Increasing prevalence of vascular risk factors in patients with stroke

A call to action

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ABSTRACT

Objective: To evaluate trends in prevalence of cardiovascular risk factors (hypertension, diabetes, dyslipidemia, smoking, and drug abuse) and cardiovascular diseases (carotid stenosis, chronic renal failure [CRF], and coronary artery disease [CAD]) in acute ischemic stroke (AIS) in the United States.

Methods: We used the 2004–2014 National Inpatient Sample to compute weighted prevalence of each risk factor in hospitalized patients with AIS and used joinpoint regression to evaluate change in prevalence over time.

Results: Across the 2004–2014 period, 92.5% of patients with AIS had ≥ 1 risk factor. Overall age- and sex-adjusted prevalence of hypertension, diabetes, dyslipidemia, smoking, and drug abuse were 79%, 34%, 47%, 15%, and 2%, respectively, while those of carotid stenosis, CRF, and CAD were 13%, 12%, and 27%, respectively. Risk factor prevalence varied by age (hypertension: 44% in 18–39 years vs 82% in 60–79 years), race (diabetes: Hispanic 49% vs white 30%), and sex (drug abuse: men 3% vs women 1.4%). Using joinpoint regression, prevalence of hypertension increased annually by 1.4%, diabetes by 2%, dyslipidemia by 7%, smoking by 5%, and drug abuse by 7%. Prevalence of CRF, carotid stenosis, and CAD increased annually by 13%, 6%, and 1%, respectively. Proportion of patients with multiple risk factors also increased over time.

Conclusions: Despite numerous guidelines and prevention initiatives, prevalence of hypertension, diabetes, dyslipidemia, smoking, and drug abuse in AIS increased across the 2004–2014 period. Proportion of patients with carotid stenosis, CRF, and multiple risk factors also increased. Enhanced risk factor modification strategies and implementation of evidence-based recommendations are needed for optimal stroke prevention. *Neurology*® 2017;89:1985–1994

GLOSSARY

AAPC = average annual percentage change; **AF** = atrial fibrillation; **AHRQ** = Agency for Healthcare Research and Quality; **AIS** = acute ischemic stroke; **APC** = annual percentage change; **CAD** = coronary artery disease; **CCS** = Clinical Classification Software; **CRF** = chronic renal failure; **HCUP** = Healthcare Cost and Utilization Project; **ICD-9** = *International Classification of Diseases-9*; **LDL** = low-density lipoprotein; **NIS** = National Inpatient Sample; **NRD** = National Readmissions Database.

Over the last decade, stroke-related mortality in the United States has declined across all age and sex groups.¹ Stroke has now dropped from the 4th to the 5th leading cause of death in men and from the 3rd to the 4th leading cause of death in women.² The American Heart Association/American Stroke Association statement lists several factors including advances in stroke treatment, better nationwide treatment of stroke risk factors including hypertension and diabetes, and declining cigarette use as potential factors responsible for this decline.³ The proportion of US adults with hypertension may have remained unchanged at approximately 30% from 1999 to 2008,⁴ but median systolic blood pressure of the US population is on the decline.⁴ Diabetes prevalence in the general population initially increased but plateaued over time,⁵ while cigarette smoking among US adults declined by 20% from 2005 to 2014.⁶ Despite these trends, actual

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data on changes in the prevalence of these cardiovascular risk factors in acute ischemic stroke (AIS) patients in the United States over the last decade are sparse.

Conditions such as chronic renal failure (CRF), coronary artery disease (CAD), and carotid stenosis may be downstream consequences of poor control of cardiovascular risk factors and influence AIS outcome.^{7–9} Understanding changes in the burden of these factors in AIS patients has major implications for public health but current temporal data on their prevalence are lacking.

The primary objective of this study is to quantify and describe racial, age, and sex-specific temporal trends in the prevalence of conventional stroke risk factors, lifestyle risk factors, and cardiovascular diseases in AIS patients in the United States, using the 2004–2014 National Inpatient Sample (NIS). Since we recently evaluated temporal trends in the prevalence of atrial fibrillation (AF) using the same database,¹⁰ we report AF prevalence but did not include AF as a primary outcome in this study.

METHODS The NIS is the largest inpatient care database in the United States. Further details on the NIS design are available at hcup-us.ahrq.gov.

Study population. We identified adults with a primary diagnosis of AIS in the 2004–2014 NIS using criteria depicted in figure e-1 at Neurology.org and described in the e-Methods.

Outcomes definition. Comorbid hypertension, diabetes, drug abuse, and CRF were all studied using Agency for Healthcare Research and Quality (AHRQ) comorbidity measures available in the NIS.¹¹ AHRQ comorbidity measures identify different comorbidities using ICD-9-CM diagnoses and the diagnosis-related group (DRG). Healthcare Cost and Utilization Project (HCUP) Clinical Classification Software (CCS) was used to obtain a constellation of codes corresponding to CAD (CCS code 101) and dyslipidemia (CCS code 53). Smoking was studied using ICD-9 codes 305.1, 649.00–649.04, and 989.84, while any carotid stenosis was determined by searching all primary and secondary ICD-9 codes for 433.10–433.11 representing carotid stenosis/occlusion without and with infarction. The subset of patients with symptomatic carotid stenosis was defined by ICD diagnosis code 433.11 representing carotid stenosis/occlusion with infarction or as AIS hospitalizations containing ICD-9 procedural codes for carotid endarterectomy (code 38.12) or stenting (code 00.63).

Statistical analysis. We computed national weighted age- and sex-adjusted prevalence of each risk factor and in subgroups stratified by sex, race, and age. Joinpoint regression models were fitted to quantify average annual percentage change (AAPC) in prevalence of each risk factor and to evaluate trends over time.¹² Generalized linear models were used to compare prevalence of

risk factors between various population subgroups with adjustment for potential confounders (see e-Methods).

Sensitivity analysis. The NIS lacks individual patient information, so multiple readmissions may account for some changes in risk factor prevalence over time. HCUP has a new National Readmissions Database (NRD) that allows for identification of unique patient readmissions. We computed the prevalence of each risk factor in unique AIS patients in the 2014 NRD and compared these estimates to those obtained using the NIS as a sensitivity analysis.

RESULTS Trends in demographic characteristics. We identified 922,451 primary AIS admissions representing 4,438,698 weighted AIS hospitalizations from the 2004–2014 NIS. Annual AIS admissions varied across the study period but total hospitalizations increased from 387,014 in 2009 to 454,065 in 2014 (table e-1).

Fewer than half (47%) of all admissions were among men. The proportion of male hospitalizations increased from 45.2% in 2004 to 49.0% in 2014 (table e-1). This increase in male hospitalizations was observed across all age groups (figure e-2) and was due to disproportionate increase in the number of AIS in men rather than decreasing female hospitalizations, as the absolute number of female admissions did not decline over time (table e-1). The majority of male admissions (48.4%) occurred in patients 60–79 years of age and the majority of female hospitalizations (42.3%) were among those ≥ 80 years of age. The proportion of AIS in the elderly ≥ 80 years of age declined over time while the proportion in the 40–59 years of age group increased in both sexes (table e-1).

Prevalence and trends of cardiovascular risk factors. Across the study period, 92.5% of patients had ≥ 1 risk factor. The proportion of patients with ≥ 1 risk factor increased from 88.3% in 2004 to 95.0% in 2014 (table e-2). Age- and sex-adjusted prevalence of all risk factors is depicted in table 1. A total of 79.1% of all AIS cases from 2004 to 2014 had comorbid hypertension (table 1). Hypertension prevalence in women (80.0%) was slightly higher compared to men (78.1%) ($p < 0.001$). Hypertension prevalence increased across the study period in all patients (relative increase of 14.7%) and across all race and age groups (table e-3 and figure 1), but prevalence was particularly high for black participants, where estimates were $\approx 90\%$ in 2014 (table e-3).

Approximately 34% of patients had comorbid diabetes. Diabetes prevalence increased by 22.2% from 30.7% in 2004 to 37.5% in 2014 in all patients (table 1). Diabetes prevalence was higher in Hispanic participants (48.7%) and black participants (44.4%) compared to white participants (30.5%) (table e-3). By 2014, $\approx 50\%$ of Hispanic participants with AIS

Table 1 Weighted sex- and age-adjusted prevalence of cardiovascular risk factors in adult acute ischemic stroke admissions in the United States from 2004 to 2014

Variables	Total	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	p Trend
Stroke risk factors, % ^a													
Hypertension, all	79.1	72.8	73.4	75.4	77.2	78.2	79.4	80.2	81.8	82.6	83.4	83.5	<0.001
Hypertension, M	78.1	70.9	71.8	73.8	76.1	77.2	78.2	79.2	81.1	81.7	82.6	82.7	<0.001
Hypertension, F	80.0	74.5	74.8	76.9	78.2	79.1	80.4	81.0	82.4	83.4	84.0	84.3	<0.001
Any DM, all	33.9	30.7	30.9	31.7	32.4	33.1	33.4	34.0	35.0	35.9	36.6	37.5	<0.001
Any DM, M	35.2	31.9	32.1	32.6	33.8	34.4	34.4	35.2	36.4	37.4	38.2	39.1	<0.001
Any DM, F	32.7	29.6	29.8	30.8	31.1	31.9	32.6	33.0	33.7	34.6	35.2	36.2	<0.001
Dyslipidemia, all	46.9	29.0	33.6	37.0	40.8	44.0	48.2	50.6	54.0	56.1	57.8	58.6	<0.001
Dyslipidemia, M	49.5	31.6	36.4	39.6	43.5	46.9	50.9	53.1	56.4	58.2	59.5	60.1	<0.001
Dyslipidemia, F	44.5	26.8	31.1	34.6	38.4	41.4	45.7	48.3	51.9	54.2	56.2	57.4	<0.001
Lifestyle risk factors, % ^a													
Smoking, all	15.1	10.6	11.6	12.7	13.3	14.6	15.4	16.2	16.6	17.3	17.6	18.0	<0.001
Smoking, M	19.2	13.5	14.9	16.4	16.9	18.7	19.9	20.5	20.8	21.5	22.1	22.5	<0.001
Smoking, F	11.5	8.0	8.6	9.4	10.1	11.0	11.5	12.3	12.9	13.6	13.7	14.1	<0.001
Drug abuse, all	2.1	1.4	1.6	1.8	2.1	1.8	2.0	2.1	2.3	2.5	2.7	2.8	<0.001
Drug abuse, M	3.0	2.1	2.2	2.5	3.0	2.5	2.8	3.0	3.2	3.4	3.8	3.9	<0.001
Drug abuse, F	1.4	0.9	1.0	1.1	1.2	1.1	1.2	1.4	1.5	1.7	1.8	1.8	<0.001
Vascular diseases, % ^a													
Afib, all	22.6	19.6	20.4	21.2	21.2	21.2	22.4	22.8	24.1	24.4	24.7	25.4	<0.001
Afib, M	19.7	17.1	17.6	18.4	18.2	18.1	19.0	19.5	21.2	21.6	21.6	22.5	<0.001
Afib, F	25.2	21.8	23.0	23.7	23.9	23.9	25.5	25.7	26.7	27.0	27.4	27.9	<0.001
CAD, all	26.5	25.2	25.0	25.5	25.9	26.4	27.3	26.5	27.1	27.9	27.3	27.3	<0.001
CAD, M	31.1	29.2	29.2	29.7	30.3	30.9	31.7	31.1	31.9	33.0	32.2	31.9	<0.001
CAD, F	22.5	21.5	21.3	21.8	22.1	22.3	23.4	22.5	22.9	23.4	23.0	23.2	<0.001
CRF, all	11.7	4.8	6.2	9.9	11.1	11.4	12.5	13.0	14.2	14.3	14.7	15.1	<0.001
CRF, M	12.9	5.1	6.8	11.1	12.4	12.7	13.7	14.3	15.4	15.4	16.1	16.2	<0.001
CRF, F	10.7	4.7	5.7	8.8	9.9	10.3	11.4	11.9	13.2	13.3	13.4	14.1	<0.001
Carotid stenosis, all	13.0	8.8	9.4	10.6	12.1	13.2	13.8	14.3	14.7	14.7	14.8	15.1	<0.001
Carotid stenosis, M	14.8	10.4	11.0	12.2	13.8	15.2	15.7	16.2	16.7	16.4	16.7	16.9	<0.001
Carotid stenosis, F	11.4	7.4	7.9	9.2	10.5	11.5	12.2	12.6	13.0	13.1	13.1	13.6	<0.001
Symptomatic stenosis, all	6.7	4.9	5.4	6.2	6.9	7.5	7.5	7.2	6.8	7.1	6.9	7.1	<0.001
Symptomatic stenosis, M	8.0	6.0	6.6	7.3	8.2	8.9	8.8	8.5	8.1	8.1	8.3	8.4	<0.001
Symptomatic stenosis, F	5.6	3.9	4.3	5.1	5.7	6.3	6.3	6.0	5.7	6.1	5.7	5.9	<0.001
Other factors, % ^a													
Any carotid revascularization ^b	1.4	0.8	1.1	1.3	1.2	1.4	1.5	1.4	1.6	1.7	1.8	1.8	<0.001
Symptomatic carotid revascularization	20.2	15.7	19.4	19.6	16.8	17.9	18.8	18.3	21.6	22.4	23.9	24.2	<0.001
Alcohol abuse, all	3.2	3.4	3.5	3.7	3.7	3.7	4.0	4.2	4.3	4.4	4.2	3.2	<0.001
Obesity, all	7.8	4.2	4.7	4.9	5.9	7.2	7.5	7.9	9.0	9.8	11.0	11.3	<0.001
Dementia, all	12.9	11.3	11.5	11.9	12.2	12.8	13.5	13.3	14.0	13.5	13.5	13.7	<0.001
Hypothyroidism, all	12.4	9.5	10.3	10.4	11.0	11.8	12.6	12.9	13.7	14.0	14.4	14.8	<0.001
Obstructive sleep apnea, all	3.0	NA	0.2	1.2	1.7	2.1	2.7	3.1	3.7	4.2	4.6	4.9	<0.001

Abbreviations: Afib = atrial fibrillation; CAD = coronary artery disease; CRF = chronic renal failure; DM = diabetes mellitus.

^aAll estimates age- and sex-adjusted in all patients or age-adjusted only in specific sex subgroups.

^bRepresents either carotid endarterectomy or carotid artery stenting in patients with symptomatic carotid stenosis diagnosis.

Figure 1 Weighted prevalence of hypertension, diabetes mellitus, dyslipidemia, and tobacco smoking in acute ischemic stroke patients hospitalized in the United States from 2004 to 2014

(A) Hypertension, (B) diabetes mellitus, (C) dyslipidemia, (D) tobacco smoking.

were diabetic (table e-3). Admissions with comorbid hypertension and diabetes increased by 36.1%, from 25.1% in 2004 to 34.2% in 2014 (table e-2).

Dyslipidemia was listed as a secondary diagnosis in 46.9% of hospitalizations (table 1). Overall dyslipidemia prevalence more than doubled during the study period (from 28.9% in 2004 to 58.6% in 2014) (table 1) across all age groups (figure 1, table e-4). Admissions with concomitant hypertension, diabetes, and dyslipidemia also increased by >200%, from 9.4% in 2004 to 23.7% in 2014 (table e-2).

Comorbid drug abuse prevalence in men (3.0%) was >2 times the prevalence in women (1.4%) while smoking prevalence in men (19.2%) was over 60% higher compared to women (11.5%). Drug abuse prevalence increased 2-fold, from 1.4% in 2004 to 2.8% in 2014 in all patients, while smoking prevalence increased by 70% over the same period. Most of this increase occurred in young and middle-aged patients (figures 1 and 2 and table e-4). By 2014, 38.3% and 44.1% of AIS patients aged 18–39 years and 40–

59 years, respectively, were using cigarettes, alcohol, or drugs (table e-2).

Prevalence and trends in chronic renal failure, carotid stenosis, and coronary artery disease. CRF prevalence increased by approximately 3-fold, from 4.8% in 2004 to 15.0% in 2014. More black participants had CRF compared to white participants (17.1% vs 10.8%) and by 2014, 20% of black participants had CRF compared to the 14.0%–14.9% prevalence in other races (table e-3). CRF prevalence increased exponentially in all age groups except in those 18–39 years of age, where rates remained unchanged over time in both sexes (table e-4) (figure 2).

Overall prevalence of CAD was 26.5% (table 1). CAD prevalence was greater in the elderly compared to other age groups and estimates in white participants (28.9%) were greater than those in black (20.7%) and Hispanic participants (23.8%) (table e-3). Prevalence also increased from 25.2% to 27.3% over the study period.

Figure 2 Weighted prevalence of drug abuse, carotid stenosis, chronic kidney disease, and coronary artery disease in acute ischemic stroke patients hospitalized in the United States from 2004 to 2014

(A) Drug abuse, (B) carotid stenosis, (C) chronic kidney disease, (D) coronary artery disease.

Prevalence of any carotid stenosis and symptomatic carotid stenosis were 12.9% and 6.7%, respectively. Proportion of patients with each condition increased over time (table 1 and figure 2). In keeping with this increased prevalence, the proportion of patients receiving either carotid endarterectomy or stenting during AIS hospitalization more than doubled during the study period, from 0.8% in 2004 to 1.8% in 2014, but the proportion of revascularizations that were endarterectomies dropped from 96.0% to 73.3% over time (data not shown).

Weighted AF prevalence increased over time, and by 2014, 1 in 4 patients with AIS had AF (table 1). AF prevalence was also greater in women (25.2%) compared to men (19.6%).

Joinpoint analysis of change in prevalence over time. In joinpoint regression, CRF (13.0%), dyslipidemia (6.9%), and drug abuse (6.7%) had the highest average annual percent increase in prevalence (AAPC), while diabetes (2.1%), hypertension (1.4%), and CAD (0.9%) had the lowest increase (table 2). Notably, unique patterns on change in risk factor

prevalence over time were also elucidated. Whereas rate of increase in hypertension prevalence slowed down, it still continued to increase after 2011 (annual percentage change [APC] in the period 2004–2011 [1.7%] > APC in the period 2011–2014 [0.6%]) (table 2, figure e-3, and figure e-4). CAD prevalence did not change after 2012 while diabetes prevalence increased considerably in the period 2010–2014 (APC 2.4%) compared to the period 2004–2010 (APC 1.9%) (table 2).

Multivariate association of each outcome with demographic, socioeconomic, and hospital characteristics. Excluding hypertension, which was more prevalent in women compared to men (prevalence ratio 1.03, 95% confidence interval 1.03–1.03), prevalence of all risk factors remained significantly lower in women compared to men (table 3). Prevalence of drug abuse and CRF in black participants were higher than in white participants (prevalence ratios 2.12 and 1.63, respectively), while diabetes prevalence in Hispanic participants was ≈ 1.5 times the prevalence in white participants. Hypertension, dyslipidemia, carotid

Table 2 Joinpoint analysis of the prevalence of the cardiovascular risk factors in acute ischemic stroke patients in the United States from 2004 to 2014

	Full range		Trend 1			Trend 2		
	AAPC	95% CI	Years	APC	95% CI	Years	APC	95% CI
Hypertension	1.4 ^a	1.2 to 1.6	2004–2011	1.7 ^a	1.4 to 2.1	2011–2014	0.6 ^a	0.1 to 1.2
Diabetes	2.1 ^a	1.9 to 2.3	2004–2010	1.9 ^a	1.6 to 2.1	2010–2014	2.4 ^a	2.0 to 2.8
Dyslipidemia	6.9 ^a	6.2 to 7.7	2004–2010	9.7 ^a	8.4 to 11.0	2010–2014	2.9 ^a	1.7 to 4.2
Smoking	5.4 ^a	5.0 to 5.8	2004–2009	7.9 ^a	7.0 to 8.8	2009–2014	3.0 ^a	2.5 to 3.5
Drug abuse	6.7 ^a	5.6 to 7.8	2004–2014	6.7 ^a	5.6 to 7.8	NA	NA	NA
Carotid stenosis	5.9 ^a	5.1 to 6.7	2004–2008	11.9 ^a	9.7 to 14.1	2008–2014	2.0 ^a	1.1 to 2.9
Chronic renal failure	13.0 ^a	10.5 to 15.5	2004–2006	40.4 ^a	32.0 to 71.5	2006–2014	5.2 ^a	4.1 to 6.3
Coronary artery disease	0.9 ^a	0.3 to 1.5	2004–2012	1.3 ^a	0.9 to 1.7	2012–2014	−0.9	−0.7 to 0.5

Abbreviations: AAPC = average annual percent change; APC = annual percentage change; NA = not applicable.

^a $p < 0.05$.

stenosis, and CRF were slightly more prevalent in hospitalizations in the South compared to the Northeast region, while smoking and drug abuse were more prevalent in the West compared to the Northeast (table 3). Interestingly, after adjusting for age, hypertension, diabetes, and dyslipidemia, the association of CAD with unit increase in time was attenuated, suggesting that observed increase in CAD prevalence is likely explained by its association with these factors. Similarly, association of hypertension with time was significantly attenuated after further adjustment for dyslipidemia and diabetes, also suggesting that some increase in prevalence of hypertension over time may be explained by increased prevalence of these risk factors (table 3).

Sensitivity analysis. In the 2014 NRD, 4.8% of AIS patients had >1 primary AIS hospitalization. After restricting analysis to the index AIS admission in 2014, estimated prevalence of risk factors in primary AIS admissions in the NRD were similar to those in the NIS (table e-5), suggesting that the high prevalence of these risk factors in 2014 was not solely due to multiple readmissions or transfers.

DISCUSSION In this contemporary analysis of adult hospitalizations from 2004 to 2014, we report a significant increase in the prevalence of conventional stroke risk factors including hypertension, diabetes, dyslipidemia, drug abuse, and smoking among stroke patients in the United States. This increase was accompanied by increased prevalence of chronic renal failure, coronary artery disease, and carotid stenosis. Prevalence of all risk factors increased across both sexes and multiple age groups, but significant heterogeneity existed by race, socioeconomic status, and hospital characteristics.

Few studies have evaluated trends in stroke risk factor prevalence in AIS patients in the United States over the last decade. These studies have either assessed

individual factors or focused on subsets of AIS patients.^{13–15} A recent British study reported a nearly 3-fold increase in hypercholesterolemia prevalence in first-ever stroke patients but no change in hypertension or diabetes prevalence from 1995 to 2011.¹⁶ Our study uniquely evaluates current US patterns of conventional stroke risk factors in various subpopulations of stroke patients and we observed widespread increase in proportion of patients with single or multiple risk factors. These results indicate that modifiable stroke risk factors continue to pose significant challenges for AIS prevention in the United States and call for intensification of proven treatment strategies and development of novel comprehensive preventive approaches.

The increased prevalence of hypertension, diabetes, and dyslipidemia noted in our study is likely multifactorial. Incidence of these conditions may have increased as a consequence of the US obesity epidemic and persistent concerns about physical inactivity and unhealthy dietary patterns.^{8,17} Black patients in the United States are more likely to have comorbid hypertension or diabetes, but less likely to have dyslipidemia, compared to white patients,⁸ as seen in this study. Diabetes prevalence in the US Hispanic population is also greater than that of white patients⁸ but the 50% diabetes prevalence in Hispanic patients with AIS in 2014 is concerning. Hispanics are the fastest growing population in the United States and have the highest projected increase in diabetes prevalence compared to other racial groups in the United States,⁹ so diabetes prevalence in Hispanic patients with AIS is likely to increase further. Black and Hispanic patients are less likely to have well-controlled diabetes and hypertension compared to white patients.^{18,19} They are also less likely to adhere to anti-hypertensive and diabetic treatments.^{19,20} Specific interventions targeting these underrepresented

Table 3 Prevalence ratio estimates for the association between hypertension, diabetes, dyslipidemia, smoking, drug abuse, any carotid stenosis, chronic renal failure, and coronary artery disease with demographic characteristics and other hospitalization characteristics in acute ischemic stroke patients in the United States from 2004 to 2014

Variables	Hypertension ^a	Diabetes ^b	Dyslipidemia	Smoking	Drug abuse	Carotid stenosis	Chronic renal failure	Coronary artery disease ^c
Year, per unit increase	1.01 (1.01-1.01) ^d	1.00 (1.00-1.01) ^d	1.06 (1.06-1.07) ^d	1.05 (1.05-1.06) ^d	1.05 (1.04-1.06) ^d	1.04 (1.04-1.05) ^d	1.08 (1.08-1.09) ^d	0.99 (0.99-0.99) ^d
Sex, female vs male	1.03 (1.03-1.03) ^d	0.98 (0.97-0.98) ^d	0.96 (0.95-0.96) ^d	0.87 (0.86-0.88) ^d	0.74 (0.72-0.77) ^d	0.85 (0.84-0.86) ^d	0.74 (0.73-0.75) ^d	0.68 (0.67-0.69) ^d
Age, y								
40-59 vs 18-39	1.64 (1.61-1.66) ^d	1.76 (1.70-1.81) ^d	1.49 (1.45-1.52) ^d	1.17 (1.14-1.20) ^d	0.66 (0.63-0.69) ^d	1.57 (1.49-1.66) ^d	0.98 (0.93-1.04)	2.51 (2.36-2.67) ^d
60-79 vs 18-39	1.78 (1.75-1.81) ^d	1.74 (1.69-1.80) ^d	1.53 (1.49-1.57) ^d	0.72 (0.71-0.74) ^d	0.16 (0.15-0.17) ^d	2.06 (1.95-2.17) ^d	0.96 (0.90-1.02)	3.30 (3.10-3.51) ^d
≥80 vs 18-39	1.83 (1.80-1.87) ^d	1.16 (1.12-1.20) ^d	1.27 (1.23-1.30) ^d	0.16 (0.15-0.16) ^d	0.02 (0.02-0.02) ^d	1.89 (1.78-1.99) ^d	1.09 (1.02-1.16) ^e	3.56 (3.35-3.79) ^d
Race								
Black vs white	1.13 (1.12-1.13) ^d	1.29 (1.27-1.30) ^d	0.90 (0.89-0.91) ^d	0.87 (0.85-0.89) ^d	2.12 (2.04-2.21) ^d	0.66 (0.64-0.67) ^d	1.63 (1.59-1.66) ^d	0.80 (0.79-0.81) ^d
Hispanic vs white	1.05 (1.05-1.06) ^d	1.47 (1.45-1.49) ^d	0.96 (0.95-0.97) ^d	0.59 (0.57-0.61) ^d	0.94 (0.88-1.01)	0.79 (0.76-0.81) ^d	1.14 (1.11-1.17) ^d	0.90 (0.88-0.92) ^d
Other vs white	1.05 (1.05-1.06) ^d	1.30 (1.29-1.32) ^d	0.99 (0.98-1.01)	0.70 (0.68-0.73) ^d	0.83 (0.75-0.92) ^d	0.84 (0.82-0.87) ^d	1.13 (1.10-1.17) ^d	0.86 (0.85-0.88) ^d
Income								
\$39,000-\$47,999 vs <\$39,000	0.99 (0.99-1.00) ^d	0.97 (0.97-0.98) ^d	1.04 (1.03-1.05) ^d	0.94 (0.93-0.96) ^d	0.81 (0.78-0.84) ^d	1.03 (1.01-1.05) ^e	1.00 (0.99-1.02)	0.97 (0.96-0.98) ^d
\$48,000-\$62,999 vs <\$39,000	0.99 (0.99-1.00) ^d	0.94 (0.93-0.95) ^d	1.08 (1.07-1.09) ^d	0.88 (0.86-0.89) ^d	0.77 (0.73-0.80) ^d	1.01 (0.99-1.03)	1.01 (0.99-1.03)	0.95 (0.94-0.97) ^d
≥\$63,000 vs <\$39,000	0.99 (0.98-0.99) ^d	0.87 (0.86-0.88) ^d	1.11 (1.10-1.12) ^d	0.71 (0.69-0.73) ^d	0.66 (0.62-0.70) ^d	0.99 (0.96-1.02)	1.00 (0.97-1.02)	0.94 (0.92-0.95) ^d
Insurance								
Medicaid vs Medicare	1.01 (1.00-1.01) ^d	1.08 (1.07-1.10) ^d	0.94 (0.93-0.95) ^d	1.44 (1.41-1.47) ^d	1.76 (1.68-1.85) ^d	1.01 (0.98-1.04)	0.76 (0.73-0.78) ^d	0.89 (0.87-0.90) ^d
Private vs Medicare	0.97 (0.97-0.97) ^d	0.93 (0.92-0.94) ^d	1.07 (1.06-1.08) ^d	1.16 (1.14-1.18) ^d	0.67 (0.63-0.71) ^d	0.99 (0.97-1.01)	0.64 (0.62-0.66) ^d	0.77 (0.76-0.78) ^d
Self-pay vs Medicare	1.03 (1.02-1.04) ^d	0.96 (0.94-0.97) ^d	0.98 (0.97-1.00) ^f	1.56 (1.53-1.59) ^d	1.54 (1.46-1.63) ^d	0.96 (0.93-0.99) ^f	0.52 (0.50-0.55) ^d	0.65 (0.63-0.67) ^d
Other vs Medicare	0.99 (0.98-1.00)	0.99 (0.97-1.01)	1.01 (0.99-1.02)	1.42 (1.39-1.46) ^d	1.35 (1.25-1.45) ^d	0.97 (0.93-1.01)	0.63 (0.59-0.66) ^d	0.78 (0.76-0.81) ^d
Hospital region								
Midwest vs Northeast	1.01 (1.00-1.02) ^e	0.98 (0.97-1.00) ^f	1.07 (1.05-1.09) ^d	1.22 (1.18-1.28) ^d	1.00 (0.92-1.08)	1.06 (1.02-1.11) ^e	1.12 (1.08-1.16) ^d	1.00 (0.97-1.02)
South vs Northeast	1.02 (1.01-1.03) ^d	0.98 (0.97-1.00) ^f	1.05 (1.03-1.07) ^d	1.18 (1.14-1.23) ^d	0.93 (0.87-1.00) ^f	1.07 (1.03-1.11) ^e	1.06 (1.03-1.10) ^d	0.97 (0.95-0.99) ^d
West vs Northeast	1.01 (1.00-1.02)	0.94 (0.92-0.95) ^d	1.06 (1.04-1.08) ^d	1.12 (1.07-1.17) ^d	1.62 (1.51-1.75) ^d	1.00 (0.95-1.04)	1.19 (1.15-1.24) ^d	0.85 (0.83-0.87) ^d

All estimates obtained from multivariable-adjusted generalized linear models with a Poisson distribution and log-link function. Models also adjusted for hypertension, diabetes, dyslipidemia, smoking drug abuse, hypothyroidism, chronic renal failure, coronary artery disease, atrial fibrillation, congestive heart failure, peripheral vascular disease, alcohol abuse, obesity, hospital location/teaching status, and yearly stroke volume.

^a Adjustment for diabetes and dyslipidemia alone in addition to age and sex significantly attenuated effect estimate for hypertension.

^b Adjustment for hypertension and dyslipidemia alone in addition to age and sex significantly attenuated effect estimate for diabetes.

^c Adjustment for hypertension, diabetes, and dyslipidemia alone in addition to age and sex significantly attenuated effect estimate for diabetes.

^d $p < 0.001$.

^e $p < 0.01$ but ≤ 0.001 .

^f $p < 0.05$ but ≤ 0.01 .

populations may potentially yield major gains for AIS prevention as improvements in cardiovascular risk factors may be associated with decreased stroke incidence.²¹ A Centers for Disease Control and Prevention report indicates that fewer than 50% of patients with dyslipidemia are on treatment for this condition and only $\approx 30\%$ have control of their low-density lipoprotein (LDL) cholesterol.²² Up to half of the 75 million patients with hypertension in the United States have uncontrolled blood pressure and $\approx 20\%$ of patients with diabetes have hemoglobin A1c >9.0 mg/dL.²² Increased awareness of these conditions,⁸ more frequent screening, improvement in detection systems, and enhanced documentation are additional factors that may have led to increased prevalence, particularly for dyslipidemia, where prevalence estimates doubled over time. Increased hypothyroidism prevalence in AIS patients in this study could also be linked with increased dyslipidemia prevalence.

Rising drug abuse prevalence seen in this study is a direct reflection of the community-wide increase in drug abuse²³ and consistent with the results of a few studies reporting increased prevalence of substance abuse in young AIS patients in the United States.^{13,24} However, our result on increased prevalence of smoking in AIS directly contradicts current reports on trend towards nationwide reduction of cigarette use. In the French Dijon Stroke registry, smoking prevalence in patients <55 years of age also increased from the period 2003–2011 compared to the period 1994–2002.²⁵ Reasons for these disparate findings are unclear and warrant prospective evaluation, but clustering of risk factors, i.e., increase in the proportion of patients with multiple risk factors over time, may have led to this increase. In our study, the proportion of smokers with concomitant hypertension or diabetes each increased by more than 2-fold over time. Smoking potentiates stroke risk associated with these factors.^{26–28} Clustering of risk factors may also in part explain the increased prevalence seen in other factors as improvements in treatment of risk factors and life expectancy over time may have allowed for many more individuals to accrue multiple risk factors that act synergistically to further increase stroke risk.²⁹

Another noteworthy finding of this study is that rising prevalence of these risk factors was independent of age. Most risk factors increased in all age groups. In fact, mean age at AIS presentation declined over time, with a significant trend towards increasing AIS burden in middle-aged patients. These findings add to those of a growing list of recent US, Chinese, and European studies^{30–32} reporting increased burden of AIS in young to middle-aged adults as opposed to increased burden in the elderly, which would be expected with aging of the population.

This study should be viewed in the context of its limitations. We cannot exclude potential inaccuracies due to ICD-9 diagnostic coding errors. Our study of trends is based on the implicit assumption that coding practices remained unchanged over time. However, trends may have been affected by upcoding, a phenomenon where discharge records in later years contain more thorough ICD-9 coding in an effort to maximize reimbursement.^{33,34} Our trend analysis may also have been affected by changes in the definition of risk factors over time. For example, changes in diabetes definition to include hemoglobin A1C $>6.5\%$ in 2009 may have contributed to increased prevalence of diabetes after this time.³⁵ LDL cholesterol targets in very high-risk atherosclerotic CVD were updated in 2004 from <100 to <70 mg/dL,³⁶ while more recent 2013 guidelines de-emphasized specific LDL cholesterol targets.³⁷ These changes are likely to have influenced reported dyslipidemia prevalence over time. Definitions of all studied risk factors are not standardized across NIS hospitals and so create considerable potential for error and misinterpretation as definitions may differ substantially between hospitals. We are unable to differentiate between first-ever and recurrent strokes. If a significant proportion of those with poor risk factor control presented with recurrent strokes, our current prevalence estimates may be an overestimation. We, however, showed using the 2014 National Readmissions Database that high prevalence of risk factors in 2014 is not solely due to readmissions or transfers. Our study evaluated risk factor prevalence among hospitalized AIS patients alone and cannot provide information on trends for the overall population. Our race-stratified analysis should be viewed with caution as up to 15.5% of patients had missing race. We cannot provide information on the degree of control of individual factors including medication use, hemoglobin A1c levels, degree of carotid stenosis, or renal impairment before AIS admission due to inherent limitations of ICD-9 databases. Although we adjusted for an extensive list of covariates in our multivariable models, we cannot exclude residual confounding due to uncontrolled factors. Obesity and alcohol abuse are underestimated in the NIS³⁸ and therefore we were unable to fully assess these factors. Increased prevalence of dyslipidemia could be related to more testing for lipid abnormalities after studies showing benefits of statins for stroke prevention.³⁹

Despite these limitations, our study represents the most comprehensive assessment to date of temporal trends in the prevalence of major stroke risk factors among hospitalized AIS patients in the United States. Important strengths of our study include better AIS case ascertainment by use of clinically diagnosed AIS as opposed to self-reported stroke and

generalizability of our results to the entire US population. Through our robust stratified analysis, we provide reference data for individual factors in various subsets of the population that may be potentially useful to clinical providers, researchers, and health care policy makers. Focusing on risk factor control is critical for stroke prevention. Our alarming findings support the call for further concerted action from all stakeholders to more effectively implement evidence-based interventions to reduce stroke risk.

AUTHOR CONTRIBUTIONS

Dr. Otite had full access to all of the study data and takes responsibility for the integrity and accuracy of the data analysis. Study concept and design: Drs. Otite and Chaturvedi. Acquisition, analysis, and interpretation of data: All authors. Drafting of the manuscript: Dr. Otite. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Dr. Otite. Administrative, technical, or material support: Drs. Malik, Chaturvedi, Sacco, and Romano. Study supervision: Dr. Chaturvedi.

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