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Weight of the Obesity Epidemic

Rising Stroke Rates Among Middle-Aged Women in the United States

Amytis Towfighi, MD; Ling Zheng, PhD; Bruce Ovbiagele, MD

Background and Purpose—Recent US nationally representative data revealed that among individuals aged 45 to 54 years, women's stroke prevalence was double that of men's. The purpose of this study was to determine if the sex disparity existed previously.

Methods—We assessed sex-specific stroke and vascular risk factor prevalence among individuals aged 35 to 64 years who participated in the National Health and Nutrition Examination Surveys (NHANES), a cross-sectional, nationally representative survey conducted in 2 waves: 1988 to 1994 (n=7234) and 1999 to 2004 (n=6499).

Results—Women aged 35 to 54 years who participated in NHANES from 1999 to 2004 were 3 times more likely to have experienced a stroke compared with similarly aged women in NHANES 1988 to 1994 (1.8% versus 0.6%, $P=0.003$), but stroke prevalence among men did not change (0.9% versus 1.0%, nonsignificant). Among women, the prevalence of obesity (15.2% versus 17.9%, $P=0.08$), morbid obesity (12.8% versus 17.5%, $P=0.003$), abdominal obesity (47.4% versus 58.9%, $P<0.0001$), hypertriglyceridemia (22.91% versus 26.78%, $P=0.035$), and hypertension (33.04% versus 37.43%, $P=0.03$) was lower in NHANES 1988 to 1994 compared with the more recent NHANES wave. Higher waist circumference was the only independent stroke risk factor for women aged 35 to 54 years in NHANES 1999 to 2004 (OR per 15-cm increase in waist circumference=1.02, 95% CI 1.00 to 1.04).

Conclusions—Stroke prevalence among women aged 35 to 54 years has tripled over the past 2 decades, at the same time remaining stable among men. Prevalence of obesity and 3 metabolic syndrome components increased; they may be key factors in the increase in women's stroke prevalence. (*Stroke*. 2010;41:1371-1375.)

Key Words: NHANES ■ middle-aged ■ sex disparity ■ stroke ■ women

An analysis of US stroke prevalence rates from 1999 to 2004 revealed that women aged 45 to 54 years were more than twice as likely as similarly aged men to report having experienced a stroke.¹ It is unclear whether this sex disparity in stroke prevalence is new or if it existed previously. In this study, we aimed to determine whether the recently noted sex disparity in midlife stroke prevalence was a new phenomenon. If indeed new, we intended to explore potential reasons for this recent rise in women's stroke prevalence by determining: (1) independent predictors of stroke; and (2) temporal trends in vascular risk factors, key physical and laboratory measurements, and medication use.

Methods

Overall Design and Study Population

The National Health and Nutrition Examination Surveys (NHANES) are cross-sectional samples of the US civilian noninstitutionalized population conducted by the National Center for Health Statistics. NHANES analyzed were conducted from 1988 to 1994 in 2 phases and from 1999 to 2004 in 3 phases; the data from the 2 phases and 3 phases, respectively, were combined following National Center for Health Statistics recommendations.^{2,3} The National Center for Health Statistics Institutional Review Board approved all protocols

for conduct and informed consent was obtained from all participants.^{4,5} The sampling plan followed a complex, stratified, multi-stage, probability cluster design with oversampling of non-Hispanic blacks, Mexican Americans, and the elderly to enhance the precision of prevalence estimates in those groups.

Interviews collected demographic, socioeconomic, dietary, and health-related information. Mobile examinations consisted of medical and dental examinations, physiological measurements, and laboratory tests. Details of the survey design and examination procedures have been previously published.^{4,5}

The respective participation rates for the questionnaire and examination components were 86% and 78% for NHANES 1988 to 1994, 82% and 76% for 1999 to 2000, 84% and 80% for 2001 to 2002, and 79% and 76% for 2003 to 2004. The numbers examined were 30 818 persons in NHANES 1988 to 1994 and 29 402 persons in NHANES 1999 to 2004. Our analysis was limited to individuals aged 35 to 64 years who answered the question regarding prior physician diagnosis of stroke (n=7234 for NHANES 1988 to 1994 and n=6499 for NHANES 1999 to 2004).

Primary Predictor Variable

Stroke history was determined by self-reported history of a physician diagnosis of stroke.

Covariates

Covariates included cardiovascular, hematologic, lifestyle, and sociodemographic variables known to be associated with stroke.

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Categorical variables included sex, age, race/ethnicity, hypertension, diabetes mellitus, history of smoking, history of myocardial infarction, current atrial fibrillation, hypercholesterolemia, elevated low-density lipoprotein (LDL) level, hypertriglyceridemia, low high-density lipoprotein (HDL) level, abdominal obesity, obesity, history of cocaine use, history of oral contraceptive pill use, history of hormone replacement therapy, elevated homocysteine level, and metabolic syndrome. Continuous covariates included waist circumference, body mass index (BMI), systolic blood pressure, diastolic blood pressure, and levels of total cholesterol, LDL cholesterol, triglyceride, HDL cholesterol, luteinizing hormone, follicle-stimulating hormone, glycosylated hemoglobin, and homocysteine.

Information on age, sex, race/ethnicity (categorized as non-Hispanic white, non-Hispanic black, Hispanic, or other), medical history, and medication use was determined by self-report. Smoking was defined by self-reported history of smoking >100 cigarettes. History of myocardial infarction was defined by self-reported physician diagnosis. Current atrial fibrillation was defined by detection of an "irregular pulse" on examination. Hypercholesterolemia was defined by a self-reported physician diagnosis, self-reported current medical therapy, or total cholesterol level >200 mg/dL. Elevated LDL was defined as LDL level >100 mg/dL. BMI was calculated from height and weight (kg/m²) measured using standardized examination protocols. Overweight was defined as BMI 25 to 29.9 kg/m², obesity was defined as BMI 30.0 to 35.0 kg/m², and morbid obesity was defined as BMI >35 kg/m². Elevated homocysteine was defined as homocysteine level ≥ 8.5 $\mu\text{mol/L}$. Metabolic syndrome was defined by the presence of ≥ 3 factors: (1) abdominal obesity (waist circumference ≥ 88 cm); (2) hypertriglyceridemia (≥ 150 mg/dL or use of fibrates or niacin); (3) low HDL (<50 mg/dL or use of fibrates or niacin); (4) hypertension (mean of first 3 blood pressure readings $\geq 130/85$ mm Hg, a self-reported physician diagnosis, or self-reported current medical therapy); and (5) insulin resistance (self-reported physician diagnosis, self-reported current medical therapy [insulin or oral agents], or glycosylated hemoglobin level >6.0%). This definition differs from the modified Adult Treatment Panel III definition with respect to insulin resistance classification.⁶ Our sample had a large number of missing fasting serum samples precluding use of fasting glucose; therefore, we used glycosylated hemoglobin, a better index of overall glycemic exposure and risk for long-term complications than fasting glucose levels.⁷ Currently, the recommended glycosylated hemoglobin cut point for a diabetes mellitus diagnosis is a level >6.5%.⁷ Individuals with a level ranging from 6.0% to 6.5% are considered at high risk for developing diabetes mellitus and have been found to have evidence of end-organ damage⁷; therefore, a cutoff of 6.0% was chosen for insulin resistance.

Multivariable Models

Tests based on the correlation matrix were conducted to rule out collinearity before running the multivariable logistic regression analysis. The following variables were excluded from the model due to the large number of missing variables: LDL cholesterol, triglyceride, homocysteine, luteinizing hormone, and follicle-stimulating hormone levels. Subjects who identified their race as "other" were excluded because none had strokes.

Statistical Analysis

Sample weights and the stratification and clustering of the design were incorporated into our analyses to get proper estimates and SEs of estimates.^{2,3} Bivariate and multivariable logistic regression analyses were performed to evaluate predictors of whether the person had experienced a stroke. The primary reported statistics are the estimated ORs. All data analyses were conducted using SAS (Version 9.1; SAS Institute Inc, Cary, NC). Statistical hypotheses were tested using $P < 0.05$ as the level of significance.

Results

The demographics of the study populations were similar in the 2 NHANES waves (Table 1). Table 2 shows age- and sex-specific stroke prevalence. During NHANES 1988 to

Table 1. Population Characteristics of US Adults Aged 35–54 Years in NHANES 1988–1994 and NHANES 1999–2004

	NHANES 1988–1994	NHANES 1999–2004
Total, no.	5112	4594
Age 35–44 years, no.	3134	2430
Age 45–54 years, no.	1978	2164
Sex		
Female, no.	2784	2361
Mean age (SE)	43.06 (0.16)	44.16 (0.20)
Male, no.	2328	2233
Mean age (SE)	43.16 (0.15)	44.16 (0.14)
Women 35–54 years		
Non-Hispanic white, no.	1009	1077
Non-Hispanic black, no.	902	528
Hispanic, no.	822	662
Other, no.	51	94
Men 35–54 years		
Non-Hispanic white, no.	851	1067
Non-Hispanic black, no.	701	487
Hispanic, no.	737	597
Other, no.	39	82

1994, there were no sex differences in stroke prevalence among individuals aged 35 to 44, 45 to 54, or 55 to 64 years. During NHANES 1999 to 2004, however, a sex disparity emerged among 45 to 54 year olds (1.04% among men versus 2.45% among women, $P = 0.0038$). Comparing stroke prevalence across NHANES waves revealed that women aged 35 to 44 years in the latter NHANES wave were >3 times as likely as women in the previous wave to report a previous stroke (1.16% versus 0.35%, $P = 0.044$), and women aged 45 to 54 were more than twice as likely as those in the previous wave to report a previous stroke (2.45% versus 1.08%, $P = 0.062$). Among men, however, there was no significant difference in stroke prevalence for each age group.

Merging the 35- to 44-year and 45- to 54-year age groups revealed that among 35 to 54 year olds, there was no midlife sex disparity prevalent stroke in NHANES 1988 to 1994 (0.6% [SE 0.2%] of 2784 women versus 0.9% [SE 0.2%] of 2328 men, $P = 0.35$), but in NHANES 1999 to 2004, women were almost twice as likely as men to report prevalent stroke (1.8% [SE 0.3] of 2360 women versus 1.0% [SE 0.2%] of 2231 men, $P = 0.01$). The tripling of stroke prevalence among women aged 35 to 54 years (1.8% versus 0.6%, $P = 0.003$), in the setting of stable stroke prevalence rates among similarly aged men, thus accounted for the observed sex disparity in midlife stroke prevalence.

Comparison of vascular risk factors across NHANES waves revealed that women aged 35 to 54 years in the more recent wave were more likely to have hypertension (37.43% versus 33.04%, $P = 0.03$), hypertriglyceridemia (26.78% versus 22.91%, $P = 0.035$), abdominal obesity (58.89% versus 47.36%, $P < 0.0001$), obesity (17.9% versus 15.2%, $P = 0.08$), morbid obesity (17.5% versus 12.8%, $P = 0.003$), and atrial fibrillation (2.0% versus 0.87%, $P = 0.0062$) than a decade prior. They were more likely to take medications for hypertension (14.8% versus 8.9%, $P < 0.0001$) and dyslipidemia (3.8% versus 1.4%,

Table 2. Age- and Sex-Specific Stroke Prevalence in NHANES 1988–1994 and NHANES 1999–2004

Age Group, Years	No.	NHANES 1988–1994 Stroke Prevalence, % (SE%)	No.	NHANES 1999–2004 Stroke Prevalence, % (SE%)	P
Women					
35–44	1732	0.35 (0.18)	1258	1.16 (0.40)	0.044
45–54	1052	1.08 (0.41)	1102	2.45 (0.58)	0.062
55–64	1089	3.02 (0.67)	980	3.38 (0.77)	0.73
Men					
35–44	1402	0.42 (0.24)	1170	0.96 (0.32)	0.19
45–54	926	1.68 (0.59)	1061	1.04 (0.29)	0.28
55–64	1033	3.15 (0.92)	928	3.02 (0.60)	0.88
Age Group, Years	No.	Stroke Prevalence Among Men, % (SE%)	No.	Stroke Prevalence Among Women, % (SE%)	P
NHANES 1988–1994					
35–44	1402	0.42 (0.24)	1732	0.35 (0.18)	0.80
45–54	926	1.68 (0.59)	1052	1.08 (0.41)	0.45
55–64	1033	3.15 (0.92)	1089	3.02 (0.67)	0.91
NHANES 1999–2004					
35–44	1170	0.96 (0.32)	1258	1.16 (0.40)	0.78
45–54	1061	1.04 (0.29)	1102	2.45 (0.58)	0.0038
55–64	928	3.02 (0.60)	980	3.38 (0.77)	0.68

P=0.0014) but were less likely to take hormone replacement therapy (23.1% versus 46.5%, *P*<0.0001). Comparison of anthropometric and laboratory values revealed that women in the more recent NHANES wave had higher mean waist circumference (93.6 cm versus 89.7 cm, *P*<0.0001), BMI (28.7 kg/m² versus 27.2 kg/m², *P*<0.0001), glycosylated hemoglobin (5.4% versus 5.3%, *P*=0.0419), HDL (57.0 mg/dL versus 55.1 mg/dL, *P*=0.0123), and luteinizing hormone (17.9 IU/L versus 10.3 IU/L, *P*<0.0001) levels and lower homocysteine (7.7 μmol/L versus 8.5 μmol/L, *P*=0.0002) levels compared with women a decade prior (Table 3). Although the prevalence of metabolic syndrome did not change, women in the more recent study were more likely to have 3 components of metabolic syndrome (abdominal obesity, hypertension, and hypertriglyceridemia; Table 3).

Numerous factors increased the odds of previous stroke on bivariate analysis (Supplemental Table I; available at <http://stroke.ahajournals.org>). After adjusting for confounders, increase in age (per 5-year increase OR 1.16, 95% CI 1.06 to 1.28), black non-Hispanic race/ethnicity (OR 4.22, 95% CI 1.19 to 14.94), history of myocardial infarction (OR 7.73, 95% CI 1.16 to 51.67), history of smoking (OR 5.27, 95% CI 1.36 to 20.37), and increase in total cholesterol level (per 40-mg/dL increase OR 1.02, 95% CI 1.01 to 1.03) were independently associated with stroke among women aged 35 to 54 years in the first NHANES wave, but waist circumference (per 15-cm increase OR 1.02, 95% CI 1.00 to 1.04) was the only independent risk factor for stroke among women aged 35 to 54 years in the more recent NHANES wave (Table 4).

Discussion

The prevalence of stroke among US women aged 35 to 54 years has tripled over the 2 most recent decades, whereas prevalence among similarly aged men has remained stable. Women aged 35

to 54 years are now almost twice as likely to report having had a stroke compared with men. Whether comparing women across epochs or with their similarly aged male counterparts, it certainly appears that the previously reported recent surge in nationwide stroke prevalence rates among women in this age group is indeed a new phenomenon.¹

Women aged 35 to 54 years are more likely to be obese and morbidly obese than in the previous decade. Not surprisingly, key components of the metabolic syndrome (abdominal obesity, hypertension, and hypertriglyceridemia) have become more prevalent among women aged 35 to 54 years.

Blood pressure levels and lipid profiles were better among women who participated in the most recent NHANES wave, perhaps as a result of increased use of antihypertensive and lipid-lowering medications. On the other hand, the lack of any changes in use of medications for diabetes mellitus, in the setting of an increase in abdominal and general obesity, was associated with higher glycosylated hemoglobin levels. In addition, women in the most recent NHANES wave had higher luteinizing hormone levels, perhaps due to the increase in obesity, which is associated with polycystic ovary syndrome.⁸ The improved homocysteine levels may be a consequence of folic acid fortification of enriched grain products, which became mandatory in 1998.

Although several vascular risk factors were independently associated with prevalent stroke among women aged 35 to 54 years who participated in NHANES 1988 to 1994, higher waist circumference was the only risk factor independently associated with prevalent stroke among midlife women who participated in NHANES 1999 to 2004. This result may lend support to our hypothesis that the increase in stroke prevalence among women aged 35 to 54 years may be related to worsening national obesity rates differentially and adversely affecting women at midlife.¹ Of course, one cannot make

Table 3. Comparison of Medical History, Biomarkers, and Medication Use Among Women Aged 35–54 Years Who Participated in NHANES 1988–1994 Versus NHANES 1999–2004

Women Aged 35–54 Years	NHANES 1988–1994		NHANES 1999–2004		P
	No.	Percent (SE)	No.	Percent (SE)	
Vascular risk factors					
History of smoking	2784	47.6 (1.5)	2359	46.0 (1.4)	0.4068
History of myocardial infarction	2583	0.73 (0.20)	2361	1.0 (0.19)	0.3803
Current atrial fibrillation	2688	0.87 (0.23)	2361	2.0 (0.36)	0.0062
Metabolic syndrome	2642	23.34 (1.49)	1859	25.00 (1.21)	0.42
Anthropometric measurements and laboratory values					
	No.	Mean (SE)	No.	Mean (SE)	P
Waist circumference, cm	2658	89.7 (0.54)	2261	93.6 (0.49)	<0.0001
BMI, kg/m ²	2779	27.2 (0.25)	2303	28.7 (0.22)	<0.0001
Systolic blood pressure, mm Hg	2698	118.9 (0.37)	2215	118.6 (0.46)	0.5341
LDL cholesterol level, mg/dL	1185	123.0 (1.8)	989	120.2 (1.5)	0.2256
Total cholesterol level, mg/dL	2651	203.5 (1.2)	2201	203.6 (1.1)	0.9907
HDL cholesterol level, mg/dL	2625	55.1 (0.47)	2202	57.0 (0.54)	0.0123
Triglyceride level, mg/dL	2644	128.0 (4.6)	1046	130.4 (4.6)	0.7214
Glycosylated hemoglobin, %	2685	5.3 (0.034)	2244	5.4 (0.025)	0.0419
Homocysteine level, μmol/L	1308	8.5 (0.13)	2237	7.7 (0.069)	0.0002
C-reactive protein level, mg/dL	2635	0.45 (0.019)	2220	0.50 (0.023)	0.0666
Follicle-stimulating hormone level, IU/L	2579	22.1 (0.91)	1469	24.2 (1.1)	0.3035
Luteinizing hormone level, IU/L	2578	10.3 (0.35)	1470	17.9 (0.71)	<0.0001
	No.	Percent (SE)	No.	Percent (SE)	P
BMI <25 kg/m ² , %	2779	46.4 (1.9)	2303	36.8 (1.5)	<0.0001
BMI 25–29 kg/m ² , %	2779	25.7 (1.2)	2303	27.9 (1.2)	0.20
BMI 30–35 kg/m ² , %	2779	15.2 (0.98)	2303	17.9 (1.11)	0.08
BMI >35 kg/m ² , %	2779	12.8 (1.2)	2303	17.5 (1.03)	0.003
Current medications					
Hormone replacement therapy	952	46.5 (2.1)	2132	23.1 (1.4)	<0.0001
Anticoagulant medication	2784	0.41 (0.20)	1612	0.57 (0.16)	0.4922
Antihypertensive medication	2784	8.9 (0.76)	1612	14.8 (1.1)	<0.0001
Antiplatelet medication	2784	0.18 (0.18)	1612	0.34 (0.15)	0.6400
Diabetes mellitus medication	2784	2.2 (0.54)	1612	3.3 (0.44)	0.1215
Lipid-lowering medication	2784	1.4 (0.41)	1612	3.8 (0.44)	0.0014
Metabolic syndrome components					
Abdominal obesity (waist circumference ≥88 cm)	2658	47.36 (1.57)	2261	58.89 (1.42)	<0.0001
Hypertriglyceridemia (≥150 mg/dL)	2644	22.91 (1.49)	1046	26.78 (1.19)	0.035
Low HDL level (<50 mg/dL)	2625	38.9 (1.52)	2202	36.99 (1.46)	0.35
Hypertension	2720	33.04 (1.42)	2260	37.43 (1.28)	0.03
Insulin resistance	2784	8.19 (0.90)	2361	8.15 (0.66)	0.97

causal associations in a cross-sectional study and future prospective studies are necessary.

This study has several limitations. First, NHANES relies on self-report of medical history, including history of stroke. Although NHANES has not validated self-reporting of stroke, previous studies have shown a sensitivity ranging from 80% to 95% and specificity ranging from 96% to 99%.^{9,10} Although enhanced media attention and stroke education may have resulted in more women than men reporting strokes, we are unaware of such a recent sex disparity in stroke reporting. Second, because NHANES does not assess incidence, it is not possible to determine if the changes in prevalence were due to changes in incidence or survival. However, data from the US

Centers for Disease Control and Prevention WONDER (Wide-ranging Online Data for Epidemiologic Research) database revealed that from 1999 to 2003, there were no sex differences in stroke mortality in individuals younger than age 45 years, suggesting that the differences observed in prevalence were due to changes in incidence.¹¹ Supporting this theory, the Greater Cincinnati–Northern Kentucky Stroke Study found that at age <35 years, women had higher stroke incidence than men.¹² Third, a substantial proportion of stroke survivors may have severe disabilities necessitating nursing home placement, thus precluding their participation in NHANES.¹³ However, it is unlikely that there were significant differences in the numbers of individuals discharged to long-term care after

Table 4. Multivariable Logistic Regression Model for Stroke Risk Among Women Aged 35–54 Years Who Participated in NHANES 1988–1994 and NHANES 1999–2004

Variable	Unit Change	NHANES 1988–1994 (n=2293)			NHANES 1999–2004 (n=2033)		
		OR	95% CI	P	OR	95% CI	P
Age	5 years	1.16	1.06–1.28	0.0024	1.07	0.99–1.16	0.1038
Black non-Hispanic (versus all others)		4.22	1.19–14.94	0.0256	1.46	0.68–3.12	0.3276
History of myocardial infarction		7.73	1.16–51.67	0.0349	3.13	0.74–13.16	0.1196
History of smoking		5.27	1.36–20.37	0.0159	2.10	1.00–4.44	0.0512
Diastolic blood pressure	20 mm Hg	1.02	0.97–1.07	0.4041	1.03	1.00–1.06	0.0813
Total cholesterol level	40 mg/dL	1.02	1.01–1.03	0.0002	1.00	1.00–1.01	0.3664
Glycosylated hemoglobin	1%	0.95	0.13–6.79	0.9594	1.03	0.75–1.4	0.8425
Waist circumference	15 cm	1.03	0.98–1.09	0.2228	1.02	1.00–1.04	0.0104

strokes in the 2 NHANES waves. In addition, women are more likely than men to be discharged to nursing homes and long-term care¹⁴; therefore, women with stroke are less likely to be captured by NHANES. Fourth, the prevalence of stroke in this age group was low, limiting the precision of estimates. Fifth, this study was cross-sectional; because both risk factors and prevalent stroke were assessed simultaneously, it is not possible to ascertain whether the risk factors preceded the stroke. Sixth, NHANES does not classify ischemic stroke subtype or differentiate hemorrhagic from ischemic strokes. Given the higher prevalence of atrial fibrillation among women aged 35 to 54 years in the most recent NHANES wave, stroke subtype classification would have been helpful. Although ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage have different risk factors, most strokes are presumably ischemic given the epidemiological breakdown of strokes. Finally, there were a large number of missing data for certain variables (such as LDL cholesterol, homocysteine, follicle-stimulating hormone, luteinizing hormone, triglyceride level, and hormone replacement therapy). Nevertheless, a strength of the study is the inclusion of a multitude of covariates (incorporating medical history, biomarkers, and medication use) and rigorous standardized biomarker assessment by trained staff within NHANES.

This study has several implications. First, it challenges the traditional thinking that men aged 35 to 54 years have a similar or higher stroke prevalence compared with their female counterparts. Although there are limited data on sex- and age-specific stroke prevalence rates, the REGARDS (REasons for Geographic And Racial Differences in Stroke) study,¹⁵ which is not nationally representative, found that fewer women than men have prevalent stroke at age 45 to 54 years.¹¹ Second, it corroborates other studies revealing a concerning trend of increasing prevalence of obesity among adults, including midlife women.¹⁶ Finally, it shows that despite improvements in vascular risk factor control, stroke prevalence has increased in midlife women. Perhaps a key to curbing this trend is to focus on mitigating the growing obesity epidemic. Nationally representative longitudinal studies are warranted to determine if the apparent increase in stroke prevalence among women aged 35 to 54 years is due to an increase in incident strokes among young and middle-aged women.

Disclosures

None.

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