ADHD Medications and Risk of Stroke

In Young and Middle-Aged Adults

Final Report

Adverse Effects of Psychostimulant Medications Working Group

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Abstract

Background: A growing number of US adults use medications labeled for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). These agents increase heart rate and blood pressure, potentially increasing risk of cerebrovascular events.

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 ADHD medications (methylphenidate, amphetamines, amphetamine salts or atomoxetine) at baseline. Each ADHD medication user was matched to two non-users on study site, birth year, gender, and calendar year of cohort entry. The primary endpoint was ischemic or hemorrhagic stroke requiring hospitalization. Poisson regression was used to compare adjusted rates in users and non-users of ADHD medications.

Findings: During 835,257 person-years of follow-up, 575 strokes occurred. ADHD medication users had 111,935 person-years of current use (average 0.74 years per user), with a crude incidence of stroke of 0.69 per 1,000 person-years. The multivariable adjusted rate ratio (RR) for any stroke for current use vs. non-use of ADHD medications was 0.77 (95% CI 0.59-1.02). RRs for ischemic and for hemorrhagic stroke were similar. Among ADHD medication users only, the adjusted RR for stroke comparing current use to remote use (> 1 year since last use) was 1.02 (95% CI 0.71-1.45). Results were similar when users were restricted to new users (no ADHD medication prescription fills in the year prior to cohort entry) and for subgroups stratified on prior cardiovascular disease, prior non-ADHD psychiatric conditions or age during follow-up (25-44 and 45-64 years).

Interpretation: Our results do not support an elevated risk of stroke associated with use of ADHD medications in young and middle-aged adults.

Introduction

In recent years, the use of medications labeled for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) appears to be increasing even more rapidly in adults than in children. Over 1.5 million U.S. adults now take stimulants[1] and approximately 25% of all prescriptions are issued to persons over 19 years old [2]. The rise in ADHD diagnoses is the primary cause of increased prescribing, although stimulants also are approved for treatment of narcolepsy[3,4] and may be used off-label to treat obesity[5] and fatigue related to depression[6,7], stroke[8,9] or traumatic brain injury[10]. In adults, commonly used ADHD medications include the stimulants methylphenidate and mixed amphetamine salts and increasingly the selective norepinephrine reuptake inhibitor, atomoxetine.

Placebo-controlled studies in children and adults indicate that stimulants and atomoxetine elevate systolic blood pressure levels by approximately 2-5 mm Hg and diastolic blood pressure by 1-3 mm Hg, and also lead to increases in heart rate[1,11-13]. Such elevation of blood pressure could potentially increase the risk of either ischemic or hemorrhagic stroke[14].

According to a summary from the U.S. Food and Drug Administration's Adverse Event Reporting System (AERS), reports of serious adverse events in adults have included sudden death, myocardial infarction and stroke[2]. Although one study among children suggested markedly elevated risks[15], cardiovascular safety data from pharmacoepidemiologic studies are limited and inconsistent[15-18], especially among adults[19,20].

The primary aim of this study was to examine whether medications used primarily to treat ADHD are associated with an increased risk of stroke in adults ages 25-64 years. The study drugs included all medications with a label indication for treatment of ADHD in children or adults as of December 31, 2005.

METHODS

Data sites

The study sites included Vanderbilt University (Tennessee State Medicaid data), Kaiser Permanente (KP) California (Northern and Southern KP regions), Ingenix-i3 (with data from the UnitedHealthcare family of health insurance plans and products) and five members of the HMO Research Network (Harvard Pilgrim Health Care; Group Health Cooperative of Puget Sound; HealthPartners; Kaiser Permanente Northwest; and Kaiser Permanente Colorado).

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 (to allow complete mortality searches to be conducted). The study was approved by the institutional review boards at each of the participating institutions.

Study participants

Eligible individuals 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 (denoted as t_0). Individuals were excluded if they had one or more of the following diagnoses during the 365 days prior to t_0: sickle cell disease, cancer (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.

At each contributing site, we assembled the eligible membership periods. Individuals entered the cohort (t_0) upon exposure or as an unexposed match. For each exposed membership period (i.e., at least one ADHD prescription), starting with the earliest t_0, we

randomly selected two membership periods with no ADHD medication use on t_0 (or in the 365 days prior to t_0) and the same gender and birth year.

Study medications and exposure categories

Medication use was based on electronic pharmacy records. ADHD medications included the amphetamine-related psychostimulants (methylphenidate, dextroamphetamines and amphetamine salts), pemoline, and atomoxetine. Each person-day of follow-up was classified according to ADHD drug use, based on prescription fill dates and days supply. Current use was the period between prescription start date and end of the days supply. Indeterminate use was the first 89 days after the end of current use. Former use began at 90 days after end of current use and ended at 365 days after last current use. Greater than 365 days since last days supply was considered remote use. Non-use referred to person-days with no current or past use (up to 365 days prior to t_0). Less than 1% of non-users became users after baseline, at which time their follow-up was categorized as current use. In some analyses, current use was categorized by specific medications or duration of use. Non-use was chosen as the reference category for all primary analyses.

Study endpoints

The primary study endpoint was any stroke, defined as an acute neurologic deficit of sudden onset that persisted more than 24 hours, corresponded to a vascular territory, and was not explained by other causes such as trauma, infection, vasculitis, extracranial hemorrhage leading to hypotension or profound hypotension from another cause. Strokes that occurred during a hospitalization were excluded. Separate analyses for ischemic and hemorrhagic stroke also were conducted.

Potential strokes (n=980) were identified from principal hospital discharge diagnoses of stroke or cause of death from death certificates using the following ICD 9/10 codes: subarachnoid hemorrhage (ICD-9 430, ICD-10 I60), intracerebral hemorrhage (ICD-9 431, ICD-10 I61, I64), non-traumatic extradural hemorrhage (ICD-9 432.0, ICD-10 I62.1), subdural

hemorrhage (ICD-9 432.1), unspecified intracranial hemorrhage (ICD-9 432.9, ICD-10 I62.0, I62.9), occlusion and stenosis of precerebral arteries (ICD-9 433.00-.01, 433.10-.11, 433.20-.21, 433.30-.31, ICD-10 I65), occlusion of cerebral arteries (ICD-9 434.00-.01, 434.10-.11, 434.90-.91, ICD-10 I63, I66), and acute, but ill-defined, cerebrovascular disease (ICD-9 436, ICD-10 I67, I68).

Charts were requested on all potential strokes. Potential strokes with charts (n=911) underwent adjudication by a team of six trained neurologists, blinded to exposure status (see Table A-1). For those with insufficient hospital or autopsy records for clinical adjudication (n=179) or for whom records were completely unavailable (n=69), we used a diagnostic code-based definition to identify probable strokes. Probable strokes had ICD-9/10 codes with a positive predictive value (PPV) of 80% or greater, based on those strokes for whom records were available. Strokes confirmed by clinical adjudication (n=451) and those with insufficient records meeting the diagnostic code-based definition (n=124), were included as events in primary analyses (see Figure A-1). In secondary analyses, we include all electronically identified strokes except those confirmed as non-strokes by clinical adjudication (i.e., strokes clinically adjudicated as cases plus all those without or with insufficient hospital or autopsy records).

Confounders

We considered the following risk factors for stroke to be potential confounders: acute MI, anticoagulants, platelet inhibitors, hypertension, prior stroke or transient ischemic attack (TIA), peripheral vascular disease, obesity, smoking, diabetes, hyperlipidemia, alcohol/substance abuse, triptan (migraine medication), oral contraceptives, and menopausal hormones. In addition, we examined potential confounding by several other variables (see Table 1a). Only number of different non-ADHD medications with at least one prescription in the year prior to t_0 resulted in a 10% or greater change in the RR for ADHD medications and was therefore included as a covariate in the fully adjusted models.

As a complement to these standard adjustment methods, we constructed a summary cardiovascular risk score (CRS). The score included the following variables based on diagnoses, claims or prescriptions in the 365 days preceding t_0: 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), 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 (prior to baseline only) 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, 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 hormones.

The cardiovascular risk scores was created from a Poisson regression model of the association of the above variables with risk of stroke 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.

We also constructed a propensity score for current vs. non-use at baseline using the same variables included in the CRS as our predictor variables. In addition, a separate propensity score, using the same variables, was constructed for the new user analyses. For both overall and new user analyses, the propensity score was created from a logistic regression model of the association of these predictor variables with current use vs. non-use at baseline, adjusted for the matching variables. The score was the linear predictor of current use vs. non-use from the coefficients of the resulting regression model.

Unmeasured confounders

In order to examine possible unmeasured confounding by variables inconsistently available in the electronic record, we used external adjustment methods[21-23] to conduct sensitivity analyses. Information on potential confounders came from two sources. Race/ethnicity, smoking, obesity, history of cardiovascular disease and drug abuse were obtained from the reviewed medical records of stroke cases. Information on race/ethnicity, income, education, smoking, obesity, family history of cardiovascular disease also was available 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 records on ADHD medications were obtained, as well.

We used multivariable logistic regression 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 associations in our study population are similar to 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 the association of ADHD medication use and risk of stroke using external adjustment methods[22].

Statistical approach

Follow-up began at cohort entry and ended at stroke, death, end of insurance coverage/pharmacy benefit, day before 65th birthday, or end of study period (December 2005), whichever came first. Poisson regression modeling was used to estimate the association of ADHD medications with risk of stroke, adjusted for potentially confounding variables. Covariates in the primary model included matching variables (study site, age (5-year dummy categories), gender, calendar year (1986-1992, 1993-1999, 2000-2001, 2002-2003, 2004-2005)). Matching variables were included 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. The full model included the following variables categorized as yes or no: acute MI, anticoagulants, platelet inhibitors, hypertension, prior stroke/TIA, peripheral vascular disease, obesity, smoking, diabetes, hyperlipidemia, alcohol/substance abuse, triptan, oral contraceptives, and menopausal hormones. Models also included number of different non-ADHD medications with at least one prescription in the year prior to t_0 (categorized as 0, 1, 2, 3, 4, 5, 6, 7-8, 9-10, 11+). In secondary analyses, ADHD medications, matching variables and either the CRS or PS were included in regression models. All analyses were done with SAS version 9.1. All p-values were two-sided.

New user analyses

In sub-analyses, 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). For these analyses, we used standard adjustment methods to adjust for non-matching variables. In secondary analyses, we used the CRS and the PS to adjust for these variables (Table A-6b).

Remote user comparison

To examine potential selection bias or unmeasured confounding that could arise from users being more or less healthy than non-users, we restricted analyses to users of ADHD

medications and compared rates in current, indeterminate and former users to rates in remote users.

Other subgroup analyses

In other analyses, users were restricted to those with a diagnosis or claim for ADHD in the 365 days prior to cohort entry. Additional subgroups were based on prior cardiovascular disease at t_0, prior non-ADHD psychiatric diagnoses or medication use at t_0, and age (25-44 vs. 45-64 years) during follow-up.

Analyses of composite endpoint –stroke/MI/SCD

We have previously conducted, and reported the results, of analyses on the association between ADHD medications and risk of myocardial infarction (MI) or sudden cardiac death. For this report, we conducted some analyses using a composite endpoint that included stroke or MI or SCD.

Within-site analyses

To examine potential heterogeneity across data sites, we conducted analyses within each of the data sites (Ingenix-i3 (I3), Tennessee Medicaid, HMORN, KPNC, KPSC).

Other sensitivity analyses

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. We also conducted analyses restricting to a single eligibility period.

RESULTS

Medication use and person-years of follow-up

During follow-up, there were 111,935 person-years of current use of ADHD medications (average of 0.74 years per user at baseline), 53,328 person-years categorized as indeterminate use (average 0.35 years per user at baseline), 47,333 person-years categorized as former use (average 0.31 years per user at baseline), 69,202 person-years categorized as remote use of ADHD medications (average 0.46 years per user at baseline), and 553,459 person-years of non

use of ADHD medications (average 1.89 years per non-user at baseline). Of the person-years of current use, methylphenidate use accounted for approximately 45%, amphetamine use accounted for 43% and atomoxetine use accounted for 7%. There was very little pemoline use (3%).

Characteristics of study population at baseline and during follow-up

Baseline characteristics of users and non-users are 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 stroke, 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%). As expected, a diagnosis or claim for ADHD was substantially more common among current users than non-users (30% vs. 0.2%, respectively). 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 were 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 835,257 person-years of follow-up, 575 cases of stroke occurred, giving a crude incidence rate of 0.69 per 1000 person-years. In analysis adjusted for matching variables only (i.e., site, age, gender, and calendar year of cohort entry), rate ratios of any stroke for current, indeterminate, former and remote users vs. non-users of ADHD medications were 0.96 (95% CI 0.73-1.25), 1.02 (95% CI 0.71-1.48), 1.32 (95% CI 0.95-1.84), and 1.06 (95% CI 0.82-1.38), respectively. In analyses adjusted for matching variables plus selected stroke risk factors (i.e., standard adjustment), rate ratios of stroke for current, indeterminate, former and remote users vs. non-users of ADHD medications were 0.77 (95% CI 0.59-1.02), 0.82 (95% CI 0.57-1.20), 0.99 (95% CI 0.71-1.40), and 0.76 (95% CI 0.58-1.00), respectively (Table 2a). Results were similar when events were restricted to either ischemic or hemorrhagic stroke alone (Tables 2c, 2d). Stroke results were similar when cases included all electronically identified cases except those confirmed as non-cases by clinical adjudication (Table 2e).

Fully adjusted rate ratios of stroke for current use of amphetamines, methylphenidate and atomoxetine vs. non-use of any ADHD medications were 0.63 (95% CI 0.40-1.01), 0.96 (95% CI 0.69-1.35), and 0.46 (95% CI 0.15-1.44), respectively (Table 3a). Results were similar when events were restricted to either ischemic or hemorrhagic stroke alone (Tables 3c, 3d). Stroke results were similar when cases included all electronically identified cases except those confirmed as non-cases by clinical adjudication (Table 3e). 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 (Table 4a).

New user analyses

The RR for current vs. non-use did not materially change when users were restricted to those without use of ADHD medications in the year prior to baseline (i.e., to new users) (Tables

2b). Likewise, the RRs for specific ADHD medications and for duration of current use in the new user analyses (Table 3b, 4b) were similar to those in analyses including both new and prevalent users.

Remote user comparison

Results of analyses comparing current, indeterminate and former users to remote users are presented in Table 5a-b. RRs were higher than those with non-users as the comparison and generally above 1.0, although none were statistically significant. As in the full cohort, there was little evidence of a difference in risk by type of ADHD medication (Table 6a, 6b).

Other subgroup analyses

Results of subgroup analyses are presented in Tables 7a-b. 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 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

Analyses of composite endpoint –stroke/MI/SCD

In analysis adjusted for matching variables only (i.e., site, age, gender, and calendar year of cohort entry), rate ratios of any stroke for current, indeterminate, former and remote users vs. non-users of ADHD medications were 0.97 (95% CI 0.84-1.12), 1.11 (95% CI 0.92-1.33), 1.07 (95% CI 0.89-1.29), and 1.02 (95% CI 0.88-1.17), respectively (Table 8a). In analyses adjusted for matching variables plus selected stroke risk factors (i.e., standard adjustment), rate ratios of stroke for current, indeterminate, former and remote users vs. non-users of ADHD medications were 0.80 (95% CI 0.69-0.92), 0.90 (95% CI 0.75-1.09), 0.83 (95%

CI 0.68-1.00), and 0.76 (95% CI 0.66-0.87), respectively. When we restricted users to new users, the RR for current use was lower (0.68, 95% CI 0.56-0.82) (Table 8b).

In analyses among ADHD medication users only, the adjusted RR for current vs. remote use was 1.05 (95% CI 0.87-1.26) (Table 9a). When we restricted users to new users, the RR for current vs. remote use was slightly lower (0.94, 95% CI 0.75-1.18) (Table 9b).

Within-site analyses

Some variation in results was observed across data sites. The crude rate of stroke was significantly higher among the Tennessee Medicaid population (Table A-2). This is expected since 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). While the RR for stroke associated with current use of ADHD medications was highest among the Tennessee Medicaid population (Table A-4a), it was not statistically significant.

Sensitivity analyses – adjustment method

The RRs for covariates included in our main model are presented in Table A-5. Results of analyses for stroke among the full cohort were similar when we used standard adjustment methods, when we used a propensity score (PS) or when we used a CRS approach (Table A-6a). In addition, there was little difference in the new user subgroup results when we used the PS or CRS to adjust for covariates (Table A-6b). We found that fixing at baseline the values of all covariates in the CRS had little impact on results (not shown).

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 stroke, then our RR estimates would be biased downward by small amounts.

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 stroke 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 stroke, then unmeasured race/ethnicity could also bias our RR estimates by amounts similar to those reported for education above.

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 countering some of the negative residual confounding from education and race.

Other 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 no evidence for an increased risk of stroke associated with current ADHD medication use. 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. Furthermore, results were similar when users were restricted to new users and when our comparison was remote use of these medications (i.e., one or more years

in the past). Results also were similar in subgroups stratified by prior cardiovascular disease or non-ADHD psychiatric conditions and among young and middle-aged adults.

Our findings of no increased risk of stroke, along with our previous findings of no increased risk of MI or SCD, are consistent with results from some, but not all, previous pharmacoepidemiologic studies of serious cardiovascular events [15-20]. Only two previous reports were from studies conducted among adults [19,20]. One study compared risk of cerebrovascular accidents (CVA) and transient ischemic attacks (TIA) among those prescribed atomoxetine with those prescribed stimulant ADHD medications, as well as with adults in the general population[19]. 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. In contrast, no increase in sudden cardiac deaths among children, adolescents or 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[20].

Our study has several strengths and limitations. 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 sources of information on longitudinal drug use. We reviewed the medical records and death certificates to confirm stroke diagnoses. However, records were unavailable for some of our electronically identified cases. We used a diagnostic code-based case definition for these strokes and some misclassification may have occurred.

We adjusted for a large number of established and potential cardiovascular risk factors. We also conducted sensitivity analyses, using a cardiovascular risk score or a propensity score

(with all covariates fixed at baseline), to examine the robustness of our primary approach. 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 stroke (or 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.

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. 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. 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[21-23].

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. Since adjustments for number of clinical encounters (physician visits, ER, hospitalization and medication use—included in CRS and PS in sensitivity analyses) 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. 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. In the new user analysis, we did not observe an elevation in risk in the period shortly after initiation, suggesting our overall results among new and prevalent users were not biased by an early depletion of susceptibles[24].

In conclusion, the results of our large, population-based study should be reassuring with respect to the cardiovascular safety of relatively short-term use of ADHD medication use in young and middle-aged adults. In primary and subgroup analyses, as well as multiple sensitivity analyses that accounted for relevant confounders, we found no evidence for an increase in the risk of stroke, MI or SCD.

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%
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 (t_0); 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	111935.5	13.4%	53327.8	6.4%	47333.0	5.7%	69202.3	8.3%	553458.5	66.3%
Demographics										
Gender										
Male	51294.6	45.8%	24147.8	45.3%	21784.1	46.0%	32323.5	46.7%	253254.0	45.8%
Female	60640.9	54.2%	29180.0	54.7%	25548.9	54.0%	36878.8	53.3%	300204.5	54.2%
Age										
25-29	8483.3	7.6%	4557.1	8.5%	3547.1	7.5%	2167.5	3.1%	36630.2	6.6%
30-34	12674.5	11.3%	6882.3	12.9%	6334.3	13.4%	7134.0	10.3%	64045.1	11.6%
35-39	15189.8	13.6%	7843.2	14.7%	7389.9	15.6%	10347.8	15.0%	79842.8	14.4%
40-44	19617.2	17.5%	9509.4	17.8%	8705.9	18.4%	13134.2	19.0%	99128.6	17.9%
45-49	21466.0	19.2%	9688.5	18.2%	8508.6	18.0%	13302.5	19.2%	103285.7	18.7%
50-54	17936.1	16.0%	7755.3	14.5%	6540.0	13.8%	11129.0	16.1%	86230.5	15.6%
55-59	11363.3	10.2%	4843.1	9.1%	4179.1	8.8%	7485.2	10.8%	56005.1	10.1%
60-64	5205.3	4.7%	2248.9	4.2%	2128.1	4.5%	4502.2	6.5%	28290.5	5.1%
Site										
KPNC	14105.0	12.6%	5150.2	9.7%	4889.7	10.3%	8039.6	11.6%	66737.0	12.1%
KPSC	5709.7	5.1%	1985.9	3.7%	1909.0	4.0%	1551.1	2.2%	23160.0	4.2%
Tennessee Medicaid	8841.5	7.9%	5426.2	10.2%	7552.5	16.0%	20629.0	29.8%	80121.0	14.5%
HMORN										
Group Health	6478.2	5.8%	2419.5	4.5%	1754.9	3.7%	2581.6	3.7%	29536.0	5.3%
Harvard Pilgrim	9919.3	8.9%	4426.3	8.3%	3216.8	6.8%	3789.8	5.5%	45958.0	8.3%
HealthPartners	4350.8	3.9%	1709.0	3.2%	1252.4	2.6%	1525.0	2.2%	23289.0	4.2%
KPCO	3114.0	2.8%	1134.7	2.1%	922.2	1.9%	1454.8	2.1%	13228.0	2.4%
KP Northwest	4472.7	4.0%	1543.7	2.9%	1110.8	2.3%	1313.0	1.9%	18488.0	3.3%
Ingenix/I3	54945.0	49.1%	29532.0	55.4%	24725.0	52.2%	28318.0	40.9%	252942.0	45.7%
Year										
2004-2005	52077.0	46.5%	23914.0	44.8%	20573.0	43.5%	30748.0	44.4%	247969.0	44.8%
2002-2003	32182.0	28.8%	14292.0	26.8%	11244.0	23.8%	22449.0	32.4%	157683.0	28.5%
2000-2001	17612.0	15.7%	9774.4	18.3%	11055.0	23.4%	9618.8	13.9%	95645.0	17.3%
1993-1999	9859.9	8.8%	5138.2	9.6%	4102.2	8.7%	5471.8	7.9%	48617.0	8.8%
1986-1992	205.2	0.2%	209.9	0.4%	359.1	0.8%	914.3	1.3%	3544.3	0.6%
ADHD at baseline	39770.6	35.5%	15776.1	29.6%	10112.9	21.4%	10020.7	14.5%	570.2	0.1%

Cardiovascular disease at baseline**										
Acute MI	196.0	0.2%	102.0	0.2%	107.9	0.2%	159.7	0.2%	1341.2	0.2%
Ischemia	2399.9	2.1%	1276.9	2.4%	1372.5	2.9%	2217.9	3.2%	12633.2	2.3%
Coronary revascularization	159.4	0.1%	76.1	0.1%	85.3	0.2%	169.5	0.2%	1271.3	0.2%
CHF	613.3	0.5%	328.5	0.6%	379.2	0.8%	646.9	0.9%	3002.1	0.5%
Arrhythmia	2283.0	2.0%	1172.2	2.2%	1143.3	2.4%	1810.1	2.6%	9201.6	1.7%
Hypertension	15012.5	13.4%	7173.6	13.5%	7024.3	14.8%	10500.4	15.2%	69893.4	12.6%
Use of cardiovascular drug at baseline**										
Loop diuretic	2889.6	2.6%	1422.9	2.7%	1539.9	3.3%	2830.9	4.1%	9594.0	1.7%
Digoxin	419.9	0.4%	205.6	0.4%	226.4	0.5%	535.6	0.8%	2490.4	0.4%
Nitrates	1291.6	1.2%	672.6	1.3%	769.0	1.6%	1491.6	2.2%	7285.1	1.3%
Anticoagulant	1099.6	1.0%	558.1	1.0%	563.0	1.2%	866.4	1.3%	4291.3	0.8%
Platelet inhibitor	523.1	0.5%	295.4	0.6%	329.4	0.7%	434.8	0.6%	2604.2	0.5%
Anti-arrhythmic agents	393.2	0.4%	183.1	0.3%	190.9	0.4%	332.5	0.5%	1287.9	0.2%
ACE inhibitor	7445.4	6.7%	3471.2	6.5%	3426.4	7.2%	5083.2	7.3%	36255.6	6.6%
Angiotensin receptor blocker	1973.5	1.8%	1028.1	1.9%	944.4	2.0%	815.3	1.2%	7746.7	1.4%
Beta-blocker	8804.3	7.9%	4103.9	7.7%	4063.2	8.6%	6265.6	9.1%	36181.3	6.5%
Calcium-channel blocker	4915.5	4.4%	2430.9	4.6%	2475.9	5.2%	4413.6	6.4%	23956.8	4.3%
Thiazide diuretic	8917.0	8.0%	4142.4	7.8%	3792.4	8.0%	5195.3	7.5%	35698.8	6.5%
Other antihypertensive	1302.3	1.2%	606.2	1.1%	609.5	1.3%	1094.0	1.6%	4707.2	0.9%
Utilization at baseline*										
Cardiovascular visits										
Emergency, 1+	3568.8	3.2%	1884.6	3.5%	2200.4	4.6%	3534.5	5.1%	15261.5	2.8%
Inpatient, 1+	3592.7	3.2%	1899.7	3.6%	2112.5	4.5%	3406.9	4.9%	12770.1	2.3%
Physician, 1-4	30456.1	27.2%	14674.9	27.5%	13233.8	28.0%	19131.1	27.6%	118654.6	21.4%
Physician, 5+	8168.1	7.3%	4187.7	7.9%	4331.1	9.2%	6586.1	9.5%	31568.0	5.7%
***Psychiatric visits**[#]										
Emergency, 1+	2793.8	2.5%	1410.2	2.6%	1781.9	3.8%	3025.6	4.4%	5810.0	1.0%
Inpatient, 1+	4918.6	4.4%	2431.5	4.6%	2862.3	6.0%	5100.5	7.4%	7043.2	1.3%
Physician, 1-4	33590.2	30.0%	15071.4	28.3%	12644.9	26.7%	16945.2	24.5%	49295.4	8.9%
Physician, 5+	29863.7	26.7%	13381.1	25.1%	12463.3	26.3%	17802.7	25.7%	21820.7	3.9%
Other visits										
Emergency, 1+	5262.2	4.7%	2729.4	5.1%	3048.5	6.4%	4893.1	7.1%	19873.2	3.6%
Inpatient, 1+	3495.2	3.1%	1778.9	3.3%	2028.7	4.3%	3425.5	4.9%	10222.3	1.8%
Physician, 1+	39434.9	35.2%	18775.1	35.2%	17356.3	36.7%	25595.0	37.0%	129160.8	23.3%

No. of different medications***										
1	17852.6	15.9%	8704.6	16.3%	7237.0	15.3%	10609.1	15.3%	117170.6	21.2%
2	17363.5	15.5%	8329.1	15.6%	7044.1	14.9%	10076.1	14.6%	75566.5	13.7%
3	14959.0	13.4%	7012.3	13.1%	6008.5	12.7%	8573.2	12.4%	49386.3	8.9%
4	11871.8	10.6%	5557.4	10.4%	4894.8	10.3%	7256.7	10.5%	32306.2	5.8%
5	9412.8	8.4%	4277.1	8.0%	3903.4	8.2%	5826.6	8.4%	21762.9	3.9%
6	7114.9	6.4%	3345.0	6.3%	3064.6	6.5%	4664.4	6.7%	13948.1	2.5%
7-8	9413.4	8.4%	4318.9	8.1%	4233.1	8.9%	6455.2	9.3%	14915.7	2.7%
9-10	5009.4	4.5%	2340.2	4.4%	2362.8	5.0%	3410.6	4.9%	6602.1	1.2%
11+	4814.9	4.3%	2315.9	4.3%	2598.4	5.5%	3435.2	5.0%	5142.2	0.9%
Medical conditions, ever/never[$]										
Obesity	11573.6	10.3%	5056.9	9.5%	5141.6	10.9%	11679.8	16.9%	48928.8	8.8%
Smoking	14557.7	13.0%	6139.2	11.5%	6704.6	14.2%	15298.8	22.1%	62401.8	11.3%
Diabetes[##]	7977.5	7.1%	3815.4	7.2%	3994.3	8.4%	9453.1	13.7%	43884.6	7.9%
Stroke/TIA	2030.1	1.8%	1031.2	1.9%	1223.7	2.6%	3567.2	5.2%	9753.7	1.8%
Hyperlipidemia[##]	27383.0	24.5%	13050.1	24.5%	12634.5	26.7%	25154.0	36.3%	123171.2	22.3%
Congenital heart disorder	391.3	0.3%	211.6	0.4%	235.6	0.5%	659.2	1.0%	2398.9	0.4%
Coronary artery anomaly	71.4	0.1%	37.7	0.1%	41.4	0.1%	143.3	0.2%	436.9	0.1%
Peripheral vascular disease	1799.6	1.6%	824.4	1.5%	853.6	1.8%	2412.4	3.5%	7911.7	1.4%
Mental health claims, time-varying[$$]										
Major depression	47972.8	42.9%	21403.4	40.1%	18520.8	39.1%	20763.6	30.0%	47844.9	8.6%
Bipolar disorder	8743.3	7.8%	3996.7	7.5%	4186.7	8.8%	5318.2	7.7%	5983.9	1.1%
Anxiety	21431.1	19.1%	9933.8	18.6%	9338.3	19.7%	11045.9	16.0%	31723.0	5.7%
Psychotic disorders	1851.8	1.7%	894.2	1.7%	1177.8	2.5%	2372.0	3.4%	5817.6	1.1%
Other selected medical conditions, time-varying[$$]										
ETOH/substance abuse	5322.3	4.8%	2429.3	4.6%	2778.8	5.9%	3386.6	4.9%	9632.7	1.7%
Suicide attempt	452.6	0.4%	238.0	0.4%	290.4	0.6%	371.1	0.5%	894.6	0.2%
Injury	21672.6	19.4%	10387.2	19.5%	9599.5	20.3%	13526.7	19.5%	72019.9	13.0%
Seizure	2057.1	1.8%	1028.9	1.9%	1187.7	2.5%	2184.8	3.2%	7180.1	1.3%
Asthma	8599.7	7.7%	4156.7	7.8%	3752.9	7.9%	5659.8	8.2%	25257.1	4.6%
Use of psychotropic medications, time-varying[$$]										
Antipsychotic, any	5857.9	5.2%	1952.0	3.7%	2138.6	4.5%	4289.4	6.2%	7110.6	1.3%
Tricyclic antidepressant	4541.8	4.1%	1702.2	3.2%	1687.3	3.6%	3167.3	4.6%	9677.6	1.7%
Antidepressants, other or SSRI/SNRI	44591.7	39.8%	15474.8	29.0%	12654.3	26.7%	18015.7	26.0%	42861.9	7.7%

Benzodiazepines	15383.8	13.7%	5507.9	10.3%	5296.3	11.2%	8626.4	12.5%	18860.0	3.4%
Lithium	1542.9	1.4%	610.7	1.1%	626.8	1.3%	917.9	1.3%	1517.3	0.3%
Modafinil	1183.3	1.1%	657.9	1.2%	899.2	1.9%	1165.3	1.7%	338.0	0.1%
Insomnia meds	4124.7	3.7%	1613.2	3.0%	1407.3	3.0%	1765.3	2.6%	3418.6	0.6%
Thioridazine	87.3	0.1%	34.9	0.1%	46.4	0.1%	182.6	0.3%	413.6	0.1%
Mood stabilizers, w/o seizure	9329.0	8.3%	3305.6	6.2%	3177.9	6.7%	5009.0	7.2%	8018.1	1.4%
Clonidine/guanfacine, w/o HT	546.8	0.5%	143.4	0.3%	96.4	0.2%	148.5	0.2%	421.3	0.1%
Use of other selected medications, time-varying[$$]										
Beta-agonist	3268.7	2.9%	1301.8	2.4%	1195.3	2.5%	2215.0	3.2%	9819.4	1.8%
Epinephrine	66.5	0.1%	28.0	0.1%	26.4	0.1%	33.9	0.0%	158.8	0.0%
Asthma med, other	7344.5	6.6%	2970.9	5.6%	2690.5	5.7%	4359.2	6.3%	20122.6	3.6%
Seizure med, any	10524.5	9.4%	3818.3	7.2%	3779.4	8.0%	6350.8	9.2%	12366.8	2.2%
Theophylline compounds (asthma med)	277.2	0.2%	137.1	0.3%	150.8	0.3%	453.2	0.7%	1466.8	0.3%
COX-2 inhibitors	2324.8	2.1%	938.6	1.8%	825.5	1.7%	1516.3	2.2%	5353.9	1.0%
Other drugs to improve blood flow	57.2	0.1%	22.2	0.0%	25.4	0.1%	85.2	0.1%	255.4	0.0%
Clonidine	848.0	0.8%	271.6	0.5%	248.7	0.5%	506.8	0.7%	2101.6	0.4%
pde5 inhibitors	1279.1	1.1%	406.0	0.8%	325.5	0.7%	471.6	0.7%	2330.7	0.4%
Triptans	1341.6	1.2%	505.4	0.9%	411.3	0.9%	536.0	0.8%	1911.2	0.3%
Oral contraceptives	7023.6	6.3%	3107.0	5.8%	2410.0	5.1%	2950.1	4.3%	26958.9	4.9%
Hormones, menopausal or misc	9139.3	8.2%	3678.6	6.9%	3152.4	6.7%	4954.0	7.2%	28407.3	5.1%
Cardiovascular Risk Score										
decile 1	11198.1	10.0%	5247.9	9.8%	4873.3	10.3%	7899.3	11.4%	54321.9	9.8%
decile 2	24730.8	22.1%	12791.1	24.0%	10605.2	22.4%	14210.3	20.5%	238950.7	43.2%
decile 3	14037.0	12.5%	6883.1	12.9%	6012.3	12.7%	8228.9	11.9%	65487.5	11.8%
decile 4	12407.0	11.1%	5790.0	10.9%	4884.8	10.3%	6428.5	9.3%	37873.1	6.8%
decile 5	11573.0	10.3%	5408.3	10.1%	4513.6	9.5%	5899.6	8.5%	37052.8	6.7%
decile 6	10062.8	9.0%	4560.4	8.6%	3946.2	8.3%	5511.7	8.0%	31738.0	5.7%
decile 7	8635.6	7.7%	3907.0	7.3%	3577.1	7.6%	5257.1	7.6%	26514.3	4.8%
decile 8	7728.7	6.9%	3470.1	6.5%	3265.5	6.9%	5018.3	7.3%	22509.7	4.1%
decile 9	6678.3	6.0%	2994.3	5.6%	3011.6	6.4%	5151.1	7.4%	21249.0	3.8%
decile 10	4884.2	4.4%	2275.8	4.3%	2643.4	5.6%	5597.5	8.1%	17761.5	3.2%

* Using the stroke model; **At baseline or cohort entry (t_0): 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 ALL strokes and by subtype

Table 2a. Rates of **ALL stroke,** by use of ADHD medications (n=150,658 total users)

Medication status	Person-yrs	Number Events	Rate/1,000 person-yrs	Unadjusted RR	95% CI	Adjusted matching variables RR*	95% CI	Adjusted RR**	95% CI
ADHD medication users	281798.7	200	0.71						
Current user	111935.5	63	0.56	0.83	0.64 - 1.08	0.96	0.73 - 1.25	0.77	0.59 - 1.02
Indeterminate user	53327.8	31	0.58	0.86	0.59 - 1.24	1.02	0.71 - 1.48	0.82	0.57 - 1.20
Former user	47333.0	39	0.82	1.22	0.87 - 1.69	1.32	0.95 - 1.84	0.99	0.71 - 1.40
Remote user	69202.3	67	0.97	1.43	1.10 - 1.85	1.06	0.82 - 1.38	0.76	0.58 - 1.00
Nonuser	553458.5	375	0.68	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, and established stroke risk factors (see Table A-5 for details)
This table excludes the two HMORN sites that did not provide data on stroke endpoints.

Table 2b. Rates of **ALL stroke,** by use of ADHD medications **(NEW USERS only, n=96,502)**

Medication status	Person-yrs	Number Events	Rate/1,000 person-yrs	Unadjusted RR	95% CI	Adjusted matching variables RR*	95% CI	Adjusted RR**	95% CI
ADHD medication users	174573.5	143	0.82						
Current user	54569.3	41	0.75	0.94	0.68 - 1.31	1.12	0.81 - 1.56	0.79	0.56 - 1.12
Indeterminate user	30657.1	20	0.65	0.82	0.52 - 1.29	1.02	0.64 - 1.60	0.71	0.45 - 1.13
Former user	34644.6	26	0.75	0.94	0.63 - 1.41	1.08	0.72 - 1.61	0.74	0.49 - 1.11
Remote user	54702.5	56	1.02	1.28	0.96 - 1.71	1.02	0.76 - 1.36	0.72	0.54 - 0.98
Nonuser	328754.2	262	0.80	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, and established stroke risk factors (see Table A-5 for details)
This table excludes the two HMORN sites that did not provide data on stroke endpoints.

Table 2c. Rates of **ISCHEMIC stroke,** by use of ADHD medications

Medication status	Person-yrs	Number Events	Rate/1,000 person-yrs	Unadjusted RR	95% CI	Adjusted matching variables RR*	95% CI	Adjusted RR**	95% CI
ADHD medication users	281798.7	148	0.53						
Current user	111935.5	46	0.41	0.86	0.63 - 1.18	1.00	0.73 - 1.37	0.79	0.57 - 1.09
Indeterminate user	53327.8	26	0.49	1.02	0.68 - 1.53	1.24	0.83 - 1.86	0.97	0.64 - 1.47
Former user	47333.0	28	0.59	1.24	0.84 - 1.83	1.37	0.93 - 2.02	1.00	0.67 - 1.48
Remote user	69202.3	48	0.69	1.45	1.07 - 1.98	1.07	0.78 - 1.46	0.72	0.53 - 1.00
Nonuser	553458.5	267	0.48	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, and established stroke risk factors (see Table A-5 for details)
This table excludes the two HMORN sites that did not provide data on stroke endpoints.

Table 2d. Rates of **HEMORRHAGIC stroke,** by use of ADHD medications

Medication status	Person-yrs	Number Events	Rate/1,000 person-yrs	Unadjusted RR	95% CI	Adjusted matching variables RR*	95% CI	Adjusted RR**	95% CI
ADHD medication users	281798.7	47	0.17						
Current user	111935.5	16	0.14	0.79	0.47 - 1.34	0.88	0.52 - 1.49	0.75	0.43 - 1.31
Indeterminate user	53327.8	5	0.09	0.52	0.21 - 1.27	0.59	0.24 - 1.46	0.51	0.20 - 1.26
Former user	47333.0	9	0.19	1.05	0.53 - 2.08	1.10	0.56 - 2.18	0.91	0.45 - 1.83
Remote user	69202.3	17	0.25	1.36	0.81 - 2.27	1.07	0.63 - 1.79	0.90	0.52 - 1.53
Nonuser	553458.5	101	0.18	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, and other established stroke risk factors (see Table A-5 for details)
This table excludes the two HMORN sites that did not provide data on stroke endpoints.

Table 2e. Rates of **ALL stroke (excluding only those adjudicated as non-cases),** by use of ADHD medications

Medication status	Person-yrs	Number Events	Rate/1,000 person-yrs	Unadjusted RR	95% CI	Adjusted matching variables RR*	95% CI	Adjusted RR**	95% CI
ADHD medication users	281716.6	256	0.91						
Current user	111919.3	80	0.71	0.89	0.70 - 1.13	1.04	0.82 - 1.33	0.84	0.66 - 1.08
Indeterminate user	53318.5	45	0.84	1.05	0.78 - 1.43	1.25	0.92 - 1.70	1.00	0.73 - 1.37
Former user	47320.9	46	0.97	1.21	0.90 - 1.64	1.30	0.96 - 1.76	0.96	0.70 - 1.31
Remote user	69157.9	85	1.23	1.54	1.22 - 1.94	1.12	0.89 - 1.42	0.78	0.61 - 0.99
Nonuser	553346.6	443	0.80	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, and established stroke risk factors (see Table A-5 for details)
This table excludes the two HMORN sites that did not provide data on stroke endpoints.

Tables of RRs – current use of specific medications, ALL strokes and by subtype

Table 3a. Rates of **ALL stroke,** by specific ADHD medication

Medication status	Person-yrs	Number Events	Rate/1,000 person-yrs	Unadjusted RR	95% CI	Adjusted matching variables RR*	95% CI	Adjusted RR**	95% CI
Current user	111935.5	63	0.56	0.83	0.64 - 1.08	0.96	0.73 - 1.25	0.77	0.59 - 1.02
Amphetamines	48672.9	19	0.39	0.58	0.36 - 0.91	0.75	0.47 - 1.19	0.63	0.40 - 1.01
Methylphenidate	50332.3	39	0.77	1.14	0.82 - 1.59	1.23	0.88 - 1.71	0.96	0.69 - 1.35
Atomoxetine	8371.1	3	0.36	0.53	0.17 - 1.65	0.58	0.19 - 1.82	0.46	0.15 - 1.44
Pemoline	3030.1	2	0.66	0.97	0.24 - 3.91	0.79	0.20 - 3.16	0.59	0.15 - 2.38
Multiple	1529.2	0	0.00	--	--	--	--	--	--
Nonuser	553458.5	375	0.68	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, and other established stroke risk factors (see Table A-5 for details)
This table excludes the two HMORN sites that did not provide data on stroke endpoints.

Table 3b. Rates of **ALL stroke,** by specific ADHD medication **(NEW USERS ONLY)**

Medication status	Person-yrs	Number Events	Rate/1,000 person-yrs	Unadjusted RR	95% CI	Adjusted matching variables RR*	95% CI	Adjusted RR**	95% CI
Current user	54569.3	41	0.75	0.94	0.68 - 1.31	1.12	0.81 - 1.56	0.79	0.56 - 1.12
Amphetamines	22965.2	10	0.44	0.55	0.29 - 1.03	0.73	0.39 - 1.38	0.54	0.28 - 1.02
Methylphenidate	23335.7	26	1.11	1.40	0.93 - 2.09	1.56	1.04 - 2.34	1.04	0.69 - 1.58
Atomoxetine	6429.4	3	0.47	0.59	0.19 - 1.83	0.67	0.21 - 2.10	0.51	0.16 - 1.61
Pemoline	1099.7	2	1.82	2.28	0.57 - 9.17	1.51	0.37 - 6.09	1.07	0.27 - 4.35
Multiple	739.3	0	0.00	--	--	--	--	--	--
Nonuser	328754.2	262	0.80	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, and established stroke risk factors (see Table A-5 for details)
This table excludes the two HMORN sites that did not provide data on stroke endpoints.

Table 3c. Rates of **ISCHEMIC stroke,** by specific ADHD medication

Medication status	Person-yrs	Number Events	Rate/1,000 person-yrs	Unadjusted RR	95% CI	Adjusted matching variables RR*	95% CI	Adjusted RR**	95% CI
Current user	111935.5	46	0.41	0.86	0.63 - 1.18	1.00	0.73 - 1.37	0.79	0.57 - 1.09
Amphetamines	48672.9	13	0.27	0.56	0.32 - 0.98	0.74	0.43 - 1.30	0.62	0.35 - 1.09
Methylphenidate	50332.3	29	0.58	1.21	0.82 - 1.77	1.29	0.87 - 1.89	0.98	0.66 - 1.45
Atomoxetine	8371.1	2	0.24	0.50	0.12 - 2.01	0.57	0.14 - 2.29	0.43	0.11 - 1.75
Pemoline	3030.1	2	0.66	1.38	0.34 - 5.56	1.11	0.27 - 4.46	0.80	0.20 - 3.21
Multiple	1529.2	0	0.00	--	--	--	--	--	--
Nonuser	553458.5	267	0.48	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, and established stroke risk factors (see Table A-5 for details)
This table excludes the two HMORN sites that did not provide data on stroke endpoints.

Table 3d. Rates of **HEMORRHAGIC stroke,** by specific ADHD medication

Medication status	Person-yrs	Number Events	Rate/1,000 person-yrs	Unadjusted RR	95% CI	Adjusted matching variables RR*	95% CI	Adjusted RR**	95% CI
Current user	111935.5	16	0.14	0.79	0.47 - 1.34	0.88	0.52 - 1.49	0.75	0.43 - 1.31
Amphetamines	48672.9	6	0.12	0.68	0.30 - 1.55	0.82	0.36 - 1.88	0.72	0.31 - 1.68
Methylphenidate	50332.3	10	0.20	1.10	0.57 - 2.11	1.17	0.61 - 2.26	0.99	0.51 - 1.93
Atomoxetine	8371.1	0	0.00	--	--	--	--	--	--
Pemoline	3030.1	0	0.00	--	--	--	--	--	--
Multiple	1529.2	0	0.00	--	--	--	--	--	--
Nonuser	553458.5	101	0.18	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, and established stroke risk factors (see Table A-5 for details)
This table excludes the two HMORN sites that did not provide data on stroke endpoints.

Table 3e. Rates of **ALL stroke (excluding only those adjudicated as non-cases),** by specific ADHD medications

Medication status	Person-yrs	Number Events	Rate/1,000 person-yrs	Unadjusted RR	95% CI	Adjusted matching variables RR*	95% CI	Adjusted RR**	95% CI
Current user	111919.3	80	0.71	0.89	0.70 - 1.13	1.04	0.82 - 1.33	0.84	0.66 - 1.08
Amphetamines	48667.9	25	0.51	0.64	0.43 - 0.96	0.85	0.57 - 1.27	0.73	0.48 - 1.10
Methylphenidate	50322.2	48	0.95	1.19	0.88 - 1.60	1.30	0.96 - 1.75	1.01	0.74 - 1.37
Atomoxetine	8370.2	3	0.36	0.45	0.14 - 1.39	0.50	0.16 - 1.57	0.40	0.13 - 1.25
Pemoline	3029.9	4	1.32	1.65	0.62 - 4.41	1.28	0.48 - 3.43	0.95	0.35 - 2.54
Multiple	1529.1	0	0.00	--	--	--	--	--	--
Nonuser	553346.6	443	0.80	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, and established stroke risk factors (see Table A-5 for details)
This table excludes the two HMORN sites that did not provide data on stroke endpoints.

Tables of RRs – duration of current use for ALL strokes

Table 4a. Rates of **ALL stroke,** by use of ADHD medications

Medication status	Person-yrs	Number Events	Rate/1,000 person-yrs	Unadjusted RR	95% CI	Adjusted matching variables RR*	95% CI	Adjusted RR**	95% CI
Duration of Current use [#]									
366+ days	51540.0	29	0.56	0.83	0.57 - 1.21	0.88	0.60 - 1.28	0.73	0.49 - 1.07
183-365 days	23938.3	9	0.38	0.55	0.29 - 1.07	0.72	0.37 - 1.39	0.58	0.30 - 1.13
91-182 days	13896.9	12	0.86	1.27	0.72 - 2.26	1.64	0.92 - 2.91	1.29	0.72 - 2.31
31-90 days	11539.6	7	0.61	0.90	0.42 - 1.89	1.16	0.55 - 2.45	0.92	0.43 - 1.95
1-30 days	7898.0	4	0.51	0.75	0.28 - 2.00	0.93	0.35 - 2.49	0.73	0.27 - 1.98
Nonuser	553458.5	375	0.68	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, and established stroke risk factors (see Table A-5 for details)
[#] Excludes current pemoline use.
This table excludes the two HMORN sites that did not provide data on stroke endpoints.

Table 4b. Rates of **ALL stroke,** by use of ADHD medications (**NEW USERS ONLY)**

Medication status	Person-yrs	Number Events	Rate/1,000 person-yrs	Unadjusted RR	95% CI	Adjusted matching variables RR*	95% CI	Adjusted RR**	95% CI
Duration of Current use [#]									
366+ days	16087.6	16	0.99	1.25	0.75 - 2.07	1.22	0.73 - 2.02	0.89	0.53 - 1.49
183-365 days	11018.6	4	0.36	0.46	0.17 - 1.22	0.57	0.21 - 1.54	0.40	0.15 - 1.08
91-182 days	9398.0	9	0.96	1.20	0.62 - 2.34	1.62	0.83 - 3.16	1.11	0.57 - 2.18
31-90 days	9511.8	6	0.63	0.79	0.35 - 1.78	1.13	0.50 - 2.54	0.78	0.34 - 1.75
1-30 days	7421.0	4	0.54	0.68	0.25 - 1.82	0.95	0.35 - 2.56	0.66	0.24 - 1.78
Nonuser	328754.2	262	0.80	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, and established stroke risk factors (see Table A-5 for details)
[#] Excludes current pemoline use.
This table excludes the two HMORN sites that did not provide data on stroke endpoints.

Tables of RRs – Remote users as reference group (Tables 5 and 6)

Table 5a. Rates of **ALL stroke,** by use of ADHD medications

Medication status	Person-yrs	Number Events	Rate/1,000 person-yrs	Unadjusted RR	95% CI	Adjusted matching variables RR*	95% CI	Adjusted RR**	95% CI
Current user	111935.5	63	0.56	0.58	0.41 - 0.82	0.90	0.63 - 1.28	1.02	0.71 - 1.45
Indeterminate user	53327.8	31	0.58	0.60	0.39 - 0.92	0.96	0.63 - 1.48	1.08	0.70 - 1.67
Former user	47333.0	39	0.82	0.85	0.57 - 1.26	1.24	0.83 - 1.85	1.31	0.88 - 1.95
Remote user	69202.3	67	0.97	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, and established stroke risk factors (see Table A-5 for details)
This table excludes the two HMORN sites that did not provide data on stroke endpoints.

Table 5b. Rates of **ALL stroke,** by use of ADHD medications **(NEW USERS ONLY)**

Medication status	Person-yrs	Number Events	Rate/1,000 person-yrs	Unadjusted RR	95% CI	Adjusted matching variables RR*	95% CI	Adjusted RR**	95% CI
Current user	54569.3	41	0.75	0.73	0.49 - 1.10	1.10	0.73 - 1.65	1.09	0.73 - 1.65
Indeterminate user	30657.1	20	0.65	0.64	0.38 - 1.06	1.00	0.60 - 1.66	0.99	0.59 - 1.65
Former user	34644.6	26	0.75	0.73	0.46 - 1.17	1.05	0.66 - 1.68	1.02	0.64 - 1.63
Remote user	54702.5	56	1.02	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, and established stroke risk factors (see Table A-5 for details)
This table excludes the two HMORN sites that did not provide data on stroke endpoints.

Table 6a. Rates of **ALL stroke,** by specific ADHD medication

Medication status	Person-yrs	Number Events	Rate/1,000 person-yrs	Unadjusted RR	95% CI	Adjusted matching variables RR*	95% CI	Adjusted RR**	95% CI
Current user	111935.5	63	0.56	0.58	0.41 - 0.82	0.90	0.63 - 1.28	1.02	0.71 - 1.45
Amphetamines	48672.9	19	0.39	0.40	0.24 - 0.67	0.70	0.42 - 1.18	0.83	0.50 - 1.40
Methylphenidate	50332.3	39	0.77	0.80	0.54 - 1.19	1.15	0.77 - 1.72	1.27	0.85 - 1.90
Atomoxetine	8371.1	3	0.36	0.37	0.12 - 1.18	0.55	0.17 - 1.75	0.60	0.19 - 1.93
Pemoline	3030.1	2	0.66	0.68	0.17 - 2.78	0.74	0.18 - 3.04	0.78	0.19 - 3.19
Multiple	1529.2	0	0.00	--	--	--	--	--	--
Remote user	69202.3	67	0.97	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, and established stroke risk factors (see Table A-5 for details)
This table excludes the two HMORN sites that did not provide data on stroke endpoints.

Table 6b. Rates of **ALL stroke,** by specific ADHD medication **(NEW USERS ONLY)**

Medication status	Person-yrs	Number Events	Rate/1,000 person-yrs	Unadjusted RR	95% CI	Adjusted matching variables RR*	95% CI	Adjusted RR**	95% CI
Current user	54569.3	41	0.75	0.73	0.49 - 1.10	1.10	0.73 - 1.65	1.09	0.73 - 1.65
Amphetamines	22965.2	10	0.44	0.43	0.22 - 0.83	0.72	0.37 - 1.41	0.74	0.38 - 1.47
Methylphenidate	23335.7	26	1.11	1.09	0.68 - 1.73	1.53	0.96 - 2.45	1.44	0.90 - 2.31
Atomoxetine	6429.4	3	0.47	0.46	0.14 - 1.46	0.66	0.20 - 2.11	0.71	0.22 - 2.27
Pemoline	1099.7	2	1.82	1.78	0.43 - 7.28	1.48	0.36 - 6.08	1.48	0.36 - 6.11
Multiple	739.3	0	0.00	--	--	--	--	--	--
Remote user	54702.5	56	1.02	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, and established stroke risk factors (see Table A-5 for details)
This table excludes the two HMORN sites that did not provide data on stroke endpoints.

Subgroup analyses

Table 7a. Rate ratios of **ALL stroke,** overall and by subgroup

Cohort/ subgroup	Person-yrs	Number Events	Rate/1,000 person-yrs	RR**	95% CI
Full cohort	835257.2	575	0.69		
Current	111935.5	63	0.56	0.77	0.58 - 1.02
Former*	169863.2	137	0.81	0.83	0.68 - 1.02
Nonuser	553458.5	375	0.68	1.00	reference
No history of CVD^	590555.2	197	0.33		
Current	73971.4	18	0.24	0.64	0.38 - 1.07
Former*	109565.1	36	0.33	0.75	0.51 - 1.12
Nonuser	407018.7	143	0.35	1.00	reference
History of CVD^	244702.0	378	1.54		
Current	37964.1	45	1.19	0.85	0.61 - 1.19
Former*	60298.1	101	1.68	0.89	0.70 - 1.13
Nonuser	146439.8	232	1.58	1.00	reference
History of non-ADHD psychiatric condition	332664.0	309	0.93		
Current	82584.4	57	0.69	0.89	0.65 - 1.23
Former*	119457.2	115	0.96	0.93	0.73 - 1.20
Nonuser	130622.4	137	1.05	1.00	reference
No history of non-ADHD psychiatric condition	502593.1	266	0.53		
Current	29351.0	6	0.20	0.44	0.19 - 0.99
Former*	50406.0	22	0.44	0.72	0.46 - 1.13
Nonuser	422836.1	238	0.56	1.00	reference
Users with ADHD	629138.7	398	0.63		
Current	39770.6	10	0.25	0.45	0.24 - 0.85
Former*	35909.7	13	0.36	0.65	0.37 - 1.15
Nonuser	553458.5	375	0.68	1.00	reference
Users with no ADHD	759576.9	552	0.73		
Current	72164.9	53	0.73	0.89	0.66 - 1.20
Former*	133953.5	124	0.93	0.86	0.69 - 1.07
Nonuser	553458.5	375	0.68	1.00	reference
Users with ADHD	236843.7	101	0.43		
Current	39770.6	10	0.25	0.48	0.25 - 0.96
Former*	35909.7	13	0.36	0.68	0.37 - 1.26
Nonuser (matched to user)	161163.5	78	0.48	1.00	reference
Users with no ADHD	603338.6	475	0.79		
Current	72164.9	53	0.73	0.89	0.65 - 1.21
Former*	133953.5	124	0.93	0.87	0.69 - 1.08
Nonuser (matched to user)	397220.2	298	0.75	1.00	reference
Ages 25-44	423164.3	104	0.25		
Current	55964.8	12	0.21	0.74	0.39 - 1.42
Former*	87552.8	26	0.30	0.84	0.52 - 1.37
Nonuser	279646.7	66	0.24	1.00	reference
Ages 45-64	412092.9	471	1.14		
Current	55970.7	51	0.91	0.77	0.57 - 1.05
Former*	82310.4	111	1.35	0.83	0.66 - 1.04
Nonuser	273811.8	309	1.13	1.00	reference

* Includes indeterminate, former and remote users

**Adjusted for site, age, sex, calendar year, and established stroke risk factors (see Table A-5 for details)

^ 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.

Subgroup analyses (remote users as reference group)

Table 7b. Rate ratios of **ALL stroke,** overall and by subgroup

Cohort/ subgroup	Person-yrs	Number Events	Rate/1,000 person-yrs	RR**	95% CI
Full cohort					
Current	111935.5	63	0.56	1.02	0.71 - 1.45
Former*	100660.9	70	0.70	1.20	0.85 - 1.69
Remote	69202.3	67	0.97	1.00	reference
No history of CVD^					
Current	73971.4	18	0.24	0.72	0.38 - 1.37
Former*	65436.8	15	0.23	0.72	0.37 - 1.41
Remote	44128.3	21	0.48	1.00	reference
History of CVD^					
Current	37964.1	45	1.19	1.16	0.76 - 1.77
Former*	35224.0	55	1.56	1.42	0.95 - 2.12
Remote	25074.0	46	1.83	1.00	reference
History of non-ADHD psychiatric condition					
Current	82584.4	57	0.69	1.03	0.70 - 1.51
Former*	71725.0	59	0.82	1.15	0.79 - 1.67
Remote	47732.2	56	1.17	1.00	reference
No history of non-ADHD psychiatric condition					
Current	29351.0	6	0.20	0.68	0.25 - 1.86
Former*	28935.8	11	0.38	1.27	0.55 - 2.96
Remote	21470.1	11	0.51	1.00	reference
Users with ADHD					
Current	39770.6	10	0.25	0.60	0.30 - 1.17
Former*	25889.0	10	0.39	0.99	0.50 - 1.93
Remote	69202.3	67	0.97	1.00	reference
Users with no ADHD					
Current	72164.9	53	0.73	1.16	0.81 - 1.68
Former*	74771.9	60	0.80	1.24	0.87 - 1.76
Remote	69202.3	67	0.97	1.00	reference
Users with ADHD – user matched to non-user					
Current	39770.6	10	0.25	0.99	0.27 - 3.64
Former*	25889.0	10	0.39	1.59	0.43 - 5.81
Remote	10020.7	3	0.30	1.00	reference
Users restricted to those with no ADHD – user matched to non-user					
Current	72164.9	53	0.73	1.12	0.77 - 1.63
Former*	74771.9	60	0.80	1.20	0.84 - 1.72
Remote	59181.6	64	1.08	1.00	reference
Ages 25-44 years					
Current	55964.8	12	0.21	0.89	0.39 - 2.05
Former*	54769.4	14	0.26	1.01	0.46 - 2.25
Remote	32783.4	12	0.37	1.00	reference
Ages 45-64 years					
Current	55970.7	51	0.91	1.04	0.71 - 1.55
Former*	45891.5	56	1.22	1.24	0.85 - 1.81
Remote	36418.9	55	1.51	1.00	reference

* Includes indeterminate and former users

**Adjusted for site, age, sex, calendar year, and established stroke risk factors (see Table A-5 for details)
^ 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.

Tables of RRs – for MI or SCD or Stroke

Table 8a. Rates of **MI or SCD or stroke,** by use of ADHD medications

Medication status	Person-yrs	Number Events	Rate/1,000 person-yrs	Unadjusted RR	95% CI	Adjusted matching variables RR*	95% CI	Adjusted RR**	95% CI
ADHD medication users	272641.8	723	2.65						
Current user	107322.4	234	2.18	0.84	0.73 - 0.96	0.97	0.84 - 1.12	0.80	0.69 - 0.92
Indeterminate user	51709.6	125	2.42	0.93	0.77 - 1.11	1.11	0.92 - 1.33	0.90	0.75 - 1.09
Former user	46120.8	121	2.62	1.01	0.84 - 1.21	1.07	0.89 - 1.29	0.83	0.68 - 1.00
Remote user	67489.0	243	3.60	1.38	1.21 - 1.58	1.02	0.88 - 1.17	0.76	0.66 - 0.87
Nonuser	533540.4	1391	2.61	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, and established stroke risk factors (see Table A-5 for details)
This table excludes the three HMORN sites that did not provide data on SCD or stroke endpoints.

Table 8b. Rates of **MI or SCD or stroke,** by use of ADHD medications **(NEW USERS only)**

Medication status	Person-yrs	Number Events	Rate/1,000 person-yrs	Unadjusted RR	95% CI	Adjusted matching variables RR*	95% CI	Adjusted RR**	95% CI
ADHD medication users	169013.3	501	2.96						
Current user	52094.6	125	2.40	0.80	0.66 - 0.96	0.96	0.80 - 1.16	0.68	0.56 - 0.82
Indeterminate user	29694.2	82	2.76	0.92	0.73 - 1.15	1.14	0.91 - 1.43	0.80	0.63 - 1.01
Former user	33774.3	97	2.87	0.95	0.77 - 1.17	1.08	0.87 - 1.33	0.74	0.60 - 0.91
Remote user	53450.1	197	3.69	1.22	1.05 - 1.43	0.96	0.82 - 1.12	0.72	0.61 - 0.84
Nonuser	317514.4	957	3.01	1.00	reference	1.00	reference	1.00	reference

* Adjusted for site, age, sex, calendar year (ie, matching variables)
**Adjusted for site, age, sex, calendar year, and established stroke risk factors (see Table A-5 for details)
This table excludes the three HMORN sites that did not provide data on SCD or stroke endpoints.

Tables of RRs – for MI or SCD or Stroke (remote users as reference group)

Table 9a. Rates of **MI or SCD or stroke,** by use of ADHD medications

Medication status	Person-yrs	Number Events	Rate/1,000 person-yrs	Unadjusted RR	95% CI	Adjusted matching variables RR*	95% CI	Adjusted RR**	95% CI
Current user	107322.4	234	2.18	0.61	0.51 - 0.72	0.96	0.80 - 1.15	1.05	0.87 - 1.26
Indeterminate user	51709.6	125	2.42	0.67	0.54 - 0.83	1.09	0.88 - 1.35	1.19	0.95 - 1.48
Former user	46120.8	121	2.62	0.73	0.59 - 0.91	1.06	0.85 - 1.32	1.09	0.87 - 1.36
Remote user	67489.0	243	3.60	1.00	reference	1.00	reference	1.00	reference

* Adjusted for site, age, sex, calendar year (ie, matching variables)
**Adjusted for site, age, sex, calendar year, and other established stroke risk factors (see Table A-5 for details)
This table excludes the three HMORN sites that did not provide data on SCD or stroke endpoints.

Table 9b. Rates of **MI or SCD or stroke,** by use of ADHD medications **(NEW USERS only)**

Medication status	Person-yrs	Number Events	Rate/1,000 person-yrs	Unadjusted RR	95% CI	Adjusted matching variables RR*	95% CI	Adjusted RR**	95% CI
Current user	52094.6	125	2.40	0.65	0.52 - 0.81	1.00	0.80 - 1.26	0.94	0.75 - 1.18
Indeterminate user	29694.2	82	2.76	0.75	0.58 - 0.97	1.19	0.92 - 1.55	1.11	0.86 - 1.44
Former user	33774.3	97	2.87	0.78	0.61 - 0.99	1.13	0.88 - 1.44	1.03	0.80 - 1.31
Remote user	53450.1	197	3.69	1.00	reference	1.00	reference	1.00	reference

* Adjusted for site, age, sex, calendar year (ie, matching variables)
**Adjusted for site, age, sex, calendar year, and established stroke risk factors (see Table A-5 for details)
This table excludes the three HMORN sites that did not provide data on SCD or stroke endpoints.

Appendices

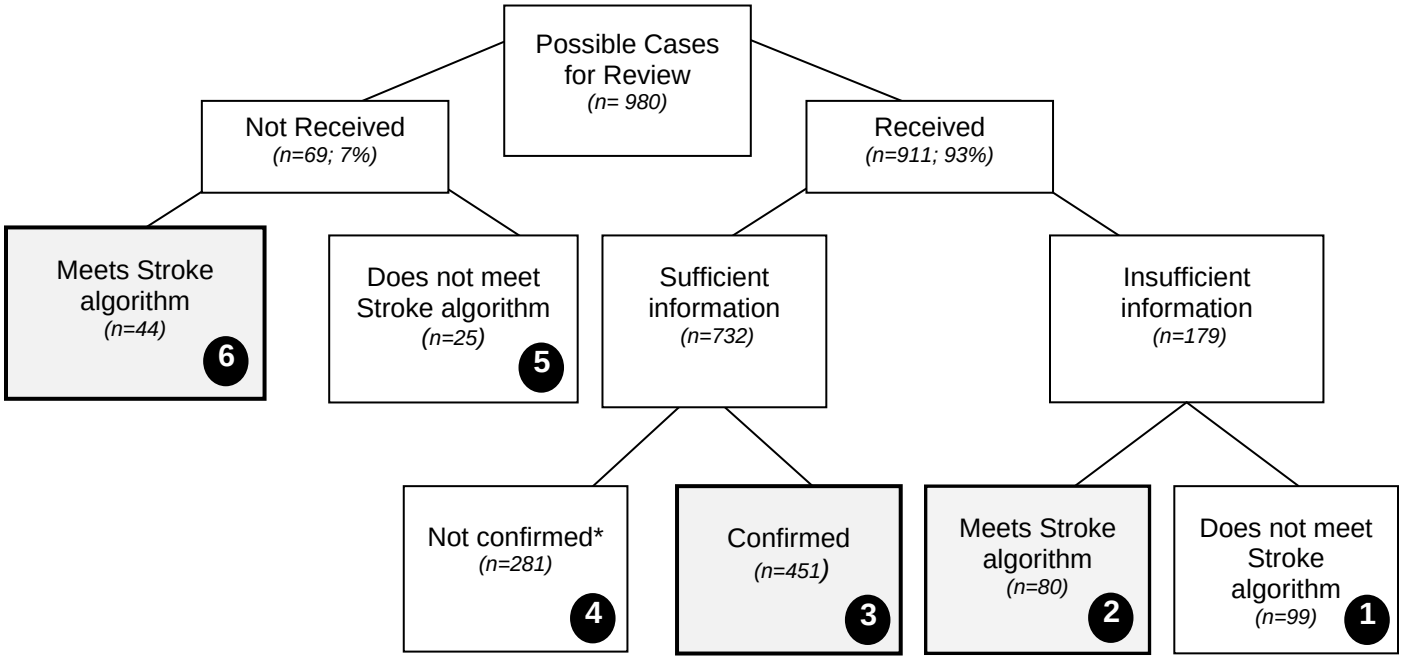
Table A-1. Case identification and adjudication by outcome

	Stroke	
	N	**%**
Total potential cases*	980	100 %
Electronic diagnosis/claims	954	
NDI search	13	
Both electronic record and NDI search	13	
Records requested	980	100 %
Records received[#]	911	93 %
Confirmed by records [a]	451	50 %
Not confirmed by records [a]	460	50 %
Inadequate information [b]	179	39 %
Evaluated and ruled out [b]	281	61 %

***** 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: STROKE Case Review Status, All sites

Note: Groups 2, 3 and 6 constitute analytic cases, groups 1 and 5 did not meet the stroke algorithm.



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

Reason for exclusion	Count
All	281
Carotid endarterectomy/ other procedure for stenosis	97
Transient ischemic attack (TIA), other transient symptoms (< 24 hours)	43
Old stroke/CVA (i.e., before t0)	22
Other head/brain condition/procedure	17
Trauma /injury	17
Syncope, fainting, dizziness, seizure	16
Negative imaging (by MRI)	15
Complications (including stroke) from surgery/procedure	14
Non- neurologic /non-brain/ non-vascular condition	11
Fever, infection	7
Other procedure (non-head/brain/neck)	6
Psychiatric or dementia, headache	6
Stenosis	5
Subdural hemorrhage	3
Vasculitis	2

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

Site	Person-yrs	Number events	Rate/1,000 person-yrs
Ingenix/I3	390461.8	168	0.50
KPNC	98921.4	71	0.61
KPSC	34316.0	29	0.77
Tennessee Medicaid	122570.1	210	1.82
HMORN	188987.9	97	
Fallon Community*	--	--	--
Group Health	42769.7	23	0.47
Harvard Pilgrim	67310.0	22	0.29
HealthPartners	32126.2	25	0.75
KP Colorado	19853.5	13	0.47
KP Mid-Atlantic*	--	--	--
KP Northwest	26928.4	14	0.41

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

Table A-2b. Rates of strokes by site (standardized to age and gender-distribution of all sites combined, NEW USERs only)

Site	Person-yrs	Number events	Rate/1,000 person-yrs
Ingenix/I3	218434.3	93	0.50
KPNC	54755.5	45	0.70
KPSC	19179.2	17	0.88
Tennessee Medicaid	115848.5	202	1.80
HMORN	95110.2	48	
Fallon Community*	--	--	--
Group Health	22128.7	10	0.46
Harvard Pilgrim	30964.0	12	0.37
HealthPartners	16477.9	15	0.91
KP Colorado	10131.1	5	0.35
KP Mid-Atlantic*	--	--	--
KP Northwest	15408.6	6	0.29

*****These sites did not contribute to the stroke 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%
Exposure					
Nonusers (N)	177,638	24,289	13,295	49,626	28,901
Current users (N)	88,868	12,150	6,652	30,725	14,470
New users (N)	52,665	7,899	4,350	18,001	13,956
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%
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 (t_0).
** Including medications
[#] Excluding ADHD visits
*** Excluding ADHD medications

Tables to examine heterogeneity of RRs by site

Table A-4a. Rate ratios **of ALL stroke** 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	0.68	0.41 - 1.14	0.53	0.23 - 1.23	1.07	0.39 - 2.99	1.23	0.76 - 2.00
Indeterminate user	0.87	0.47 - 1.59	1.03	0.39 - 2.69	1.04	0.23 - 4.81	0.54	0.22 - 1.32
Former user	1.03	0.57 - 1.87	1.03	0.39 - 2.72	1.53	0.41 - 5.66	0.96	0.54 - 1.72
Remote user	0.44	0.21 - 0.92	0.59	0.24 - 1.46	1.95	0.52 - 7.26	0.88	0.61 - 1.26
Nonuser	1.00	reference	1.00	reference	1.00	reference	1.00	reference

Adjusted for age, sex, calendar year, and other variables in Table A-5 (some variables are time-varying)

Table A-4b. Rate ratios **of ALL stroke** by site **(NEW USERs only)**

	I3		KPNC		KPSC		Tennessee Medicaid	
Medication status	**RR**	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**
ADHD medication users								
Current user	0.55	0.24 - 1.22	0.81	0.29 - 2.27	0.82	0.20 - 3.45	1.31	0.80 - 2.14
Indeterminate user	0.71	0.30 - 1.67	1.50	0.49 - 4.61	0.66	0.08 - 5.61	0.57	0.23 - 1.40
Former user	0.69	0.31 - 1.54	1.01	0.29 - 3.55	1.10	0.21 - 5.70	0.92	0.50 - 1.68
Remote user	0.14	0.03 - 0.57	0.70	0.23 - 2.14	2.33	0.54 - 10.1	0.89	0.62 - 1.29
Nonuser	1.00	reference	1.00	reference	1.00	reference	1.00	reference

Adjusted for age, sex, calendar year, and other variables in Table A-5 (some variables are time-varying)

Table A-5. Rate ratios of **ALL stroke – standard adjustment**

Variable in model	**Person-yrs**	**Number Events**	**Rate/1,000 person-yrs**	**RR***	**95% CI**
Exposure					
Amphetamines	48672.9	19	0.39	0.63	0.40-1.01
Methylphenidate	50332.3	39	0.77	0.96	0.69-1.35
Atomoxetine	8371.1	3	0.36	0.46	0.15-1.44
Pemoline	3030.1	2	0.66	0.59	0.15-2.38
Multiple	1529.2	0	0.00	0.00	--
Indeterminate	53327.8	31	0.58	0.82	0.57-1.20
Former	47333.0	39	0.82	0.99	0.71-1.39
Remote	69202.3	67	0.97	0.76	0.58-1.00
Non-user	553458.5	375	0.68	1.00	reference
Demographics					
Gender					
Male	382804.1	274	0.72	1.30	1.08-1.56
Female	452453.1	301	0.67	1.00	reference
Age					
25-29	55385.2	3	0.05	0.05	0.01-0.15
30-34	97070.3	22	0.23	0.18	0.11-0.30
35-39	120613.6	27	0.22	0.17	0.11-0.27
40-44	150095.3	52	0.35	0.25	0.18-0.36
45-49	156251.2	92	0.59	0.39	0.29-0.52
50-54	129590.9	125	0.96	0.55	0.43-0.72
55-59	83875.8	129	1.54	0.72	0.56-0.92
60-64	42375.0	125	2.95	1.00	reference
Site					
KPNC	98921.4	71	0.72	1.33	1.00-1.79
KPSC	34316.0	29	0.85	1.45	0.97-2.17
Tennessee Medicaid	122570.1	210	1.71	1.76	1.39-2.23
HMORN					
Group Health	42769.7	23	0.54	0.99	0.63-1.54
Harvard Pilgrim	67310.0	22	0.33	0.63	0.40-0.99
HealthPartners	32126.2	25	0.78	1.63	1.07-2.49
KP Colorado	19853.5	13	0.65	1.10	0.62-1.96
KP Northwest	26928.4	14	0.52	0.88	0.51-1.52
Ingenix/I3	390461.8	168	0.43	1.00	reference
Year					
2004-2005	375280.3	242	0.64	1.46	0.53-3.97
2002-2003	237850.0	166	0.70	1.67	0.61-4.58
2000-2001	143704.8	81	0.56	1.41	0.51-3.89
1993-1999	73189.4	82	1.12	2.23	0.81-6.12
1986-1992	5232.7	4	0.76	1.00	reference
Cardiovascular disease in 365 days prior to baseline **					
Acute MI, primary	858.9	3	3.49	0.85	0.27-2.70
Acute MI, other	1047.8	6	5.73	1.58	0.70-3.60
Hypertension	109604.2	233	2.13	1.50	1.22-1.84
***Use of cardiovascular drug in 365 days prior to baseline ** ***					
Anticoagulant	7378.3	46	6.23	2.15	1.55-2.99
Platelet inhibitor	4186.9	31	7.40	1.32	0.88-1.97

Medication utilization in 365 days prior to baseline **					
No. of different medications***					
1	161573.7	59	0.37	1.08	0.77-1.51
2	118379.3	60	0.51	1.27	0.90-1.79
3	85939.2	51	0.59	1.23	0.86-1.78
4	61886.9	53	0.86	1.53	1.05-2.21
5	45182.9	46	1.02	1.52	1.03-2.25
6	32137.0	44	1.37	1.84	1.23-2.76
7-8	39336.1	82	2.08	2.21	1.53-3.18
9-10	19725.1	41	2.08	1.71	1.10-2.66
11+	18306.6	59	3.22	1.78	1.14-2.78
Medical conditions, ever/never[$]					
Obesity	82380.8	112	1.36	1.13	0.90-1.41
Smoking	105102.2	154	1.47	1.19	0.97-1.46
Diabetes[##]	69124.9	195	2.82	1.96	1.60-2.41
TIA, primary	2860.5	40	13.98	1.92	1.33-2.78
TIA, other	16577.4	126	7.60	3.45	2.69-4.44
Hyperlipidemia[##]	201392.8	289	1.44	0.96	0.78-1.17
Peripheral vascular disease	13801.6	57	4.13	1.11	0.82-1.51
Other selected medical conditions, time-varying[$$]					
ETOH/substance abuse, primary	3698.8	4	1.08	1.11	0.41-2.99
ETOH/substance abuse, other	19850.9	29	1.46	1.49	1.01-2.19
Use of other selected medications, time-varying[$$]					
Triptans	4705.5	5	1.06	1.67	0.69-4.06
Oral contraceptives	42449.6	27	0.64	1.58	1.06-2.36
Hormones, menopausal	49331.7	63	1.28	1.04	0.78-1.39

*RRs adjusted for site, age, sex, calendar year, exposure, and each of the other variables in the table
**At baseline or cohort entry (t_0): if 'on' at baseline, remains on; if 'off' at baseline but goes 'on' during follow-up, stays off
*** 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'
*RRs adjusted for all other variables in the table; All variables except the utilization variable, no. of different medications, are must-haves. Only the utilization variable earned its way in using the 10% change in RR rule.

Comparison of RRs by Adjustment Method

Table A-6a. RR of ALL Strokes, by use of ADHD Medications

	Unadjusted		Adjusted (matching variables)		Adjusted (standard)		Adjusted (Propensity Score)		Adjusted (Stroke Risk Score)	
Current User	0.83	0.64 - 1.08	0.96	0.73 - 1.25	0.77	0.59 - 1.02	0.75	0.55 - 1.00	0.76	0.58 - 1.00
Indeterminate	0.86	0.59 - 1.24	1.02	0.71 - 1.48	0.82	0.57 - 1.20	0.81	0.55 - 1.19	0.83	0.57 - 1.19
Former	1.22	0.87 - 1.69	1.32	0.95 - 1.84	0.99	0.71 - 1.40	1.05	0.74 - 1.49	1.01	0.73 - 1.41
Remote	1.43	1.10 - 1.85	1.06	0.82 - 1.38	0.76	0.58 - 1.00	0.88	0.66 - 1.17	0.82	0.63 - 1.07
Nonuser	1.00	reference	1.00	reference	1.00	reference	1.00	reference	1.00	reference

Table A-6b. RR of ALL Strokes, by use of ADHD Medications (NEW USERS only)

	Unadjusted		Adjusted (matching variables)		Adjusted (standard)		Adjusted (Propensity Score)		Adjusted (Stroke Risk Score)	
Current User	0.94	0.68 - 1.31	1.12	0.81 - 1.56	0.79	0.56 - 1.12	0.89	0.61 - 1.28	0.87	0.62 - 1.21
Indeterminate	0.82	0.52 - 1.29	1.02	0.64 - 1.60	0.71	0.45 - 1.13	0.82	0.51 - 1.33	0.80	0.50 - 1.26
Former	0.94	0.63 - 1.41	1.08	0.72 - 1.61	0.74	0.49 - 1.11	0.88	0.57 - 1.35	0.83	0.55 - 1.24
Remote	1.28	0.96 - 1.71	1.02	0.76 - 1.36	0.72	0.54 - 0.98	0.86	0.63 - 1.18	0.80	0.59 - 1.07
Nonuser	1.00	reference	1.00	reference	1.00	reference	1.00	reference	1.00	reference

Comparison of RRs by Adjustment Method

For analyses with Composite Endpoint: Stroke, MI or SCD

Table A-7a. RR of ALL MI or SCD or Strokes, by use of ADHD Medications

	Unadjusted		Adjusted (matching variables)		Adjusted (standard)		Adjusted (Propensity Score)		Adjusted (Stroke Risk Score)	
Current User	0.84	0.73 - 0.96	0.97	0.84 - 1.12	0.80	0.69 - 0.92	0.81	0.69 - 0.94	0.83	0.72 - 0.96
Indeterminate	0.93	0.77 - 1.11	1.11	0.92 - 1.33	0.90	0.75 - 1.09	0.93	0.77 - 1.13	0.94	0.78 - 1.13
Former	1.01	0.84 - 1.21	1.07	0.89 - 1.29	0.83	0.68 - 1.00	0.91	0.75 - 1.10	0.86	0.72 - 1.04
Remote	1.38	1.21 - 1.58	1.02	0.88 - 1.17	0.76	0.66 - 0.87	0.88	0.76 - 1.01	0.81	0.70 - 0.93
Nonuser	1.00	reference	1.00	reference	1.00	reference	1.00	reference	1.00	reference

Table A-7b. RR of ALL MI or SCD or Strokes, by use of ADHD Medications (NEW USERS only)

	Unadjusted		Adjusted (matching variables)		Adjusted (standard)		Adjusted (Propensity Score)		Adjusted (Stroke Risk Score)	
Current User	0.80	0.66 - 0.96	0.96	0.80 - 1.16	0.68	0.56 - 0.82	0.77	0.63 - 0.94	0.77	0.64 - 0.93
Indeterminate	0.92	0.73 - 1.15	1.14	0.91 - 1.43	0.80	0.63 - 1.01	0.94	0.74 - 1.19	0.92	0.73 - 1.16
Former	0.95	0.77 - 1.17	1.08	0.87 - 1.33	0.74	0.60 - 0.91	0.89	0.72 - 1.11	0.84	0.68 - 1.03
Remote	1.22	1.05 - 1.43	0.96	0.82 - 1.12	0.72	0.61 - 0.84	0.81	0.68 - 0.95	0.76	0.65 - 0.88
Nonuser	1.00	reference	1.00	reference	1.00	reference	1.00	reference	1.00	reference

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