Research

Temporal trends in risk of future cardiac events among stroke survivors in the United States

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Background **Long term, stroke survivors have a higher risk of death from cardiac causes than incident stroke. However, little is known about temporal trends in age- and gender-specific risk of future cardiac events among stroke survivors.**
Aims **To determine temporal trends in 10-year risk of future major cardiac events (measured using the Framingham Cardiovascular Risk Score) and components of the Framingham Cardiovascular Risk Score among a nationally representative population of stroke survivors in the United States.**
Methods **Framingham Cardiovascular Risk Score was assessed among individuals with a self-reported history of stroke ($n = 748$) who participated in the National Health and Nutrition Examination Surveys in the United States during the years 1988–1994 and 1999–2006.**
Results **In both National Health and Nutrition Examination Surveys waves, male stroke survivors had higher mean Framingham Cardiovascular Risk Scores than their female counterparts. This gender disparity was driven by the >64 years age group, where men had a threefold higher Framingham Cardiovascular Risk Scores compared to women ($P < 0{\cdot}01$). Analysis of temporal trends revealed that mean Framingham Cardiovascular Risk Scores was lower in 1999–2006 compared to 1988–1994 in men (21% (standard error 1%) vs. 28% (standard error 0·2%), $P = 0{\cdot}01$) and women (9% (standard error 1%) vs. 11% (standard error 1%), $P = 0{\cdot}06$). Temporal comparisons revealed that diastolic blood pressure and total cholesterol levels were better in 1999–2006 compared to 1988–1994 for both genders.**
Conclusions **Male stroke survivors, particularly those over the age of 64, are at higher risk for future cardiac events than their female counterparts. For both genders, the risk of future cardiac events after stroke has declined in recent years; this reduction is most pronounced in men and likely due to improvements in blood pressure and cholesterol levels.**

Key words: cardiac, FCRS, gender-specific, NHANES, stroke, trends

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Background

With a five-year mortality risk as high as 58%, stroke survivors have significantly higher mortality rates than the general population (1). The majority of deaths during the first 30 days poststroke are due to the incident stroke; however, in the long term, stroke survivors are at a higher risk of death from cardiac causes than from incident or recurrent stroke (2). The Northern Manhattan Study showed that the adjusted five-year risk of fatal cardiac events was 6·4% (95% confidence interval (CI), 4·1 to 8·6%), whereas the adjusted five-year risk of fatal stroke was 3·7% (95% CI, 2·1 to 5·4%) (3). Characterization of cardiovascular risk among stroke survivors may be an important first step for curbing long-term mortality after stroke. In particular, determining age- and gender-specific risk may help to identify specific populations that are at particularly high risk for coronary heart disease (CHD) after stroke and enable policy makers and health professionals to target interventions at high-risk populations.

In recent years, cardiovascular mortality has decreased in the United States (4). However, nationwide trends in future cardiovascular risk among stroke survivors have not been studied. The goals of this study were twofold: (i) to determine temporal trends in age- and gender-specific 10-year risk of a future major cardiovascular event (measured using the Framingham Cardiovascular Risk Score (FCRS)), and (ii) to determine temporal trends in age- and gender-specific components of FCRS among a nationally representative population of stroke survivors in the United States, who participated in the National Health and Nutrition Examination Surveys (NHANES) in 1988–1994 and 1999–2006.

Methods

Study population

NHANES are cross-sectional samples of the US civilian noninstitutionalized population conducted by the National Center for Health Statistics (NCHS). The protocols for conduct were approved by the NCHS institutional review board; informed consent was obtained from all participants (5). The sampling plan followed a complex, stratified, multistage, probability cluster design, with oversampling of non-Hispanic blacks, Mexican-Americans, and the elderly, to enhance the precision of prevalence estimates in those groups. Details of the survey design and examination procedures have been previously published (5).

The sample included 20 050 adults who participated in NHANES 1988–1994 and 22 624 adults who participated in NHANES 1999–2006. Of the total sample, 1442 individuals reported prevalent stroke. After excluding 339 individuals with prevalent myocardial infarction, 202 individuals with nonpositive weights, and 153 individuals missing FCRS components, the final sample size was 748.

Study variables

Prevalent myocardial infarction and stroke were determined by self-report. FCRS was determined using formulas published by Wilson *et al.* (6) The FCRS was analyzed as a continuous variable and in dichotomized form using a cutoff of 10% or greater and a cutoff of 20% or greater. The secondary outcomes were the individual FCRS components including age, systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol, high-density lipoprotein (HDL) cholesterol, diabetes mellitus, and current smoking. Diabetes mellitus was determined by self-report, current medication use, or non-fasting glucose >150 mg/dl consistent with the definition used by Wilson *et al.* (6).

Statistical analysis

There were four main comparison groups: female stroke survivors in NHANES 1988–1994, female stroke survivors in NHANES 1999–2006, male stroke survivors in NHANES 1988–1994, and male stroke survivors in NHANES 1999–2006. Outcomes were compared between men vs. women in each time period and between time periods within each gender. In addition, gender-specific FCRS were calculated in the following racial/ethnic groups: Hispanic, non-Hispanic White, and non-Hispanic Black.

For each continuous outcome, we computed the weighted population estimate for the mean and the corresponding standard error (SE) in each of the four comparison groups. The *P*-values for between-group mean comparisons were computed under the analysis of variance/regression model while taking into account the complex survey design. For each binary outcome, we computed the weighted population estimate for the proportion and the corresponding SE in each of the four comparison groups. The *P*-values for between-group comparisons were computed under the logistic regression model while adjusting for the survey design. To summarize the relationship between group and the odds of experiencing the binary outcome, we computed the corresponding odds ratios (OR) with the 95% CIs.

Results

Mean FCRS was significantly higher in men than in women in both NHANES 1988–1994 and NHANES 1999–2006 (both $P < 0{\cdot}01$) (Table 1). The odds of FCRS >10% was significantly higher in men than in women in both NHANES 1988–1994 (OR = 5·94, $P < 0{\cdot}01$) and NHANES 1999–2006 (OR = 7·25, $P < 0{\cdot}01$). Similarly, the odds of FCRS >20% was significantly higher in men than in women in both NHANES 1988–1994 (OR = 7·20, $P < 0{\cdot}01$) and NHANES 1999–2006 (OR = 7·81, $P < 0{\cdot}01$).

Assessment of temporal trends in FCRS revealed that mean FCRS was lower in the latter time period than in the earlier time period in both men ($P = 0{\cdot}01$) and women ($P = 0{\cdot}06$), although in women, the improvement was not as pronounced and was not significant at the $P < 0{\cdot}05$ level (Table 2). In addition, the odds of FCRS >10% was significantly higher in the earlier time period than in the latter time period among women (OR = 1·86, $P = 0{\cdot}01$), whereas the corresponding

Table 1 Gender differences in FCRS in NHANES 1988–1994 and 1999–2006

Variable	*n*	Women	*n*	Men	OR (95% CI)	*P* value
NHANES 1988–1994						
FCRS, %, mean (SE)	153	11 (1)	152	28 (2)		<0.01
FCRS >10%, proportion (SE)	153	0.47 (0.05)	152	0.84 (0.05)	5.94 (2.45–14.40)	<0.01
FCRS >20%, proportion (SE)	153	0.17 (0.03)	152	0.60 (0.06)	7.20 (3.52–14.72)	<0.01
NHANES 1999–2006						
FCRS, %, mean (SE)	225	9 (1)	218	21 (1)		<0.01
FCRS >10%, proportion (SE)	225	0.32 (0.04)	218	0.77 (0.05)	7.25 (3.74–14.06)	<0.01
FCRS >20%, proportion (SE)	225	0.08 (0.02)	218	0.41 (0.04)	7.81 (4.36–13.97)	<0.01

CI, confidence interval; FCRS, Framingham Cardiovascular Risk Score; NHANES, National Health and Nutrition Examination Surveys; OR, odds ratio; SE, standard error.

Table 2 Temporal trends in FCRS in NHANES 1988–1994 vs. 1999–2006

Variable	*n*	1988–1994	*n*	1999–2006	OR (95% CI)	*P* value
Women						
FCRS, %, mean (SE)	153	11 (1)	225	9 (1)		0·06
FCRS >10%, proportion (SE)	153	0·47 (0·05)	225	0·32 (0·04)	1·86 (1·14–3·04)	0·01
FCRS >20%, proportion (SE)	153	0·17 (0·03)	225	0·08 (0·02)	2·35 (1·18–4·68)	0·02
Men						
FCRS, %, mean (SE)	152	28 (2)	218	21 (1)		<0·01
FCRS >10%, proportion (SE)	152	0·84 (0·05)	218	0·77 (0·05)	1·53 (0·61–3·82)	0·37
FCRS >20%, proportion (SE)	152	0·60 (0·06)	218	0·41 (0·04)	2·16 (1·18–3·98)	0·01

CI, confidence interval; FCRS, Framingham Cardiovascular Risk Score; NHANES, National Health and Nutrition Examination Surveys; OR, odds ratio; SE, standard error.

Table 3 Gender differences in FCRS among individuals aged 35–64 and >65 years

Variable	Women 35–64	Men 35–64	OR (95% CI)	*P*
NHANES 1988–1994				
FCRS, %, mean (SE)	14 (2)	18 (2)		0·18
FCRS >20%, proportion (SE)	0·30 (0·10)	0·31 (0·08)	1·08 (0·28–4·12)	0·91
NHANES 1999–2006				
FCRS, mean (SE)	10 (1)	13 (1)		0·02
FCRS >20%, proportion (SE)	0·09 (0·03)	0·10 (0·03)	1·10 (0·39–3·07)	0·86
	Women >64	Men >64	OR (95% CI)	*P*
NHANES 1988–1994				
FCRS, mean (SE)	11 (1)	37 (2)		<0·01
FCRS >20%, proportion (SE)	0·13 (0·04)	0·84 (0·06)	35·61 (8·62–147·21)	<0·01
NHANES 1999–2006				
FCRS, mean (SE)	9 (1)	27 (1)		<0·01
FCRS >20%, proportion (SE)	0·08 (0·03)	0·62 (0·05)	18·82 (7·21–49·13)	<0·01

CI, confidence interval; FCRS, Framingham Cardiovascular Risk Score; NHANES, National Health and Nutrition Examination Surveys; OR, odds ratio; SE, standard error.

results in men were not statistically significant. Similarly, the odds of having FCRS >20% was significantly higher in the earlier time period than in the latter time period in women (OR = 2·35, $P = 0·02$) and in men (OR = 2·16, $P = 0·01$).

Analysis of FCRS in individuals aged 35–64 and >64 years revealed that the gender disparity in FCRS was much more pronounced among older individuals (Table 3). Among stroke survivors aged 35–64 who participated in NHANES 1988–1994, there was no gender disparity in mean FCRS. Among stroke survivors aged 35–64 years who participated in NHANES 1999–2006, mean FCRS was slightly lower in women than in men. Among those >64 years, in NHANES 1988–1994, the odds of having FCRS >20% was 36 times greater in men than in women (OR = 35·61, 95% CI 8·62–147·21, $P < 0·01$) and in NHANES 1999–2006, the odds of having FCRS >20% was 19 times greater in men than in women (OR = 18·82, 95% CI 7·21–49·13, $P < 0·01$).

Analysis of individual FCRS components revealed that the mean age was comparable among both men and women who participated in NHANES 1988–1994 and NHANES 1999–2006 and ranged from 63·8 to 67·8 years (Tables 4 and 5). Mean SBP was comparable across the four groups. While there were no significant differences in mean DBP between the genders in any of the time periods, mean DBP was significantly lower in the latter time period than in the earlier time period in both men and in women ($P < 0·01$) (Table 5). Mean total cholesterol and HDL levels were significantly higher in women than in men in both NHANES 1988–1994 (both $P < 0·01$) and NHANES 1999–2006 (both $P < 0·01$) (Table 4). Mean total cholesterol was lower in the latter time period than in the earlier time period in both men and women (both $P < 0·01$) (Table 5). Mean HDL was slightly higher in the latter time period than in the earlier time period, approaching statistical significance in women ($P = 0·05$) (Table 5). The proportions with diabetes mellitus were comparable across the four groups and ranged from 0·25 to 0·27. None of the differences in serum glucose levels were statistically significant. The proportions that smoked ranged from 0·19 to 0·26, and there

Table 4 Gender differences in FCRS components among stroke survivors in NHANES 1988–1994 and 1999–2006

Variable	*n*	Women	*n*	Men	OR (95% CI)	*P* value
NHANES 1988–1994						
Age, years, mean (SE)	182	67·8 (2·1)	180	64·4 (1·8)		0·26
Systolic blood pressure, mmHg, mean (SE)	170	142·7 (3·0)	168	137·2 (2·4)		0·17
Diastolic blood pressure, mmHg, mean (SE)	167	76·8 (1·1)	166	77·4 (1·0)		0·40
Total cholesterol, mg/dl, mean (SE)	167	237·7 (4·2)	169	210·6 (3·8)		<0·01
HDL cholesterol, mg/dl, mean (SE)	166	50·8 (1·4)	168	43·3 (1·9)		<0·01
Diabetes mellitus, proportion (SE)	167	0·27 (0·04)	166	0·27 (0·04)	0·99 (0·54–1·82)	0·97
Current smoker, proportion (SE)	182	0·19 (0·05)	180	0·24 (0·05)	1·38 (0·61–3·14)	0·44
NHANES 1999–2006						
Age, years, mean (SE)	278	63·8 (1·1)	261	64·1 (1·4)		0·84
Systolic blood pressure, mmHg, mean (SE)	251	138·9 (1·7)	238	134·8 (1·7)		0·10
Diastolic blood pressure, mmHg, mean (SE)	244	72·2 (1·0)	233	73·2 (1·0)		0·40
Total cholesterol, mg/dl, mean (SE)	246	213·9 (3·5)	238	195·9 (3·3)		<0·01
HDL cholesterol, mg/dl, mean (SE)	246	54·5 (1·2)	237	46·0 (1·3)		<0·01
Diabetes mellitus, proportion (SE)	264	0·26 (0·03)	243	0·25 (0·04)	0·94 (0·56–1·59)	0·83
Current smoker, proportion (SE)	278	0·27 (0·03)	261	0·19 (0·04)	0·66 (0·39–1·10)	0·11

CI, confidence interval; FCRS, Framingham Cardiovascular Risk Score; HDL, high-density lipoprotein; NHANES, National Health and Nutrition Examination Surveys; OR, odds ratio; SE, standard error.

Table 5 Temporal trends in FCRS components in NHANES 1988–1994 vs. 1999–2006

Variable	*n*	1988–1994	*n*	1999–2006	OR (95% CI)	*P* value
Women						
Age, years, mean (SE)	182	67·8 (2·1)	278	63·8 (1·1)		0·10
Systolic blood pressure, mmHg, mean (SE)	170	142·7 (3·0)	251	138·9 (1·7)		0·28
Diastolic blood pressure, mmHg, mean (SE)	167	76·8 (1·1)	244	72·2 (1·0)		<0·01
Total cholesterol, mg/dl, mean (SE)	167	237·7 (4·2)	246	213·9 (3·5)		<0·01
HDL cholesterol, mg/dl, mean (SE)	166	50·8 (1·4)	246	54·5 (1·2)		0·05
Diabetes mellitus, proportion (SE)	167	0·27 (0·04)	264	0·26 (0·03)	1·04 (0·63–1·73)	0·87
Current smoker, proportion (SE)	182	0·19 (0·05)	278	0·27 (0·03)	0·63 (0·31–1·27)	0·19
Men						
Age, years, mean (SE)	180	64·4 (1·8)	261	64·1 (1·4)		0·89
Systolic blood pressure, mmHg, mean (SE)	168	137·2 (2·4)	238	134·8 (1·7)		0·42
Diastolic blood pressure, mmHg, mean (SE)	166	77·4 (1·0)	233	73·2 (1·0)		<0·01
Total cholesterol, mg/dl, mean (SE)	169	210·6 (3·8)	238	195·9 (3·3)		<0·01
HDL cholesterol, mg/dl, mean (SE)	168	43·3 (1·9)	237	46·0 (1·3)		0·25
Diabetes mellitus, proportion (SE)	166	0·27 (0·04)	243	0·25 (0·04)	1·09 (0·61–1·96)	0·76
Current smoker, proportion (SE)	180	0·24 (0·05)	261	0·19 (0·04)	1·33 (0·68–2·61)	0·41

CI, confidence interval; FCRS, Framingham Cardiovascular Risk Score; HDL, high-density lipoprotein; NHANES, National Health and Nutrition Examination Surveys; OR, odds ratio; SE, standard error.

were no significant differences in the proportions of current smokers between the groups.

Evaluation of FCRS among Hispanics, non-Hispanic Whites, and non-Hispanic Blacks revealed that mean FCRS and the proportion of individuals with FCRS >20% did not differ by race/ethnicity, after adjustment for age. In addition, while the sample sizes are generally inadequate to formally assess all possible interactions between race/ethnicity, gender, time, and age, the results indicated that the effects of time and gender in each racial/ethnic group were similar to the analysis that did not take race/ethnicity into account. As in the previous analysis, the age-adjusted mean FCRS was significantly worse in men than in women, regardless of race/ethnicity and the age-adjusted FCRS were better in the more recent time period, regardless of race/ethnicity, except for in Hispanic women in whom the FCRS has worsened (Supporting Information Table S1).

Discussion

Analysis of this nationally representative sample of the US population revealed that among stroke survivors, (i) the

10-year risk of a major cardiovascular events has decreased among both men and women, coincident with improvements in DBP, total cholesterol, and HDL cholesterol over the past two decades (with the exception of Hispanic women, in whom FCRS has actually increased), and (ii) among individuals older than 64 years, there is a gender disparity in future cardiovascular risk favoring female stroke survivors.

As expected, FCRS among stroke survivors are substantially higher than FCRS among the general population. Although recent gender-specific trends in FCRS among individuals over 64 years in the general population have not been reported, the gender differential in FCRS among older stroke survivors mirrors the incidence of myocardial infarction in the general population (7). We observed only a modest difference in mean FCRS between men and women at midlife assessed from 1999 to 2006, and did not find any gender differences in mean FCRS at midlife from 1988 to 1994, or any gender differences in FCRS >20% at midlife during either epoch. This lack of a consistently robust gender difference in mean FCRS or high cardiac risk among midlife stroke survivors is somewhat at odds with findings among midlife individuals in the general population, where men consistently have a higher FCRS (8) and higher incidence of CHD (9) than women. The reasons for this inconsistency in cardiovascular risk by gender between the midlife general population and midlife stroke survivor population are not immediately clear and will require further investigation, but we speculate that, perhaps, those midlife men at very high vascular risk may have been less likely to survive their stroke, or were too sick to be captured in this ambulatory nationwide survey.

Analysis of temporal trends in FCRS components corroborates studies that have shown improvements in total cholesterol (10–12), HDL cholesterol (10), and blood pressure (13,14) in the United States. Also, the higher total and HDL cholesterol among female stroke survivors compared to male stroke survivors is consistent with general population data (7).

Although there were temporal improvements in DBP and total cholesterol in both male and female stroke survivors and HDL among female stroke survivors, total cholesterol levels remained in the high normal range in men and elevated range in women, leaving room for improvement. In addition, the lack of any recent improvements in SBP, diabetes mellitus, and smoking rates are concerning. Finally, the worsening of FCRS among Hispanic women should be noted, as this population may need targeted interventions for reducing cardiovascular risk.

This is the first study to our knowledge to assess FCRS among stroke survivors in a nationally representative sample of the US population. Our study's strengths include its inclusion of various racial/ethnic groups and standardized rigorous biomarker assessment. The study has several limitations. First, NHANES is a cross-sectional study that assesses, among other conditions, prevalence of stroke. Information regarding stroke subtype, stroke severity, time since stroke, and number of previous strokes are lacking. Second, NHANES is limited by volunteer bias and only assesses the noninstitutionalized civilian population in the United States. As a result, stroke survivors living in skilled nursing facilities were precluded from participating in NHANES. Third, there may be minor differences in study conduct between the years, which can limit interpretation of temporal trends. Fourth, NHANES relies on self-report of medical history, including stroke and myocardial infarction. However, while NHANES has not validated self-report of stroke or myocardial infarction, previous studies have shown a sensitivity of 73% to 95% (15–17) and specificity of 96% to 99% for stroke (15,16) and sensitivity of 80% to 82% (17,18) and specificity of 99·4% (18) for myocardial infarction. Fifth, FCRS was derived in a predominantly white population in a suburb of Boston, Massachusetts limiting its generalizability. Analysis of the validity of FCRS in six prospectively studied, ethnically diverse cohorts revealed that FCRS prediction functions performed well among whites and blacks in different settings, but required recalibration for differing prevalences of risk factors and underlying rates of CHD events among other ethnic groups (19). In addition, FCRS was derived from a healthy population and has not been validated among stroke survivors. In addition, gender differences in FCRS in individuals younger than 45 years must be interpreted with caution, as the score assumes that male gender confers a higher risk of coronary heart disease in individuals younger than 45-years. For example, with all other risk factors being equal, a man younger than 45 years will receive a higher FCRS than a woman of the same age. Finally, one should keep in mind that this study presents the FCRS estimates of CHD risk in stroke survivors and does not show observed longitudinal risks of CHD. It will be important to validate these risk scores with future longitudinal cohort studies among stroke survivors. Despite its limitations, this study fills a knowledge gap by providing estimates of future risk of future cardiac events among male and female stroke survivors from 1988 to 2006.

In conclusion, this study showed that male stroke survivors over the age of 64 years have a higher 10-year risk of a hard cardiovascular event than similarly aged female stroke survivors. More intensive efforts to bridge this gender disparity via better vascular risk factor control may be warranted. Furthermore, despite impressive improvements in overall FCRS and certain FCRS components over the past two decades, substantial improvements are likely required to curb the risk of a major cardiovascular event after stroke.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Age-adjusted FCRS by race/ethnicity and gender among stroke survivors in NHANES 1988–1994 and NHANES 1999–2006.

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