

# Persistent Sex Disparity in Midlife Stroke Prevalence in the United States

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## Key Words

Sex disparity · Midlife stroke prevalence · National Health and Nutrition Examination Survey

## Abstract

**Background:** A recent study found that US women aged 45–54 years in 1999–2004 were twice as likely as men to report previous stroke. The aim of this study was to evaluate the validity of this finding by assessing the sex-specific midlife stroke prevalence in the most recent nationally representative, cross-sectional sample of US individuals. **Methods:** Sex-specific stroke prevalence, sex-specific vascular risk factor prevalence and sex-specific independent predictors of stroke were assessed among 35- to 64-year olds who participated in the National Health and Nutrition Examination Surveys in 2005–2006 (n = 2,274). **Results:** Women aged 35–64 years were almost 3 times more likely than men to report prior stroke (2.90 vs. 1.07%; p < 0.001). This disparity was driven by the 45- to 54-year age group, where women had thrice the odds of prior stroke compared with men (OR 3.12, 95% CI 1.30–7.50). Among 45- to 54-year olds, men were more likely than women to have a history of smoking, elevated homocysteine and elevated triglyceride levels, but less likely to be abdominally obese (p < 0.001). Independent stroke risk factors among women aged 35–64 years were a homocysteine level >8.5 μmol/l (OR 6.19, 95% CI 2.57–14.93), a history of

myocardial infarction (OR 5.35, 95% CI 1.09–26.27) and diabetes mellitus (OR 6.63, 95% CI 2.47–17.81). **Conclusion:** The midlife sex disparity in US stroke prevalence persists. Greater emphasis on prompt recognition and treatment of cardiovascular risk factors among young and middle-aged women may ameliorate this worrisome trend.

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## Introduction

Stroke in women is an important public health concern [1]. Since women have greater longevity than men and stroke is more common in older individuals, more women than men are affected by stroke [2, 3]. In addition, women have poorer clinical outcomes after stroke [4–9] and may have less robust responses to stroke prevention therapies compared with men [10]. Although the 2005 Behavioral Risk Factor Surveillance System survey showed that the prevalence of stroke was similar among men (2.7%) and women (2.5%) [11], little information exists on sex differences in age-specific stroke prevalence rates, particularly amongst individuals under the age of 45 years [3].

The consequences of stroke in middle-aged individuals are not trivial: 30-day mortality after stroke among persons 45–64 years old is as high as 12% for ischemic

and 38% for hemorrhagic stroke [12]. A better understanding of sex-specific characteristics in prevalence and predictors of midlife stroke may help guide prioritization and timely implementation of stroke prevention efforts [1].

We recently reported that women aged 45–54 years were twice as likely as men to report previous stroke among a nationally representative sample of US individuals assessed and surveyed in 1999–2004 [13]. A sex disparity in stroke prevalence was not apparent only a decade prior (1988–1994); however, men's stroke prevalence remained stable, while women's stroke prevalence increased [14]. The validity, nature and direction of this evolving sex disparity in midlife stroke prevalence require further investigation. To accomplish this, the aims of our study were to assess – among a cross-sectional sample of US individuals aged 35–64 years – (1) sex-specific stroke prevalence rates in 2005–2006, (2) sex differences in prevalence of vascular risk factors, and (3) association of vascular risk factors with odds of prior stroke.

## Methods

### *Study Population*

The National Health and Nutrition Examination Surveys (NHANES) are cross-sectional samples of the US civilian non-institutionalized population conducted by the National Center for Health Statistics (NCHS), a branch of the Centers for Disease Control and Prevention. The surveys randomly select subjects using a stratified, multistage probability cluster design and oversample certain groups including the elderly, non-Hispanic blacks and Mexican-Americans. Since 1999, NHANES has been planned and conducted as a continuous annual survey; however, the continuous NHANES survey data are released on public use data files in 2-year increments (e.g. NHANES 2005–2006). The study sample is not the same for each survey; therefore, the sample surveyed in 1999–2004 is not the same as the sample surveyed in 2005–2006. The protocols for conduct were approved by the NCHS institutional review board and informed consent was obtained from all participants [15].

Subjects were interviewed in sampled households and examined in mobile examination centers. Details of the survey design and examination procedures have been previously published [15]. Data were collected for 10,348 individuals who participated in NHANES 2005–2006. Response rates were 80.5% for the interview and 77.4% for the examination. Of 2,198 men and women aged 35–64 years who participated in NHANES 2005–2006, 2,136 (97.2%) answered the question regarding a previous physician diagnosis of stroke.

### *Datasets*

NHANES datasets were downloaded from the website of the National Center for Health Statistics (<http://www.cdc.gov/nchs>) for the survey years 2005 and 2006.

### *Primary Predictor Variable*

History of stroke was determined by self-reported history of physician diagnosis of stroke. Given the sex disparity in stroke prevalence noted among individuals aged 45–54 years in 1999–2004 [13], the primary age group of interest in this study was 35–64 years, categorized by decile.

### *Covariates*

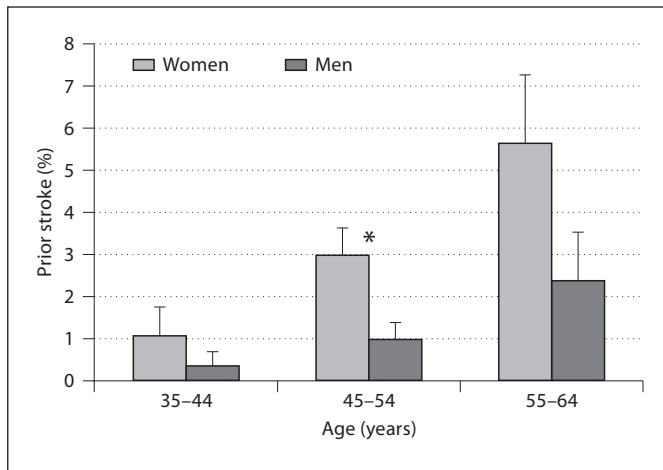
Covariates were assessed as continuous and categorical variables. Categorical variables included race/ethnicity, hypertension, diabetes mellitus (DM), smoking, history of myocardial infarction (MI), hypercholesterolemia, hypertriglyceridemia, history of illicit drug use, history of oral contraceptive pill use, history of hormone replacement therapy, abdominal obesity, obesity, elevated serum low-density lipoprotein cholesterol level, low serum high-density lipoprotein (HDL) cholesterol level, and elevated serum homocysteine level. The variable for low-density lipoprotein cholesterol had a large amount of missing data (58%) and was therefore not included in the final analysis.

Information on age, sex, race/ethnicity, medical history and medication use was determined by self-report. Race/ethnicity was categorized as non-Hispanic white, non-Hispanic black, Hispanic, or other. The 'other' ethnicity was rare and was grouped with the Hispanics for the purpose of the analysis. Hypertension was defined by self-reported physician diagnosis, self-reported current anti-hypertensive medication use, or presence of hypertension on examination (mean of the first 3 blood pressure readings, measured by NHANES technicians, >140 mm Hg systolic or 90 mm Hg diastolic). DM was defined by self-reported physician diagnosis, self-reported current medical therapy, or a glycosylated hemoglobin level >7%. Hypercholesterolemia was defined by self-reported physician diagnosis, self-reported current medical therapy, or a total cholesterol level >200 mg/dl. Hypertriglyceridemia was defined as a triglyceride level >150 mg/dl. A low HDL level was defined as a HDL level <40 mg/dl in men and <50 mg/dl in women. An elevated homocysteine level was defined as a homocysteine level >8.5  $\mu\text{mol/l}$ . This cutoff was selected because the introduction of mandatory folic acid fortification in 1998 reduced the mean plasma homocysteine levels to approximately 8–10  $\mu\text{mol/l}$  [16, 17] and homocysteine is directly correlated with vascular risk across a wide range of values [18, 19]. Smoking was defined by self-reported history of smoking >100 cigarettes. History of MI was defined by self-reported physician diagnosis of heart attack. Illicit drug use was defined by self-report. Body mass index (BMI) was calculated from height and weight measured using standardized examination protocols. The BMI was investigated as a continuous and a categorical variable (overweight, BMI 25–29.9; obese, BMI 30.0–39.0; morbidly obese, BMI >39). Abdominal obesity was defined as a waist circumference >88 cm in women and >102 cm in men.

### *Statistical Analysis*

#### *Comparison of Stroke Prevalence*

For each sex, the weighted population estimate and corresponding standard error were computed for individuals with a history of stroke in the following age groups: 35–44, 45–54, 55–64 and 35–64 years. Odds of previous stroke in women versus men within each age group, and across age groups within each sex, were compared under the logistic regression model while adjusting for the survey design variables.



**Fig. 1.** Comparison by decile of sex-specific stroke prevalence among 35- to 64-year olds in the US in 2005–2006. Women were more likely than men to report prior stroke across all deciles; the difference was significant (\*) only among 45- to 54-year olds. Age 35–44 years: OR 3.12, 95% CI 0.34–28.46,  $p = 0.31$ ; age 45–54 years: OR 3.12, 95% CI 1.30–7.50,  $p = 0.01$ ; age 55–64 years: OR 2.44, 95% CI 0.76–7.88,  $p = 0.14$ .

**Table 1.** Demographic characteristics of women and men aged 35–64 years who participated in NHANES 2005–2006

	Men (n = 1,102)		Women (n = 1,096)		P value
	n	%	n	%	
<b>Race/ethnicity</b>					
White non-Hispanic	547	73.3	505	71.7	0.22
Black non-Hispanic	267	10.7	286	12.0	0.05
Hispanic	240	10.0	247	9.7	0.78
Other	48	6.0	58	6.5	0.55
<b>Age group</b>					
35–44 years	408	36.5	401	37.6	0.66
45–54 years	389	40.1	377	38.1	0.44
55–64 years	305	23.3	318	24.3	0.65

#### Bivariate Assessment of Risk Factors

To assess the sex-specific relationship between each cardiovascular risk factor and stroke, the logistic regression model stratifying by age group was used, taking into account the complex survey design. Given the small number of strokes, bivariate analyses were also assessed collapsing across the age strata in each sex, in order to increase power and improve the precision of estimates.

#### Comparison of Anthropometric and Laboratory Measures

For each sex, the age-specific weighted population mean estimate and corresponding standard error were determined for each

of the following 9 measures: BMI, waist circumference, systolic blood pressure, diastolic blood pressure, homocysteine level, glycohemoglobin level, total cholesterol level, HDL cholesterol level, and triglyceride level. The  $p$  values for comparing the means in men versus women in each age group were computed under the regression model while adjusting for the survey design variables.

#### Multivariable Assessment of Risk Factors

The low frequency of previous stroke among men aged 35–64 years and all individuals aged 45–54 years precluded multivariable analysis due to sample size limitations. We used multivariable logistic regression analysis to determine independent predictors of stroke in women aged 35–64 years, adjusting for significant cardiovascular risk factors in the bivariate analysis and the complex survey design. A backward procedure with a  $p$  level of significance  $< 0.25$  was used for variable selection. The sample size was too small to formally test and/or adjust for potential interaction effects with the age group.

## Results

Men and women who participated in NHANES 2005–2006 had similar demographic characteristics (table 1). Women aged 35–64 years were more likely than men to report previous stroke (2.90 vs. 1.07%;  $p < 0.001$ ). This disparity was driven by differences in the 45- to 54-year age group, where women had thrice the odds of previous stroke compared with men (OR 3.12, 95% CI 1.30–7.50; fig. 1). The sex differences in the 35- to 44-year and 55- to 64-year age groups, although unfavorable to women, did not meet statistical significance (fig. 1).

In bivariate analysis, among women aged 35–64 years, significant predictors of prior stroke included overweight (vs. normal weight), abdominal obesity, elevated homocysteine level, history of MI, history of illicit drug use, DM, hypercholesterolemia, and hypertension (table 2). Among similarly aged men, significant predictors of prior stroke included morbid obesity, higher BMI, abdominal obesity, history of MI, and DM, while white race was protective (table 2).

Bivariate assessment of stroke risk factors among women aged 45–54 years revealed that DM (OR 3.49, 95% CI 1.02–11.96) and elevated homocysteine (OR 4.25, 95% CI 1.44–12.60) were associated with higher odds of prior stroke whereas white race was marginally significantly associated with lower odds of prior stroke (OR 0.35, 95% CI 0.11–1.07). In men aged 45–54 years, BMI (OR per 1 point increase 1.13, 95% CI 1.07–1.19) and a history of MI (OR 6.60, 95% CI 1.37–31.75) were associated with higher odds of previous stroke. All 6 men with stroke had hypertension and abdominal obesity and none were of normal weight.

**Table 2.** Bivariate analysis of stroke risk factors in men and women aged 35–64 years in the US in 2005–2006

Variable	Women		Men	
	OR	p value	OR	p value
White non-Hispanic versus Hispanic	1.19 (0.55–2.58)	0.65	0.29 (0.08–0.98)	0.05
Black non-Hispanic versus Hispanic	1.35 (0.45–4.08)	0.59	1.21 (0.27–5.32)	0.80
Overweight versus normal weight	4.07 (1.42–11.68)	0.009	1.18 (0.19–7.17)	0.86
Obese versus normal weight	2.59 (0.66–10.11)	0.17	6.83 (0.75–62.06)	0.09
Morbid obese versus normal weight	2.20 (0.55–8.79)	0.26	9.70 (1.67–56.43)	0.01
BMI (per 1 point increase)	1.01 (0.96–1.06)	0.71	1.05 (1.01–1.08)	0.006
Abdominal obesity	3.40 (1.19–9.69)	0.02	7.58 (1.81–31.79)	0.006
Elevated homocysteine level	4.85 (1.88–12.54)	0.001	1.26 (0.41–3.83)	0.68
Low HDL level	0.99 (0.28–3.43)	0.98	1.72 (0.49–6.08)	0.34
History of MI	9.52 (2.81–32.25)	<0.001	10.69 (4.28–26.68)	<0.001
History of smoking	2.58 (0.95–6.98)	0.06	1.83 (0.45–7.40)	0.40
History of illicit drug use	2.62 (1.14–6.02)	0.02	1.81 (0.21–15.25)	0.59
Diabetes mellitus	5.37 (1.86–15.44)	0.002	5.14 (2.74–9.65)	<0.001
Hypercholesterolemia	3.03 (1.10–8.35)	0.03	1.23 (0.38–4.00)	0.73
Hypertension <sup>1</sup>	3.66 (1.50–8.91)	0.004	–	–
Hypertriglyceridemia	1.61 (0.67–3.89)	0.29	1.54 (0.41–5.73)	0.52
History of hormone replacement or oral contraceptive therapy	0.98 (0.27–3.57)	0.97	–	–

Figures in parentheses are 95% CIs.

<sup>1</sup> OR is undefined in men because all men with stroke had hypertension.

Multivariable logistic regression modeling revealed that among women aged 35–64 years, an elevated homocysteine level (OR 7.44, 95% CI 2.95–18.73), a history of MI (OR 5.70, 95% CI 1.04–31.13) and DM (OR 6.47, 95% CI 2.14–19.54) were associated with higher odds of prior stroke.

Table 3 shows comparisons of cardiovascular risk factors between men and women aged 35–64 years. Compared with women, men were more likely to have a history of smoking, hypercholesterolemia, hypertriglyceridemia, and elevated homocysteine. In addition, men had higher systolic and diastolic blood pressures, and higher mean homocysteine and triglyceride levels than women. On the other hand, women were more likely than men to have abdominal obesity (61.9 vs. 50.0%;  $p < 0.001$ ). Other risk factors and laboratory measures were comparable between sexes. A similar pattern was observed among those aged 45–54 years, with men being more likely to have a history of smoking and higher levels of homocysteine and triglycerides compared with women. As in the 35- to 64-year age group, women aged 45–54 years were more likely than similarly aged men to have abdominal obesity (62.2 vs. 49.2%;  $p < 0.001$ ).

## Discussion

This recent analysis of a nationally representative, cross-sectional sample of the US population shows that the sex disparity in midlife stroke prevalence noted in the 1999–2004 NHANES wave [13, 14] has persisted. Specifically, in 1999–2004, women aged 45–54 years were more than twice as likely as similarly aged men to report a history of stroke (OR 2.39, 95% CI 1.32–4.32); in 2005–2006, they were 3 times more likely to report previous stroke (OR 3.12, 95% CI 1.30–7.50). These data at the very least lend credence to a persistent sex disparity in stroke prevalence among persons aged 45–54 years.

The exact reasons behind this persistent sex disparity may be difficult to decipher precisely. Naturally, the disparity could be due to lower mortality or higher stroke incidence among women or higher mortality or lower stroke incidence among men. We suspect that the disparity is due to a higher incidence of stroke in women compared with men and a recent increase in stroke incidence among women under the age of 54 years. There are 2 lines of evidence supporting this theory. First, several studies show a lack of sex differences in survival after stroke, par-

**Table 3.** Comparison of cardiovascular risk factors among men and women aged 35–64 years in the US in 2005–2006

Variable	Men			Women			Difference		
	sample, n	mean	SE	sample, n	mean	SE	mean	SE	p value
BMI, kg/m <sup>2</sup>	1,084	29.27	0.30	1,086	29.24	0.39	0.03	0.36	0.93
SBP, mm Hg	1,050	124.33	0.61	1,040	120.62	0.74	3.71	0.78	<0.001
DBP, mm Hg	1,048	74.94	0.46	1,038	72.27	0.50	2.67	0.61	<0.001
Homocysteine, mg/dl	1,039	9.18	0.16	1,048	7.68	0.17	1.50	0.25	<0.001
Glycohemoglobin, %	1,043	5.54	0.03	1,056	5.50	0.04	0.05	0.04	0.18
Total cholesterol, mg/dl	1,046	203.93	1.23	1,048	207.09	1.76	-3.16	1.84	0.11
Triglycerides, mg/dl	1,038	185.35	5.56	1,046	144.00	5.33	41.35	8.09	<0.001
		%	SE		%	SE			
Abdominal obesity	1,049	50.0	2.7	1,061	61.9	2.0			<0.001
Low HDL level	1,046	25.8	1.4	1,048	26.6	1.7			0.73
Elevated homocysteine level	1,039	51.9	2.4	1,048	25.4	1.8			<0.001
History of MI	1,102	3.0	0.8	1,093	2.0	0.5			0.22
History of smoking	1,102	55.1	2.4	1,096	44.5	2.2			<0.001
DM	1,050	9.7	1.0	1,062	9.0	1.0			0.64
Hypercholesterolemia	944	74.8	2.0	950	68.9	1.9			0.003
Hypertension	1,064	38.7	2.1	1,064	36.9	3.1			0.48
Hypertriglyceridemia	1,038	46.9	1.6	1,046	32.1	1.8			<0.001

SBP = Systolic blood pressure; DBP = diastolic blood pressure.

ticularly in those under the age of 45 years [3–5, 12, 20, 21]; therefore, it seems unlikely that men at midlife are dying from strokes at a higher rate than similarly aged women. Also, the lack of any corresponding recent national increase in cardiovascular mortality rates among men aged 35–54 years [22] indicates that a cardiac sex survival bias is unlikely to be a factor. Second, while data are sparse regarding sex- and age-specific stroke incidence, the Greater Cincinnati/Northern Kentucky Stroke Study, with a population closely resembling the US demographic profile, showed that among individuals younger than age 35, the incidence of stroke was higher among women than among men [3, 23]. In addition, observational data from the Rochester community study indicate a growing incidence of stroke among women in their midlife years [24], and data from the Swedish Hospital Discharge Register showed that among individuals aged 30–65 years, average stroke incidence increased by only 19% among men and by 33% among women between 1989 and 1991 versus 1998 and 2000, with the biggest increase among those younger than 60 years [25]. However, the Framingham Heart Study showed that among individuals aged 45–84 years, stroke incidence was higher in men than in women ( $p < 0.001$ ), but the study did not

evaluate sex differences in stroke incidence rates in individuals younger than age 45 years [26].

If a higher stroke incidence among women is driving the sex disparity in midlife stroke prevalence, potential reasons may include higher prevalence of sex-specific risk factors (such as oral contraceptive/hormone replacement use), improved detection of stroke in women, or higher prevalence/poorer control of cardiovascular risk factors among women compared with men. With regard to sex-specific risk factors, this study corroborated studies of prior NHANES epochs showing no association between use of oral contraceptives or hormone replacement therapy and prior stroke [14]. Although stroke detection has improved in recent years, studies have not revealed a major sex differential impact on detection [3]. In addition, there is no evidence to suggest a sex differential in self-report of stroke. With respect to cardiovascular risk factors, this study showed that men were more likely than women to have traditional cardiovascular risk factors (such as hypertension, dyslipidemia and history of smoking); however, women were more likely than men to be abdominally obese. In this study, without a multivariable logistic regression analysis in the 45- to 54-year age group, it was not possible to investigate whether abdominal obe-

sity independently predicted stroke among women in this age group, a finding which was noted in our larger prior study [13] and by others [27]. In fact, it has been suggested that women approaching menopause are especially vulnerable to steep rises in waist circumference due to ovarian aging [28]. As we previously suggested [13], it is possible that the midlife sex disparity in stroke rates may in part reflect the impact of the growing obesity epidemic [29]. More research is required to understand potential sex differences in the pathophysiological mechanisms of stroke in the setting of obesity; the hormonal and inflammatory milieu conceivably plays an important role.

With respect to temporal patterns in cardiovascular risk factors, our previous research revealed no worsening in prevalence or control of dyslipidemia, hypertension or smoking among midlife women [14]. However, women's prevalence of DM and MI has significantly increased over the past 2 decades [14, 30]. Correspondingly, both a history of MI and DM were independent predictors of prior stroke among women in this sample, suggesting that the increasing frequency of these factors could be playing a role in the rise in stroke prevalence. This is in accord with our 1999–2004 analysis, where we found a history of MI to be a strong independent predictor of stroke occurrence [13]. Interestingly, it has been suggested that DM may have a stronger effect on stroke risk in women than in men [31].

In this sample, elevated homocysteine was also an independent predictor of prevalent stroke among women. Elevated homocysteine likely represents a cardiovascular risk marker [32], although the results of a large homocysteine-lowering stroke prevention trial are pending [33]. It is not clear whether there might be a sex-differential impact of homocysteine on stroke risk.

This study has several limitations. First, although NHANES is a nationwide sample, it is limited in the number of US communities sampled and the small sample size, particularly when studying events as rare as midlife stroke. Second, the cross-sectional nature of the study precludes the ability to determine temporal relationships between potential risk factors and events and precludes any causal inferences. Although corroboration of these findings requires prospective studies, the advantage of NHANES is its national representation. Third, NHANES does not differentiate between hemorrhagic and ischemic stroke. However, the purpose of this study was to assess overall stroke burden. Fourth, unlike our prior study that covered a 6-year period (1999–2004), this study only covered a 2-year period, further limiting our sample size and ability to conduct a specific multivariable logistic regression analysis in the 45- to 54-year age group. Fifth, NHANES relies on self-reported history of stroke (which in other studies has shown a sensitivity ranging from 80 to 95% and a specificity of 96–99%) [34, 35] and there may be sex differences in the self-report of prevalent stroke.

This study corroborates our previous findings of a midlife sex disparity in stroke prevalence. Although reasons behind this disparity remain speculative, this study suggests that the obesity epidemic may be playing a role. Further research is required to determine if stroke incidence rates are increasing among young and middle-aged women in the US and to explore if there are physiologic reasons why obesity may have a differential association with stroke in women compared with men.

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