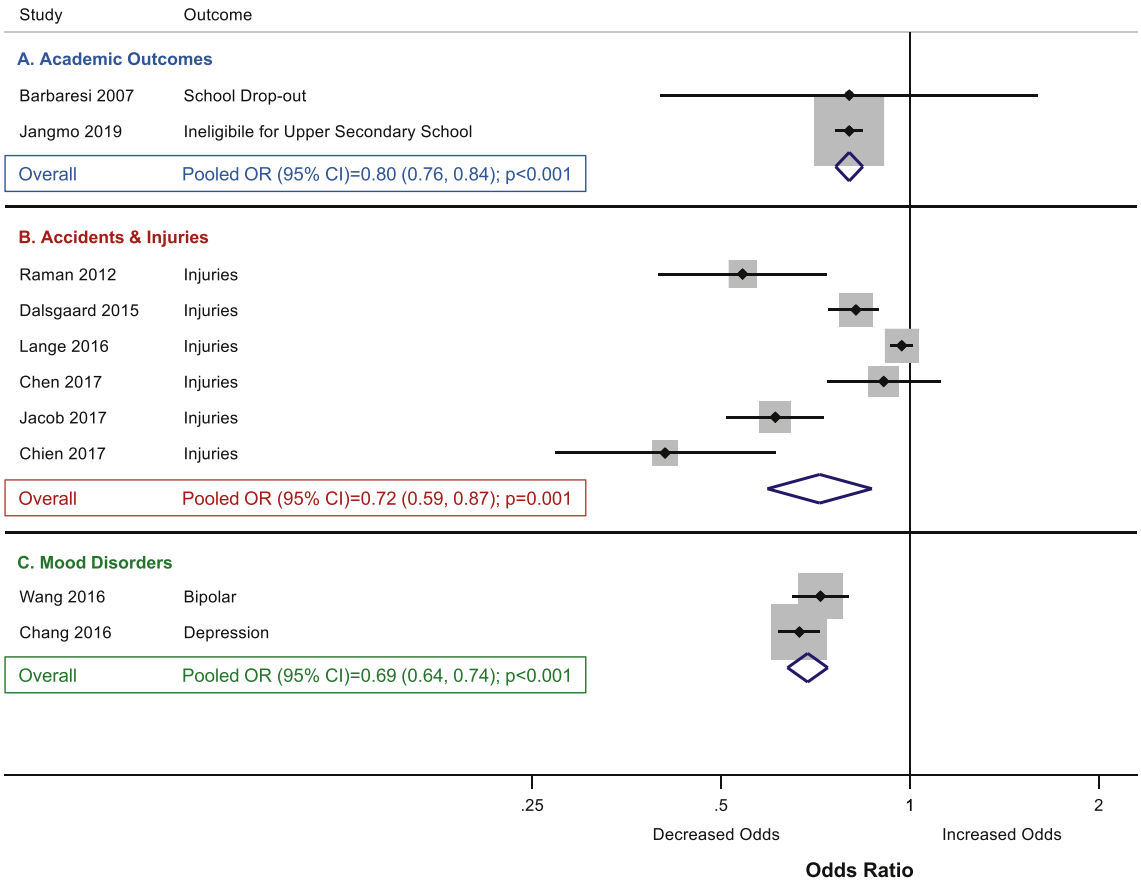

Fig. 2. Odds ratio forest plot.

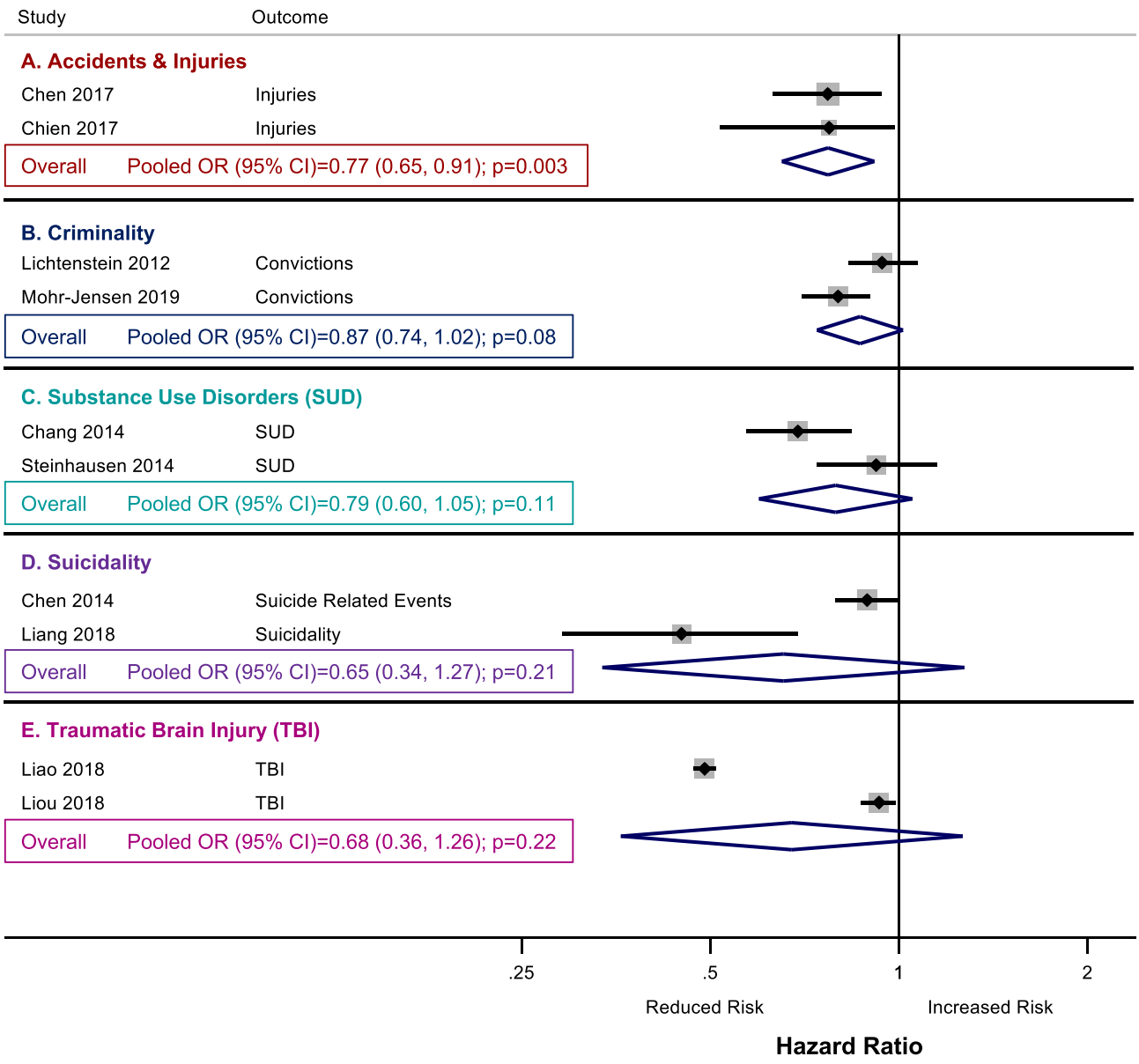

Fig. 3. Hazard ratio forest plot.

0.87; p = 0.001) (Fig. 2B). Heterogeneity was high and significant (I^2_5 = 91.6%, p < 0.001), suggesting that these studies were not estimating a common OR. Similarly, the two studies with available HR data for meta-analysis of accidents and injuries showed that the pooled HR was < 1 and statistically significant, indicating that mediated ADHD subjects were at **significantly reduced risk** for accidents and injuries compared to unmedicated ADHD (pooled HR = 0.77, 95% CI = 0.65, 0.91; p = 0.003) (Fig. 3A). Overall heterogeneity was low and not significant (I^2 = 0.0%, p = 0.98), suggesting that they were estimating a common OR.

Traumatic Brain Injury (TBI): Consistent with the qualitative review, the pooled HR for the two studies with available HR data for meta-analysis examining TBI showed that although this risk was reduced, it did not attain statistical significance (pooled HR = 0.68, 95% CI = 0.36, 1.26; p = 0.22) (Fig. 3E). Overall heterogeneity was high and significant (I^2 = 99.6%, p < 0.001), suggesting that they were not estimating a common HR.

3.3.3. Academic outcomes

In the two studies with available OR data for meta-analysis examining academic outcomes, the pooled OR was < 1 and statistically significant, indicating **significantly decreased odds** of poor academic outcomes in medicated ADHD subjects compared to unmedicated ADHD subjects (pooled OR = 0.80, 95% CI = 0.76, 0.84; p < 0.001) (Fig. 2A). Overall heterogeneity was low and not significant (I^2 = 0.0%, p = 1.00), suggesting that they were estimating a common OR. In contrast, in the three studies with available continuous data for meta-analysis of academic performance, the pooled SMD showed neutral effects of ADHD medication (Lu et al., 2017: SMD = −0.23, 95% CI = −0.31, −0.16; van der Schans et al., 2017: SMD = 0.23, 95% CI = 0.12, 0.33; Keilow et al., 2018: SMD = −0.05, 95% CI = −0.10, 0.00; pooled SMD = −0.02, 95% CI = −0.23, 0.19; p = 0.84). This is not surprising given the mix of positive, negative, and neutral findings in the qualitative analysis and as shown in the heterogeneity test that was high and significant (I^2_2 = 96.1%, p < 0.001). The Egger test showed no signs of publication bias (p = 0.75).

4. Discussion

Our systematic literature review of big database studies examining

the effects of medication on several important and morbid ADHD-associated functional outcomes documented major benefits of ADHD medication, particularly stimulant, treatment in mitigating the risks for mood disorders, suicidality, criminality, SUDs, accidents and injuries, TBI, automobile crashes, and academic impairments. Furthermore, in studies that examined within-individual effects of medications, protective effects of ADHD medications were observed during periods when subjects were compliant with their pharmacological treatment when compared with periods of non-adherence. The results of the meta-analysis were largely consistent with the qualitative findings providing together strong support for the protective effects of stimulants against the development of costly and highly morbid adverse functional outcomes in individuals with ADHD.

While some studies we reviewed included non-stimulant medications, the overwhelming majority of the pharmacological treatment for ADHD consisted of stimulants and none of the available studies reported findings on non-stimulants alone. This is not surprising considering the large literature documenting efficacy and tolerability of stimulants in the management of ADHD as well as their strong effect sizes (Bhat and Hechtman, 2018; Shier et al., 2013; Faraone, 2009).

The preponderance of evidence showing the reduction in the risks for depression and bipolar disorder associated with ADHD treatment (largely stimulants) is consistent with our previous results from longitudinal case-controlled studies of youth with and without ADHD of both sexes that also documented that treatment with stimulants in childhood was associated with protective effects against the subsequent development of mood disorders in adult years (Biederman et al., 2009). Further efforts to quantify the protective effects of treatment with stimulants using the number needed to treat (NNT) statistic showed NNTs in the single digits indicating very robust protective effects (Biederman et al., 2019).

The finding of an inverse association between stimulant treatment and rate of suicide related events (Liang et al., 2018) is highly noteworthy considering the strong associations between ADHD (Elkins, 2011) with both suicidality (Huang et al., 2018)) and mood disorders (Katzman et al., 2017) and the association between mood disorders with suicidality (Balazs and Kereszteny, 2017). Although it remains unclear whether this ADHD medication-associated protective effect against suicidality in ADHD is direct or indirect (through their protective effects in mitigating mood disorders), it remains a finding of high clinical and public health relevance.

The results showing a reduction in the risk of criminality and delinquent behaviors associated with stimulant treatment (Lichtenstein et al., 2012) in ADHD is consistent with our findings from longitudinal follow up studies documenting that early stimulant therapy reduces the subsequent risk for developing conduct disorder in both boys and girls with ADHD grown up (Biederman et al., 2019). Considering the poor prognosis associated with conduct disorder, antisocial disorders, and criminality, the protective effects of stimulants on these risks are likely to have large beneficial impact to individuals with ADHD.

The finding that stimulant treatment mitigates the risk for the subsequent development of SUDs in ADHD in the majority of the reviewed literature is also consistent with our longitudinal studies documenting similar effects in ADHD children grown up (Biederman et al., 2008, 2019) and with other studies (McCabe et al., 2016, 2017) showing similar findings. Given the evidence that ADHD is a significant risk for SUDs (Yule et al., 2017), that this serious risk may be mitigated by early treatment with stimulants is of great importance to clinicians and families.

The majority of the reviewed literature in both the qualitative review and meta-analysis showed medicated ADHD subjects were at decreased risk for accidents and injuries, particularly when they are adherent to treatment. Considering the high morbidity and costs associated with accidents and injuries, these findings have very practical clinical implications and may help in decreasing unnecessary medical expenditures by increasing efforts to support medication treatment for ADHD and adherence to it.

The protective effects of stimulants on car crashes derived from registry and big data studies are consistent with results from our randomized, placebo-controlled clinical trial of lisdexamfetamine on driving behavior and performance in a driving simulator (Biederman et al., 2019; Biederman et al., 2012; Biederman et al., 2012b). This study (Biederman et al., 2012) documented significant improvements on lisdexamfetamine over placebo in rates of collisions as well as driving errors and driving lapses. These findings emphasize the critical importance of stimulants on the prevention of MVCs and support of safe driving in individuals with ADHD.

The finding in most registry studies examining the effects of ADHD medications on educational outcomes showing improved academic outcomes is consistent with results from our longitudinal studies (Biederman et al., 2009, 2019). However, a few studies reported worsening educational outcomes or neutral effects and the meta-analysis showed an overall neutral effect of treatment. These overall mixed findings on the effects of medications for ADHD on educational outcomes are not surprising considering that ADHD symptoms represent only one of many factors contributing to academic difficulties in individuals with ADHD including cognitive abilities, executive dysfunction, learning disabilities and social class (Erikson, 2016; Miller and Hinshaw, 2010; Rohde and Thompson, 2007; Hampton and Mason, 2003), factors that may not be as responsive to medications for ADHD as those of ADHD symptoms. Nevertheless, considering the critical importance of academic success for employment opportunities in our society, even if academic improvement were to be limited to ADHD patients without other cognitive comorbidities, it would still have a large beneficial societal effect.

As noted in many registry studies, the aforementioned protective effects of ADHD medication were most prominent when individuals were compliant with their medication treatment. Chang et al. (2017) reported that rates of MVCs were lower during periods of ADHD medication compliance, while another registry study noted a 20% decreased risk for depression during periods of medication adherence (Chang et al., 2016). Lu et al. (2017) reported that patient test scores were significantly higher during medicated versus non-medicated periods. Likewise, a registry study from Taiwan noted a 59% suicide attempt risk reduction among ADHD youths prescribed methylphenidate for 180 days and a 72% risk reduction in those prescribed for more than 180 days (Liang et al., 2018). These findings underscore the importance of compliance enhancement interventions as part of any ADHD management.

While highly noteworthy, the protective effects associated with ADHD medications on a wide range of ADHD-associated adverse functional outcomes do not necessarily imply that pharmacological treatments for ADHD are the only factor influencing functional outcomes. Future research can benefit from more widespread examination of additional moderators of functional outcomes in individuals with ADHD.

Moreover, medication treatments for ADHD are associated with a wide range of adverse effects (Swanson et al., 2017), highlighting the critical importance of careful examination of risks versus benefits when prescribing medications to patients ADHD of any age. However, this essential calculus requires knowledge of the benefits of medication treatment and whether these benefits are expected to exceed those of the potential risks.

Our results must be considered in light of some methodological limitations. Data in registry studies are limited to coded diagnoses and treatments (Liang et al., 2018; Chang et al., 2014) and do not include all affected subjects. Additionally, most of the available registry studies used data from international samples with different assessment and treatment traditions for ADHD, which may not generalize to the United States. Because findings from registry studies are naturalistic, causality cannot be inferred and the effects of medication treatment on different outcomes are vulnerable to potential confounding (Mendes et al.,

2017), although the within patient analyses are not affected by such confounding. Moreover, although the analytic approaches used in registry studies do not provide an in-depth view of treatment effects, it adds to the general understanding of the effectiveness of medication in the ADHD population that is complementary to other methods of analysis derived from treatment studies.

Despite these considerations, results from this systematic review and meta-analysis using data derived from registries and large datasets suggest that medication treatments for ADHD and stimulants in particular, are associated with decreases in the risks for a wide range of highly morbid and costly ADHD-associated functional outcomes supporting efforts aimed at early diagnosis and treatment of individuals with ADHD. Considering that the documented protective effects of medication for ADHD on functional outcomes were particularly marked when treatment was adhered to, these findings also support the critical need to develop innovative methods to improve adherence to medications in ADHD.

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CRediT authorship contribution statement

Heidi Boland: Conceptualization, Methodology, Investigation, Data curation. **Maura DiSalvo:** Methodology, Data curation, Formal analysis. **Ronna Fried:** Conceptualization, Supervision. **K. Yvonne Woodworth:** Supervision. **Timothy Wilens:** Data curation, Resources. **Stephen V. Faraone:** Methodology, Supervision. **Joseph Biederman:** Conceptualization, Methodology, Investigation, Supervision, Resources.

Declaration of competing interest

All authors report no potential conflicts of interest to disclose above the ones reported in the financial disclosures.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2020.01.006.

References

Balazs, J., Kereszteny, A., 2017. Attention-deficit/hyperactivity disorder and suicide: a systematic review. World J. Psychiatr. 7 (1), 44–59.
Barbaresi, W.J., Katusic, S.K., Colligan, R.C., Weaver, A.L., Jacobsen, S.J., 2007. Modifiers of long-term school outcomes for children with attention-deficit/hyperactivity disorder: does treatment with stimulant medication make a difference? Results from a population-based study. J. Dev. Behav. Pediatr. 28 (4), 274–287.
Barkley, R.A., Anastopoulos, A.D., Guevremont, D.C., Fletcher, K.E., 1991. Adolescents with ADHD: patterns of behavioral adjustment, academic functioning, and treatment utilization. J. Am. Acad. Child Adolesc. Psychiatry 30 (5), 752–761.
Bhat, V., Hechtman, L., 2018. Considerations in selecting pharmacological treatments for attention deficit hyperactivity disorder. Pharm. J. 8 (2).
Biederman, J., DiSalvo, M., Fried, R., Woodworth, K.Y., Biederman, I., Faraone, S.V., 2019. Quantifying the protective effects of stimulants on functional outcomes in ADHD: a focus on number needed to treat (NNT) statistic and sex effects. J. Adolesc. Health 65 (6), 784–789.
Biederman, J., Fried, R., Hammerness, P., et al., 2012. The effects of lisdexamfetamine dimesylate on the driving performance of young adults with ADHD: a randomized, double-blind, placebo-controlled study using a validated driving simulator paradigm. J. Psychiatr. Res. 46 (4), 484–491.
Biederman, J., Fried, R., Hammerness, P., et al., 2012b. The effects of lisdexamfetamine dimesylate on driving behaviors in young adults with ADHD assessed with the Manchester driving behavior questionnaire. J. Adolesc. Health 51 (6), 601–607.
Biederman, J., Monuteaux, M.C., Spencer, T., Wilens, T.E., Faraone, S.V., 2009. Do stimulants protect against psychiatric disorders in youth with ADHD? A 10-year follow-up study. Pediatrics 124 (1), 71–78.
Biederman, J., Monuteaux, M.C., Spencer, T., Wilens, T.E., Macpherson, H.A., Faraone, S.V., 2008. Stimulant therapy and risk for subsequent substance use disorders in male adults with ADHD: a naturalistic controlled 10-year follow-up study. Am. J. Psychiatr. 165 (5), 597–603.
Biederman, J., Monuteaux, M.C., Mick, E., et al., 2006. Young adult outcome of attention deficit hyperactivity disorder: a controlled 10-year follow-up study. Psychol. Med. 36 (2), 167–179.
Brandl, C., Brucklmayer, C., Gunther, F., et al., 2019. Retinal layer thicknesses in early age-related macular degeneration: results from the German AugUR study. *Invest. Ophthalmol. Vis. Sci.* 60 (5), 1581–1594.
Chang, Z., Ghirardi, L., Quinn, P.D., et al., 2019. Risks and benefits of attention-deficit/hyperactivity disorder medication on behavioral and neuropsychiatric outcomes: a qualitative review of pharmacoepidemiology studies using linked prescription databases. Biol. Psychiatr S0006-3223(19)31274-0. doi: 10.1016.
Chang, Z., Quinn, P.D., Hur, K., et al., 2017. Association between medication use for attention-deficit/hyperactivity disorder and risk of motor vehicle crashes. JAMA Psychiatry 74 (6), 597–603.
Chang, Z., D'Onofrio, B.M., Quinn, P.D., Lichtenstein, P., Larsson, H., 2016. Medication for attention-deficit/hyperactivity disorder and risk for depression: a nationwide longitudinal cohort study. Biol. Psychiatr. 80 (12), 916–922.
Chang, Z., Lichtenstein, P., D'Onofrio, B.M., Sjolander, A., Larsson, H., 2014b. Serious transport accidents in adults with attention-deficit/hyperactivity disorder and the effect of medication: a population-based study. JAMA Psychiatry 71 (3), 319–325.
Chang, Z., Lichtenstein, P., Halldner, L., et al., 2014. Stimulant ADHD medication and risk for substance abuse. JCPP (J. Child Psychol. Psychiatry) 55 (8), 878–885.
Chen, V.C., Yang, Y.H., Liao, Y.T., et al., 2017. The association between methylphenidate treatment and the risk for fracture among young ADHD patients: a nationwide population-based study in Taiwan. PloS One 12 (3), e0173762.
Chen, Q., Sjolander, A., Runeson, B., D'Onofrio, B.M., Lichtenstein, P., Larsson, H., 2014. Drug treatment for attention-deficit/hyperactivity disorder and suicidal behaviour: register based study. BMJ 348, g3769.
Chien, W.C., Chung, C.H., Lin, F.H., et al., 2017. The risk of injury in adults with attention-deficit hyperactivity disorder: a nationwide, matched-cohort, population-based study in Taiwan. Res. Dev. Disabil. 65, 57–73.
Claster, S., Termuhlen, A., Schrager, S.M., Wolfson, J.A., Iverson, E., 2013. Pitfalls of using administrative data sets to describe clinical outcomes in sickle cell disease. Pediatr. Blood Canc. 60 (12), 1936–1939.
Currie, J., Stabile, M., Jones, L., 2014. Do stimulant medications improve educational and behavioral outcomes for children with ADHD? J. Health Econ. 37, 58–69.
Dalsgaard, S., Leckman, J.F., Mortensen, P.B., Nielsen, H.S., Simonsen, M., 2015. Effect of drugs on the risk of injuries in children with attention deficit hyperactivity disorder: a prospective cohort study. Lancet Psychiatry 2 (8), 702–709.
Dalsgaard, S., Nielsen, H.S., Simonsen, M., 2014. Consequences of ADHD medication use for children's outcomes. J. Health Econ. 37, 137–151.
DerSimonian, R., Laird, N., 1986. Meta-analysis in clinical trials. Contr. Clin. Trials 7, 177–188.
Egger, M., Davey Smith, G., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. BMJ 315 (7109), 629–634.
Elkins, I.J., 2011. Young children with ADHD are at increased risk of depression and suicidal behaviour in adolescence. Evid. Base Ment. Health 14 (1), 15.
Erikson, R., 2016. Is it enough to be bright? Parental background, cognitive ability and educational attainment. Eur. Soc. 18 (2), 117–135.
Faraone, S.V., Glatt, S.J., 2010. A comparison of the efficacy of medications for adult attention-deficit/hyperactivity disorder using meta-analysis of effect sizes. J. Clin. Psychiatr. 71 (6), 754–763.
Faraone, S.V., 2009. Using meta-analysis to compare the efficacy of medications for attention-deficit/hyperactivity disorder in youths. P T 34 (12), 678–694.
Faraone, S.V., Biederman, J., Spencer, T.J., Aleardi, M., 2006. Comparing the efficacy of medications for ADHD using meta-analysis. MedGenMed 8 (4), 4.
Faraone, S.V., Sergeant, J., Gillberg, C., Biederman, J., 2003. The worldwide prevalence of ADHD: is it an American condition? World Psychiatr. 2 (2), 104–113.
Hampton, N.Z., Mason, E., 2003. Learning disabilities, gender, sources of efficacy, self-efficacy beliefs, and academic achievement in high school students. J. Sch. Psychol. 41 (2), 101–112.
Higgins, J.P., Thompson, S.G., Deeks, J.J., Altman, D.G., 2003. Measuring inconsistency in meta-analyses. BMJ 327 (7414), 557–560.
Huang, K.L., Wei, H.T., Hsu, J.W., et al., 2018. Risk of suicide attempts in adolescents and young adults with attention-deficit/hyperactivity disorder: a nationwide longitudinal study. Br. J. Psychiatry 212 (4), 234–238.
Jacob, L., Kostev, K., 2017. Impact of attention deficit hyperactivity disorder therapy on fracture risk in children treated in German pediatric practices. Osteoporos. Int. 28 (4), 1265–1269.
Jangmo, A., Stalhandske, A., Chang, Z., et al., 2019. Attention-deficit/hyperactivity disorder, school performance, and effect of medication. J. Am. Acad. Child Adolesc. Psychiatry 58 (4), 423–432.
Jerrell, J.M., McIntyre, R.S., Park, Y.M., 2015. Risk factors for incident major depressive disorder in children and adolescents with attention-deficit/hyperactivity disorder. Eur. Child Adolesc. Psychiatr. 24 (1), 65–73.
Katzman, M.A., Bilkey, T.S., Chokka, P.R., Fallu, A., Klassen, L.J., 2017. Adult ADHD and comorbid disorders: clinical implications of a dimensional approach. BMC Psychiatr. 17 (1), 302.
Keilow, M., Holm, A., Fallesen, P., 2018. Medical treatment of Attention Deficit/Hyperactivity Disorder (ADHD) and children's academic performance. PloS One 13 (11), e0207905.
Lange, H., Buse, J., Bender, S., Siegert, J., Knopf, H., Roessner, V., 2016. Accident proneness in children and adolescents affected by ADHD and the impact of medication. J. Atten. Disord. 20 (6), 501–509.
Lee, M.J., Yang, K.C., Shyu, Y.C., et al., 2016. Attention-deficit hyperactivity disorder, its treatment with medication and the probability of developing a depressive disorder: a

nationwide population-based study in Taiwan. J. Affect. Disord. 189, 110–117.
Leibson, C.L., Barbaresi, W.J., Ransom, J., et al., 2006. Emergency department use and costs for youth with attention-deficit/hyperactivity disorder: associations with stimulant treatment. Ambul. Pediatr. 6 (1), 45–53.
Liao, Y.T., Yang, Y.H., Kuo, T.Y., et al., 2018. Dosage of methylphenidate and traumatic brain injury in ADHD: a population-based study in Taiwan. Eur. Child Adolesc. Psychiatr. 27 (3), 279–288.
Liang, S.H., Yang, Y.H., Kuo, T.Y., et al., 2018. Suicide risk reduction in youths with attention-deficit/hyperactivity disorder prescribed methylphenidate: a Taiwan nationwide population-based cohort study. Res. Dev. Disabil. 72, 96–105.
Lichtenstein, P., Halldner, L., Zetterqvist, J., et al., 2012. Medication for attention deficit-hyperactivity disorder and criminality. N. Engl. J. Med. 367 (21), 2006–2014.
Liou, Y.J., Wei, H.T., Chen, M.H., et al., 2018. Risk of traumatic brain injury among children, adolescents, and young adults with attention-deficit hyperactivity disorder in taiwan. J. Adolesc. Health 63 (2), 233–238.
Lu, Y., Sjölander, A., Cederlöf, M., et al., 2017. Association between medication use and performance on higher education entrance tests in individuals with attention-deficit/hyperactivity disorder. JAMA Psychiatry 74 (8), 815–822.
Man, K.K.C., Coghill, D., Chan, E.W., et al., 2017. Association of risk of suicide attempts with methylphenidate treatment. JAMA Psychiatry 74 (10), 1048–1055.
Man, K.K., Chan, E.W., Coghill, D., et al., 2015. Methylphenidate and the risk of trauma. Pediatrics 135 (1), 40–48.
Marcus, S.C., Durkin, M., 2011. Stimulant adherence and academic performance in urban youth with attention-deficit/hyperactivity disorder. J. Am. Acad. Child Adolesc. Psychiatry 50 (5), 480–489.
Marcus, S.C., Wan, G.J., Zhang, H.F., Olfson, M., 2008. Injury among stimulant-treated youth with ADHD. J. Atten. Disord. 12 (1), 64–69.
McCabe, S.E., Veliz, P., Wilens, T.E., Schulenberg, J.E., 2017. Adolescents' prescription stimulant use and adult functional outcomes: a national prospective study. J. Am. Acad. Child Adolesc. Psychiatry 56 (3), 226–233 e224.
McCabe, S.E., Dickinson, K., West, B.T., Wilens, T.E., 2016. Age of onset, duration, and type of medication therapy for attention-deficit/hyperactivity disorder and substance use during adolescence: a multi-cohort national study. J. Am. Acad. Child Adolesc. Psychiatry 55 (6), 479–486.
Mendes, D., Alves, C., Batel-Marques, F., 2017. Number needed to treat (NNT) in clinical literature: an appraisal. BMC Med. 15 (1), 112.
Merrill, R.M., Thygerson, S.M., Palmer, C.A., 2016. Risk of injury according to attention deficit hyperactivity disorder, comorbid mental illness, and medication therapy. Pharmacopsychiatry 49 (2), 45–50.
Merrill, R.M., Lyon, J.L., Baker, R.K., Gren, L.H., 2009. Attention deficit hyperactivity disorder and increased risk of injury. Adv. Med. Sci. 54 (1), 20–26.
Mikolajczyk, R., Horn, J., Schmedt, N., Langner, I., Lindemann, C., Garbe, E., 2015. Injury prevention by medication among children with attention-deficit/hyperactivity disorder: a case-only study. JAMA Pediatr 169 (4), 391–395.
Miller, M., Hinshaw, S.P., 2010. Does childhood executive function predict adolescent functional outcomes in girls with ADHD? J. Abnorm. Child Psychol. 38 (3), 315–326.
Mohr-Jensen, C., Muller Bisgaard, C., Boldsen, S.K., Steinhausen, H.C., 2019. Attention-deficit/hyperactivity disorder in childhood and adolescence and the risk of crime in young adulthood in a Danish nationwide study. J. Am. Acad. Child Adolesc. Psychiatry 58 (4), 443–452.
Polanczyk, G.V., Willcutt, E.G., Salum, G.A., Kieling, C., Rohde, L.A., 2014. ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis. Int. J. Epidemiol. 43 (2), 434–442.
Quinn, P.D., Chang, Z., Hur, K., et al., 2017. ADHD medication and substance-related problems. Am. J. Psychiatr. 174 (9), 877–885.
Raman, S.R., Marshall, S.W., Haynes, K., Gaynes, B.N., Naftel, A.J., Sturmer, T., 2013. Stimulant treatment and injury among children with attention deficit hyperactivity disorder: an application of the self-controlled case series study design. Inj. Prev. 19 (3), 164–170.
Rice, H.E., Englum, B.R., Gulack, B.C., et al., 2015. Use of patient registries and administrative datasets for the study of pediatric cancer. Pediatr. Blood Canc. 62 (9), 1495–1500.
Rohde, T.E., Thompson, L.A., 2007. Predicting academic achievement with cognitive ability. Intelligence 35 (1), 83–92.
Shier, A.C., Reichenbacher, T., Ghuman, H.S., Ghuman, J.K., 2013. Pharmacological treatment of attention deficit hyperactivity disorder in children and adolescents: clinical strategies. J. Cent. Nerv. Syst. Dis. 5, 1–17.
Stata Statistical Software, 2017. Release, vol. 15 StataCorp LLC.
Stein, M.A., Waldman, I., Newcorn, J., Bishop, J., Kittles, R., Cook Jr., E.H., 2014. Dopamine transporter genotype and stimulant dose-response in youth with attention-deficit/hyperactivity disorder. J. Child Adolesc. Psychopharmacol. 24 (5), 238–244.
Steinhausen, H.C., Bisgaard, C., 2014. Substance use disorders in association with attention-deficit/hyperactivity disorder, co-morbid mental disorders, and medication in a nationwide sample. Eur. Neuropsychopharmacol 24 (2), 232–241.
Sundquist, J., Ohlsson, H., Sundquist, K., Kendler, K.S., 2015. Attention-deficit/hyperactivity disorder and risk for drug use disorder: a population-based follow-up and corelative study. Psychol. Med. 45 (5), 977–983.
Swanson, J.M., Arnold, L.E., Molina, B.S.G., et al., 2017. Young adult outcomes in the follow-up of the multimodal treatment study of attention-deficit/hyperactivity disorder: symptom persistence, source discrepancy, and height suppression. JCPP (J. Child Psychol. Psychiatry) 58 (6), 663–678.
Swensen, A., Birnbaum, H.G., Ben Hamadi, R., Greenberg, P., Cremieux, P.Y., Secnik, K., 2004. Incidence and costs of accidents among attention-deficit/hyperactivity disorder patients. J. Adolesc. Health 35 (4), 346 e341–349.
Thompson, A.L., Molina, B.S., Pelham Jr., W., Gnagy, E.M., 2007. Risky driving in adolescents and young adults with childhood ADHD. J. Pediatr. Psychol. 32 (7), 745–759.
van den Ban, E., Souverein, P., Meijer, W., et al., 2014. Association between ADHD drug use and injuries among children and adolescents. Eur. Child Adolesc. Psychiatr. 23 (2), 95–102.
van der Schans, J., Cicek, R., Vardar, S., et al., 2017. Methylphenidate use and school performance among primary school children: a descriptive study. BMC Psychiatr. 17 (1), 116.
Wang, L.J., Shyu, Y.C., Yuan, S.S., et al., 2016. Attention-deficit hyperactivity disorder, its pharmacotherapy, and the risk of developing bipolar disorder: a nationwide population-based study in Taiwan. J. Psychiatr. Res. 72, 6–14.
Yule, A.M., Martelon, M., Faraone, S.V., Carrellas, N., Wilens, T.E., Biederman, J., 2017. Examining the association between attention deficit hyperactivity disorder and substance use disorders: a familial risk analysis. J. Psychiatr. Res. 85, 49–55.
Zoega, H., Rothman, K.J., Huybrechts, K.F., et al., 2012. A population-based study of stimulant drug treatment of ADHD and academic progress in children. Pediatrics 130 (1), e53–62.

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Dr. Timothy Wilens within the past two years has received research support from NIH; and has been a consultant to Ironshore, KemPharm Otsuka, Minor/Major League Baseball, and the National Football League (ERM Associates). He has a co-licensed rating scale with Ironshore and MHJ. He provides clinical care at MGH, BayCove Human Services and Gavin Foundation. He receives royalties for a co-edited book: *Straight Talk About Psychiatric Medication in Kids* (Guilford Press).

In the past year, **Dr. Stephen V. Faraone** received income, potential income, travel expenses continuing education support and/or research support from Lundbeck, Rhodes, Arbor, KenPharm, Ironshore, Shire, Akili Interactive Labs, CogCubed, Alcobra, VAYA, Sunovion, Genomind and Neurolifesciences. With his institution, he has US patent US20130217707 A1 for the use of sodium-hydrogen exchange inhibitors in the treatment of ADHD. In previous years, he received support from: Shire, Neurovance, Alcobra, Otsuka, McNeil, Janssen, Novartis, Pfizer and Eli Lilly. Dr. Faraone receives royalties from books published by Guilford Press: *Straight Talk about Your Child's Mental Health*, Oxford University Press: *Schizophrenia: The Facts* and Elsevier: ADHD: *Non-Pharmacologic Interventions.* He is principal investigator of www.adhdinadults.com.

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