Factors Associated With Geographic Variations in Stroke Incidence Among Older Populations in Four US Communities

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Background and Purpose—In the Cardiovascular Health Study (CHS), we previously observed lower stroke incidence in Allegheny County, PA compared with the other 3 study sites. The purpose of this study was to study possible reasons for the lower stroke incidence in Allegheny County.

Methods—CHS participants 65 years or older who were stroke-free at baseline (n=5639) were followed between 1989 to 1990 and 2000 for the development of stroke. Risk factors at baseline and their subsequent control were compared among both groups. Site-specific hazard ratios for stroke incidence were calculated using Cox regression models.

Results—The unadjusted hazard ratio for total stroke incidence in Forsyth County, NC; Sacramento County, CA; and Washington County, MD combined compared with Allegheny County, PA was 1.74 (95% CI: 1.42, 2.14). After adjustment for age and other traditional risk factors, there was modest reduction of the excess hazard in non-Allegheny sites compared with Allegheny County (hazard ratio 1.52, 95% CI: 1.17, 1.98). Between baseline and the seventh-year visits, control of hypertension, diabetes, lipids, smoking, atrial fibrillation and transient ischemic attack were similar across sites. White matter grade on the baseline brain MRI was less common in Allegheny County (25.8% versus 36.3%, respectively; P<0.001) and accounted for 25% of the excess hazard in non-Allegheny sites compared with Allegheny County.

Conclusions—Site differences in stroke risk factors at baseline and subsequent control only partially explain site differences in stroke incidence. White matter grade as a possible integrated measure of exposure and control of risk factors may help in explaining geographic variations in stroke incidence. (Stroke. 2006;37:1980-1985.)

Key Words: epidemiology ■ geography ■ incidence ■ magnetic resonance imaging ■ risk factors ■ stroke

Geographic variation in stroke incidence and mortality remain unexplained in the US. Studying variations in stroke incidence and its causes may be an important step in improving preventive practices especially among older population who experience the majority of stroke burden. Few studies have examined the association between geographic variations in multiple stroke risk factors and stroke incidence and mortality among Americans, showing relatively inconsistent patterns. In addition to a paucity of recent data, prior studies frequently included only a few traditional cardiovascular risk factors and typically did not incorporate the effect of potentially important markers of subclinical cardiovascular disease such as carotid artery stenosis or MRI findings. Most US studies of geographic variation have focused on the southeast regions of the US, or “stroke belt”, which has had a consistent excess in stroke mortality over the past half-century. This pattern has been attributed to less favorable stroke risk factors profiles and less desirable response to medications. For example, hypertension prevalence, less desirable response to antihypertensive medications, and hypertension-related mortality and morbidity were all reported to be high among southeastern states.

We previously reported a significantly lower stroke incidence in Allegheny County, Pa, in the Cardiovascular Health Study (CHS), a prospective cohort study of older adults in 4 US communities. Here we report analyses examining reasons for the CHS site differences in stroke incidence. We compared a large number of stroke risk factors and their control between higher stroke incidence sites (non-Allegheny sites) and lower stroke incidence site (Allegheny site).
Methods

Study Population
The CHS design, including recruitment techniques, definitions of risk factors and outcomes, has been described in detail.4,5 In brief, 5888 men and women aged 65 years and older were recruited from a random sample of Health Care Financing Administration (HCFA) Medicare eligibility lists type B in 4 US communities: Forsyth, NC; Sacramento County, CA; Washington County, MD; and Allegheny County, PA. Potentially eligible participants were excluded if they were institutionalized, wheelchair-bound in the home, or receiving cancer treatment. Participants were recruited in 2 waves. A total of 5201 participants were recruited in 1989 to 1990 in the first wave (original cohort). An additional 687 black participants were recruited in 1992 to 1993 in the second wave (new cohort) to improve black representation in the study.

Risk Factors and Outcome Assessments
Extensive historical, physical and laboratory evaluations were performed at baseline and thereafter annually to identify the presence and severity of stroke risk factors. ICD-9-CM codes 430 to 438 were investigated for possible stroke events. Ascertainment of new stroke events was carried out by questionnaire at the annual visits and interim telephone contacts, from notification of events by participants, and reviewing Medicare hospitalization data.7,8 Hypertension was defined as systolic blood pressure ≥140, diastolic blood pressure ≥90, or a history of hypertension plus use of antihypertensive medication. Diabetes was defined as fasting glucose ≥126 mg/dL or taking insulin or oral hypoglycemics. Current smoking was defined as smoking cigarettes in the last 30 days. Self-reported previous coronary heart disease (CHD), atrial fibrillation (AF), or transient ischemic attacks (TIA) were validated by examination or medical records. Control of risk factors was evaluated by the rate of medication use (eg, hypertension medications) among appropriate participants (eg, those with hypertension) or improving risk factor levels (eg, blood pressure) with medication use. Carotid ultrasounds were obtained at baseline, third-year, and ninth-year visits to detect subclinical atherosclerosis. Cerebral MRIs were performed twice, once in years 4, 5 or 6 and again in years 10 or 11. White matter grade was scored with a value of 0 to 9 with 0 = no changes and 9 = most pronounced changes. Any MRI lesion with a maximum diameter of at least 3 mm was considered a large infarct. We defined “any sub-clinical cardiovascular disease” as a composite measure including any of the following: ankle arm index ≤0.9, internal or carotid wall thickness >80th percentile, carotid stenosis >25%, major ECG abnormalities or claudication or angina from the Rose questionnaire.

Statistical Analysis
Participants were included in the analyses at baseline (1989 to 1990 for the original cohort and 1992 to 1993 for the new cohort), the seventh-year visit (1996–1997), and at the time of their cerebral MRI or carotid ultrasound only if they were stroke-free at the time of visit and stroke follow-up data were available after that specified visit time. Incident stroke cases were adjudicated from the baseline examination for each cohort through June 30, 2000. Years of follow-up were defined as the time from the baseline visit to occurrence of stroke for those who had a stroke and as the time from the baseline visit to censoring (death or drop out) for those who did not have a stroke.

Potential stroke risk factors and their control were compared between Allegheny County and the other 3 sites combined. Data were checked for normality. For continuous variables, the t test was used to test differences for risk factors that were normally distributed and the Mann-Whitney test was used to test differences for risk factors that were not normally distributed. The Pearson χ2 test was used for the testing of categorical risk factors. Stroke incidence hazard ratios at different visits were calculated using Cox regression models. After adjustment for age, gender and race, hazards in Forsyth, Sacramento and Washington Counties were compared with that in Allegheny County, separately, and then combined. The effects of traditional cardiovascular risk factors (including hypertension, diabetes, smoking, body mass index, low-density lipoprotein (LDL) and high-density lipoprotein cholesterol, alcohol drinking, previous CHD, AF, or TIA) on stroke incidence between non-Allegheny sites combined and Allegheny County were then evaluated. Subclinical cardiovascular diseases, specific MRI findings, and the use of medications (including aspirin, oral anticoagulants, and medications for hypertension, diabetes, or hyperlipidemia) were evaluated in age-adjusted models. The percentage of excess hazard reduction in a specific model was calculated by comparing the excess hazard reduction for that model to a reference model.

Results

Subjects and Stroke Risk
Compared with the other 3 sites, the population at Allegheny Countype had similar age (72.8 years in both groups) and gender (females were 56.8% and 58.8%, respectively; P = 0.173) but not race (whites were 79.0% and 86.6%, respectively; P < 0.001) or education (those who had >12 years schooling were 49.4% and 41.7%, respectively; P < 0.001). The total number of participants at risk for incident stroke at all sites who were able to complete the visits was 5639 at baseline, 3918 at the third-year visit and 3345 at the seventh-year visit. There

![Figure 1. Total stroke adjusted hazard ratio at different CHS visits in non-Allegheny sites separately and combined compared with Allegheny County.](image-url)
were 665 incident stroke events with 10 or 7 years of follow-up in predominantly white \( (n=5002) \) and black \( (n=637) \) cohorts, respectively. A total of 359 incident stroke events developed after the third-year visit, and 164 after the seventh-year visit. After adjustment for age, gender and race, the hazard ratio of stroke for non-Allegheny sites combined compared with Allegheny County was 1.75 \((95\% \text{ CI}: 1.42, 2.14; P<0.001)\) at baseline, 2.01 \((95\% \text{ CI}: 1.49, 2.71; P<0.001)\) at the third year, and 2.39 \((95\% \text{ CI}: 1.54, 3.73; P<0.001)\) at the seventh year (Figure 1).

### Traditional Risk Factors and Markers of Subclinical Disease

Both Allegheny County and the other 3 sites had similar prevalence of hypertension, diabetes and current smoking across visits (Table 1). There were no significant differences at baseline and the third year between the 2 groups in the percentage of those who had high LDL \((\geq 100 \text{ mg/dL})\), low high-density lipoprotein \((\leq 35 \text{ mg/dL})\), and high triglycerides \((\geq 200 \text{ mg/dL})\); Table 1). The number of alcoholic drinks per week was higher in Allegheny County compared with the other 3 sites at all visits (Table 1). Both Allegheny County and the other 3 sites had similar rates of any subclinical disease at baseline (68.4\% and 67.5\%, respectively; \(P=0.504\)). Common and internal carotid wall thickness were similar in both groups at all visits (Table 1).

### Control of Risk Factors

With the exception of use of any hypertension medication at baseline which was slightly lower at Allegheny County \( (P=\)
(0.05), both groups had similar rates of medication use across visits (Table 2). Controlled hypertension (blood pressure <140/90 mm Hg), diabetes (fasting glucose <126 mg/dL), and LDL levels (<100 mg/dL) were similar in both groups across visits (Table 2).

### MRI White Matter Grade
White matter grade (WMG) ≥3 was lower in Allegheny County than the other 3 sites for both the first (25.8%, 36.3%, P<0.001) and second MRI (37.8%, 44.2%, P=0.009; Table 1). After controlling for site and age, WMG was a strong stroke predictor for both the first (hazard ratio = 2.61, 95%CI: 2.06, 3.31; P<0.001; Figure 2) and second MRI (hazard ratio = 2.97, 95%CI: 1.65, 5.35; P<0.001).

### Explaining Stroke Hazard Variations
After adjustment for age, hypertension, diabetes, education, body mass index, LDL cholesterol and previous CHD, TIA, and AF, there was about 30% reduction of the excess stroke hazard in non-Allegheny sites compared with Allegheny County (P=0.002; Table 3). After controlling for WMG and age, the excess stroke hazard in non-Allegheny sites compared with Allegheny County was reduced for both the first (25.2%; P<0.001; Figure 2) and second MRI (20.1%; P=0.24). Adjust-

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**Table 2. Control of Stroke Risk Factors in CHS Participants Completed Their Baseline, Third-Year, and Seventh-Year Visits by Site**

<table>
<thead>
<tr>
<th></th>
<th>Baseline, n=5639</th>
<th>Third Year, n=3918</th>
<th>Seventh Year, n=3345</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Other 3 Sites</td>
<td>Allegheny County</td>
<td>Other 3 Sites</td>
</tr>
<tr>
<td></td>
<td>(4210)</td>
<td>(1429)</td>
<td>(3010)</td>
</tr>
<tr>
<td><strong>P Value</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any hypertension medication with hypertension</td>
<td>1696 (519)</td>
<td>0.05</td>
<td>1125 (335)</td>
</tr>
<tr>
<td>Blood pressure &lt;140/90 mm Hg with medication</td>
<td>1048 (335)</td>
<td>0.51</td>
<td>774 (244)</td>
</tr>
<tr>
<td>Any diabetic medication with diabetes</td>
<td>347 (119)</td>
<td>0.39</td>
<td>258 (78)</td>
</tr>
<tr>
<td>Fasting glucose &lt;126 mg/dl with medication</td>
<td>61 (23)</td>
<td>0.78</td>
<td>55 (13)</td>
</tr>
<tr>
<td>Any lipid-lowering medication</td>
<td>235 (68)</td>
<td>0.23</td>
<td>214 (72)</td>
</tr>
<tr>
<td>LDL &lt;100 mg/dl with medication</td>
<td>28 (3)</td>
<td>0.53</td>
<td>44 (16)</td>
</tr>
<tr>
<td>Use of aspirin</td>
<td>1385 (478)</td>
<td>0.77</td>
<td>1122 (345)</td>
</tr>
<tr>
<td>Use of oral anticoagulants</td>
<td>49 (18)</td>
<td>0.78</td>
<td>84 (27)</td>
</tr>
</tbody>
</table>
| **N/A indicates not applicable.**

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**Figure 2.** Total stroke hazard ratio at first MRI among CHS participants.
ment for medication use or any subclinical disease in age-adjusted models did not have any impact on stroke hazard ratios between both groups (Table 3).

Discussion

Traditional Risk Factors and Their Control

Allegheny County, which had the lowest stroke hazard among the 4 sites across all visits, had similar distributions of traditional stroke risk factors compared with the other 3 sites with few exceptions, such as education level and amount of alcohol use. Our findings may not be attributed to differential loss of follow-up between Allegheny and non-Allegheny sites as there was virtually no loss to follow-up in the CHS cohort irrespective of site; in addition, both groups had similar rates of missed visits at the third and the seventh years. The current findings indicated that traditional stroke risk factors can only partially explain the site differences in stroke risk. Similarly, most previous reports with adjustment of different sets of variables have shown that traditional stroke risk factors play a minor role in explaining geographic differences in stroke incidence and mortality. In a report from Sweden, however, cardiovascular score (based on hypertension, diabetes, smoking, and being overweight) and socioeconomic status together accounted for 44% of the geographic variation of stroke incidence among men and 63% among women.

Although several clinical trials and epidemiological studies suggested that stroke risk is reduced by control of potential stroke risk factors, particularly hypertension and high LDL, medication usage in this cohort was similar among groups and had little association with site differences in stroke risk. Moreover, the percentage of those who self-reported ability to be seen by a doctor within 3 days of developing new illness/symptoms were similar in both groups (67.3% versus 66%; \( P=0.365 \)) suggesting similar access to medical care. The inability to measure the site-specific true medication usage compliance rates over time may explain, in part, our failure to link control of traditional risk factors at 1 or 2 points in time and geographic variation in stroke. It is possible that Allegheny County which had better education at baseline than non-Allegheny sites was more medication compliant over time.

Subclinical Disease

Given the similar rates for Allegheny County and the other 3 sites of any subclinical disease at baseline and symptomatic (with TIA) carotid stenosis (≥25% or ≥50%) at all visits (data not shown), it is not surprising that subclinical disease measured in CHS participants by history, ultrasound, and ECG fail to explain differences in stroke incidence.

MRI WMG

Recent reports from prospective studies indicated that higher WMG by MRI is a strong independent predictor of stroke, especially lacunar infarction. In this report, likewise, WMG was a strong stroke predictor irrespective of site. Moreover, WMG measured at the baseline MRI examination probably explained a quarter of the excess stroke hazard in the non-Allegheny sites (Figure 2), suggesting that WMG may help in explaining geographic variations in stroke incidence. It is possible that white matter lesions, which were associated with older age, hypertension and silent brain infarcts in the CHS population, simply reflect the contributions of these factors to stroke risk. The WMG may be a better marker of the duration of exposure to a risk factor such as hypertension, and its control, than a single measure of blood pressure or even multiple measurements of risk factors. As such, it may represent the cumulative effect of risk factor management before enrollment in the CHS. It may be helpful in future geographic studies of stroke to measure WMG on brain MRI.

Study Strengths and Limitations

This study has many strengths, including a population based elderly cohort, prospective design, large sample size, long-term follow-up, and central adjudication of events from 4 geographically separated sites. Although we could analyze in a detailed
way the reasons for site differences in stroke incidence in this study, we cannot generalize conclusions to different parts of the US. Also, we could not study reasons for existence of the “stroke belt” in this dataset because the Forsyth site (located in the stroke belt) had similar stroke incidence to the non-Forsyth sites (located outside the stroke belt).

Conclusions
Site differences in stroke risk factors at baseline and subsequent control only partially explain site differences in stroke incidence observed in this observational study. Factors represented by WMG on brain MRI may help in explaining geographic variations in stroke incidence. The current findings require replication in other studies before any public health significance could be considered for use of WMG as marker of stroke risk in different communities and regions.

Disclosures
None.

References
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