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ORIGINAL RESEARCH ARTICLE

Psychostimulants/Atomoxetine and Serious Cardiovascular Events in Children with ADHD or Autism Spectrum Disorder

Richard Houghton[1,2,3] · **Frank de Vries**[2,3] · **Georg Loss**[1]

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Abstract

Background Psychostimulants and atomoxetine have been shown to increase blood pressure, heart rate, and QT interval in children and adolescents; however, based on current literature, it is unclear if these "attention-deficit/hyperactivity disorder (ADHD) medications" are also associated with serious cardiovascular (SCV) events. We addressed this question in commonly exposed groups of children and adolescents with either ADHD or autism spectrum disorder (ASD).

Methods Using commercial (years 2000–2016) and Medicaid (years 2012–2016) administrative claims data from the United States (US), we conducted two case–control studies, nested within respective cohorts of ADHD and ASD children aged 3–18 years. We defined cases by a composite outcome of stroke, myocardial infarction, or serious cardiac arrhythmia. For each case, we matched ten controls on age, sex, and insurance type. We conducted conditional logistic regression models to test associations between SCV outcomes and a primary exposure definition of current ADHD medication use. Additionally, we controlled for resource use, cardiovascular and psychiatric comorbidities, and use of medications in a variety of sensitivity analyses.

Results We identified 2,240,774 children for the ADHD cohort and 326,221 children for the ASD cohort. For ADHD, 33.9% of cases (63 of 186) versus 32.2% of controls (598 of 1860) were exposed, which yielded an odds ratio (OR) and 95% confidence interval (CI) of 1.08 (0.78–1.49). For ASD, 12.5% of cases (6 of 48) versus 22.1% of controls (106 of 480) were exposed [OR 0.49 (0.20–1.20)]. Covariate-adjusted results and results for individual outcomes and other exposure definitions were consistent with no increased risk of SCV events.

Conclusion Using large US claims data, we found no evidence of increased SCV risk in children and adolescents with ADHD or ASD exposed to ADHD medications.

1 Introduction

Prescription stimulants such as methylphenidate and non-stimulants such as atomoxetine are labeled for the treatment of attention-deficit/hyperactivity disorder (ADHD) from age

Key Points

Attention-deficit/hyperactivity disorder (ADHD) medications increase blood pressure, heart rate, and QT interval. It is unclear if they increase serious cardiovascular event rates.

Current literature is based mainly on pre-2006 data and small samples, and has not considered subgroups of children with different medical diagnoses.

Using data from 2000–2016, for US children aged 3–18 years, we found no evidence of increased serious cardiovascular risk in those exposed to ADHD medications.

Findings were consistent for children with either ADHD or autism spectrum disorder.

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✉ Richard Houghton
richard.houghton@roche.com

[1] Personalized Health Care Data Science, Real World Data, F. Hoffmann-La Roche Ltd., Grenzacherstrasse. 124, 4070 Basel, Switzerland

[2] Department of Clinical Pharmacy and Toxicology, Maastricht University Medical Center+, Maastricht, The Netherlands

[3] Cardiovascular Research Institute Maastricht, Maastricht University Medical Center+, Maastricht, The Netherlands

approximately 6 and above years, and are also commonly used in medical practice for the management of non-core symptoms of autism spectrum disorder (ASD) [1]. In the USA and in Europe, there has been a trend toward higher prescription rates of these drugs (hereon referred to as "ADHD medications") for both children and adults over the past 2 decades; nevertheless, use remains most common in middle childhood, and not all ADHD diagnosed individuals are prescribed ADHD medications [2–7].

Despite evidence for short-term effectiveness [8], both placebo-controlled and open-label extension trials have repeatedly shown ADHD medication-induced increases in mean blood pressure, heart rate, and QT interval in children, adolescents, and adults [9–11]. Although these increases were described as relatively minor, their existence has raised concern to what degree ADHD medication could influence the likelihood of serious cardiovascular (SCV) events such as stroke, myocardial infarction (MI), and cardiac arrhythmia, especially in people with underlying heart problems [11]. Furthermore, ADHD medications have been linked to sudden cardiac death in case reports and currently carry a US Food and Drug Administration (FDA) class-specific warning regarding these potential increased risks [12–14].

A limited number of observational studies have generally found no increased risk of SCV events with ADHD medication use, but results have not been consistent [14]. The majority of such studies were conducted on data from over a decade ago, and due to the low absolute numbers of SCV events, the ability to rule out such an association has been limited [15, 16]. To the best of our knowledge, no studies have specifically studied this question in the growing subgroup of exposed children with ASD, who frequently use other psychotropic co-medications such as antidepressants or antipsychotics [17], which may further increase heart rate, QT interval, and consequently the risk of SCV events.

Given the uncertainty described above, which surrounds the relationship between SCV events and ADHD medications, plus the increasing number of children and adolescents with ADHD and ASD that are exposed, our study aimed to quantify this risk, in large cohorts, representative of these populations.

2 Methods

2.1 Study Design and Data

This was a retrospective, nested case–control study using the Truven Health MarketScan® administrative insurance claims database. At the time of analysis, the full database contained billed records of care on 184 million commercially insured and 19 million Medicaid insured individuals between calendar years 2000 and 2016 (with at least some coverage from each US state) and 2012 and 2016 (ten to 12 states), respectively.

2.2 Cohort Selection and Follow-Up

From within the whole MarketScan database, we defined two main cohorts of interest: (1) individuals with ADHD (but not ASD) and (2) individuals with ASD (with or without ADHD). Eligibility requirements were two or more claims for ASD or ADHD respectively, age between 3 and 18 years, and individuals were excluded from the ASD cohort if they ever had any claim for Rett's syndrome, to avoid possibly misdiagnosed cases [17–19]. To avoid overlap between the two cohorts, individuals with ASD claims were removed from the ADHD cohort, but not vice versa. This decision was made because previous studies have shown over one in three autistic people have an ADHD comorbidity versus a lower proportion (around one in eight) of the ADHD population with comorbid ASD [20, 21]. We also excluded individuals with any previous SCV event of interest prior to diagnosis and the start of follow-up. Individuals in both cohorts were followed from first diagnosis claim (minimum age of 3 years) until first SCV event, the end of database enrollment, or the end of the calendar year marking their 18th birthday, whichever occurred first.

2.3 Outcomes and Case/Control Selection

From within each of the two cohorts, we conducted a nested case–control study. Cases were identified by the first inpatient primary diagnosis claim for any of the three secondary SCV outcomes, namely, (1) stroke, (2) MI, and (3) serious cardiac arrhythmia (SCA). SCA included cardiac arrest, complete atrioventricular block, and ventricular tachycardia, ventricular fibrillations or flutter. Definitions were based upon previously published studies and systematic reviews, which show high positive predictive values (PPV > 85%) [15, 22–27]. For each case, we defined the index date as the date of the composite (first) event.

For each case, ten controls were matched, randomly and without replacement, using the risk set sampling technique [28]. Matching was based on age, sex, insurance type, and calendar time, so controls were assigned the same index date as their case. Finally, both cases and controls were required to have at least 30 days' continuous enrollment in the database, directly prior to the index date. This was needed in order to establish baseline risk factors and to observe exposures.

2.4 Exposure Definitions

Based on dispense date and days' supply, the primary exposure variable was defined as currently versus not currently

exposed to any ADHD medication on the index date. As per previous studies [15, 23], current use was deemed to be the most etiologically relevant exposure, as the half-life of stimulants/atomoxetine is short (hours opposed to days).

2.5 Statistical Analysis

After matching, we used conditional logistic regression to perform the crude (matched) analysis. Beyond the crude analysis, a causal diagram was used to identify other covariates to be included in a minimal adjustment set (see Figure S1 in the electronic supplementary material and Greenland et al. [29] and Textor et al. [30] for diagram theory). We refer to this set as adjustment set 1, which included the concepts of underlying cardiovascular risk and healthcare resource use (HCRU). We defined underlying cardiovascular risk by taking prior record of the following comorbidities into account: congenital circulatory system disorders, congestive heart failure (CHF), essential hypertension, disorders of lipid metabolism, peripheral artery disease, asthma, chronic obstructive pulmonary disease (COPD), diabetes, and obesity [15, 23]. We approximated HCRU via presence/absence of a visit to the emergency department, cardiology specialist, behavioral therapist, inpatient visit for any reason, and the total number of medical claims pro-rated to the past year. When deriving these variables, we ignored data during the month prior to index, in order to avoid over-adjustment bias by using data potentially collected after exposure. The total number of medical claims in the past year was pro-rated for individuals with less than 12 months prior follow-up. Covariate adjustment was made by selecting a weighted subset of the controls that had characteristics most similar to the cases. To achieve optimal covariate balance between cases and controls, weights were assigned by a generalized boosted model algorithm [31], before unmatched logistic regression was applied to test the exposure-outcome association (also see supplementary methods information in the electronic supplementary material).

2.6 Sensitivity Analyses

We conducted two sets of sensitivity analyses and a post-hoc subgroup analysis. In the first sensitivity analysis, we adjusted exposure definitions to within 90 days and "ever use" prior to index. In the second sensitivity analysis, we additionally controlled for an expanded set of other covariates. Adjustment set 2 included all covariates from adjustment set 1 as well as severe medical comorbidities, common psychiatric comorbidities, psychotropic medications, and beta-blocker use. Psychotropic and beta-blocker medication use were based on prescriptions in the 6 months prior to index. These covariates were selected a priori using potential confounders and clinical assumptions from the literature (but not using causal diagrams like adjustment set 1). Additionally, we adjusted for both adjustment sets via adjusted conditional logistic regression to test if model specification had an impact on findings.

Lastly, in a post-hoc subgroup analysis, we excluded cases and controls with congenital circulatory system disorders, CHF, or any cardiology specialty visit in the past year (and their matched pairs). We also repeated crude and weighted analysis by individual endpoints (stroke, MI, and SCA). Throughout, results were deemed statistically significant, or not, based upon 95% confidence intervals (CIs).

3 Results

A total of 2,240,774 children and adolescents were identified for the ADHD cohort and 326,221 were identified for the ASD cohort (see Table 1). The ADHD cohort had 1,531,687 males (68.4%), and the mean [standard deviation (SD)] age at first ADHD claim was 11.1 (3.7) years. This cohort had 186 composite SCV events over a mean (SD) 2.66 (2.11) years of at-risk time, resulting in an incidence rate (95% CI) of 3.12 (2.70–3.60) per 100,000 person years. The ASD cohort had 262,434 males (80.4%), and the mean (SD) age at first ASD claim was 9.3 (4.4) years. This cohort had 48 composite SCV events over a mean (SD) 2.62 (2.14) years of at-risk time, resulting in an incidence rate (95% CI) of 5.62 (4.23–7.45) per 100,000 person years. The most common specific event in both cohorts was stroke, and MI was the rarest. See Table S1a and S1b in the electronic supplementary material for full listings of events.

Characteristics of cases and controls, selected from the ADHD and ASD cohorts based on the composite SCV endpoint, are presented in Table 2. We found ten controls for each case as planned regarding the matching characteristics (age, sex, and insurance). Cases in both cohorts more often had underlying cardiovascular comorbidities and higher amounts of inpatient, emergency, and cardiology resource use than controls. ADHD cases were on average slightly older at time of SCV event compared to ASD cases (mean 13.9 vs 12.5 years) and received fewer psychotropic drugs. By design, none of the ADHD cases had comorbid ASD, but nine (18%) of the ASD cases had comorbid ADHD.

Table 3 shows that for both ADHD and ASD, there was no increased risk of SCV events associated with ADHD medication use. For ADHD, the proportion of cases currently exposed was 33.9% (63 of 186 cases) versus 32.2% of controls (598 of 1860 controls). This translated to no association of ADHD medication use with SCV events in the crude analysis [odds ratio (OR) (95% CI) 1.08 (0.78–1.49)]. For ASD, the proportion of cases currently exposed was 12.5% (6 of 48 cases) versus 22.1% of controls (106 of 480 controls). This also translated to no crude association of

Table 1 Attrition table and selection of cohorts

	ADHD	ASD
At least 1 claim for ASD/ADHD at age at least 3 years	5,978,601	612,856
At least 2 claims for ASD/ADHD at age at least 3 years	4,428,572	452,851
Exclude individuals with claim for ASD (from ADHD cohort) and Rett's syndrome (from ASD cohort)	4,211,082	451,832
Only include individuals enrolled for some time between age 3 and 18 (inclusive) and first claim for ASD/ADHD at age before 19 years	2,240,854	326,246
Exclude individuals with event of interest (stroke, myocardial infarction, serious cardiac arrhythmia) prior to first ASD/ADHD diagnosis claim	2,240,774	326,221
Total SCV events	186	48
Stroke	102	25
Myocardial infarction	10	1
Serious cardiac arrhythmia	75	22

Composite event was the main event of interest, defined as the first of individual events

ADHD attention-deficit/hyperactivity disorder, *ASD* autism spectrum disorder, *SCV events* serious cardiovascular events

ADHD medication use with SCV events in the ASD cohort [OR (95% CI) 0.49 (0.20–1.20)].

Furthermore, based on the current exposure definition, and across both ADHD and ASD cohorts, all results statistically adjusted for covariates were consistent with these findings (see Table 3). For weighted cohort characteristics, see Tables S2a and S2b in the electronic supplementary material. After we completely excluded individuals with underlying congenital circulatory system disorders, CHF, or recent cardiology visits, ORs were closer to a null association than in crude (and most adjusted) analyses.

Point estimates for associations between the outcomes and exposures were also stable (and without trend) regardless of the exposure definition used. Due to small sample sizes, some of the associated CIs were wide, especially in the ASD cohort. There were no obvious differences in specific drugs or dosages used between cases and controls nor ASD and ADHD (see Table S3 in the electronic supplementary material).

Finally, Table 4 demonstrates that crude and adjusted results based upon the individual outcomes (stroke, MI, and SCA) were not materially different than those for the composite endpoint.

4 Discussion

Results of this study indicate that there is no association between the use of ADHD medications and increased risk of SCV events in children and adolescents with ADHD and ASD. Strengths of our study lie in the large number of individuals observed (234 events in total vs 81 in the largest previous study with similar outcomes) [15], representivity across all states of the USA, and the objectivity of administrative claims data (e.g., no recall bias). Moreover, our results were stable across a series of sensitivity analyses, which adjusted for different covariates (demographics, resource use, comorbidities, and concomitant treatment use) and used different statistical models. There was no increased risk found for the composite endpoint, regardless of the timing of exposure, nor for any individual SCV events. Overall, in both cohorts, SCV events were extremely rare.

These findings are largely in line with former research. Indeed, seven of the nine previous studies included in a recent literature review also found no associations between stimulants and pediatric cardiovascular risk [14]. This included three studies perhaps most comparable to ours, also based on US claims data and with similar outcome definitions [15, 16, 32]. Another study in claims data found no associations between current, former, or non-use of stimulants and cardiovascular-related hospitalizations and emergency room visits [33]. The two studies with findings contrary to ours had different outcome definitions. Gould et al. [34] took an unconventional approach in comparing cases of any unexpected deaths to victims of road traffic accidents, while Dalsgaard et al. [35] analyzed a cohort of children from Danish national data, but used a much wider event definition that included any hospital contact for any cardiovascular reason. A study by Shin et al. [36] found an increased association between methylphenidate use and arrhythmia among children and adolescents in Korea, but again, the definition of arrhythmia was also much wider and included less serious events. No consistent increased risks were found for MI, stroke, heart failure, or hypertension. These data, on the whole, are consistent with a recent meta-analysis of methylphenidate, atomoxetine, and/or placebo in controlled trials that showed a pre–post exposure elevation of systolic blood pressure and heart rate in children and adolescents, but no increase of serious cardiac adverse events

Table 2 ADHD and ASD cases and control characteristics (based on composite serious cardiovascular event)

	ADHD			ASD		
	Cases $n=186$	Controls $n=1860$	SMD	Cases $n=48$	Controls $n=480$	SMD
Demographics (initial matching criteria)						
Female	53 (28.5)	530 (28.5)	NA	10 (20.8)	100 (20.8)	NA
Age in years, mean (SD)	13.9 (3.4)	13.9 (3.4)	NA	12.5 (4.4)	12.5 (4.4)	NA
Age category in years			NA			NA
3–4	0 (0.0)	0 (0.0)		4 (8.3)	40 (8.3)	
5–9	20 (10.8)	200 (10.8)		9 (18.8)	90 (18.8)	
10–14	78 (41.9)	780 (41.9)		15 (31.3)	150 (31.3)	
15–18	88 (47.3)	880 (47.3)		20 (41.7)	200 (41.7)	
Medicaid	58 (31.2)	580 (31.2)	NA	14 (29.2)	140 (29.2)	NA
Capitated insurance	52 (28.0)	520 (28.0)	NA	14 (29.2)	140 (29.2)	NA
History of cardiovascular comorbidities						
Congenital circulatory system disorders	29 (15.6)	20 (1.1)	0.544	9 (18.8)	11 (2.3)	0.557
Congestive heart failure	11 (5.9)	1 (0.1)	0.350	6 (12.5)	0 (0.0)	0.535
Essential hypertension	11 (5.9)	32 (1.7)	0.220	2 (4.2)	14 (2.9)	0.068
Disorders of lipid metabolism	5 (2.7)	30 (1.6)	0.074	2 (4.2)	9 (1.9)	0.134
Peripheral artery disease	3 (1.6)	1 (0.1)	0.172	1 (2.1)	0 (0.0)	0.206
Asthma	38 (20.4)	295 (15.9)	0.119	9 (18.8)	85 (17.7)	0.027
Chronic obstructive pulmonary disease	1 (0.5)	5 (0.3)	0.042	1 (2.1)	7 (1.5)	0.047
Diabetes	2 (1.1)	12 (0.6)	0.047	2 (4.2)	7 (1.5)	0.164
Overweight or obese	8 (4.3)	70 (3.8)	0.027	4 (8.3)	24 (5.0)	0.134
HCRU						
1 or more emergency room visit	71 (38.2)	350 (18.8)	0.439	21 (43.8)	93 (19.4)	0.543
1 or more inpatient hospital visit	32 (17.2)	51 (2.7)	0.497	6 (12.5)	18 (3.8)	0.324
1 or more cardiology specialty visit	35 (18.8)	33 (1.8)	0.584	9 (18.8)	21 (4.4)	0.461
Received behavior therapy	57 (30.6)	452 (24.3)	0.142	7 (14.6)	163 (34.0)	0.464
Days with any medical claim, mean (SD)	21.5 (31.6)	12.0 (22.4)	0.349	28.6 (39.3)	22.7 (33.7)	0.160
Psychiatric comorbidities						
ADHD	NA	NA	NA	9 (18.8)	191 (39.8)	0.475
Anxiety	31 (16.7)	231 (12.4)	0.121	10 (20.8)	107 (22.3)	0.035
Depression	31 (16.7)	215 (11.6)	0.147	5 (10.4)	54 (11.3)	0.027
Epilepsy	13 (7.0)	32 (1.7)	0.260	9 (18.8)	41 (8.5)	0.301
Sleep disturbances	13 (7.0)	95 (5.1)	0.079	6 (12.5)	31 (6.5)	0.207
Other serious medical conditions						
Cancer	12 (6.5)	7 (0.4)	0.339	0 (0.0)	1 (0.2)	0.065
Renal disease	2 (1.1)	4 (0.2)	0.108	0 (0.0)	1 (0.2)	0.065
Liver disease	4 (2.2)	6 (0.3)	0.166	1 (2.1)	4 (0.8)	0.104
Human immunodeficiency virus	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
Psychotropic medications						
Antidepressants	33 (17.7)	222 (11.9)	0.164	8 (16.7)	123 (25.6)	0.221
Antipsychotics	7 (3.8)	110 (5.9)	0.100	13 (27.1)	98 (20.4)	0.157
Anxiolytics/sedatives/hypnotics	4 (2.2)	38 (2.0)	0.008	6 (12.5)	14 (2.9)	0.365
Benzodiazepines	13 (7.0)	16 (0.9)	0.320	8 (16.7)	21 (4.4)	0.409
Beta-blockers	12 (6.5)	3 (0.2)	0.357	2 (4.2)	2 (0.4)	0.253

Results are *n* (%) unless stated otherwise

ADHD attention-deficit/hyperactivity disorder, *ASD* autism spectrum disorder, *HCRU* healthcare resource use, *NA* not applicable, *SD* standard deviation, *SMD* standardized mean difference between cases and controls

Table 3 Use of ADHD medication and risk of composite serious cardiovascular event in children and adolescents with ADHD and ASD

	Odds ratios (95% confidence intervals)	
	ADHD	ASD
Crude (matched only) analyses		
Current exposure (reference: not currently exposed)	1.08 (0.78–1.49)	0.49 (0.20–1.20)
Exposed in past 90 days (reference: not exposed in past 90 days)[a]	1.06 (0.72–1.54)	0.30 (0.10–0.89)
Ever prior exposed (reference: never prior exposed)[b]	1.15 (0.39–3.39)	0.41 (0.08–2.06)
Control for adjustment set 1, current exposure (reference: not currently exposed)		
Weighted analysis	0.97 (0.68–1.38)	0.49 (0.20–1.25)
Conditional logistic regression	1.11 (0.78–1.59)	0.48 (0.17–1.40)
Control for adjustment set 2, current exposure (reference: not currently exposed)		
Weighted analysis	0.97 (0.68–1.39)	0.71 (0.28–1.83)
Conditional logistic regression	1.10 (0.75–1.61)	1.20 (0.33–4.41)
Crude (matched only) in subgroup, current exposure (reference: not currently exposed)		
Exclude individuals with CCSD, CHF, or cardiology visit[c]	1.01 (0.66–1.56)	0.57 (0.16–2.04)

Covariate set 1: matching variables, underlying cardiovascular risk, and healthcare resource use

Covariate set 2: covariate set 1, serious medical and psychiatric comorbidities, psychotropic medications, and beta-blocker use

Logistic regression for ASD adjustment set 1 is without CHF or PAD, else model cannot converge. Likewise, logistic regression for ASD adjustment set 2 is without CHF, PAD, cancer, or renal disease

ADHD attention-deficit/hyperactivity disorder, *ASD* autism spectrum disorder, *CCSD* congenital circulatory system disorders, *CHF* congestive heart failure, *PAD* peripheral artery disease

[a]Where cases and 10 matched controls have at least 120 days pre-index enrollment (ADHD cases: $n=123$; ASD cases $n=33$)

[b]Where cases and 10 matched controls have at least 365 days pre-index enrollment (ADHD cases: $n=30$; ASD cases $n=9$)

[c]Where cases and 10 matched controls have no CCSD, CHF, or cardiology visit (ADHD cases: $n=106$; ASD cases $n=19$)

Table 4 Current use of ADHD medication and risk of specific serious cardiovascular events in children and adolescents with ADHD and ASD

	Odds ratios (95% confidence intervals)					
	ADHD			ASD		
	Stroke	Serious cardiac arrhythmia	Myocardial infarction	Stroke	Serious cardiac arrhythmia	Myocardial infarction[a]
Current use (reference: not currently exposed)	1	1	1	1	1	–
Crude (matched only) analyses	0.99 (0.64–1.54)	1.20 (0.72–1.98)	0.84 (0.17–4.13)	0.52 (0.14–1.84)	0.62 (0.17–2.24)	–
Control for adjustment set 1	0.90 (0.57–1.41)	0.96 (0.55–1.68)	1.07 (0.21–5.60)	0.59 (0.16–2.14)	0.43 (0.10–1.74)	–
Control for adjustment set 2	0.84 (0.53–1.31)	1.03 (0.57–1.83)	0.83 (0.15–4.51)	0.68 (0.19–2.47)	0.90 (0.23–3.54)	–

Covariate set 1: matching variables, underlying cardiovascular risk, and healthcare resource use

Covariate set 2: covariate set 1, serious medical and psychiatric comorbidities, psychotropic medications, and beta-blocker use

ADHD attention-deficit/hyperactivity disorder, *ASD* autism spectrum disorder

[a]Unable to fit models due to only 1 case with myocardial infarction in the ASD cohort (who was unexposed, compared to 2 out of 10 controls exposed)

[10]. In general, these more minor cardiovascular effects during treatment with ADHD medications are thought to be manageable, although should not be underestimated [37]. For consistency with abovementioned previous systematic reviews of ADHD medications on SCV events [13, 14] as well as blood pressure and heart rate [9, 10], we did not include guanfacine and clonidine as exposures in our analyses. However, given that these medications have been more

recently been approved in some countries for treatment of ADHD, this could be an area for further research.

A novel aspect of our study is the contemporaneous nature of the data used (up until the end of 2016). In contrast, the most recent data used by any of the studies included in the Zito and Burcu review [14] was from 2007, only 1 year after an FDA advisory committee first advised that a class-specific warning for stimulants and SCV risk be introduced [12]. Regardless of these policy statements or subsequent debate about limiting use in people with heart problems [38–40] inference from our study results remains the same compared to the majority of earlier observational studies: no association found between SCV events and ADHD medications. In any case, across both ADHD and ASD, cases were more likely to already have underlying serious cardiac conditions than controls, which may indicate the class-wide warnings are not always followed.

The overall incidence rate of SCV events was extremely low. Our incidence rate estimate of 3.1/100,000 person years in the ADHD cohort is consistent with the rates observed in other cohorts that primarily comprised ADHD children and adolescents (3.1/100,000 by Cooper et al. [15] and 2.8/100,000 by Winterstein et al. [32]). Underlying risk for the subgroup of children and adolescents with ASD in our study was slightly higher (5.6/100,000 person years), which may be partially explained by a higher prevalence of other psychotropic drugs within this group [41]. The lower point estimate for the exposure–outcome relationship found in the ASD group may also be a consequence of this group's higher concurrent treatment use, with more caution exercised by prescribing doctors deciding whether to suggest ADHD medication as an additional treatment or not.

Designing this study presented different methodological considerations. Due to the expected rarity of events, we used a nested case–control study design to include as many events in the analyses as possible. However, this meant there was a possibility of over-adjustment via inclusion of post-exposure variables, and hence we emphasized results of the crude matched analyses. When we did adjust for covariates, we tried to mitigate the risk of over-adjustment by not counting medical diagnoses and HCRU variables within the month prior to index. Furthermore, as logistic regression adjustment for many covariates and small sample sizes is known to increase the chance of unstable results [42], we opted for a weighted analysis as our primary adjusted model. Attaching weights to observations from the control group, such that this group is more similar to the cases, is an extension of simple matching, with the same theoretical motivation. In matched cohort studies, propensity scores are commonly used to find suitable weights, but here we preferred the gradient boosted method because the algorithm directly assigns weights for optimum balance without the need to model the propensity of group assignment in the first place. This has two advantages: firstly, that many covariates can be controlled for without considering the functional form of their relationships to each other and to group assignment [31], and secondly, that there are known difficulties in estimating propensity scores for case–control studies [43].

Other limitations of our study include the inability to confirm outcomes by linking claims data to medical records, or assessing medication adherence beyond prescription filing; however, we expect such misclassifications to be few, non-differential between groups, and have little bearing on our results. The case–control design also limits interpretation to the subgroup of ADHD and ASD children and adolescents reflective of those who experience SCV events. Confounding by contraindication means that cases with more severe underlying cardiac conditions and inpatient, emergency, and cardiology resource use may actually have been least likely to receive ADHD medication, biasing results away from a positive association. Finally, despite controlling for many factors, it is possible that residual confounding remained, either through unobserved variables (e.g., diet/exercise) or limited detail in the database (e.g., severity of comorbid conditions). Such limitations are common to many epidemiological studies, but since the SCV event rate is low and ADHD medications are widely used, randomized studies to address this question are unpractical, and analysis of large-scale, real-world observational data is meaningful and relevant.

5 Conclusion

In conclusion, in a large, contemporary insurance database, we found low rates of SCV events in children and adolescents with ADHD (3.1/100,000 person years) and ASD (5.6/100,000 person years). Furthermore, we found no evidence of an increased SCV risk when exposed to ADHD medications.

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Presentation Information A partly similar analysis to the one shown here (ASD cohort only) has been accepted for poster presentation at the American Academy of Child and Adolescent Psychiatry's 66th Annual Meeting, Chicago, IL, October 14–19, 2019.

Compliance with Ethical Standards

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Conflict of interest RH and GL are full time employees of F. Hoffman-La Roche Ltd (Roche), and Roche has molecules for ASD in development. FV supervises two Ph.D. students who are employed with Roche (Basel, Switzerland (RH) and Welwyn Garden City, UK). He has not received any funding or reimbursements related to this.

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