

Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Description of Kaiser Permanente Postal Survey

Participants in the Research Program in Genes, Environment and Health (RPGEH) cohort were initially enrolled through completion of a mailed survey of all adult members of KPNC (~1.9 million) conducted in 2007. Survey materials in English, Spanish, and Chinese described the RPGEH and invited participation. The six-page survey, with pre-specified categorical responses for most questions, asked for information on demographic factors (e.g., education, race-ethnicity, income, and marital status); indicators for self- and family history of the occurrence of about 35 conditions and diseases; behavioral factors, including a diet, physical activity, smoking, and alcohol consumption; and reproductive history for women, as well as urinary and reproductive health for men. Approximately 393,000 (21% response) men and women completed the survey. Survey response rates were higher among older compared with younger individuals (average age of survey respondents is 65 years); women responded at higher rates than men (64% of respondents were women). Non-Hispanic White individuals responded at higher rates than non-white individuals. Approximately 12% reported their race or ethnicity as Asian; 6.8% were African American; 9% were Hispanic or Latino; 4.9% were designated “Other” or “Missing”, and 67% of respondents reported their race or ethnicity as non-Hispanic White.

eTable 1. ICD Codes Used to Identify Potential Serious Cardiovascular Events

Event	ICD codes	
	ICD-9 codes	ICD-10 codes
MI	410.x	I21.x, I22.x
SCD		
Death certificate (underlying cause of death)		
Any cardiac system cause of death	390-429 (402.9 ^a , 414.0 ^a , 414.9 ^a , 425.4 ^a , 429.2 ^a)	I01, I05-09, I11(I11.9 ^a), I13, I20-I52 (I20.1 ^a , I25.0 ^a , I25.1 ^a , I25.5 ^a , I42.9 ^a , I46.1 ^a , I46.9 ^a , I49.9 ^a , I51.9 ^a)
Congenital cardiac anomaly	745-746	Q20-28
Collapse	780.2	R55
Sudden death, unknown cause	798.0-798.9 (798.2 ^a , 798.9 ^a)	R96
Respiratory arrest	799.1	R09.2
Death from ill-defined condition	799.8	R98
Unknown cause of death	799.9	R99
Hospitalization (primary diagnosis) with death		
Cardiac arrest	427.5 ^a	
Ventricular fibrillation, flutter or tachycardia	427.4x (427.41 ^a), 427.1	
Collapse ^b	780.2	
Sudden death, unknown cause ^b	798.0-798.9 (798.2 ^a , 798.9 ^a)	
Respiratory arrest ^b	799.1	
Resuscitated cardiac arrests (primary hospital discharge with discharge status other than dead)		
Cardiac arrest	427.5 ^a	
Ventricular fibrillation, flutter or tachycardia ^c	427.4x (427.41 ^a), 427.1	
Stroke		
Subarachnoid hemorrhage	430 ^a	I60
Intracerebral hemorrhage	431 ^a	I61, I64
Non-traumatic extradural hemorrhage	432.0	I62.1
Subdural hemorrhage	432.1	
Unspecified intracranial hemorrhage	432.9 ^a	I62.0, I62.9
Occlusion and stenosis of precerebral arteries	433.00, 433.01 ^a , 433.10, 433.11 ^a , 433.20, 433.21 ^a , 433.30, 433.31	I65
Occlusion of cerebral arteries	434.00, 434.01 ^a , 434.10 ^a , 434.11 ^a , 434.9 ^a , 434.90 ^a , 434.91 ^a	I63, I66
Acute, but ill-defined, cerebrovascular disease	436	I67, I68

Abbreviations: MI, myocardial infarction; ICD, International Classification of Diseases; SCD, sudden cardiac death

^aUsed in ICD-9/10 code-based definition (for those without sufficient records for adjudication).

^bMust be accompanied by a secondary diagnosis of cardiac disease (ICD-9 codes 390-429).

^cFor non-fatal hospitalizations, ventricular tachycardia diagnoses, but not ventricular fibrillation or flutter, must be accompanied by secondary discharge diagnosis of cardiac arrest.

eTable 2A. Identification and Disposition of Potential Serious Cardiovascular Events

	Sudden cardiac death		Myocardial infarction		Stroke	
	N	%	N	%	N	%
Potential cases- method of identification^a	411	100 %	1,375	100 %	980	100 %
Electronic diagnosis/claims	56	14 %	1,247	91 %	954	97 %
NDI search	268	65 %	107	8 %	13	1 %
Both electronic record and NDI search	87	21 %	21	2 %	13	1 %
Records requested	411	100 %	433	100 %	980	100 %
Records not received (1)	106	26 %	23	5 %	69	7 %
Records received ^b	305	74 %	410	95 %	911	93 %
Clinical Adjudication	305	100 %	410	100%	911	100 %
Confirmed as case ^c	139	46 %	353	86 %	451	50 %
Not confirmed as case ^c	166	54 %	57	14 %	460	50 %
Not confirmed as case	166	100 %	57	100 %	460	100 %
Inadequate information ^d (2)	97	58 %	39	68 %	179	39 %
Evaluated and ruled out (non-case) ^d	64	39 %	18	32 %	281	61 %
Not a death/arrest (non-case) ^d	5	3 %	--	--	--	--
With no or inadequate records (1) + (2)	203	100 %	--	--	248	100 %
Meets algorithm	157	77 %	--	--	124	50 %
Does not meet algorithm	46	23 %	--	--	124	50 %
Cases confirmed by clinical adjudication	139	46 %	353	86 %	451	50 %
Cases with insufficient records meeting algorithm	157	77 %	--	--	124	50 %
Final cases in primary analyses (confirmed by adjudication or meets algorithm)	296	72%	1,357^e	99%	575	59 %

Abbreviations: NDI, National Death Index; MI, myocardial infarction
^aCases identified from electronic diagnosis/claims and NDI searches.
^bReceived includes emergency department records, inpatient records, autopsy records, and death certificates.
^cPercent of records received
^dPercent of records not confirmed
^eIncludes all MIs identified from electronic records except those determined to be non-cases by clinical adjudication

eTable 2B. Disposition of Excluded Serious Cardiovascular Events

Reasons for exclusion for MI	N
All	18
Ruled out: symptomatic, test negative	14
Miscode/other diagnosis	4
Reasons for exclusion for SCD	
All	69
Cardiac death, non-arrhythmic	22
Miscode	4
Procedure-related	2
Overdose	7
Injury/accident	2
Drowning	1
Non-cardiac death, other	26
Non-death, non-cardiac	5
Reasons for exclusion for stroke	
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 t ₀)	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

Abbreviations: MI, myocardial infarction; SCD, sudden cardiac death; CVA, cerebrovascular accident; MRI, magnetic resonance imaging

eTable 3. Characteristics of Person-Time (After Baseline), by Medication Use

Characteristic	Current Use (N= 149,821)		Indeterminate Use (N= 137,574)		Former Use (N= 78,324)		Remote Use (N = 38,622)		Nonuse (N= 282,812)	
	Person-yr ^a	%	Person-yr ^a	%	Person-yr ^a	%	Person-yr ^a	%	Person-yr ^a	%
Total	107,322.4	13.3%	51,709.6	6.4%	46,120.8	5.7%	67,489.0	8.4%	533,540.4	66.2%
Demographics										
Gender										
Male	49,174.2	45.8%	23,408.6	45.3%	21,215.3	46.0%	31,463.2	46.6%	244,056.7	45.7%
Female	58,148.2	54.2%	28,301.0	54.7%	24,905.5	54.0%	36,025.8	53.4%	289,483.7	54.3%
Age										
25-29	8,286.7	7.7%	4,475.3	8.7%	3,491.5	7.6%	2,137.6	3.2%	35,939.1	6.7%
30-34	12,241.0	11.4%	6,718.7	13.0%	6,205.3	13.5%	6,993.2	10.4%	62,254.9	11.7%
35-39	14,663.3	13.7%	7,647.3	14.8%	7,251.2	15.7%	10,182.8	15.1%	77,495.5	14.5%
40-44	18,916.0	17.6%	9,269.4	17.9%	8,518.2	18.5%	12,896.4	19.1%	95,977.6	18.0%
45-49	20,635.7	19.2%	9,405.8	18.2%	8,287.8	18.0%	12,998.5	19.3%	99,655.9	18.7%
50-54	17,035.8	15.9%	7,461.9	14.4%	6,319.0	13.7%	10,778.9	16.0%	82,443.1	15.5%
55-59	10,702.0	10.0%	4,613.8	8.9%	4,012.4	8.7%	7,169.8	10.6%	53,140.8	10.0%
60-64	4,841.9	4.5%	2,117.4	4.1%	2,035.4	4.4%	4,331.8	6.4%	26,633.5	5.0%
Site										
KPNC	14,076.0	13.1%	5,138.1	9.9%	4,876.1	10.6%	7,974.3	11.8%	66,565.0	12.5%
KPSC	5,703.9	5.3%	1,983.2	3.8%	1,905.4	4.1%	1,545.0	2.3%	23,120.0	4.3%
Tennessee Medicaid	8,812.3	8.2%	5,411.8	10.5%	7,524.7	16.3%	20,426.0	30.3%	79,603.0	14.9%
HMORN										
Group Health	6,463.8	6.0%	2,415.6	4.7%	1,753.2	3.8%	2,579.7	3.8%	29,421.0	5.5%
Harvard Pilgrim	9,915.7	9.2%	4,423.0	8.6%	3,210.1	7.0%	3,779.8	5.6%	45,842.0	8.6%
HealthPartners	4,349.4	4.1%	1,706.9	3.3%	1,246.6	2.7%	1,504.9	2.2%	23,202.0	4.3%
KPCO	3,109.6	2.9%	1,131.6	2.2%	917.9	2.0%	1,448.5	2.1%	13,195.0	2.5%
OptumInsight	54,892.0	51.1%	29,499.0	57.0%	24,687.0	53.5%	28,231.0	41.8%	252,591.0	47.3%
Year										

Characteristic	Current Use (N= 149,821)		Indeterminate Use (N= 137,574)		Former Use (N= 78,324)		Remote Use (N = 38,622)		Nonuse (N= 282,812)	
	Person-yr ^a	%	Person-yr ^a	%	Person-yr ^a	%	Person-yr ^a	%	Person-yr ^a	%
2004-2005	49,986.0	46.6%	23,194.0	44.9%	19,997.0	43.4%	29,816.0	44.2%	238,947.0	44.8%
2002-2003	30,868.0	28.8%	13,825.0	26.7%	10,903.0	23.6%	21,920.0	32.5%	151,671.0	28.4%
2000-2001	16,753.0	15.6%	9,456.0	18.3%	10,805.0	23.4%	9,417.0	14.0%	91,905.0	17.2%
1993-1999	9,511.1	8.9%	5,024.9	9.7%	4,057.0	8.8%	5,427.1	8.0%	47,483.0	8.9%
1986-1992	205.2	0.2%	209.9	0.4%	358.8	0.8%	908.8	1.3%	3,534.8	0.7%
ADHD at baseline^b	37,564.9	35.0%	15,056.7	29.1%	9,662.7	21.0%	9,545.3	14.1%	556.2	0.1%
Cardiovascular disease at baseline^b										
Acute myocardial infarction	178.7	0.2%	96.9	0.2%	100.9	0.2%	153.2	0.2%	1,275.3	0.2%
Ischemia	2,320.4	2.2%	1,246.9	2.4%	1,339.1	2.9%	2,142.5	3.2%	12,179.0	2.3%
Coronary revascularization	147.9	0.1%	72.9	0.1%	83.0	0.2%	160.4	0.2%	1,196.5	0.2%
Congestive heart failure	599.2	0.6%	320.9	0.6%	368.0	0.8%	630.2	0.9%	2,911.1	0.5%
Arrhythmia	2,223.8	2.1%	1,149.5	2.2%	1,119.4	2.4%	1,768.9	2.6%	8,966.5	1.7%
Hypertension	14,479.1	13.5%	6,989.4	13.5%	6,861.1	14.9%	10,264.7	15.2%	67,797.0	12.7%
Use of cardiovascular drug at baseline^b										
Loop diuretic	2,779.1	2.6%	1,385.5	2.7%	1,503.4	3.3%	2,762.0	4.1%	9,274.7	1.7%
Digoxin	405.4	0.4%	200.8	0.4%	221.4	0.5%	515.1	0.8%	2,390.2	0.4%
Nitrates	1,196.6	1.1%	632.3	1.2%	734.9	1.6%	1,424.2	2.1%	6,820.6	1.3%
Anticoagulant	1,059.3	1.0%	542.4	1.0%	548.0	1.2%	844.8	1.3%	4,132.9	0.8%
Platelet inhibitor	502.5	0.5%	287.8	0.6%	321.0	0.7%	424.0	0.6%	2,504.8	0.5%
Anti-arrhythmic agents	340.2	0.3%	160.5	0.3%	173.1	0.4%	314.1	0.5%	1,194.4	0.2%
ACE inhibitor	7,080.4	6.6%	3,354.2	6.5%	3,329.2	7.2%	4,933.9	7.3%	34,858.0	6.5%
Angiotensin receptor blocker	1,935.9	1.8%	1,014.9	2.0%	930.7	2.0%	801.2	1.2%	7,589.5	1.4%
Beta-blocker	8,373.1	7.8%	3,953.6	7.6%	3,922.8	8.5%	6,055.1	9.0%	34,341.5	6.4%
Calcium-channel blocker	4,754.2	4.4%	2,371.2	4.6%	2,416.7	5.2%	4,296.6	6.4%	23,279.9	4.4%
Thiazide diuretic	8,546.5	8.0%	3,999.4	7.7%	3,684.2	8.0%	5,041.4	7.5%	34,384.4	6.4%
Other antihypertensive	1,250.7	1.2%	581.5	1.1%	589.4	1.3%	1,074.8	1.6%	4,550.0	0.9%
Utilization at baseline^b										
Cardiovascular visits										
Emergency, 1+	3,369.5	3.1%	1,804.8	3.5%	2,128.6	4.6%	3,423.7	5.1%	14,642.6	2.7%
Inpatient, 1+	3,463.2	3.2%	1,838.2	3.6%	2,052.6	4.5%	3,305.5	4.9%	12,324.1	2.3%
Physician, 1-4	29,248.3	27.3%	14,279.3	27.6%	12,937.1	28.1%	18,696.5	27.7%	115,197.5	21.6%

Characteristic	Current Use (N= 149,821)		Indeterminate Use (N= 137,574)		Former Use (N= 78,324)		Remote Use (N = 38,622)		Nonuse (N= 282,812)	
	Person-yr ^a	%	Person-yr ^a	%	Person-yr ^a	%	Person-yr ^a	%	Person-yr ^a	%
		%				%				
Physician, 5+	7,952.7	7.4%	4,110.6	7.9%	4,251.5	9.2%	6,448.1	9.6%	30,873.7	5.8%
Psychiatric visits^c										
Emergency, 1+	2,533.4	2.4%	1,324.6	2.6%	1,706.4	3.7%	2,917.2	4.3%	5,665.6	1.1%
Inpatient, 1+	4,776.4	4.5%	2,374.0	4.6%	2,800.2	6.1%	4,996.4	7.4%	6,920.2	1.3%
Physician, 1-4	31,727.4	29.6%	14,428.9	27.9%	12,187.1	26.4%	16,366.3	24.3%	47,137.7	8.8%
Physician, 5+	28,716.7	26.8%	12,988.0	25.1%	12,112.7	26.3%	17,325.5	25.7%	21,401.0	4.0%
Other visits										
Emergency, 1+	4,982.4	4.6%	2,630.3	5.1%	2,967.6	6.4%	4,757.1	7.0%	19,279.6	3.6%
Inpatient, 1+	3,364.0	3.1%	1,726.1	3.3%	1,981.6	4.3%	3,356.5	5.0%	9,904.8	1.9%
Physician, 1+	37,665.8	35.1%	18,196.8	35.2%	16,925.9	36.7%	24,984.2	37.0%	124,378.8	23.3%
No. of different medications^d										
1	17,180.1	16.0%	8,474.3	16.4%	7,092.5	15.4%	10,415.8	15.4%	113,144.6	21.2%
2	16,734.8	15.6%	8,107.4	15.7%	6,875.9	14.9%	9,810.4	14.5%	72,609.6	13.6%
3	14,222.2	13.3%	6,759.8	13.1%	5,846.8	12.7%	8,343.0	12.4%	47,365.8	8.9%
4	11,371.7	10.6%	5,381.4	10.4%	4,763.0	10.3%	7,098.0	10.5%	30,903.7	5.8%
5	8,992.8	8.4%	4,123.9	8.0%	3,783.6	8.2%	5,649.6	8.4%	20,801.0	3.9%
6	6,768.3	6.3%	3,221.8	6.2%	2,966.3	6.4%	4,531.6	6.7%	13,370.5	2.5%
7-8	8,925.5	8.3%	4,172.1	8.1%	4,115.0	8.9%	6,305.1	9.3%	14,304.7	2.7%
9-10	4,764.9	4.4%	2,252.2	4.4%	2,283.3	5.0%	3,285.2	4.9%	6,365.7	1.2%
11+	4,648.9	4.3%	2,249.0	4.3%	2,528.3	5.5%	3,322.9	4.9%	4,990.9	0.9%
Medical conditions, ever/never^e										
Obesity	10,845.7	10.1%	4,820.0	9.3%	4,939.3	10.7%	11,221.7	16.6%	46,320.0	8.7%
Smoking	13,489.8	12.6%	5,791.2	11.2%	6,373.8	13.8%	14,670.8	21.7%	58,244.0	10.9%
Diabetes ^f	7,594.4	7.1%	3,691.6	7.1%	3,887.0	8.4%	9,225.6	13.7%	42,165.3	7.9%
Stroke/TIA	1,970.2	1.8%	1,005.1	1.9%	1,194.2	2.6%	3,436.3	5.1%	9,381.2	1.8%
Hyperlipidemia ^f	26,571.0	24.8%	12,762.9	24.7%	12,370.4	26.8%	24,518.6	36.3%	119,329.8	22.4%

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	Person-yr ^a	%	Person-yr ^a	%	Person-yr ^a	%	Person-yr ^a	%	Person-yr ^a	%
Congenital heart disorder	371.0	0.3%	207.9	0.4%	232.8	0.5%	655.2	1.0%	2,284.7	0.4%
Coronary artery anomaly	64.7	0.1%	36.1	0.1%	40.0	0.1%	124.4	0.2%	386.4	0.1%
Peripheral vascular disease	1,730.3	1.6%	799.2	1.5%	827.7	1.8%	2,310.6	3.4%	7,540.5	1.4%
Mental health claims, time-varying^g										
Major depression	45,642.2	42.5%	20,608.2	39.9%	17,895.6	38.8%	20,063.3	29.7%	45,863.5	8.6%
Bipolar disorder	8,501.1	7.9%	3,904.3	7.6%	4,095.6	8.9%	5,181.6	7.7%	5,880.4	1.1%
Anxiety	20,389.9	19.0%	9,570.1	18.5%	9,032.1	19.6%	10,690.0	15.8%	30,632.9	5.7%
Psychotic disorders	1,814.8	1.7%	878.7	1.7%	1,154.4	2.5%	2,321.8	3.4%	5,741.7	1.1%
Other selected medical conditions, time-varying^g										
Alcohol/substance abuse	5,076.5	4.7%	2,358.2	4.6%	2,695.5	5.8%	3,295.8	4.9%	9,248.8	1.7%
Suicide attempt	445.7	0.4%	233.8	0.5%	285.4	0.6%	366.3	0.5%	887.2	0.2%
Injury	20,643.6	19.2%	10,029.1	19.4%	9,307.2	20.2%	13,142.4	19.5%	68,973.3	12.9%
Seizure	2,010.6	1.9%	1,015.2	2.0%	1,173.0	2.5%	2,150.2	3.2%	7,043.9	1.3%
Asthma	8,245.0	7.7%	4,033.4	7.8%	3,657.1	7.9%	5,513.5	8.2%	24,354.6	4.6%
Use of psychotropic medications, time-varying^g										
Antipsychotic, any	5,658.7	5.3%	1,896.8	3.7%	2,076.4	4.5%	4,158.0	6.2%	6,980.9	1.3%
Tricyclic antidepressant	4,269.5	4.0%	1,632.9	3.2%	1,632.4	3.5%	3,085.0	4.6%	9,250.4	1.7%
Antidepressants, other or SSRI/SNRI	42,370.8	39.5%	14,860.2	28.7%	12,186.3	26.4%	17,394.0	25.8%	40,600.0	7.6%
Benzodiazepines	14,849.1	13.8%	5,348.8	10.3%	5,134.7	11.1%	8,330.4	12.3%	18,342.3	3.4%
Lithium	1,485.0	1.4%	591.3	1.1%	610.0	1.3%	890.6	1.3%	1,489.5	0.3%
Modafinil	1,146.1	1.1%	633.8	1.2%	860.7	1.9%	1,116.7	1.7%	333.6	0.1%
Insomnia medications	4,047.0	3.8%	1,584.2	3.1%	1,377.8	3.0%	1,723.3	2.6%	3,375.5	0.6%
Thioridazine	86.4	0.1%	34.2	0.1%	45.7	0.1%	181.8	0.3%	407.3	0.1%
Mood stabilizers, w/o seizure	9,038.4	8.4%	3,212.0	6.2%	3,086.5	6.7%	4,868.1	7.2%	7,798.1	1.5%
Clonidine/guanfacine, w/o HT	530.1	0.5%	139.6	0.3%	94.2	0.2%	144.7	0.2%	394.2	0.1%
Use of other selected medications, time-varying^g										
Beta-agonist	3,116.7	2.9%	1,256.0	2.4%	1,157.8	2.5%	2,149.3	3.2%	9,413.1	1.8%
Epinephrine	63.4	0.1%	26.6	0.1%	26.1	0.1%	32.6	0.0%	149.0	0.0%
Asthma medications, other	6,939.2	6.5%	2,852.9	5.5%	2,603.3	5.6%	4,238.4	6.3%	19,084.2	3.6%

Characteristic	Current Use (N= 149,821)		Indeterminate Use (N= 137,574)		Former Use (N= 78,324)		Remote Use (N = 38,622)		Nonuse (N= 282,812)	
	Person-yr ^a	%	Person-yr ^a	%	Person-yr ^a	%	Person-yr ^a	%	Person-yr ^a	%
Seizure medications	10,209.1	9.5%	3,717.1	7.2%	3,679.2	8.0%	6,190.7	9.2%	12,057.8	2.3%
Theophylline compounds	271.0	0.3%	135.3	0.3%	149.7	0.3%	443.4	0.7%	1,442.1	0.3%
COX-2 inhibitors	2,300.5	2.1%	931.1	1.8%	820.1	1.8%	1,492.2	2.2%	5,289.0	1.0%
Other drugs to improve blood flow	50.7	0.0%	21.1	0.0%	24.5	0.1%	74.1	0.1%	249.1	0.0%
Clonidine	815.8	0.8%	262.7	0.5%	241.7	0.5%	496.0	0.7%	1,987.4	0.4%
pde5 inhibitors	1,241.7	1.2%	396.5	0.8%	317.8	0.7%	460.0	0.7%	2,271.2	0.4%
Triptans	1,263.7	1.2%	484.6	0.9%	397.3	0.9%	520.1	0.8%	1,800.4	0.3%
Oral contraceptives	6,747.2	6.3%	3,015.6	5.8%	2,341.8	5.1%	2,875.2	4.3%	25,795.1	4.8%
Hormones, menopausal	8,637.9	8.0%	3,511.9	6.8%	3,030.6	6.6%	4,799.0	7.1%	26,811.2	5.0%
Cardiovascular Risk Score^h										
decile 1 (rate/1,000 pyr= 0.92)	23,146.4	21.6%	10,962.0	21.2%	9,018.2	19.6%	11,919.5	17.7%	198,686.2	37.2%
decile 2 (rate/1,000 pyr= 1.10)	19,234.4	17.9%	9,682.9	18.7%	8,060.6	17.5%	9,768.2	14.5%	93,651.1	17.6%
decile 3 (rate/1,000 pyr= 1.28)	13,224.8	12.3%	6,489.3	12.5%	5,472.0	11.9%	6,828.7	10.1%	50,797.0	9.5%
decile 4 (rate/1,000 pyr= 1.49)	11,419.8	10.6%	5,617.7	10.9%	4,731.8	10.3%	6,409.9	9.5%	45,804.0	8.6%
decile 5 (rate/1,000 pyr= 2.24)	9,375.3	8.7%	4,423.8	8.6%	3,971.6	8.6%	5,688.7	8.4%	31,782.5	6.0%
decile 6 (rate/1,000 pyr= 2.55)	8,259.3	7.7%	3,856.5	7.5%	3,561.4	7.7%	5,345.7	7.9%	28,300.0	5.3%
decile 7 (rate/1,000 pyr= 3.46)	7,269.0	6.8%	3,411.0	6.6%	3,302.6	7.2%	5,388.3	8.0%	25,439.9	4.8%
decile 8 (rate/1,000 pyr= 5.08)	6,504.3	6.1%	2,966.1	5.7%	3,018.5	6.5%	5,392.2	8.0%	22,297.2	4.2%
decile 9 (rate/1,000 pyr= 8.46)	5,294.4	4.9%	2,504.2	4.8%	2,682.7	5.8%	5,404.1	8.0%	20,531.7	3.8%
decile 10 (rate/1,000 pyr= 20.25)	3,594.7	3.3%	1,796.0	3.5%	2,301.4	5.0%	5,343.8	7.9%	16,250.8	3.0%

Abbreviations: KPNC, Kaiser Permanente Northern California; KPSC, Kaiser Permanente Southern California; HMORN, Health Maintenance Organization Research Network; KPCO, Kaiser Permanente Colorado; ADHD, attention deficit hyperactivity disorder; MI, myocardial infarction; SCD, sudden cardiac death; ACE, angiotensin-converting enzyme; TIA, transient ischemic attack; SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin and norepinephrine reuptake inhibitors; w/o, without; HT, hypertension; COX, cyclooxygenase; pde5, phosphodiesterase type 5; pyr, person-years

^aBased on time to first event (MI, SCD, or stroke); Numbers are for unique individuals for all sites except the three HMORN sites (Fallon Community, KP Georgia, KP Northwest) that did not provide data on SCD and/or stroke endpoints

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

^cExcluding ADHD visits

^dExcluding ADHD medications

^eEver/never: once 'on' at baseline or during follow-up, remains on

^fIncluding medications

^gDiagnosis: 'on' if any day in prior 365 is 'on', else 'off'; Meds: 'on' if has supply on the day, else 'off'

^hIncludes all variables in table except demographics.

eTable 4. Adjusted Rate Ratios for Serious Cardiovascular Events Associated With Use vs Nonuse of Attention-Deficit/Hyperactivity Disorder Medications

Medication Status	Person- Years	Number of Events	Rate/1000 Person-Years	Adjusted RR (95% CI) ^a
MI				
Current use	113324.2	152	1.34	0.88 (0.74 - 1.05)
Amphetamines	49080.1	59	1.20	0.92 (0.70 - 1.19)
Methylphenidate	51232.8	77	1.50	0.89 (0.71 - 1.13)
Atomoxetine	8424.8	11	1.31	0.87 (0.48 - 1.57)
Pemoline	3047.3	5	1.64	0.71 (0.29 - 1.71)
Multiple	1539.1	0	0.00	NA
Indeterminate use	53896.7	86	1.60	1.07 (0.85 - 1.33)
Former use	47858.5	65	1.36	0.78 (0.61 - 1.00)
Remote use	69792.9	147	2.11	0.82 (0.68 - 0.97)
Nonuse	559743.1	907	1.62	1 [Reference]
SCD^b				
Current use	107525.0	32	0.30	0.80 (0.55 - 1.18)
Amphetamines	46910.0	13	0.28	0.93 (0.52 - 1.63)
Methylphenidate	47887.1	13	0.27	0.67 (0.38 - 1.18)
Atomoxetine	8257.6	4	0.48	1.04 (0.38 - 2.82)
Pemoline	2995.7	2	0.67	1.08 (0.27 - 4.37)
Multiple	1474.5	0	0.00	NA
Indeterminate use	51814.0	14	0.27	0.73 (0.42 - 1.26)
Former use	46263.5	20	0.43	0.90 (0.57 - 1.44)
Remote use	68102.6	50	0.73	0.98 (0.71 - 1.35)
Nonuse	535515.5	180	0.34	1 [Reference]
Stroke^c				
Current use	111935.5	63	0.56	0.76 (0.58 - 1.00)
Amphetamines	48672.9	19	0.39	0.63 (0.40 - 1.01)
Methylphenidate	50332.3	39	0.77	0.94 (0.68 - 1.32)
Atomoxetine	8371.1	3	0.36	0.44 (0.14 - 1.38)
Pemoline	3030.1	2	0.66	0.59 (0.15 - 2.39)
Multiple	1529.2	0	0.00	NA
Indeterminate use	53327.8	31	0.58	0.83 (0.57 - 1.19)
Former use	47333.0	39	0.82	1.01 (0.73 - 1.41)
Remote use	69202.3	67	0.97	0.82 (0.63 - 1.07)
Nonuse	553458.5	375	0.68	1 [Reference]
MI, SCD or Stroke^{b,c}				

Current use	107322.4	234	2.18	0.83 (0.72 - 0.96)
Amphetamines	46826.5	88	1.88	0.85 (0.68 - 1.05)
Methylphenidate	47792.3	120	2.51	0.87 (0.72 - 1.04)
Atomoxetine	8248.2	17	2.06	0.74 (0.46 - 1.19)
Pemoline	2985.2	9	3.01	0.75 (0.39 - 1.45)
Multiple	1470.1	0	0.00	NA
Indeterminate use	51709.6	125	2.42	0.94 (0.78 - 1.13)
Former use	46120.8	121	2.62	0.86 (0.72 - 1.04)
Remote use	67489.0	243	3.60	0.81 (0.70 - 0.93)
Nonuse	533540.4	1391	2.61	1 [Reference]

Abbreviations: MI, myocardial infarction; NA, not applicable; RR, rate ratio; SCD, sudden cardiac death.

^aAdjusted for site, age, sex, calendar year, and cardiovascular risk score (some variables within score are time-varying).

^bAnalyses excluded the 3 Health Maintenance Organization Research Network (HMORN) sites (Fallon Community, Kaiser Permanente [KP] Georgia, KP Northwest) that did not provide data on SCD end points.

^cAnalyses excluded the 2 HMORN sites (Fallon Community, KP Georgia) that did not provide data on stroke end points.

eTable 5A. 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^a	95% CI	Adjusted RR^b	95% CI
Current use	111,935.5	46	0.41	0.86	0.63 - 1.18	1.00	0.73 - 1.37	1.08	0.79 - 1.49
Amphetamines	48,672.9	13	0.27	0.56	0.32 - 0.98	0.74	0.43 - 1.30	0.75	0.42 - 1.33
Methylphenidate	50,332.3	29	0.58	1.21	0.82 - 1.77	1.29	0.87 - 1.89	1.60	1.08 - 2.38
Atomoxetine	8,371.1	2	0.24	0.50	0.12 - 2.01	0.57	0.14 - 2.29	0.56	0.14 - 2.29
Indeterminate use	53,327.8	26	0.49	1.02	0.68 - 1.53	1.24	0.83 - 1.86	1.01	0.67 - 1.52
Former use	47,333.0	28	0.59	1.24	0.84 - 1.83	1.37	0.93 - 2.02	1.11	0.75 - 1.65
Remote use	69,202.3	48	0.69	1.45	1.07 - 1.98	1.07	0.78 - 1.46	0.95	0.69 - 1.31
Nonuse	553,458.5	267	0.48	1.00	reference	1.00	reference	1.00	reference

Abbreviations: ADHD, attention deficit hyperactivity disorder; RR, rate ratio; CI, confidence interval; CRS, cardiovascular risk score

^aAdjusted for site, age, sex, and calendar year (i.e., matching variables).

^bAdjusted for site, age, sex, calendar year, and CRS (some variables are time-varying).

This table excludes the two HMORN sites (Fallon Community and KP Georgia) that did not provide data on stroke endpoints.

eTable 5B. 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 ^a	95% CI	Adjusted RR ^b	95% CI
Current use	111,935.5	16	0.14	0.79	0.47 - 1.34	0.88	0.52 - 1.49	0.85	0.46 - 1.56
Amphetamines	48,672.9	6	0.12	0.68	0.30 - 1.55	0.82	0.36 - 1.88	1.09	0.45 - 2.63
Methylphenidate	50,332.3	10	0.20	1.10	0.57 - 2.11	1.17	0.61 - 2.26	0.73	0.35 - 1.54
Atomoxetine	8,371.1	0	0.00	--	--	--	--	--	--
Indeterminate use	53,327.8	5	0.09	0.52	0.21 - 1.27	0.59	0.24 - 1.46	0.57	0.23 - 1.43
Former use	47,333.0	9	0.19	1.05	0.53 - 2.08	1.10	0.56 - 2.18	0.84	0.42 - 1.72
Remote use	69,202.3	17	0.25	1.36	0.81 - 2.27	1.07	0.63 - 1.79	2.34	1.32 - 4.14
Nonuse	553,458.5	101	0.18	1.00	reference	1.00	reference	1.00	reference

Abbreviations: ADHD, attention deficit hyperactivity disorder; RR, rate ratio; CI, confidence interval; CRS, cardiovascular risk score

^aAdjusted for site, age, sex, and calendar year (i.e., matching variables).

^bAdjusted for site, age, sex, calendar year, and CRS (some variables are time-varying).

This table excludes the two HMORN sites (Fallon Community and KP Georgia) that did not provide data on stroke endpoints.

eTable 6A. Rates of SCD (Excluding Only Those Adjudicated as Noncases), by Use of ADHD Medications

Medication status	Person- yrs	Number Events	Rate/1,000 person-yrs	Unadjusted RR	95% CI	Adjusted matching variables RR ^a	95% CI	Adjusted RR ^b	95% CI
ADHD medication use	273,705.1	140	0.51						
Current use	107,525.0	40	0.37	0.99	0.70 – 1.38	1.24	0.88 – 1.74	0.84	0.59 – 1.19
Indeterminate use	51,814.0	17	0.33	0.87	0.53 – 1.43	1.07	0.65 – 1.76	0.75	0.46 – 1.23
Former use	46,263.5	28	0.61	1.60	1.08 – 2.38	1.65	1.11 – 2.45	1.08	0.72 – 1.61
Remote use	68,102.6	55	0.81	2.14	1.59 – 2.88	1.42	1.05 – 1.93	0.96	0.71 – 1.30
Nonuse	535,515.5	202	0.38	1.00	reference	1.00	reference	1.00	reference

Abbreviations: SCD, sudden cardiac death; ADHD, attention deficit hyperactivity disorder; RR, rate ratio; CI, confidence interval; CRS, cardiovascular risk score

^aAdjusted for site, age, sex, and calendar year (i.e., matching variables).

^bAdjusted for site, age, sex, calendar year, and CRS (some variables within score are time-varying).

This table excludes the three HMORN sites (Fallon Community, KP Georgia, and KP Northwest) that did not provide data on SCD endpoints.

eTable 6B. Rates of Stroke (Excluding Only Those Adjudicated as Noncases), by Use of ADHD Medications

Medication status	Person- yrs	Number Events	Rate/1,000 person-yrs	Unadjusted RR	95% CI	Adjusted matching variables RR ^a	95% CI	Adjusted RR ^b	95% CI
ADHD medication use	281,716.6	256	0.91						
Current use	111,919.3	80	0.71	0.89	0.70 - 1.13	1.04	0.82 - 1.33	0.83	0.65 - 1.06
Indeterminate use	53,318.5	45	0.84	1.05	0.78 - 1.43	1.25	0.92 - 1.70	1.00	0.74 - 1.36
Former use	47,320.9	46	0.97	1.21	0.90 - 1.64	1.30	0.96 - 1.76	0.98	0.72 - 1.32
Remote use	69,157.9	85	1.23	1.54	1.22 - 1.94	1.12	0.89 - 1.42	0.84	0.67 - 1.07
Nonuse	553,346.6	443	0.80	1.00	reference	1.00	reference	1.00	reference

Abbreviations: ADHD, attention deficit hyperactivity disorder; RR, rate ratio; CI, confidence interval

^aAdjusted for site, age, sex, and calendar year (i.e., matching variables).

^bAdjusted for site, age, sex, calendar year, and CRS (some variables within score are time-varying).

This table excludes the two HMORN sites (Fallon Community and KP Georgia) that did not provide data on stroke endpoints.

eTable 7. Rates of MI, SCD, or Stroke, by Use of ADHD Medications, CRS Variables Fixed at Baseline

Medication status	Person- yrs	Number Events	Rate/1,000 person-yrs	Unadjusted RR	95% CI	Adjusted matching variables RR ^a	95% CI	Adjusted RR ^b	95% CI
ADHD medication use	272,641.8	723	2.65						
Current use	107,322.4	234	2.18	0.84	0.73 - 0.96	0.97	0.84 - 1.12	0.81	0.71 - 0.94
Indeterminate use	51,709.6	125	2.42	0.93	0.77 - 1.11	1.11	0.92 - 1.33	0.92	0.76 - 1.10
Former use	46,120.8	121	2.62	1.01	0.84 - 1.21	1.07	0.89 - 1.29	0.86	0.71 - 1.03
Remote use	67,489.0	243	3.60	1.38	1.21 - 1.58	1.02	0.88 - 1.17	0.89	0.77 - 1.02
Nonuse	533,540.4	1391	2.61	1.00	reference	1.00	reference	1.00	reference

Abbreviations: MI, myocardial infarction; SCD, sudden cardiac death; ADHD, attention deficit hyperactivity disorder, CRS, cardiovascular risk score; RR, rate ratio; CI, confidence interval

^aAdjusted for site, age, sex, and calendar year (i.e., matching variables).

^bAdjusted for site, age, sex, calendar year, and CRS (*all variables fixed at baseline*).

This table excludes the three HMORN sites (Fallon Community, KP Georgia, and KP Northwest) that did not provide data on SCD and/or stroke endpoints.

eTable 8. Selected Characteristics of Study Cohort at Baseline, New Users Only

Characteristic	Current Use		Nonuse	
Number of unique individuals	91,742		178,618	
Number of membership periods^a	91,958		178,922	
Median year of cohort entry	2003		2003	
Person-years during follow-up^b	52,095		317,514	
Demographics				
Median age in years (interquartile range)	42	34 - 49	42	34 - 49
Male gender (%)	40,814	44.4%	79,530	44.4%
Medicaid enrollment (%)	13,877	15.1%	27,547	15.4%
ADHD Medication				
Amphetamines	31,238	34.0%	0	0.0%
Methylphenidate	43,006	46.8%	0	0.0%
Atomoxetine	15,648	17.0%	0	0.0%
Pemoline	1,861	2.0%	0	0.0%
Multiple	205	0.2%	0	0.0%
Cardiovascular disease within past year				
Acute myocardial infarction	235	0.3%	447	0.2%
Ischemia	2,798	3.0%	4,626	2.6%
Coronary revascularization	170	0.2%	439	0.2%
Congestive heart failure	878	1.0%	1,323	0.7%
Arrhythmia	2,368	2.6%	3,299	1.8%
Stroke/transient ischemic attack	1,365	1.5%	1,469	0.8%
Congenital heart disorder	231	0.3%	359	0.2%
Coronary artery anomaly	48	0.1%	61	0.0%
Peripheral vascular disease	820	0.9%	1,164	0.7%
Hypertension	14,729	16.0%	25,501	14.3%
Hyperlipidemia ^c	18,561	20.2%	27,157	15.2%
Mental health claims within past year				
ADHD	19,276	21.0%	353	0.2%
Major depression	38,810	42.2%	15,877	8.9%
Bipolar disorder	7,503	8.2%	2,080	1.2%
Anxiety	20,600	22.4%	10,716	6.0%
Psychotic disorders	1,920	2.1%	1,532	0.9%
Other selected medical conditions within past year				
Diabetes ^c	6,162	6.7%	10,548	5.9%
Obesity	6,577	7.2%	7,892	4.4%
Smoking	8,257	9.0%	10,311	5.8%
Alcohol/substance abuse	5,771	6.3%	3,397	1.9%
Suicide attempt	592	0.6%	306	0.2%
Injury	19,771	21.5%	24,080	13.5%
Seizure	2,217	2.4%	2,129	1.2%
Asthma	7,329	8.0%	8,100	4.5%
Use of cardiovascular drug within past year				
Loop diuretic	3,241	3.5%	3,707	2.1%
Digoxin	434	0.5%	809	0.5%
Nitrates	1,463	1.6%	2,430	1.4%
Anticoagulant	1,273	1.4%	1,664	0.9%
Platelet inhibitor	766	0.8%	1,222	0.7%
Anti-arrhythmic agents	392	0.4%	424	0.2%
ACE inhibitor	7,109	7.7%	13,121	7.3%
Angiotensin receptor blocker	2,354	2.6%	3,894	2.2%
Beta-blocker	8,311	9.0%	12,525	7.0%
Calcium-channel blocker	4,716	5.1%	8,252	4.6%
Thiazide diuretic	7,990	8.7%	12,900	7.2%

Characteristic	Current Use		Nonuse	
Other antihypertensive	1056	1.1%	1476	0.8%
Use of psychotropic medications within past year				
Antipsychotic, any	10,452	11.4%	4,317	2.4%
Tricyclic antidepressant	10,009	10.9%	7,100	4.0%
Antidepressants, other or SSRI/SNRI	50,966	55.4%	25,425	14.2%
Benzodiazepines	28,585	31.1%	17,758	9.9%
Lithium	2,820	3.1%	765	0.4%
Modafinil	3,178	3.5%	296	0.2%
Insomnia medications	9,671	10.5%	4,575	2.6%
Thioridazine	248	0.3%	160	0.1%
Mood stabilizers, w/o seizure	14,968	16.3%	6,330	3.5%
Clonidine/guanfacine, w/o hypertension	1,214	1.3%	465	0.3%
Use of other selected medications within past year				
Beta-agonist	12,352	13.4%	14,016	7.8%
Epinephrine	822	0.9%	816	0.5%
Asthma medications, other	25,093	27.3%	29,036	16.2%
Seizure medications, any	16,339	17.8%	7,718	4.3%
Theophylline compounds (asthma medications)	728	0.8%	926	0.5%
COX-2 inhibitors	6,993	7.6%	7,164	4.0%
Other drugs to improve blood flow	150	0.2%	174	0.1%
Clonidine	1,784	1.9%	1,333	0.7%
pde5 inhibitors	2,977	3.2%	2,801	1.6%
Triptans	4,610	5.0%	3,470	1.9%
Oral contraceptives	11,026	12.0%	17,421	9.7%
Hormones, menopausal	11,256	12.2%	14,554	8.1%
Utilization within past year				
Cardiovascular visits				
Emergency, 1+	4,513	4.9%	5,763	3.2%
Inpatient, 1+	4,595	5.0%	5,167	2.9%
Physician, 1-4	27,074	29.4%	40,864	22.8%
Physician, 5+	9,323	10.1%	12,023	6.7%
Psychiatric visits^d				
Emergency, 1+	3,566	3.9%	2,405	1.3%
Inpatient, 1+	5,878	6.4%	2,973	1.7%
Physician, 1-4	27,019	29.4%	17,660	9.9%
Physician, 5+	26,188	28.5%	8,081	4.5%
Other visits				
Emergency, 1+	5,900	6.4%	7,104	4.0%
Inpatient, 1+	4,381	4.8%	4,097	2.3%
Physician, 1+	35,396	38.5%	44,448	24.8%
Number of different medications^e				
1	13,261	14.4%	36,304	20.3%
2+	67,642	73.6%	75,236	42.0%

Abbreviations: ADHD, attention deficit hyperactivity disorder; MI, myocardial infarction; SCD, sudden cardiac death; ACE, angiotensin-converting enzyme; SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin and norepinephrine reuptake inhibitors; w/o, without; COX, cyclooxygenase; pde5, phosphodiesterase type 5

^aPercents are calculated from membership periods.

^bFollow-up time based on combined endpoint (MI, SCD or stroke).

^cIncluding medications

^dExcluding ADHD visits

^eExcluding ADHD medications

All variables in table included in CRS, except demographics and ADHD

eTable 9. Subgroup Analyses for Combined End Point (Myocardial Infarction, Sudden Cardiac Death, or Stroke), Use vs Nonuse of ADHD Medications

Subgroup and ADHD Medication Use	Person-Years	Number of Events	Rate/1000 Person-Years	Adjusted RR (95% CI) ^a
Full cohort				
Current	107322.4	234	2.18	0.83 (0.72 - 0.95)
Past	165319.4	489	2.96	0.85 (0.77 - 0.95)
Nonuse	533540.4	1391	2.61	1 [Reference]
New use cohort ^b				
Current	52094.6	125	2.40	0.77 (0.63 - 0.94)
Past	116918.7	376	3.22	0.85 (0.75 - 0.98)
Nonuse	317514.4	957	3.01	1 [Reference]
No history of CVD				
Current	70748.1	79	1.12	0.79 (0.62 - 1.00)
Past	106497.1	148	1.39	0.79 (0.65 - 0.95)
Nonuse	391881.9	562	1.43	1 [Reference]
History of CVD				
Current	36574.2	155	4.24	0.87 (0.73 - 1.03)
Past	58822.3	341	5.80	0.89 (0.79 - 1.01)
Nonuse	141658.5	829	5.85	1 [Reference]
No non-ADHD psychiatric conditions				
Current	28355.6	43	1.52	0.76 (0.56 - 1.04)
Past	49324.2	103	2.09	0.82 (0.67 - 1.01)
Nonuse	407981.5	884	2.17	1 [Reference]
Non-ADHD psychiatric conditions				
Current	78966.8	191	2.42	0.87 (0.73 - 1.03)
Past	115995.3	386	3.33	0.88 (0.77 - 1.01)
Nonuse	125558.9	507	4.04	1 [Reference]
Use without ADHD diagnoses				
Current	69757.4	177	2.54	0.86 (0.74 - 1.01)
Past	131054.7	434	3.31	0.87 (0.78 - 0.97)
Nonuse	385962.7	1113	2.88	1 [Reference]
Use with ADHD diagnoses				
Current	37564.9	57	1.52	0.76 (0.57 - 1.01)
Past	34264.7	55	1.61	0.79 (0.59 - 1.05)
Nonuse	152357.3	283	1.86	1 [Reference]
Age 25-44 years				
Current	54106.9	47	0.87	0.78 (0.57 - 1.06)
Past	85786.7	102	1.19	0.79 (0.63 - 1.00)
Nonuse	271667.1	250	0.92	1 [Reference]
Age 45-64 years				
Current	53215.5	187	3.51	0.83 (0.71 - 0.97)
Past	79532.7	387	4.87	0.86 (0.76 - 0.97)
Nonuse	261873.3	1141	4.36	1 [Reference]

Abbreviations: RR, rate ratio.

^aAdjusted for site, age, sex, calendar year, and cardiovascular risk score (some variables within score are time-varying) except for new use cohort.

^bAdjusted for site, age, sex, calendar year, and propensity score.

Analyses excluded the 3 Health Maintenance Organization Research Network (HMORN) sites (Fallon Community, Kaiser Permanente [KP] Georgia, KP Northwest) that did not provide data on SCD and/or stroke end points.

eTable 10. End Points by Site (Standardized to Age and Gender Distribution of All Sites Combined)

Site	Sudden cardiac death ^a			Myocardial infarction			Stroke ^b		
	Person-yrs	Number events	Rate/1,000 person-yrs	Person-yrs	Number events	Rate/1,000 person-yrs	Person-yrs	Number events	Rate/1,000 person-yrs
OptumInsight	390,657.4	86	0.25	390,090.3	451	1.26	390,461.8	168	0.50
KP California	133,346.3	41	0.27	132,999.1	201	1.23	133,237.4	100	0.65
Tennessee Medicaid	123,028.2	150	1.34	122,204.9	446	4.20	122,570.1	210	1.82
HMORN	162,188.7	19	0.10	199,321.0	259	1.12	188,987.9	97	0.44

Abbreviations: yrs, years; KP, Kaiser Permanente; HMORN, Health Maintenance Organization Research Network

^aFallon Community, KP Georgia, and KP Northwest did not contribute to the SCD endpoint.

^bFallon Community and KP Georgia did not contribute to the stroke endpoint.

eTable 11. Characteristics of Users and Nonusers (Combined) at Baseline, by Site

Characteristics	OptumInsight	KP California	HMORN	Tennessee Medicaid
Number of Unique Individuals	265,078	55,943	78,943	43,234
Number of Membership Periods^a	266,787	56,397	80,351	43,371
Study Period	1998-2005	1999-2005	1999-2005	1986-2005
Person-years during follow-up^b	389,900	132,887	161,617	121,778
Demographics				
Median age in years (interquartile range)	41 (34-48)	44 (36-51)	43 (36-50)	39 (32-48)
Male gender (%)	47.7%	46.6%	46.2%	34.0%
Medicaid enrollment (%)	--	1.1%	--	100.0%
ADHD Medication				
Amphetamines	14.2%	10.9%	12.8%	8.1%
Methylphenidate	13.7%	17.7%	22.2%	15.0%
Atomoxetine	4.5%	3.5%	2.3%	8.3%
Pemoline	0.7%	1.1%	0.8%	1.9%
Multiple	0.2%	0.2%	0.2%	0.1%
Nonuser	66.6%	66.6%	61.8% ^c	66.6%
Cardiovascular disease within past year				
Acute myocardial infarction	0.2%	0.1%	0.2%	0.5%
Ischemia	2.3%	1.2%	1.7%	6.5%
Coronary revascularization	0.2%	0.1%	0.2%	0.5%
Congestive heart failure	0.4%	0.4%	0.3%	3.1%
Arrhythmia	1.9%	0.8%	1.8%	3.9%
Stroke/TIA	0.7%	0.3%	0.6%	2.8%
Congenital heart disorder	0.2%	0.1%	0.2%	0.4%
Coronary artery anomaly	0.0%	0.0%	0.0%	0.1%
Peripheral vascular disease	0.6%	0.3%	0.5%	2.0%
Hypertension	13.2%	10.5%	10.8%	27.1%
Hyperlipidemia ^d	16.5%	11.4%	14.0%	22.2%
Mental health claims within past year				
ADHD	9.6%	15.1%	14.1%	3.1%
Major depression	15.9%	21.1%	23.1%	27.4%
Bipolar disorder	2.2%	3.2%	3.0%	8.9%
Anxiety	8.7%	11.0%	11.1%	18.3%
Psychotic disorders	0.4%	0.8%	0.6%	5.3%
Other selected medical conditions within past year				
Diabetes ^d	4.6%	5.6%	4.6%	13.1%
Obesity	2.6%	13.5%	4.3%	6.1%
Smoking	3.6%	8.1%	6.9%	15.4%
Alcohol/substance abuse	1.6%	4.1%	2.7%	8.9%
Suicide attempt	0.2%	0.1%	0.2%	1.2%
Injury	14.0%	14.5%	14.9%	25.0%
Seizure	0.9%	0.6%	0.9%	5.7%
Asthma	4.8%	5.3%	5.4%	9.4%
Use of cardiovascular drug within past year				
Loop diuretic	1.4%	1.2%	1.1%	9.1%
Digoxin	0.2%	0.4%	0.3%	1.6%
Nitrates	0.7%	1.0%	1.0%	4.7%
Anticoagulant	0.6%	1.4%	0.8%	2.6%

Platelet inhibitor	0.5%	0.3%	0.3%	2.2%
Anti-arrhythmic agents	0.1%	0.2%	0.6%	0.6%
ACE inhibitor	5.9%	6.7%	5.9%	14.3%
Angiotensin receptor blocker	2.5%	0.8%	0.9%	4.0%
Beta- blocker	5.9%	7.8%	7.3%	13.0%
Calcium-channel blocker	3.9%	3.0%	3.0%	11.1%
Thiazide diuretic	7.0%	7.8%	6.2%	10.6%
Other antihypertensive	0.7%	1.2%	0.7%	1.9%
<i>Use of psychotropic medications within past year</i>				
Antipsychotic, any	2.6%	4.4%	4.0%	17.0%
Tricyclic antidepressant	3.5%	5.8%	5.9%	16.0%
Antidepressants, other or SSRI/SNRI	22.3%	28.0%	31.8%	41.2%
Benzodiazepines	14.3%	13.3%	14.1%	29.4%
Lithium	0.8%	1.2%	1.2%	3.1%
Modafinil	1.2%	1.0%	0.9%	1.8%
Insomnia medications	5.7%	1.7%	2.5%	9.0%
Thioridazine	0.0%	0.1%	0.1%	0.9%
Mood stabilizers, w/o seizure	5.6%	6.1%	6.4%	17.4%
Clonidine/guanfacine, w/o HT	0.5%	0.4%	0.6%	1.5%
<i>Use of other selected medications within past year</i>				
Beta-agonist	6.7%	10.7%	9.5%	19.1%
Epinephrine	0.5%	0.4%	0.8%	0.8%
Asthma medications, other	18.3%	11.2%	21.3%	29.2%
Seizure medications, any	6.1%	6.5%	6.8%	21.3%
Theophylline compounds	0.2%	0.2%	0.3%	2.7%
COX-2 inhibitors	5.9%	0.9%	1.2%	10.3%
Other drugs for blood flow	0.1%	0.1%	0.1%	0.4%
Clonidine	0.6%	0.8%	0.8%	3.7%
pde5 inhibitors	2.3%	3.2%	1.9%	0.5%
Triptans	2.8%	2.6%	2.4%	3.9%
Oral contraceptives	10.3%	10.0%	11.7%	10.7%
Hormones, menopausal	8.6%	10.1%	9.6%	11.7%

Utilization within past year				
Cardiovascular visits				
Emergency, 1+	1.4%	2.3%	3.2%	13.6%
Inpatient, 1+	2.0%	2.2%	2.3%	11.1%
Physician, 1-4	25.2%	19.0%	22.9%	29.0%
Physician, 5+	6.6%	2.2%	4.9%	18.9%
Psychiatric visits^e				
Emergency, 1+	0.6%	1.0%	1.7%	9.0%
Inpatient, 1+	1.6%	1.9%	2.0%	10.7%
Physician, 1-4	14.0%	18.5%	17.3%	19.8%
Physician, 5+	9.4%	9.9%	13.6%	22.5%
Other visits				
Emergency, 1+	2.0%	2.7%	4.2%	16.9%
Inpatient, 1+	1.6%	2.3%	1.9%	9.9%
Physician, 1+	25.9%	30.2%	25.9%	40.9%
No. of different medications^f				
1	19.9%	20.9%	19.8%	10.8%
2+	47.8%	47.4%	50.3%	72.0%

Abbreviations: KP, Kaiser Permanente; HMORN, Health Maintenance Organization Research Network; ADHD, attention deficit hyperactivity disorder; MI, myocardial infarction; SCD, sudden cardiac death; TIA, transient ischemic attack; ACE, angiotensin-converting enzyme; SSRI, Selective serotonin re-uptake inhibitors; SNRI, serotonin and norepinephrine re-uptake inhibitors; w/o, without; HT, hypertension; COX, cyclooxygenase; pde5, phosphodiesterase type 5

^aPercents are calculated from membership periods.

^bFollow-up time based on combined endpoint (MI, SCD or stroke).

^cA small percent of users at HMORN sites had only one match.

^dIncluding medications

^eExcluding ADHD visits

^fExcluding ADHD medications

Tables to examine heterogeneity of RRs by site

eTable 12A. Rate Ratios of MI by Site

Medication status	<u>OptumInsight</u>				<u>KP California</u>			
	Person-yr	n	RR ^a	95% CI	Person-yr	n	RR ^a	95% CI
ADHD medication use								
Current use	54,912.2	61	0.93	0.71 - 1.23	19,785.5	25	0.87	0.57 - 1.34
Indeterminate use	29,509.4	31	0.89	0.61 - 1.29	7,125.2	18	1.85	1.13 - 3.04
Former use	24,700.7	19	0.58	0.36 - 0.92	6,788.8	9	0.96	0.49 - 1.89
Remote use	28,259.8	43	0.95	0.69 - 1.31	9,541.6	21	1.37	0.86 - 2.18
Nonuse	252,708.2	297	1.00	reference	89,758.1	128	1.00	reference

Abbreviations: MI, myocardial infarction; KP, Kaiser Permanente; yr, year; RR, rate ratio; CI, confidence interval; ADHD, attention deficit hyperactivity disorder; CRS, cardiovascular risk score

^aAdjusted for age, sex, calendar year, and CRS (some variables within score are time-varying).

Medication status	<u>HMORN</u>				<u>Tennessee Medicaid</u>			
	Person-yr	n	RR ^a	95% CI	Person-yr	n	RR ^a	95% CI
ADHD medication use								
Current use	29,794.7	44	1.05	0.75 - 1.46	8,831.8	22	0.63	0.41 - 0.97
Indeterminate use	11,841.8	17	1.08	0.66 - 1.78	5,420.3	20	0.98	0.63 - 1.55
Former use	8,828.8	5	0.42	0.17 - 1.02	7,540.1	32	1.08	0.75 - 1.56
Remote use	11,434.1	13	0.71	0.40 - 1.25	20,557.5	70	0.69	0.53 - 0.90
Nonuse	137,421.6	180	1.00	reference	79,855.2	302	1.00	reference

Abbreviations: HMORN, Health Maintenance Organization Research Network; yr, year; RR, rate ratio; CI, confidence interval; ADHD, attention deficit hyperactivity disorder; CRS, cardiovascular risk score

^aAdjusted for age, sex, calendar year, and CRS (some variables within score are time-varying).

eTable 12B. Rate Ratios of SCD by Site

Medication status	<u>OptumInsight</u>				<u>KP California</u>			
	Person-yr	n	RR ^a	95% CI	Person-yr	n	RR ^a	95% CI
ADHD medication use								
Current use	54,965.5	14	0.89	0.49 - 1.62	19,820.0	8	1.03	0.45 - 2.36
Indeterminate use	29,542.3	5	0.62	0.25 - 1.56	7,139.9	2	0.75	0.17 - 3.23
Former use	24,738.7	3	0.39	0.12 - 1.24	6,804.4	3	1.02	0.30 - 3.47
Remote use	28,349.3	9	0.97	0.48 - 1.99	9,613.0	4	0.86	0.29 - 2.54
Nonuse	253,061.6	55	1.00	reference	89,968.9	24	1.00	reference

Abbreviations: SCD, sudden cardiac death; KP, Kaiser Permanente; yr, year; RR, rate ratio; CI, confidence interval; ADHD, attention deficit hyperactivity disorder; CRS, cardiovascular risk score

^aAdjusted for age, sex, calendar year, and CRS (some variables within score are time-varying).

This table excludes the three HMORN sites (Fallon Community, KP Georgia, and KP Northwest) that did not provide data on SCD endpoints.

Medication status	<u>HMORN</u>				<u>Tennessee Medicaid</u>			
	Person-yr	n	RR ^a	95% CI	Person-yr	n	RR ^a	95% CI
ADHD medication use								
Current use	23,878.1	2	0.63	0.14 - 2.82	8,861.5	8	0.62	0.30 - 1.29
Indeterminate use	9,697.2	0	--	--	5,434.6	7	0.95	0.44 - 2.07
Former use	7,151.6	4	4.03	1.29 - 12.6	7,568.7	10	0.93	0.48 - 1.80
Remote use	9,364.5	0	--	--	20,775.8	37	1.07	0.72 - 1.58
Nonuse	112,097.3	13	1.00	reference	80,387.6	88	1.00	reference

Abbreviations: HMORN, Health Maintenance Organization Research Network; yr, year; RR, rate ratio; CI, confidence interval; ADHD, attention deficit hyperactivity disorder; CRS, cardiovascular risk score

^aAdjusted for age, sex, calendar year, and CRS (some variables within score are time-varying).

This table excludes the three HMORN sites (Fallon Community, KP Georgia, and KP Northwest) that did not provide data on SCD endpoints.

eTable 12C. Rate Ratios of Stroke by Site

Medication status	OptumInsight				KP California			
	Person-yr	n	RR ^a	95% CI	Person-yr	n	RR ^a	95% CI
ADHD medication use								
Current use	54,944.7	18	0.60	0.36 - 0.98	19,814.2	13	0.73	0.40 - 1.33
Indeterminate use	29,532.3	12	0.78	0.43 - 1.41	7,136.1	7	1.14	0.52 - 2.50
Former use	24,724.8	13	0.95	0.53 - 1.69	6,798.7	8	1.33	0.63 - 2.80
Remote use	28,318.2	8	0.43	0.21 - 0.89	9,590.7	9	0.93	0.46 - 1.88
Nonuse	252,941.8	117	1.00	reference	89,897.7	63	1.00	reference

Abbreviations: KP, Kaiser Permanente; yr, year; RR, rate ratio; CI, confidence interval; ADHD, attention deficit hyperactivity disorder; CRS, cardiovascular risk score

^aAdjusted for age, sex, calendar year, and CRS (some variables within score are time-varying).

This table excludes the two HMORN sites (Fallon Community and KP Georgia) that did not provide data on stroke endpoints.

Medication status	HMORN				Tennessee Medicaid			
	Person-yr	n	RR ^a	95% CI	Person-yr	n	RR ^a	95% CI
ADHD medication use								
Current use	28,335.1	12	0.59	0.32 - 1.11	8,841.5	20	1.23	0.77 - 1.98
Indeterminate use	11,233.2	7	0.92	0.42 - 2.01	5,426.2	5	0.55	0.22 - 1.34
Former use	8,257.0	5	0.84	0.34 - 2.10	7,552.5	13	1.00	0.57 - 1.78
Remote use	10,664.2	8	0.98	0.46 - 2.06	20,629.3	42	0.98	0.69 - 1.39
Nonuse	130,498.4	65	1.00	reference	80,120.6	130	1.00	reference

Abbreviations: HMORN, Health Maintenance Organization Research Network; yr, year; RR, rate ratio; CI, confidence interval; ADHD, attention deficit hyperactivity disorder;

CRS, cardiovascular risk score

^aAdjusted for age, sex, calendar year, and CRS (some variables within score are time-varying).

This table excludes the two HMORN sites (Fallon Community and KP Georgia) that did not provide data on stroke endpoints.

eTable 12D. Rate Ratios of MI, SCD, or Stroke by Site

Medication status	<u>OptumInsight</u>				<u>KP California</u>			
	Person-yr	n	RR ^a	95% CI	Person-yr	n	RR ^a	95% CI
ADHD medication use								
Current use	54,891.8	92	0.85	0.68 - 1.07	19,779.7	46	0.86	0.62 - 1.18
Indeterminate use	29,499.4	48	0.85	0.63 - 1.14	7,121.3	26	1.43	0.95 - 2.15
Former use	24,686.8	35	0.66	0.47 - 0.94	6,781.5	19	1.05	0.65 - 1.68
Remote use	28,230.6	55	0.78	0.59 - 1.03	9,519.2	33	1.13	0.78 - 1.64
Nonuse	252,591.2	456	1.00	reference	89,685.3	209	1.00	reference

Abbreviations: MI, myocardial infarction; SCD, sudden cardiac death; KP, Kaiser Permanente; yr, year; RR, rate ratio; CI, confidence interval; ADHD, attention deficit hyperactivity disorder; CRS, cardiovascular risk score

^aAdjusted for age, sex, calendar year, and CRS (some variables within score are time-varying).

This table excludes the three HMORN sites (Fallon Community, KP Georgia, and KP Northwest) that did not provide data on SCD and/or stroke endpoints.

Medication status	<u>HMORN</u>				<u>Tennessee Medicaid</u>			
	Person-yr	n	RR ^a	95% CI	Person-yr	n	RR ^a	95% CI
ADHD medication use								
Current use	23,838.5	47	0.85	0.62 - 1.17	8,812.3	49	0.77	0.58 - 1.04
Indeterminate use	9,677.1	20	0.94	0.60 - 1.49	5,411.8	31	0.85	0.59 - 1.22
Former use	7,127.8	12	0.72	0.40 - 1.30	7,524.7	55	1.04	0.79 - 1.37
Remote use	9,312.9	20	0.77	0.48 - 1.22	20,426.3	135	0.78	0.64 - 0.95
Nonuse	111,660.9	219	1.00	reference	79,603.0	507	1.00	reference

Abbreviations: HMORN, Health Maintenance Organization Research Network; yr, year; RR, rate ratio; CI, confidence interval; ADHD, attention deficit hyperactivity disorder; CRS, cardiovascular risk score

^aAdjusted for age, sex, calendar year, and CRS (some variables within score are time-varying).

This table excludes the three HMORN sites (Fallon Community, KP Georgia, and KP Northwest) that did not provide data on SCD and/or stroke endpoints.