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Attention Deficit Hyperactivity Disorder Medications and Risk of Serious Cardiovascular Disease in Children and Youth

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Attention Deficit Hyperactivity Disorder Medications and Risk of Serious Cardiovascular Disease in Children and Youth

Abstract

Background. Recent reviews of U.S. Food and Drug Administration (FDA) Adverse Event Reporting System data have raised concern that attention-deficit hyperactivity disorder (ADHD) medication use might be associated with increased risk of serious cardiovascular disease.

Objective. To examine the association between use of ADHD medications and the risk for serious cardiovascular disease, including sudden cardiac death, acute myocardial infarction, and stroke, in children and youth of age 2-24 years.

Design. Retrospective cohort study using automated data from four health plans (Tennessee Medicaid, Kaiser Permanente California, OptumInsight Epidemiology, Washington State Medicaid) in which ADHD medication users were compared to nonusers.

Patients. 1,200,438 children and youth contributed 2,579,104 person-years of follow-up, including 373,667 person-years of current ADHD medication use.

Measurements. Baseline and follow-up drug use was assessed from automated records of dispensed prescriptions. The primary outcome was serious cardiovascular disease (sudden cardiac death, acute myocardial infarction, or stroke) identified from computerized databases and confirmed through medical record review.

Results. Cohort members had 81 serious cardiovascular events (3.1/100,000 person-years). Current ADHD medication users had no increased risk for serious cardiovascular events (adjusted hazard ratio 0.75; 95% confidence interval [CI] 0.31 to 1.85). Risk was not increased for any of the individual endpoints, or for current users compared to former users (adjusted hazard ratio 0.70; 95% CI 0.29 to 1.72). Alternative analyses addressing several study assumptions also found no significant association between ADHD medication use and the risk of study endpoints.

Conclusions. Although there was no evidence of increased risk of serious cardiovascular events for current users of ADHD medications, the upper bound of the 95 percent confidence interval indicates that up to a two-fold increased risk cannot be ruled out. However, the absolute magnitude of such an increased risk would be low.

Contents

Introduction.....1
Methods.....2
Data Sources.....2
Study Population.....2
Study Medications.....2
Study Endpoints.....3
Analysis.....3
Human Subjects Protection.....4
Results.....5
Discussion.....7
References.....14

Tables

Table 1. Study Cohort, by Site.....10
Table 2. Cohort Characteristics by Baseline ADHD Medication Use.....10
Table 3. Occurrence of Serious Cardiovascular Disease by Current Use of ADHD Medications.....11
Table 4. Occurrence of Individual Endpoints by Current Use of ADHD Medications.....11
Table 5. Alternative Analyses, ADHD Medication Use, and Serious Cardiovascular Disease.....12

Figure

Figure 1. Adjusted Hazard Ratios for Serious Cardiovascular Disease (Sudden Cardiac Death, Acute Myocardial Infarction, or Stroke) for Current and Non-Current Users of ADHD Medications Compared to Non-Users of ADHD Medications.....13

Appendixes

Appendix A. Serious Illness Exclusions
Appendix B. Study Person-Time
Appendix C. Case Definitions and Identification
Appendix D. Medical Record Review
Appendix E. Computer Algorithm for Cases in Which Records Were Unavailable or Had Insufficient Information
Appendix F. Propensity Score Diagnostics
Appendix G. Full Model
Appendix H. Clinical Characteristics of Confirmed Cases
Appendix I. Analysis in Which Former Users Served as the Reference
Appendix J. Adjusted Rates of Serious Cardiovascular Events for Individual ADHD Medications
Appendix K. Alternative Analyses
Appendix L. Comparisons of Medicaid and Non-Medicaid Sites

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Introduction

There now are more than 2.7 million children in the United States who receive ADHD medications each year.[1] Although some of the stimulant medications used to treat ADHD have a well-known potential for toxicity in overdose or abuse, the current ADHD medications in the doses prescribed for ADHD have been thought to be relatively safe.[2-5] However, doubts about the safety of ADHD medication use were raised by an FDA review of its Adverse Event Reporting System (AERS) for cases of sudden death and arrhythmias in conjunction with use of these drugs, which occurred in children and adults.[6,7] Although the case reports have raised doubts about the cardiovascular safety of ADHD medications, these reports cannot determine the existence of or reliably quantify the magnitude of any increased risk. The FDA reviews were followed by studies that provided additional information but were limited by small sample size, concerns about possible recall bias, and lack of validation of all potential endpoints.[8-11]

Thus, there is an urgent clinical and public health need to obtain better safety data for these medications. We conducted a retrospective cohort study using data from four large health plans which included validation of study outcomes to assess the relationship between use of ADHD medications and the risk of serious cardiovascular disease in children and youth.

Methods

Data Sources

Study data were obtained from the computerized health records of four study sites [Tennessee State Medicaid, Washington State Medicaid, Kaiser Permanente California (Northern and Southern regions), and OptumInsight Epidemiology] augmented with linkage to state death certificates (Tennessee, Washington State, Kaiser Permanente California) or the National Death Index (all sites). The beginning of follow-up differed by site based on the earliest availability of the site's computerized data (ranging from 1986 to 2002); follow-up concluded for all sites at the end of 2005 to allow for ascertainment of deaths. To ensure ascertainment of deaths occurring in youth of ages 18 to 24 years (who may have moved away for college or early careers while still insured by a parent) for sites using state death certificates, we also performed National Death Index searches for any cohort member who was age 18-24 years during follow-up, ended enrollment prior to another reason for end of follow-up, and had no evidence of being alive after the end of enrollment based on subsequent re-enrollment, other healthcare claims, or births. All deaths that were potential cases identified in the National Death Index search had already been identified from state vital records.

Study Population

A cohort of person-time eligible for the study was assembled from enrollees in each health plan who had: (1) age of 2 to 24 years (to correspond with the World Health Organization's definition of youth)[12]; (2) availability of data needed for the study; and, (3) absence of serious illness (Appendix 1). In addition, cohort members could not have a hospital discharge in the preceding 365 days with a primary diagnosis of acute myocardial infarction or stroke. Cohort eligibility ended at the earliest of: (1) the last day of the study, (2) when the cohort member reached the upper age limit for the study, (3) the last day of membership of pharmacy benefits in a plan, (4) the day prior to development of an exclusion illness, or (5) the day of death. A given child or youth was allowed to contribute more than one eligible period to the study, as long as all of the cohort eligibility requirements were met.

To improve logistic efficiency, eligible person-time was sampled to form the final study cohort (Appendix 2). The sample included all eligible person-time with use of ADHD medications (with the earliest day of ADHD medication use during a period of qualifying eligibility defined as t_0) and a random sample of person-time from two cohort members with no evidence of ADHD medication use on that date matched at t_0 for calendar year, age, and gender.

Study Medications

ADHD medications and other drugs of interest were identified from pharmacy records, which included the date a prescription was dispensed, drug name, dose, quantity and days supply. ADHD medications included the amphetamine-related psychostimulants (methyphenidate, dexmethylphenidate, dextroamphetamines and amphetamine salts), other stimulants (pemoline), and the selective norepinephrine reuptake inhibitor, atomoxetine.

Every person-day during study follow-up was classified according to use of ADHD medications (Appendix 2). *Current use* was defined as the period between the prescription start date and the end of the days of supply (including up to a 7-day carryover from previous

prescriptions). *Former use* included person-time that occurred following current use through the end of study follow-up. *Nonuse* included person-time with no prescribed use of ADHD medications on the day being classified or any preceding days. Former users and nonusers could become current users of ADHD medications during follow-up, and when this occurred their user person-time was classified as described above.

Study Endpoints

The primary study endpoint was serious cardiovascular disease (defined as sudden cardiac death, myocardial infarction, or stroke). Sudden cardiac death was defined as a sudden, pulseless condition or collapse consistent with a ventricular tachyarrhythmia occurring in a community setting that was fatal or resuscitated (i.e., requiring cardiopulmonary resuscitation and defibrillation).[13-17] Acute myocardial infarction (MI) was defined as an acute cardiac event meeting the international diagnostic criteria for myocardial infarction (a combination of clinical symptoms, diagnostic cardiac enzyme elevation, or electrocardiogram changes) for which a cohort member was hospitalized.[18,19,20] Stroke was defined as an acute neurologic deficit of sudden onset that persisted more than 24 hours, corresponded to a vascular territory, and was not explained by other causes such as trauma, infection, vasculitis, extracranial hemorrhage leading to hypotension or profound hypotension from another cause.[18,21,22]

All endpoints were identified from computer data sources and confirmed through review of hard copies of all pertinent medical records, including hospitalizations, emergency medical services reports, autopsy reports, and death certificates (Appendix 3). Case adjudication was conducted by at least two adjudicators from the lead site (Vanderbilt) (two cardiologists for sudden cardiac death and myocardial infarction and two neurologists for stroke), who reviewed potential cases from all sites and were unaware of exposure status (Appendix 4).

For potential cases for whom we were unable to adjudicate medical records (21% of potential cases), case status was determined from a computer case definition (Appendix 5). This definition was based on the positive predictive value of the diagnosis codes that lead to being a potential case. Among the potential cases for whom we were unable to adjudicate medical records, we added 1 sudden cardiac death, 1 acute myocardial infarction, and 6 strokes using the computer-based definition.

Analysis

We calculated the hazard ratio for users of ADHD medications compared to nonusers from Cox regression models, using robust sandwich variance estimators to account for the matched study design and for persons entering the cohort multiple times.[23] The hazard ratio was adjusted for both baseline characteristics and changes in characteristics that occurred during follow-up. We calculated the adjusted incidence of endpoints by multiplying the incidence rate in the nonusers by the hazard ratio.

Because the number of covariates reflecting baseline cohort characteristics was large relative to the number of endpoints, we adjusted for these covariates by including a site-specific propensity score in the regression models. The propensity score was defined as the probability that the patient was a current ADHD medication user on the first day of study follow-up, estimated for each site using logistic regression.[24] The baseline variables in the propensity score included sociodemographic characteristics as well as information on medical care encounters consistent with psychiatric disorders, asthma and other respiratory illnesses, seizure and other neurologic disorders, unintentional injuries, cardiovascular diseases, and other diseases. For each

site, we tested the adequacy of the propensity score models by calculating the propensity-score adjusted means of baseline variables for users and nonusers of ADHD medications; these were comparable (Appendix 6).

In our primary analysis, we adjusted for site, propensity score decile, and several time-dependent covariates (medical and psychiatric conditions, healthcare utilization, age, and calendar year) (Appendix 7). Additional analyses stratified by age (2-17 years, 18-24 years) and using alternative exposure groups, cohort inclusion criteria, and endpoint exclusions were performed to test key study assumptions. We performed all statistical analyses with SAS 9.1 (SAS Institute, Cary, North Carolina).

Human Subjects Protection

The study was approved by the institutional review boards at each of the participating institutions, and the Food and Drug Administration Research in Human Subjects Committee. In addition, permission was obtained from each of the data sources (TennCare Bureau, Tennessee Department of Health, Washington Department of Health and Human Services, Kaiser Permanente, OptumInsight Epidemiology).

Results

The study cohort included 1,200,438 children and youth. The mean age of cohort members at baseline was 11.1 years, and ranged from 8.7 to 12.0 years at the study sites (Table 1). The mean length of follow-up for the cohort was 2.1 years, and ranged from 1.5-3.9 years at the study sites. Characteristics of current users and nonusers at baseline are shown in Table 2. Generally, current users had more evidence of healthcare utilization of all types. In addition, current users had greater prevalence of psychiatric comorbidities and greater use of psychotropic medications. Current users were also more likely to have asthma, seizures, and congenital heart defects. For both current users and nonusers, alcohol and drug use, as determined from medical care encounter records, were uncommon.

The 2,579,104 person-years of follow-up included 373,667 person-years of follow-up for current use of ADHD medications, 607,475 person-years of follow-up for former use, and 1,597,962 years of follow-up for nonusers. There were 81 cohort members with serious cardiovascular events, or 3.1/100,000 person-years: 33 sudden cardiac deaths (1.3/100,000 person-years), 9 acute myocardial infarctions (0.3/100,000 person-years), and 39 strokes (1.5/100,000 person-years). Characteristics of the confirmed cases according to study drug exposure are shown in Appendix 8. In the multivariate model, older age, current antipsychotic use, major psychiatric illness, serious cardiovascular conditions, and chronic illness were associated with increased risk for serious cardiovascular events (Appendix 7).

Current users of ADHD medications had an adjusted rate of serious cardiovascular events that was not statistically significantly different from that of nonusers (hazard ratio [HR] 0.75; 95% confidence interval [CI] 0.31 to 1.85) (Table 3). The risk for former users did not differ materially from that for nonusers (HR 1.03; 95% CI 0.57-1.89). When former users served as the reference, which assessed the possible effect of unmeasured confounding, current users of ADHD medications had no increased risk of serious cardiovascular events (HR 0.70; 95% CI 0.29-1.72) (Appendix 9). There was also no evidence of increased risk for the individual endpoints of sudden cardiac death, acute myocardial infarction, or stroke (Table 4). We found no evidence of increased risk for methylphenidate (HR 0.96; 95% CI 0.31-2.97), the most frequently used ADHD medication (Appendix 10). Data were too sparse for other individual drugs to fit regression models.

We performed several alternative analyses to test the robustness of study findings (Table 5). To assess possible bias from inclusion of persons who used ADHD medications before the beginning of follow-up,[25] we restricted the current users of ADHD medications to new users (no ADHD medications during the 365 days preceding t_0). Findings were essentially identical to those of the primary analysis (HR 0.73; 95% CI 0.24-2.10) (Appendix 11). When we included seven cases excluded from the primary analysis because they had evidence of severe underlying cardiac disease for which sudden cardiac death would not be unexpected, we found no increased risk for current users (HR 0.71; 95% CI 0.29-1.72) (Appendix 11). In analyses including only children 2-17 years of age, we found no association between ADHD medication use and serious cardiovascular events (HR 0.98; 95% CI 0.41-2.36) (Appendix 11). When children with evidence of serious psychiatric disease were excluded, we also found no association (HR 0.66, 95% CI 0.20-2.16) (Appendix 11).

We also performed analyses to test other key study assumptions. A site-specific analysis (Appendix 12) suggested a potential difference between Medicaid and non-Medicaid sites, although numbers were very small. However, a pooled Medicaid versus non-Medicaid analysis

found no statistical evidence of heterogeneity. Another analysis expanded the definition of current use to include the 89 days after the end of current use to account for possible exposure misclassification related to clinical use of ADHD medications or for medications stopped following prodromal symptoms of an endpoint (e.g. headache preceding stroke). Finally, we performed an analysis where time-dependent variables were fixed at baseline. The findings of these analyses were essentially identical to those reported here.

Discussion

Recent case reports from the Food and Drug Administration and studies from other populations have raised concern that ADHD medications might be associated with increased risk of sudden cardiac death, acute myocardial infarction, and stroke. In this study of 1,200,438 children and youth from four geographically diverse health plans, we assessed the risk of serious cardiovascular disease for current use of ADHD medications and found that such use was not associated with increased risk for these outcomes,although the 95% confidence interval was consistent with up to a two-fold increased risk.

Our findings of no increased risk of serious cardiovascular disease in children and youth with ADHD drug use are consistent with some, but not all previous reports. Three recent cohort studies using Florida Medicaid data and General Practice Research Database data reported no increased risk for serious cardiovascular disease in children and youth.[8-10] The two Florida Medicaid studies included 42,612 person-years and 28,285 person-years of current ADHD medication use, while the United Kingdom study included 18,637 total person-years of follow-up (current use exposure time was not reported). Thus, even though the cohorts were large, it is possible that the studies were underpowered to detect a difference given the rarity of serious cardiovascular disease in children and youth. By comparison, our study included over 1.2 million children and youth with more than 2.5 million person-years of follow-up and 373,667 person years of current ADHD medication use. A recent case-control study suggested a 7-fold increased risk for sudden cardiac death for users of ADHD medications,[11] but there were distinct methodological differences between the case-control study and our study which may have affected the results.

The findings of our study should be viewed in the context of several limitations, including potential limitations of the comparison group for the primary analysis, the exposure group definition, the handling of covariates in the analyses, the case definition, and the differences in the populations contributing data to the study. We employed several strategies to address these potential limitations.

After weighing several options, we considered non-users of ADHD medications to represent the best choice for a comparison group in our primary analysis. We considered drawing the comparison group from children and youth diagnosed with ADHD who had no medication use, but ultimately decided that this group would differ systematically from current users because of potential misdiagnosis of ADHD, less serious ADHD, and non-adherence (i.e., prescribed ADHD medications but did not fill prescriptions). Importantly, all persons who were non-users at baseline had the possibility of becoming users during follow-up. To address bias that would be introduced if ADHD medication users were healthier than non-users or sought and received preventive healthcare more frequently than non-users,[26] we performed an alternative analysis with former users (those who were users of ADHD medications and stopped) as the comparison group. The findings of this analysis were not materially different from our primary analysis.

To maximize study power, the planned primary analysis included person-time for prevalent use of study drugs, defined as using ADHD medications at the time of entrance into the cohort. To address bias that would be introduced if the exposure conferred a period of high initial risk, if there was substantial "depletion of susceptibles," or if important covariates were modified by the exposure,[26] we performed an analysis restricted to new users. We also performed a recent user analysis, which included indeterminate person time and current use person time as the primary exposure. In this analysis, we accounted for the possibility that prodromal symptoms

could result in a change in exposure status (i.e., headache symptoms before a stroke could lead a child to stop ADHD medications). Finally, we performed additional analyses where we carried over the most recent user status for the small number of persons who left and re-entered the cohort. All of these additional analyses yielded results similar to the primary analysis.

We used propensity scores to adjust for a large number of study covariates. Given the small number of study end points, we considered this preferable to fitting regression models relating ADHD use to study end points and directly adjusting for the individual covariates. We also considered this preferable to deriving more parsimonious models that would adjust for a smaller number of study covariates. While visual inspection of the site specific propensity scores might suggest that non-users had propensity scores that largely grouped around 0, the range of propensity scores for both current users and non-users included the full distribution from 0 to 1. Furthermore, our comparisons of users and non-users at baseline would suggest that the propensity scores were able to balance the exposure groups. In addition, analyses in which we created models with important covariates and no propensity score did not differ from the primary models. We also performed analyses in which we held time dependent variables at baseline values to avoid the possible bias that would be introduced if variables on the causal pathway between exposure and outcome were affected by exposure. Again, these analyses did not differ materially from our primary analysis.

The case definition was defined prospectively, ascertained with attention to quality assurance, and included masked adjudication. We excluded cases where there was evidence of severe underlying cardiac disease (i.e., end-stage congestive heart failure). Alternative analyses including these cases did not differ from the primary analysis.

Although the study population was large, the endpoints considered are very rare in children and youth. The rate of confirmed sudden cardiac death in our study (1.3/100,000 person-years) was comparable to previous population-based estimates of pediatric sudden cardiac death (1.3-8.5/100,000 person-years).[27] Similarly, our rate of acute myocardial infarction (0.3/100,000 person-years) was comparable to previously described rates in adolescents (0.6/100,000 person-years)[28] and our rate of stroke (1.7/100,000 person-years) was comparable to previous estimates of pediatric stroke (1.2-2.7/100,000 person-years).[29,30] Even so, despite the very large population, power was limited for many analyses. In particular, the study had limited power to examine factors such as individual drug and duration of use, or effects in small subpopulations at potentially increased risk.

To minimize bias resulting from possible site differences from the four health plans included in the study, we created common data models and performed numerous quality checks at each step of data processing. We also performed site specific analyses and did not demonstrate an association between use of ADHD medications and serious cardiovascular disease at any of the individual sites. In addition, analyses restricted to the years in which all sites had data (2000-2005) did not demonstrate any association.

Despite these limitations, the findings of this study provide important information to patients, families, providers, and policy makers who may consider the use of medications in the treatment of ADHD. The study included over 1.2 million children and youth from four geographically diverse health plans. The study endpoints were carefully constructed and hard copies of medical records were reviewed to confirm endpoints. Thus, even if unmeasured confounding resulting from differences between users of ADHD medications and the non-user comparison group were present, it seems unlikely that our study would have missed an association of the magnitude suggested by some studies.[11]

In conclusion, this population of children and youth with 2.5 million person-years of followup had 3.1 serious cardiovascular events per 100,000 person years. Although the point estimates of the relative risks for ADHD medications did not indicate increased risk, the upper bound of the 95 percent confidence interval indicates that up to a two-fold increased risk cannot be ruled out. However, the absolute magnitude of any increased risk would be low.

Table 1. Study cohort, by site

	Tennessee Medicaid	Kaiser Permanente California	OptumInsight Epidemiology	Washington Medicaid	Total
Study Period	1986-2005	1999-2005	1998-2005	2000-2005	1986-2005
N in cohort	200,198	191,772	692,187	116,281	1,200,438
% Medicaid	100.0	4.4	0	100.0	27.0
Age in years, mean	8.7	11.1	12.0	10.0	11.1
First day of follow-up, mean	1999.0	2002.1	2002.3	2002.2	2001.7
Follow-up in years, mean	3.9	2.6	1.5	2.1	2.1

Table 2. Cohort characteristics by baseline ADHD medication use[*]

	Nonuser	Current User
Demographic characteristics		
Age in years, mean	11.1	11.1
Male, %	70.9	71.1
Non-white-, %	50.5	36.8
Reside in metropolitan area, %	78.4	77.1
Psychiatric conditions[†]		
ADHD diagnosis, %	1.3	57.4
Major depression, %	1.6	10.4
Bipolar disorder, %	0.2	2.1
Psychosis, %	0.1	0.5
Autism, %	0.2	1.4
Mental retardation, %	0.6	4.0
Prior suicide attempt, %	0.1	0.3
Psychotropic medication use[†]		
Antidepressants, %	1.8	15.0
Mood stabilizers, %	0.5	4.2
Antipsychotics, %	0.4	5.2
Benzodiazepines, %	0.1	0.5
Medical conditions[†]		
Asthma, %	16.1	22.1
Seizures, %	0.6	2.1
Obesity, %	0.9	1.2
Major congenital heart defect, %[‡]	0.5	0.8
Minor congenital heart defect, %[‡]	3.6	6.9
Diabetes, %	0.4	0.5
Other serious health conditions, %[§]	0.9	1.3
Alcohol and drug use[†]		
Alcohol or drug use, %	0.4	1.5
Smoking, %	0.6	0.9
Use of health services[†]		
Psychiatric hospitalization, %	0.3	1.9
Medical hospitalization, %	2.5	4.1
Medical emergency department visit, %	12.9	15.8
Any psychiatric care, %	5.4	63.1
Any cardiovascular care, %	4.0	6.0
Any outpatient visit, %	75.1	92.9
Any prescription, %	22.0	31.7

*Adjusted for age, sex, and site.

†Measured from claims and medications used in the 365 days before study entry.

‡Major congenital heart defects included common truncus, transposition of the great vessels, Tetrology of Fallot, common ventricle, endocardial cushion defect, pulmonary atresia, tricuspid atresia, hypoplastic left heart syndrome, coarctation of the aorta, and total anomalous pulmonary venous return. Minor congenital heart defects included any other congenital heart anomaly.

§Other serious health conditions included pneumonia, thyroid disease, and kidney disease.

Table 3. Occurrence of serious cardiovascular disease by current use of ADHD medications

ADHD medication use	Person-years	Events	Rate/100,000	Hazard Ratio†	95% confidence interval low	95% confidence interval high
Non-user	1,597,962	49	3.07	1.00	Ref	Ref
Former user	607,475	25	4.12	1.03	0.57	1.89
Current User, any ADHD drug	373,667	7	1.87	0.75	0.31	1.85

†Hazard ratios estimated with Cox regression models, which included site-specific propensity score decile, site, medical conditions (serious cardiovascular disease, serious chronic illness), psychiatric conditions (major psychiatric illness, substance abuse, and antipsychotic use), utilization variables (medical hospitalization and general medical care access), age, and calendar year. Regression models were not fit for amphetamines, atomoxetine, and pemoline, because there was only one event per medication class.

Table 4. Occurrence of individual endpoints by current use of ADHD medications

ADHD medication use	Person-years	Events	Rate/100,000 person-years	Hazard Ratio†	95% confidence interval
Sudden Cardiac Death					
Nonuser	1,597,962	17	1.06	1.00	Reference
Former user	607,475	13	2.14	1.52	0.65-3.56
Current User	373,667	3	0.80	0.88	0.23-3.35
Acute Myocardial Infarction†					
Nonuser	1,597,962	6	0.38	1.00	Reference
Former user	607,475	3	0.49	0.88	0.16-4.71
Current User	373,667	0	0	-	-
Stroke					
Nonuser	1,597,962	26	1.63	1.00	Reference
Former user	607,475	9	1.48	0.80	0.33-1.96
Current User	373,667	4	1.07	0.93	0.29-2.97

†Hazard ratios estimated with Cox regression models which included site-specific propensity score decile, site, medical conditions (serious cardiovascular disease, serious chronic illness), psychiatric conditions (major psychiatric illness, substance abuse, and antipsychotic use), utilization variables (medical hospitalization and general medical care access), age, and calendar year. Because there were no events in the current user group, models were not calculated for acute myocardial infarction.

Table 5. Alternative analyses, ADHD medication use, and serious cardiovascular disease

Alternative Analyses, Adjusted Hazard Ratios for Serious Cardiovascular Events, According to Use of ADHD Medications

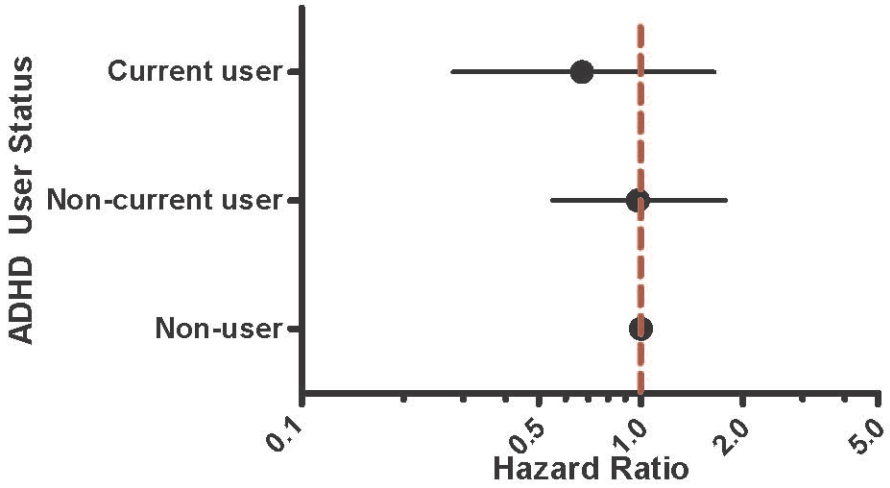
Analysis	Exposure	Reference	Hazard Ratio†	95% Confidence Interval
Primary Analysis	Current User	Nonuser	0.75	0.31-1.85
Exposures were restricted to new ADHD medication users§	New User	Nonuser	0.73	0.24-2.10
Cases included those with severe underlying cardiac disease for which sudden cardiac death would not be unexpected	Current User	Nonuser	0.71	0.29-1.72
Restricted to children of age 2-17 years	Current User	Nonuser	0.98	0.41-2.36
Restricted to children without evidence of serious psychiatric disorders‡	Current User	Nonuser	0.66	0.20-2.16

†Hazard ratios estimated with Cox regression models which included site-specific propensity score decile, site, medical conditions (serious cardiovascular disease, serious chronic illness), psychiatric conditions (major psychiatric illness, substance abuse, and antipsychotic use), utilization variables (medical hospitalization and general medical care access), age, and calendar year.

§New users included individuals who had no ADHD medication use in the 365 days prior to t0.

‡This analysis excluded cohort members who had any of the following at baseline or during follow-up: use of psychotropic medications (antipsychotics, mood stabilizers or lithium), or evidence of treated mental illness (major depression, bipolar disorder, psychotic disorder, autism or hospitalization with a psychiatric diagnosis).

Figure 1. Adjusted hazard ratios for serious cardiovascular disease (sudden cardiac death, acute myocardial infarction, or stroke) for current and non-current users of ADHD medications compared to non-users of ADHD medications



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Appendixes: Attention Deficit-Hyperactivity Disorder Medications and Risk of Serious Cardiovascular Events in Children and Youth

Appendixes

These appendixes provide supplementary material for the paper, including a more detailed presentation of several methodologic points and secondary analyses. They should be read in conjunction with the primary paper.

Appendix A. Serious Illness Exclusions

Children and youth with serious illnesses were excluded from the study because they were felt to have a substantially increased mortality risk. It would thus be inefficient to review deaths for these children as potential cases. It was also considered likely that the use of ADHD medications would be less frequent in this population. For example, none of the FDA cases of sudden cardiac death in persons under 25 years of age were reported to have these exclusion illnesses.[33] Persons were thus excluded from the cohort if they had the following during the period 365 days prior to the qualifying date:

1. One inpatient claim with a diagnosis for the exclusion disease (Table A-1), with the claim of interest appearing anywhere in the primary and secondary diagnoses; or,
2. Two outpatient claims separated by at least 30 days for the exclusion disease; or,
3. One prescription for a medication used to treat the exclusion disease; or,
4. One claim with a procedure for the exclusion disease.

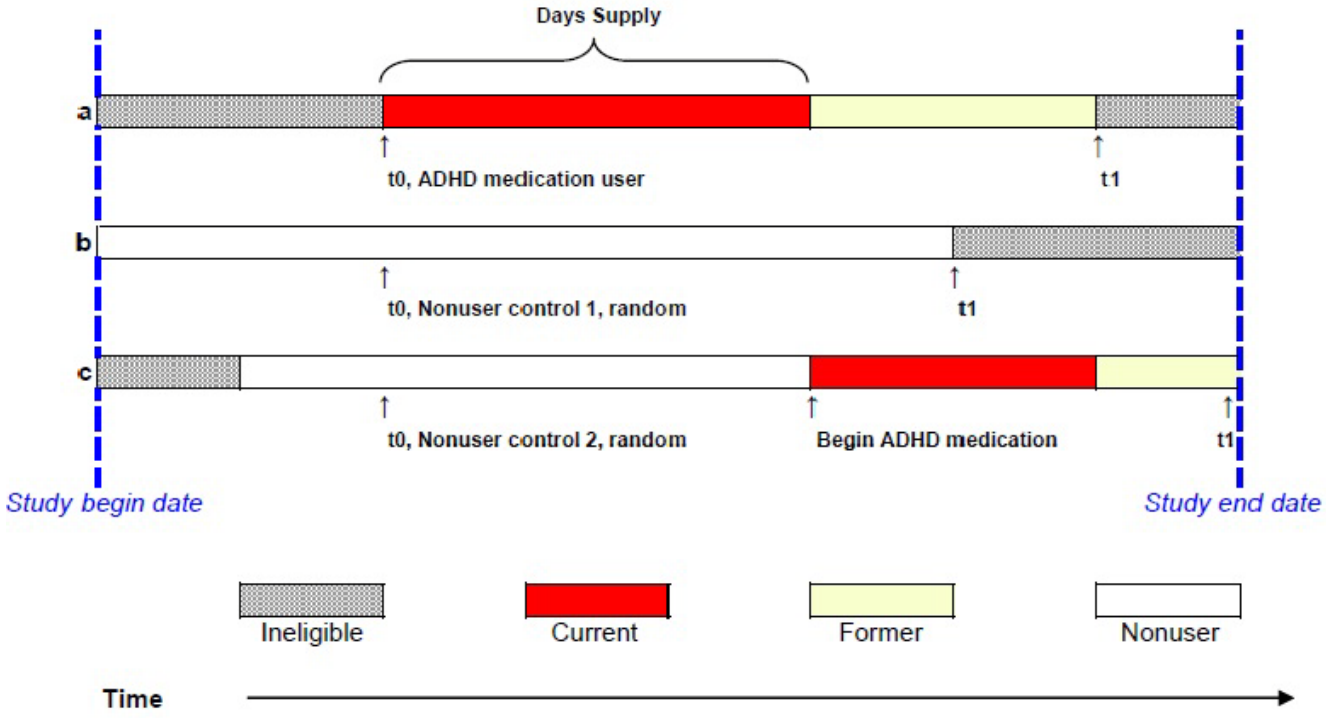
Table A-1. Exclusion illnesses

Sickle cell disease
Cystic fibrosis
Cerebral Palsy
Cancer
HIV
Organ transplant
Liver failure
Renal dialysis (except single inpatient episode)
Respiratory failure
Other potentially lethal diseases of childhood (metabolic diseases, aplastic anemia, congenital immune deficiencies, lethal chromosomal anomalies)

Appendix B. Study Person-Time

All study person-time was classified according to ADHD medication use as current, former, or nonuser. Figure B-1 illustrates how this classification was performed.

Figure B-1. Study person-time



To assemble the cohort, we first identified ADHD medication users who met study criteria (Figure B-1, Person a). The first day of qualifying use was defined as t_0. Study follow-up ended at the end of the study or when the person no longer met study criteria, defined as t_1. For each ADHD user, we then randomly selected up to two control persons with no ADHD medication use on t_0 (Figure B-1, Persons b and c). Controls were from the same site's health plan members enrolled on t_0 matched for calendar year, age, and gender who also met the study inclusion criteria for users. Follow-up for nonusers began on t_0 for the matched ADHD medication user and ended when the nonuser left the cohort, t_1.

For each cohort member, every person-day during study follow-up was classified according to probable use of ADHD medications. *Current use* was defined as the period between the prescription start date and the end of the days of supply (including up to a 7-day carryover from previous prescriptions). *Former use* included person-time following current use through the end of study follow-up that was not classified as current use. *Nonuse* included person-time with no prescribed use of ADHD medications on these days or at any time in the past. Nonusers could become users of ADHD medications during follow-up (Person c), but they did not re-enter the cohort. Rather, their person-time was classified as described above.

Appendix C. Case Definitions and Identification

Because we planned to review medical records for potential cases and anticipated that serious cardiovascular events in children and youth would be rare, initial definitions for potential cases selected for review and adjudication were intentionally broad to increase the sensitivity of our case finding. We first created a clinical definition for each endpoint (described in the Methods section) and then created a search definition of potential cases for review.

Sudden Cardiac Death

Potential sudden cardiac death (SCD) cases were identified from state death certificates (Tennessee, Washington State, Kaiser) or the National Death Index (Tennessee, Kaiser, OptumInsight Epidemiology). To ensure ascertainment of deaths occurring in youth 18 to 24 years of age (who may have moved away for college or early careers while still insured by a parent) for sites using state death certificates, we also performed National Death Index searches for any cohort member who was 18-24 years of age during follow-up, ended enrollment prior to another reason for end of follow-up, and had no evidence of being alive subsequently based on re-enrollment, other healthcare claims, or births. All deaths that were potential cases identified in the National Death Index search were already identified from state vital records.

We included the following underlying causes of death on death certificates and national death index searches: any cardiac system cause of death (ICD-9 390-459, ICD-10 I00-I99); congenital anomaly (ICD-9 740-759, ICD-10 Q00-89); diabetes (ICD-9 250, ICD10-E10-E14, collapse (ICD-9 780.2, ICD-10 R55); sudden death, unknown cause (ICD-9 798.0-798.9, ICD-10 R96); respiratory arrest (ICD-9 799.1, ICD-10 R09.2); death from ill-defined condition (ICD-9 799.8, ICD-10 R98); and unknown cause of death (ICD-9 799.9, ICD-10 R99). A secondary source was hospital discharge data, including Emergency Department (ED) records. We included the following primary diagnoses for hospitalizations with death: cardiac arrest (ICD-9 427.5), sudden death, unknown cause (ICD-9 798.0-798.9); respiratory arrest (ICD-9 799.1), and cardiac arrest due to a procedure (ICD-9 997.1).

Acute Myocardial Infarction

Potential cases of acute myocardial infarction were identified from principal hospital discharge diagnoses of acute myocardial infarction or cause of death from death certificates using the following codes: acute myocardial infarction (ICD-9 410, ICD-10 I21, I22), intermediate coronary syndrome (ICD-9 411.1, ICD-10 I20.0), acute coronary occlusion (ICD-9 411.8, ICD-10 I24), old myocardial infarction (ICD-9 412, ICD-10 I25.2), angina pectoris (ICD-9 413, ICD-10 I20.1, I20.8, I20.9), coronary atherosclerosis (ICD-9 414.0, ICD-10 I25.0, I25.1), aneurysm of heart (ICD-9 414.1, ICD-10 I25.3, I25.4), other specified forms of chronic ischemic heart disease (ICD-9 414.8, ICD-10 I25.5-I25.9), and sequelae of myocardial infarction (ICD-9 429.7, ICD-10 I23).

Stroke

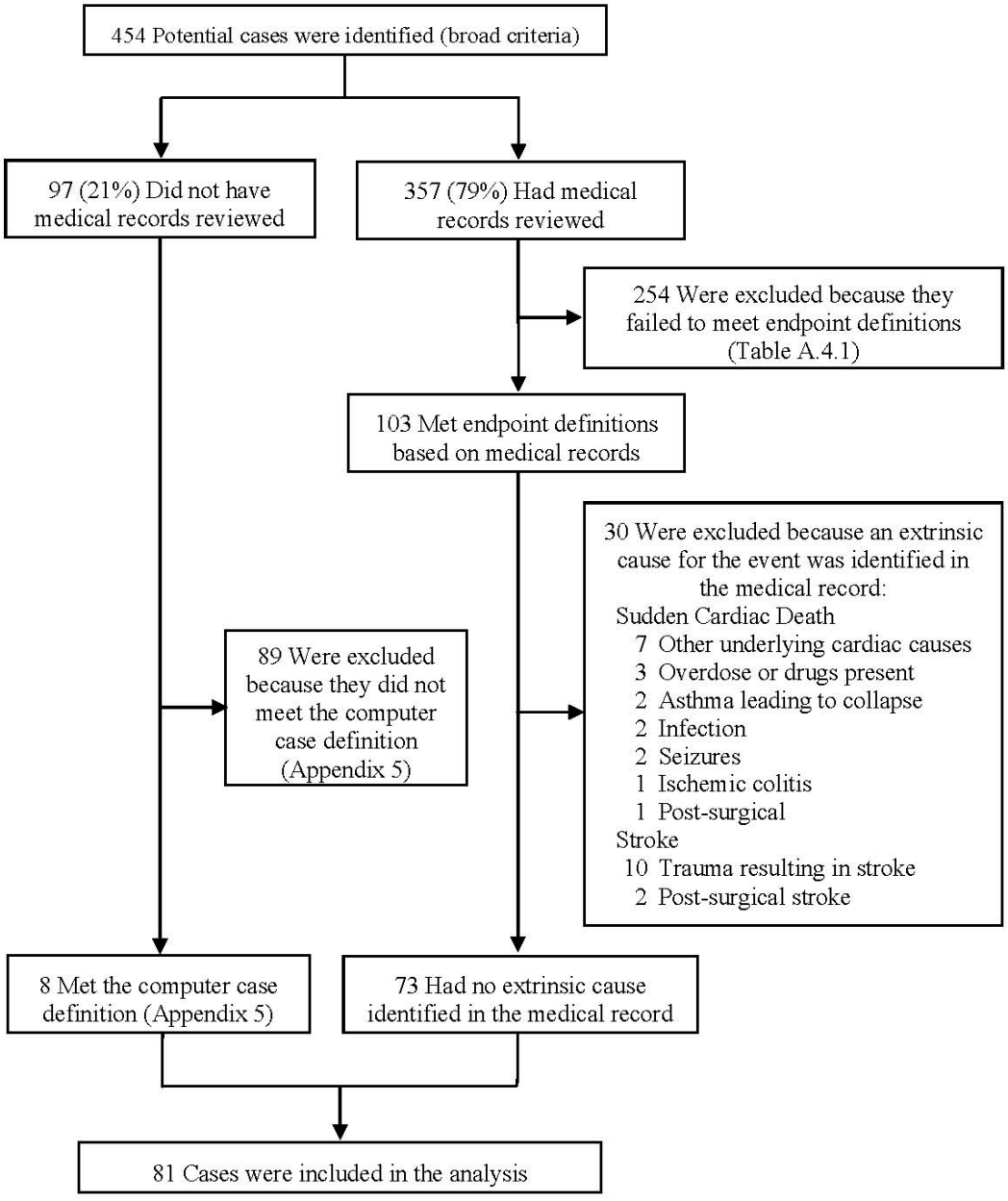
Potential stroke cases were identified from principal hospital discharge diagnoses of stroke or cause of death from death certificates using the following codes: intracerebral hemorrhage (ICD-9 431, ICD-10 I61, I64), nontraumatic extradural hemorrhage, (ICD-9 432.0 ICD-10 I62.1), unspecified intracranial hemorrhage, (ICD-9 432.9, ICD-10 I62.0, I62.9),

occlusion and stenosis of precerebral arteries, (ICD-9 433, ICD-10 I65), occlusion of cerebral arteries, (ICD-9 434, ICD-10 I63, I66), transient cerebral ischemia, (ICD-9 435, ICD-10 G45.9), acute, but ill-defined, cerebrovascular disease, (ICD-9 436, ICD-10 I67, I68), late effects of cerebrovascular disease, (ICD-9 438, ICD-10 I-69), hemiplegia, (ICD-9 342, ICD-10 G81), other paralytic syndromes, [ICD-9 344 (not 344.6), ICD-10 G83].

Appendix D. Medical Record Review

Medical records were reviewed by two adjudicators at the lead site (two cardiologists for sudden death and acute myocardial infarction and two neurologists for stroke) based on clinical criteria for the outcome of interest and to exclude cases due to non-cardiac causes (e.g. overdose, other underlying illnesses). For the <5% of cases in which the adjudicators differed on any element of the adjudication [either whether the event was a case or the type of outcome (i.e., hemorrhagic stroke vs. thromboembolic stroke)], the study principal investigator met with the adjudicators for resolution. Final case status is shown below (Figure D-1).

Figure D-1. Identification of cases and medical record review



Exclusion of Potential Cases Based on Medical Record Review

Table D-1. Reasons for exclusion of potential cases

Reason	All	Sudden Cardiac Death	Acute Myocardial Infarction	Stroke
All	254	149	28	77
Syncope/Weakness/Dizziness only[§]	86	75	0	11
Trauma	34	14	0	20
Evaluated and found not to have the condition	26	7	12	7
Miscode	16	2	6	8
Other diagnoses	15	11	1	3
Prior event	10	0	0	10
Suicide	9	9	0	0
Procedure Related	9	4	5	0
Spinal cord injury	8	0	0	8
Overdose	8	6	1	1
Gunshot wound	7	6	1	0
Seizure only	5	2	0	3
Drowning	5	5	0	0
Infection	4	1	1	2
Transient Ischemic Attack	4	0	0	4
Undetermined	3	3	0	0
House fire	2	2	0	0
Snake bite	1	0	1	0
Homicide	1	1	0	0
Choking	1	1	0	0

[§]In cases where the child/youth did not die.

Appendix E. Computer Algorithm for Cases in Which Medical Records Were Unavailable or Had Insufficient Information

This appendix describes the computer algorithm developed for cases for which medical records were sought, but were not available or where the record was reviewed but had insufficient information for adjudication. The positive predictive value of the algorithm across all three endpoints was 91 percent.

Decision Rule for Sudden Cardiac Death

For sudden cardiac death, the computer-based definition was based on prior literature[34] and the predictive value of codes in the present study, and included the following:

1. Evidence of death (death certificate or national death index), AND
2. No evidence of other explanatory cause in the causes of death [(i.e., motor vehicle collision, gunshot wound, drowning, suicide, post-operative death, or cocaine use/abuse (ICD-9 304.2, 305.6, 968.5)], AND
3. Cause of death included any of the codes below[34]:

ICD9		ICD10	
From previous literature[34]			
401.9	Essential hypertension, NOS	I10	Essential hypertension
402	Hypertensive heart disease, NOS	I11.9	Hypertensive heart disease w/o heart failure
410	Acute myocardial infarction	I21	Acute myocardial infarction
		I22	Subsequent myocardial infarction
		I23	Certain complications following AMI
411	Other acute/subacute ischemic heart disease	I24	Other acute ischemic heart disease
412	Old myocardial infarction	I25.2	Old myocardial infarction (incl. With I25)
413	Angina pectoris	I20	Angina pectoris
414	Other forms of chronic ischemic heart disease	I25, I25.1	Chronic ischemic heart disease
425.4	Primary cardiomyopathy, other	I42, I42.9,I42.8	Cardiomyopathy, Not otherwise specified
427.5	Cardiac arrest	I46	Cardiac arrest
		I47.0	Reentry ventricular arrhythmia
427.1	Paroxysmal ventricular tachycardia	I47.2	Ventricular tachycardia
427.4	Ventricular fibrillation and flutter	I49.0	Ventricular fibrillation and flutter
427.8	Arrhythmia, other but not specified	I49.8	Other specified cardiac arrhythmias
427.9	Arrhythmia (cardiac), NOS	I49.9	Cardiac arrhythmia, unspecified
429.2	Cardiovascular disease, unspecified	I51.6	Cardiovascular disease, unspecified
429.9	Heart disease, unspecified	I51.9	Heart disease, unspecified
440.9	Arteriosclerosis, NOS	I70.9	Atherosclerosis, NOS
798.2	Death in <24 hours	R96.1	Death in <24 hours
798.9	Unattended death	R98	Unattended death
From the present study			
745.0	Common truncus	Q20	Anomalies of cardiac chambers
745.1	Transposition of great vessels	Q20.3	Transposition of great vessels
745.2	Tetrology of Fallot	Q21.3	Tetrology of Fallot
745.3	Common ventricle	Q20.0	Common ventricle
745.6	Endocardial cushion defects	Q21.2	Endocardial cushion defects
746, 745	Other congenital anomalies of heart	Q22, Q23	Other congenital anomalies of heart

Among 241 potential sudden cardiac deaths, records for 45 were unavailable or had insufficient information. Among these cases, one additional case met the computer algorithm definition and was included as a case in the analysis. The positive predictive value of the algorithm as applied to the found cases was 86%.

Decision Rule for Acute Myocardial Infarction

For acute myocardial infarction, the computer-based definition was based on prior literature[35] and the predictive value of codes in the present study and included the following:

1. Hospitalization with at least 2 days stay (i.e., including at least three calendar days) OR Death, AND
2. Discharge diagnosis or Cause of Death = 410 (acute myocardial infarction).

Of 66 potential acute myocardial infarctions, records for 29 were unavailable or had insufficient information (mostly cases that were only treated in the emergency department and did not result in hospital admission or death). Of these, one additional case met the computer algorithm definition and was included as a case in the analysis. The positive predictive value of this algorithm as applied to cases where records were obtained and reviewed was 100 percent.

Decision Rule for Stroke

For stroke, the computer-based definition was based on prior literature[35] and the predictive value of codes in the present study and included the following:

1. Hospitalization with at least 2 days stay (i.e., including at least three calendar days) OR death, AND
2. No other codes in the discharge or death records indicate an alternate explanation (i.e., trauma, gunshot wound), AND
3. The following ICD-9 codes were included in the discharge listing or causes of death:

Description	ICD-9 codes	ICD-10 codes
Intracerebral hemorrhage	431	I61, I64
Occlusion and stenosis of precerebral arteries	433	I65
Occlusion of cerebral arteries	434 (not 434.xo)	I63, I66
Acute, but ill-defined, cerebrovascular disease	436	I67, I68

Of 147 stroke potential cases, records for 23 were unavailable or had insufficient information. Of these, 6 met the computer algorithm definition and were included as cases. The positive predictive value of this algorithm as applied to the found cases was 91 percent.

Records Unavailable or Had Insufficient Information, Case Included Based on Computer Algorithm

Endpoint*	ICD-9 code	Description	N cases with records unavailable or with insufficient information	Estimated positive predictive value from found cases
AMI	410.11	Acute myocardial infarction with prolonged hospitalization	1	100%
STK	431	Intracerebral hemorrhage and hospitalization	3	92%
STK	433.21	Occlusion, vertebral arteries and hospitalization	2	92%
STK	434.91	Occlusion, cerebral arteries and hospitalization	1	92%
SCD	I49.9	Death with cardiac arrhythmia as cause of death	1	86%

Records Unavailable or Had Insufficient Information, Case Excluded Based on Computer Algorithm

Endpoint*	ICD-9 code	Description	N cases with records unavailable or with insufficient information	Estimated positive predictive value from found cases
AMI	410	Acute myocardial infarction, 1 day stay (no death)	4	0%
AMI	411.1	Intermediate coronary syndrome	2	0%
AMI	413	Angina pectoris	7	0%
AMI	414.00	Coronary Atherosclerosis	12	0%
AMI	414.8	Other ischemic heart disease	2	0%
AMI	429.71	Sequelae of acute myocardial infarction	1	0%
SCD	427.5	Cardiac arrest, no death, no hospitalization	8	0%
SCD	780.2	Collapse	28	3%
SCD	799.1	Respiratory arrest	1	0%
SCD	799.9	Unknown cause of death	1	25%
SCD	R99	Other ill defined mortality	4	26%
SCD	I80.2	Phlebitis	1	10%
SCD	I51.4	Myocarditis	1	0%
STK	342	Hemiplegia	2	0%
STK	344	Other paralytic syndromes	6	0%
STK	431	Intracerebral hemorrhage, no death, no hospitalization	1	0%
STK	432.0	Extradural hemorrhage	1	0%
STK	432.9	Unspecified cerebrovascular disease	1	30%
STK	433.10	Occlusion carotid arteries	1	33%
STK	434.91	Occlusion cerebral arteries, no hospitalization	1	0%
STK	435.9	Transient ischemic attack	2	0%
STK	436	Acute ill defined cerebrovascular disease, no death, no hospitalization	1	0%
STK	I60.7	Subarachnoid hemorrhage	1	30%

*SCD=sudden cardiac death, AMI=acute myocardial infarction, STK=stroke

Appendix F. Propensity Score Diagnostics

One important check of the specification of the propensity score model is whether or not, after adjustment for propensity score, the distribution of the covariates is balanced. We performed this check for the ADHD medication user propensity score[36] using a variant of the inverse probability of treatment method described by Brenner.[37, 38] The advantage of this method is that it standardizes the distribution of the nonuser group to that of the current user group, which is left unadjusted. The method of Brenner works as follows: for patient i, let r_i be the variable value in the group providing the standard and s_i that in the group being standardized. Then the weight is defined as r_i/s_i. Thus, for the nonuser:user propensity scores, considering the ith patient in the nonuser group, r_i is the probability of treatment with ADHD medications, given a comparable covariate pattern. This is simply the propensity score for that patient. Similarly, s_i is the probability of being a nonuser, which is 1-propensity score. Table F-1 shows the covariate balance after adjusting the nonuser distribution. Unadjusted distributions of the study covariates by exposure group are shown in Table 2.

Table F1. Characteristics of nonusers and current users by study site, adjusted for propensity score

	Tennessee Medicaid		Kaiser Permanente Northern & Southern California		OptumInsight Epidemiology		Washington State Medicaid	
Characteristic	**Nonuser**	**Current**	**Nonuser**	**Current**	**Nonuser**	**Current**	**Nonuser**	**Current**
Demographic characteristics								
Age in years, mean	8.8	8.7	11.2	11.1	12.5	12.0	10.1	10.0
Male	70.9%	70.1%	74.0%	74.0%	69.5%	70.3%	72.0%	72.4%
Nonwhite	26.1%	29.8%	50.0%	56.4%	0.0%	0.0%	16.2%	16.5%
Reside in metropolitan area, %	62.2%	63.7%	95.9%	95.6%	-	-	70.7%	69.4%
Psychiatric conditions								
Major depression	10.0%	9.4%	13.3%	11.6%	12.4%	11.1%	8.3%	6.0%
Bipolar disorder	2.0%	2.2%	1.7%	1.7%	1.9%	2.2%	1.7%	1.8%
Psychosis	1.1%	1.0%	0.6%	0.4%	0.5%	0.4%	1.1%	0.6%
Autism	1.0%	0.9%	2.3%	2.5%	1.0%	1.2%	1.5%	1.2%
Mental Retardation	5.9%	5.4%	1.2%	2.1%	2.3%	4.2%	3.5%	3.6%
Prior suicide attempt	0.4%	0.4%	0.3%	0.2%	0.3%	0.3%	0.1%	0.1%
Psychotropic medication use								
Antidepressant	16.5%	17.5%	17.8%	14.7%	17.2%	13.8%	18.5%	18.5%
Mood stabilizers	4.5%	4.8%	3.4%	3.4%	3.9%	4.1%	5.2%	5.6%
Antipsychotics	6.0%	7.3%	4.4%	4.5%	3.7%	4.8%	5.4%	5.6%
Benzodiazepines	0.5%	0.4%	0.4%	0.3%	0.7%	0.6%	0.4%	0.2%
Medical Conditions								
Asthma	31.1%	27.6%	24.8%	21.1%	26.5%	21.4%	23.0%	18.4%
Seizures	4.4%	3.6%	1.3%	1.1%	2.3%	1.9%	2.6%	2.1%
Obesity	1.4%	1.3%	3.4%	3.1%	0.8%	0.8%	0.5%	0.5%
Major congenital heart disease‡	2.2%	2.0%	0.9%	0.8%	0.5%	0.5%	0.5%	0.4%
Minor congenital heart disease‡	8.0%	7.5%	4.3%	3.8%	8.1%	7.6%	6.4%	6.5%
Diabetes	0.9%	0.7%	0.3%	0.2%	0.5%	0.5%	0.6%	0.5%
Other serious health condition§	1.8%	1.4%	1.2%	0.90%	1.8%	1.5%	1.6%	1.1%
Alcohol and drug use								
Alcohol or drug use	1.2%	1.1%	1.5%	1.5%	0.9%	1.0%	2.1%	1.2%
Smoking	1.6%	1.4%	1.6%	1.2%	1.0%	0.8%	1.0%	0.7%
Use of health services								
Psychiatric hospitalization	3.3%	3.2%	2.1%	1.5%	1.9%	1.7%	2.3%	2.1%
Psychiatric outpatient visits	54.3%	59.0%	57.4%	67.9%	55.5%	63.7%	47.7%	58.7%
Cardiovascular hospitalization	0.5%	0.4%	0.4%	0.3%	0.2%	0.2%	0.3%	0.3%
Cardiovascular ED Visit	1.4%	1.3%	0.3%	0.3%	0.3%	0.3%	1.3%	1.0%
Cardiovascular outpatient visits	9.3%	8.4%	3.5%	2.8%	7.1%	6.5%	4.9%	4.3%
Other outpatient visits	95.9%	95.4%	93.7%	91.8%	92.8%	92.8%	90.3%	91.2%
Any prescription	37.9%	33.8%	28.1%	24.7%	40.5%	34.4%	20.8%	23.5%
Propensity Score								
Site specific propensity score	55.8%	58.2%	60.4%	67.2%	56.7%	61.9%	51.8%	60.1%

*Adjusted for propensity score using the method of Brenner.[37]

†Measured in the 365 days before study entry.

‡Major congenital heart defects included common truncus, transposition of the great vessels, Tetrology of Fallot, common ventricle, endocardial cushion defect, pulmonary atresia, tricuspid atresia, hypoplastic left heart syndrome, coarctation of the aorta, and total anomalous pulmonary venous return. Minor congenital heart defects included any other congenital heart anomaly.

§Other serious health conditions included pneumonia, thyroid disease, and kidney disease.

Appendix G. Full Model

Parameter	Chi Squared	Hazard Ratio	95% confidence interval
Age	<.0001	1.15	1.09-1.22
Current antipsychotic use	0.4271	1.52	0.54-4.24
Major psychiatric illness	0.0010	2.72	1.50-4.95
Substance abuse	0.5837	0.67	0.16-2.83
Serious cardiovascular	0.0001	5.36	2.26-12.71
Serious chronic illness	0.0002	5.12	2.19-11.93
Medical hospitalization	0.3421	0.64	0.25-1.61
General medical care access	0.4883	1.26	0.66-2.42
Site Washington State	0.2030	0.57	0.24-1.35
Site Tennessee Medicaid	0.8231	0.92	0.42-1.98
Site OptumInsight Epidemiology	0.0008	0.24	0.11-0.55
Propensity Score Decile 9	0.1989	0.50	0.17-1.44
Propensity Score Decile 8	0.0775	0.30	0.08-1.14
Propensity Score Decile 7	0.2462	0.55	0.20-1.51
Propensity Score Decile 6	0.1326	0.42	0.14-1.30
Propensity Score Decile 5	0.7971	1.12	0.47-2.69
Propensity Score Decile 4	0.7579	1.15	0.47-2.81
Propensity Score Decile 3	0.1411	0.41	0.13-1.34
Propensity Score Decile 2	0.4329	0.67	0.25-1.83
Propensity Score Decile 1	0.3400	0.60	0.21-1.71
Current user	0.5342	0.75	0.31-1.85
Former user	0.8999	1.04	0.57-1.89

Appendix H. Clinical Characteristics of Confirmed Cases

	Nonuser	Former ADHD Medication User	Current ADHD Medication User
Sudden cardiac death†			
Number of cases	17	12	3
Age, mean (standard deviation)	14.6 (4.2)	18.7 (4.3)	14.0 (8.0)
Autopsy reviewed	13 (76.5%)	9 (75.0%)	3 (100.0%)
Cardiac abnormalities found at autopsy	Left ventricular hypertrophy (1) Hypertrophic Obstructive Cardiomyopathy (3) No abnormality (9)	Left ventricular hypertrophy (1) Dilated cardiomyopathy (2) Tunneling of left anterior descending coronary artery (1) No abnormality (6)	Dilated cardiomyopathy (1) Fibro-fatty change sino-atrial node (1) Dysplasia of atrioventricular node artery (1)
Acute myocardial infarction†			
Number of cases	6	2	0
Age, mean (standard deviation)	18.7 (2.7)	18.0 (1.4)	-
ST segment elevation on electrocardiogram	6 (100%)	1 (50%)	-
Coronary artery occlusion noted at cardiac catheterization (among those who underwent the procedure)	3 of 5 who had cardiac catheterization performed	1 of 2 who had cardiac catheterization performed	
Stroke†			
Number of cases	21	8	4
Age, mean (standard deviation)	14.9 (4.1)	16.3 (2.2)	14.5 (5.1)
Etiology, Number (%)			
Hemorrhagic stroke	15 (71.4%)	2 (25.0%)	2 (50.0%)
Stroke from vessel occlusion or vessel abnormality	2 (9.5%)	2 (25.0%)	1 (25.0%)
Embolic stroke	1 (4.8%)	1 (12.5%)	1 (25.0%)
Unknown despite imaging	2 (9.5%)	-	-
Ischemic	1 (4.8%)	3 (37.5%)	

†Cases where outcomes were validated with medical records. Note that this table excludes cases where medical records were not reviewed, including one sudden cardiac death, one acute myocardial infarction, and six strokes.

For sudden cardiac death, the mean age at time of death was comparable across the study medication groups. Autopsy reports were reviewed for 78.1% of the sudden cardiac death cases and revealed occasional structural abnormalities, including left ventricular hypertrophy, hypertrophic obstructive cardiomyopathy, coronary artery anomalies, and fibro-fatty changes of the sino-atrial node. For acute myocardial infarction, the mean age for cases was greater than that for sudden cardiac death. All but one of the cases of acute myocardial infarction (87.5%) had electrocardiogram ST segment elevation. Seven of the cases of acute myocardial infarction underwent cardiac catheterization and coronary vessel occlusion was noted in 4 (57%). For strokes, the mean age of cases across the drug exposure groups was comparable. Hemorrhagic strokes were the most common stroke type for all three groups.

Appendix I. Analysis in Which Former Users Served as the Reference.

In this analysis, former users of ADHD medications were the reference group to account for possible unmeasured confounding.

Table I-1. Adjusted hazard ratios for serious cardiovascular events, according to use of ADHD medications, former Users as the Reference.

ADHD medication use	Person-years	Events	Rate/100,000 person-years	Hazard Ratio†	95% confidence interval
Former user	607,475	25	4.12	1.00	Reference
Nonuser	1,597,962	49	3.07	1.24	0.73-2.08
Current User	373,667	7	1.87	0.70	0.29-1.72

†Hazard ratios estimated with Cox regression models which included site-specific propensity score decile, site, medical conditions (serious cardiovascular disease, serious chronic illness), psychiatric conditions (major psychiatric illness, substance abuse, and antipsychotic use), utilization variables (medical hospitalization and general medical care access), age, and calendar year.

Appendix J. Adjusted Rates of Serious Cardiovascular Events for Individual ADHD Medications

ADHD medication use	Person-years	Events	Rate/100,000 person-years	Hazard Ratio†	95% confidence interval
Nonuser	1,597,962	49	3.07	1.00	Reference
Former user	607,475	25	4.12	1.03	0.57-1.89
Current User	373,667	7	1.87	0.75	0.31-1.85
Methylphenidate	192,257	4	2.08	0.96	0.31-2.97
Amphetamines‡	137,448	1	0.73	-	-
Atomoxetine‡	29,330	1	3.41	-	-
Pemoline‡	14,632	1	6.83	-	-

†Hazard ratios estimated with Cox regression models which included site-specific propensity score decile, site, medical conditions (serious cardiovascular disease, serious chronic illness), psychiatric conditions (major psychiatric illness, substance abuse, and antipsychotic use), utilization variables (medical hospitalization and general medical care access), age, and calendar year.

‡Because of low numbers of events for use of amphetamines, atomoxetine, and pemoline, regression models were not fit for these individual medications.

Appendix K. Alternative Analyses

Alternative Analysis Addressing Exposure Group Definitions

In this analysis, we restricted the analysis to individuals who had no ADHD medication use in the 365 days prior to t_0. Thus, covariates were measured at drug initiation.

Table K-1a. Adjusted hazard ratios for serious cardiovascular events, according to use of ADHD medications, restricted to new users of ADHD medications

ADHD medication use	Person-years	Events	Rate/100,000 person-years	Hazard Ratio†	95% confidence interval
Nonuser	1,597,962	49	3.07	1.00	Reference
Former user	376,456	19	5.05	1.13	0.60-2.13
Current User	192,040	4	2.08	0.73	0.24-2.10

†Hazard ratios estimated with Cox regression models which included site-specific propensity score decile, site, medical conditions (serious cardiovascular disease, serious chronic illness), psychiatric conditions (major psychiatric illness, substance abuse, and antipsychotic use), utilization variables (medical hospitalization and general medical care access), age, and calendar year.

In this analysis, the analysis was restricted to new users and focused on the individual endpoints, sudden cardiac death, acute myocardial infarction, and stroke.

Table K-1b. Adjusted hazard ratios for individual cardiovascular endpoints, according to use of ADHD medications, restricted to new users of ADHD medications

ADHD medication use	Person-years	Events	Rate/100,000 person-years	Hazard Ratio†	95% confidence interval
Sudden Cardiac Death					
Nonuser	1,597,962	17	1.06	1.00	Reference
Former user	376,456	8	2.13	1.13	0.41-3.10
Current User	192,040	2	1.04	0.76	0.18-3.26
Acute Myocardial Infarction					
Nonuser	1,597,962	6	0.38	1.00	Reference
Former user	376,456	3	0.80	-	-
Current User	192,040	0	0	-	-
Stroke					
Nonuser	1,597,962	26	1.63	1.00	Reference
Former user	376,456	8	2.13	1.14	0.47-2.76
Current User	192,040	2	1.04	0.97	0.22-4.27

†Hazard ratios estimated with Cox regression models which included site-specific propensity score decile, site, medical conditions (serious cardiovascular disease, serious chronic illness), psychiatric conditions (major psychiatric illness, substance abuse, and antipsychotic use), utilization variables (medical hospitalization and general medical care access), age, and calendar year. Because there were no events in the current user group, acute myocardial infarction models were calculated for former users and nonusers only.

Alternative Analyses Addressing Case Definitions

The case definitions for sudden cardiac death excluded potential cases with severe underlying cardiac disease that would likely be the cause of any sudden death event rather than a medication exposure. In reviewing the clinical characteristics of cases excluded due to other cardiac disease, we found five patients with severe congestive heart failure, several who were awaiting heart transplant; 1 patient with an arrest event in whom a post-mortem discovered a ruptured aortic aneurysm, and 1 patient with a history of viral illness who collapsed while running and had confirmed viral myocarditis on post-mortem. In this alternative analysis, we included all of these cases as confirmed events.

Table K-2. Adjusted hazard ratios for serious cardiovascular events, according to use of ADHD medications, including cardiac cases excluded for having severe underlying cardiac disease

ADHD medication use	Person-years	Events	Rate/100,000 person-years	Hazard Ratio†	95% confidence interval
Nonuser	1,597,962	54	3.38	1.00	Reference
Former user	607,475	27	4.44	1.01	0.58-1.78
Current User	373,667	7	1.87	0.71	0.29-1.72

†Hazard ratios estimated with Cox regression models which included site-specific propensity score decile, site, medical conditions (serious cardiovascular disease, serious chronic illness), psychiatric conditions (major psychiatric illness, substance abuse, and antipsychotic use), utilization variables (medical hospitalization and general medical care access), age, and calendar year.

Alternative Analyses Addressing Age

These analyses were stratified by age 2-17 years and age 18-24 years.

Table K-3. Adjusted hazard ratio for serious cardiovascular events, according to use of ADHD medications, stratified by age

ADHD medication use	Person-years	Events	Rate/100,000 person-years	Hazard Ratio†	95% confidence interval
Age 2-17 years					
Nonuser	1,516,662	45	2.97	1.00	Reference
Former user	576,553	21	3.64	1.03	0.55-1.95
Current User	355,360	7	1.97	0.98	0.41-2.36
Age 18-24 years					
Nonuser	81,300	4	4.92	1.00	Reference
Former user	30,922	4	12.94	0.92	0.14-6.24
Current User	18,307	0	0	-	-

†Hazard ratios estimated with Cox regression models which included site-specific propensity score decile, site, medical conditions (serious cardiovascular disease, serious chronic illness), psychiatric conditions (major psychiatric illness, substance abuse, and antipsychotic use), utilization variables (medical hospitalization and general medical care access), and calendar year. Because there were no events in the current user group for cohort members of age 18-24 years, full models were calculated for age 2-17 years and models for former users only for age 18-24 years.

Alternative Analyses Excluding Children with Serious Psychiatric Illness

These analyses excluded children with evidence of serious psychiatric illness, defined as use of psychotropic medications (antipsychotics, lithium or mood stabilizers) or claims evidence of major psychiatric illness (depression, bipolar disorder, psychotic disorder, autism, or psychiatric hospitalizations for any psychiatric diagnosis in the past 365 days) at baseline or children who developed evidence of these conditions during follow-up, who were excluded from the date that they met evidence of serious psychiatric illness through the end of their follow-up.

Table K-4. Adjusted hazard ratio for serious cardiovascular events, according to use of ADHD medications, excluding children with serious psychiatric illness

ADHD medication use	Person-years	Events	Rate/100,000	Hazard Ratio†	95% confidence interval low	95% confidence interval high
Non-user	1,534,206	43	2.80	1.00	Ref	Ref
Former user	457,171	10	2.19	0.82	0.36	1.86
Current user	280,306	3	1.07	0.66	0.20	2.16

†Hazard ratios estimated with Cox regression models which included site-specific propensity score decile, site, medical conditions (serious cardiovascular disease, serious chronic illness), utilization variables (medical hospitalization and general medical care access), and calendar year.

Appendix L. Comparison of Outcomes by Site and Medicaid vs. Non-Medicaid Enrollment

We compared the occurrence of serious cardiovascular events for the exposure groups (ADHD medication nonusers and current users) according to individual site. Given the rarity of these events and the small numbers of events for the individual sites, these data are unadjusted. For those sites that had at least one case in each of the exposure groups, we calculated the unadjusted incidence rate-ratios (IRRs) and 95% confidence intervals (CIs), using as the estimated variance of the log (IRR) the square root of the sum of the reciprocals of the numbers of exposed and unexposed cases.

For those sites for which there were no cases in one of exposure groups, we calculated the difference in unadjusted incidence (RD) between current users and nonusers. The 95% CI for the RD was calculated using a test-based method. The statistical test was a standard chi-square test for heterogeneity, calculated as follows:

$$[(I*L_0-N_0)^2]/[\ I*L_0] + [(I*L_1-N_1)^2]/[\ I*L_1]$$ [1]

where

N_0, N_1 are the numbers of cases in ADHD medication nonusers and current users

L_0, L_1 are the corresponding person-years of exposure

I is the pooled incidence in the nonusers and current users.

The square-root of the chi-square statistic (1 degree of freedom), or z, is the absolute value of a standard normal random variable with mean 0 and standard deviation 1. The test-based 95% confidence interval is thus:

$$RD*(1\pm 1.96/z).$$

The data presented here should be interpreted as a qualitative evaluation of potential differences between the sites. There are two factors that limit precision. First, these data are unadjusted for potential differences between the ADHD medication exposure groups. Second, for both the IRR and the RD, the accuracy of the 95% CIs requires an adequate number of events. The standard criterion is that there should be at least 5 events expected in each group. For some of the sites, this criterion was not met. For these sites, the 95% confidence intervals presented here, for both the IRR and the RD, are likely to be too narrow.

The total number of cases at the individual sites was small, ranging from 32 (Tennessee Medicaid) to 6 (Washington Medicaid). All of the sites had events in the nonuser group. However, two of the sites (Kaiser, Optuminsight Epidemiology) had no events among current users; thus, IRRs could not be calculated for these sites.

[1] This is equivalent to the standard formula $(N_0-I*L_0)^2/(N*L_0*L_1/L^2)$, where N is the total of events and L total person-years, see, for example, *Modern Epidemiology*

For three of the sites, the 95% confidence intervals for the RD included 0, indicating no difference in the occurrence of serious cardiovascular events between ADHD nonusers and current users. The 95% confidence interval for the RD in Washington Medicaid did not include zero; nor did it overlap with those for Kaiser and OptumInsight Epidemiology. However, given the small numbers, this nominal confidence interval for Washington is likely to be too narrow.

Given that the incidence of serious cardiovascular events among ADHD users was higher in the Medicaid sites than in the non-Medicaid sites, we conducted a post-hoc analysis of a potential interaction between Medicaid:non-Medicaid sites. This analysis pooled the data according to type of site and is unadjusted. Given that there were no cases in ADHD current users for the non-Medicaid sites, the IRR could not be calculated. With regard to the RD, the 95% confidence interval for the pooled Medicaid sites includes the RD for the pooled other sites, thus indicating absence of heterogeneity.

Table L-1. Comparison of outcomes by site and Medicaid vs. Non-Medicaid enrollment

	Nonuser			Current User			Incidence Rate Ratio			Incidence Difference		
	Events	Person Years	$I/10^5$	Events	Person Years	$I/10^5$	IRR	95% CI		RD	95% CI	
Tennessee	29	470,853	6.16	3	77,541	3.87	0.63	0.19	2.06	-2.29	-8.09	3.51
Kaiser	10	329,872	3.03	0	77,773	0.00	n/a	n/a	n/a	-3.03	-6.90	0.84
OptumInsight	11	651,489	1.69	0	176,264	0.00	n/a	n/a	n/a	-1.69	-3.61	0.23
Washington	2	145,748	1.37	4	42,088	9.50	6.93	1.27	37.86	8.13	2.00	14.26
Medicaid	31	616,601	5.03	7	119,629	5.85	1.16	0.51	2.64	0.82	-3.61	5.25
Other	21	981,361	2.14	0	254,037	0.00	n/a	n/a	n/a	-2.14	-3.94	-0.34

I=Incidence
PY=Person years
IRR=Incidence rate ratio
CI=confidence interval
RD=Rate difference