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Stimulants and Cardiovascular Events in Youth with Attention-Deficit/Hyperactivity Disorder

Mark Olfson, MD, MPH,
New York State Psychiatric Institute and the College of Physicians and Surgeons of Columbia University.

Cecilia Huang, PhD,
Institute for Health, Health Care Policy and Aging Research of Rutgers University, New Jersey

Tobias Gerhard, PhD,
Rutgers University.

Almut G. Winterstein, PhD,
College of Pharmacy and the Colleges of Medicine and Public Health and Health Professions at the University of Florida in Gainesville, Florida.

Stephen Crystal, PhD,
Institute for Health, Health Care Policy and Aging Research of Rutgers University, New Jersey.

Paul D. Allison, PhD, and
University of Pennsylvania.

Steven C. Marcus, PhD
Center for Health Equity Research and Promotion, Philadelphia Veterans Affairs Medical Center, and the School of Social Policy and Practice, University of Pennsylvania.

Abstract

Objective—This study examines associations between stimulant use and risk of cardiovascular events and symptoms among youth with attention-deficit/hyperactivity disorder and compares the risks associated with methylphenidate and amphetamines.

Method—Claims were reviewed of privately insured young people, ages 6 to 21 years, without known cardiovascular risk factors (n=171,126). A day-level cohort analysis evaluated risk of cardiovascular events following a diagnosis of ADHD in relation to stimulant exposures. On the basis of filled stimulant prescriptions, follow-up days were classified as current, past, and no stimulant use. End points included emergency department or inpatient diagnosis of 1) angina

Correspondence to Dr. Olfson, New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY 10032; mo49@columbia.edu.

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pectoris, cardiac dysrhythmia, or transient cerebral ischemia (cardiac events) or 2) tachycardia, palpitations, or syncope (cardiac symptoms).

Results—There were 0.92 new cardiac events and 3.08 new cardiac symptoms per 1,000,000 days of current stimulant use. Compared to no stimulant use (reference group), the adjusted odds ratio of cardiac events was 0.69 (95%CI=0.42–1.12) during current stimulant use and 1.18 (95%CI=0.83–1.66) during past stimulant use. The corresponding adjusted odds ratios for cardiac symptoms were 1.18 (95%CI=0.89–1.59) for current and 0.93 (95%CI=0.71–1.21) for past stimulant use. No significant differences were observed in risks of cardiovascular events (2.14, 95%CI=0.82–5.63) or symptoms (1.08, 95%CI=0.66–1.79) for current methylphenidate use compared with amphetamine use (reference group).

Conclusions—Clinical diagnoses of cardiovascular events and symptoms were rare and not associated with stimulant use. The results help to allay concerns over the cardiovascular safety of stimulant treatment for ADHD in young people without known pre-existing risk factors.

Keywords

attention-deficit/hyperactivity disorder; stimulants; cardiovascular events; drug safety; pharmacoepidemiology

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With an estimated prevalence in youth of approximately 5 to 9 percent, attention-deficit/hyperactivity disorder (ADHD) is one of the most common mental disorders of childhood and adolescence.[1–3] Stimulants are widely considered the first-line pharmacological treatment for children and adolescents with ADHD.[4–5] Approximately 3.2% of youth in the United States are treated with stimulants each year.[6] The clinical importance of stimulant medications is underscored by the limited clinical effectiveness of even intensive alternative non-pharmacological interventions for ADHD.[7]

The FDA labeling of all stimulants includes a warning regarding sudden death. Specifically, the labeling warns that "sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems."[8] A recent FDA drug safety communication also indicates that patients treated with ADHD medications should be periodically monitored for changes in heart rate or blood pressure.[9] Case reports from the FDA Adverse Event Reporting System[10] and reviews of stimulant adverse events in emergency department records[11] have coincided with concerns regarding the cardiovascular safety of stimulants in the broader population of youth without known cardiac problems.[12]

Cardiovascular symptoms, such as palpitations and tachycardia which are likely related to direct stimulant adrenergic agonist effects,[13] should be distinguished from more serious cardiovascular events that have poorly understood potential pathophysiological pathways. Whether stimulant mediated elevations in heart rate and blood pressure are harmful to the cardiovascular system of otherwise healthy young people is not known.[14] One potential pathway for severe cardiac events is acute tachycardia-induced cardiomyopathy, a reversible form of cardiomyopathy in children and adults.[15–16] It is more often associated with supraventricular or ventricular tachycardia and tachycardia-induced cardiomyopathy than with sinus tachycardia.[17] Controlling the arrhythmia and the heart rate usually results in rapid improvement in cardiac function with normalization of the ejection fraction within one to two weeks.[18]

The incidence of cardiovascular events is sufficiently rare that randomly controlled trials are unlikely to ever provide sufficient power to assess this aspect of stimulant safety. One retrospective cohort study focused on youth 3 to 20 years who were newly diagnosed with

ADHD (n=55,383), using 10 consecutive years of Florida Medicaid claims data.[19] Compared with nonuse, stimulant use was associated with a small though significant increase in the hazard for emergency department visits and physician office visits, respectively, for cardiac causes or symptoms. No cardiac deaths and very few hospital admissions for circulatory disease were reported in over 40,000 person-years of stimulant use.[19] In a second analysis of the same data set, risk for cardiac emergency department visits was similar among children and adolescents who were currently using methylphenidate or amphetamines.[20] A second study that included almost 20,000 person-years of follow-up found no association between stimulant treatment and sudden death in young people.[21] A recent third large cohort analysis also reported that youth prescribed ADHD medications (n=241,417) were not significantly more likely than matched youth who had not been prescribed ADHD medications (n=965,668) to have a stroke, myocardial information, or ventricular arrhythmia.[22] A fourth cohort study of 1.2 million children and young adults including over 370,00 person-years of current use of ADHD drugs revealed 7 serious cardiovascular events among current medication users and no evidence of increased risk of serious cardiovascular events associated with ADHD medication use.[23] Despite their large size, limited numbers of events in these studies constrain their ability to exclude small relative increases in risk.

The current analysis focuses on the treatment of ADHD with methylphenidate and mixed salts of amphetamine. Claims records from a large privately insured population are examined for cardiovascular events and symptoms. Associations are examined between stimulant treatment and risk of cardiovascular events among youth with ADHD without known risk factors.

METHOD

Study Cohort

Service and pharmacy claims were examined from the MarketScan Research Databases (1996–2007). These data are collected directly from over 150 large employers including 80 health plans and representing enrollees from all 50 states and over 30 million covered lives.[24] All study procedures were approved by the Institutional Review Board of the New York State Psychiatric Institute.

We first limited the cohort to patients who were aged 6 to 21 years age and who had an initial first or second listed service claim for ADHD (ICD-9-CM:314) after a period of eligibility of at least 180 days without an ADHD medical claim diagnosis. This date is referred to as time zero (t_0). We further required patients not to have filled any prescriptions for stimulants during the 180 day period before t_0.[25] A day-level cohort analysis was conducted to evaluate risk of cardiovascular events and symptoms in relation to stimulant exposures starting at t_0 and continuing until the time of an event or end of study period, loss of eligibility, or death, whatever came first.

Cohort eligibility criteria sought to assure the availability of necessary information and to exclude patients likely to have events related to underlying general medical disorders. During the 180 days before t_0, cohort members had to be enrolled in a health plan with pharmacy coverage. Patients were excluded if they received a “High Risk Exclusion Condition” diagnosis at any time before or after t_0. Patients were also excluded if they were diagnosed with a “High Risk Censored Event” during the 180 day period before t_0. Patients who first received a “High Risk Censored Event” diagnosis following t_0 were censored at that point. The list of high risk censored events and high risk exclusion conditions was developed from a review of risk factors for stroke,[26] myocardial infarction,[27] and other

cardiovascular events and following consultation with medical subspecialists (see Table 1 for lists of high risk censored events and exclusions).

From an initial cohort of age and service eligible patients with qualifying ADHD diagnoses (n=268,606), the most common exclusions were for stimulant use (n=75,722) and high risk exclusion conditions (n=20,342) during the 180 day pre-period. Other common exclusions included high risk censoring events (n=9,403), chest pain (n=2,260), and syncope (n=1,074) during the preperiod. Less common exclusions were tachycardia (n=318), less severe cardiovascular events (angina, dysrhythmia, or transient cerebral ischemia) (n=130), and severe cardiovascular events (n=31) during the preperiod.

Cardiovascular Events

We initially planned to study three levels of cardiovascular events: severe cardiovascular events, less severe cardiovascular events, and cardiovascular symptoms. Severe cardiovascular events were defined by an inpatient claim for acute myocardial infarction (ICD-9-CM: 410), subarachnoid or intracerebral hemorrhage (ICD-9-CM: 430, 431), occlusion or stenosis of cerebral arteries (ICD-9-CM: 433-434), acute cerebrovascular disease (ICD-9-CM: 436), ischemic heart disease (ICD-9-CM: 411.89), sudden death (ICD-9-CM: 798), and respiratory arrest (ICD-9-CM: 799.1). These codes have established validity in adults.[28–31] A preliminary analysis revealed only one incident case, which occurred during a period of current methylphenidate use, and no further analyses of severe cardiovascular events were performed.

Less severe events included angina pectoris (ICD-9-CM: 413),[32] cardiac dysrhythmias (ICD-9-CM: 427),[33] or transient cerebral ischemia (ICD-9-CM: 435)[34] that is listed on any position in an emergency department or inpatient claim. Secondly, the cardiovascular symptom tachycardia (ICD-9-CM: 785.0), palpitations (ICD-9-CM:785.1) or syncope (ICD-9-CM: 780.2) listed in any position on an emergency department or inpatient claim was studied separately as an endpoint.

Stimulant Exposure

The independent variable of interest was exposure to stimulants, which included all methylphenidate and amphetamine preparations. Using available information on the dates of prescriptions and the days of supply, we classified each *patient-day* into one of the following three categories: 1) Non-use defined as days of patients who never used stimulants from time t_0 to the current day, 2) Current use defined as patient-days occurring between the filling of a stimulant prescription through the end of the days of supply, and 3) Former use defined as patient-days with stimulant use in the past (on or after t_0) but not current stimulant use. Over the course of observation, a patient could switch from non-use to current use, and then could alternate between current use and former use.

Propensity Score

In order to help balance the exposure groups with respect to measured covariates, a propensity score for each day of stimulant treatment was developed that included a wide range of potentially confounding variables. The propensity score summarizes associations of selected observed covariates with treatment assignment. Adjusting for the propensity score efficiently removes bias due to these covariates and improves control of measured confounding over a conventional multivariate model when the outcome is scarce.[35] Because general medical conditions and medications that affect cardiovascular function may influence clinical decisions to initiate stimulants,[36] they were entered into the propensity score model (see Diseases and Drugs in Propensity Score in Table 1). These conditions and medications were based on literature reviews[37] and discussions with colleagues. Calendar

month was included to accommodate seasonal stimulant treatment variation over the course of a year.[38] Receipt of one or more well child visits, which served as a proxy for preventive care, as well as patient age and sex were also entered as covariates into the propensity score. Day-level propensity scores were estimated by logistic regressions in which stimulant use time was the dependent variable and correlates of stimulant use were covariates (Table 1).[39] Separate propensity scores were calculated for propensity to stimulant non-use or current use and propensity to stimulant non-use or past use. These propensity scores were separately calculated for overall stimulant use, methyphenidate use, and amphetamine use. In adjusted models, the propensity quintile score for current as compared with non-use was inversely related to risk of the cardiovascular outcomes (data not shown).

Analytic Strategy

Rates of first claim for less severe cardiovascular events and for cardiovascular symptoms per million days were first determined for current, past, and non-use of stimulants during the follow-up period. Day-level logistic regressions were then performed to derive adjusted odds ratios with associated 95% confidence intervals. These logistic regression analyses closely resemble time dependent covariate Cox regression analyses but are computationally more efficient.[40] Stimulant use was the independent variable of interest, cardiovascular event was the dependent variable, and propensity score (quintiles), patient age category, and days from index diagnosis were covariates. Within an individual patient, stimulant use was a time varying variable.

Corresponding analyses were performed with first onset of cardiovascular symptom as the outcome. Separate corresponding analyses were also performed to compare rates for cardiovascular outcomes for the two stimulant groups, methylphenidate and amphetamine salts. In these analyses, current methylphenidate and amphetamine use were compared, controlling for past use of the other stimulant, in unadjusted and adjusted models. Comparable models compared past methylphenidate and amphetamine use excluding all days with current or no stimulant use. Because the outcomes were infrequent, a disease risk score was not utilized.[35]

RESULTS

Background Characteristics

The study sample included 171,126 youth who contributed 304,310 person years (111,073,077 days) of follow-up to the analysis. Background characteristics were compared for patients who did or did not use stimulants at any point during follow-up (Table 2). As compared to patients who did not use stimulants, patients who used stimulants were significantly younger and more likely to be male. During the 180 days prior to the visit for ADHD, a significantly smaller percentage of stimulant-using than non-using patients had markers of cardiovascular risk. Significant group differences were evident for inpatient treatment for any reason, diagnosis of obesity, diabetes, asthma, depression, anxiety, and substance use disorders as well as prescription of any of the medications associated with risk of cardiovascular events (Table 2).

Exposure Groups

The patient cohort was distributed among patients who received no stimulants (48.0%), methylphenidate only (26.3%), amphetamine salts only (17.1%) and both stimulant classes (8.6%) during follow-up. Days of follow-up were distributed across no stimulant use (46.6%), past stimulant use (32.9%) and current stimulant use (20.5%).

Stimulant Exposure and Cardiovascular Outcomes

Among the current stimulant use group, the rate of less severe cardiovascular events was 0.92 events per 1,000,000 days of stimulant use or 1 event per 2,978 years of stimulant treatment (n=21). In the unadjusted model, current stimulant use as compared with no stimulant use was associated with significantly lower odds of a less severe cardiovascular event. This association was no longer significant after controlling for the propensity score, patient age, and days from the index ADHD diagnosis. Past stimulant use was not associated with less severe cardiovascular events in either unadjusted or adjusted regressions (Table 3).

Among periods of current stimulant use, inpatient or emergency department diagnoses of cardiovascular symptoms occurred at a rate of 3.08 events per 1,000,000 days of stimulant use or 1 event per 890 years of stimulant treatment (n=70). As compared with no stimulant use, neither current nor past stimulant use was significantly related to cardiovascular symptoms in either the adjusted or unadjusted model (Table 3).

A direct comparison of current amphetamine and current methylphenidate use revealed no significant associations with either less severe cardiovascular events or cardiovascular symptoms (Table 4). However, there was a non-significant trend toward greater risk of event with current methylphenidate than amphetamine. The analogous comparison of past amphetamine and methylphenidate use also revealed no significant associations with either adverse outcome (Table 4).

DISCUSSION

Severe cardiovascular events were quite uncommon among privately insured young people who have received a clinical diagnosis of ADHD and have no known cardiovascular risk factors. Only one such event was observed yielding an incidence approximately 0.3 per 100,000 years of follow-up. This compares with a previously published corresponding incidence of severe cardiovascular events of 0.5 per 100,000 person-years in youth not receiving ADHD medications[22] and an incidence of 3.1 serious cardiovascular events per 100,000 person-years in a cohort that included children and young adults, ages 2 to 24 years, without known pre-existing potentially life-threatening diseases.[23] Less severe cardiovascular events including angina, dysrhythmia, or transient cerebral ischemia, which occurred at rate of roughly 1 per 3,000 years of follow-up in the present study, were not significantly related to stimulant use in the final models. Current stimulant use trended toward a protective effect of these events which is likely a consequence of residual confounding. No significant associations were also reported between stimulant use and emergency or inpatient diagnosis of cardiovascular symptoms. In keeping with an earlier report, the risk of less severe cardiovascular events and symptoms did not significantly differ between periods of current amphetamine and methylphenidate use.[19] These findings help to allay concerns over the cardiovascular safety of stimulant therapy for ADHD in young people without known pre-existing risk factors.

The absence of a positive association between stimulant use and cardiovascular outcomes differs slightly with results from the earlier claims-based study of Florida Medicaid data.[19] In this study, the adjusted association between current stimulant use and emergency department visits for cardiac symptoms and circulatory disease achieved statistical significance (hazard ratio=1.20; 95% CI=1.04–1.38). This finding was driven largely by the far more common cardiac symptoms than cardiac disease events. The comparable finding from the present study (hazard ratio=1.18; 95% CI=0.89–1.59) was similar in magnitude but failed to achieve statistical significance. This pattern suggests that stimulants may make a small contribution to the risk of palpitations or other minor symptoms,[41] but these risks do

not seem to translate into more clinically significant outcomes such as angina, dysrhythmias, or transient cerebral ischemia.

In the present study, the observed non-significant tendency for current stimulant use to lower risk of less severe cardiovascular events is likely a spurious consequence of residual confounding. Some evidence from adults with ADHD indicates that physicians tend to avoid prescribing stimulants to patients with cardiovascular risk factors.[35.42] Physicians may have greater concerns over the safety of amphetamines than methylphenidate and tend to avoid prescribing to youth who have known or suspected drug abuse problems out of concern over stimulant misuse or diversion.[43] Young people with greater vulnerability to cardiovascular disease may be relatively unlikely to receive stimulants, especially amphetamines, or to receive a shorter duration or lower dose of stimulant treatment. Without random assignment, it is not possible to exclude the possibility of confounding by cardiovascular risk which might explain the observed trend towards a protective effect of current stimulant use over no use and current amphetamine use over methylphenidate use. Several important risk factors, such as smoking, physical inactivity, diet, family history of cardiovascular disease, undiagnosed cardiovascular disease, and lifetime history of previous events are not available in claims data. Other risk factors, such as obesity and hypertension, are poorly measured in claims data. Importantly, even if residual confounding were present, as appears likely, a dramatic stimulant safety signal should have offset this effect and resulted in a safety signal.

It is unlikely that stimulants actually protect from cardiovascular events. Amphetamines are adrenergic agonists with acute chronotropic and pressor effects.[41] Centrally, amphetamines mediate release of norepinephrine and dopamine. Peripherally, amphetamines are sympathomimetic agents that stimulate alpha and beta receptors, leading to blood pressure and heart rate elevation. In adults, persistent hypertension is a well accepted risk factor for coronary artery disease, stroke, and several other cardiovascular diseases[4,44] and a fast heart rate is a predictor of cardiovascular morbidity and mortality.[45] Although moderate tea and coffee consumption provide examples of compounds with mild chronotropic and pressor effects that nevertheless have been found to decrease risks of cerebral vascular events[46] and myocardial infarction[47] in adults, these effects are thought to be mediated by antioxidant phenolic compounds[48] that do not occur in amphetamines or methylphenidate.[49]

The present report has several limitations beyond potential confounding by unmeasured cardiovascular risk. First, claims data only capture cardiovascular events that receive medical treatment. Asymptomatic arrhythmias,[50] for example, commonly escape detection and treatment. Second, the validity and clinical significance of claims for cardiovascular events, which have been studied in adults, have not been well documented in young people. Palpitations are a common presenting clinical complaint in young people that are usually benign and may be non-cardiac in origin[51] and syncope in young people is almost always benign.[52] Some of the outcome events under study, therefore, may not be cardiovascular in origin. Third, a more sensitive measure of stimulant use, such as pill counts, might have yielded more accurate information, but is clearly impractical on the scale required for a study of such rare events. Nevertheless, there is reasonable concordance between drug claims records and self-report medication use[33] and between administrative drug claims and the medications actually dispensed.[53] Fourth, the analysis is limited to patients in private health insurance plans. Because risk of cardiovascular disease tends to be inversely related to social class,[54] the risk profile of privately insured patients likely differs from that of Medicaid patients. However, more than one-half of all children in the United States have private health insurance coverage.[55] Fifth, the results should not be extended to illicit use of stimulants.[56–57] Finally, despite the large size of the base population, it was not large enough to assess associations between stimulant exposures and severe cardiovascular events.

An analysis of over 100 million days of follow-up of young people diagnosed with ADHD demonstrated no significant increase in risk of angina, cardiac dysrhythmia, transient cerebral ischemia, or more common cardiovascular symptoms associated with stimulant use. The present study did not address the question of sudden and unexplained death. In a matched case control study of youth who died of unexplained causes or as passengers in motor vehicle accidents, an association was reported between methylphenidate use and sudden unexplained death.[58] Because this study specifically excluded sudden death due stroke or myocardial infarction and because only a minority of sudden and unexplained deaths in young people are ultimately determined to be cardiovascular in origin,[59–60] it is difficult compare the two studies. Although the reassuring results of the present study are generally consistent with other recent pharmaco-epidemiologic safety studies,[19–23] they do not exclude the possibility raised by the case-control study of exceedingly rare, poorly understood, catastrophic stimulant associated adverse events.

In the present analysis, stimulant treatment was not associated with a substantially increased risk of cardiovascular events in otherwise apparently healthy young people receiving treatment for ADHD for an average follow-up of one and three quarters years. In view of safety concerns in higher risk patients, however, it is prudent before initiating stimulant therapy to follow current recommendations that include taking a personal and family cardiovascular history with special attention to a family history of premature sudden death and a personal history of syncope, dizziness, palpitations, and chest pain and to perform a physical examination including a careful cardiac examination.[61]

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Table 1

High risk exclusion conditions and potentially confounding factors entered into propensity score

High Risk Exclusion Conditions	**High Risk Exclusion Conditions (cont)**	**Diseases in Propensity Score**
Congenital anomalies, nervous system	Malignant essential hypertension	Prothrombotic state
Congenital anomalies, heart	Pailledema	Atherosclerosis
Congential anomalies, circulatory system	Cardiac or respiratory complications, NEC	Hyperlipidemia
Cardiac valvular disease	Cardiac pacemaker	Collagen vascular disease
Cystic fibrosis	Nervous system device	Obesity
Neoplasms		Diabetes
Immune deficiencies and HIV	**High Risk Censored Events**	Asthma
Hemolytic and aplastic anemias;	Concussion	Renal disease
Disorders of amino acid transport	Cerebral laceration and contusion	Hypertension
Thrombosis or embolism	Cerebral hemorrhage, injury	Depression
Heart Failure	Intracranial injury	Anxiety
Pericarditis or related diseases	Traumatic pneumothorax	Substance use disorder
Endocarditis or related diseases	Injury to heart and lung	
Myocarditis and cardiomyopathies	Facture of skull	**Drugs in Propensity Score**
Conduction disorders	Injury of head/neck, blood vessels	Clonidine
Intracranial abscess or related diseases	Injury thorax blood vessels	Xanthines
Cerebral degeneration	Injury to skull	Adrenergic bronchodilators
Anoxic brain damage or related diseases	Injury to nervous system	Inotropic agents
Chronic liver disease or hepatitis	Contusion to chest wall	Systemic corticosteroids
Mental retardation, moderate or severe	Spinal cord injury, thoracic level	Oral contraceptives
Cerebral palsy or other paralyses	Injury to face and neck	Highly active antiretrovirals
Muscular dystrophy	Injury to trunk and chest wall	Anthracyclines
Chromosomal anomalies	Poisoning	Selective COX-2 inhibitors
Lupus erythematosus	Toxicities	Antipsychotic medications
Coagulation defects	Foreign body gastrointestinal tract	Monoamine oxidase inhibitors
Diseases of white blood cells	Open wound of head	Erythromycin
Schizophrenia and autism	Open wound of chest wall	Ciprofloxacin
Meningitis or encephalitis	Coma and stupor	Antihypertensives
Spinocerebellar diseases	Fracture of thoracic vertebrae	Lipid lowering drugs
Syringomyelia	Fracture of ribs or sternum	Anticoagulants
Multiple sclerosis or related diseases	Sprain of ribs or sternum	Antiarrythmic drugs
Rheumatic heart disease	Transient organic psychotic state	Antianginal agents
Aortic or cerebral aneurysm	Obstructive sleep apnea	Other stimulants
Peripheral vascular disease		
Pancreatitis		
Acute pulmonary heart disease		

Note: HIV = Human immunodeficiency virus; NEC = necrotizing enterocolitis.

Table 2

Background characteristics of privately insured youth diagnosed with attention-deficit/hyperactivity disorder by stimulant use during the follow-up period

Characteristic	Patients with Stimulant Use % (n=89,031)	Patients without Stimulant Use % (n=82,095)	Statistics
Sex			X^2=28.6, df=1, p<0.001
Male	67.68	66.47	
Female	32.32	33.53	
Age, years			X^2=438.5, df=1, p<0.001
6–12	60.71	55.71	
13–21	39.29	44.29	
Any selected medication[a]	6.00	6.42	X^2=12.9, df=1, p=0.003
Selected diseases[a]			
Prothrombotic state	1.41	1.38	X^2=0.4, df=1, p=0.51
Atherosclerosis	0.02	0.02	X^2=0.2, df=1, p=0.68
Hyperlipidemia	0.28	0.31	X^2=1.0, df=1, p=0.32
Collagen vascular disease	0.06	0.07	X^2=1.0, df=1, p=0.32
Obesity	0.33	0.38	X^2=4.1, df=1, p=0.04
Diabetes mellitus	0.28	036	X^2=7.3, df=1, p=0.007
Asthma	3.44	3.69	X^2=8.2, df=1, p=0.004
Renal disease	0.12	0.15	X^2=4.0, df=1, p=0.05
Hypertension	0.12	0.13	X^2=1.2, df=1, p=0.28
Depression	4.17	5.60	X^2=189.4, df=1, p<0.0001
Anxiety	2.83	3.32	X^2=34.7, df=1, p<0.0001
Substance use disorder	0.62	1.35	X^2=237.1, df=1, p<0.0001
Any inpatient treatment	0.65	1.27	X^2=178.5, df=1, p<0.0001

Note:

[a]Selected medications and selected diseases are based on claims during the 180 day period before the index attention-deficit/hyperactivity disorder visit. Variables representing these medications, diseases, and inpatient treatment were entered into the propensity score. See Table 1 for list of the medications and diseases that were entered into the propensity score.

Table 3

Rates and adjusted odds ratios of less severe cardiovascular events and cardiovascular symptoms by stimulant use groups for privately insured youth diagnosed with attention-deficit/hyperactivity disorder

Stimulant Use Group	Day Level Event Rate per Million Days (n)	Odds Ratio (95% CI)	Adjusted Odds Ratio[a] (95% CI)
Less Severe Cardiovascular Event			
Current stimulant use	0.92 (n=21)	0.60 (0.37–0.97)	0.69 (0.42–1.12)
Past stimulant use	1.67 (n=61)	1.08 (0.78–1.51)	1.18 (0.83–1.66)
No stimulant use	1.55 (n=80)	1.00	1.00
Cardiovascular Symptoms			
Current stimulant use	3.08 (n=70)	1.06 (0.80–1.41)	1.18 (0.89–1.59)
Past stimulant use	2.53 (n=92)	0.87 (0.67–1.13)	0.93 (0.71–1.21)
No stimulant use	2.90 (n=150)	1.00	1.00

Note: See text for definition of stimulant use groups. Less severe cardiovascular events include angina pectoris, cardiac dysrhythmias, or transient cerebral ischemia. Cardiovascular symptoms include tachycardia, palpitations, and syncope. CI = confidence interval.

[a] All adjusted odds ratios are adjusted for propensity score, patient age, and days from index attention-deficit/hyperactivity disorder diagnosis. In addition, the adjusted odds ratios of less severe cardiovascular events are also adjusted for cardiovascular symptoms.

Table 4

Rates and adjusted odds ratios of less severe cardiovascular events and cardiovascular symptoms for privately insured youth diagnosed with attention-deficit/hyperactivity disorder by current, former, and non-use of stimulants, by stimulant class

Stimulant Use Group	Day Level Event Rate per Million Days (n)	Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)[a]
Less Severe Cardiovascular Events			
Current methylphenidate use	1.06 (n=14)	1.57 (0.62–3.96)	2.14 (0.82–5.63)
Current amphetamine use	0.72 (n=7)	1.00	1.00
Past methylphenidate use	1.70 (n=45)	1.06 (0.59–1.91)	1.23 (0.67–2.25)
Past amphetamine use	1.84 (n=37)	1.00	1.00
Cardiovascular Symptoms			
Current methylphenidate use	2.58 (n=34)	0.69 (0.43–1.10)	1.08 (0.66–1.79)
Current amphetamine use	3.72 (n=36)	1.00	1.00
Past methylphenidate use	2.57 (n=68)	0.98 (0.62–1.54)	1.13 (0.72–1.79)
Past amphetamine use	2.59 (n=52)	1.00	1.00

Note: See text for definition of stimulant use groups. Less severe event analyses also adjusted for cardiovascular symptoms. Less severe cardiovascular events include angina pectoris, cardiac dysrhythmias, or transient cerebral ischemia. Cardiovascular symptoms include tachycardia, palpitations, and syncope. CI = confidence interval.

[a] All adjusted odds ratios are adjusted for propensity score, patient age, and days from index ADHD diagnosis. In addition, the adjusted odds ratios of less severe cardiovascular events are also adjusted for cardiovascular symptoms.