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Temporal Trends of Sex Differences in Transient Ischemic Attack Incidence Within a Population

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Abstract

Objective: Previously we reported that ischemic stroke incidence is declining over time for men but not women. We sought to describe temporal trends of sex differences in incidence of transient ischemic attack (TIA) within the same large, biracial population.

Methods: Among the population of 1.3 million in the Greater Cincinnati Northern Kentucky Stroke Study (GCNKSS) region, TIAs among area residents (≥20 years old) were identified at all local hospitals. Out of hospital cases were ascertained using a sampling scheme. First-ever cases and first within each study period for a patient were included in incidence rates. All cases were physician-adjudicated. Incidence rates (during 7/93-6/94 and calendar years 1999, 2005, and 2010) were calculated using the age-, race-, and sex-specific number of TIAs divided by the GCNKSS population in that group; rates were standardized to the 2010 U.S. population. T-tests with Bonferroni correction were used to compare rates over time.

Results: There were a total of 4746 TIA events; 53% were female, and 12% were black. In males, incidence decreased from 153 (95%CI 139-167) per 100,000 in 1993/4 to 117 (95%CI

107-128) in 2010 (p<0.05 for trend test) but was similar over time among females (107 (95%CI 97-116) to 102 (95%CI 94-111), p>0.05).

Conclusions: Within the GCNKSS population, TIA incidence decreased significantly over time in males but not females, data which parallels trends in ischemic stroke in the GCNKSS over the same time period. Future research is needed to determine if these sex differences in incidence over time continue past 2010.

Keywords

sex-specific; incidence; transient ischemic attack; stroke

INTRODUCTION

Previous data from the Greater Cincinnati Northern Kentucky Stroke Study (GCNKSS) suggests that there are sex differences in how ischemic stroke incidence is changing over time; data from 1993/4 through 2010 suggests that stroke incidence in women is decreasing to a lesser extent than stroke incidence in men over the same time period.[1] These data conflict with other studies showing similarly decreasing rates of stroke over time in women and men.[2-4]

Reasons for conflicting data on temporal trends as well as the possible contributors to sex differences in stroke incidence over time are unclear, though sex differences in the prevalence and/or control of conventional stroke risk factors could be contributing.[5] It is plausible to hypothesize that there might also be sex differences in the incidence of transient ischemic attack (TIA) over time given that TIAs are known to be a significant predictor of subsequent ischemic stroke.[6-9] TIAs are potentially high risk events, with associated 90-day stroke risks ranging from 8.5 to 14.6% depending on the study population.[6, 7, 10, 11]

Previous incidence data from the GCNKSS showed higher TIA rates among men compared with women and blacks compared with whites but did not evaluate trends over time.[6] Data on TIA incidence over time is generally lacking, as TIAs are often excluded from longitudinal epidemiologic studies of stroke.[2-4] One study of TIA incidence and stroke risk following TIA in a population based study in Australia reported a difference in temporal trends of TIA by age but not sex; this same study, however, found that stroke risk following TIA increased more in women than men between 2001 and 2011.[12] If significant sex differences in TIA incidence are identified, we may identify opportunities to improve stroke prevention strategies in a sex-specific manner among TIA patients, a high risk group for stroke and poor outcomes.

The primary objective of the present study was to investigate temporal trends in TIA incidence over time by sex in the GCNKSS. Our secondary objective was to evaluate sex differences in short term outcomes following TIA.

MATERIALS AND METHODS

Study Population/ Setting/ Design

The GCNKSS is a population-based epidemiologic study tracking stroke events among approximately 1.3 million people living in a 5-county region of southern Ohio and northern Kentucky. This is an area whose population is representative of the U.S. with regards to percent black, age, and socioeconomic status. During each study period (1993/4, 1999, 2005, 2010), all events among adults at least 20 years old presenting to one of the area hospitals are ascertained along with those ascertained in outpatient settings; coroner's offices, hospital-based and public health clinics, plus a weighted sample of events occurring in nursing homes and doctor's offices. The number of hospitals in the region ranged from 14 to 17 depending on the study period. Further details of study methodology, including out of hospital sampling procedures, can be found in previously published papers.[13,14]

Case definition/ Adjudication

TIA was defined as a focal neurologic deficit lasting less than 24 hours. Potential events were first identified using discharge ICD9 codes (430-436). Trained study nurses reviewed records from all potential events as determined by ICD9 codes and abstracted data on patient demographics, presenting symptoms, risk factors and co-morbidities, and neuroimaging characteristics. Nurses decided whether an event had occurred, keeping all borderline or possible events; however, cases were excluded by nurses if the patient was not a resident of the 5-county study region. All cases were then adjudicated by trained study physicians, including determination of stroke type (for example, infarct, TIA, intracerebral hemorrhage); only TIAs were included in the present analysis. Physician adjudicators used a clinical case definition of TIA, a focal neurologic deficit lasting less than 24 hours, in order to be able to compare incidence over time. A subset of all cases were also reviewed by lead study physicians. To be included in the current analysis as an incident event, TIAs must have been a first event during the individual study period. Subsequent TIAs within the same study period were not included in the incidence rates. Methods for screening and adjudication of TIA events were consistent across the 4 study periods.

Statistical Analyses

Demographic characteristics of patients with TIA (age, sex, race) were reported by sex and study period. To examine other possible sex differences influencing TIA incidence over time, history of stroke risk factors (hypertension, diabetes, hyperlipidemia) were also reported by sex and year. Weighted means and associated standard errors were reported for continuous variables, while raw frequencies with weighted percentages were reported for categorical variables. Weighting was used to account for the sampling scheme for out-of-hospital events.

To calculate TIA incidence rates in each study period, an event was counted only if it was the first event during the individual study period for the patient, as per our previous methodology.[6] An event was considered recurrent if it occurred following the initial adjudicated event within a given study period so was not included in the current analysis. Sex-specific TIA incidence rates in each of four study periods (July 1993-June 1994 and

calendar years 1999, 2005, and 2010) were determined. Incidence rates were calculated using the age-, race-, and sex-specific number of TIAs divided by the relevant GCNKSS population, and then standardized to the 2010 U.S. population. Incidence rates were reported per 100,000 with 95% confidence intervals estimated assuming a Poisson distribution. Statistical testing for differences over time for demographic and clinical variables was performed using generalized linear models adjusted for age and race, and p-values for the interaction of time period and sex were reported. Incidence rates were compared using t-test with a Bonferroni correction as we were comparing the four time periods. The delta method was then used to estimate the ratio of female to male TIA incidence and the associated standard error (SE) in each study period. A sensitivity analysis was performed using only events ascertained from local hospitals (excluding all events ascertained only in the out-of-hospital setting) in order to account for possible over-estimation of event rates due to the diagnostic uncertainty around outpatient events. In secondary analyses, incidence rates over all years, in -sex and -age stratified groups, were calculated to further investigate the effect of age on sex differences in TIA trends over time. Bonferroni-adjusted p-values were used to compare sex-specific incidence rates between years to account for multiple comparisons.

Outcomes in our study were ascertained within 6 months of TIA and included recurrent TIA, subsequent infarct, all-cause mortality, and composite outcomes (TIA/infarct and TIA/infarct/death). In addition to reporting sex-specific crude rates of each outcome, outcomes were analyzed using a Cox proportional hazards regression, adjusted for age and race. For adjusted results, hazards ratios with 95% confidence intervals were reported. Unless otherwise noted above, p values less than 0.05 were considered significant. Statistical analyses were completed using SAS® version 9.4 (SAS Institute, Cary, NC).

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the institutional review boards of each of the participating hospitals and/or outpatient institutions. Because data were analyzed retrospectively, written informed consent was not obtained; the study was approved by the IRBs/ethics committees.

Data Availability Policy

Data are housed at the University of Cincinnati College of Medicine. External requests for data from the Greater Cincinnati/ Northern Kentucky Population-Based Epidemiology of Stroke study should be submitted to the principal investigators via the official website (https://www.gcnkss.com).

RESULTS

There were 4746 total TIA events over the 4 time periods, and 53% occurred in female patients. At the time of the incident TIA event, females were older than males in all 4 time periods by an average of 4.6 years (Table 1). The race of patients with TIA differed by sex as well; a greater proportion of females compared with males were black in all years with the exception of 1999. The distribution of hypertension, diabetes, and high cholesterol differed by sex within study periods, but not in any clear pattern across the four study periods.

Table 2 shows our primary outcome, TIA incidence rates (both inpatient and out of hospital ascertained) by sex, adjusted by age and race. Overall, TIA incidence decreased over time, from 127 (95%CI 119-135) per 100,000 in 1993/4 to 110 (95% CI 103-117) per 100,000 in 2010 ($p<0.05$ for trend). In men, incidence decreased from 153 (95%CI 139-167) per 100,000 in 1993/4 to 117 (95%CI 107-128) in 2010 ($p<0.05$ for trend) but there was no significant change over time among females (107 (95%CI 97-116) to 102 (95%CI 94-111), $p>0.05$) (Figure 1). For men, this is a 23.5% reduction in incidence compared to a 4.7% reduction in incidence for women. The male/female rate ratio of TIA incidence over the course of the 4 study periods changed as well, increasing from 0.70 (95%CI 0.61-0.79) in 1993/4 to 0.87 (0.75-0.99) in 2010. Similar sex differences in trends over time were seen when only inpatient ascertained events (patients with events found in the hospital records) were included (data in Table S1 in online supplement).

Crude, unadjusted rates of outcomes at 2 days, 7 days, 1 month, 2 months, 3 months, and 6 months post stroke are displayed in Table 3. In Cox proportional Hazards models adjusted for age and race, females have a lower risk of post-TIA infarct (HR 0.82, 95% CI 0.69-0.98), TIA/infarct (HR 0.86, 95% CI 0.76-0.98), and of the composite outcome of TIA, infarct, or death compared with males (HR 0.86, 95%CI 0.76-0.98) but similar risk of recurrent TIA compared with males (HR 0.93, 95% CI 0.78-1.11).

In our age stratified analysis of TIA incidence (Table S2 in online supplement), our data show that the majority of events are occurring in those in the four oldest age groups (55-64, 65-74, 75-84, and over 85). Incidence rates in these age groups decreased between the first and last study periods in males. For example, in the 65-74 group, among males, TIA rates decreased from 378 (95% CI 317-439) per 100,000 in 1993/4 to 230 (183-277) per 100,000 in 2010. Similarly, in the 85+ group, among males, TIA rates decreased from 722 (95% CI 471-974) in 1993/4 to 503 (95%CI 338-668) per 100,000 in 2010. In females, however, rates appear to be stable or increasing slightly over time in each of these four age groups. Incidence rates are higher in males than females in most age groups, though by 2010, rates appear to be similar by sex or higher in females in the majority of age categories with the exception of ages 45-64 and 75-84.

DISCUSSION

In our analysis of TIA incidence rates over time in the GCNKSS between 1993/4 and 2010, while overall incidence rates decreased, the trend over time differed by sex: there were significant decreases in TIA incidence over time among males but not females. In addition, when data were stratified by age, by 2010 females had similar or higher rates of TIA in several age groups including 55-64 years, 65-74 years, and over 85 years compared with males. Outcomes also differed by sex; females were less likely to have subsequent infarcts and death after adjustment for age and race compared with males.

Not only does our study demonstrate sex difference in how TIA rates may be changing over time, but it also adds to the current knowledge of trends in overall TIA incidence over time, something few studies have investigated in recent years. Recent cohort and/or population based studies of stroke over time have largely excluded TIAs[1-4] or have focused on

obtaining TIA incidence data over a single time period.[6, 15] In a population-based study out of Rochester, TIA incidence rates appeared to be stable between the 1970s and 1980s,[16] and data from a population-based study in Russia showed a trend toward an increase in TIA incidence among both females and males between 1987 and 1997.[17] Another study of TIA incidence over time between the 1980s and 1990s showed widely varying rates of TIA in both females and males with no clear trends over time.[18] Finally, in a population-based cohort study out of Australia, TIA incidence rates in both sexes decreased between 2001 and 2011 but only among individuals older than 65 years old. In the same study rates of TIA increased among females and males under the age of 65.[12]

Our findings of post-TIA outcomes are consistent with prior estimates. Previous studies of 3-month outcomes after TIA have demonstrated infarct rates between 8 to 15% [6,7,11] with some as high as 17.3%[8] and some as low as 3-4%.[12,19] In general, though, our findings from the current study combined with previous data continue to suggest that TIAs are potentially high risk events and should continue to trigger aggressive management of risk factors. Other previous studies have demonstrated sex differences in outcomes after TIA which conflict with our findings. Sundarajan et al. performed a temporal analysis of the 90-day risk of stroke after TIA between 2001 and 2011 and found that male sex was a predictor of decreasing risk of stroke after TIA over this 10 year time period.[12] In the present study, we did not aim to describe whether outcomes after TIA were changing over time but did find that over all time periods, females had a lower risk of TIA or TIA/infarct following the incident TIA compared with males. These findings require further investigation.

Our finding that decreases in TIA incidence rates over time are driven by decreases in males parallel our previous findings of sex differences in stroke incidence over time,[1] which is logical given the known association between TIA and incident stroke. Drivers behind these sex differences in rates of cerebrovascular events over time are not clear, and this study was not specifically designed to evaluate specific contributors to TIA risk. Though there were sex differences in the prevalence of risk factors such as hypertension and hyperlipidemia within individual study periods, there were no clear sex differences in trends over time. Our findings do, however, still have implications going forward. Most notably, if the trend of a sex difference in TIA risk over time continues, it follows that women may experience a relative increase in stroke events compared with men. Guidelines for stroke prevention in women have been previously published, but more sex-specific research is needed with regard to the management of the risk factors accounting for the bulk of stroke risk. [5,20] These may include hypertension, diabetes, and hyperlipidemia, among others.

Our study has several limitations to consider. First, though TIAs were adjudicated by trained study physicians, TIA event rates in general may be more difficult to estimate than ischemic stroke rates given the brief nature and lower severity of many TIAs. Our standardized process of ascertaining and adjudicating these events over the 4 study periods did not change over time, which is a strength of the GCNKSS. Our findings were similar when we conducted sensitivity analyses with only inpatient ascertained events, indicating that our trends are unlikely to be a result of any biases arising from misclassification of events in the outpatient setting. It is also known that practice patterns, particularly the use of MRI imaging, has increased over time. Though increasing MRI use has the potential to change

the rates of diagnosed TIAs,[21] it is unlikely that MRI use is accounting for the changes over time in our study as TIA adjudication in the GCNKSS is based on a clinical definition of TIA (not imaging) and has remained consistent over time. In addition, prior work from the GCNKSS demonstrated that MRI did not significantly change incidence rates and that the use of MRI ruled out a diagnosis of stroke as often as it confirmed a stroke diagnosis.[22]

In conclusion, in our study of TIA incidence between 1993/4 and 2010, there was a significant decrease among males over time but no significant decrease among females. Outcomes post-TIA in both sexes were comparable to prior literature and remain high. It is critical to continue to investigate TIA trends over time both overall and by sex and age in order to confirm whether our findings of sex differences in temporal trends continue and to guide research on effective stroke prevention strategies for both women and men.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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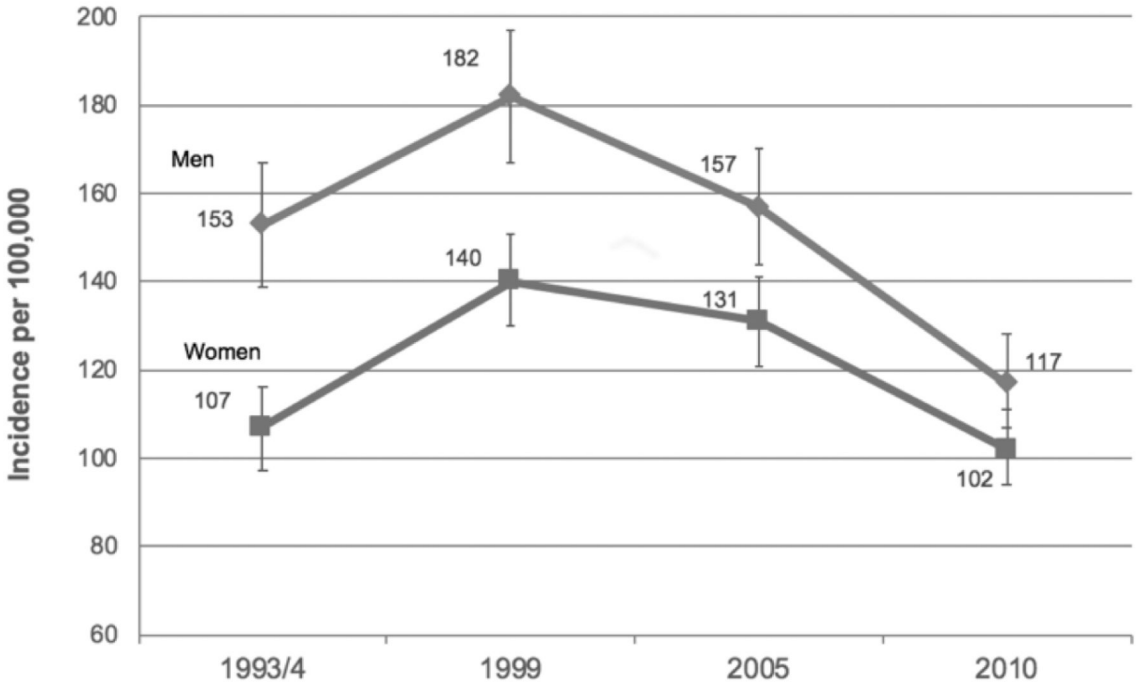

Figure:

TIA Incidence per 100,000, Men vs. Women, Adjusted by Age and Race and Standardized to 2010 US Census

Table: 1

Demographics by year and sex, Inpatient and Out-of-Hospital Ascertained

Variable	1993/4		1999		2005		2010		
	Male	Female	Male	Female	Male	Female	Male	Female	p-value*
Age (years)	69.1 (1.12)	71.8 (0.90)	68.1 (1.06)	73.5 (0.92)	65.5 (0.84)	70.1 (1.34)	64.6 (1.39)	70.4 (0.68)	0.13
Race (black)	55 (12.4)	84 (15.4)	49 (11.5)	65 (12.0)	43 (7.2)	83 (14.0)	59 (12.0)	100 (17.6)	0.14
Hypertension	189 (47.9)	245 (51.1)	268 (57.7)	373 (72.9)	321 (71.9)	413 (65.9)	322 (75.7)	443 (82.2)	<0.0001
Diabetes	82 (19.8)	98 (18.0)	111 (18.)	126 (26.6)	126 (26.0)	151 (23.7)	120 (26.4)	161 (30.2)	0.01
High Cholesterol	48 (22.9)	58 (16.7)	124 (27.2)	130 (33.2)	212 (48.0)	217 (41.8)	235 (58.0)	290 (54.7)	0.007

*p-value for interaction of sex with year

Data presented as weighted mean (weighted standard error) or raw n (weighted %).

Table 2:

TIA incidence Rates (95% confidence interval), per 100,000 for those 20 years and older, Inpatient and Out-of-Hospital ascertained, standardized to the 2010 US population, Adjusted by age and race

	N	Weighted N	Overall Incidence (95% CI)	Male Incidence (95% CI)	Female Incidence (95% CI)	Ratio female/male (95% CI)
1993/94	907	1043	127 (119, 135)	153 (139, 167)	107 (97, 116)	0.70 (0.61, 0.79)
1999	1003	1339	159 (150, 168)	182 (167, 197)	140 (130, 151)	0.77 (0.68, 0.85)
2005	1005	1304	144 (136,152)	157 (144, 170)	131 (121, 141)	0.83 (0.74, 0.93)
2010	955	1060	110 (103, 117)	117 (107, 128)	102 (94, 111)	0.87 (0.75, 0.99)
P value for trend over time *			<0.05	<0.05	>0.05	

* Bonferroni corrections were used for testing differences between years:

Overall 2010 < 1993/4, 1999 and 2005 and 1993/4 < 1999 and 2005 ($p<0.05$)

Male 2010 < 1993/4, 1999 and 2005 and 1993/4 < 1999 ($p<0.05$)

Female 2010 < 1999 and 2005 and 1993/4 < 1999 and 2005 ($p<0.05$)

Table 3:

Short–term prognosis after Transient Ischemic Attack: Over all study time periods by sex, crude unadjusted rates and adjusted hazards ratios (Inpatient and Out-of-Hospital Ascertained)

Recurrent events	**TIA %**	**Infarct %**	**TIA/Infarct %**	**Death %**	**TIA/Infarct/Death %**
Sex (p-value)	**Female / Male**	**Female / Male**	**Female / Male**	**Female / Male**	**Female / Male**
2 day	2.7 / 2.1 (0.19)	3.7 / 3.1 (0.45)	5.7 / 5.7 (0.99)	0.04 / 0 (1.00)	5.7 / 5.7 (0.99)
7 day	4.6 / 4.0 (0.28)	5.4 / 5.1 (0.80)	9.3 / 9.7 (0.71)	0.28 / 0.32 (0.80)	9.4 / 10.0 (0.63)
1 month	9.8 / 8.0 (0.31)	8.6 / 7.9 (0.58)	18.2 / 15.5 (0.21)	1.3 / 1.7 (0.25)	18.8 / 16.7 (0.35)
2 months	11.7 / 10.4 (0.56)	10.6 / 9.5 (0.50)	21.7 / 19.1 (0.28)	2.4 / 2.6 (0.63)	22.8 / 20.6 (0.37)
3 months	13.5 / 12.0 (0.54)	12.6 / 11.7 (0.59)	25.0 / 22.4 (0.34)	3.6 / 3.9 (0.64)	26.6 / 24.6 (0.45)
6 months	19.5 / 19.4 (0.99)	21.4 / 19.2 (0.45)	37.1 / 34.6 (0.48)	7.8 / 10.4 (0.04)	40.0 / 39.5 (0.89)
HR (95% CI) * [p-value] for female vs male	0.93 (0.78, 1.11) [0.43]	0.82 (0.69, 0.98) [0.03]	0.86 (0.76, 0.98) [0.02]	Non-estimable	0.90 (0.80, 1.01) [0.07]

The rates account for incomplete follow-up and competing risks (if death occurs, not possible to have TIA or Infarct).

* HR: Hazard Ratio (95% confidence interval), adjusted for age and race