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Age- and Ethnic-specific Sex Differences in Stroke Risk

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INTRODUCTION

Age-adjusted stroke risk is higher for men than women.¹ However, age-adjusted sex comparisons obscure the more complex relationship between sex and stroke risk at specific ages. Among whites, age appears to modify the effect of sex on stroke risk such that women compared to men are protected from stroke until roughly age 75 to 85, at which point the protection is lost or reversed, although findings across studies have not been consistent.^{2–6} A similar pattern has also been reported for African Americans,¹ but comparable age and sex-specific stroke incidence data are currently not available for Hispanics.

Hispanic Americans make up the largest minority group in the United States, with Mexican Americans (MAs) being the largest subgroup.⁷ In the United States, MAs are among the fastest growing populations.⁷ MAs have a higher incidence of ischemic stroke, and intracerebral hemorrhage (ICH) compared with non-Hispanic whites (NHWs), especially at younger ages.^{8–10} The objective of this study was to assess age-specific stroke incidence in women and men and to compare these patterns across ethnic groups, using data from a population-based stroke surveillance study in a bi-ethnic population.

MATERIALS AND METHODS

The details of the methods of the Brain Attack Surveillance in Corpus Christi (BASIC) Project have been published previously.^{11, 12} In brief, the BASIC Project conducts population-based stroke surveillance in a bi-ethnic community in south Texas (Nueces County). Of the nearly 314,000 residents in Nueces County, 56% are MA, and NHWs make up 44%.⁷ Case ascertainment in the BASIC Project includes both active and passive surveillance to identify stroke events. In active surveillance (or “hot pursuit”), identification

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of cases occurs through screening hospital admission logs, emergency department records, medical wards, intensive care units and out-of-hospital sources. Passive surveillance (or “cold pursuit”), identifies cases by searching hospital discharge diagnoses, using International Classification of Diseases, Ninth Revision (ICD-9) codes for stroke (430–438). All possible stroke events underwent validation by a stroke neurologist, blinded to race/ethnicity and age, using source documentation and based on published international standards.^{13, 14}

All incident strokes (ischemic, ICH and subarachnoid hemorrhage (SAH)) occurring between January 1, 2000– May 25, 2007 in individuals at least 45 years old were included in the current study. Stroke was defined as an acute onset of a focal neurologic deficit specifically referable to a cerebrovascular distribution that persisted for more than 24 hours. For ICH and SAH the case definition included the same symptoms mentioned above plus neuroimaging showing a spontaneous focal collection of blood in either the parenchyma/ventricle for ICH or the subarachnoid space for SAH. For SAH a spinal fluid definition including xanthochromia and/or greater than 1,000 red blood cells per cubic millimeter without a decrement from first to last tubes of greater than 25 percent was also accepted.¹⁵ Only the first stroke occurring in an individual during the study period was considered. Age, sex and race/ethnicity were ascertained from medical records by trained abstractors. We have previously demonstrated high agreement between race/ethnicity documented in the medical record and self-reported race/ethnicity.¹¹ Population counts were from the 2000 Census.

Statistical Analysis

Descriptive statistics were calculated for demographics and stroke risk factors stratified by race/ethnicity (NHW and MA). Annual stroke incidence rates by sex, age, and race/ethnicity were calculated as the number of strokes within each sex, age and race/ethnicity group divided by the population counts from the 2000 US Census for each group and the study time period in years, with rates expressed as incidence per 1,000 persons per year. Poisson regression using the generalized additive models (GAM) framework was used to analyze the relationship between sex, age (5 year intervals), and race/ethnicity (MA and NHW) and incident stroke risk. GAM is an extension of generalized linear modeling that allows for flexible modeling of the predictors’ effects without having to specify its functional form. Age was treated as a continuous variable, using the midpoint of the 5-year age category as representative for the age group. The outcome was the number of strokes within each sex, age and race/ethnicity group, with the population counts from the 2000 US Census for each group serving as the offset. As it was of interest to understand whether the pattern of sex differences in age-specific stroke incidence rates differed for the two race/ethnic groups, the model included main effects for sex, race/ethnicity and age as well as the following effect modification terms: age*race/ethnicity, age*sex, race/ethnicity*sex and age*race/ethnicity*sex. The continuous age variable was modeled non-parametrically to fit a non-linear age relationship without having to specify a parametric form (e.g., quadratic).¹⁶ Sex differences in stroke risk were summarized as relative risks (RR) and 95% confidence intervals (CI). Models were run for all strokes combined (ischemic, ICH, SAH) and for ischemic strokes separately. Sensitivity analyses were also performed by restricting the analysis to those less than 90 years of age to examine whether the observed patterns of sex differences in stroke risk with advancing age were primarily due to the longer lifespan in women (i.e., the oldest age group exerting undue influence). All tests were two-sided, with alpha values < 0.05 considered statistically significant. The GAM package in R was used for these analyses.

This project was approved by the institutional review boards of the University of Michigan and the Corpus Christi/Nueces County hospitals.

RESULTS

Study Population Characteristics

A total of 2,421 validated incident strokes occurred between January 1, 2000 and May 25, 2007 in the study community. This included 652 strokes in MA men, 657 in MA women, 525 in NHW men and 587 in NHW women. Table 1 depicts the demographic and risk factor data for the stroke cases by sex and race/ethnicity.

Stroke Incidence Rates by Sex, Age and Race/ethnicity

Stroke incidence rates by sex, age and race/ethnicity are presented in Table 2. Stroke incidence increased with advancing age in all sex and race/ethnicity groups. Among both men and women, MAs had increased stroke incidence compared with NHWs until advanced ages when differences were attenuated. For both race/ethnic groups, men had greater stroke incidence than women until advanced age where the sex difference was reversed. The two-way interactions between sex and age and between race/ethnicity and age were significant ($P < 0.001$ for both).

Sex Differences in Stroke Incidence by Age and Race/ethnicity

RRs comparing men with women by age and race/ethnicity are included in Table 3. Among NHWs, men had a higher stroke risk than women in the 45 to 79 age group. The magnitude of increased stroke risk in men compared with women diminished with age such that after age 79 no sex difference in stroke risk remained. Figure 1a suggests a clear decreasing linear relationship in the RR with age among NHWs. Among MAs, a similar pattern of an increased stroke risk in men compared with women in the younger age groups were seen. However, there appeared to be some lack of linearity, where the steady decrease in RR comparing men and women began somewhat later than that in NHWs, at around age 70 (Figure 1b). The three-way interaction formally tests if the shape of the age association comparing men to women differs by race/ethnicity, i.e., if the shape depicted in Figure 1a is different from the shape depicted in Figure 1b. Although the formal test of the three-way interaction was not significant ($P = 0.27$), a post-hoc test of the apparent non-linear association among MAs did reveal a trend ($P = 0.06$).

DISCUSSION

Among NHWs and MAs, we observed a significant interaction between age and sex such that women compared with men experienced protection from incident stroke until roughly 80 years of age, at which point no sex difference in stroke risk remained. Consistent with previous reports, we also observed a significant interaction between age and race/ethnicity on stroke risk.^{8, 10, 17, 18}

Although the patterns of sex differences in stroke risk with age were similar for the two race/ethnic groups as evidenced by an insignificant three-way interaction term ($P = 0.21$), we found some indication of a non-linear association in MAs when considering ischemic and hemorrhagic strokes combined, driven in part by hemorrhages, as the same non-linear pattern was not present when limited to ischemic strokes. In previous work in this community, we demonstrated that SAH is more common among women and MAs.¹⁹ While SAH is the least common stroke type overall, it is a more common stroke type among younger stroke patients.²⁰ The greater burden of SAH in women and in particular MAs may have contributed to the non-linear age trend with respect to sex differences in stroke risk observed for MAs. Our analysis did not include separate models for ICH or SAH strokes due to a small number of events for these stroke types.

The current literature on age-specific sex differences in stroke risk is primarily limited to white populations and is somewhat inconsistent. In a study from Framingham, men had higher stroke risk compared with women until age 84, when risk in women exceeded that in men.⁵ Data from a population-based study in Sweden also showed a reversal in the sex difference with advanced age.⁴ Others have reported that stroke risk in men remains higher than that in women throughout the life-course, although the magnitude of the sex difference diminishes with age.^{2, 3} Still, others have reported that the sex differences no longer exist at older ages.^{6, 21} Our findings are in general agreement with the studies that suggest that women are protected from stroke, at younger ages, and that this protection is lost with advancing age but not reversed. Our study further extends this observation to MAs, a subgroup of the US population with an excess stroke burden.⁸

Although during midlife women have a lower risk of stroke than men, their risk doubles in the decade after menopause. Changes in cardiovascular risk factors with menopause may contribute to this increase in stroke risk and the attenuation of sex differences in stroke with advancing age. Changes that occur with menopause include increasing low density lipid and triglyceride levels, decreasing high density lipid levels, changes in body fat distribution, changes in insulin action, increasing blood pressure levels, increased prevalence of metabolic syndrome, and increases in fibrinolytic and inflammatory markers with.^{22, 23} These risk factors could mediate the pathway from changing hormone levels with the menopausal transition and stroke risk as low levels of sex hormone binding globulin and estradiol and high levels of free androgen index have been associated with risk factor levels in the peri-menopause.²⁴ Data on endogenous hormone levels and risk factors, measured throughout the menopausal transition, as well as subsequent stroke endpoints would be needed to formally address this hypothesis. Alternatively, age and sex-specific differences in the prevalence, treatment and control of stroke risk factors may contribute to the observed pattern of sex differences in stroke risk in midlife. Another mechanism that may contribute to the decline in sex differences in stroke risk with age pertains to selective survival in men. Markides and Machalek introduced the idea that mortality differences among populations could decrease or reverse with advancing age due to selective survival.²⁵ In the context of sex differences in stroke, men who survive to older ages may have a different susceptibility to stroke than men who suffered a stroke at younger ages, thus contributing to the lack of a sex difference in stroke risk among the oldest old.

There are several strengths to the current analysis including the nearly eight-year period of case ascertainment and large number of stroke events, which increased our power to detect sex differences in stroke risk by age and race/ethnicity. Another strength is the focus on sex and age-specific differences in stroke risk in the MA population, a growing population with disparate stroke rates.^{7, 8} Further, we used GAM models for our analysis, which allowed greater flexibility in modeling the effect of nonlinear predictors, such as age, on stroke risk.

The current study has limitations that should be considered. First, the study is limited to one, urban, non-immigrant community in southeast Texas and thus, the results may have limited generalizability to immigrant populations and geographic regions with different demographic and stroke risk factor profiles. However, our study population has a similar risk factor profile to those reported in other studies of stroke risk in Hispanics.^{26, 27} There is some potential for missing events, especially in MAs who may have reduced access to medical care services and/or who have access, but do not seek medical attention for stroke. However, we have previously shown the number of out of hospital strokes and medical insurance coverage to be roughly similar in the two ethnic groups in this community reducing the likelihood of this bias.^{28, 29}

Summary

We observed that women were protected from incident stroke compared with men until roughly 80 years old, at which point no sex difference in stroke risk remained, and that similar patterns exist for MAs and NHWs. Reasons for the loss of protection from stroke in aging women are not fully understood and warrant further study.

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Figure 1.

Men:Women relative risk of stroke (ischemic and hemorrhagic) by age in non-Hispanic whites (A) and Mexican Americans; (B) and of the Men:Women relative risk ischemic stroke in non-Hispanic whites; (C) and Mexican Americans (D) in the BASIC (Brain Attack Surveillance in Corpus Christi) Project, Nueces County Texas, 2000–2007.

Table 1

Baseline Demographic and Risk Factor Data for Stroke Cases by Race/Ethnicity and Sex; BASIC Project, Nueces County, Texas (2000–2007); Percent (n).

	NHW		MA	
	Male	Female	Male	Female
N	525	587	652	657
Age *	70.0(12.5)	75.8(12.4)	65.6(11.9)	69(12.8)
NIH Stroke Scale Score †	4(2, 8)	4(2, 10)	4(2, 8)	4(2, 8)
Stroke Type				
Ischemic	84.9%(446)	81.4%(478)	79.3%(517)	79.0%(519)
ICH	12.4%(65)	14.1%(83)	17.8%(116)	13.9%(91)
SAH	2.7%(14)	4.4%(26)	2.9%(19)	7.2%(47)
Atrial fibrillation	12.6%(66)	16.9%(99)	5.1%(33)	9.6%(63)
Coronary artery disease	33.9%(178)	26.7%(157)	27.6%(180)	26.8%(176)
High cholesterol	25.5%(134)	23.3%(137)	24.8%(162)	24.4%(160)
Diabetes	23.8%(125)	21.5%(126)	44.9%(293)	50.2%(330)
Hypertension	67.0%(352)	70.5%(414)	70.2%(458)	75.0%(493)
Excessive alcohol	10.1%(53)	2.7%(16)	13.7%(89)	1.8%(12)
Current smoker	24.9%(127)	15.5%(88)	27.6%(175)	11.7%(76)

* Mean (Standard deviation(SD)).

† Median (Inter-quartile range(IQR)).

Table 2

Age-specific Stroke Incidence Rates (per 1,000 population per year) in MA and NHW Women and Men by Stroke Type; BASIC Project, Nueces County Texas (2000–2007).

Age	Women				Men			
	Total Stroke		Ischemic Stroke		Total Stroke		Ischemic Only	
	NHW	MA	NHW	MA	NHW	MA	NHW	MA
45–49	0.42	1.05	0.28	0.77	0.89	1.33	0.71	1.12
50–54	1.03	1.61	0.77	1.08	1.37	2.83	1.09	2.06
55–59	1.44	2.89	1.10	2.34	1.74	4.35	1.26	3.14
60–64	1.59	3.20	1.38	2.42	3.08	4.32	2.78	3.41
65–69	2.23	4.04	1.94	3.57	2.91	5.66	2.45	4.60
70–74	4.26	5.26	3.51	4.24	3.84	8.09	3.43	6.57
75–79	4.91	6.54	4.01	5.16	6.91	9.00	6.40	7.56
80–84	7.96	10.66	6.88	8.76	9.89	11.18	8.27	9.17
85–89	12.8	12.79	10.06	10.40	11.41	11.83	9.31	9.93
90plus	17.10	16.16	13.68	12.01	15.77	14.75	12.62	12.64

Abbreviations: MA, Mexican American; NHW, Non-Hispanic White

Table 3

Age-Specific Relative Risk (RR) Estimates of Stroke Comparing Men with Women by Race/Ethnicity and Stroke type; BASIC Project, Nueces County, Texas (2000–2007).

Age	Total Stroke				Ischemic Only			
	NHW	95% CI	MA	95% CI	NHW	95% CI	MA	95% CI
45–49	1.70	1.28, 2.24	1.43	0.90, 2.28	1.81	1.32, 2.49	1.62	0.97, 2.69
50–54	1.59	1.26, 2.02	1.50	1.03, 2.19	1.69	1.30, 2.21	1.57	1.03, 2.40
55–59	1.49	1.23, 1.82	1.53	1.12, 2.10	1.58	1.27, 1.97	1.52	1.07, 2.16
60–64	1.40	1.19, 1.64	1.52	1.16, 1.99	1.48	1.24, 1.77	1.46	1.09, 1.96
65–69	1.31	1.15, 1.50	1.48	1.16, 1.87	1.38	1.19, 1.60	1.41	1.10, 1.80
70–74	1.23	1.09, 1.39	1.40	1.12, 1.75	1.29	1.13, 1.48	1.34	1.06, 1.69
75–79	1.16	1.02, 1.32	1.28	1.01, 1.62	1.21	1.05, 1.39	1.27	0.99, 1.64
80–84	1.09	0.93, 1.26	1.15	0.87, 1.52	1.13	0.95, 1.33	1.20	0.89, 1.62
85–89	1.02	0.84, 1.23	1.02	0.71, 1.46	1.05	0.86, 1.29	1.13	0.78, 1.64
90plus	0.96	0.76, 1.20	0.90	0.56, 1.45	0.98	0.77, 1.26	1.06	0.67, 1.69

Abbreviations: CI, Confidence Interval; MA, Mexican American; NHW, Non-Hispanic White; RR, Relative Risk.