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ADHD Medications and Risk of Serious Coronary Heart Disease in Young and Middle-Aged Adults

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Contents

Tables

Appendix

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ADHD Medications and Risk of Serious Coronary Heart Disease in Young and Middle-Aged Adults

Abstract

Background. More than 1.5 million US adults use stimulants and other medications labeled for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD). These agents are known to increase heart rate and blood pressure.

Methods. Using computerized health records from four study sites (Ingenix-3, Tennessee Medicaid, Kaiser Permanente California, and the HMO Research Network), we identified 150,658 adults aged 25-64 years with prescriptions for methylphenidate, amphetamines (and amphetamine salts) or atomoxetine at baseline. Each medication user was matched to two non-users on study site, birth year, gender and calendar year of cohort entry. Study endpoints were acute myocardial infarction (MI) and/or sudden cardiac death (SCD). Poisson regression was used to compare adjusted rates in users and non-users of ADHD medications.

Findings. During 844,615 person-years of follow-up, 1357 cases of MI and 296 cases of SCD occurred. We had 113,324 person years of current use (average 0.74 years per user), with a crude incidence of MI of 1.34 per 1000 person-years and of SCD of 0.30 per 1000. Multi-variable adjusted rate ratio of MI/SCD for current use vs. non-use of ADHD medications was 0.87 (95% CI 0.74-1.02). Adjusted rate ratios for current use of methylphenidate, amphetamines or atomoxetine vs. non-use of any ADHD medications were 0.85 (95% CI 0.68-1.07), 0.93 (95% CI 0.73-1.19), and 0.88 (95% CI 0.52-1.49), respectively. There was no evidence of increasing risk with increasing duration of use. The adjusted rate ratio for MI/SCD for current vs. remote use (> 1 year since last use) was 1.04 (95% CI 0.85-1.29). Results were similar when users were restricted to new users (no dispensing for ADHD medications in the year prior to cohort entry), when the cohort was restricted to those with or to those without evidence of prior cardiovascular disease, or when we restricted the cohort to those aged 25-44 years or 45-64 years during follow-up.

Interpretation. Our results do not support an association between the use of ADHD medications in young and middle-aged adults and the risk of MI or SCD.

Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a common condition in children and adolescents that is characterized by developmentally inappropriate inattention, hyperactivity, and impulsivity[1-4] and usually is associated with academic, behavioral, and social impairment.[3] Although data are more limited, symptoms in adults have been reported to be similar but more subtle and heterogeneous and subtle than those in children and adolescents.

In children, use of stimulants to treat ADHD has increased dramatically over the last 30 years. However in recent years, the use of stimulants appears to be increasing even more rapidly in adults than in children. More than 1.5 million U.S. adults now take stimulants.[5] For the period 1999 to 2003, national prescribing data suggest that approximately 25% of all stimulant prescriptions were issued to persons over 19 years old.[6] Commonly used products in adults include methylphenidate, mixed amphetamine salts (Adderall) and, increasingly, atomoxetine. The leading indication is ADHD and the rise in the frequency of this diagnosis is the primary cause of increased prescribing. However, psychostimulants are also used in the treatment of narcolepsy, obesity, fatigue and for recovery after stroke or traumatic brain injury.

While these drugs have been demonstrated to be effective for the treatment of symptoms of ADHD, two important effects of the sympathomimetic stimulants (amphetamines and methylphenidate) are of particular concern with respect to myocardial infarction (MI) and sudden cardiac death (SCD). Placebo-controlled studies indicate that in both children and adults these agents elevate systolic blood pressure levels by approximately 2-5 mm Hg and diastolic blood pressure by 1-3 mm Hg.[5,7,8] They also commonly lead to increases in heart rate. Similar effects on blood pressure and heart rate have been found with the selective norepinephrine reuptake inhibitor (SNRI), atomoxetine.[9] This degree of elevation of blood pressure would be expected to slightly increase risk for both MI and SCD.[10] The effects of increased heart rate are less clear, but may be associated with both an increased susceptibility to arrhythmias and of cardiomyopathy and congestive heart failure, both of which increase the risk for SCD.

According to a summary from the FDA's Adverse Event Reporting System (***AERS***), cardiac arrest, myocardial infarction, and death are among the top 50 most commonly reported adverse events for both amphetamines and methylphenidate.[6] Of all reported deaths, a substantial number were cardiac deaths, associated either with sudden collapse or with symptoms of MI. Deaths were reported in both children and adults. Cardiac safety data from post-marketing pharmacoepidemiologic studies are limited and inconsistent[11-13] and more studies are needed.[5,7]

The primary aim of this study was to examine whether medications used primarily to treat ADHD are associated with risk of serious coronary heart disease in adults 25-64 years of age. The two primary endpoints for this study were myocardial infarction (MI) and sudden cardiac death (SCD). The study drugs included all medications with a label indication for treatment of ADHD as of December 31, 2005.

Methods

Data Sites

Study data were obtained from the computerized files of four study sites. These sites included Tennessee State Medicaid, Kaiser Permanente (KP) California (Northern and Southern KP regions), Ingenix-i3 (with data from a large health insurance plan) and the HMO Research Network (Harvard Pilgrim Health Care (Boston, MA); Fallon Community Health Plan (Worcester, MA); Group Health Cooperative of Puget Sound (Seattle, WA); HealthPartners (Minneapolis, MN); Kaiser Permanente Georgia (Atlanta, GA); Kaiser Permanente Northwest (Portland, OR); and Kaiser Permanente Colorado (Denver, CO)). All seven sites in the HMO Research Network contributed data to the MI outcome (electronically identified cases were considered valid), but only four sites (see Table A-2 for sites) contributed data to the SCD outcome (because chart reviews and thus adjudication of electronically identified cases were too logistically complex at three sites). The study files included: health plan or program enrollment data; demographic information; complete ambulatory prescription records or claims; hospital admission/discharge databases with diagnoses; and outpatient visit or claims databases with diagnoses. Mortality data were obtained by linkage with state mortality files or with files from the National Death Index. The study was approved by the institutional review boards at each of the participating institutions.

Because the computerized data systems at study sites had differing start-up dates, ranging from 1986 for Tennessee Medicaid to 2002 for KP Southern California, the start of observation differed by site. Follow-up concluded for all sites at the end of 2005 so that complete mortality searches could be conducted.

Study Participants

Individuals were eligible for the study if they were aged 25-64 years with at least 12 months of continuous health plan coverage and pharmacy benefits prior to the time of cohort entry (which we denote as t0). We did not include patients aged 65 years or older because their numbers are small among exposed persons; the indications for stimulant use become much more varied in this age group and shift away from the most common indication, ADHD; and the incidence of cardiovascular disease rises due to the increasing prevalence of cardiovascular disease risk factors.

Given the very low prevalence of use of ADHD medications in adults and the relatively low rates of the selected endpoints in those less than 65 years of age, we maximized efficiency to detect medication-outcome associations by using all available eligible exposed person-time at each study site, and then sampling on unexposed person-time.

Individuals were excluded if they had one or more of the following diagnoses during the 365 days prior to t0: sickle cell disease, cancer diagnosis (other than non-melanoma skin cancer), HIV infection, organ transplant, liver failure or hepatic coma, end-stage renal disease, respiratory failure, or severe congestive heart failure. For most of these diagnoses, their occurrence following cohort entry resulted in censoring. In addition, any study endpoints noted simultaneously with the appearance of an excluding illness diagnosis were removed from consideration, with the exception of severe congestive heart failure. Since severe congestive

heart failure may well be a consequence of the endpoint (i.e., myocardial infarction) or an acute condition leading immediately to SCD, it was not grounds for exclusion of the event.

At each contributing site, we initially assembled a cohort of eligible members, without respect to exposure to ADHD medications. For each eligible member, we identified periods during which all eligibility criteria (i.e., continuous enrollment, prescription benefit, and age <65 years) were met. We then selected all eligible periods with at least one prescription for an ADHD medication (methylphenidate, amphetamine, atomoxetine, pemoline). For every eligible exposed period, starting with the earliest exposure (or t0), we randomly selected two periods with no exposure to ADHD medications on that same day (t0), or in the past, from among all eligible individuals of the same gender and birth year, including from among those who were exposed in the future.

Study Medications

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

Each person-day of follow-up for cohort members was classified according to probable use of study ADHD drugs. The number of days of drug use per prescription was estimated based on the fill date and days supply. To avoid misclassification of current use, overlapping days of supply were adjusted to account for up to 7 days of stockpiling of medication. Current use was defined as the period between the prescription start date and the end of the days supply. An indeterminate use category was included to reduce the potential for misclassification and referred to the first 30 days after the end of a window of current use. This category also allowed us to examine whether recent discontinuation of ADHD medications was associated with risk of MI or SCD. The former use category began after indeterminate use ended (i.e., at 31 days after end of current use) and ended at 365 days after last current use. Person-days greater than 365 days since last days supply were considered remote use. Non-use referred to those person-days with no prescribed ADHD medication on those days or at any time in the past. A small number (less than 1%) of non-users became users after baseline, at which time their follow-up was categorized as current use. Current use was further categorized based on specific medications (amphetamines, methylphenidate, atomoxetine, multiple ADHD drugs, or pemoline) and on duration of use (1-30 days, 31-90 days, 91-182 days, 183-365 days, 366+ days). The non-use exposure category was chosen as the reference category for all primary analyses.

Study Endpoints

The primary study endpoints were acute myocardial infarction requiring hospital admission and/or sudden cardiac death. Note, results of a separate analysis with stroke as the primary endpoint will be presented in a future report.

Acute myocardial infarction (MI) was identified from principal hospital discharge diagnoses of ICD-9 code 410.x. Many previous studies have relied on this hospital discharge code to identify endpoints. Several recent studies, including studies within participating health plans of this study, have confirmed the accuracy of this hospital discharge code against chart review validation.[14-19] Additional potential MIs were identified by searching mortality files

(either a National Death Index (NDI) search or linkage with state mortality files) for ICD-9 codes of 410.x or ICD-10 codes (I21.x, I22.x).

The primary source of potential sudden cardiac death (SCD) cases was death certificates obtained by the mortality searches described above for all members not known to be alive on December 31, 2005. We included the following underlying causes of death on death certificates: any cardiac system cause of death (ICD-9 390-429, ICD-10 I01,I05-09, I11, I13, I20-I52); congenital cardiac anomaly (ICD-9 745-746, ICD-10 Q20-28); 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); 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), ventricular fibrillation, flutter or tachycardia (ICD-9 427.4x, 427.1); cardiac arrest due to a procedure (ICD-9 997.1). We also included collapse (ICD-9 780.2), sudden death, unknown cause (ICD-9 798.0-798.9), and respiratory arrest (ICD-9 799.1), if there was a secondary discharge diagnosis of cardiac disease (ICD-9 390.x – 429.x). Resuscitated cardiac arrests were identified from the following primary hospital discharge diagnoses with discharge status other than dead: cardiac arrest (ICD-9 427.5) and ventricular fibrillation, flutter or tachycardia (ICD-9 427.4x, 427.1). To be included, ventricular tachycardia needed to be accompanied by a secondary discharge diagnosis of cardiac arrest (ICD-9 427.5).

Charts were requested on all potential sudden cardiac deaths (n=411) and 31% (n=433) of potential MIs for adjudication by a trained clinician who was blinded to exposure status (see Table A-1). For potential cases identified by NDI or other mortality records, copies of death certificates were requested. For deaths occurring in hospital, hospital records were obtained. For out-of-hospital deaths in which an autopsy was performed, autopsy records were requested.

For potential SCD cases without hospital or autopsy records, we used a computer case definition, based on ICD-9 and ICD-10 codes, developed and validated in a retrospective cohort study of SCD that included medical record review and clinical adjudication.[20] In that study, the positive predictive value (PPV) for the computer case definition was 86 percent.

Confounders

To control for potential differences in the risk of coronary heart disease among those exposed to ADHD medications compared to those unexposed to ADHD medications, we constructed a cardiovascular risk score (CRS).[21,22] The score included the following variables based on diagnoses, claims or prescriptions in the 365 days preceding t0: acute myocardial infarction, coronary ischemia, coronary revascularization, congestive heart failure (CHF), arrhythmia, hypertension; utilization of relevant medical services (psychiatric visits, cardiovascular visits, other visits, number of different medications (see Table A-9b for categories)), and one or more prescriptions (yes/no) for cardiovascular drugs such as loop diuretic, digoxin, nitrates, anticoagulant, platelet inhibitor, anti-arrhythmic agents, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, beta-blocker, calcium-channel blocker, thiazide diuretic, and other antihypertensive drugs. The score also included ever/never (time-varying during follow-up) indicators of smoking, diabetes, obesity, hyperlipidemia, stroke or transient ischemic attack, congenital heart disorder, coronary artery anomaly, and peripheral vascular disease. In addition, several variables not believed to be in any plausible causal pathway from ADHD medications to the outcomes were treated as time-varying and included the

following: alcohol (ETOH)/substance abuse, suicide attempt, injury, seizure, asthma, major depression, bipolar disorder, anxiety, psychotic disorders, and several drugs such as antipsychotics, tricyclic antidepressants, other or SSRI/SNRI antidepressants, benzodiazepines, lithium, modafinil, insomnia medications, thioridazine, mood stabilizers, clonidine, guanfacine, beta-agonists, theophylline compounds, epinephrine, asthma medications, seizure medications, COX-2 inhibitors, other drugs to improve blood flow, pde5 inhibitors, triptans, oral contraceptives, and menopausal or miscellaneous hormones. In secondary analyses, all variables in the CRS were fixed at baseline to address concerns that some variables may lie on the causal pathway between medication use and the outcomes of interest.

Separate cardiovascular risk scores were created from a Poisson regression model of the association of the above variables with risk of each endpoint (i.e., a separate CRS for MI, SCD, or combined MI/SCD), among all patients, adjusted for use of ADHD medications and the matching variables. The score was the linear predictor from the coefficients of the resulting regression model, excluding the coefficients for ADHD medications and the matching variables. As a complement to the CRS and per request from the FDA, we constructed a propensity score for current vs. non-use at baseline using the same variables included in the CRS as our predictor variables. The score was the linear predictor from the coefficients of the resulting regression model.

Unmeasured Confounders

In order to examine the potential for unmeasured confounding by variables not available or inconsistently available in the electronic record, we used external adjustment methods[23-25] to conduct sensitivity analyses. We obtained information on potential confounders from two sources. First, information on race/ethnicity, smoking, obesity, history of cardiovascular disease and drug abuse was obtained from the review of available medical records and death certificates on all SCD cases (records available on 305 of 411 requested) and the medical records of a sample of MI cases (records available on 410 of 433 requested). Second, we obtained information on race/ethnicity, income, education, smoking, obesity, family history of cardiovascular disease on approximately 200,000 KP Northern California members aged 25-64 years who took a mailed survey in 2006. On this survey population, electronic pharmacy data on prescriptions for ADHD medications was obtained, as well.

We used multivariable logistic regression modeling to examine the association between potential confounders and use of ADHD medications. Obesity, smoking, family history of cardiovascular disease were not or were only very weakly associated with use of these medications and, therefore, would not be important confounders (if these associations in our study population are similar to what we found in our external samples). For variables that were associated with use of ADHD medications (race/ethnicity, income and education), we assessed the extent of their potential confounding effect on our RRs for MI or SCD associated with ADHD medications. Once we had estimates of the prevalence of exposure to ADHD medications in 25-64 year olds, the prevalence of the confounders in those exposed and unexposed to ADHD medications (chart review and survey), the confounder-exposure associations (chart review and survey) and the confounder-disease associations (from the literature), we used external adjustment methods to estimate the extent of their potential confounding effect on our RRs for MI or SCD associated with ADHD medications.[24]

Cohort Entry and Follow-Up

Follow-up began at cohort entry and ended at MI or SCD, death, end of insurance coverage/pharmacy benefit, day before 65th birthday, or end of study period (December 2005), whichever came first. Subjects could re-enter the cohort as long as they met the entry criteria. Thus each subject could contribute more than one period of observation (or membership period) to the study. Of the 443,198 unique patients in the study, only 3,647 (0.8%) left and re-entered the cohort. Of the 3,647, there were 1,148 (31.5%) who left as non-users and re-entered and stayed as non-users, while 2,409 (66.1%) left as current users and re-entered and stayed as current users. Less than 3% changed ADHD medication status upon re-entry. Furthermore, of the 3,647 who left and re-entered the cohort, only 12 (0.3%) had an MI at either the first period or second period (not both periods). None of those who left and re-entered had an SCD. Of the 12 who had an MI, ten were current users and two were non-users.

Statistical Approach

Poisson regression modeling, which is appropriate for rare events, was used to estimate the effect of ADHD medications on the rate of MI and/or SCD, adjusted for several potentially confounding variables. A key assumption is a constant hazard function within the strata defined by the study covariates. Experience suggests that under these conditions, Poisson regression provides results that are virtually identical to Cox regression, but is several times more computationally efficient than Cox regression. Covariates in the full model included study site, age (5-year dummy categories), gender, calendar year (1986-1992, 1993-1999, 2000-2001, 2002-2003, 2004-2005), and cardiovascular risk score (specified as a linear variable in deciles). In some analyses, the propensity score (specified as a linear variable in deciles) was used instead of the CRS. Note, results were unchanged when CRS was treated as 9 dummy variables. Matching variables were included in the full model because, while matching assured balance with respect to these variables at baseline (point at which matching was done), it did not assure balance during follow-up as there may have been differential changes in medication use categories or censoring by these factors. All analyses were done with SAS version 9.1. All p-values were two sided.

In addition to analyses on the full cohort of users and non-users, we conducted several analyses within subgroups. First, we restricted users of ADHD medications to those who had no use of these medications in the 365 days prior to cohort entry (i.e., new users). Second, users were restricted to those with a diagnosis or claim for ADHD in the 365 days prior to cohort entry. Third, we restricted some analyses to those who had and to those who did not have evidence of prevalent cardiovascular disease and some analyses to those who had and to those who did not have non-ADHD psychiatric diagnoses or medication use (as assessed during the 365 days prior to cohort entry). Fourth, to examine whether results might be different for young adults and for middle-aged adults, we conducted separate analyses for those who were 25-44 years and for those who were 45-64 years during follow-up. Fifth, to examine potential heterogeneity of results across sites, we conducted within-site analyses.

Finally, to examine the potential for selection bias or confounding by indication that could arise from users being more or less healthy than non-users due to unmeasured variables, we compared rates in current, indeterminate and in former users to rates in remote users. Remote users may be more similar to current users than to non-users with respect to these unmeasured variables.

Results

Medication Use and Person-Years of Follow-Up

The total follow-up time in person-years for those who were non-users of ADHD medications at baseline was approximately twice the number of person-years of follow-up for those who were users at baseline, which given the 2:1 matching ratio, indicates that there was equivalent follow-up and retention for adults in the two initial exposure groups. During follow-up, there were 107,383 person-years of current use of ADHD medications (average of 0.71 years per user at baseline), 51,739 person-years categorized as indeterminate use (average 0.34 years per user at baseline), 46,163 person-years categorized as former use (average 0.30 years per user at baseline), 67,689 person-years categorized as remote use of ADHD medications (average 0.45 years per user at baseline), and 534,070 person-years of non use of ADHD medications (average 1.82 years per non-user at baseline). Of the person-years of current use, methylphenidate use accounted for approximately 45%, amphetamine use accounted for 44% and atomoxetine use accounted for 8%. There was very little pemoline use (3%).

Characteristics of Study Population at Baseline and During Follow-Up

As expected because of matching, users and non-users were similar at baseline with respect to study site, age, gender, and calendar year of entry. Other baseline characteristics of users and non-users are also shown in Table 1a. Other than hypertension and hyperlipidemia, the prevalences of various cardiovascular disease conditions in the year prior to baseline were rare and less than 3%. Prevalences in the year prior to baseline of most cardiovascular disease conditions and cardiovascular medications were generally similar, although some such as hypertension, hyperlipidemia, arrhythmia, and stroke/TIA were slightly more common in current users than non-users of ADHD medications. While the prevalences of other established risk factors for MI or SCD, such as diabetes, obesity, and smoking, were fairly similar, substance abuse was more common in the users than non-users (5.2% vs. 1.5%, respectively). As expected, a diagnosis or claim for ADHD was substantially more common among current users than non-users (30% vs. 0.2%, respectively), though it is important to note that more than two thirds of current users did not have an ADHD diagnosis. The prevalences of other mental health conditions were also higher in current users than non-users. During the year prior to baseline, several non-cardiovascular conditions, such as injury and asthma, also were more common among current users than among non-users of ADHD medications. As with mental health conditions, use of psychotropic medications in the year prior to diagnosis was substantially more common in current users than non-users of ADHD medications. Use of several other selected medications, such as those for seizures, was also more common among current users than non-users.

Characteristics of person-time by medication use are presented in Table 1b. The prevalences of cardiovascular risk factors are slightly higher among the remote users than among the current users – or the non-users. This risk distribution is summarized by the CRS deciles (bottom of Table 1b). Remote users are less likely to be in the lowest 3 deciles of the CRS (1, 2, 3) and more likely to be in the highest 3 deciles compared to either current users or non-users.

Number of Events and Rate Ratios in the Full Cohort

During 844,615 person-years of follow-up, 1357 cases of MI and 296 cases of SCD occurred, or 1.6 per 1000 person-years and 0.4 per 1000 person-years, respectively. In analysis adjusted for matching variables only (i.e., site, age, gender, and calendar year of cohort entry), rate ratios of MI or SCD for current, indeterminate, former and remote users vs. non-users of ADHD medications were 0.97 (95% CI 0.83-1.14), 1.15 (95% CI 0.93-1.41), 0.99 (95% CI 0.79-1.24), and 1.03 (95% CI 0.88-1.20), respectively. In analyses adjusted for matching variables plus the cardiovascular risk score, rate ratios of MI or SCD for current, indeterminate, former and remote users vs. non-users of ADHD medications were 0.87 (95% CI 0.74-1.02), 1.02 (95% CI 0.83-1.26), 0.83 (95% CI 0.66-1.03), and 0.83 (95% CI 0.71-0.98), respectively (Table 2c). Results were similar when events were restricted to either MI or SCD alone (Tables 2a, 2b). SCD results were similar when cases included all electronically identified cases except those confirmed as non-cases by clinical adjudication (Table 2b-2).

Tables 3a, 3b, 3b-2, and 3c show rate ratios of MI and SCD for current use of specific ADHD medications. Fully adjusted rate ratios of MI or SCD for current use of amphetamines, methylphenidate and atomoxetine vs. non-use of any ADHD medications were 0.93 (95% CI 0.73-1.19), 0.85 (95% CI 0.68-1.07), and 0.88 (95% CI 0.52-1.49), respectively (Table 3c). Analyses of duration among current users did not suggest any pattern of increasing risk associated with increasing time on ADHD medications or for any windows of time for any of the three endpoints (Table 4a-c). Duration results were similar when we restricted users to those without a prescription for ADHD medication in the 365 days prior to baseline (i.e., new users) (Table 4d).

Analyses of Subgroups—New User, History of CVD, History of ADHD, History of Psychiatric Conditions, Age

Results of subgroup analyses are presented in Tables 5a-c. RRs were not materially changed when the cohort was restricted to patients with or to those without cardiovascular disease in the year prior to baseline or to patients with or without non-ADHD psychiatric conditions in the year prior to baseline. Results also were not materially changed when users were restricted to those without use of ADHD medications in the year prior to baseline (i.e., to new users) or to those with ADHD-related health encounters in the year prior to baseline. Note, these RRs were similar when we included all non-users as the comparison or just those non-users matched to the new users or to users with ADHD, respectively. RRs for current vs. non-use of ADHD medications were similar for young and middle-aged adults. There was a suggestion that the rate of SCD was lower for former users vs. non-users of ADHD medications among young adults but not among middle-aged adults. However, the number of events in young adults was small and this subgroup difference may have been due to chance alone.

Remote Use as Comparison Group

Results of analyses comparing current, indeterminate and former users to remote users are presented in Table 6a-c and 7a-c. Indeterminate users were at slightly increased risk of MI or MI/SCD, compared to remote users, although the elevated RRs were only borderline statistically significant (Table 6a-c). There was little evidence of a difference in risk by type of ADHD medication (Table 7a-c).

Within-Site Analyses

Some variation in results was observed across data sites. The rates of incident MI and SCD also were significantly higher among the Tennessee Medicaid population (Table A-2). As expected, the Tennessee Medicaid population was generally sicker, with greater prevalence at baseline of most medical conditions and prescription medication use, compared to those at other sites (Table A-3). The rate ratios for MI or SCD for use vs. non-use of ADHD medications also differed somewhat by site, with the lowest rate ratios for MI/SCD associated with current or remote use observed among the Tennessee Medicaid population (Tables A-4a-c). The low RRs for Tennessee Medicaid did not materially change when we used standard adjustment methods instead of the CRS (see IRR^6 in Table A-7) or when we restricted analyses to later calendar years (1999-2005) (see Adjusted IRR^3 in Table A-7). In contrast to other sites, we had race/ethnicity on a substantial proportion of the Medicaid patients (95.3%). However, we saw little evidence of confounding by this factor when we included it as a co-variate (Table A-7). As in the full cohort, when we used remote use instead of non-use as the reference group, the RR for current use in the Tennessee Medicaid population was closer to 1.0 for MI and MI/SCD (Table A-6a, 6c). However, the RR was lower for SCD (Table A-6b).

Sensitivity Analyses—Adjustment Method

In sensitivity analyses to examine the effect of allowing the values of some variables in our CRS to vary during follow-up (i.e., time-varying covariates), we found that results were virtually identical to those when we fixed the values of all covariates in the CRS at baseline (not shown). Results (for MI/SCD) for the full cohort were similar when we used standard adjustment methods instead of the CRS or when we used a propensity score (PS) approach (Tables A-9a-9c). In addition, there was little difference in the new user subgroup results when we used the CRS or PS to adjust for covariates (Tables 5a-5c).

Sensitivity Analyses—Unmeasured Confounding

When we used external survey data to examine the association of ADHD medication use with sociodemographic factors that could not be systematically assessed on the study population using electronic data, we found that stimulant users were less likely than nonusers to lack any college education (10% v. 17%). If this pattern was similar in our study population, and if lack of any college education doubled the risk of MI and SCD, then our RR estimates would be biased downward by small amounts: from a "true" RR of 0.95 to an estimate of 0.88 (such as is reported in Table 2a for the association of current use with MI), or from a "true" RR of 0.88 to an estimate 0.80 (such as is reported in Table 2b for the association of current use with SCD). Although lack of any college education may well be much more prevalent in our overall study population than in our external sample of survey respondents, it would require a profound disparity in educational attainment—for example, a disparity such that 20% of users versus 50% of nonusers lack any college education—for residual confounding (from unmeasured education) to drive an RR estimate from 1.0 to 0.80 (assuming not only such a profound disparity in education between users and non-users, but also assuming that lack of any college education doubles the risk of MI or SCD).

We similarly found evidence in the external survey data that only 5% of the stimulant users were black or Hispanic versus 12% of the nonusers. Our chart reviews to validate MI and SCD cases also found evidence that among the reviewed cases, use of ADHD medications is

more common among whites than among minorities. If black or Hispanic race/ethnicity were as prevalent in our study population as in our survey sample, and if it also doubled the risk of MI and SCD, then unmeasured race/ethnicity could also bias our RR estimates by amounts similar to those reported for education above.

Unexpectedly, low income was more prevalent in users than in non-users among the survey respondents (19% of the users had annual income < $40,000 versus 13% of non-users). This would suggest that residual confounding from unmeasured income would bias our RR estimates upwards (toward an apparent RR higher than the true RR), and thereby "cancel out" some of the negative residual confounding from education and race.

Sensitivity Analyses—Single Eligibility Period

Less than 1% of the cohort had multiple eligibility periods (i.e., left and re-entered the cohort). Results were virtually identical in sensitivity analyses in which we restricted eligibility periods to one per individual (not shown).

Discussion

In our large cohort of over 440,000 young and middle-aged adults aged 25-64 years, including over 150,000 users of ADHD medications, we found little evidence of an increased risk of MI or SCD associated with current ADHD medication use when comparing to non-use or to remote use of ADHD medications. We also found little evidence of an increased risk for current use of any of the specific medications examined (i.e., methylphenidate, amphetamines or atomoxetine) or for an increase in risk with increasing duration of current use of ADHD medications. Furthermore, results were similar when users were restricted to new users or to those with or without ADHD. Results also were similar when the cohort was restricted to those with or to those without evidence of prior cardiovascular disease or to those with or to those without evidence of prior non-ADHD psychiatric conditions. In addition, results were similar for ages 25-44 years and for 45-64 years during follow-up.

Our study has several limitations. While use of ADHD medications was based on electronic pharmacy records of filled prescriptions, filled prescriptions may not represent medications actually consumed and days supply may not represent actual periods of use. Nonetheless, electronic pharmacy databases have been found to be excellent unbiased sources of information on drug use and it seems unlikely that any misclassification of use would be differential with respect to the endpoints of interest. As in our study, electronic diagnoses of MI have been found to be accurate by several others.[14-19] Furthermore, our MI rate (1.62/1000 person-years for non-users of ADHD medications) is comparable to that reported by others for this age group.[26] In contrast, the electronic diagnosis of SCD has not been similarly validated. While we reviewed the medical records and death certificates to confirm diagnoses, as in other studies, this information was unavailable for many of our electronically identified cases of SCD. We used a computer case definition with a high PPV[20] for these cases, but misclassification of some cases may have occurred. Nonetheless, the rate of SCD among non-users of ADHD medications in our study (0.34 /1000 person-years) is comparable to that reported for other similarly aged adults.[27]

The chief limitation of this study is that it is observational and results could therefore be subject to unrecognized and uncontrolled confounding. We adjusted for a large number of established and potential cardiovascular risk factors. However there were some factors, primarily psychiatric conditions and/or medications, for which the prevalence was substantial in the users of ADHD medications but rare in the non-users. Therefore, we had limited ability to adjust for these variables. Important confounding by these psychiatric conditions and/or medications seems unlikely though, since they are not considered established risk factors for cardiovascular disease, they were not or were only modestly related to risk of MI or SCD in our cohort, and results were similar when we restricted our analyses to those with or to those without a history of non-ADHD psychiatric conditions or medication use.

We had no or incomplete information on several potentially important factors, including race/ethnicity, socioeconomic status, smoking, obesity, substance abuse and family history of serious cardiovascular disease. When we examined the association between these variables and use of ADHD medications among the cases for which there was a chart review or among respondents to a survey conducted among the KP Northern California membership, we observed little association between ADHD medication use and smoking, obesity or family history of serious cardiovascular disease. However, we did observe that use of ADHD medications was more common in non-Hispanic whites and less common among minorities. We also found that

use of ADHD medications was more common among the more educated. Results of sensitivity analyses suggest that unmeasured confounding by education and race/ethnicity may account for the slightly lower rates of our endpoints among users vs. non-users of these medications, such that we cannot confidently rule out an elevated rate ratio below 1.2 or so. If stimulants increase systolic blood pressure by 5mm Hg (5), and risk of MI doubles for each additional 20mm Hg, as has been reported for mortality from ischemic heart disease (10), then stimulants might be expected to multiply the risk of MI by 1.19 (because $1.19^{20/5} = 2.0$). The limitations to our sensitivity analysis approach to evaluating the extent of unmeasured confounding include assumptions that associations between the confounder and the exposure in the external population parallel those in the study population and this approach does not address joint confounding by several unmeasured covariates.[23-25]

To help minimize unmeasured confounding or selection bias, ideally our primary comparison would have been use of another medication with an identical indication and patient profile to that of the medications of interest but without the same concern about cardiovascular risk. However, all medications approved for the treatment of ADHD increase blood pressure and heart rate. While not an established risk factor, if an ADHD diagnosis itself is related to risk of cardiovascular disease, either directly or indirectly, our choice of individuals unexposed to ADHD medications as our primary comparison may have resulted in some confounding by indication. While using untreated ADHD patients as our primary comparison group might have allowed us to disentangle the risk of cardiovascular disease associated with ADHD from the risk associated with ADHD medications, we were concerned that such patients would be relatively rare. Further, untreated patients are likely to have less severe disease and so confounding by severity would still be a potential issue. Instead, we chose to conduct secondary analyses using remote users as our comparison group. Remote users may be more similar to current users than our non-user group or untreated ADHD patients with respect to some unmeasured confounders or selection factors. If so, using them as the comparison group would reduce the related confounding and bias. We did not choose remote users as our primary comparison, as reasons for stopping use may include misdiagnosis of ADHD, less serious ADHD, non-adherence, and adverse effects, some of which may be related to risk of cardiovascular disease. Further, if there are long-term consequences of ADHD medication use, associations would be attenuated when remote users are the comparison.

Some variation in results across data sites would be expected by chance alone. Variation also could result from differences across sites in the prevalence of unmeasured confounders or selection factors. Such differences may explain the lower RRs for current and remote medication use in the Tennessee Medicaid population. As expected from our within-site analyses, the overall RRs for current and remote use vs. non-use were substantially closer to 1.0 when we excluded the Medicaid population.

Differential misclassification of confounders is another potential source of bias. It is possible that users of stimulants were more or less likely than non-users to have their cardiovascular disease conditions (or other risk factors for our outcomes) captured in the electronic medical record. If this information was more frequently captured for the users, such differential misclassification could result in RR estimates that were biased downward (i.e., more "protective"). Since we adjusted for number of clinical encounters (physician visits, ER, hospitalization and medication use) and these adjustments did not materially change our estimates, this issue seems unlikely to be of significant concern.

As with any observational study of medications, some healthy user and provider bias may have influenced results. In our cohort, users and non-users of ADHD medications appeared to be quite similar with respect to the prevalence of most cardiovascular disease risk factors at baseline, although it did appear that these risk factors were generally more prevalent in those who discontinued use. While the results of our remote user comparisons are consistent with some healthy user or provider bias, the results of our new user subgroup analyses suggest that our overall results were not appreciably biased by covariates that changed after use of ADHD medications or by early depletion of susceptibles. In the new users, we did not observe an elevation in risk in the period shortly after initiation.

Clinical trials have provided limited information on the cardiovascular safety of ADHD medications in children and adults, due mostly to the fact that they have not been large enough and sufficiently powered to assess risk of rare events, such as myocardial infarction or sudden cardiac death.[28,29] Nonetheless, trials have demonstrated that methylphenidate and amphetamine increase blood pressure and heart rate in children and adults.[5,28] Atomoxetine, an SNRI, also increases blood pressure and heart rate in these groups.[9]

Post-marketing surveillance data from AERS[6] and from the National Electronic Injury Surveillance System[30] have suggested that serious cardiovascular events among users of medications used to treat ADHD may be of concern. However, with these surveillance systems, which are known to only capture a small percent of adverse events, false signals may occur if clinicians suspect, and are thus more likely to report, adverse events for a particular drug (i.e., detection bias). Relatively few observational pharmacoepidemiologic studies have been conducted on the cardiovascular safety of stimulants or atomoxetine.

Our findings of no increased risk of serious coronary heart disease in young or middle-aged adults associated with use of ADHD medications are consistent with some, but not all previous reports. These studies were smaller than ours and most were conducted using electronic records on pharmacy and medical encounter data, with similarly limited information on some potentially important cardiovascular risk factors. Cohort studies conducted among the Florida Medicaid population found that stimulant use was associated with a slight increase in emergency department (ED) visits for cardiac symptoms and circulatory disease among children and adolescents between the ages of 3 and 20 years (hazard ratio=1.2; 95% CI 1.0-1.4)[11] and that risks for ED visits were similar among users of amphetamines and methylphenidate.[13] A cohort study conducted among adults ages 18 years and older within a large insurance database, compared risk of cerebrovascular accidents (CVA) and transient ischemic attacks (TIA) among those prescribed atomoxetine and those prescribed stimulant ADHD medications, as well as adults in the general population.[31] There was a suggestion of higher rates of CVA and lower rates of TIA in current users of atomoxetine compared to users of stimulants, although the number of events was small and RRs were not statistically significant. Compared to rates in the general population, users of ADHD medications had higher rates of TIAs and lower rates of CVA, although the latter was not statistically significant. Gould et al used a case-control design to examine the association between ADHD medications and risk of sudden death in children and youths aged 7-19 years.[12] Each case of sudden death (n=564), identified from state vital records, was matched on age and gender to a control who died in a motor vehicle accident. There were 10 cases and 2 controls with a history of stimulant use, giving an unstable, but quite elevated, odds ratio of 7.4 (95% CI 1.4-74.9). In contrast, no increase in sudden cardiac deaths among children, adolescents and young adults using ADHD medications (methylphenidate, dexamphetamines or

atomoxetine) was observed in a cohort study conducted in the General Practice Research Database in the UK.[32]

In conclusion, although our results are in conflict with some previous reports, we believe they should be reassuring with respect to the cardiac safety of relatively short-term use of ADHD medication use in young and middle-aged adults. We do not believe the true RR for MI/SCD associated with current use of ADHD medications is less than 1.0, as we think it is biologically implausible that, given their effect on blood pressure and heart rate, they would be protective against MI or SCD. We find it more likely that any of the RRs less than 1.0 are due to a combination of residual confounding and chance. Given our adjustment for multiple established and potential CVD risk factors, our findings from several secondary analyses (including remote user comparison and new user analyses) and the results of our sensitivity analyses, we believe that at most a modestly elevated risk of MI or SCD associated with use of ADHD medications is plausible.

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Tables

Table 1a. Cohort characteristics by baseline medication use

Characteristic	Current Use* (n= 152,852)		Non-use* (n= 293,749)	
Median year of cohort entry	2003		2003	
Demographics				
Median age (years)	42		42	
Male gender (%)	70245	46.0%	135002	46.0%
Medicaid enrollment (%)	14786	9.7%	29171	9.9%
Cardiovascular disease within past year				
Acute MI	340	0.2%	689	0.2%
Ischemia	3998	2.6%	6857	2.3%
Coronary revascularization	253	0.2%	643	0.2%
CHF	1112	0.7%	1759	0.6%
Arrhythmia	3560	2.3%	5076	1.7%
Stroke/TIA	1826	1.2%	2075	0.7%
Congenital heart disorder	331	0.2%	556	0.2%
Coronary artery anomaly	66	0.0%	89	0.0%
Peripheral vascular disease	1225	0.8%	1651	0.6%
Hypertension	22562	14.8%	39011	13.3%
Hyperlipidemia**	28613	18.7%	42601	14.5%
Mental health claims within past year				
ADHD	46356	30.3%	455	0.2%
Major depression	61417	40.2%	23296	7.9%
Bipolar disorder	11196	7.3%	2682	0.9%
Anxiety	30472	19.9%	15670	5.3%
Psychotic disorders	2494	1.6%	1833	0.6%
Other selected medical conditions within past year				
Diabetes**	8972	5.9%	15862	5.4%
Obesity	9119	6.0%	11439	3.9%
Smoking	11579	7.6%	14717	5.0%
ETOH/substance abuse	7965	5.2%	4514	1.5%
Suicide attempt	795	0.5%	410	0.1%
Injury	30655	20.1%	37559	12.8%
Seizure	3062	2.0%	2854	1.0%
Asthma	11627	7.6%	12432	4.2%
Use of cardiovascular drug within past year				
Loop diuretic	4328	2.8%	4932	1.7%
Digoxin	587	0.4%	1130	0.4%
Nitrates	1941	1.3%	3298	1.1%
Anticoagulant	1768	1.2%	2421	0.8%
Platelet inhibitor	996	0.7%	1675	0.6%
Anti-arrhythmic agents	556	0.4%	631	0.2%
ACE inhibitor	10719	7.0%	19796	6.7%
Angiotensin receptor blocker	3652	2.4%	5988	2.0%
Beta-blocker	12431	8.1%	19091	6.5%
Calcium-channel blocker	7028	4.6%	12233	4.2%
Thiazide diuretic	12471	8.2%	20008	6.8%
Other antihypertensive	1668	1.1%	2192	0.7%

Table 1a. Cohort characteristics by baseline medication use (continued)

Characteristic	Current Use* (n= 152,852)		Non-use* (n= 293,749)	
Use of psychotropic medications within past year				
Antipsychotic, any	14618	9.6%	5371	1.8%
Tricyclic antidepressant	14224	9.3%	9907	3.4%
Antidepressants, other or SSRI/SNRI	81639	53.4%	36962	12.6%
Benzodiazepines	43695	28.6%	25956	8.8%
Lithium	4177	2.7%	1002	0.3%
Modafinil	4732	3.1%	383	0.1%
Insomnia meds	15270	10.0%	6732	2.3%
Thioridazine	307	0.2%	181	0.1%
Mood stabilizers, w/o seizure	22426	14.7%	8631	2.9%
Clonidine/guanfacine, w/o HT	2000	1.3%	659	0.2%
Use of other selected medications within past year				
Beta-agonist	18971	12.4%	20835	7.1%
Epinephrine	1342	0.9%	1274	0.4%
Asthma med, other	39645	25.9%	45102	15.4%
Seizure med, any	24139	15.8%	10397	3.5%
Theophylline compounds (asthma med)	960	0.6%	1200	0.4%
COX-2 inhibitors	10666	7.0%	10838	3.7%
Other drugs to improve blood flow	216	0.1%	250	0.1%
Clonidine	2602	1.7%	1787	0.6%
pde5 inhibitors	5183	3.4%	4504	1.5%
Triptans	7164	4.7%	5298	1.8%
Oral contraceptives	18379	12.0%	28590	9.7%
Hormones, menopausal or misc	18026	11.8%	23388	8.0%
Utilization within past year				
Cardiovascular visits				
Emergency, 1+	5728	3.7%	7697	2.6%
Inpatient, 1+	6022	3.9%	7130	2.4%
Physician, 1-4	43474	28.4%	65256	22.2%
Physician, 5+	13242	8.7%	17713	6.0%
Psychiatric visits[#]				
Emergency, 1+	4417	2.9%	2897	1.0%
Inpatient, 1+	7761	5.1%	3827	1.3%
Physician, 1-4	43538	28.5%	26703	9.1%
Physician, 5+	40176	26.3%	11048	3.8%
Other visits				
Emergency, 1+	7885	5.2%	9594	3.3%
Inpatient, 1+	5812	3.8%	5595	1.9%
Physician, 1+	55386	36.2%	69134	23.5%
No. of different medications***				
1	24309	15.9%	61193	20.8%
2+	108955	71.3%	116680	39.7%

*Numbers are for membership periods at baseline or cohort entry (t0); actual counts of unique individuals are 150,359 for current users and 292,540 for non-users at baseline. Note, there were 299 indeterminate and former users at baseline (for a total of 150,658 users at baseline)

** Including medications

[#] Excluding ADHD visits

*** Excluding ADHD medications

Table 1b. Characteristics of person-time (after baseline), by medication use

Characteristic	Current Use		Indeterminate-use		Former Use		Remote Use		Non-use	
	Pr-yr*	%	Pr-yr*	%	Pr-yr*	%	Pr-yr*	%	Pr-yr*	%
Total	107383.3	13.3%	51739.1	6.4%	46163.0	5.7%	67688.6	8.4%	534070.5	66.2%
Demographics										
Gender										
Male	49205.2	45.8%	23424.6	45.3%	21237.6	46.0%	31546.6	46.6%	244253.8	45.7%
Female	58178.1	54.2%	28314.5	54.7%	24925.4	54.0%	36142.1	53.4%	289816.8	54.3%
Age										
25-29	8286.7	7.7%	4475.3	8.6%	3491.5	7.6%	2137.6	3.2%	35940.2	6.7%
30-34	12243.8	11.4%	6719.8	13.0%	6206.1	13.4%	6999.7	10.3%	62269.6	11.7%
35-39	14674.6	13.7%	7650.8	14.8%	7253.6	15.7%	10194.0	15.1%	77516.7	14.5%
40-44	18916.9	17.6%	9271.6	17.9%	8522.5	18.5%	12911.5	19.1%	96018.3	18.0%
45-49	20639.4	19.2%	9408.6	18.2%	8293.9	18.0%	13018.7	19.2%	99735.3	18.7%
50-54	17043.7	15.9%	7467.4	14.4%	6328.8	13.7%	10822.4	16.0%	82543.6	15.5%
55-59	10719.9	10.0%	4621.5	8.9%	4023.6	8.7%	7237.2	10.7%	53275.6	10.0%
60-64	4858.3	4.5%	2124.2	4.1%	2043.0	4.4%	4367.8	6.5%	26771.2	5.0%
Site										
KPNC	14081.0	13.1%	5141.7	9.9%	4881.9	10.6%	7992.3	11.8%	66623.0	12.5%
KPSC	5704.7	5.3%	1983.5	3.8%	1906.1	4.1%	1549.2	2.3%	23133.0	4.3%
Tennessee Medicaid	8831.8	8.2%	5420.1	10.5%	7540.2	16.3%	20557.5	30.4%	79855.1	15.0%
HMORN										
Group Health	6470.2	6.0%	2417.1	4.7%	1754.2	3.8%	2580.8	3.8%	29454.0	5.5%
Harvard Pilgrim	9915.9	9.2%	4423.7	8.6%	3211.0	7.0%	3782.6	5.6%	45868.0	8.6%
HealthPartners	4356.8	4.1%	1711.3	3.3%	1250.1	2.7%	1511.4	2.2%	23222.0	4.3%
KPCO	3110.9	2.9%	1132.3	2.2%	918.9	2.0%	1455.0	2.1%	13206.0	2.5%
Ingenix/I3	54912.0	51.1%	29509.0	57.0%	24701.0	53.5%	28260.0	41.7%	252708.0	47.3%
Year										
2004-2005	50010.0	46.6%	23203.0	44.8%	20014.0	43.4%	29904.0	44.2%	239181.0	44.8%
2002-2003	30881.0	28.8%	13833.0	26.7%	10914.0	23.6%	21971.0	32.5%	151820.0	28.4%
2000-2001	16763.0	15.6%	9463.0	18.3%	10814.0	23.4%	9454.6	14.0%	91985.0	17.2%
1993-1999	9523.6	8.9%	5029.9	9.7%	4062.1	8.8%	5450.7	8.1%	47545.0	8.9%
1986-1992	205.2	0.2%	209.9	0.4%	358.8	0.8%	908.8	1.3%	3539.1	0.7%
ADHD at baseline	37577.3	35.0%	15062.1	29.1%	9667.6	20.9%	9554.9	14.1%	556.5	0.1%

Table 1b. Characteristics of person-time (after baseline), by medication use (continued)

Characteristic	Current Use		Indeterminate-use		Former Use		Remote Use		Non-use	
Cardiovascular disease at baseline**										
Acute MI	180.1	0.2%	97.2	0.2%	100.9	0.2%	153.2	0.2%	1276.6	0.2%
Ischemia	2326.5	2.2%	1250.3	2.4%	1344.3	2.9%	2161.2	3.2%	12226.3	2.3%
Coronary revascularization	147.9	0.1%	72.9	0.1%	83.1	0.2%	160.4	0.2%	1198.0	0.2%
CHF	608.6	0.6%	323.8	0.6%	371.4	0.8%	656.2	1.0%	2926.2	0.5%
Arrhythmia	2230.7	2.1%	1151.5	2.2%	1121.2	2.4%	1772.5	2.6%	8976.4	1.7%
Hypertension	14497.1	13.5%	7001.4	13.5%	6879.0	14.9%	10349.7	15.3%	68010.9	12.7%
Use of cardiovascular drug at baseline**										
Loop diuretic	2789.2	2.6%	1389.9	2.7%	1509.4	3.3%	2808.4	4.1%	9333.9	1.7%
Digoxin	405.6	0.4%	201.5	0.4%	222.6	0.5%	520.2	0.8%	2440.5	0.5%
Nitrates	1200.8	1.1%	635.4	1.2%	738.8	1.6%	1448.9	2.1%	6840.1	1.3%
Anticoagulant	1071.0	1.0%	547.6	1.1%	552.2	1.2%	866.4	1.3%	4190.0	0.8%
Platelet inhibitor	503.5	0.5%	289.4	0.6%	323.2	0.7%	434.8	0.6%	2529.2	0.5%
Anti-arrhythmic agents	341.4	0.3%	161.4	0.3%	174.3	0.4%	315.4	0.5%	1213.8	0.2%
ACE inhibitor	7091.1	6.6%	3360.5	6.5%	3341.5	7.2%	4973.1	7.3%	34988.8	6.6%
Angiotensin receptor blocker	1938.1	1.8%	1015.8	2.0%	932.9	2.0%	803.0	1.2%	7594.9	1.4%
Beta-blocker	8388.8	7.8%	3961.1	7.7%	3935.4	8.5%	6097.2	9.0%	34439.5	6.4%
Calcium-channel blocker	4759.6	4.4%	2374.4	4.6%	2424.0	5.3%	4345.2	6.4%	23405.0	4.4%
Thiazide diuretic	8554.0	8.0%	4002.7	7.7%	3692.3	8.0%	5083.8	7.5%	34454.8	6.5%
Other antihypertensive	1255.6	1.2%	584.0	1.1%	593.4	1.3%	1088.9	1.6%	4580.3	0.9%
Utilization at baseline**										
Cardiovascular visits										
Emergency, 1+	3382.0	3.1%	1812.2	3.5%	2137.2	4.6%	3444.2	5.1%	14690.1	2.8%
Inpatient, 1+	3482.2	3.2%	1847.8	3.6%	2063.8	4.5%	3350.5	4.9%	12381.2	2.3%
Physician, 1-4	29264.5	27.3%	14285.0	27.6%	12948.5	28.0%	18757.1	27.7%	115420.0	21.6%
Physician, 5+	7975.1	7.4%	4123.3	8.0%	4268.7	9.2%	6524.8	9.6%	30989.7	5.8%
Psychiatric visits[#]										
Emergency, 1+	2541.8	2.4%	1328.0	2.6%	1712.0	3.7%	2924.9	4.3%	5686.6	1.1%
Inpatient, 1+	4789.1	4.5%	2382.0	4.6%	2809.2	6.1%	5029.6	7.4%	6937.8	1.3%
Physician, 1-4	31761.8	29.6%	14444.5	27.9%	12201.5	26.4%	16434.4	24.3%	47217.7	8.8%
Physician, 5+	28735.9	26.8%	12997.4	25.1%	12127.7	26.3%	17390.2	25.7%	21417.8	4.0%
Other visits										
Emergency, 1+	4987.2	4.6%	2632.2	5.1%	2970.3	6.4%	4768.6	7.0%	19330.8	3.6%
Inpatient, 1+	3375.4	3.1%	1730.3	3.3%	1985.6	4.3%	3377.2	5.0%	9929.0	1.9%
Physician, 1+	37697.0	35.1%	18209.7	35.2%	16943.8	36.7%	25062.0	37.0%	124542.4	23.3%

Table 1b. Characteristics of person-time (after baseline), by medication use (continued)

Characteristic	Current Use		Indeterminate-use		Former Use		Remote Use		Non-use	
No. of different medications***										
1	17180.9	16.0%	8475.5	16.4%	7094.3	15.4%	10419.9	15.4%	113216.3	21.2%
2	16738.0	15.6%	8108.6	15.7%	6879.3	14.9%	9821.8	14.5%	72675.4	13.6%
3	14225.8	13.2%	6762.9	13.1%	5852.0	12.7%	8357.6	12.3%	47432.8	8.9%
4	11382.4	10.6%	5386.8	10.4%	4765.3	10.3%	7112.6	10.5%	30936.1	5.8%
5	8998.5	8.4%	4126.5	8.0%	3786.7	8.2%	5676.3	8.4%	20846.7	3.9%
6	6778.7	6.3%	3225.6	6.2%	2969.0	6.4%	4544.4	6.7%	13414.8	2.5%
7-8	8935.2	8.3%	4176.1	8.1%	4124.2	8.9%	6368.4	9.4%	14380.5	2.7%
9-10	4769.2	4.4%	2254.1	4.4%	2287.8	5.0%	3295.8	4.9%	6386.5	1.2%
11+	4661.3	4.3%	2254.8	4.4%	2537.9	5.5%	3362.5	5.0%	5008.8	0.9%
Medical conditions, ever/never[$]										
Obesity	10859.0	10.1%	4826.7	9.3%	4947.7	10.7%	11277.5	16.7%	46458.1	8.7%
Smoking	13510.0	12.6%	5802.9	11.2%	6390.7	13.8%	14768.0	21.8%	58481.4	11.0%
Diabetes[##]	7614.5	7.1%	3705.6	7.2%	3907.5	8.5%	9308.2	13.8%	42398.6	7.9%
Stroke/TIA	2031.0	1.9%	1034.5	2.0%	1236.2	2.7%	3635.8	5.4%	9910.2	1.9%
Hyperlipidemia[##]	26614.9	24.8%	12785.1	24.7%	12403.9	26.9%	24691.1	36.5%	119781.9	22.4%
Congenital heart disorder	375.2	0.3%	209.8	0.4%	235.5	0.5%	662.1	1.0%	2316.1	0.4%
Coronary artery anomaly	64.7	0.1%	36.1	0.1%	40.0	0.1%	128.3	0.2%	387.5	0.1%
Peripheral vascular disease	1738.7	1.6%	804.4	1.6%	835.2	1.8%	2352.8	3.5%	7646.4	1.4%
Mental health claims, time-varying[$$]										
Major depression	45677.5	42.5%	20625.7	39.9%	17921.1	38.8%	20142.8	29.8%	45976.7	8.6%
Bipolar disorder	8510.1	7.9%	3908.2	7.6%	4103.5	8.9%	5198.7	7.7%	5891.4	1.1%
Anxiety	20400.6	19.0%	9576.3	18.5%	9046.4	19.6%	10731.7	15.9%	30681.5	5.7%
Psychotic disorders	1815.3	1.7%	880.5	1.7%	1158.6	2.5%	2340.0	3.5%	5761.1	1.1%
Other selected medical conditions, time-varying[$$]										
ETOH/substance abuse	5079.2	4.7%	2359.9	4.6%	2699.3	5.8%	3307.9	4.9%	9286.0	1.7%
Suicide attempt	446.3	0.4%	234.4	0.5%	286.0	0.6%	368.1	0.5%	888.1	0.2%
Injury	20660.1	19.2%	10037.0	19.4%	9319.1	20.2%	13205.7	19.5%	69082.6	12.9%
Seizure	2023.4	1.9%	1020.2	2.0%	1178.9	2.6%	2187.0	3.2%	7103.4	1.3%
Asthma	8253.3	7.7%	4037.1	7.8%	3661.9	7.9%	5532.8	8.2%	24401.9	4.6%
Use of psychotropic medications, time-varying[$$]										
Antipsychotic, any	5665.0	5.3%	1900.5	3.7%	2083.5	4.5%	4194.6	6.2%	7008.3	1.3%
Tricyclic antidepressant	4272.6	4.0%	1635.9	3.2%	1635.7	3.5%	3101.6	4.6%	9298.4	1.7%
Antidepressants, other or SSRI/SNRI	42400.5	39.5%	14870.6	28.7%	12202.9	26.4%	17477.7	25.8%	40710.5	7.6%
Benzodiazepines	14864.4	13.8%	5355.8	10.4%	5145.6	11.1%	8375.1	12.4%	18408.6	3.4%

Table 1b. Characteristics of person-time (after baseline), by medication use (continued)

Characteristic	Current Use		Indeterminate-use		Former Use		Remote Use		Non-use	
Lithium	1485.0	1.4%	591.3	1.1%	610.0	1.3%	891.1	1.3%	1495.3	0.3%
Modafinil	1147.5	1.1%	634.9	1.2%	862.9	1.9%	1122.8	1.7%	334.7	0.1%
Insomnia meds	4047.9	3.8%	1585.3	3.1%	1379.7	3.0%	1736.5	2.6%	3382.2	0.6%
Thioridazine	86.4	0.1%	34.2	0.1%	45.7	0.1%	181.9	0.3%	407.4	0.1%
Mood stabilizers, w/o seizure	9046.2	8.4%	3215.6	6.2%	3093.5	6.7%	4895.9	7.2%	7838.5	1.5%
Clonidine/guanfacine, w/o HT	530.2	0.5%	139.6	0.3%	94.2	0.2%	145.6	0.2%	397.3	0.1%
Use of other selected medications, time-varying [$$]										
Beta-agonist	3120.6	2.9%	1256.8	2.4%	1158.7	2.5%	2166.0	3.2%	9445.3	1.8%
Epinephrine	63.6	0.1%	26.6	0.1%	26.1	0.1%	33.1	0.0%	150.6	0.0%
Asthma med, other	6946.0	6.5%	2855.3	5.5%	2607.3	5.6%	4257.8	6.3%	19124.6	3.6%
Seizure med, any	10225.2	9.5%	3723.2	7.2%	3689.3	8.0%	6246.7	9.2%	12134.1	2.3%
Theophylline compounds (asthma med)	273.2	0.3%	135.7	0.3%	149.9	0.3%	448.7	0.7%	1446.6	0.3%
COX-2 inhibitors	2301.9	2.1%	931.8	1.8%	821.1	1.8%	1500.0	2.2%	5307.0	1.0%
Other drugs to improve blood flow	50.7	0.0%	21.1	0.0%	24.5	0.1%	74.3	0.1%	249.5	0.0%
Clonidine	816.8	0.8%	263.7	0.5%	243.6	0.5%	512.0	0.8%	2029.6	0.4%
pde5 inhibitors	1242.2	1.2%	396.6	0.8%	317.9	0.7%	460.7	0.7%	2278.3	0.4%
Triptans	1265.5	1.2%	484.9	0.9%	397.5	0.9%	521.3	0.8%	1800.8	0.3%
Oral contraceptives	6747.6	6.3%	3015.9	5.8%	2342.6	5.1%	2877.7	4.3%	25804.4	4.8%
Hormones, menopausal or misc	8643.0	8.0%	3514.0	6.8%	3035.7	6.6%	4821.3	7.1%	26849.8	5.0%
Cardiovascular Risk Score										
decile 1	14555.0	13.6%	6163.4	11.9%	4872.3	10.6%	6168.8	9.1%	45003.8	8.4%
decile 2	22077.1	20.6%	10621.7	20.5%	8626.5	18.7%	10667.8	15.8%	191506.4	35.9%
decile 3	16459.8	15.3%	8598.3	16.6%	7398.3	16.0%	9168.2	13.5%	86101.3	16.1%
decile 4	12312.2	11.5%	6322.5	12.2%	5458.9	11.8%	6764.0	10.0%	46379.0	8.7%
decile 5	10232.0	9.5%	4950.7	9.6%	4377.6	9.5%	6377.2	9.4%	40920.8	7.7%
decile 6	8812.5	8.2%	4228.4	8.2%	3967.1	8.6%	6216.2	9.2%	32823.2	6.1%
decile 7	7469.7	7.0%	3552.5	6.9%	3425.2	7.4%	5671.4	8.4%	29000.0	5.4%
decile 8	6596.1	6.1%	3040.5	5.9%	3066.7	6.6%	5635.4	8.3%	24185.2	4.5%
decile 9	5342.2	5.0%	2487.7	4.8%	2727.2	5.9%	5742.1	8.5%	21633.3	4.1%
decile 10	3526.6	3.3%	1773.4	3.4%	2243.3	4.9%	5277.6	7.8%	16517.5	3.1%

* Using the MI or SCD model; **At baseline or cohort entry (t0): if 'on' at baseline, remains on; if 'off' at baseline but goes 'on' during follow-up, stays off;
[#] Excluding ADHD visits; *** Excluding ADHD medications; [$] Ever/never: once 'on' at baseline or during follow-up, remains on
[##] Including medications; [$$] Diagnosis: 'on' if any day in prior 365 is 'on', else 'off'; Meds: 'on' if has supply on the day, else 'off'

Tables of RRs—for Each of 3 Endpoints

Table 2a. Rates of acute myocardial infarction, by use of ADHD medications

Medication status	Person-yrs	Number Events	Rate/1,000 person-yrs	Unadjusted IRR	95% CI	Adjusted matching variables IRR*	95% CI	Adjusted IRR**	95% CI
ADHD medication users	284872.2	450	1.58						
Current user	113324.2	152	1.34	0.83	0.70 – 0.98	0.95	0.80 – 1.12	0.88	0.74 - 1.05
Indeterminate user	53896.7	86	1.60	0.98	0.79 – 1.23	1.15	0.92 – 1.44	1.07	0.85 - 1.33
Former user	47858.5	65	1.36	0.84	0.65 – 1.08	0.89	0.69 – 1.14	0.78	0.61 - 1.00
Remote user	69792.9	147	2.11	1.30	1.09 – 1.55	0.97	0.81 – 1.16	0.82	0.68 – 0.97
Nonuser	559743.1	907	1.62	1.00	reference	1.00	reference	1.00	reference

* Adjusted for site, age, sex, calendar year (i.e., matching variables)
**Adjusted for site, age, sex, calendar year, CRS (some variables within score are time-varying)

Table 2b. Rates of sudden cardiac death, by use of ADHD medications

Medication status	Person-yrs	Number Events	Rate/1,000 person-yrs	Unadjusted IRR	95% CI	Adjusted matching variables IRR*	95% CI	Adjusted IRR**	95% CI
ADHD medication users	273705.1	116	0.42						
Current user	107525.0	32	0.30	0.89	0.61 – 1.29	1.13	0.77 – 1.64	0.80	0.55 – 1.18
Indeterminate user	51814.0	14	0.27	0.80	0.47 – 1.38	1.01	0.58 – 1.74	0.73	0.42 – 1.26
Former user	46263.5	20	0.43	1.29	0.81 – 2.04	1.34	0.84 – 2.13	0.90	0.57 – 1.44
Remote user	68102.6	50	0.73	2.18	1.60 – 2.99	1.43	1.04 – 1.97	0.98	0.71 – 1.35
Nonuser	535515.5	180	0.34	1.00	reference	1.00	reference	1.00	reference

* Adjusted for site, age, sex, calendar year (i.e., matching variables)
**Adjusted for site, age, sex, calendar year, CRS (some variables within score are time-varying)
This table excludes the three HMORN sites that did not provide data on SCD endpoints.

Table 2b-2. Rates of sudden cardiac death (excluding only those adjudicated as non-cases), by use of ADHD medications

Medication status	Person-yrs	Number Events	Rate/1,000 person-yrs	Unadjusted IRR	95% CI	Adjusted matching variables IRR*	95% CI	Adjusted IRR**	95% CI
ADHD medication users	273705.1	140	0.51						
Current user	107525.0	40	0.37	0.99	0.70 – 1.38	1.24	0.88 – 1.74	0.84	0.59 – 1.19
Indeterminate user	51814.0	17	0.33	0.87	0.53 – 1.43	1.07	0.65 – 1.76	0.75	0.46 – 1.23
Former user	46263.5	28	0.61	1.60	1.08 – 2.38	1.65	1.11 – 2.45	1.08	0.72 – 1.61
Remote user	68102.6	55	0.81	2.14	1.59 – 2.88	1.42	1.05 – 1.93	0.96	0.71 – 1.30
Nonuser	535515.5	202	0.38	1.00	reference	1.00	reference	1.00	reference

* Adjusted for site, age, sex, calendar year (i.e., matching variables)
**Adjusted for site, age, sex, calendar year, CRS (some variables within score are time-varying)
This table excludes the three HMORN sites that did not provide data on SCD endpoints.

Table 2c. Rates of acute myocardial infarction or sudden cardiac death, by use of ADHD medications

Medication status	Person-yrs	Number Events	Rate/1,000 person-yrs	Unadjusted IRR	95% CI	Adjusted matching variables IRR*	95% CI	Adjusted IRR**	95% CI
ADHD medication users	272974.0	541	1.98						
Current user	107383.3	174	1.62	0.83	0.71 – 0.98	0.97	0.83 – 1.14	0.87	0.74 - 1.02
Indeterminate user	51739.1	97	1.87	0.96	0.78 – 1.18	1.15	0.93 – 1.41	1.02	0.83- 1.26
Former user	46163.0	84	1.82	0.93	0.75 – 1.17	0.99	0.79 – 1.24	0.83	0.66 - 1.03
Remote user	67688.6	186	2.75	1.41	1.21 – 1.65	1.03	0.88 – 1.20	0.83	0.71 – 0.98
Nonuser	534070.5	1041	1.95	1.00	reference	1.00	reference	1.00	reference

* Adjusted for site, age, sex, calendar year (i.e., matching variables)
**Adjusted for site, age, sex, calendar year, CRS (some variables within score are time-varying)
This table excludes the three HMORN sites that did not provide data on SCD endpoints.

Tables of RRs—Current Use of Specific Medications and Each of 3 Endpoints

Table 3a. Rates of acute myocardial infarction, by specific ADHD medication

Medication status	Person-yrs	Number Events	Rate/1,000 person-yrs	Unadjusted IRR	95% CI	Adjusted matching variables IRR*	95% CI	Adjusted IRR**	95% CI
Current user	113324.2	152	1.34	0.83	0.70 – 0.98	0.95	0.80 – 1.12	0.88	0.74 - 1.05
Amphetamines	49080.1	59	1.20	0.74	0.57 – 0.97	0.95	0.73 – 1.24	0.92	0.70 - 1.19
Methylphenidate	51232.8	77	1.50	0.93	0.74 – 1.17	0.97	0.77 – 1.23	0.89	0.71 - 1.13
Atomoxetine	8424.8	11	1.31	0.81	0.44 – 1.46	0.96	0.53 – 1.75	0.87	0.48 - 1.57
Pemoline	3047.3	5	1.64	1.01	0.42 – 2.44	0.85	0.35 – 2.04	0.71	0.29 - 1.71
Multiple	1539.1	0	0.00	--	--	--	--	--	--
Nonuser	559743.1	907	1.62	1.00	reference	1.00	reference	1.00	reference

* Adjusted for site, age, sex, calendar year (i.e., matching variables)
**Adjusted for site, age, sex, calendar year, CRS (some variables within score are time-varying)

Table 3b. Rates of sudden cardiac death, by specific ADHD medication

Medication status	Person-yrs	Number Events	Rate/1,000 person-yrs	Unadjusted IRR	95% CI	Adjusted matching variables IRR*	95% CI	Adjusted IRR**	95% CI
Current user	107525.0	32	0.30	0.89	0.61 – 1.29	1.13	0.77 – 1.64	0.80	0.55 - 1.18
Amphetamines	46910.0	13	0.28	0.82	0.47 – 1.45	1.22	0.69 – 2.14	0.93	0.52 - 1.63
Methylphenidate	47887.1	13	0.27	0.81	0.46 – 1.42	0.95	0.54 – 1.68	0.67	0.38 - 1.18
Atomoxetine	8257.6	4	0.48	1.44	0.54 – 3.88	1.63	0.60 – 4.42	1.04	0.38 - 2.82
Pemoline	2995.7	2	0.67	1.99	0.49 – 8.00	1.59	0.39 – 6.44	1.08	0.27 - 4.37
Multiple	1474.5	0	0.00	--	--	--	--	--	--
Nonuser	535515.5	180	0.34	1.00	reference	1.00	reference	1.00	reference

* Adjusted for site, age, sex, calendar year (i.e., matching variables)
**Adjusted for site, age, sex, calendar year, CRS (some variables within score are time-varying)
This table excludes the three HMORN sites that did not provide data on SCD endpoints.

Table 3b-2. Rates of sudden cardiac death (excluding only those adjudicated as non-cases), by specific ADHD medication

Medication status	Person-yrs	Number Events	Rate/1,000 person-yrs	Unadjusted IRR	95% CI	Adjusted matching variables IRR*	95% CI	Adjusted IRR**	95% CI
Current user	107525.0	40	0.37	0.99	0.70 – 1.38	1.24	0.88 – 1.74	0.84	0.59 - 1.19
Amphetamines	46910.0	15	0.32	0.85	0.50 – 1.43	1.23	0.72 – 2.08	0.88	0.52 - 1.50
Methylphenidate	47887.1	19	0.40	1.05	0.66 – 1.68	1.23	0.77 – 1.98	0.82	0.51 - 1.32
Atomoxetine	8257.6	4	0.48	1.28	0.48 – 3.45	1.43	0.53 – 3.87	0.85	0.32 – 2.31
Pemoline	2995.7	2	0.67	1.77	0.44 – 7.13	1.43	0.35 – 5.76	0.97	0.24 – 3.92
Multiple	1474.5	0	0.00	--	--	--	--	--	--
Nonuser	535515.5	202	0.38	1.00	reference	1.00	reference	1.00	reference

* Adjusted for site, age, sex, calendar year (i.e., matching variables)
**Adjusted for site, age, sex, calendar year, CRS (some variables within score are time-varying)
This table excludes the three HMORN sites that did not provide data on SCD endpoints.

Table 3c. Rates of acute myocardial infarction or sudden cardiac death by specific ADHD medication

Medication status	Person-yrs	Number Events	Rate/1,000 person-yrs	Unadjusted IRR	95% CI	Adjusted matching variables IRR*	95% CI	Adjusted IRR**	95% CI
Current user	107383.3	174	1.62	0.83	0.71 – 0.98	0.97	0.83 – 1.14	0.87	0.74 - 1.02
Amphetamines	46844.2	69	1.47	0.76	0.59 – 0.96	1.00	0.78 – 1.28	0.93	0.73 - 1.19
Methylphenidate	47829.9	84	1.76	0.90	0.72 – 1.13	0.96	0.77 – 1.20	0.85	0.68 - 1.07
Atomoxetine	8249.0	14	1.70	0.87	0.51 – 1.48	1.04	0.61 – 1.76	0.88	0.52 - 1.49
Pemoline	2989.8	7	2.34	1.20	0.57 – 2.53	1.01	0.48 – 2.13	0.83	0.39 - 1.75
Multiple	1470.5	0	0.00	--	--	--	--	--	--
Nonuser	534070.5	1041	1.95	1.00	reference	1.00	reference	1.00	reference

* Adjusted for site, age, sex, calendar year (i.e., matching variables)
**Adjusted for site, age, sex, calendar year, CRS(some variables within score are time-varying)
This table excludes the three HMORN sites that did not provide data on SCD endpoints.

Tables of RRs—Duration of Current Use and Each of 3 Endpoints

Table 4a. Rates of acute myocardial infarction, by use of ADHD medication

Medication status	Person-yrs	Number Events	Rate/1,000 person-yrs	Unadjusted IRR	95% CI	Adjusted matching variables IRR*	95% CI	Adjusted IRR**	95% CI
Duration of Current use [#]									
366+ days	52135.0	73	1.40	0.86	0.68 – 1.10	0.89	0.70 – 1.13	0.84	0.66 – 1.06
183-365 days	24237.3	38	1.57	0.97	0.70 – 1.34	1.24	0.90 – 1.72	1.17	0.85 – 1.62
91-182 days	14096.5	12	0.85	0.53	0.30 – 0.93	0.69	0.39 – 1.22	0.64	0.36 – 1.13
31-90 days	11704.9	12	1.03	0.63	0.36 – 1.12	0.83	0.47 – 1.47	0.77	0.44 – 1.37
1-30 days	8009.5	12	1.50	0.92	0.52 – 1.63	1.15	0.65 – 2.04	1.07	0.61 – 1.89
Nonuser	559743.1	907	1.62	1.00	reference	1.00	reference	1.00	reference

* Adjusted for site, age, sex, calendar year (i.e., matching variables)
**Adjusted for site, age, sex, calendar year, CRS(some variables within score are time-varying)
[#] Excludes current pemoline use.

Table 4b. Rates of sudden cardiac death, by use of ADHD medication

Medication status	Person-yrs	Number Events	Rate/1,000 person-yrs	Unadjusted IRR	95% CI	Adjusted matching variables IRR*	95% CI	Adjusted IRR**	95% CI
Duration of Current use [#]									
366+ days	49222.4	19	0.39	1.15	0.72 – 1.84	1.40	0.87 – 2.25	1.03	0.64 – 1.66
183-365 days	23046.0	2	0.09	0.26	0.06 – 1.04	0.37	0.09 – 1.48	0.26	0.07 – 1.07
91-182 days	13371.1	5	0.37	1.11	0.46 – 2.71	1.53	0.63 – 3.74	1.05	0.43 – 2.57
31-90 days	11140.0	2	0.18	0.53	0.13 – 2.15	0.72	0.18 – 2.91	0.49	0.12 – 1.96
1-30 days	7660.5	2	0.26	0.78	0.19 – 3.13	0.96	0.24 – 3.87	0.63	0.16 – 2.56
Nonuser	535515.5	180	0.34	1.00	reference	1.00	reference	1.00	reference

* Adjusted for site, age, sex, calendar year (i.e., matching variables)
**Adjusted for site, age, sex, calendar year, CRS(some variables within score are time-varying)
[#] Excludes current pemoline use.
This table excludes the three HMORN sites that did not provide data on SCD endpoints.

Table 4c. Rates of acute myocardial infarction or sudden cardiac death, by use of ADHD medication

Medication status	Person-yrs	Number Events	Rate/1,000 person-yrs	Unadjusted IRR	95% CI	Adjusted matching variables IRR*	95% CI	Adjusted IRR**	95% CI
Duration of Current use [#]									
366+ days	49112.8	88	1.79	0.92	0.74 – 1.14	0.98	0.79 – 1.22	0.89	0.71 – 1.10
183-365 days	23030.1	37	1.61	0.82	0.59 – 1.14	1.08	0.78 – 1.51	0.98	0.71 – 1.36
91-182 days	13364.9	15	1.12	0.58	0.35 – 0.96	0.76	0.46 – 1.27	0.68	0.41 – 1.13
31-90 days	11136.9	14	1.26	0.64	0.38 – 1.09	0.85	0.50 – 1.44	0.75	0.44 – 1.28
1-30 days	7659.5	13	1.70	0.87	0.50 – 1.50	1.09	0.63 – 1.88	0.95	0.55 – 1.64
Nonuser	534070.5	1041	1.95	1.00	reference	1.00	reference	1.00	reference

* Adjusted for site, age, sex, calendar year (i.e., matching variables)
**Adjusted for site, age, sex, calendar year, CRS(some variables within score are time-varying)
[#] Excludes current pemoline use.
This table excludes the three HMORN sites that did not provide data on SCD endpoints.

Table 4d. Rates of acute myocardial infarction or sudden cardiac death, by use of ADHD medication (new users only)

Medication status	Person-yrs	Number Events	Rate/1,000 person-yrs	Unadjusted IRR	95% CI	Adjusted matching variables IRR*	95% CI	Adjusted IRR**	95% CI
Duration of Current use [#]									
366+ days	15077.8	33	2.19	0.98	0.69 - 1.39	0.97	0.68 - 1.37	0.82	0.58 - 1.16
183-365 days	10500.2	16	1.52	0.68	0.42 - 1.12	0.89	0.54 - 1.46	0.75	0.45 - 1.23
91-182 days	9020.6	10	1.11	0.50	0.27 - 0.93	0.70	0.37 - 1.30	0.58	0.31 - 1.09
31-90 days	9193.0	13	1.41	0.63	0.37 - 1.10	0.92	0.53 - 1.60	0.78	0.45 - 1.34
1-30 days	7216.4	12	1.66	0.74	0.42 - 1.32	1.05	0.59 - 1.86	0.88	0.50 - 1.55
Nonuser	317903.0	710	2.23	1.00	reference	1.00	reference	1.00	reference

* Adjusted for site, age, sex, calendar year (i.e., matching variables)
**Adjusted for site, age, sex, calendar year, CRS (some variables within score are time-varying)
[#] Excludes current pemoline use.
This table excludes the three HMORN sites that did not provide data on SCD endpoints.

Subgroup Analyses

Table 5a. Rate ratios of acute myocardial infarction, overall and by subgroup

Cohort/ subgroup	Person-yrs	Number Events	Rate/1,000 person-yrs	IRR**	95% CI
Full cohort	844615.3	1357	1.61		
Current	113324.2	152	1.34	0.88	0.74 – 1.05
Former*	171548.0	298	1.74	0.87	0.76 – 0.99
Nonuser	559743.1	907	1.62	1.00	reference
Excluding pts with history of CVD^	597679.9	529	0.89		
Current	74944.5	57	0.76	0.87	0.65 – 1.15
Former*	110860.6	98	0.88	0.82	0.66 – 1.03
Nonuser	411874.8	374	0.91	1.00	reference
Including pts with history of CVD^	246935.4	828	3.35		
Current	38379.7	95	2.48	0.88	0.70 – 1.09
Former*	60687.4	200	3.30	0.89	0.76 – 1.05
Nonuser	147868.3	533	3.60	1.00	reference
Including pts with non-ADHD psychiatric diagnosis or medications	335690.0	661	1.97		
Current	83597.7	116	1.39	0.85	0.68 - 1.05
Former*	120563.2	227	1.88	0.86	0.72 - 1.02
Nonuser	131529.1	318	2.42	1.00	reference
Excluding pts with non-ADHD psychiatric diagnosis or medications	508925.3	696	1.37		
Current	29726.5	36	1.21	0.93	0.67 - 1.31
Former*	50984.8	71	1.39	0.85	0.67 - 1.09
Nonuser	428214.0	589	1.38	1.00	reference
Excluding prevalent users (CRS)	510404.1	906	1.78		
Current	55533.9	77	1.39	0.80	0.63 – 1.02
Former*	121371.9	222	1.83	0.80	0.68 – 0.93
Nonuser	333498.3	607	1.82	1.00	reference
Excluding prevalent users (PS)	510404.1	906	1.78		
Current	55533.9	77	1.39	0.77	0.59 - 1.00
Former*	121371.9	222	1.83	0.84	0.71 - 1.00
Nonuser	333498.3	607	1.82	1.00	reference
Users restricted to those with ADHD	636461.0	990	1.56		
Current	40340.4	44	1.09	0.85	0.62 – 1.15
Former*	36377.5	39	1.07	0.83	0.60 – 1.15
Nonuser	559743.1	907	1.62	1.00	reference
Users restricted to those with no ADHD	767897.3	1274	1.66		
Current	72983.7	108	1.48	0.88	0.72 – 1.08
Former*	135170.5	259	1.92	0.87	0.76 – 1.00
Nonuser	559743.1	907	1.62	1.00	reference
Users restricted to those with ADHD	240093.6	278	1.16		
Current	40340.4	44	1.09	0.87	0.63 - 1.22
Former*	36377.5	39	1.07	0.87	0.62 - 1.23
Nonuser (matched to user)	163375.7	195	1.19	1.00	reference
Users restricted to those with no ADHD	609486.8	1084	1.78		
Current	72983.7	108	1.48	0.88	0.72 - 1.08
Former*	135170.5	259	1.92	0.86	0.75 - 1.00
Nonuser (matched to user)	401332.6	717	1.79	1.00	reference
Restricted to ages 25-44	428064.5	239	0.56		
Current	56642.9	28	0.49	0.89	0.59 – 1.34
Former*	88442.5	64	0.72	0.92	0.68 – 1.24
Nonuser	282979.1	147	0.52	1.00	reference
Restricted to ages 45-64	416550.8	1118	2.68		
Current	56681.2	124	2.19	0.87	0.72 – 1.06
Former*	83105.5	234	2.82	0.85	0.73 – 0.98
Nonuser	276764.0	760	2.75	1.00	reference

* Includes indeterminate, former and remote users

**Adjusted for site, age, sex, calendar year, CRS(some variables within score are time-varying)

^ Definition of CVD included the following diagnoses/claims and medications within the year prior to baseline: acute myocardial infarction, ischemia, coronary revascularization, CHF, arrhythmia, stroke/TIA, congenital heart disorder, coronary artery anomaly, peripheral vascular disease, hyperlipidemia, hypertension, loop diuretic, digoxin, nitrates, anticoagulant, platelet inhibitor, anti-arrhythmic agents, ACE inhibitor, angiotensin receptor blocker, beta-blocker, calcium-channel blocker, thiazide diuretic, and other antihypertensive drugs.

Table 5b. Rate ratios of sudden cardiac death, overall and by subgroup

Cohort/ subgroup	Person-yrs	Number Events	Rate/1,000 person-yrs	IRR**	95% CI
Full cohort	809220.6	296	0.37		
Current	107525.0	32	0.30	0.81	0.55 – 1.18
Former*	166180.1	84	0.51	0.91	0.70 – 1.18
Nonuser	535515.5	180	0.34	1.00	reference
Excluding pts with history of CVD^	570372.7	102	0.18		
Current	70840.5	9	0.13	0.74	0.36 – 1.49
Former*	106783.9	22	0.21	0.80	0.49 – 1.31
Nonuser	392748.3	71	0.18	1.00	reference
Including pts with history of CVD^	238847.9	194	0.81		
Current	36684.5	23	0.63	0.87	0.55 – 1.38
Former*	59396.2	62	1.04	0.99	0.72 – 1.35
Nonuser	142767.2	109	0.76	1.00	reference
Including pts with non-ADHD psychiatric diagnosis or medications	321989.4	175	0.54		
Current	79128.1	28	0.35	0.89	0.57 - 1.39
Former*	116646.1	70	0.60	0.96	0.69 - 1.33
Nonuser	126215.2	77	0.61	1.00	reference
Excluding pts with non-ADHD psychiatric diagnosis or medications	487231.2	121	0.25		
Current	28396.9	4	0.14	0.64	0.24 - 1.76
Former*	49534.0	14	0.28	0.88	0.50 - 1.55
Nonuser	409300.3	103	0.25	1.00	reference
Excluding prevalent users (CRS)	488581.1	222	0.45		
Current	52203.2	15	0.29	0.63	0.37 – 1.08
Former*	117556.8	74	0.63	0.99	0.74 – 1.32
Nonuser	318821.1	133	0.42	1.00	reference
Excluding prevalent users (PS)	488581.1	222	0.45		
Current	52203.2	15	0.29	0.62	0.35 - 1.10
Former*	117556.8	74	0.63	1.06	0.76 - 1.46
Nonuser	318821.1	133	0.42	1.00	reference
Users restricted to those with ADHD	607491.7	192	0.32		
Current	37621.3	7	0.19	0.78	0.36 – 1.68
Former*	34354.8	6	0.17	0.68	0.30 – 1.54
Nonuser	535515.5	180	0.34	1.00	reference
Users restricted to those with no ADHD	737244.5	283	0.38		
Current	69903.7	25	0.36	0.83	0.54 – 1.26
Former*	131825.3	78	0.59	0.93	0.71 – 1.23
Nonuser	535515.5	180	0.34	1.00	reference
Users restricted to those with ADHD	224736.4	43	0.19		
Current	37621.3	7	0.19	0.78	0.34 - 1.80
Former*	34354.8	6	0.17	0.67	0.28 - 1.63
Nonuser (matched to user)	152760.2	30	0.20	1.00	reference
Users restricted to those with no ADHD	589275.8	253	0.43		
Current	69903.7	25	0.36	0.83	0.54 - 1.28
Former*	131825.3	78	0.59	0.95	0.71 - 1.25
Nonuser (matched to user)	387546.8	150	0.39	1.00	reference
Restricted to ages 25-44	412049.0	62	0.15		
Current	54141.3	9	0.17	0.78	0.37 – 1.65
Former*	85960.3	14	0.16	0.54	0.29 – 1.02
Nonuser	271947.4	39	0.14	1.00	reference
Restricted to ages 45-64	397171.6	234	0.59		
Current	53383.7	23	0.43	0.79	0.50 – 1.23
Former*	80219.8	70	0.87	1.02	0.76 – 1.36
Nonuser	263568.1	141	0.53	1.00	reference

*Includes indeterminate, former and remote users

**Adjusted for site, age, sex, calendar year, CRS(some variables within score are time-varying)

^ See definition of CVD in Table 5a.

This table excludes the three HMORN sites that did not provide data on SCD endpoints.

Table 5c. Rate ratios of acute myocardial infarction or sudden cardiac death, overall and by subgroup

Cohort/ subgroup	Person-yrs	Number Events	Rate/1,000 person-yrs	IRR**	95% CI
Full cohort	807044.6	1582	1.96		
Current	107383.3	174	1.62	0.87	0.74 – 1.02
Former*	165590.8	367	2.22	0.87	0.78 – 0.99
Nonuser	534070.5	1041	1.95	1.00	reference
Excluding pts with history of CVD^	569399.6	602	1.06		
Current	70766.5	62	0.88	0.87	0.66 – 1.14
Former*	106563.6	115	1.08	0.82	0.67 – 1.01
Nonuser	392069.5	425	1.08	1.00	reference
Including pts with history of CVD^	237645.0	980	4.12		
Current	36616.7	112	3.06	0.87	0.71 – 1.07
Former*	59027.2	252	4.27	0.91	0.78 – 1.05
Nonuser	142001.1	616	4.34	1.00	reference
Including pts with non-ADHD psychiatric diagnosis or medications	321012.2	800	2.49		
Current	79020.3	136	1.72	0.86	0.70 - 1.05
Former*	116231.9	284	2.44	0.87	0.75 - 1.02
Nonuser	125760.0	380	3.02	1.00	reference
Excluding pts with non-ADHD psychiatric diagnosis or medications	486032.3	782	1.61		
Current	28363.0	38	1.34	0.90	0.65 - 1.25
Former*	49358.8	83	1.68	0.87	0.69 - 1.10
Nonuser	408310.5	661	1.62	1.00	reference
Excluding prevalent users (CRS)	487157.1	1082	2.22		
Current	52129.2	87	1.67	0.76	0.61 – 0.95
Former*	117124.9	285	2.43	0.83	0.73 – 0.96
Nonuser	317903.0	710	2.23	1.00	reference
Excluding prevalent users (PS)	487157.1	1082	2.22		
Current	52129.2	87	1.67	0.74	0.58 - 0.94
Former*	117124.9	285	2.43	0.87	0.75 - 1.02
Nonuser	317903.0	710	2.23	1.00	reference
Users restricted to those with ADHD	605930.3	1130	1.86		
Current	37577.2	47	1.25	0.84	0.63 – 1.13
Former*	34282.5	42	1.23	0.80	0.59 – 1.09
Nonuser	534070.5	1041	1.95	1.00	reference
Users restricted to those with no ADHD	735182.7	1493	2.03		
Current	69806.0	127	1.82	0.88	0.73 – 1.06
Former*	131306.2	325	2.48	0.89	0.78 – 1.01
Nonuser	534070.5	1041	1.95	1.00	reference
Users restricted to those with ADHD	224304.0	302	1.35		
Current	37577.2	47	1.25	0.85	0.62 - 1.17
Former*	34284.5	42	1.23	0.82	0.58 - 1.14
Nonuser (matched to user)	152442.2	213	1.40	1.00	reference
Users restricted to those with no ADHD	587526.3	1284	2.19		
Current	69806.0	127	1.82	0.88	0.73 - 1.06
Former*	131306.2	325	2.48	0.89	0.78 - 1.01
Nonuser (matched to user)	386414.1	832	2.15	1.00	reference
Restricted to ages 25-44	411700.6	296	0.72		
Current	54122.0	35	0.65	0.85	0.59 -1.22
Former*	85833.7	77	0.90	0.83	0.63 – 1.08
Nonuser	271744.9	184	0.68	1.00	reference
Restricted to ages 45-64	395344.1	1286	3.25		
Current	53261.3	139	2.61	0.87	0.73 – 1.04
Former*	79757.0	290	3.64	0.88	0.77 – 1.01
Nonuser	262325.7	857	3.27	1.00	reference

* Includes indeterminate, former and remote users

**Adjusted for site, age, sex, calendar year, CRS(some variables within score are time-varying)

^ See definition of CVD in Table 5a.

This table excludes the three HMORN sites that did not provide data on SCD endpoints.

Tables of RRs—Remote Users as Reference Group (Tables 6 and 7)

Table 6a. Rates of acute myocardial infarction, by use of ADHD medication

Medication status	Person- yrs	Number Events	Rate/1,000 person-yrs	Unadjusted IRR	95% CI	Adjusted matching variables IRR**	95% CI	Adjusted IRR**	95% CI
Current user	113324.2	152	1.34	0.64	0.51 – 0.80	0.98	0.78 – 1.23	1.08	0.86 - 1.36
Indeterminate user	53896.7	86	1.60	0.76	0.58 – 0.99	1.19	0.91 – 1.56	1.31	1.00 - 1.71
Former user	47858.5	65	1.36	0.64	0.48 – 0.86	0.92	0.68 – 1.23	0.96	0.71 - 1.28
Remote user	69792.9	147	2.11	1.00	reference	1.00	reference	1.00	reference

* Adjusted for site, age, sex, calendar year (i.e., matching variables)
**Adjusted for site, age, sex, calendar year, CRS(some variables within score are time-varying)

Table 6b. Rates of sudden cardiac death, by use of ADHD medication

Medication status	Person- yrs	Number Events	Rate/1,000 person-yrs	Unadjusted IRR	95% CI	Adjusted matching variables IRR**	95% CI	Adjusted IRR**	95% CI
Current user	107525.0	32	0.30	0.41	0.26 – 0.63	0.79	0.50 – 1.24	0.82	0.52 – 1.29
Indeterminate user	51814.0	14	0.27	0.37	0.20 – 0.67	0.70	0.39 – 1.28	0.74	0.41 – 1.35
Former user	46263.5	20	0.43	0.59	0.35 – 0.99	0.94	0.56 – 1.58	0.92	0.55 – 1.55
Remote user	68102.6	50	0.73	1.00	reference	1.00	reference	1.00	reference

* Adjusted for site, age, sex, calendar year (i.e., matching variables)
**Adjusted for site, age, sex, calendar year, CRS(some variables within score are time-varying)
This table excludes the three HMORN sites that did not provide data on SCD endpoints.

Table 6c. Rates of acute myocardial infarction or sudden cardiac death, by use of ADHD medication

Medication status	Person- yrs	Number Events	Rate/1,000 person-yrs	Unadjusted IRR	95% CI	Adjusted matching variables IRR**	95% CI	Adjusted IRR**	95% CI
Current user	107383.3	174	1.62	0.59	0.48 – 0.73	0.95	0.77 – 1.17	1.04	0.85 - 1.29
Indeterminate user	51739.1	97	1.87	0.68	0.53 – 0.87	1.12	0.87 – 1.43	1.22	0.95 - 1.57
Former user	46163.0	84	1.82	0.66	0.51 – 0.86	0.96	0.74 – 1.25	0.99	0.76- 1.28
Remote user	67688.6	186	2.75	1.00	reference	1.00	reference	1.00	reference

* Adjusted for site, age, sex, calendar year (i.e., matching variables)
**Adjusted for site, age, sex, calendar year, CRS(some variables within score are time-varying)
This table excludes the three HMORN sites that did not provide data on SCD endpoints.

Table 7a. Rates of acute myocardial infarction, by specific ADHD medication

Medication status	Person- yrs	Number Events	Rate/1,000 person-yrs	Unadjusted IRR	95% CI	Adjusted matching variables IRR**	95% CI	Adjusted IRR**	95% CI
Current user	113324.2	152	1.34	0.64	0.51 – 0.80	0.98	0.78 – 1.23	1.08	0.86 – 1.36
Amphetamines	49080.1	59	1.20	0.57	0.42 – 0.77	0.99	0.73 – 1.34	1.12	0.83 – 1.52
Methylphenidate	51232.8	77	1.50	0.71	0.54 – 0.94	1.00	0.76 – 1.32	1.10	0.83 – 1.45
Atomoxetine	8424.8	11	1.31	0.62	0.34 – 1.14	0.99	0.54 – 1.84	1.06	0.57 – 1.96
Pemoline	3047.3	5	1.64	0.78	0.32 – 1.90	0.87	0.36 – 2.13	0.87	0.36 – 2.12
Multiple	1539.1	0	0.00	--	--	--	--	--	--
Remote user	69792.9	147	2.11	1.00	reference	1.00	reference	1.00	reference

* Adjusted for site, age, sex, calendar year (i.e., matching variables)
**Adjusted for site, age, sex, calendar year, CRS(some variables within score are time-varying)

Table 7b. Rates of sudden cardiac death, by specific ADHD medication

Medication status	Person- yrs	Number Events	Rate/1,000 person-yrs	Unadjusted IRR	95% CI	Adjusted matching IRR**	95% CI	Adjusted IRR**	95% CI
Current user	107525.0	32	0.30	0.41	0.26 – 0.63	0.79	0.50 – 1.24	0.82	0.52 - 1.29
Amphetamines	46910.0	13	0.28	0.38	0.21 – 0.69	0.85	0.46 – 1.58	0.94	0.51 - 1.76
Methylphenidate	47887.1	13	0.27	0.37	0.20 – 0.68	0.66	0.36 – 1.23	0.68	0.37 - 1.27
Atomoxetine	8257.6	4	0.48	0.66	0.24 – 1.83	1.14	0.41 – 3.18	1.06	0.38 – 2.95
Pemoline	2995.7	2	0.67	0.91	0.22 – 3.74	1.11	0.27 – 4.59	1.10	0.27 - 4.56
Multiple	1474.5	0	0.00	--	--	--	--	--	--
Remote user	68102.6	50	0.73	1.00	reference	1.00	reference	1.00	reference

* Adjusted for site, age, sex, calendar year (i.e., matching variables)
**Adjusted for site, age, sex, calendar year, CRS(some variables within score are time-varying)
This table excludes the three HMORN sites that did not provide data on SCD endpoints.

Table 7c. Rates of acute myocardial infarction or sudden cardiac death by specific ADHD medication

Medication status	Person- yrs	Number Events	Rate/1,000 person-yrs	Unadjusted IRR	95% CI	Adjusted matching IRR**	95% CI	Adjusted IRR**	95% CI
Current user	107383.3	174	1.62	0.59	0.48 – 0.73	0.95	0.77 – 1.17	1.04	0.85 – 1.29
Amphetamines	46844.2	69	1.47	0.54	0.41 – 0.71	0.97	0.74 – 1.29	1.12	0.84 – 1.48
Methylphenidate	47829.9	84	1.76	0.64	0.49 – 0.83	0.94	0.72 – 1.22	1.02	0.79 – 1.33
Atomoxetine	8249.0	14	1.70	0.62	0.36 – 1.06	1.01	0.59 – 1.74	1.05	0.61 – 1.81
Pemoline	2989.8	7	2.34	0.85	0.40 – 1.81	0.99	0.46 – 2.10	0.99	0.47 – 2.12
Multiple	1470.5	0	0.00	--	--	--	--	--	--
Remote user	67688.6	186	2.75	1.00	reference	1.00	reference	1.00	reference

* Adjusted for site, age, sex, calendar year (i.e., matching variables)
**Adjusted for site, age, sex, calendar year, CRS(some variables within score are time-varying)
This table excludes the three HMORN sites that did not provide data on SCD endpoints.

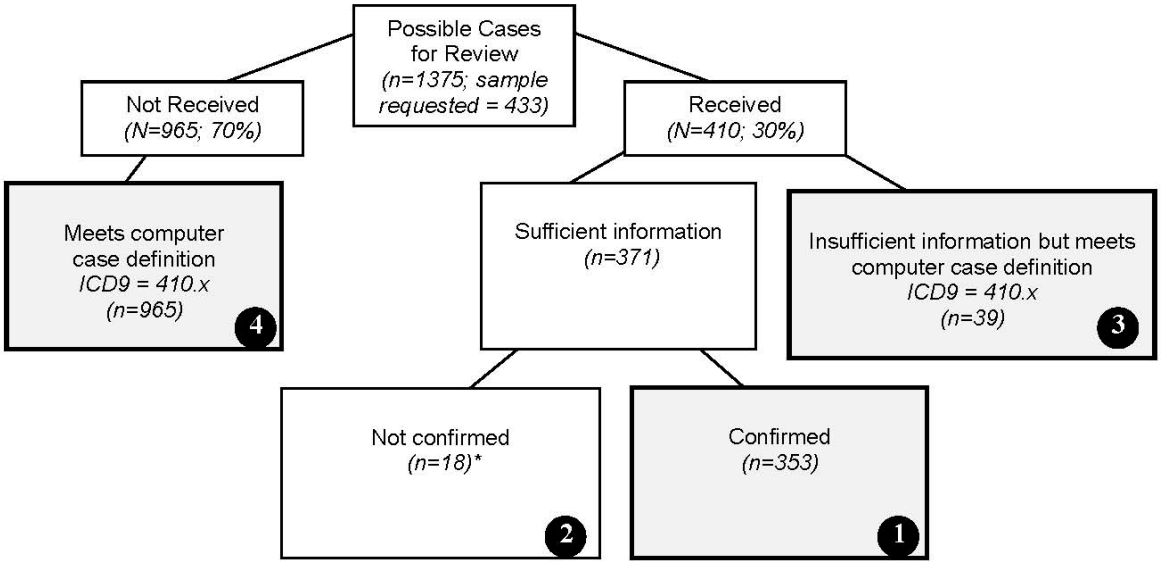
Appendix A. Supplementary Tables and Figures

Table A-1. Case identification and adjudication by outcome

	Sudden cardiac death		Myocardial infarction	
	N	**%**	**N**	**%**
Total potential cases*	411	100 %	1375	100 %
Electronic diagnosis/claims	56		1247	
NDI search	268		107	
Both electronic record and NDI search	87		21	
Records requested	411	100 %	433	31%
Records received[#]	305	74 %	410	95 %
Confirmed by records [a]	139	46 %	353	86 %
Not confirmed by records [a]	166	54 %	57	14 %
Inadequate information [b]	97	58 %	39	68 %
Evaluated and ruled out [b]	67	40 %	18	32 %
Not a death/arrest (SCD only) [b]	2	1 %	--	--

* Cases identified from electronic diagnosis/claims and National Death Index searches.
[#] Received includes ED records, inpatient records, autopsy records, and death certificates.
[a] Percent of records received
[b] Percent of records not confirmed

Figure A-1. Flowchart of MI case review status: all sites combined

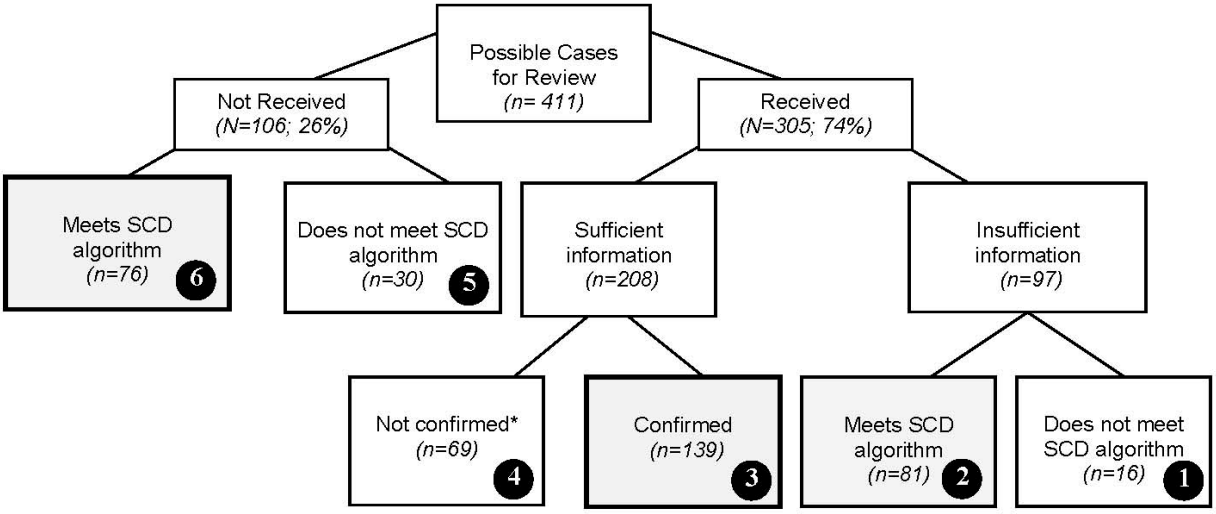


*Reasons for cases not being confirmed (Adjudication status=2)

Reason	MI
All	18
Ruled out: symptomatic, test negative	14
Miscode/other diagnosis	4

Note: Groups 1, 3 and 4 constitute analytic cases, group 2 was identified by the computer but not confirmed by chart review.

Figure A-2. Flowchart of SCD case review status: all sites combined



*Reasons for cases not being confirmed (Adjudication status=4)

Reason	SCD
All	69
Cardiac death, non-arrhythmic	22
Miscode	2
Procedure related	2
Overdose	7
Injury/accident	2
Drowning	1
Non-cardiac death, other	26
Non-death, non-cardiac	5
Undetermined	2

Note: Groups 2, 3 and 6 constitute analytic cases; groups 1, 4 and 5 were not confirmed by adjudication or did not meet the SCD algorithm.

Table A-2. Endpoints by site (standardized to age and gender-distribution of all sites combined)

	Sudden cardiac death			Myocardial infarction		
Site	**Person-yrs**	**Number events**	**Rate/1,000 person-yrs**	**Person-yrs**	**Number events**	**Rate/1,000 person-yrs**
Ingenix/I3	390657.4	86	0.25	390090.3	451	1.26
KPNC	99011.0	23	0.19	98722.4	161	1.33
KPSC	34335.3	18	0.51	34276.7	40	0.97
Tennessee Medicaid	123028.2	150	1.34	122204.9	446	4.20
HMORN	162188.7	19		199321.0	259	
Fallon Community*	--	--	--	5009.4	3	0.48
Group Health	42813.0	5	0.09	42676.3	68	1.32
Harvard Pilgrim	67340.5	2	0.02	67201.5	74	0.94
HealthPartners	32161.6	8	0.24	32057.7	52	1.56
KPCO	19873.7	4	0.17	19823.2	29	1.26
KP Mid-Atlantic*	--	--	--	5651.0	4	0.70
KPNW*	--	--	--	26902.0	29	0.90

*****These sites did not contribute to the SCD endpoint.

Table A-3. Characteristics of study cohort at baseline, by site

Characteristics	I3* N=266,787	KPNC* N=36,450	KPSC* N=19,947	HMORN* N=80,351	Tennessee Medicaid* N=43,371
Demographics					
Median age (years)	41	44	45	43	39
Male gender (%)	47.7%	46.3%	47.3%	46.2%	34.0%
Medicaid enrollment (%)	--	1.2%	0.9%	--	100.0%
Cardiovascular disease within past year					
Acute MI	0.2%	0.1%	0.2%	0.2%	0.5%
Ischemia	2.3%	1.1%	1.4%	1.7%	6.5%
Coronary revascularization	0.2%	0.1%	0.1%	0.1%	0.5%
CHF	0.4%	0.3%	0.4%	0.3%	3.1%
Arrhythmia	1.9%	0.6%	1.0%	1.7%	3.9%
Stroke/TIA	0.7%	0.3%	0.5%	0.6%	2.8%
Congenital heart disorder	0.2%	0.1%	0.1%	0.2%	0.4%
Coronary artery anomaly	0.0%	0.0%	0.0%	0.0%	0.1%
Peripheral vascular disease	0.5%	0.3%	0.3%	0.5%	2.0%
Hypertension	13.2%	10.0%	11.3%	10.8%	27.1%
Hyperlipidemia**	16.5%	9.4%	15.0%	13.9%	22.2%
Mental health claims within past year					
ADHD	9.6%	15.2%	14.9%	14.1%	3.1%
Major depression	15.9%	21.6%	20.2%	23.1%	27.4%
Bipolar disorder	2.2%	3.2%	3.0%	3.0%	8.9%
Anxiety	8.7%	11.0%	10.8%	11.1%	18.3%
Psychotic disorders	0.4%	0.8%	0.9%	0.6%	5.3%
Other selected medical conditions within past year					
Diabetes**	4.6%	5.2%	6.3%	4.6%	13.1%
Obesity	2.6%	17.6%	5.9%	4.3%	6.1%
Smoking	3.6%	10.9%	2.9%	6.9%	15.4%
ETOH/substance abuse	1.6%	4.5%	3.4%	2.7%	8.9%
Suicide attempt	0.2%	0.1%	0.2%	0.2%	1.2%
Injury	14.0%	15.0%	13.6%	14.9%	24.9%
Seizure	0.9%	0.6%	0.6%	0.9%	5.7%
Asthma	4.8%	5.9%	4.3%	5.4%	9.4%
Use of cardiovascular drug within past year					
Loop diuretic	1.4%	1.2%	1.3%	1.1%	9.1%
Digoxin	0.2%	0.3%	0.4%	0.3%	1.6%
Nitrates	0.7%	1.0%	1.1%	1.0%	4.7%
Anticoagulant	0.6%	0.6%	2.9%	0.8%	2.6%
Platelet inhibitor	0.5%	0.3%	0.4%	0.3%	2.2%
Anti-arrhythmic agents	0.1%	0.1%	0.2%	0.6%	0.5%
ACE inhibitor	5.9%	6.0%	8.0%	5.9%	14.3%
Angiotensin receptor blocker	2.5%	0.7%	1.1%	0.9%	4.0%
Beta- blocker	5.9%	7.5%	8.4%	7.3%	13.0%
Calcium-channel blocker	3.9%	3.0%	3.0%	3.0%	11.1%
Thiazide diuretic	7.0%	7.3%	8.5%	6.2%	10.6%
Other antihypertensive	0.7%	1.0%	1.5%	0.7%	1.9%
Use of psychotropic medications within past year					
Antipsychotic, any	2.6%	4.3%	4.5%	4.0%	17.0%
Tricyclic antidepressant	3.5%	6.0%	5.5%	5.9%	16.0%
Antidepressants, other or SSRI/SNRI	22.3%	28.2%	27.6%	31.8%	41.2%
Benzodiazepines	14.3%	12.9%	14.1%	14.1%	29.4%
Lithium	0.8%	1.4%	0.9%	1.2%	3.1%
Modafinil	1.1%	0.6%	1.6%	0.9%	1.8%

Table A-3. Characteristics of study cohort at baseline, by site (continued)

Characteristics	I3* N=266,787	KPNC* N=36,450	KPSC* N=19,947	HMORN* N=80,351	Tennessee Medicaid* N=43,371
Insomnia meds	5.7%	1.7%	1.7%	2.5%	9.0%
Thioridazine	0.0%	0.1%	0.1%	0.1%	0.9%
Mood stabilizers, w/o seizure	5.6%	6.3%	5.7%	6.4%	17.4%
Clonidine/guanfacine, w/o HT	0.5%	0.4%	0.5%	0.6%	1.5%
Use of other selected medications within past year					
Beta-agonist	6.7%	11.0%	10.0%	9.5%	19.1%
Epinephrine	0.5%	0.4%	0.4%	0.8%	0.8%
Asthma med, other	18.3%	10.8%	11.8%	21.3%	29.2%
Seizure med, any	6.1%	6.7%	6.1%	6.8%	21.3%
Theophylline compounds	0.2%	0.3%	0.2%	0.3%	2.7%
COX-2 inhibitors	5.9%	0.8%	1.0%	1.2%	10.3%
Other drugs to improve blood flow	0.1%	0.1%	0.0%	0.1%	0.4%
Clonidine	0.6%	0.7%	0.9%	0.8%	3.7%
pde5 inhibitors	2.3%	3.0%	3.7%	1.9%	0.5%
Triptans	2.8%	2.5%	2.7%	2.4%	3.9%
Oral contraceptives	10.3%	9.8%	10.3%	11.7%	10.7%
Hormones, menopausal or misc	8.6%	10.4%	9.4%	9.6%	11.7%
Utilization within past year					
Cardiovascular visits					
Emergency, 1+	1.4%	2.3%	2.2%	3.2%	13.6%
Inpatient, 1+	2.0%	1.7%	3.1%	2.3%	11.1%
Physician, 1-4	25.2%	18.7%	19.4%	22.9%	29.0%
Physician, 5+	6.6%	2.1%	2.4%	4.9%	18.9%
***Psychiatric visits**[#]*					
Emergency, 1+	0.6%	1.0%	0.9%	1.7%	9.0%
Inpatient, 1+	1.6%	1.7%	2.3%	2.0%	10.7%
Physician, 1-4	14.0%	18.2%	19.0%	17.3%	19.8%
Physician, 5+	9.4%	10.5%	8.8%	13.6%	22.5%
Other visits					
Emergency, 1+	2.0%	2.7%	2.8%	4.2%	16.9%
Inpatient, 1+	1.6%	1.9%	3.1%	1.9%	9.9%
Physician, 1+	25.9%	34.1%	22.9%	25.9%	40.9%
No. of different medications*					
1	19.9%	21.1%	20.7%	19.8%	10.8%
2+	47.8%	47.2%	47.9%	50.3%	72.0%

*Numbers are for membership periods at baseline or cohort entry (t0).

** Including medications

[#] Excluding ADHD visits

*** Excluding ADHD medications

Tables To Examine Heterogeneity of RRs by Site

Table A-4a. Rate ratios of acute myocardial infarction by site

	I3		KPNC		KPSC		Tennessee Medicaid	
Medication status	**RR**	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**
ADHD medication users								
Current user	0.93	0.71 - 1.23	0.85	0.51 - 1.40	0.97	0.42 - 2.26	0.63	0.41 - 0.97
Indeterminate user	0.89	0.61 - 1.29	2.04	1.18 - 3.52	1.32	0.40 - 4.37	0.98	0.63 - 1.55
Former user	0.58	0.36 - 0.92	0.85	0.37 - 1.94	1.36	0.41 - 4.51	1.08	0.75 - 1.56
Remote user	0.95	0.69 - 1.31	1.46	0.90 - 2.37	0.53	0.07 - 3.96	0.69	0.53 - 0.90
Nonuser	1.00	reference	1.00	reference	1.00	reference	1.00	reference

Adjusted for age, sex, calendar year, CRS (some variables within score are time-varying)
Using the CRS created from the full cohort

Table A-4b. Rate ratios of sudden cardiac death by site

	I3		KPNC		KPSC		Tennessee Medicaid	
Medication status	**RR**	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**
ADHD medication users								
Current user	0.89	0.49 - 1.62	1.51	0.52 - 4.44	0.56	0.15 - 2.05	0.62	0.30 - 1.29
Indeterminate user	0.62	0.25 - 1.56	0.87	0.11 - 6.77	0.56	0.07 - 4.42	0.95	0.44 - 2.07
Former user	0.39	0.12 - 1.24	2.26	0.61 - 8.30	--	--	0.93	0.48 - 1.80
Remote user	0.97	0.48 - 1.99	0.84	0.18 - 3.83	1.78	0.38 - 8.40	1.07	0.72 - 1.58
Nonuser	1.00	reference	1.00	reference	1.00	reference	1.00	reference

Adjusted for age, sex, calendar year, CRS (some variables within score are time-varying)

Table A-4c. Rate ratios of acute myocardial infarction or sudden cardiac death by site

	I3		KPNC		KPSC		Tennessee Medicaid	
Medication status	**RR**	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**
ADHD medication users								
Current user	0.96	0.74 - 1.23	0.93	0.59 - 1.47	0.88	0.44 - 1.78	0.65	0.45 - 0.95
Indeterminate user	0.88	0.62 - 1.24	1.88	1.11 - 3.19	1.09	0.39 - 3.06	1.01	0.68 - 1.49
Former user	0.56	0.36 - 0.87	1.06	0.53 - 2.09	0.81	0.25 - 2.63	1.08	0.78 - 1.49
Remote user	0.93	0.69 - 1.26	1.28	0.80 - 2.05	1.05	0.32 - 3.44	0.77	0.62 - 0.96
Nonuser	1.00	reference	1.00	reference	1.00	reference	1.00	reference

Adjusted for age, sex, calendar year, CRS (some variables within score are time-varying)

Table A-5. Characteristics of person-time (after baseline), by medication use (Tennessee Medicaid only)

Characteristic	Current Use		Indeterminate-use		Former Use		Remote Use		Non-use	
	Pr-yr*	%	Pr-yr*	%	Pr-yr*	%	Pr-yr*	%	Pr-yr*	%
Total	8831.8	7.2%	5420.1	4.4%	7540.2	6.2%	20557.5	16.8%	79855.1	65.3%
Demographics										
Gender										
Male	3125.9	35.4%	1844.9	34.0%	2615.6	34.7%	7632.5	37.1%	29348.3	36.8%
Female	5705.9	64.6%	3575.3	66.0%	4924.6	65.3%	12925.0	62.9%	50506.8	63.2%
Age										
25-29	895.7	10.1%	686.8	12.7%	945.1	12.5%	937.1	4.6%	6378.4	8.0%
30-34	1232.4	14.0%	910.4	16.8%	1309.2	17.4%	2906.1	14.1%	11616.7	14.5%
35-39	1480.9	16.8%	903.2	16.7%	1332.8	17.7%	3817.7	18.6%	13672.7	17.1%
40-44	1463.3	16.6%	868.8	16.0%	1195.6	15.9%	3823.6	18.6%	13386.4	16.8%
45-49	1423.9	16.1%	744.2	13.7%	981.9	13.0%	3118.2	15.2%	12033.1	15.1%
50-54	1083.0	12.3%	579.7	10.7%	771.9	10.2%	2510.8	12.2%	9581.2	12.0%
55-59	786.7	8.9%	435.4	8.0%	579.0	7.7%	1892.2	9.2%	7455.8	9.3%
60-64	465.8	5.3%	291.7	5.4%	424.7	5.6%	1551.9	7.5%	5730.9	7.2%
Year										
2004-2005	4052.4	45.9%	2258.4	41.7%	3050.7	40.5%	5731.5	27.9%	27282.7	34.2%
2002-2003	1620.1	18.3%	935.1	17.3%	1039.6	13.8%	4808.6	23.4%	15516.9	19.4%
2000-2001	888.4	10.1%	639.0	11.8%	1118.1	14.8%	4061.1	19.8%	12812.0	16.0%
1993-1999	2065.6	23.4%	1377.8	25.4%	1973.0	26.2%	5047.4	24.6%	20704.5	25.9%
1986-1992	205.2	2.3%	209.9	3.9%	358.8	4.8%	908.8	4.4%	3539.1	4.4%
ADHD at baseline*	1188.5	13.5%	568.3	10.5%	587.1	7.8%	1044.1	5.1%	82.1	0.1%
Cardiovascular disease at baseline*										
Acute MI	27.2	0.3%	21.9	0.4%	31.6	0.4%	74.7	0.4%	315.2	0.4%
Ischemia	502.0	5.7%	337.0	6.2%	501.9	6.7%	1117.0	5.4%	3881.3	4.9%
Coronary revascularization	22.0	0.2%	17.8	0.3%	34.4	0.5%	104.0	0.5%	313.3	0.4%
CHF	217.3	2.5%	149.7	2.8%	218.5	2.9%	448.1	2.2%	1463.1	1.8%
Arrhythmia	363.3	4.1%	223.2	4.1%	333.5	4.4%	880.3	4.3%	2191.1	2.7%
Hypertension	2372.0	26.9%	1467.1	27.1%	2101.8	27.9%	4633.4	22.5%	16868.8	21.1%
Use of cardiovascular drug at baseline*										
Loop diuretic	1018.0	11.5%	588.2	10.9%	800.0	10.6%	1993.3	9.7%	5117.9	6.4%
Digoxin	122.3	1.4%	84.5	1.6%	117.3	1.6%	381.5	1.9%	1140.6	1.4%
Nitrates	351.3	4.0%	250.9	4.6%	371.0	4.9%	956.2	4.7%	3176.6	4.0%
Anticoagulant	193.2	2.2%	134.3	2.5%	181.1	2.4%	464.7	2.3%	1216.1	1.5%
Platelet inhibitor	154.0	1.7%	105.8	2.0%	150.7	2.0%	258.4	1.3%	1032.2	1.3%

Table A-5. Characteristics of person-time (after baseline), by medication use (Tennessee Medicaid only) (continued)

Characteristic	Current Use		Indeterminate-use		Former Use		Remote Use		Non-use	
Anti-arrhythmic agents	51.5	0.6%	30.9	0.6%	51.6	0.7%	174.1	0.8%	303.9	0.4%
ACE inhibitor	1147.7	13.0%	726.1	13.4%	1039.8	13.8%	2225.8	10.8%	8686.8	10.9%
Angiotensin receptor blocker	265.0	3.0%	180.5	3.3%	232.8	3.1%	178.9	0.9%	1350.3	1.7%
Beta-blocker	1308.5	14.8%	745.9	13.8%	1089.1	14.4%	2563.3	12.5%	7395.3	9.3%
Calcium-channel blocker	990.6	11.2%	598.7	11.0%	874.6	11.6%	2254.1	11.0%	7639.6	9.6%
Thiazide diuretic	953.6	10.8%	598.6	11.0%	833.0	11.0%	1801.0	8.8%	6283.8	7.9%
Other antihypertensive	191.5	2.2%	115.1	2.1%	176.9	2.3%	492.6	2.4%	1444.5	1.8%
Utilization at baseline*										
Cardiovascular visits										
Emergency, 1+	1113.2	12.6%	753.0	13.9%	1101.8	14.6%	1960.5	9.5%	6440.1	8.1%
Inpatient, 1+	1038.3	11.8%	685.2	12.6%	972.3	12.9%	2091.4	10.2%	5290.5	6.6%
Physician, 1-4	3050.1	34.5%	1793.2	33.1%	2458.6	32.6%	6298.5	30.6%	19908.6	24.9%
Physician, 5+	1865.2	21.1%	1144.9	21.1%	1627.3	21.6%	3609.5	17.6%	11013.3	13.8%
Psychiatric visits[#]										
Emergency, 1+	1132.0	12.8%	696.8	12.9%	1042.0	13.8%	2061.1	10.0%	3972.8	5.0%
Inpatient, 1+	1562.8	17.7%	944.2	17.4%	1395.1	18.5%	3510.8	17.1%	4367.6	5.5%
Physician, 1-4	2370.3	26.8%	1449.6	26.7%	1943.1	25.8%	5212.9	25.4%	12460.2	15.6%
Physician, 5+	4216.2	47.7%	2273.7	41.9%	3108.4	41.2%	7411.8	36.1%	10142.3	12.7%
Other visits										
Emergency, 1+	1587.4	18.0%	1037.9	19.1%	1491.5	19.8%	2842.8	13.8%	9120.0	11.4%
Inpatient, 1+	1000.2	11.3%	654.1	12.1%	982.0	13.0%	2299.9	11.2%	4576.7	5.7%
Physician, 1+	4644.0	52.6%	2778.9	51.3%	3962.7	52.6%	9925.6	48.3%	27014.2	33.8%
No. of different medications***										
1	536.8	6.1%	389.2	7.2%	548.9	7.3%	1950.0	9.5%	11965.3	15.0%
2	684.0	7.7%	455.3	8.4%	624.6	8.3%	2118.5	10.3%	9748.3	12.2%
3	766.6	8.7%	476.8	8.8%	636.6	8.4%	2055.7	10.0%	7903.8	9.9%
4	723.5	8.2%	497.5	9.2%	722.5	9.6%	2332.0	11.3%	6202.5	7.8%
5	811.1	9.2%	462.0	8.5%	660.2	8.8%	1998.4	9.7%	5449.1	6.8%
6	756.4	8.6%	461.4	8.5%	643.3	8.5%	1892.6	9.2%	4339.3	5.4%
7-8	1426.5	16.2%	837.4	15.4%	1182.6	15.7%	2966.2	14.4%	5633.4	7.1%
9-10	1073.4	12.2%	592.4	10.9%	821.4	10.9%	1679.8	8.2%	3232.6	4.0%
11+	1696.6	19.2%	970.4	17.9%	1334.0	17.7%	2107.1	10.2%	3387.6	4.2%
Medical conditions, ever/never[$]										
Obesity	1206.3	13.7%	699.8	12.9%	1027.4	13.6%	3917.4	19.1%	8208.1	10.3%
Smoking	2521.3	28.5%	1403.2	25.9%	2128.3	28.2%	7073.8	34.4%	17273.6	21.6%
Diabetes[##]	1578.6	17.9%	928.8	17.1%	1374.4	18.2%	5238.6	25.5%	13773.2	17.2%
Stroke/TIA	602.4	6.8%	325.2	6.0%	488.5	6.5%	2286.7	11.1%	4746.7	5.9%
Hyperlipidemia[##]	3195.5	36.2%	1734.2	32.0%	2496.0	33.1%	8603.9	41.9%	22836.4	28.6%

Table A-5. Characteristics of person-time (after baseline), by medication use (Tennessee Medicaid only) (continued)

Characteristic	Current Use		Indeterminate-use		Former Use		Remote Use		Non-use	
Congenital heart disorder	87.4	1.0%	50.7	0.9%	66.4	0.9%	346.4	1.7%	849.5	1.1%
Coronary artery anomaly	16.3	0.2%	7.6	0.1%	14.4	0.2%	79.3	0.4%	154.9	0.2%
Peripheral vascular disease	414.8	4.7%	223.2	4.1%	336.4	4.5%	1468.6	7.1%	3539.0	4.4%
Mental health claims, time-varying[$$]										
Major depression	4459.5	50.5%	2530.8	46.7%	3402.5	45.1%	7212.1	35.1%	12940.6	16.2%
Bipolar disorder	1907.5	21.6%	1024.5	18.9%	1412.6	18.7%	2618.3	12.7%	3328.7	4.2%
Anxiety	2609.7	29.5%	1499.9	27.7%	2079.2	27.6%	4618.3	22.5%	9287.8	11.6%
Psychotic disorders	673.8	7.6%	406.0	7.5%	646.5	8.6%	1794.5	8.7%	4583.1	5.7%
Other selected medical conditions, time-varying[$$]										
ETOH/substance abuse	1059.8	12.0%	677.9	12.5%	968.6	12.8%	1881.7	9.2%	4685.7	5.9%
Suicide attempt	134.4	1.5%	88.9	1.6%	128.3	1.7%	236.4	1.1%	460.6	0.6%
Injury	2541.3	28.8%	1598.7	29.5%	2212.1	29.3%	5237.7	25.5%	14952.3	18.7%
Seizure	710.0	8.0%	416.2	7.7%	591.4	7.8%	1594.3	7.8%	4493.2	5.6%
Asthma	1126.5	12.8%	703.4	13.0%	960.5	12.7%	2323.6	11.3%	5921.8	7.4%
Use of psychotropic medications, time-varying[$$]										
Antipsychotic, any	1724.7	19.5%	689.1	12.7%	1025.7	13.6%	2916.0	14.2%	5318.2	6.7%
Tricyclic antidepressant	914.7	10.4%	406.4	7.5%	582.7	7.7%	1726.9	8.4%	4151.6	5.2%
Antidepressants, other or SSRI/SNRI	4609.5	52.2%	1910.9	35.3%	2583.5	34.3%	6479.5	31.5%	11442.3	14.3%
Benzodiazepines	2743.8	31.1%	1203.2	22.2%	1723.2	22.9%	4505.7	21.9%	8815.7	11.0%
Lithium	296.9	3.4%	133.3	2.5%	187.0	2.5%	392.9	1.9%	856.4	1.1%
Modafinil	216.7	2.5%	121.8	2.2%	175.3	2.3%	269.4	1.3%	122.6	0.2%
Insomnia meds	689.1	7.8%	279.0	5.1%	362.0	4.8%	753.1	3.7%	1216.4	1.5%
Thioridazine	50.2	0.6%	27.5	0.5%	40.4	0.5%	177.0	0.9%	382.3	0.5%
Mood stabilizers, w/o seizure	1656.4	18.8%	646.5	11.9%	861.6	11.4%	2158.4	10.5%	3608.7	4.5%
Clonidine/guanfacine, w/o HT	104.9	1.2%	32.0	0.6%	34.6	0.5%	76.8	0.4%	166.2	0.2%
Use of other selected medications, time-varying[$$]										
Beta-agonist	611.2	6.9%	285.7	5.3%	392.0	5.2%	1169.1	5.7%	3418.2	4.3%
Epinephrine	17.9	0.2%	9.7	0.2%	13.5	0.2%	17.2	0.1%	56.5	0.1%
Asthma med, other	1321.7	15.0%	677.2	12.5%	900.4	11.9%	2044.0	9.9%	6066.1	7.6%
Seizure med, any	2124.7	24.1%	880.2	16.2%	1191.6	15.8%	3187.1	15.5%	6471.6	8.1%
Theophylline compounds (asthma med)	123.4	1.4%	69.4	1.3%	97.7	1.3%	375.8	1.8%	1011.9	1.3%
COX-2 inhibitors	383.7	4.3%	176.2	3.3%	220.3	2.9%	718.5	3.5%	1714.5	2.1%
Other drugs to improve blood flow	14.0	0.2%	9.8	0.2%	15.3	0.2%	50.9	0.2%	168.9	0.2%

Table A-5. Characteristics of person-time (after baseline), by medication use (Tennessee Medicaid only) (continued)

Characteristic	Current Use		Indeterminate-use		Former Use		Remote Use		Non-use	
Clonidine	233.5	2.6%	89.5	1.7%	120.4	1.6%	360.2	1.8%	1112.8	1.4%
pde5 inhibitors	7.5	0.1%	2.6	0.0%	2.7	0.0%	6.5	0.0%	18.1	0.0%
Triptans	103.9	1.2%	41.7	0.8%	50.0	0.7%	92.5	0.5%	182.2	0.2%
Oral contraceptives	450.6	5.1%	267.5	4.9%	351.7	4.7%	705.4	3.4%	2583.7	3.2%
Hormones, menopausal or misc	918.9	10.4%	459.0	8.5%	644.0	8.5%	1858.8	9.0%	5541.0	6.9%
Cardiovascular Risk Score										
decile 1	653.7	7.4%	371.9	6.9%	473.7	6.3%	1167.4	5.7%	4125.1	5.2%
decile 2	798.6	9.0%	541.8	10.0%	732.5	9.7%	1787.8	8.7%	18667.5	23.4%
decile 3	743.6	8.4%	536.4	9.9%	721.5	9.6%	1798.4	8.7%	9428.4	11.8%
decile 4	696.0	7.9%	471.5	8.7%	627.4	8.3%	1493.4	7.3%	6272.7	7.9%
decile 5	750.6	8.5%	454.5	8.4%	603.7	8.0%	1555.9	7.6%	6298.2	7.9%
decile 6	782.3	8.9%	471.1	8.7%	659.7	8.7%	1722.3	8.4%	6016.9	7.5%
decile 7	849.0	9.6%	509.9	9.4%	733.0	9.7%	1943.4	9.5%	6519.5	8.2%
decile 8	1020.6	11.6%	573.7	10.6%	784.2	10.4%	2368.4	11.5%	6657.1	8.3%
decile 9	1153.4	13.1%	670.6	12.4%	964.1	12.8%	3032.2	14.7%	7285.2	9.1%
decile 10	1384.0	15.7%	818.7	15.1%	1240.4	16.5%	3688.3	17.9%	8584.6	10.8%

*Using the MI or SCD model.
**At baseline or cohort entry (t0): if 'on' at baseline, remains on; if 'off' at baseline but goes 'on' during follow-up, stays off
[#]Excluding ADHD visits
***Excluding ADHD medications
[$]Ever/never: once 'on' at baseline or during follow-up, remains on
[##]Including medications
[$$]Diagnosis: 'on' if any day in prior 365 is 'on', else 'off'; Meds: 'on' if has supply on the day, else 'off'

Tables of RRs—Remote User Comparison (Tennessee Medicaid only)

Table A-6a. Rates of acute myocardial infarction, by use of ADHD medications—Tennessee Medicaid only

Medication status	Person- yrs	Number Events	Rate/1,000 person-yrs	Unadjusted IRR	95% CI	Adjusted matching variables IRR**	95% CI	Adjusted IRR**	95% CI
Current user	8831.8	22	2.49	0.73	0.45 - 1.18	0.81	0.50 - 1.31	0.91	0.56 - 1.48
Indeterminate user	5420.3	20	3.69	1.08	0.66 - 1.78	1.30	0.79 - 2.14	1.43	0.87 - 2.35
Former user	7540.1	32	4.24	1.25	0.82 - 1.89	1.50	0.99 - 2.29	1.57	1.03 - 2.38
Remote user	20557.5	70	3.41	1.00	reference	1.00	reference	1.00	reference

* Adjusted for site, age, sex, calendar year (i.e., matching variables)

**Adjusted for site, age, sex, calendar year, CRS (some variables within score are time-varying)

Table A-6b. Rates of sudden cardiac death, by use of ADHD medications—Tennessee Medicaid only

Medication status	Person- yrs	Number Events	Rate/1,000 person-yrs	Unadjusted IRR	95% CI	Adjusted matching variables IRR**	95% CI	Adjusted IRR**	95% CI
Current user	8861.5	8	0.90	0.51	0.24 - 1.09	0.56	0.26 - 1.21	0.58	0.27 - 1.25
Indeterminate user	5434.6	7	1.29	0.72	0.32 - 1.62	0.86	0.38 - 1.93	0.89	0.40 - 2.01
Former user	7568.7	10	1.32	0.74	0.37 - 1.49	0.88	0.44 - 1.78	0.88	0.43 - 1.76
Remote user	20775.8	37	1.78	1.00	reference	1.00	reference	1.00	reference

* Adjusted for site, age, sex, calendar year (i.e., matching variables)

**Adjusted for site, age, sex, calendar year, CRS (some variables within score are time-varying)

This table excludes the three HMORN sites that did not provide data on SCD endpoints.

Table A-6c. Rates of acute myocardial infarction or sudden cardiac death, by use of ADHD medications—Tennessee Medicaid

Medication status	Person- yrs	Number Events	Rate/1,000 person-yrs	Unadjusted IRR	95% CI	Adjusted matching variables IRR**	95% CI	Adjusted IRR**	95% CI
Current user	8831.8	30	3.40	0.70	0.46 - 1.05	0.77	0.51 - 1.17	0.85	0.56 - 1.28
Indeterminate user	5420.1	27	4.98	1.02	0.67 - 1.57	1.23	0.80 - 1.88	1.31	0.86 - 2.01
Former user	7540.1	42	5.57	1.15	0.80 - 1.64	1.38	0.96 - 1.97	1.40	0.98 - 2.02
Remote user	20557.5	100	4.86	1.00	reference	1.00	reference	1.00	reference

* Adjusted for site, age, sex, calendar year (i.e., matching variables)
**Adjusted for site, age, sex, calendar year, CRS (some variables within score are time-varying)
This table excludes the three HMORN sites that did not provide data on SCD endpoints.

Additional Analyses of Tennessee Medicaid Data

Models With Different Covariate Adjustment

Table A-7. Rates of acute myocardial infarction or sudden cardiac death, by use of ADHD medications, Tennessee Medicaid

Medication status	Person- yrs	Number Events	Rate/1,000 person-yrs	Unadjusted IRR	95% CI	Adjusted matching variables IRR*	95% CI	Adjusted Matching variables IRR**	95% CI
Current user	8831.8	30	3.40	0.71	0.49 - 1.02	0.76	0.52 - 1.10	0.75	0.52 - 1.09
Indeterminate user	5420.1	27	4.98	1.04	0.70 - 1.53	1.20	0.81 - 1.77	1.19	0.81 - 1.76
Former user	7540.1	42	5.57	1.16	0.84 - 1.59	1.34	0.98 - 1.85	1.34	0.98 - 1.85
Remote user	20557.5	100	4.86	1.01	0.81 - 1.26	0.98	0.78 - 1.22	0.98	0.78 - 1.22
Nonuser	79855.1	384	4.81	1.00	reference	1.00	reference	1.00	reference

* Adjusted for site, age (categorical), sex, calendar year (ie, matching variables)
**Adjusted for site, age (continuous – linear and quadratic), sex, calendar year. (ie, matching variables)

Table A-7. Rates of acute myocardial infarction or sudden cardiac death, by use of ADHD medications, Tennessee Medicaid

Medication status	Person- yrs	Number Events	Rate/1,000 person-yrs	Adjusted IRR[1]	95% CI	Adjusted IRR[2]	95% CI	Adjusted IRR[3]	95% CI
Current user	8831.8	30	3.40	0.75	0.52 - 1.09	0.72	0.49 - 1.05	0.64	0.39 - 1.05
Indeterminate user	5420.1	27	4.98	1.19	0.81 - 1.76	1.09	0.74 - 1.61	1.16	0.71 - 1.88
Former user	7540.1	42	5.57	1.34	0.97 - 1.84	1.16	0.84 - 1.60	1.26	0.84 - 1.89
Remote user	20557.5	100	4.86	0.97	0.78 - 1.21	0.82	0.66 - 1.03	0.74	0.49 - 1.14
Nonuser	79855.1	384	4.81	1.00	reference	1.00	reference	1.00	reference

[1] Adjusted for site, age (continuous), sex, calendar year *plus* race
[2]Adjusted for site, age (continuous), sex, calendar year, race *plus* diabetes, obesity, smoking, cardiovascular diagnoses and medications
[3]Adjusted for site, age (continuous), sex, calendar year, year at t0 restricted to 1999-2005

Table A- 7. Rates of acute myocardial infarction or sudden cardiac death, by use of ADHD medications, Tennessee Medicaid

Medication status	Person- yrs	Number Events	Rate/1,000 person-yrs	Adjusted IRR[4]	95% CI	Adjusted IRR[5]	95% CI	Adjusted IRR[6]	95% CI
Current user	8831.8	30	3.40	0.68	0.46 - 0.99	0.66	0.45 - 0.98	0.67	0.45 - 0.99
Indeterminate user	5420.1	27	4.98	1.01	0.68 - 1.51	1.00	0.66 - 1.49	1.01	0.67 - 1.51
Former user	7540.1	42	5.57	1.07	0.77 - 1.49	1.05	0.75 - 1.47	1.07	0.76 - 1.49
Remote user	20557.5	100	4.86	0.79	0.62 - 0.99	0.78	0.61 - 0.99	0.79	0.62 - 1.00
Nonuser	79855.1	384	4.81	1.00	reference	1.00	reference	1.00	reference

[4] Adjusted for site, age (continuous), sex, calendar year, race, diabetes, obesity, smoking, cardiovascular diagnoses and medications *plus* mental health claims and psychotropic drugs
[5]Adjusted for site, age (continuous), sex, calendar year, race, diabetes, obesity, smoking, cardiovascular diagnoses and medications, mental health claims and psychotropic drugs *plus* utilization variables
[6]Adjusted for site, age (continuous), sex, calendar year, race, diabetes, obesity, smoking, cardiovascular diagnoses and medications, mental health claims and psychotropic drugs, utilization variables *plus* other variables in the CRS

Table A-8. RRs of MI/SCD—Propensity score (PS) adjustment (PS has same variables as CRS)—Tennessee Medicaid

Variable in model	Person-yrs	Number Events	Rate/1,000 person-yrs	RR*	95% CI
Exposure					
Amphetamines	2813.2	8	2.84	0.53	0.26 - 1.08
Methylphenidate	3747.3	17	4.54	0.76	0.46 - 1.25
Atomoxetine	1509.6	3	1.99	0.41	0.13 - 1.29
Pemoline	597.2	2	3.35	0.59	0.15 - 2.37
Multiple	164.5	0	0.00	0.00	--
Indeterminate	5420.1	27	4.98	0.99	0.66 - 1.48
Former	7540.1	42	5.57	1.12	0.80 - 1.56
Remote	20557.5	100	4.86	0.81	0.64 - 1.03
Non-user	79855.1	384	4.81	1.00	reference
Demographics					
Gender					
Male	44567.1	336	7.54	2.32	1.97 - 2.74
Female	77637.5	247	3.18	1.00	reference
Age					
25-29	9843.2	2	0.20	0.01	0.00 - 0.06
30-34	17974.7	16	0.89	0.06	0.04 - 0.11
35-39	21207.2	44	2.07	0.15	0.10 - 0.21
40-44	20737.6	65	3.13	0.22	0.16 - 0.30
45-49	18301.3	110	6.01	0.42	0.32 - 0.54
50-54	14526.6	116	7.99	0.56	0.43 - 0.72
55-59	11149.0	108	9.69	0.68	0.53 - 0.88
60-64	8465.0	122	14.41	1.00	reference
Year					
2004-2005	42375.7	203	4.79	1.15	0.75 - 1.76
2002-2003	23920.4	121	5.06	1.07	0.69 - 1.67
2000-2001	19518.5	105	5.38	1.21	0.77 - 1.89
1993-1999	31168.3	130	4.17	1.00	0.65 - 1.55
1986-1992	5221.8	24	4.60	1.00	reference
Propensity Score					
Decile 10	12679.2	70	5.52	3.32	1.91 - 5.76
Decile 9	12274.7	54	4.40	2.29	1.31 - 4.00
Decile 8	12227.4	59	4.83	2.40	1.38 - 4.14
Decile 7	12677.9	81	6.39	2.93	1.73 - 4.98
Decile 6	13519.7	78	5.77	2.64	1.55 - 4.48
Decile 5	14240.7	76	5.34	2.33	1.37 - 3.96
Decile 4	12357.3	61	4.94	2.26	1.32 - 3.88
Decile 3	11355.3	43	3.79	1.82	1.03 - 3.20
Decile 2	12297.0	44	3.58	1.67	0.95 - 2.93
Decile 1	8575.6	17	1.98	1.00	reference

*RRs adjusted for all other variables in the table

Table A-9a. Rate ratios of MI/SCD—for ADHD medications and other variables in the final Poisson regression model

Variable in model	Person-yrs	Number Events	Rate/1,000 person-yrs	RR*	95% CI
Exposure					
Amphetamines	46844.2	69	1.47	0.93	0.73 - 1.19
Methylphenidate	47829.9	84	1.76	0.85	0.68 - 1.07
Atomoxetine	8249.0	14	1.70	0.88	0.52 - 1.49
Pemoline	2989.8	7	2.34	0.83	0.39 - 1.75
Multiple	1470.5	0	0.00	0.00	--
Indeterminate	51739.1	97	1.87	1.02	0.83-1.26
Former	46163.0	84	1.82	0.83	0.66-1.03
Remote	67688.6	186	2.75	0.83	0.71-0.98
Non-user	534070.5	1041	1.95	1.00	reference
Demographics					
Gender					
Male	369667.8	1109	3.00	2.76	2.48-3.08
Female	437376.7	473	1.08	1.00	reference
Age					
25-29	54331.2	5	0.09	0.03	0.01-0.08
30-34	94438.9	37	0.39	0.13	0.09-0.19
35-39	117289.5	84	0.72	0.22	0.17-0.29
40-44	145640.9	170	1.17	0.34	0.28-0.42
45-49	151095.9	298	1.97	0.54	0.46-0.65
50-54	124205.9	393	3.16	0.77	0.66-0.91
55-59	79877.8	342	4.28	0.88	0.74-1.03
60-64	40164.6	253	6.30	1.00	reference
Site					
KPNC	98720.0	181	1.83	1.09	0.92-1.29
KPSC	34276.7	57	1.66	1.07	0.81-1.41
Tennessee Medicaid	122204.7	583	4.77	1.96	1.72-2.24
HMORN					
Group Health	42676.3	71	1.66	1.03	0.80-1.32
Harvard Pilgrim	67201.5	76	1.13	0.65	0.51-0.83
HealthPartners	32051.9	57	1.78	1.19	0.91-1.57
KPCO	19823.2	33	1.67	0.84	0.59-1.19
Ingenix/I3	390090.3	524	1.34	1.00	reference
Year					
2004-2005	362312.0	609	1.68	0.62	0.41-0.94
2002-2003	229419.8	455	1.98	0.78	0.51-1.18
2000-2001	138479.5	298	2.15	0.89	0.59-1.37
1993-1999	71611.5	196	2.74	0.93	0.60-1.42
1986-1992	5221.8	24	4.60	1.00	reference
Cardiovascular Risk Score					
Decile 10	29338.5	451	15.37	17.15	11.61-25.32
Decile 9	37932.5	221	5.83	7.99	5.37-11.88
Decile 8	42523.9	146	3.43	5.27	3.51-7.92
Decile 7	49118.8	144	2.93	4.98	3.32-7.48
Decile 6	56047.4	106	1.89	3.44	2.27-5.23
Decile 5	66858.3	94	1.41	2.68	1.75-4.09
Decile 4	77236.6	103	1.33	2.73	1.80-4.16
Decile 3	127725.8	103	0.81	1.98	1.30-3.01
Decile 2	243499.4	186	0.76	1.73	1.16-2.58
Decile 1	76763.3	28	0.36	1.00	reference

*RRs adjusted for all other variables in the table

Table A-9b. Rate ratios of MI/SCD—standard adjustment (all variables, including those in the CRS)

Variable in model	Person-yrs	Number Events	Rate/1,000 person-yrs	RR*	95% CI
Exposure					
Amphetamines	46844.2	69	1.47	0.94	0.73-1.22
Methylphenidate	47829.9	84	1.76	0.85	0.67-1.07
Atomoxetine	8249.0	14	1.70	0.89	0.52-1.52
Pemoline	2989.8	7	2.34	0.83	0.39-1.76
Multiple	1470.5	0	0.00	0.00	--
Indeterminate	51739.1	97	1.87	1.01	0.81-1.26
Former	46163.0	84	1.82	0.81	0.64-1.02
Remote	67688.6	186	2.75	0.83	0.70-0.99
Non-user	534070.5	1041	1.95	1.00	reference
Demographics					
Gender					
Male	369667.8	1109	3.00	2.78	2.47-3.14
Female	437376.7	473	1.08	1.00	reference
Age					
25-29	54331.2	5	0.09	0.03	0.01-0.08
30-34	94438.9	37	0.39	0.13	0.09-0.19
35-39	117289.5	84	0.72	0.22	0.17-0.29
40-44	145640.9	170	1.17	0.35	0.28-0.43
45-49	151095.9	298	1.97	0.55	0.46-0.66
50-54	124205.9	393	3.16	0.78	0.66-0.92
55-59	79877.8	342	4.28	0.89	0.75-1.04
60-64	40164.6	253	6.30	1.00	reference
Site					
KPNC	98720.0	181	1.83	1.10	0.92-1.32
KPSC	34276.7	57	1.66	1.08	0.82-1.43
Tennessee Medicaid	122204.7	583	4.77	1.86	1.60-2.16
HMORN					
Group Health	42676.3	71	1.66	1.03	0.80-1.32
Harvard Pilgrim	67201.5	76	1.13	0.65	0.51-0.83
HealthPartners	32051.9	57	1.78	1.18	0.90-1.56
KPCO	19823.2	33	1.67	0.87	0.61-1.25
Ingenix/I3	390090.3	524	1.34	1.00	reference
Year					
2004-2005	362312.0	609	1.68	0.55	0.36-0.85
2002-2003	229419.8	455	1.98	0.71	0.46-1.09
2000-2001	138479.5	298	2.15	0.82	0.53-1.26
1993-1999	71611.5	196	2.74	0.87	0.57-1.34
1986-1992	5221.8	24	4.60	1.00	reference
Cardiovascular disease at baseline*					
Acute MI, primary	816.7	15	18.37	0.89	0.48-1.64
Acute MI, other	991.2	26	26.23	1.77	1.16-2.71
Ischemia, primary	2807.8	62	22.08	1.18	0.80-1.73
Ischemia, other	16500.9	224	13.57	1.56	1.29-1.89
Coronary revascularization	1662.3	39	23.46	1.11	0.68-1.79
CHF, primary	542.9	19	35.00	1.39	0.83-2.33
CHF, other	4343.4	83	19.11	1.25	0.96-1.64
Arrhythmia, primary	1221.8	15	12.28	0.99	0.56-1.73
Arrhythmia, other	14030.4	83	5.92	0.89	0.70-1.14
Hypertension	106738.1	547	5.12	1.00	0.85-1.17

Table A-9b. Rate ratios of MI/SCD—standard adjustment (all variables, including those in the CRS) (continued)

Variable in model	Person-yrs	Number Events	Rate/1,000 person-yrs	RR*	95% CI
Use of cardiovascular drug at baseline**					
Loop diuretic	17830.8	190	10.66	1.25	1.02-1.52
Digoxin	3790.4	74	19.52	1.41	1.07-1.87
Nitrates	10864.0	197	18.13	1.30	1.06-1.60
Anticoagulant	7227.3	75	10.38	1.14	0.88-1.48
Platelet inhibitor	4080.1	68	16.67	1.08	0.81-1.43
Anti-arrhythmic agents	2206.4	25	11.33	1.04	0.67-1.61
ACE inhibitor	53754.9	345	6.42	1.10	0.95-1.28
Angiotensin receptor blocker	12284.7	68	5.54	1.29	0.99-1.67
Beta-blocker	56822.0	335	5.90	1.27	1.10-1.47
Calcium-channel blocker	37308.2	272	7.29	1.19	1.02-1.39
Thiazide diuretic	55787.6	209	3.75	0.93	0.79-1.09
Other antihypertensive	8102.2	54	6.66	0.82	0.62-1.09
Utilization at baseline**					
Cardiovascular visits					
Emergency, 1+	23125.4	237	10.25	1.17	0.97-1.42
Inpatient, 1+	25465.8	177	6.95	1.05	0.85-1.31
Physician, 1-4	190675.1	498	2.61	1.00	0.87-1.16
Physician, 5+	53881.5	413	7.66	0.93	0.76-1.15
Psychiatric visits[#]					
Emergency, 1+	21947.8	131	5.97	0.99	0.74-1.32
Inpatient, 1+	14193.2	67	4.72	1.19	0.94-1.51
Physician, 1-4	122060.0	251	2.06	0.87	0.74-1.02
Physician, 5+	92668.8	248	2.68	0.85	0.70-1.03
Other visits					
Emergency, 1+	20397.6	124	6.08	1.23	1.00-1.52
Inpatient, 1+	34689.0	126	3.63	1.00	0.80-1.27
Physician, 1+	222454.9	517	2.32	0.83	0.73-0.94
No. of different medications***					
1	156387.0	198	1.27	1.17	0.97-1.41
2	114223.1	182	1.59	1.27	1.04-1.55
3	82631.0	159	1.92	1.32	1.07-1.64
4	59583.2	135	2.27	1.28	1.02-1.63
5	43434.6	131	3.02	1.43	1.12-1.84
6	30932.4	94	3.04	1.19	0.90-1.58
7-8	37984.4	155	4.08	1.32	1.00-1.73
9-10	18993.4	106	5.58	1.36	0.99-1.87
11+	17825.4	152	8.53	1.19	0.83-1.71
Medical conditions, ever/never[$]					
Obesity	78369.0	260	3.32	1.12	0.97-1.30
Smoking	98952.9	491	4.96	1.61	1.42-1.82
Diabetes[##]	66934.5	488	7.29	1.74	1.53-1.98
Stroke/TIA, primary	3574.6	43	12.03	0.99	0.71-1.38
Stroke/TIA, other	16593.4	153	9.22	1.00	0.82-1.22
Hyperlipidemia[##]	196276.9	856	4.36	1.38	1.22-1.56
Congenital heart disorder	3798.7	20	5.27	1.02	0.65-1.60
Coronary artery anomaly	656.6	14	21.32	1.58	0.92-2.70
Peripheral vascular disease	13377.5	171	12.78	1.68	1.40-2.01
Mental health claims, time-varying[$$]					
Major depression, primary	7407.6	40	5.40	1.37	0.95-1.97
Major depression, other	142936.2	345	2.41	1.30	1.11-1.52

Table A-9b. Rate ratios of MI/SCD—standard adjustment (all variables, including those in the CRS) (continued)

Variable in model	Person-yrs	Number Events	Rate/1,000 person-yrs	RR*	95% CI
Bipolar disorder, primary	3576.9	18	5.03	1.08	0.65-1.81
Bipolar disorder, other	24035.1	54	2.25	0.85	0.63-1.14
Anxiety, primary	2359.3	12	5.09	1.10	0.61-1.99
Anxiety, other	78077.3	194	2.48	1.06	0.90-1.25
Psychotic disorders, primary	2614.3	24	9.18	1.63	1.04-2.54
Psychotic disorders, other	9341.2	55	5.89	1.35	1.00-1.82
Other selected medical conditions, time-varying[$$]					
ETOH/substance abuse, primary	3633.8	14	3.85	0.86	0.50-1.49
ETOH/substance abuse, other	19098.5	84	4.40	1.19	0.94-1.51
Suicide attempt	2184.3	6	2.75	0.67	0.29-1.54
Injury, primary	19455.2	85	4.37	1.16	0.91-1.47
Injury, other	109801.6	235	2.14	0.98	0.85-1.13
Seizure, primary	1973.7	15	7.60	1.97	1.08-3.59
Seizure, other	11539.3	50	4.33	1.39	0.95-2.03
Asthma, primary	2475.0	17	6.87	1.51	0.92-2.48
Asthma, other	43412.0	120	2.76	1.03	0.84-1.26
Use of psychotropic medications, time-varying[$$]					
Antipsychotic, any	20851.9	103	4.94	1.17	0.92-1.49
Tricyclic antidepressant	19944.2	80	4.01	0.94	0.75-1.19
Antidepressants, other or SSRI/SNRI	127662.2	298	2.33	0.78	0.67-0.91
Benzodiazepines	52149.6	231	4.43	1.25	1.07-1.46
Lithium	5072.6	14	2.76	1.02	0.59-1.77
Modafinil	4102.8	6	1.46	0.52	0.23-1.17
Insomnia meds	12131.6	46	3.79	1.26	0.93-1.70
Thioridazine	755.5	3	3.97	0.68	0.22-2.14
Mood stabilizers, w/o seizure	28089.7	107	3.81	1.77	1.05-2.99
Clonidine/guanfacine, w/o HT	1306.8	5	3.83	1.13	0.43-2.94
Use of other selected medications, time-varying[$$]					
Beta-agonist	17147.4	93	5.42	1.19	0.93-1.52
Epinephrine	299.9	5	16.67	5.42	2.23-13.13
Asthma med, other	35790.9	148	4.14	1.11	0.91-1.35
Seizure med, any	36018.5	141	3.91	0.70	0.43-1.14
Theophylline compounds (asthma med)	2454.0	34	13.85	1.22	0.85-1.76
COX-2 inhibitors	10861.8	42	3.87	0.88	0.64-1.20
Other drugs to improve blood flow	420.0	9	21.43	1.37	0.70-2.67
Clonidine	3865.7	29	7.50	1.13	0.75-1.69
pde5 inhibitors	4695.6	22	4.69	1.20	0.79-1.84
Triptans	4469.9	5	1.12	0.87	0.36-2.10
Oral contraceptives	40788.2	21	0.51	0.81	0.52-1.26
Hormones, menopausal or misc	46863.9	65	1.39	0.65	0.50-0.84

*RRs adjusted for site, age, sex, calendar year, exposure, and each of the CRS variables in the table

**At baseline or cohort entry (t0): if 'on' at baseline, remains on; if 'off' at baseline but goes 'on' during follow-up, stays off

[#] Excluding ADHD visits

*** Excluding ADHD medications

[$] Ever/never: once 'on' at baseline or during follow-up, remains on

[##] Including medications

[$$] Diagnosis: 'on' if any day in prior 365 is 'on', else 'off'; Meds: 'on' if has supply on the day, else 'off'

Table A-9c. Rate ratios of MI/SCD—Propensity score (PS) adjustment (PS has same variables as CRS)

Variable in model	Person-yrs	Number Events	Rate/1,000 person-yrs	RR*	95% CI
Exposure					
Amphetamines	46844.2	69	1.47	0.84	0.65 - 1.09
Methylphenidate	47829.9	84	1.76	0.82	0.65 - 1.04
Atomoxetine	8249.0	14	1.70	0.87	0.51 - 1.48
Pemoline	2989.7	7	2.34	0.89	0.42 - 1.87
Multiple	1470.5	0	0.00	0.00	--
Indeterminate	51739.1	97	1.87	0.98	0.79 - 1.22
Former	46163.0	84	1.82	0.85	0.68 - 1.07
Remote	67688.6	186	2.75	0.89	0.76 - 1.06
Non-user	534070.5	1041	1.95	1.00	reference
Demographics					
Gender					
Male	369667.8	1109	3.00	3.05	2.73 - 3.41
Female	437376.7	473	1.08	1.00	reference
Age					
25-29	54331.2	5	0.09	0.01	0.01 - 0.04
30-34	94438.9	37	0.39	0.06	0.04 - 0.09
35-39	117289.5	84	0.72	0.12	0.09 - 0.15
40-44	145640.9	170	1.17	0.20	0.17 - 0.25
45-49	151095.9	298	1.97	0.36	0.31 - 0.43
50-54	124205.9	393	3.16	0.59	0.50 - 0.69
55-59	79877.8	342	4.28	0.76	0.65 - 0.90
60-64	40164.6	253	6.30	1.00	reference
Site					
KPNC	98720.0	181	1.83	1.05	0.88 - 1.24
KPSC	34276.7	57	1.66	0.97	0.74 - 1.28
Tennessee Medicaid	122204.6	583	4.77	3.77	3.30 - 4.31
HMORN					
Group Health	42676.3	71	1.66	0.88	0.68 - 1.13
Harvard Pilgrim	67201.5	76	1.13	0.63	0.50 - 0.81
HealthPartners	32051.9	57	1.78	1.12	0.85 - 1.47
KPCO	19823.2	33	1.66	0.95	0.66 - 1.35
Ingenix/I3	390090.3	524	1.34	1.00	reference
Year					
2004-2005	362312.0	609	1.68	0.95	0.63 - 1.45
2002-2003	229419.8	455	1.98	1.12	0.74 - 1.71
2000-2001	138479.5	298	2.15	1.19	0.78 - 1.83
1993-1999	71611.5	196	2.74	1.08	0.70 - 1.65
1986-1992	5221.8	24	4.60	1.00	reference
Propensity Score					
Decile 10	74731.2	165	2.21	1.61	1.26 - 2.06
Decile 9	77764.3	153	1.97	1.26	1.00 - 1.60
Decile 8	80574.4	201	2.49	1.45	1.17 - 1.81
Decile 7	81660.8	167	2.05	1.19	0.95 - 1.50
Decile 6	83837.3	217	2.59	1.39	1.12 - 1.72
Decile 5	81447.1	131	1.61	1.34	1.05 - 1.70
Decile 4	84492.3	101	1.20	0.91	0.70 - 1.18
Decile 3	76456.4	132	1.73	0.93	0.73 - 1.18
Decile 2	85338.8	153	1.79	1.06	0.84 - 1.32
Decile 1	80741.9	162	2.01	1.00	reference

*RRs adjusted for all other variables in the table

Additional Analyses of SCD

Models With Different Covariate Adjustment

Table A-10. Rates of sudden cardiac death, by use of ADHD medications

Medication status	Person- yrs	Number Events	Rate/1,000 person-yrs	Adjusted IRR[1]	95% CI	Adjusted IRR[2]	95% CI	Adjusted IRR[3]	95% CI
Current user	107525.0	32	0.30	1.04	0.71 - 1.52	1.17	0.79 - 1.74	0.84	0.56 - 1.25
Indeterminate user	51814.0	14	0.27	0.91	0.53 - 1.57	1.08	0.61 - 1.90	0.76	0.44 - 1.33
Former user	46263.5	20	0.43	1.14	0.72 - 1.82	1.18	0.70 - 2.01	0.93	0.58 - 1.51
Remote user	68102.6	50	0.73	1.16	0.84 - 1.61	1.20	0.83 - 1.74	1.01	0.72 - 1.41
Nonuser	535515.5	180	0.34	1.00	reference	1.00	reference	1.00	reference

[1]Adjusted for site, age (continuous), sex, calendar year *plus* diabetes, obesity, smoking, cardiovascular diagnoses and medications
[2]Adjusted for site, age (continuous), sex, calendar year restricted to 1999-2005
[3] Adjusted for site, age (continuous), sex, calendar year, diabetes, obesity, smoking, cardiovascular diagnoses and medications *plus* mental health claims and psychotropic drugs

Table A-10. Rates of sudden cardiac death, by use of ADHD medications

Medication status	Person- yrs	Number Events	Rate/1,000 person-yrs	Adjusted IRR[4]	95% CI	Adjusted IRR[5]	95% CI	Adjusted IRR[6]	95% CI
Current user	107525.0	32	0.30	0.81	0.53 - 1.22	0.83	0.55 - 1.25	0.80	0.55 – 1.18
Indeterminate user	51814.0	14	0.27	0.73	0.41 - 1.28	0.74	0.42 - 1.30	0.73	0.42 – 1.26
Former user	46263.5	20	0.43	0.89	0.55 - 1.45	0.89	0.55 - 1.46	0.90	0.57 – 1.44
Remote user	68102.6	50	0.73	0.96	0.68 - 1.35	0.98	0.70 - 1.39	0.98	0.71 – 1.35
Nonuser	535515.5	180	0.34	1.00	reference	1.00	reference	1.00	reference

[4]Adjusted for site, age (continuous), sex, calendar year, race, diabetes, obesity, smoking, cardiovascular diagnoses and medications, mental health claims and psychotropic drugs *plus* utilization variables
[5]Adjusted for site, age (continuous), sex, calendar year, race, diabetes, obesity, smoking, cardiovascular diagnoses and medications, mental health claims and psychotropic drugs, utilization variables *plus* other variables in the CRS
[6]Adjusted for site, age (continuous), sex, calendar year *plus* CRS (SCD model with CRS in *Table 2b*)