

Research Report

Coprescribing of Benzodiazepines and Opioids in Older Adults: Rates, Correlates, and National Trends

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Abstract

Background: To estimate prescribing trends of and correlates independently associated with coprescribing of benzodiazepines and opioids among adults aged 65 years or older in office-based outpatient visits.

Methods: I examined a nationally representative sample of office-based physician visits by older adults between 2006 and 2015 ($n = 109,149$ unweighted) using data from the National Ambulatory Medical Care Surveys (NAMCS). National rates and prescribing trends were estimated. Then, I used multivariable logistic regression analyses to identify demographic and clinical factors associated with coprescriptions of benzodiazepines and opioids.

Results: From 2006 to 2015, 15,954 (14.6%) out of 109,149 visits, representative of 39.3 million visits nationally, listed benzodiazepine, opioid, or both medications prescribed. The rate of prescription benzodiazepines only increased monotonically from 4.8% in 2006–2007 to 6.2% in 2014–2015 ($p < .001$), and the rate of prescription opioids only increased monotonically from 5.9% in 2006–2007 to 10.0% in 2014–2015 ($p < .001$). The coprescribing rate of benzodiazepines and opioids increased over time from 1.1% in 2006–2007 to 2.7% in 2014–2015 ($p < .001$). Correlates independently associated with a higher likelihood of both benzodiazepine and opioid prescriptions included: female sex, a visit for chronic care, receipt of six or more concomitantly prescribed medications, and clinical diagnoses of anxiety and pain ($p < .01$ for all).

Conclusion: The coprescribing rate of benzodiazepines and opioids increased monotonically over time in outpatient care settings. Because cause of benzodiazepines and opioids is associated with medication burdens and potential harms, future research is needed to address medication safety in these vulnerable populations.

Keywords: Benzodiazepine, Opioid, Older adults, Prescribing, Outpatient care

In the past two decades, the opioid crisis has been one of the most serious public health problems in the United States (1). In 2016, about 46 people died every day from overdoses involving prescription opioids, and more than 40% of all opioid overdose deaths in the United States involved a prescription opioid (2). In addition, benzodiazepines, as one of the most frequently used coprescribed central nervous system depressants, contribute to nearly one third of all opioid overdose deaths in the United States (3–7). Coprescribing of benzodiazepines and opioids is common in diverse clinical settings (4,8), and the concomitant use of both benzodiazepines and opioids may pose even greater risks of morbidity and mortality in older adults.

The Beers criteria recommend against the use of *all* benzodiazepines because they can increase the risk of cognitive impairment,

delirium, falls, and fractures in older adults (9). Furthermore, opioid analgesics are not recommended as they can cause central nervous system adverse effects, such as confusion and hallucinations (9). For these reasons, the concomitant use of benzodiazepines and opioids is considered potentially inappropriate prescribing in older adults (10).

There are a few pharmaco-epidemiologic studies investigating the concomitant use of benzodiazepines and opioids (4,6,7,11,12). Their findings suggest that the concomitant use of benzodiazepines and opioids was associated with the risks of overdose (7,11) and mortality (12). However, these studies focused on the Veterans Health Administration setting (12), emergency department (ED) setting (4), or nonelderly patients who are privately insured (11).

To address current gaps in the literature, I sought to address the following questions: (i) What are national rates and longitudinal trends of benzodiazepine-opioid coprescribing among older adults in office-based outpatient visits? (ii) What are demographic and clinical factors associated with coprescribing of benzodiazepines and opioids? This study is, thus, the first descriptive pharmaco-epidemiologic study investigating rates, correlates, and national trends of coprescribing of benzodiazepines and opioids among older adults in office-based outpatient settings.

Methods

Data Source and Study Sample

I used data from the 2006–2015 National Ambulatory Medical Care Survey (NAMCS), an annual cross-sectional survey of office-based physician visits. The NAMCS nationally represents ambulatory medical care services, including prescription trends (13). I limited the sample to all visits by adults aged 65 years or older ($n = 109,149$ unweighted). Using publicly available deidentified data, this study was exempted from the Institutional Review Board (#2000021850) at Yale School of Medicine. Further details of the survey, including descriptions, questionnaires, sampling methodology and data sets, are publicly available on the NAMCS website (13).

Measures

Medications list

In NAMCS, up to eight medications prescribed in a randomly selected visit are recorded between 2006 and 2011. The number of prescription medications documented increased up to 10 in 2012 and 2013, and then up to 30 in 2014 and 2015. I examined all medications listed as prescribed in each visit. I included 13 *benzodiazepine* medications using their generic names (14): alprazolam; chloridiazepoxide (hydrochloride); clonazepam; clorazepate dipotassium; diazepam; estazolam; flurazepam hydrochloride; lorazepam; midazolam hydrochloride; oxazepam; quazepam; temazepam; and triazolam. For opioids, I only considered *opiate agonists* because opiate partial agonists (eg, buprenorphine) and opiate antagonists (eg, naloxone hydrochloride and naltrexone) are used to treat opiate use disorders (15,16). The following opiate agonists were included: alfentanil; butorphanol; codeine phosphate or codeine sulfate; dihydrocodeine; fentanyl, fentanyl citrate, or fentanyl hydrochloride; hydrocodone bitartrate; hydromorphone hydrochloride; levorphanol tartrate; meperidine hydrochloride; methadone hydrochloride; morphine sulfate; nalbuphine; opium; oxycodone, oxycodone hydrochloride, or oxycodone myrist; oxymorphone hydrochloride; pentazocine; propoxyphene; remifentanyl hydrochloride; sufentanil citrate; tapentadol hydrochloride; tramadol hydrochloride; and their combined products (eg, droperidol-fentanyl). Based on these medications, I constructed an indicator variable for benzodiazepines only, opioids only, or both.

Covariates

Similar to previous pharmaco-epidemiologic studies using NAMCS, I selected covariates based on the potential for clinically relevant confounding (17–21). Demographic variables included: age; gender; race/ethnicity; primary source of payment (Private, Medicare, Medicaid, or other); and metropolitan statistical area (%) (22). Clinical characteristics included: physician specialty (primary care, psychiatry, or other); reason for visit (acute problem, routine chronic problem, preventive care, or surgical care); number of repeated visits

within the past 12 months; and time spent with a doctor (in minutes). I also included number of chronic conditions (eg, arthritis, congestive heart failure, and diabetes), and number of concomitant medications prescribed as they are provided by the NAMCS.

In addition, I included visit diagnoses relevant to benzodiazepines or opioids. The NAMCS provides up to three clinical diagnoses at each visit using the *International Classification of Diseases, 9th edition, Clinical Modification* (ICD-9-CM) diagnostic codes. Using ICD-9-CM diagnostic codes, I constructed five diagnosis variables relevant to benzodiazepines or opioids: (i) cancer-related pain (140–239, 338.3X); (ii) pain other than cancer (338.XX, 350.1X–350.2X, 354.4X, 355.71, 379.91, 388.7X, 719.4X, 724.1X–724.2X, 729.1X, 780.96, 786.5X, 789.XX); (iii) anxiety disorder, including panic disorder (300.00–300.02, 300.09); (iv) insomnia (327.00–327.02, 327.09, 780.51); and (v) seizure (345.XX, 780.31–780.33, 780.39).

Data Analysis

I estimated if demographic and clinical characteristics differed by prescription status (no prescription, benzodiazepines only, opioids only, or both). For each characteristic, I used cross-tabulations and weight-corrected Pearson's chi-squared statistics (ie, design-based F -tests) to investigate the differences in each prescription group. Using these raw p -values, I adjusted for and reported p -values using the false discovery rate (FDR) method to perform multiple comparisons across different prescription groups (23). Second, I assessed overall trends of benzodiazepine prescriptions, opioid prescriptions, and both prescriptions, and compared prescription rate changes between 2006 and 2007 and 2014 and 2015. Finally, I performed multivariable-adjusted logistic regression analyses to identify demographic and clinical correlates independently associated with a prescription of benzodiazepines, opioids, and both. I conducted all analysis using Stata MP/6-Core version 15.1 (College Station, TX) (24). I used *svy* commands to account for the survey sample design (eg, unequal probability of selection, clustering, and stratification). For multiple comparison tests, I used the *Proc MULTTEST* procedure in SAS 9.4 (Cary, NC) (25).

Results

Selected Characteristics of the Sample

Between 2006 and 2015, 15,954 (14.6%) out of 109,149 visits by older adults, representative of 39.3 million visits nationally, had benzodiazepine, opioid, or both medications prescribed in outpatient settings (Table 1). Patient visits in which these medications prescribed were more likely to be made by younger older adults (65–74), women, non-Hispanic whites, Medicare beneficiaries, and those living in metropolitan areas. Furthermore, the majority of patient visits, in which these medications prescribed, listed a routine chronic problem as the main reason for visit, had two or more chronic conditions. More than 50% of visits in which benzodiazepines, opioids, or both medications prescribed had six or more medications prescribed at that visit, meeting the definition of a polypharmacy. This proportion was significantly higher than for visits where neither benzodiazepines nor opioids were prescribed ($p < .001$).

National Trends of Benzodiazepine and Opioid Prescriptions

Figure 1 shows national trends of benzodiazepine and opioid prescriptions from 2006 to 2015. The overall rates increased from 11.7% of visits in 2006–2007 to 18.9% of visits in 2014–2015 (p

Table 1. Selected Characteristics (weighted column %) of Older Adults by Benzodiazepine and Opioid Prescription Status in Office-Based Outpatient Settings, 2006–2015 NAMCS

	Total	No Prescription	<i>p</i> Value	Benzodiazepines (BZDs) Only	<i>p</i> Value	Opioids Only	<i>p</i> Value	Both BZDs and Opioids	<i>p</i> Value
Sample size									
Unweighted sample	109,149	93,195		5,740		8,295		1,919	
Weighted visits	262,142,969	222,799,164		14,271,289		20,658,478		4,414,038	
Age									
65–74	50.9	51.0	.604	46.9	.007	52.6	.358	54.4	.322
75–84	35.8	35.8		38.3		34.4		31.5	
85+	13.3	13.2		14.8		13.0		14.1	
Gender									
Female	57.0	55.8	<.001	67.5	<.001	61.4	<.001	65.6	<.001
Male	43.0	44.2		32.5		38.6		34.4	
Race/ethnicity									
Non-Hispanic White	79.0	78.9	.300	81.8	.006	77.3	.118	83.7	.011
Non-Hispanic Black	7.9	7.9		5.8		9.6		6.7	
Hispanic	8.4	8.4		9.7		7.8		7.6	
Other ^a	4.7	4.8		2.7		5.4		2.0	
Primary source of payment									
Private	15.3	15.6	<.001	11.7	<.001	13.7	.112	14.9	.709
Medicare	77.0	76.7		79.8		77.9		77.3	
Medicaid	2.5	2.5		2.5		2.5		2.0	
Other ^b	2.1	2.0		2.6		2.0		1.9	
Undocumented	3.2	3.2		3.4		3.9		3.9	
Metropolitan Statistical Area (%)	88.5	88.6	.420	87.2	.420	87.9	.423	87.0	.423
Physician specialty									
Primary care	39.9	37.9	<.001	51.4	<.001	51.5	<.001	54.0	<.001
Psychiatry	1.3	1.0		7.7		0.2		0.7	
Other ^c	58.7	61.1		40.9		48.3		45.3	
Reason for visit									
Acute problem	25.1	25.1	<.001	25.0	<.001	26.1	<.001	19.8	<.001
Routine chronic problem	52.3	51.6		57.7		55.1		58.5	
Preventive care	10.4	10.8		8.5		7.6		7.1	
Pre- or postsurgery	7.1	7.3		3.8		7.2		5.3	
Undocumented	5.2	5.2		5.0		4.0		9.4	
Repeat of visits in the past 12 mo									
0 visit	5.4	5.7	<.001	4.2	<.001	3.0	<.001	4.8	<.001
1–2 visits	30.8	31.8		26.4		24.9		23.2	
3–5 visits	29.8	29.6		32.4		30.5		27.0	
6+ visits	22.6	21.2		28.9		31.2		33.3	
Undocumented	11.4	11.7		8.2		10.5		11.8	
Time spent with doctor									
< 15 min	18.1	18.7	<.001	14.6	<.001	14.8	<.001	15.6	.055
15–20 min	48.7	48.6		48.7		50.7		46.4	
21–30 min	21.4	21.1		22.6		23.8		25.5	
> 30 min	11.7	11.6		14.1		10.7		12.5	
≥2 chronic conditions (%) ^d	59.3	57.5	<.001	68.4	<.001	68.6	<.001	74.0	<.001
≥6 medications (%)	31.4	26.5	<.001	63.6	<.001	59.7	<.001	73.3	<.001
Visit diagnosis									
Cancer-related pain (%)	8.1	8.2	.453	6.3	.010	8.3	.986	8.1	.986
Pain other than cancer (%)	4.0	3.3	<.001	3.8	.134	10.6	<.001	11.4	<.001
Anxiety disorder (%)	1.3	0.6	<.001	11.4	<.001	0.5	.488	5.9	<.001
Insomnia (%)	0.6	0.5	<.001	2.3	<.001	0.5	.996	1.1	.034
Seizure (%)	0.3	0.3	.930	0.5	.183	0.1	.026	0.2	.868

Note: ^aincludes Asians, American Indian/Alaska Natives (AIANs), Native Hawaiian or Other Pacific Islanders (NHOPI), or 2+ reported racial/ethnic groups; ^bincludes worker's compensation, self-pay, no charge, or others; ^cincludes obstetrics/gynecology, cardiovascular diseases, dermatology, urology, neurology, ophthalmology, otolaryngology, and others; and ^dwas based on 14 chronic conditions (yes/no) collected by the NAMCS (eg, arthritis, congestive heart failure, and diabetes).

< .001). In prescription benzodiazepines only, the prescribing rate increased monotonically from 4.8% of visits in 2006–2007 to 6.2% of visits in 2014–2015 ($p < .001$) among older adults. Similarly, the

rate of prescription opioids only increased monotonically from 5.9% of visits in 2006–2007 to 10.0% of visits in 2014–2015 ($p < .001$). The coprescribing of benzodiazepines and opioids also increased

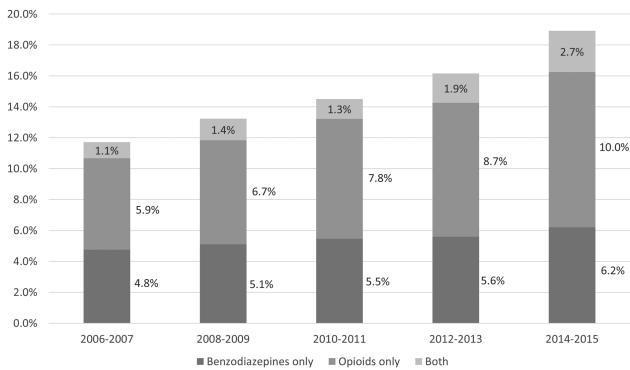


Figure 1. National trends of prescription benzodiazepines and opioids among older adults in office-based outpatient settings, 2006–2015 National Ambulatory Medical Care Surveys (NAMCS).

monotonically from 1.1% of visits in 2006–2007 to 2.7% of visits in 2014–2015 ($p < .001$).

Multivariable Logistic Regression Analysis

Table 2 presents the results of multivariable-adjusted logistic regression analyses, which estimated the odds of receiving a benzodiazepine, an opioid, or both medications, respectively. For a benzodiazepine prescription only, being female and having Medicare as a primary source of payment was associated with a greater likelihood of receiving benzodiazepines when compared to older male adults and those covered by a private insurance plan, respectively ($p < .05$). When compared to non-Hispanic whites, both non-Hispanic blacks and other minority groups were associated with a lower likelihood of receiving benzodiazepines ($p < .01$). Turning to clinical factors, visits to psychiatrists were more likely to receive benzodiazepines (adjusted odds ratio [AOR] = 8.43; 95% confidence interval [CI] = 6.32, 11.25), whereas visits to other specialists were less likely to receive benzodiazepines (AOR = 0.71; 95% CI = 0.63, 0.80). Older adults taking six or more medications prescribed were more likely to receive benzodiazepines (AOR = 4.83; 95% CI = 4.25, 5.48). Visits in which anxiety disorders or insomnia were diagnosed had at least two times more likely to receive benzodiazepines ($p < .001$).

For opioid prescriptions only, being older than those aged between 65 and 74 was less likely to receive opioids ($p < .001$). Being female and having the other type of insurance as a primary source of payment were more likely to receive opioids ($p < .01$). Turning to clinical factors, visits to psychiatrists and other specialists were less likely to involve with opioid prescriptions when compared to primary care visits ($p < .001$). Compared to those with acute problems, surgery-related visits were more likely to receive opioid prescriptions (AOR = 1.29; 95% CI = 1.05, 1.58). Those who had at least six visits in the past year were more likely to receive opioids than those who had not visited at all (AOR = 2.03; 95% CI = 1.63, 2.52). Older adults taking six or more medications prescribed were more likely to receive opioids (AOR = 3.53; 95% CI = 3.20, 3.91). Visits in which cancer-related pain and pain other than cancer diagnosed were more likely to receive opioids ($p < .001$).

In coprescriptions of both benzodiazepines and opioids, patterns were similar to that of the opioid prescriptions only, with two exceptions. In reason for visit, it was routine chronic problem, not surgery-related visits, which was associated with a greater likelihood of having coprescriptions (AOR = 1.41; 95% CI = 1.15, 1.71). Second, having a diagnosis of anxiety disorder, along with all other

pain diagnoses, was associated with a greater likelihood of coprescriptions (AOR = 6.36; 95% CI = 3.82, 10.58).

Discussion

This study investigated national rates, trends, and correlates of coprescribing of benzodiazepines and opioids among older adults in a nationally representative sample of office-based outpatient visits between 2006 and 2015. Prescribing rates of individual drug classes and the coprescribing rate increased monotonically over time. The coprescribing rate is lower than those of previous studies (3,4,11,12), which reported prevalence rates of 2.7% in ED settings (4), 9% among privately insured adults (11), and 27% among male veterans (12). The finding cannot be compared directly to these studies due in part to different populations of interest, settings, data sources (eg, survey-based vs claims-based), and inclusion criteria of medications.

Among demographic factors, while being older was associated with a lower likelihood of coprescribing, being female was associated with a higher likelihood of coprescribing. Among clinical factors, chronic care visits were associated with a higher likelihood of coprescribing. Furthermore, visits in which polypharmacy documented, and anxiety and pain diagnosed were also associated with a higher likelihood of coprescribing of benzodiazepines and opioids. These patterns are similar to previous studies (3,6,26), but direct comparisons could not be made as this study focuses primarily on older adults in office-based outpatient settings.

There are several implications from this study. First, because individual benzodiazepine and opioid classes of medication are increasingly prescribed over time, further pharmaco-vigilance studies are needed to track the coprescribing trends and adverse drug events among older adults. Further, as the Food and Drug Administration issued its warnings on cause of benzodiazepines and opioids in 2016 (27), physicians and other healthcare providers (eg, nurse practitioners and physician assistants) should be more cautious about the use of these medications concomitantly. Evidence-based interventions (eg, academic detailing and computerized prescribing alerts) (28–31) may also be effective in reducing the cause of these medications since these interventions allow healthcare providers to prescribe safer pharmacological alternatives (eg, nonopioid analgesics for pain management).

Second, among visits in which the cause of benzodiazepines and opioids was documented, older adults often take more than six medications concomitantly. While such polypharmacy can be justified by multimorbidities, it may still carry potential harms due to medication burdens in older adults. Thus, older adults with polypharmacy, who are exposed to the cause of benzodiazepines and opioids, may be particularly vulnerable, and therefore, future research is needed to address their quality of care and quality of life.

Several methodological limitations deserve a comment. First, the NAMCS does not capture outpatient visits from hospital-affiliated clinics or ED visits, which account for about 8.5% of all outpatient visits (19). Furthermore, it excludes any prescriptions ordered by phone. Second, NAMCS selected information in a randomly selected visit, and thus, incomplete patient information is inevitable. These factors may underestimate the magnitude of current findings in this study.

Strengths of this study are generalizability using nationally representative data, as NAMCS represents prescribing patterns in office-based care at the national level. Findings from this study lay the foundation for future research to improve better prescribing practices among older adults taking either benzodiazepines or opioids, or both.

Table 2. Adjusted Odds Ratios (AOR) of Receiving Benzodiazepine and Opioid Prescriptions Among Older Adults in Office-Based Outpatient Settings, 2006–2015 NAMCS

(Reference group in a parenthesis)	Benzodiazepines (BZDs) Only			Opioids Only			Both BZDs and Opioids		
	AOR	95% CI	p Value	AOR	95% CI	p Value	AOR	95% CI	p Value
Age (65–74)									
75–84	1.15	1.03, 1.29	.017	0.84	0.75, 0.93	.001	0.77	0.65, 0.92	.003
85+	1.04	0.90, 1.21	.601	0.79	0.70, 0.89	<.001	0.70	0.53, 0.94	.016
Gender (Male)									
Female	1.53	1.40, 1.67	<.001	1.22	1.12, 1.33	<.001	1.45	1.19, 1.77	<.001
Race/ethnicity (Non-Hispanic White)									
Non-Hispanic Black	0.67	0.55, 0.82	<.001	1.17	1.01, 1.37	.040	0.80	0.54, 1.18	.262
Hispanic	1.14	0.91, 1.42	.269	0.97	0.81, 1.15	.701	0.79	0.56, 1.10	.166
Other ^a	0.58	0.40, 0.84	.004	0.93	0.70, 1.24	.623	0.37	0.18, 0.79	.010
Primary source of payment (Private)									
Medicare	1.25	1.08, 1.44	.003	1.08	0.96, 1.22	.205	1.05	0.79, 1.39	.759
Medicaid	1.35	0.97, 1.89	.074	1.15	0.89, 1.49	.289	1.17	0.64, 2.15	.611
Other ^b	0.99	0.70, 1.40	.963	1.54	1.19, 2.00	.001	1.57	0.85, 2.84	.148
Metropolitan Statistical Area (No)	0.97	0.82, 1.14	.677	1.03	0.84, 1.27	.783	0.91	0.68, 1.22	.531
Physician specialty (Primary care)									
Psychiatry	8.43	6.32, 11.25	<.001	0.14	0.08, 0.23	<.001	0.56	0.22, 1.42	.222
Other ^c	0.71	0.63, 0.80	<.001	0.74	0.65, 0.83	<.001	0.74	0.60, 0.91	.005
Reason for visit (Acute problem)									
Routine chronic problem	0.96	0.85, 1.09	.559	0.96	0.87, 1.06	.401	1.41	1.15, 1.71	.001
Preventive care	0.83	0.70, 0.97	.023	0.73	0.62, 0.85	<.001	0.94	0.68, 1.31	.715
Pre- or postsurgery	0.73	0.57, 0.94	.015	1.29	1.05, 1.58	.014	1.42	1.02, 1.98	.038
Repeat of visits in the past 12 mo (Never)									
1–2 visits	0.94	0.75, 1.19	.624	1.31	1.06, 1.61	.011	0.59	0.41, 0.84	.003
3–5 visits	1.02	0.81, 1.29	.837	1.52	1.23, 1.87	<.001	0.69	0.48, 1.00	.053
6+ visits	0.99	0.79, 1.25	.949	2.03	1.63, 2.52	<.001	1.03	0.71, 1.50	.871
Time spent with a doctor (<15 min)									
15–20 min	1.06	0.93, 1.22	.378	1.17	1.03, 1.32	.013	0.93	0.73, 1.19	.569
21–30 min	1.05	0.89, 1.24	.580	1.18	1.01, 1.38	.035	1.03	0.75, 1.42	.842
> 30 min	1.10	0.90, 1.34	.345	1.01	0.86, 1.19	.876	1.07	0.76, 1.51	.696
≥2 chronic conditions ^d	1.00	0.89, 1.11	.934	0.94	0.85, 1.04	.204	0.94	0.79, 1.12	.483
≥6 medications	4.83	4.25, 5.48	<.001	3.53	3.20, 3.91	<.001	7.25	5.62, 9.36	<.001
Visit diagnosis									
Cancer-related pain	1.08	0.90, 1.30	.392	1.26	1.10, 1.43	.001	1.45	1.10, 1.92	.009
Pain other than cancer	0.91	0.72, 1.16	.460	3.33	2.86, 3.89	<.001	3.81	2.84, 5.11	<.001
Anxiety disorder	12.90	9.72, 17.13	<.001	0.39	0.22, 0.68	.001	6.36	3.82, 10.58	<.001
Insomnia	2.96	1.77, 4.94	<.001	0.72	0.43, 1.21	.220	1.47	0.68, 3.19	.332
Seizure	1.53	0.80, 2.91	.199	0.44	0.25, 0.79	.005	0.2	0.06, 0.68	.011

Note: ^aincludes Asians, American Indian/Alaska Natives (AIANs), Native Hawaiian or Other Pacific Islanders (NHOPI), or 2+ reported racial/ethnic groups; ^bincludes worker's compensation, self-pay, no charge, or others; ^cincludes obstetrics/gynecology, cardiovascular diseases, dermatology, urology, neurology, ophthalmology, otolaryngology, and others; and ^dwas based on 14 chronic conditions (yes/no) collected by the NAMCS (eg, arthritis, congestive heart failure, and diabetes).

Author Contributions

Study concept and design: T.G.R.; Data acquisition and statistical analyses: T.G.R.; Interpretation of data: T.G.R.; Drafting of manuscript: T.G.R.; Critical revision of manuscript for important intellectual content: T.G.R.

Data Access and Responsibility

T.G.R. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflict of Interest

T.G.R. completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest, and none were reported.

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