NEUROLOGY

A midlife stroke surge among women in the United States

Amytis Towfighi, Jeffrey L. Saver, Rita Engelhardt and Bruce Ovbiagele

Neurology 2007;69;1898-1904; originally published online Jun 20, 2007;
DOI: 10.1212/01.wnl.0000268491.89956.c2

This information is current as of November 15, 2007

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://www.neurology.org/cgi/content/full/69/20/1898

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2007 by AAN Enterprises, Inc. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.

Downloaded from www.neurology.org by NERSES SANOSSIAN on November 15, 2007

A midlife stroke surge among women in the United States

Amytis Towfighi, MD
Jeffrey L. Saver, MD
Rita Engelhardt, DrPH
Bruce Ovbiagele, MD

Address correspondence and reprint requests to Dr. Amytis Towfighi, Stroke Center and Department of Neurology, University of California at Los Angeles, 710 Westwood Plaza, Los Angeles, CA 90095
towfighi@usc.edu

ABSTRACT

Background: We assessed sex differences in stroke prevalence among individuals of midlife age (35 to 64 years) in the United States and determined factors predicting stroke.

Methods: Data from 1999 to 2004 (n = 17,061) from the National Health and Nutrition Examination Survey, a nationally representative sample of US adults, were used to assess sex differences in stroke prevalence and to identify independent predictors of stroke occurrence among middle-aged individuals.

Results: Women aged 45 to 54 years had significantly higher odds of having experienced a stroke vs men of the same age (odds ratio [OR] 2.39, 95% CI 1.32 to 4.32). No other significant midlife stroke differences between sexes were noted. A higher stroke trend was seen in 45- to 54-year-old women vs 35- to 44-year-old women (OR 2.13, 95% CI 0.95 to 4.80, $p = 0.067$), but no difference was seen in stroke rates in 55- to 64-year-old women vs 45- to 54-year-old women (OR 1.40, 95% CI 0.6912 to 2.8229, $p = 0.352$). Independent predictors of stroke in women aged 45 to 54 years were coronary artery disease (OR 12.790, 95% CI 1.901 to 86.063, $p = 0.009$) and waist circumference (OR 1.543, 95% CI 1.002 to 2.376, $p = 0.049$). Several vascular risk factors including systolic blood pressure and total cholesterol levels increased at higher rates among women compared with men in each successively older cohort from 35 to 64 years.

Conclusions: A higher prevalence of stroke may exist among women aged 45 to 54 years compared with similarly aged men. This potential disparity could be due in part to inadequate stroke risk factor modification in women and is deserving of further study.
Neurology® 2007;69:1898–1904

GLOSSARY

ABPI = ankle-brachial pressure index; **CAD** = coronary artery disease; **DM** = diabetes mellitus; **NHANES** = National Health and Nutrition Examination Survey.

Although the majority of strokes occur in individuals aged 65 years or older, younger persons, particularly those in their midlife years (aged 35 to 64 years), are also at risk.[1] In particular, women younger than 65 years harbor unique risk factors for stroke, including pregnancy, oral contraceptive use, higher prevalence of migraines, and use of hormone replacement therapy,[2] and with recent data suggesting a sex differential in response to certain stroke prevention therapies,[3] further understanding of the sex-specific differences in the frequency and predictors of stroke among persons at midlife could be important.[4]

The objective of this study was twofold. The first aim was to assess sex differences in stroke prevalence rates in the midlife years and to identify potential determinants of these differences. The second aim was to assess stroke and vascular risk factor rates across successive decades in the midlife years in both men and women and determine independent predictors of stroke.

Editorial, see page 1894

e-Pub ahead of print on June 20, 2007, at www.neurology.org.

From the Stroke Center and Department of Neurology (A.T., J.L.S., B.O.) and Department of Biomathematics (R.E.), UCLA Medical Center, Los Angeles, California.

Disclosure: The authors report no conflicts of interest.

Copyright © 2007 by AAN Enterprises, Inc.
Downloaded from www.neurology.org by NERSES SANOSSIAN on November 15, 2007
Copyright © by AAN Enterprises, Inc. Unauthorized reproduction of this article is prohibited.

Table 1 Comparison of stroke prevalence in men vs women and across age groups 35 to 64 years in NHANES 1999 to 2004

Variable	Comparators		Odds ratio	95% CI	*p* Value
Age group	Women*	Men*			
35-44 years	1.2%	1.0%	1.2142	0.4715-3.1268	0.6876
45-54 years	2.5%	1.0%	2.3903	1.3205-4.3267	0.0040
55-64 years	3.4%	3.0%	1.1256	0.6218-2.0376	0.6961
Sex	Age group	Age group			
Female	45-54 years	35-44 years	2.1346	0.9491-4.8011	0.0667
Female	55-64 years	45-54 years	1.3969	0.6912-2.8229	0.3518
Female	55-64 years	35-44 years	2.9818	1.3329-6.6704	0.0078
Sex	Age group	Age group			
Male	45-54 years	35-44 years	1.0843	0.4303-2.7322	0.8637
Male	55-64 years	45-54 years	2.9665	1.5407-5.7115	0.0011
Male	55-64 years	35-44 years	3.2165	1.4735-7.0213	0.0034

* Mobile Exam Center weighted percentages.
NHANES = National Health and Nutrition Examination Survey.

METHODS **Subjects and methods.** The Centers for Disease Control and Prevention conducted the National Health and Nutrition Examination Surveys (NHANES) 1999 to 2000, 2001 to 2002, and 2003 to 2004 to estimate the prevalence of common chronic conditions and associated risk factors among a nationally representative sample of the civilian, noninstitutionalized US population. The surveys included oversampling of low-income persons, adolescents aged 12 to 19 years, persons older than age 60 years, African Americans, and Mexican Americans.

The NHANES detailed interview included demographic, socioeconomic, dietary, and health-related questions. The examination component consisted of medical and dental examinations, physiologic measurements, and laboratory tests.

The study sample included 17,061 subjects, aged 18 years and older, who participated in the NHANES surveys from 1999 to 2004. During the household interview, participants were asked whether a physician had ever told them that they had experienced a stroke; persons who answered in the affirmative were defined as having the condition.

Statistical analysis. NHANES data sets were downloaded from the National Center for Health Statistics Web site (http://www.cdc.gov/nchs) for the survey years 1999 to 2000, 2001 to 2002, and 2003 to 2004. We analyzed demographic, clinical, and biomarker data, based on previous literature depicting major stroke risk factors.[5,6] The demographic variables analyzed included age, sex, race, ethnicity, and education. Medical history variables studied included history of migraine or headache within the 3 months preceding the survey, history of hypertension, diabetes mellitus (DM), coronary artery disease (CAD), myocardial infarction, smoking, illicit drug use, and history or current use of hormone replacement therapy. NHANES did not specifically ask about history of TIA; therefore, this variable could not be evaluated. Biomarkers evaluated included body mass index, waist circumference, systolic blood pressure, ankle–brachial pressure index (ABPI), homocysteine, glycohemoglobin, total cholesterol, low-density lipoprotein cholesterol, follicle-stimulating hormone, and luteinizing hormone.

Data analysis was performed in SAS 9.1. A sampling weight was calculated according to the NHANES Analytic and Reporting Guidelines.[7] The multivariable logistic regression analysis evaluated predictors of whether the person had experienced a stroke. The primary reported statistics are the estimated odds ratios (ORs).

RESULTS Of 17,061 adults surveyed from 1999 to 2004, 15,309 (90%) responded to the interview question about stroke. Among the respondents, 606 (4%) individuals reported having experienced a stroke; 51% were men and 49% were women. Men and women had a similar prevalence of stroke at age 35 to 44 years, but women aged 45 to 54 years were more than twice as likely to have had a stroke than men (table 1). At age 55 to 64 years, there was again almost equal sex prevalence of stroke. Not surprisingly, because increasing age is a well-established predictor of higher stroke risk, the highest age groups in both men and women were significantly more likely to have reported having experienced a stroke compared with the lowest age groups (table 1).

In the 45- to 54-year age group, single stroke presence predictors in women included increased waist circumference, higher glycohemoglobin, occurrence of severe headache or migraine in the 3 months preceding the survey, and history of hypertension, DM, or CAD (table 2). Stroke predictors in men of this age group included nonwhite race/non-Hispanic ethnicity, low ABPI, higher glycohemoglobin, occurrence of severe headache or migraine in the 3 months preceding the survey, and history of hypertension, DM, or CAD (table 2). The frequency of stroke in subjects with atrial

Downloaded from www.neurology.org by NERSES SANOSSIAN on November 15, 2007
Copyright © by AAN Enterprises, Inc. Unauthorized reproduction of this article is prohibited.

Table 2	Bivariate analysis for predictors of stroke in men and women aged 45 to 54 years			
	Men, n = 1,117		Women, n = 1,155	
Variable	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value
Other race (vs white)	4.503 (1.389-14.597)	0.0121	2.345 (0.949-5.798)	0.0649
Hispanic	2.557 (0.451-14.503)	0.2889	0.542 (0.169-1.739)	0.3034
Waist circumference, Δ = 15 cm*	1.321 (0.717-2.435)	0.3716	1.564 (1.144-2.138)	0.0051
Average systolic blood pressure, Δ = 20 mm Hg*	1.369 (0.627-2.987)	0.4302	1.085 (0.660-1.787)	0.7470
Homocysteine, Δ = 5 μmol/L*	1.160 (0.955-1.409)	0.1341	1.037 (0.711-1.511)	0.8508
Glycohemoglobin, Δ = 1%*	1.301 (1.082-1.564)	0.0052	1.388 (1.102-1.749)	0.0054
Total cholesterol, Δ = 40 mg/dL*	0.846 (0.533-1.341)	0.4757	1.574 (0.941-2.634)	0.0840
LDL cholesterol, Δ = 36 mg/dL*	0.725 (0.489-1.073)	0.1076	1.676 (0.760-3.698)	0.2005
Follicle stimulating hormone, Δ = 30 IU/L*	Not applicable	—	0.959 (0.562-1.636)	0.8784
Luteinizing hormone, Δ = 20 IU/L*	Not applicable	—	1.074 (0.750-1.538)	0.6974
Recent severe headache or migraine	3.781 (1.255-11.385)	0.0181	3.749 (1.627-8.639)	0.0019
History of atrial fibrillation	†	—	3.200 (0.490-20.907)	0.2246
History of hypertension	5.728 (1.505-21.803)	0.0105	3.808 (1.591-9.114)	0.0027
History of diabetes	2.842 (1.014-7.965)	0.0469	3.502 (1.161-10.568)	0.0261
History of smoking	‡	—	1.276 (0.595-2.736)	0.5318
History of coronary artery disease	8.966 (1.519-52.939)	0.0155	6.425 (1.348-30.630)	0.0196
History of illicit drug use	0.179 (0.023-1.416)	0.1030	0.845 (0.144-4.951)	0.8521
Hormone replacement treatment	Not applicable	—	0.976 (0.393-2.425)	0.9584

* Odds ratio (OR) is based on specified change, Δ, in variable units.
† No subjects with atrial fibrillation had a stroke in this group.
‡ All subjects who had strokes had smoked; therefore, OR is undefined.
LDL = low-density lipoprotein.

fibrillation was low; no men aged 45 to 54 years with atrial fibrillation had a stroke, and only two women aged 45 to 54 years with atrial fibrillation had a stroke (table 2). Because of the low frequencies of atrial fibrillation and stroke, atrial fibrillation was not included in the multivariable logistic regression model. In the sex-specific multivariable logistic regression model (after adjustment for race, ethnicity, waist circumference, average systolic blood pressure, homocysteine, glycohemoglobin, total cholesterol, history of hypertension, history of DM, history of smoking, and history of CAD), a history of smoking was the only independent predictor of stroke in men aged 45 to 54 years to the extent that all stroke victims had smoked. In women, after multivariable analyses (including all of the aforementioned variables adjusted for in men, plus any use of hormone replacement therapy), CAD (OR 12.79, 95% CI 1.901 to 86.063, $p = 0.0088$) and waist circumference (OR 1.543 95% CI 1.002 to 2.376, $p = 0.0489$) were the only independent predictors of stroke. History or current use of hormone replacement therapy was not a significant predictor of stroke in 45- to 54-year-old women in bivariate or multivariable analyses.

We created a separate sex-specific multivariable logistic regression model with occurrence of severe headache or migraine in the preceding 3 months added to the model. This analysis was conducted separately because although migraine has been associated with a higher risk of stroke[8] as was confirmed in our bivariate analysis, the nature of the NHANES survey question for migraines also included any severe nonspecific headache, and excluded persons who had not experienced migraine within the 3 months preceding the survey. When this migraine variable was included in the multivariable analysis for women, it was an independent predictor of stroke (OR 4.859, 95% CI 1.864 to 12.669, $p = 0.0012$), with presence of coronary artery disease still an independent stroke predictor (OR 7.062, 95% CI 1.226 to 40.670, $p = 0.0287$) and greater waist circumference showing a trend toward higher stroke risk (OR 1.448, 95% CI 0.981 to 2.137, $p = 0.0627$). Otherwise, in women, this headache-inclusive multivariable model was similar to the main multivariable model. Adding the NHANES migraine variable to the multivariable analysis for men did not change the previous results.

Comparison of vascular risk factors over the

Downloaded from www.neurology.org by NERSES SANOSSIAN on November 15, 2007
Copyright © by AAN Enterprises, Inc. Unauthorized reproduction of this article is prohibited.

Table 3 Physiologic stroke risk variable comparisons in men vs women across midlife (35 to 64 years) decades

	Age group/Sex			Age group/Sex			Age group/Sex		
	35 to 44 years			45 to 54 years			55 to 64 years		
Variable	Men	Women	*p* Value	Men	Women	*p* Value	Men	Women	*p* Value
Body mass index, kg/m^2	28.2361	28.403	0.5696	28.6298	28.9570	0.3380	28.7233	29.5843	0.0202
Waist circumference, cm	99.2731	92.3403	<0.0001	102.0670	94.9395	<0.0001	104.2316	97.5505	<0.0001
Average SBP, mm Hg	119.9254	113.9440	<0.0001	124.7098	123.5454	0.1767	128.6503	131.9976	0.0082
Left ABPI	1.1697	1.4673	0.0062	1.1666	1.1292	<0.0001	1.1496	1.1099	<0.0001
Right ABPI	1.1653	1.1330	<0.0001	1.1643	1.1209	<0.0001	1.1439	1.0980	<0.0001
Homocysteine, μmol/L	8.9176	7.2259	<0.0001	9.5591	7.9580	<0.0001	9.9227	8.5289	<0.0001
Glycohemoglobin, %	5.3997	5.2765	0.0018	5.6511	5.5240	0.0146	5.8065	5.7548	0.3494
Total cholesterol, mg/dL	208.6748	197.5985	<0.0001	213.40723	209.8612	0.1277	208.7677	219.7549	<0.0001
HDL cholesterol, mg/dL	45.7805	55.6920	<0.0001	45.7156	56.6862	<0.0001	47.2561	58.4132	<0.0001
Triglycerides, mg/dL	178.0621	125.7701	<0.0001	191.5534	135.4046	<0.0001	178.5280	160.3469	0.1952

SBP = systolic blood pressure; ABPI = ankle–brachial pulsatility index; HDL = high-density lipoprotein.

three successive midlife decades showed that women in each successively older cohort had worsening in waist circumference, systolic blood pressure, homocysteine, glycohemoglobin, total cholesterol and triglyceride levels, and ABPI with each consecutive decade (table 3). For men, however, successively older cohorts exhibited worsening in waist circumference, systolic blood pressure, homocysteine, and glycohemoglobin with each subsequent decade (table 3). Certain traditional vascular risk factors in women increased at a higher rate than the same risk factors for stroke in men (table 3). For instance, with each decade, men's blood pressure increased by an average of 4 to 5 points, whereas women's blood pressure increased by 7 to 10 points, so that at age 35 to 54 years, men had a significantly higher blood pressure than women, whereas by age 55 to 64 years, women had a significantly higher average blood pressure than men. Similarly, men had significantly higher total cholesterol levels than women at age 35 to 44 years, but men's total cholesterol remained stable, whereas women's total cholesterol increased by 10 to 12 points with each decade, so that by age 55 to 64 years, women had a significantly higher total cholesterol level than men. Homocysteine, glycohemoglobin, and triglyceride levels also increased at higher rates in women compared with men with each successive midlife decade. ABPI, a biomarker of atherosclerosis, also seemed to worsen at a greater rate in women than men across midlife decades. Comparison of biomarker risk factors by successive midlife decade showed that the steepest increases in premier stroke risk biomarkers such as systolic blood pressure and total cholesterol occurred between women aged 35 to 44 years vs women aged 45 to 54 years (table 4).

When comparing historic risk factors for stroke, men had significantly higher per capita prevalence rates of CAD than women across all ages except between 45 and 54 years, where there was no significant difference (OR 1.6433, 95% CI 0.7684 to 3.5143) between sexes. Among women, transitioning from the 35- to 44-year to the 45- to 54-year age group resulted in four times the odds of having CAD (OR 4.2470, 95% CI 1.466 to 12.30, $p = 0.008$), and although there was an increase in CAD prevalence when transitioning from the 45- to 54-year to the 55- to 64-year age group, this difference did not reach significance. Furthermore, comparing the presence of a history of the premier modifiable risk factor for stroke, hypertension, in men vs women, there were no differences between 35 and 44 years, but after age 45 years, men had lower rates of hypertension history than women (OR 0.7854, 95% CI 0.6310 to 0.9777, $p = 0.0306$).

DISCUSSION In this nationally representative cohort, we found that in the years 1999 to 2004, women aged 45 to 54 years had twice the odds of having experienced a stroke compared with men of the same age, and that the transition from ages 35 to 44 years to 45 to 54 years marked the steepest increase in stroke prevalence over successive midlife decades for women. This 6-year study period is too short for any conclusions to be drawn about overall sex-specific secular trends in stroke in the United States, but longer term observational data from the Rochester community study suggest a rising incidence of stroke among women in their midlife years,[9] and a more recent analysis

Downloaded from www.neurology.org by NERSES SANOSSIAN on November 15, 2007
Copyright © by AAN Enterprises, Inc. Unauthorized reproduction of this article is prohibited.

Table 4	Physiologic stroke risk variable comparisons in women across midlife (35 to 64 years) decades					
	Age in years			Age in years		
Variable	35 to 44	45 to 54	*p* Value	45 to 54	55 to 64	*p* Value
Body mass index, kg/m^2	28.4031	28.9570	0.1356	28.9570	29.5843	0.1541
Waist circumference, cm	92.3403	94.9395	0.0010	94.9395	97.5505	0.0065
Average SBP, mm Hg	113.9440	123.5454	<0.0001	123.5454	131.9976	<0.0001
Left ABPI	1.1467	1.1292	0.0222	1.1292	1.1099	0.0046
Right ABPI	1.1330	1.1209	0.0955	1.1209	1.0980	0.0006
Homocysteine, μmol/L	7.2259	7.9581	<0.0001	7.9581	8.5289	<0.0001
Glycohemoglobin, %	5.2765	5.5240	<0.0001	5.5240	5.7548	<0.0001
Total cholesterol, mg/dL	197.5985	209.8612	<0.0001	209.8612	219.7549	0.0002
HDL cholesterol, mg/dL	55.6920	56.6862	0.3667	56.6862	58.4132	0.1005
Triglycerides, mg/dL	125.7701	135.4046	0.3121	135.4046	160.3469	0.0007

SBP = systolic blood pressure; ABPI = ankle–brachial pulsatility index; HDL = high-density lipoprotein.

from another Westernized population study, the Swedish Hospital Discharge Register, also revealed that among individuals aged 30 to 65 years, the average stroke incidence increased by 19% among men and by 33% among women between 1989 and 1991 vs 1998 to 2000, with the largest increase among those younger than 60 years.[10] The midlife sex disparity in stroke prevalence in the NHANES data would seem more likely due to an increased stroke incidence in women, rather than differential survival of women poststroke. Stroke outcomes do not seem to be any worse in men,[11] with several studies indicating that women may actually come off worse.[12-16] Furthermore, our results among middle-aged women alone (without the male comparisons) point to a sharp increase in stroke after age 45 years.

It is not immediately clear why there is a growing sex disparity in stroke prevalence rates among individuals aged 45 to 54 years, and the cross-sectional nature of the study may limit any strong inferences from being drawn at this time. However, on multivariable analyses, different independent predictors of stroke prevalence within this age range were noted: history of coronary artery disease and increasing waist circumference for women vs smoking for men. This sex difference in stroke predictors may not be surprising because we observed a steeper rise in several conventional vascular biomarkers over the course of midlife in women compared with men, with the biggest changes frequently occurring between 45 and 54 years. For instance, the rise of systolic blood pressure in women after the age of 35 years, at twice the rate of men of comparable age, was striking. Indeed, previous NHANES analyses of other time periods have shown that systolic blood pressures and pulse pressures, although higher in men than in women among persons younger than 45 years, became higher in women compared with men after age 45 years.[17] Furthermore, among just the women in this study, the steepest rise in systolic blood pressure over successive midlife decades was seen when women aged 35 to 44 years were compared with women aged 45 to 54 years. Because it has previously been shown that the risk of stroke increases continuously above systolic blood pressure levels of approximately 115 mm Hg, with even small increases translating to greater stroke risk especially in middle-aged subjects (45 to 69 years),[18] these blood pressure disparities may be resulting in deleterious consequences for women in their midlife.

Abdominal obesity is a known predictor of stroke in women younger than 60 years,[19] and it has been suggested that women nearing menopause are particularly susceptible to steep increases in waist circumference due to ovarian aging.[20] In addition, estrogen deficiency during menopause can contribute to the metabolic syndrome with a resultant increase in cerebrovascular disease risk.[20-22] Being overweight or obese has been shown to exert substantially greater morbidity on women compared with men, and interestingly, this sex disparity is most marked from age 45 years.[23] As such, it is conceivable that the widening midlife sex disparity in stroke rates noted in our study, and those of others,[10] may in part reflect the impact of the growing obesity epidemic,[24] which would likely exert a higher cardiovascular toll on middle-aged women compared with men.[23,25]

A history of any migraine or severe nonspecific headache within 3 months of the NHANES survey was an independent risk factor for stroke in

Downloaded from www.neurology.org by NERSES SANOSSIAN on November 15, 2007
Copyright © by AAN Enterprises, Inc. Unauthorized reproduction of this article is prohibited.

women aged 45 to 54 years, but not men in additional multivariable analyses. These results are in accord with an NHANES study of a different time period than ours, which showed a nonrandom association of both headache and migraine with stroke, especially among young women.[8] However, prospectively collected data have shown no relationship between overall migraine and incidence of stroke,[26] but a positive association between migraineurs with aura aged < 55 years and ischemic stroke.[26] Unable to distinguish migraines from other headache types within this study, let alone the different types of migraines, and limited by the headache time cutoff of 3 months, we did not include the NHANES migraine variable in the final multivariable analysis. Another explanation for the association between recent nonspecific headache and history of stroke could be that those who experienced a stroke may have been more attentive to headaches, leading to overreporting, particularly because recent educational campaigns have emphasized this symptom as a major stroke warning sign.

Despite the preeminence of cardiovascular disease as the leading killer of women, women seem generally ill informed about its attendant risks.[27,28] Unfortunately, health care practitioners also tend to underestimate women's cardiovascular disease risk,[29] with only a minority of women achieving national guideline recommended target biomarker goals and receiving recommended drug therapy.[30] Specific to stroke, even after controlling for explanatory variables in one study, women with stroke were less likely to receive standard diagnostic tests vs men.[31]

Our finding of a relatively low prevalence of stroke in men aged 45 to 54 years was unexpected, and we cannot exclude a decreasing stroke incidence among men of this age, or a cardiac survival bias contributing to our results, where in the latter situation men with extensive cardiovascular disease may be dying earlier than age 45 years. However, the lack of any corresponding recent national increase in cardiovascular mortality rates among men aged 35 to 54 years[32] would indicate that a cardiac sex survival bias is unlikely to be a factor. Furthermore, it is conceivable that men aged 45 to 54 years who had experienced a stroke were less likely to participate in NHANES than women aged 45 to 54 years who had experienced a stroke; however, it is unclear why a sex difference in participation would manifest only among persons between 45 and 54 years, and not other age groups. Another interesting and unexpected finding in this study was a late midlife stroke acceleration among men. Men aged 55 to 64 years were three times more likely than men aged 45 to 54 years to have experienced a stroke. The reasons behind this precipitous rise in stroke certainly warrant further investigation.

This study has some other limitations in addition to those already mentioned. We did not distinguish hemorrhagic from ischemic strokes, and unmeasured confounding or the play of chance could still explain our results. Furthermore, NHANES has not validated self-reporting of stroke, but other studies have found self-reporting of stroke to have a sensitivity ranging from 80% to 95% and a specificity of 96% to 99%.[33,34] Additional study is certainly needed, and calls for a nationwide, systematic mechanism for tracking the incidence of heart disease and stroke in the United States may help facilitate a prompt and more in-depth understanding of burgeoning public health issues like the one raised in this study.[35]

In the meantime, our study suggests a substantial toll of stroke among women aged 45 to 54 years that may be amenable to optimal control of modifiable vascular risk factors. Prompt and close attention may need to be paid to the cardiovascular health of women in their mid-30s to mid-50s with a goal of mitigating this burden.

ACKNOWLEDGMENT

The authors thank Teresa Seeman, PhD, for her critical review of the manuscript.

Received January 7, 2007. Accepted in final form April 16, 2007.

REFERENCES

1. Rosamond W, Flegal K, Friday G, et al. Heart disease and stroke statistics—2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2007;115: e69–e171.
2. Bousser MG. Stroke in women: the 1997 Paul Dudley White International Lecture. Circulation 1999;99:463–467.
3. Ridker PM, Cook NR, Lee IM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med 2005; 352:1293–1304.
4. Bushnell CD, Hurn P, Colton C, et al. Advancing the study of stroke in women: summary and recommendations for future research from an NINDS-Sponsored Multidisciplinary Working Group. Stroke 2006;37:2387–2399.
5. Goldstein LB, Adams R, Alberts MJ, et al. Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and

Downloaded from www.neurology.org by NERSES SANOSSIAN on November 15, 2007
Copyright © by AAN Enterprises, Inc. Unauthorized reproduction of this article is prohibited.

Outcomes Research Interdisciplinary Working Group: the American Academy of Neurology affirms the value of this guideline. Stroke 2006;37:1583–1633.
6. Sacco RL, Adams R, Albers G, et al. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. Stroke 2006;37:577–617.
7. National Center for Health Statistics. National Health and Nutrition Examination Survey. Available at: http://www.cdc.gov/nchs/nhanes.htm. Accessed January 1, 2007.
8. Merikangas KR, Fenton BT, Cheng SH, Stolar MJ, Risch N. Association between migraine and stroke in a large-scale epidemiological study of the United States. Arch Neurol 1997;54:362–368.
9. Brown RD, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Stroke incidence, prevalence, and survival: secular trends in Rochester, Minnesota, through 1989. Stroke 1996;27:373–380.
10. Medin J, Nordlund A, Ekberg K. Increasing stroke incidence in Sweden between 1989 and 2000 among persons aged 30 to 65 years: evidence from the Swedish Hospital Discharge Register. Stroke 2004;35:1047–1051.
11. Holroyd-Leduc JM, Kapral MK, Austin PC, Tu JV. Sex differences and similarities in the management and outcome of stroke patients. Stroke 2000;31:1833–1837.
12. Di Carlo A, Lamassa M, Baldereschi M, et al. Sex differences in the clinical presentation, resource use, and 3-month outcome of acute stroke in Europe: data from a multicenter multinational hospital-based registry. Stroke 2003;34:1114–1119.
13. Wyller TB, Sodring KM, Sveen U, Ljunggren AE, Bautz-Holter E. Are there gender differences in functional outcome after stroke? Clin Rehabil 1997;11:171–179.
14. Roquer J, Campello AR, Gomis M. Sex differences in first-ever acute stroke. Stroke 2003;34:1581–1585.
15. Arboix A, Oliveres M, Garcia-Eroles L, Maragall C, Massons J, Targa C. Acute cerebrovascular disease in women. Eur Neurol 2001;45:199–205.
16. Sharma JC, Fletcher S, Vassallo M. Characteristics and mortality of acute stroke patients: are there any gender differences? J Gend Specif Med 2002;5:24–7.
17. Martins D, Nelson K, Pan D, Tareen N, Norris K. The effect of gender on age-related blood pressure changes and the prevalence of isolated systolic hypertension among older adults: data from NHANES III. J Gend Specif Med 2001;4:10–13, 20.
18. Lawes CM, Bennett DA, Feigin VL, Rodgers A. Blood pressure and stroke: an overview of published reviews. Stroke 2004;35:1024–1033.
19. Lu M, Ye W, Adami HO, Weiderpass E. Prospective study of body size and risk for stroke amongst women below age 60. J Intern Med 2006;260:442–450.
20. Sowers M, Zheng H, Tomey K, et al. Changes in body composition in women over six years at mid-life: ovarian and chronological aging. J Clin Endocrinol Metab 2007;92:895–901.
21. Carr MC. The emergence of the metabolic syndrome with menopause. J Clin Endocrinol Metab 2003;88:2404–2411.
22. Spencer CP, Godsland IF, Stevenson JC. Is there a menopausal metabolic syndrome? Gynecol Endocrinol 1997;11:341–355.
23. Muennig P, Lubetkin E, Jia H, Franks P. Gender and the burden of disease attributable to obesity. Am J Public Health 2006;96:1662–1668.
24. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999-2004. JAMA 2006;295:1549–1555.
25. Li C, Engstrom G, Hedblad B, Calling S, Berglund G, Janzon L. Sex differences in the relationships between BMI, WHR and incidence of cardiovascular disease: a population-based cohort study. Int J Obes (Lond) 2006;30:1775–1781.
26. Kurth T, Slomke MA, Kase CS, et al. Migraine, headache, and the risk of stroke in women: a prospective study. Neurology 2005;64:1020–1026.
27. Mosca L, Jones WK, King KB, Ouyang P, Redberg RF, Hill MN. Awareness, perception, and knowledge of heart disease risk and prevention among women in the United States. American Heart Association Women's Heart Disease and Stroke Campaign Task Force. Arch Fam Med 2000;9:506–515.
28. Robertson RM. Women and cardiovascular disease: the risks of misperception and the need for action. Circulation 2001;103:2318–2320.
29. Mosca L, Linfante AH, Benjamin EJ, et al. National study of physician awareness and adherence to cardiovascular disease prevention guidelines. Circulation 2005;111:499–510.
30. Mosca L, Merz NB, Blumenthal RS, et al. Opportunity for intervention to achieve American Heart Association guidelines for optimal lipid levels in high-risk women in a managed care setting. Circulation 2005;111:488–493.
31. Smith MA, Lisabeth LD, Brown DL, Morgenstern LB. Gender comparisons of diagnostic evaluation for ischemic stroke patients. Neurology 2005;65:855–858.
32. Health, United States 2005: with Chartbook on Trends in the Health of Americans. Available at: http://www.ncbi.nlm.nih.gov/books/bookres.fcgi/healthus05/healthus05.pdf. Pages 193–196. Accessed January 1, 2007.
33. Engstad T, Bonaa KH, Viitanen M. Validity of self-reported stroke: the Tromso Study. Stroke 2000;31:1602–1607.
34. O'Mahony PG, Dobson R, Rodgers H, James OF, Thomson RG. Validation of a population screening questionnaire to assess prevalence of stroke. Stroke 1995;26:1334–1337.
35. Goff DC Jr, Brass L, Braun LT, et al. Essential features of a surveillance system to support the prevention and management of heart disease and stroke: a scientific statement from the American Heart Association Councils on Epidemiology and Prevention, Stroke, and Cardiovascular Nursing and the Interdisciplinary Working Groups on Quality of Care and Outcomes Research and Atherosclerotic Peripheral Vascular Disease. Circulation 2007;115:127–155.

Downloaded from www.neurology.org by NERSES SANOSSIAN on November 15, 2007
Copyright © by AAN Enterprises, Inc. Unauthorized reproduction of this article is prohibited.

A midlife stroke surge among women in the United States

Amytis Towfighi, Jeffrey L. Saver, Rita Engelhardt and Bruce Ovbiagele

Neurology 2007;69;1898-1904; originally published online Jun 20, 2007;

DOI: 10.1212/01.wnl.0000268491.89956.c2

This information is current as of November 15, 2007

Updated Information & Services	including high-resolution figures, can be found at: http://www.neurology.org/cgi/content/full/69/20/1898
Related Articles	A related article has been published: http://www.neurology.org/cgi/content/full/69/20/1894
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): **Outcome research** http://www.neurology.org/cgi/collection/outcome_research **All Cerebrovascular disease/Stroke** http://www.neurology.org/cgi/collection/all_cerebrovascular_disease_stroke **Stroke in young adults** http://www.neurology.org/cgi/collection/stroke_in_young_adults **Other cerebrovascular disease/ Stroke** http://www.neurology.org/cgi/collection/other_cerebrovascular_disease__stroke **All epidemiology** http://www.neurology.org/cgi/collection/all_epidemiology **Prevalence studies** http://www.neurology.org/cgi/collection/prevalence_studies **Risk factors in epidemiology** http://www.neurology.org/cgi/collection/risk_factors_in_epidemiology
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.neurology.org/misc/Permissions.shtml
Reprints	Information about ordering reprints can be found online: http://www.neurology.org/misc/reprints.shtml

Downloaded from www.neurology.org by NERSES SANOSSIAN on November 15, 2007

NEUROLOGY

Sex and stroke: Are they really different in midlife?

Kevin M. Barrett and Bradford B. Worrall

Neurology 2007;69;1894-1895
DOI: 10.1212/01.wnl.0000290698.62620.a9

This information is current as of November 15, 2007

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://www.neurology.org/cgi/content/full/69/20/1894

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2007 by AAN Enterprises, Inc. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.

Downloaded from www.neurology.org by NERSES SANOSSIAN on November 15, 2007

EDITORIAL

Sex and stroke

Are they really different in midlife?

Kevin M. Barrett, MD
Bradford B. Worrall, MD, MSc

Address correspondence and reprint requests to Dr. Bradford B. Worrall, Department of Neurology, University of Virginia Health System, P.O. Box 800394, Charlottesville, VA 22908-0394
bbw9r@virginia.edu

Neurology® 2007;69:1894–1895

Whether in social or academic circles, discussing the differences between men and women is a fairly easy way to generate lively conversation. In this issue, Dr. Towfighi and colleagues[1] report provocative findings obtained from the National Health and Nutrition Examination Surveys (NHANES). Using results from three consecutive surveys spanning the years 1999 to 2004, the authors found that women aged 45 to 54 years were more than twice as likely to have had a stroke than men of the same age. This midlife surge in stroke prevalence was paralleled by the observation that some traditional vascular risk factors, such as blood pressure and total cholesterol, increased at a greater rate in women than in men through successive decades between 35 and 64 years. The authors propose that the observed difference in midlife stroke prevalence may, in part, be explained by inadequate stroke risk factor modification in women. Important epidemiologic findings such as these, if substantiated, have the potential to impact prevention, detection, and management of cardiovascular disease and stroke in both sexes.

Sex differences have been previously recognized in stroke. Similar to women with acute coronary syndromes, there are data to suggest that women with stroke may present to emergency departments with atypical symptoms more commonly than men.[2] Women have unique stroke risk factors that include oral contraceptive use, hormone replacement therapy, and changes in risk associated with pregnancy. Differential responses to both acute interventions[3] and preventive strategies have been reported,[4,5] in addition to sex differences in coagulation and fibrinolytic cascades.[6] The influence of sex steroids (estrogens and androgens) on the vascular environment, as well as the unique genetic backgrounds of men and women, may partly explain these clinical observations. However, our current knowledge is incomplete, and there is room to promote further understanding. This was recently highlighted by the identification of research gaps related to the study of stroke in women by a National Institute of Neurological Disease and Stroke–sponsored multidisciplinary working group.[7]

Perhaps more relevant than the stroke prevalence data in the present study are the changes in vascular risk noted with advancing age. The NHANES data are noteworthy for changes in measured blood pressure with age: for men, blood pressure increased by an average of 4 to 5 mm Hg per decade, and for women, blood pressure increased by an average of 7 to 10 mm Hg per decade. Total cholesterol levels in men remained relatively stable, but for women a brisk increase was seen with advancing age. These differences are difficult to explain. However, the widely held stereotype that premenopausal women have a favorable vascular risk profile could result in less vigilant screening or treatment of vascular risk factors in midlife. The data do not provide insight into the potential effects of oral contraceptive use, but their impact on blood pressure and triglyceride levels cannot be overlooked. By including younger patients in their analysis, Towfigi and colleagues have helped shift our attention to this age group, in which stroke is not uncommon and of particular consequence to those affected during their productive working years.

Despite the potential importance of the findings reported here, the results should be interpreted with caution. The NHANES dataset is an important epidemiologic tool, but the cross-sectional design and use of self-reporting to estimate disease prevalence impose clear limitations on conclusions drawn from the survey results. One remarkable feature of the NHANES stroke prevalence data are the notably low prevalence among men aged 45 to 54 years. As increasing age is an established independent predictor of higher stroke risk,[8] the static prevalence of stroke in men between the decades of 35 to 44 and 45 to 54 is

See also page 1898

From the Departments of Neurology (K.M.B., B.B.W.) and Public Health Sciences (B.B.W.), University of Virginia Health System, Charlottesville.
Disclosure: The authors report no conflicts of interest.

Copyright © 2007 by AAN Enterprises, Inc.
Downloaded from www.neurology.org by NERSES SANOSSIAN on November 15, 2007
Copyright © by AAN Enterprises, Inc. Unauthorized reproduction of this article is prohibited.

unexpected. This apparent plateau across successive decades in men, coupled with the anticipated age-related increase through the same decades in women, largely accounts for the observed sex differences in stroke prevalence. It is difficult to measure the extent to which recall bias (which itself may be differentially affected by sex) may have influenced the results. Misinterpretation of TIA or mini-stroke by participants when reporting stroke could represent an important source of confounding. Despite these limitations, the results may offer a preliminary glimpse onto a changing dynamic in US stroke prevalence, especially among a population perceived as younger than the prime age for stroke (>55 years).

Further exploration of the interplay of sex and age on the distribution and determinants of stroke occurrence is necessary. It is not inconceivable that ongoing efforts to address cardiovascular and stroke risk factors could be altering the epidemiologic landscape. Changes in the rates of cerebral infarction, with differential rates of decline for men and women, were recently reported in another North American population.[9] Attempts to reproduce the findings of Towfighi and colleagues in a prospective US cohort should be a priority. Validation of the observations in a population-based cohort, ideally with clinical or radiographically confirmed stroke, would add substantially to our knowledge. If the NHANES data truly represent an initial glimpse onto a shifting burden of stroke in younger women, then greater emphasis might be placed on surveillance and modification of vascular risk factors in premenopausal women. As our current understanding of the influence imparted by sex, age, and ethnicity on disease occurrence grows, one might imagine future recommendations for blood pressure goals and management of other vascular risk factors based on age and sex. Sex differences could be highlighted and emphasized among our primary care colleagues, those on the front lines of primary and secondary stroke prevention. In light of the current results, we should heed the admonishment of Towfighi and colleagues to improve risk factor control among women in an attempt to close any gap that may exist for stroke in men and women. At the same time, these findings should provide incentive to confirm and further study the basis of sex differences in stroke prevalence.

REFERENCES

1. Towfighi A, Saver JL, Engelhardt R, Ovbiagele B. A midlife stroke surge among women in the United States. Neurology 2007;69:1898–1904.
2. Labiche LA, Chan W, Saldin KR, Morgenstern LB. Sex and acute stroke presentation. Ann Emerg Med 2002;40:453–460.
3. Savitz SI, Schlaug G, Caplan L, Selim M. Arterial occlusive lesions recanalize more frequently in women than in men after intravenous tissue plasminogen activator administration for acute stroke. Stroke 2005;36:1447–1451.
4. Final report on the aspirin component of the ongoing Physicians' Health Study. Steering Committee of the Physicians' Health Study Research Group. N Engl J Med 1989;321:129–135.
5. Ridker PM, Cook NR, Lee IM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med 2005;352:1293–1304.
6. Kain K, Carter AM, Bamford JM, Grant PJ, Catto AJ. Gender differences in coagulation and fibrinolysis in white subjects with acute ischemic stroke. J Thromb Haemost 2003;1:390–392.
7. Bushnell CD, Hurn P, Colton C, et al. Advancing the study of stroke in women: summary and recommendations for future research from an NINDS-Sponsored Multidisciplinary Working Group. Stroke 2006;37:2387–2399.
8. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. Stroke 1991;22:312–318.
9. Mayo NE, Nadeau L, Daskalopoulou SS, Cote R. The evolution of stroke in Quebec: a 15-year perspective. Neurology 2007;68:1122–1127.

Downloaded from www.neurology.org by NERSES SANOSSIAN on November 15, 2007
Copyright © by AAN Enterprises, Inc. Unauthorized reproduction of this article is prohibited.

Sex and stroke: Are they really different in midlife?

Kevin M. Barrett and Bradford B. Worrall

Neurology 2007;69;1894-1895
DOI: 10.1212/01.wnl.0000290698.62620.a9

This information is current as of November 15, 2007

Updated Information & Services	including high-resolution figures, can be found at: http://www.neurology.org/cgi/content/full/69/20/1894
Related Articles	A related article has been published: http://www.neurology.org/cgi/content/abstract/69/20/1898
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): **All Cerebrovascular disease/Stroke** http://www.neurology.org/cgi/collection/all_cerebrovascular_disease_stroke **Risk factors in epidemiology** http://www.neurology.org/cgi/collection/risk_factors_in_epidemiology
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.neurology.org/misc/Permissions.shtml
Reprints	Information about ordering reprints can be found online: http://www.neurology.org/misc/reprints.shtml

Downloaded from www.neurology.org by NERSES SANOSSIAN on November 15, 2007