

# Factors Associated with the Steep Increase in Late Midlife Stroke Occurrence among US Men

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*Background:* Data on recent stroke prevalence rates among middle-aged men in the United States indicate that men aged 55 to 64 years are 3 times more likely than men aged 45 to 54 years to have experienced a stroke. We aimed to determine potential risk factors that may contribute to this steep increase in late midlife stroke occurrence. *Methods:* We analyzed the National Health and Nutrition Examination Survey 1999 to 2004 data sets, assessing stroke prevalence, predictors of stroke occurrence, and vascular risk factors in men across their midlife years. *Results:* Crudely, higher glycohemoglobin, history of hypertension, history of diabetes, and history of coronary artery disease significantly predicted stroke in 45- to 54- and 54- to 64-year-old men. Significant stroke risk factors unique to each age group were non-white race, lower ankle-brachial pulsatility index, and occurrence of recent severe headache in the 45- to 54-year age group, whereas elevated serum homocysteine (HCY) level predicted stroke in those aged 55 to 64 years. In multivariable regression analysis, lower ankle-brachial pulsatility index (odds ratio [OR] 1.69, 95% confidence interval [CI] 1.47-1.83,  $P < .001$ ) and recent severe headache (OR 5.12, 95% CI 1.3-20.1,  $P = .019$ ) were the only independent predictors of stroke in the 45- to 54-year age group, whereas only elevated HCY predicted stroke in the 55- to 64-year age group (OR 1.708, 95% CI 1.103-2.643,  $P = .0163$ ). *Conclusion:* Elevated serum HCY level is the sole independent predictor of stroke among men aged 55 to 64 years in the United States. Further study to assess the efficacy of HCY-lowering treatment in mitigating a steep increase in late midlife stroke occurrence among men may be warranted. **Key Words:** Men—stroke—risk factors—midlife—National Health and Nutrition Examination Survey.

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Although stroke primarily affects people older than age 65 years, most of the established risk factors associated with stroke appear much earlier in life.<sup>1</sup> Indeed, the midlife years (35-65 years) may represent a period of life for

which identification of stroke predictors and understanding of prevailing stroke patterns could lead to the timely administration of therapeutic interventions geared not only at reducing the risk of stroke during middle age, but also in the years beyond. For men, who generally tend to have higher stroke incidence rates than women during the midlife years, but not at older ages,<sup>1</sup> such knowledge could allow health care professionals to optimally manage stroke risk in a targeted manner to reduce their overall burden of stroke.

In a recent study of the prevalence of stroke in middle-aged persons, we found that men in the United States aged 55 to 64 years were 3 times more likely than men aged 45 to 54 years to have experienced a stroke.<sup>2</sup> In this study, we aimed to determine potential causes for this rapid increase in late midlife stroke prevalence among men.

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## 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, non-institutionalized US population. The surveys included oversampling of low-income persons, adolescents aged 12 to 19 years, persons older than 60 years, African Americans, and Mexican Americans.

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

During the 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. The study sample included 7213 men, aged 18 years and older, who answered the question regarding stroke in the NHANES interview from 1999 to 2004.

### Statistical Analysis

NHANES data sets for the survey years 1999 to 2000, 2001 to 2002, and 2003 to 2004 were analyzed. Variables investigated for association with stroke included demographic, clinical, and biomarker factors, selected based on prior literature depicting major stroke risk factors.<sup>3,4</sup> The demographic variables included age, sex, race/ethnicity, and education. Medical history variables included history of hypertension, diabetes mellitus, coronary artery disease, atrial fibrillation, occurrence of severe headache or migraine in the 3 months preceding the survey, myocardial infarction, smoking, and illicit drug use. Biomarkers evaluated included body mass index, waist circumference, systolic blood pressure, ankle-brachial pressure index (ABPI), serum homocysteine (HCY), glycohemoglobin, serum total cholesterol, and serum low-density lipoprotein cholesterol. Data analysis was performed with software (SAS 9.1, Chicago, IL) survey routines, using the sampling stratification, clustering, and a 6-year sampling weight, according to the NHANES Analytic and Reporting Guidelines.<sup>5</sup> The multivariable logistic regression analysis evaluated predictors of whether the person had experienced a stroke. The primary reported statistics are the estimated odds ratios (OR).

## Results

In all, 17,061 adults were surveyed from 1999 to 2004. Of 2045 men in the 45- to 64-year age group who responded to the question about stroke, 16 of the 1117 men aged 45 to 54 years and 49 of the 928 men aged

55 to 64 years reported having experienced a stroke (1.0% and 3.0%, respectively; OR 2.967, 95% confidence interval [CI] 1.541-5.711,  $P = .0011$ ) as was previously reported.<sup>2</sup>

The 45- to 54-year-old men and 55- to 64-year-old men shared the following single predictors of stroke: higher glycohemoglobin, history of hypertension, history of diabetes, and history of coronary artery disease (Table 1). Stroke factors unique to each age group were non-white race, lower ABPI, and occurrence of severe headache or migraine in the 3 months preceding the survey in the 45- to 54-year age group and higher serum HCY level in the 55- to 64-year age group (Table 1).

A multivariable logistic regression model adjusting for race/ethnicity, waist circumference, average systolic blood pressure, HCY, glycohemoglobin, total cholesterol, ABPI, history of hypertension, history of diabetes mellitus, recent severe headache, and history of coronary artery disease revealed that in the 45- to 54-year age group, lower ABPI (OR 1.696, 95% CI -1.47-1.826,  $P < .001$ ) and recent severe headache (OR 5.118, 95% CI 1.303-20.097,  $P = .0193$ ) were the only independent predictors of stroke risk, whereas higher HCY was the only independent predictor of stroke in the 55- to 64-year age group (OR 1.708, 95% CI -1.103-2.643,  $P = .0163$ ).

Because all stroke victims in the 45- to 54-year age group smoked, a multivariable model that included smoking could not be analyzed given limited variability. When we included smoking in a multivariable model of the 55- to 64-year age group (not all those aged 55-64 years with stroke had smoked), higher serum HCY remained the only independent predictor of stroke in this age group (OR 1.640, 95% CI = 1.087-2.475,  $P = .0183$ ). There were no significant interaction terms between covariates from logistic regression models predicting the odds of stroke.

Comparing stroke risk factors across age groups revealed that men aged 55 to 64 years had significantly larger waist circumference, higher systolic blood pressure, lower ABPI, higher glycohemoglobin, and higher prevalence of coronary artery disease, hypertension, smoking, and diabetes mellitus than men age 45 to 54 years (Table 2). The older age group, however, had significantly lower low-density lipoprotein levels and fewer headaches than the younger group (Table 2). A higher proportion of the older age group compared with the younger age group was on lipid-lowering medication (22.97% *v* 11.74%,  $P < .0001$ ). This difference was driven by the higher use of lipid-lowering medications in the 55- to 64-year age group in 2001 to 2002, compared with 1999 to 2000 (26.31% *v* 11.22%,  $P < .0001$ ).

## Discussion

In exploring the recently observed steep increase in late midlife stroke prevalence among US men, we found that in crude analysis several established vascular risk factors, such as hypertension and diabetes mellitus, were

**Table 1.** Bivariate analysis for predictors of stroke in men aged 45 to 54 versus 55 to 64 years

Variable	Men aged 45-54 y (n = 1061)		Men aged 55-64 y (n = 928)	
	OR (95% CI)	P value	OR (95% CI)	P value
Other race (v white)	4.094 (1.332-12.597)	.0139	1.745 (0.714-4.264)	.2220
Waist circumference, $\Delta = 15$ cm*	1.321 (0.717-2.435)	.3716	1.143 (0.802-1.627)	.4601
Average SBP, $\Delta = 20$ mm Hg*	1.369 (0.627-2.987)	.4302	1.162 (0.686-1.967)	.5770
Homocysteine, $\Delta = 5$ $\mu$ mol/L*	1.170 (0.966-1.418)	.1085	1.303 (1.034-1.643)	.0251
Glycohemoglobin, $\Delta = 1\%$ *	1.301 (1.082-1.564)	.0052	1.284 (1.030-1.600)	.0265
Total cholesterol, $\Delta = 40$ mg/dL*	0.846 (0.533-1.341)	.4757	0.903 (0.542-1.504)	.6952
LDL cholesterol, $\Delta = 36$ mg/dL*	0.725 (0.489-1.073)	.1076	0.593 (0.161-2.181)	.4315
Right ankle-brachial pressure index, $\Delta = 0.14$	0.288 (0.160-0.519)	<.0001	0.613 (0.343-1.096)	.0987
History of atrial fibrillation	†	—	0.283 (0.057-1.401)	.1220
History of hypertension	5.728 (1.505-21.803)	.0105	5.184 (2.009-13.374)	.0007
History of diabetes mellitus	2.842 (1.014-7.965)	.0469	3.048 (1.185-7.838)	.0207
History of smoking	‡	—	0.712 (0.275-1.845)	.4849
History of coronary artery disease	8.966 (1.519-52.939)	.0155	5.775 (2.175-15.331)	.0004
Occurrence of severe headache or migraine in the 3 mo preceding the survey	3.781 (1.255-11.385)	.0181	1.477 (0.560-3.890)	.4304

Abbreviations: CI, confidence interval; LDL, low-density lipoprotein; OR, odds ratio; SBP, systolic blood pressure.

\*OR is based on specified change,  $\Delta$ , in variable units.

†No subjects with stroke had atrial fibrillation in this group.

‡In this group all subjects with stroke also smoked, therefore OR undefined.

associated with a greater risk of stroke in men aged 45 to 54 and 55 to 64 years. However, this analysis also revealed that certain factors were unique to each age group: non-white race, lower ABPI, and having a history of recent severe headache predicted stroke in the 45- to 54-year age group, whereas serum HCY predicted stroke in the 55- to 64-year age group. Multivariable analysis largely

confirmed the importance of these unique predictors noted in bivariate analysis showing that only lower ABPI and a recent severe headache were independently associated with stroke in men aged 45 to 54 years, and serum HCY was the sole independent predictor of stroke in men aged 55 to 64 years. These results suggest that specific vascular factors in middle-aged men could be

**Table 2.** Stroke risk factor comparisons across age groups in men aged 45 to 64 (n = 2045)

Variable	Men aged 45-54 y	Men aged 55-64 y	P
Body mass index, kg/m <sup>2</sup>	28.63	28.72	.7387
Waist circumference, cm	102.07	104.23	.0046
Average systolic blood pressure	124.71	128.65	<.0001
Left ankle-brachial pressure index	1.1666	1.1496	.0121
Right ankle-brachial pressure index	1.1643	1.1439	.0008
Homocysteine, $\mu$ mol/L	9.67	10.03	.0973
Glycohemoglobin, %	5.65	5.81	.0205
Total cholesterol, mg/dL	213.41	208.77	.0829
LDL cholesterol, mg/dL	131.60	125.99	.0292
Taking lipid-lowering medication, %*	11.74	22.97	<.0001
History of CAD, %	2.66	11.72	<.0001
History of hypertension, %	29.22	40.65	<.0001
History of smoking, %	62.79	69.74	.0052
History of diabetes, %	7.69	14.17	<.0001
Occurrence of severe headache or migraine in the 3 mo preceding the survey, %	17.17	12.06	.0035
Atrial fibrillation, %	3.00	5.10	.0719

Abbreviations: CAD, coronary artery disease; LDL, low-density lipoprotein.

\*Lipid-lowering medication information not available for survey years 2003-2004.

valuable markers of stroke risk or perhaps even amenable to modification to reduce stroke risk.

In this study, we were especially interested in discovering any clues behind the 3 times higher odds of stroke in 54- to 65-year-old men compared with 45- to 54-year-old men. Coupled with an increased trend in serum HCY levels in the older age group versus the younger age group, and the role of serum HCY as the only independent predictor of stroke in older group, it would appear that HCY may be a crucial factor in the late midlife stroke acceleration among men. This finding is in accord with other studies, which have suggested the relevance of serum HCY in predicting stroke among middle-aged persons,<sup>6</sup> and once again raises the often-debated issue of whether reducing elevated HCY levels may reduce future vascular risk.

Several observational studies support an association between elevated HCY levels and atherosclerotic disease including stroke.<sup>4</sup> However, so far, HCY-lowering trials in persons at high vascular risk have not shown that this strategy reduces vascular risk,<sup>7-9</sup> although one of these trials that did not meet its primary end point found that significantly fewer patients who received the HCY-lowering intervention experienced a stroke.<sup>9</sup> It must, however, be pointed out that these trials had a subject mean age of 66 to 68 years, and although other trials are ongoing,<sup>10</sup> it is possible that relatively younger adults may benefit more from such treatment.<sup>11,12</sup> Indeed, a detailed review of the HOPE-2 trial data and reanalysis of the VISP trial restricted to patients capable of responding to vitamin therapy indicated that higher doses of vitamin B12 and possibly novel methods of reducing total HCY besides routine vitamin therapy could potentially reduce the risk of stroke.<sup>13</sup> This notion is further supported by a recent meta-analysis suggesting that the benefit of HCY-lowering in reducing stroke risk may not apply broadly, but to targeted groups of individuals.<sup>13</sup> At the very least, serum HCY may serve as a useful marker of underlying vascular disease, and further study will be needed to confirm its role as a potential routine screening tool in middle-aged men.

Our study has limitations: it was cross-sectional, NHANES did not distinguish between ischemic and hemorrhagic stroke, and unmeasured confounding may have influenced it. We also relied on self-reporting of stroke, although other studies have found self-reporting of stroke to have high sensitivity and specificity.<sup>14</sup> The study's strengths are in its nationally representative sample and standardized biomarker assessment.

In conclusion, we found that among middle-aged men in the United States, serum HCY level may be an important predictor of stroke in 55- to 64-year-old men, and may influence or reflect the steep increase in stroke risk observed in late midlife. Further study is needed to investigate the relevance of serum HCY measurements in delineating vascular risk in middle-aged men.

## 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. Towfighi A, Saver J, Liebeskind D, et al. Does overall atherosclerotic burden contribute to late midlife acceleration of stroke in men? *Stroke* 2007;38:533 (abstr).
3. 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.
4. 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 Outcomes Research Interdisciplinary Working Group, the American Academy of Neurology affirms the value of this guideline. *Stroke* 2006;37:1583-1633.
5. National Center for Health Statistics. National health and nutrition examination survey. Available from: URL:<http://www.cdc.gov/nchs/nhanes.htm>. Accessed January 1, 2007.
6. Virtanen JK, Voutilainen S, Happonen P, et al. Serum homocysteine, folate and risk of stroke: Kuopio ischemic heart disease risk factor (KIHD) study. *Eur J Cardiovasc Prev Rehabil* 2005;12:369-375.
7. Toole JF, Malinow MR, Chambless LE, et al. Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death: The vitamin intervention for stroke prevention (VISP) randomized controlled trial. *JAMA* 2004;291:565-575.
8. Bonna KH, Njolstad I, Ueland PM, et al. Homocysteine lowering and cardiovascular events after acute myocardial infarction. *N Engl J Med* 2006;354:1578-1588.
9. Lonn E, Yusuf S, Arnold MJ, et al. Homocysteine lowering with folic acid and B vitamins in vascular disease. *N Engl J Med* 2006;354:1567-1577.
10. Dusitanond P, Eikelboom JW, Hankey GJ, et al. Homocysteine-lowering treatment with folic acid, cobalamin, and pyridoxine does not reduce blood markers of inflammation, endothelial dysfunction, or hypercoagulability in patients with previous transient ischemic attack or stroke: A randomized substudy of the VITATOPS trial. *Stroke* 2005;36:144-146.
11. Virtanen JK, Voutilainen S, Alfthan G, et al. Homocysteine as a risk factor for CVD mortality in men with other CVD risk factors: The Kuopio ischemic heart disease risk factor (KIHD) study. *J Intern Med* 2005;257:255-262.
12. Bos MJ, van Goor ML, Koudstaal PJ, et al. Plasma homocysteine is a risk factor for recurrent vascular events in young patients with an ischemic stroke or TIA. *J Neurol* 2005;252:332-337.
13. Spence JD. Homocysteine-lowering therapy: A role in stroke prevention? *Lancet Neurol* 2007;6:830-838.
14. Engstad T, Bonna KH, Viitanen M. Validity of self-reported stroke: The Tromso study. *Stroke* 2000;31:1602-1607.