VARIATIONS IN STROKE INCIDENCE IN FOUR US COMMUNITIES: THE CARDIOVASCULAR HEALTH STUDY (CHS)

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VARIATIONS IN STROKE INCIDENCE IN FOUR US COMMUNITIES: THE CARDIOVASCULAR HEALTH STUDY (CHS)

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BACKGROUND: Although stroke rates are much higher in old age, recent data on geographic variation in stroke incidence in older American populations were rare. Moreover, geographic variation in stroke incidence and mortality remain unexplained in United States.

OBJECTIVES: To compare stroke incidence rates and stroke risk factors and their control in four US communities

METHODS: Participants in the Cardiovascular Health Study (CHS) who had no history of stroke at baseline (n=5639) were followed for 10 years for the development of stroke events. Site specific stroke incidence and mortality rates were calculated. Possible risk factors at baseline and their control across the visits were compared among the four CHS sites.

RESULTS: Age and sex standardized total stroke incidence rates per 1000 person-years were 9.6 (CI 7.7, 11.5) in Allegheny, 19.2 (CI 15.6, 22.8) in Forsyth, 20.7 (CI 16.9, 24.5) in Sacramento, and 19.8 (CI 16.1, 23.5) in Washington Counties. Although Allegheny County had the lowest stroke incidence among the 4 sites, risk factor distributions at baseline were similar. After adjustment for age, hypertension, diabetes, education, BMI, LDL cholesterol and previous coronary heart disease, transient ischemic attack (TIA), and atrial fibrillation (AF), there was modest reduction of the excess hazard in the other 3 sites compared to Allegheny County (HR=1.52, CI 1.17, 1.98 compared to 1.74 CI 1.42, 2.14). Moreover, between baseline and year

9, control of hypertension, diabetes, lipids, smoking, AF, and TIA were similar across sites. White matter grade (WMG) $\geq$ 3 on the baseline brain MRI was less common in Allegheny County than the other 3 sites (25.8%and 36.3% respectively, $p< 0.001$) and accounted for 25% of the excess hazard in the other 3 sites compared to Allegheny County (HR=1.65, CI 1.20-2.26 compared to 1.87 CI 1.36-2.55)

CONCLUSION: Site-differences in stroke risk factors at baseline and their subsequent control only partially explain site-differences in stroke incidence.

PUBLIC HEALTH SIGNIFICANCE: White matter grade may be a marker of integrated exposure and control of stroke risk factors and its progression could be used as a marker of the efficacy of different stroke prevention strategies on a community level.

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*This work is dedicated to my wonderful wife **Reda**,*
*my beautiful daughter **Lena**, and lovely son **Ahmad***

1. INTRODUCTION

1.1. Stroke morbidity statistics:

From the early 1970s to early 1990s, the estimated number of non-institutionalized stroke survivors among Americans 25-74 years of age, increased from 1.5 million to 2.4 million, probably due to population growth, population aging, and substantial improvement of survival after stroke during the 1970s and 1980s.[1] In 2002, the number of non-institutionalized American adults 18 years or more who ever had a stroke was 4.83 million with 2.4% prevalence rate (48.9% for males and 51.1% for females).[2] Stroke incidence, on the other hand, declined during the 1970s in several population-based studies and did not decline or even increased during the 1980s or 1990s in these populations.[3-5]

Based on recently published stroke incidence epidemiologic studies as “Greater Cincinnati/Northern Kentucky Stroke Study” and “Atherosclerosis Risk in Communities Study” American Heart Association reported that, each year about 700,000 people experience a new or recurrent stroke. About 500,000 of these are first attacks, and 200,000 are recurrent attacks. [6] On average, every 45 seconds someone in the United States has a stroke .The age-adjusted stroke incidence rates per 100,000 for first-ever strokes were estimated from population-based studies to be 167 for white males, 138 for white females, 323 for black males and 260 for black females.[6]

1.2. Stroke mortality statistics:

A substantial decline in stroke mortality in United States since the 1950s has been reported in several population-based studies, the decline showed an acceleration in the 1970s.[7-11] However, national data and data from selected communities have suggested that the rate of decline in stroke mortality rates slowed down during the latter half of the 1980s. [3, 7, 11, 12] Stroke continues as the third leading cause of death among the US population in 2001, after heart diseases and cancer. Stroke accounted for more than 1 of every 15 deaths in the United States in 2001 (about 164,000 or 6.8% of total 2,416,000 deaths).[11] World-wide, it is even worse; stroke was the second among the 30 leading causes of global mortality in 1990 with 4.38 million deaths, almost 3 million in developing countries. [13] On average, every 3 minutes someone dies of a stroke in United States. The 2001 overall death rate for stroke for all Americans of all ages per 100,000 was 57.9. Death rates were 56.5 for white males and 85.4 for black males, and 54.5for white females and 73.7 for black females. [6]

1.3. Stroke disability:

Stroke is a leading cause of serious, long-term disability in the United States. In 1999 more than 1,100,000 American adults reported some form of disability resulting from stroke.[11, 14] Stroke imposes a substantial economic burden on individuals and society. In 2004, the estimated total cost of stroke was 53.6 $ billion, of which 33.0 $ billion direct cost (hospital stay, nursing homes, physicians/other professionals, drugs/other medical durables, and home health care) and 20.6 $ billion, indirect cost (loss of productivity due to morbidity and/or mortality). [6] After converted to 1999 dollars, the mean lifetime cost of ischemic stroke in the United States is estimated at $140,048.[15]

1.4. Stroke incidence studies versus mortality data

The majority of stroke studies in United States and worldwide are mortality hospital-based studies which may lead to problems in comparing geographic stroke rates on a national or international scale. Mortality data are limited by inaccuracy of death certificate stroke diagnosis with reported false positive range between 21% and 35%, [16-18] variability of stroke subtypes reporting in death certificates with over-reporting of cerebral hemorrhage and under-reporting of cerebral embolus,[16] limited reliability to distinguish between ischemic stroke versus primary intra-cerebral hemorrhage, [13] and the absence of information on mild or nonfatal strokes (e.g. lacunar stroke) excluding the significant proportion of stroke patients who survive.[19] Accuracy can also be compromised by variations in how stroke is recorded and coded, especially if it appears in part two of the death certificate, in different countries or in different times in the same country.[13]

Community-based stroke incidence studies can overcome at least some of the above mortality data limitations. To be comparable, studies of stroke incidence must use the same definitions, methods, and mode of data presentation. These studies allow more valid geographic comparisons of stroke rates; may yield data that can be used to follow stroke trends with time. Also they can be utilized in stroke follow-up in terms of case fatality, recurrence, and disability; in conducting case-control studies of various incident stroke risk factors; in assessment of stroke services; and in assisting in healthcare planning within communities.[20] However, community-based studies require considerable resources and rigorous methods, and it is difficult to be sure that all the cases have been found and accurately diagnosed. Also, sample sizes have nowhere been all that large, which makes comparisons of incidence by time and place imprecise.[21]

1.5. Comparability of stroke incidence studies

As stroke incidence geographic or secular comparisons are only meaningful if they are based on studies that use similar definitions, methods, and data presentation, Sudlow and Warlow [20] reviewed and refined the original criteria proposed by Malmgren and colleagues [22] to consider stroke incidence studies comparable with each other. Most recently, these criteria were further updated by Feigin and colleagues.[23] It seems that ideal study does not exist in reality or at least very challenging.[20] However, to make sense of geographic and secular comparisons, it should be recognize that the studies that come close to the ideal are the most likely to provide reliable and comparable results. [20] The main criteria described by researchers were: [20, 22, 23] (1) Using a standard stroke definitions based on WHO clinical definition of stroke. (2) Using standardized definitions for classifying stroke (pathological types and first ever versus recurrent) (3) Using several overlapping sources of information to ensure complete case ascertainment with at least 80% verification of stroke type using CT or MRI (4) Using a prospective design that pursue stoke cases as they occur "hot pursuit". (5) Using a well defined and stable population of appropriately large size (6) Assessing the completeness of case ascertainment by performing either a cross-sectional survey or the capture-recapture technique. (7) Using a standard data presentation for men and women separately and with rates calculated for mid-decade 10-year age bands (e.g. 45 to 54, 55 to 64 years).

1.6. International geographic variation in stroke incidence

Despite the fact there are many stroke incidence studies worldwide, the number of comparable studies on a worldwide scale remains limited, being largely confined to developed, westernized countries. In a recent review article, Feigin and colleagues [23] used the same criteria described before [20] in reviewing worldwide population-based stroke studies conducted at 1990 or later and with no upper age limit, 15 population-based stroke incidence studies that met their eligibility criteria were identified and included in the analysis. Age-standardised incidence of total stroke per 1000 person-years for people of all age ranges included in the fifteen stroke incidence studies ranged from 1.3 to 4.1. The highest rates were reported in Oyabe, Japan 4·1 (3·8–4·4),[24] Arcadia, Greece 3·4 (3·1–3·7), [25] and Frederiksberg, Denmark 3·1 (2·7–3·4).[26] On the other hand, the lowest rates were reported in South London, UK 1·3 (1·2–1· 4),[27] Erlangen, Germany 1·3 (1·2–1·4),[28, 29] and Auckland, New Zealand 1·4 (1·3–1·5).[30]

WHO MONICA investigators published a report [31]that compares stroke incidence, case fatality, and mortality rates, during the first years of the study, among 18 populations in 10 mainly European countries (Germany, Italy, Denmark, Sweden, Finland, Lithuania, Yugoslavia, Poland, Russia, China). There was a three-fold differential among men with the highest stroke attack rate reported in Finland 359 (328-392), Russia 344 (300-393), and Lithuania 286 (256-319), and the lowest stroke attack rate in Italy 121 (112-130), Sweden 128 (114-143), and Germany 136 (117-157). In women, a five-fold differential with the highest stroke attack rate reported in Russian 294 (260-332) and Finland 194 (172-217), and the lowest stroke attack rate in Germany 58 (51-67) and Italy 63 (57-70).

1.7. Stroke Belt and its contributing factors

Excess stroke mortality in the Southeastern region of the United States was first documented in 1965 and has existed at least since 1940. Although there is no "official" definition for the boundaries of the stroke belt, definitions of the "stroke belt" frequently include the entire Southeastern region of the United States excluding the state of Florida (ie, North Carolina, South Carolina, Georgia, Tennessee, Arkansas, Mississippi, Alabama, and Louisiana). Depending on the specific geographic boundaries used (which vary between reports) and the time period of the analysis, the stroke belt has a stroke mortality that is 1.3-1.5 times the risk in the remainder of the nation.[32]

Despite the persistence of the stroke belt over the past six decades and the dramatic magnitude of the excess stroke mortality, the contributing cause or causes remains a mystery. [32] Many studies tried to explain the causes of this geographical difference in stroke mortality. A number of reports showed higher prevalence of hypertension, lower anti-hypertensive drug efficacy, and poor hypertension control in the Southeastern region of the United States.[33-37] Higher stroke incidence rates were also reported.[38] Elevated blood glucose levels,[37] lower educational achievements,[39] and lower socioeconomic status [40] were reported in studies from stroke belt states. A graded risk of stroke mortality by birthplace was reported, with the highest among individuals born in South Carolina, intermediate in those born in the Southeast other than South Carolina, and lowest for those born outside the Southeast.[41] Dietary and environmental factors such as high salt intake, low potassium and calcium intake and soft water consumption have been hypothesized as important factors.[34]

1.8. Stroke risk factors prevalence and regional variation in stroke incidence

According to NHANES I data, [38] age adjusted stroke risk in white men aged 45-74 years was significantly higher in the Southeast than the Northeast or the West. After adjustment of baseline risk factors that included age, sex for blacks, smoking status, history of diabetes, history of heart disease, education, systolic blood pressure, alcohol use , and physical activity; the risk still lower in Northeast but not the West compared to Southeast. The same data showed that the prevalence of current smoking and abstinence from alcohol were higher in the Southeast than other regions of the United States, but the highest rates of diabetes prevalence were in the Northeast in women and Midwest in men. In the Three-area epidemiological study,[37] only blood pressure in white men and black women and glucose intolerance in both races mirrored a gradient observed for stroke mortality in 3 areas in the United States; Savannah, Georgia (high stroke rates), Hagerstown, Maryland (intermediate stroke rates) and Pueblo, Colorado (low stroke rates). No consistent pattern was found correlating stroke mortality with other cerebrovascular risk factors, including the prevalence of transient ischemic attacks, angina, cigarette smoking, cholesterol levels, or height and weight.

1.9. Control of stroke risk factors and stroke risk

There is strong evidence from epidemiological studies and clinical trials that control of modifiable traditional stroke risk factors specially hypertension, diabetes, blood lipids, smoking, atrial fibrillation, and carotid stenosis were associated with subsequent reduced risk of stroke.[42] Data from randomized controlled trials in older population indicated that a 10 mm Hg reduction in systolic BP was associated with a reduction in risk of stroke of approximately one third. [43] Tight control of hypertension in diabetics significantly reduces stroke incidence.[44] Angiotensin-converting-enzyme (ACE) was reported to reduce the risk of stroke in high-risk diabetic patients by one third.[45]

The double stroke risk associated with current smoking was shown to disappear about 5 years after cessation.[46] Several meta-analysis of large randomized trials suggests that statins reduce the incidence of stroke by about 20-25% in patients with and without coronary heart disease. [47-49] Carotid endarterectomy was repeatedly reported as a highly effective stroke preventive measure among patients with severe carotid stenosis and recent transient ischemic attack.[50, 51] Warfarin and to a less extent aspirin were reported in clinical trials to be highly effective in reducing stroke in atrial fibrillation patients.[52]

1.10. The Cardiovascular Health Study (CHS)

The Cardiovascular Health Study (CHS) is a population-based, longitudinal study of coronary heart disease and stroke in adults aged 65 years and older. Participants of the CHS were recruited from a random sample of Health Care Financing Administration (HCFA) Medicare eligibility lists in four US communities: Forsyth County, NC; Sacramento County, CA; Washington County, MD; and Allegheny County, PA. 5888 men and women 65 years of age or older at study entry, were recruited in 2 waves. A total of 5,201 participants were recruited in 1989 to 1990 in the first wave (original cohort) and additional 687 black participants were recruited in 1992 to 1993 in the second wave (new cohort). The main study outcomes were myocardial infarction, angina pectoris, congestive heart failure, peripheral vascular disease, stroke, transient ischemic attack, and all-cause mortality. Extensive historical, physical and laboratory evaluations were performed at baseline examination for each cohort to identify the presence and severity of the cardiovascular risk factors. 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.

1.11. Research Hypothesis

First: Stroke incidence rates (crude and adjusted for age, gender, race, and follow up years) were lower in Allegheny County site compared to the other three CHS sites (Forsyth County, Sacramento County, and Washington County). This hypothesis will be tested in the first article.

Second: Those differences in stroke incidence rates were related to the variations in the prevalence of potential stroke risk factors at baseline (hypertension, diabetes, smoking, atrial fibrillation, transient ischemic attacks, carotid stenosis, MRI findings, educational levels...etc) between Allegheny County and the other three CHS sites (Forsyth County, Sacramento County, and Washington County). This hypothesis will be tested in the second article.

Third: Control of potentially modifiable stroke risk factors (hypertension, diabetes, smoking, atrial fibrillation, transient ischemic attacks, and carotid stenosis…etc) across visits (baseline, year 5, and year9) was better in Allegheny County compared to the other three CHS sites (Forsyth County, Sacramento County, and Washington County). This hypothesis will be tested in the third article.

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2. FIRST ARTICLE: Variations in stroke incidence and mortality in four US communities: The Cardiovascular Health Study (CHS)

2.1. ABSTRACT

BACKGROUND: Stroke continues as a leading cause of death and disability in the United States. Although stroke rates are much higher in old age, recent data on geographic variation in stroke incidence in older populations were rare.

OBJECTIVES: To compare stroke incidence and mortality rates in four US communities

METHODS: Participants in the Cardiovascular Health Study (CHS) who had no history of stroke at baseline (n=5639) were followed for 10 years in a predominantly whites cohort (n=5002) and 7 years in black cohort (n=637). Incident stroke was ascertained by questionnaire at annual visits and interim telephone contacts, and review of Medicare hospitalization data. All reported stroke cases were reviewed and adjudicated by a cerebrovascular endpoint committee.

RESULTS: Total stroke incidence rate for all CHS participants, age and sex standardized to the year 2000 US population, was 17.7 per 1000 person-years (95% CI 15.9, 19.5). The rates per 1000 person-years were significantly lower in Allegheny County, Pennsylvania 9.6 (95% CI 7.7, 11.5) than Forsyth County, North Carolina 19.2 (95% CI 15.6, 22.8), Sacramento County, California 20.7 (95% CI 16.9, 24.5), and Washington County, Maryland 19.8 (95% CI 16.1, 23.5). The lower stroke incidence rate in Allegheny County was consistent by cohort, gender, race, and age groups. Though not statistically significant, the total stroke mortality rates were also lower in Allegheny County than other three sites. The one month case fatality percentages were similar in the four sites for all strokes (p=0.947) and stroke types (p=0.871 for ischemic and p=0.234 for hemorrhagic).

CONCLUSION: Further investigation is needed to clarify the cause of lower stroke incidence in Allegheny County. This may provide insight into stroke etiology, prevention, and treatment differences among these four communities

2.2. INTRODUCTION

Stroke continues as the third leading cause of death among the US population, after heart diseases and cancer. In 2001, about 164,000 Americans died from stroke (6.8% of all deaths). [1] Stroke is a leading cause of serious, long-term disability in the United States. In 1999 more than 1,100,000 American adults reported some form of disability resulting from stroke.[1, 2] The American Heart Association reported that each year about 700,000 people experience a new or recurrent stroke. About 500,000 of these were first events, and 200,000 were recurrent. [3]

Excess stroke mortality (RR=1.3-1.5) in the Southeastern region of the United States than the remainder of the nation "stroke belt" was first documented in 1965 and has existed at least since 1940. Despite the persistence of the stroke belt over the past half-century, the contributing cause or causes remain a mystery.[4] Geographic or secular comparisons of stroke incidence or mortality are only meaningful if they are based on studies that use similar definitions, methods, and data presentation.[5] In United States in the last three decades, a number of studies assessed stroke incidence in different regions, with a two-fold reported variation in stroke incidence.[6-16] The incidence rates calculated from most of these studies, based on populations from localized geographical areas, have limited potential to assess geographic or secular comparisons of stroke incidence across the United States, due to different methodologies used for case ascertainment, and different population characteristics (race and upper age limit, or time periods of data collection). The ARIC study [8] was the first study to use a standard multi-center prospective cohort design, which allowed stroke incidence comparisons in four geographically-separated US communities. More than 2.5 fold difference in stroke incidence between sites was reported. However, old people (65 years or more), who suffer approximately 75% of the stroke burden, were excluded from the study.

There is a need for a stroke incidence study including older men and women enrolled in geographically-separated US communities, and using a standardized prospective design for case ascertainment and validation. All these requirements have been fulfilled in the current study, the Cardiovascular Health Study (CHS), a multi-center population-based cohort study, with a main objective of identifying factors related to the onset and course of coronary heart disease and stroke in the elderly. We hypothesized that stroke incidence rates (crude and adjusted for age, gender, race, and follow up years) were lower in Allegheny County site compared to the other three CHS sites (Forsyth County, Sacramento County, and Washington County).

2.3. METHODS

2.3.1. Study population:

The Cardiovascular Health Study (CHS) design, including recruitment techniques, definitions of risk factors and outcomes, has been described in detail.[17, 18] CHS is a population-based, longitudinal study of coronary heart disease and stroke in adults aged 65 years and older. Participants of the CHS were recruited from a random sample of Health Care Financing Administration (HCFA) Medicare eligibility lists in four US communities: Forsyth County, 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 were receiving cancer treatment. The Allegheny County field center population was entirely urban; and the other three centers recruited a mixture of urban and rural populations. 5888 men and women 65 years of age or older at study entry, were recruited in 2 waves. A total of 5,201 participants were recruited in 1989 to 1990 in the first wave (original cohort) and additional 687 black participants were recruited in 1992 to 1993 in the second wave (new cohort), to improve the racial representativeness of the study. No second wave participants were recruited in Washington County, MD.

2.3.2. Outcome assessment:

The main study outcomes were myocardial infarction, angina pectoris, congestive heart failure, peripheral vascular disease, stroke, transient ischemic attack, and all-cause mortality. Extensive historical, physical and laboratory evaluations were performed at baseline examination for each cohort to identify the presence and severity of cardiovascular risk factors.[17]

Ascertainment methods of stroke and other CHS endpoints, either incident or prevalent have been described. [19-21] Prevalent stroke at baseline line was assessed by answering “yes” to a question “has a doctor ever told that you had stroke?” These self reported events were then validated using other information from baseline examination, from medical records or a physician questionnaire.[20] Some undetected pre-baseline events were later detected during investigation of potential incident events and added to the prevalent cases.[20] 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. For suspected stroke events clinical records were sought, and copies including admission and discharge notes, results of pertinent tests, and copies of any brain images (CT and MRI) were obtained. [19, 21]

Provisional diagnoses of stroke were assigned by the field center principal investigator, and then reviewed and adjudicated at periodic meetings of the cerebrovascular disease endpoint committee. The committee also classified the stroke types and determined if death was caused by stroke.[19] Stroke was classified as hemorrhagic if there was bloody spinal fluid by lumber puncture, or evidence of hemorrhage at surgery or autopsy. Stroke was classified as ischemic infarction if there was evidence of focal brain deficit without evidence of primary hemorrhage.[19] Information for classification of death was obtained from death certificates, autopsy and coroners’ forms (if available), hospital records, and interviews with attending physicians, next-of-kin, and witnesses.[17]

2.3.3. Statistical analysis:

Participants with pre-baseline stroke were excluded from all analyses. Incident stroke cases were adjudicated from the baseline examination for each cohort through June 30, 2000. Years of follow up were classified 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 or the end of follow up for those who did not have a stroke. Participants who died and never had a stroke were censored at time of death. Participants who survived to June 30, 2000 were censored at that time if they were still under active follow-up in the study. If lost to follow-up prior to that time, they were censored at the maximum of the last contact plus 6 months and Dec 31, 1999.

Stroke incidence rates per 1000 person-years were calculated by dividing new stroke events by the person years at risk. The 95% confidence interval for stroke incidence rates per 1000 person-years were created by calculating the lower (C1) and upper limits (C2) of the 95% confidence interval for the expected number of the new stroke events (x) using this formula $\{x \pm z_{1-\alpha/2} \sqrt{x}\}$. C1 & C2 were then divided by the person years at risk and multiplied by 1000. Stroke mortality rate was calculated in the same way as the incidence rate except that, the numerator consisted of those with fatal stroke events rather than all new stroke events. Incidence rates were compared across the sites for all participants and also by cohort, race, gender, and age groups at baseline (65-74 years, 75-84 years, and 85 years and older).

Stroke rates were either age specific or age standardized. Rates were also sex standardized when applicable. Age standardization was done using the 2000 US census population distribution [22] using the direct method (Appendix A). The weight for those 65-74 years at baseline was 52.6%, for those 75-84 years 35.3%, and for those 85 years and older was 12.1%. The 95% confidence intervals for standardized stroke incidence rates per 1000 person-years (R-adj) were created by calculating the standard error for the standardized rates (se R-adj) as described by Breslow and Day [23]. The upper and lower 95% confidence interval, are then were calculated using this formula $\{R\ x \pm z_{1-\alpha/2} * \text{se R-adj}\}$.

Stroke case fatality rates were calculated by dividing the number of fatal strokes by all new strokes. The cumulative stroke incidence and mortality over the total follow up period were calculated using a Cox regression (Appendix B). The following covariates were entered simultaneously in the model for adjustment; age, race, gender. The model was then stratified by field center.

2.4. RESULTS

2.4.1. Demographics:

The total number of participants at risk for incident stroke at baseline in the four sites was 5639. There were 5002 (88.7%) recruited between 1989 and 1990 (original cohort) and 637 (11.3%) recruited between 1992 and 1993 (new cohort). The mean age at baseline was 72.8 years (median 72 years, range 65-100 years); 3759 (66.7%) participants were aged 65-74 years, 1668 (29.6%) were 75-84 years, and 212 (3.8%) were 85 or more years old. 58% of the participants were women. There were no significant age or gender differences between sites. Approximately 85% of the participants were white and 15% were black with a significantly low percentage of blacks at the Washington County site (Table 1).

2.4.2. Crude incidence rates:

There were 665 incident strokes in the four sites together, in 46,976 years of follow up, with an average 8.6 years (median = 10.2 years) of follow up in the original cohort and 6.3 years (median = 7.2 years) in the new cohort. The number of stroke events and the crude incidence rates were lower in Allegheny County (110 events and 9.1 per 1000 person-yeas, 95% CI 7.4, 10.8) than Forsyth County (185 events and 15.1 per 1000 person-yeas, 95% CI 13.0, 17.3), Sacramento County (200 events and 16.2 per 1000 person-yeas, 95% CI 14.0, 18.5) and Washington County (170 events and 16.4 per 1000 person-yeas, 95% CI 13.9, 18.8). The lower number of total stroke events in Allegheny County compared to the other three sites was consistently observed in each of the three age groups, both sexes, both cohorts, and in whites and blacks (Table 2).

2.4.3. Age standardized incidence rates:

Total stroke incidence rate for all CHS participants, age and sex standardized to the year 2000 US population, was 17.7 per 1000 person-years (95% CI 15.9, 19.5). The rates per 1000 person-years were significantly lower in Allegheny County, Pennsylvania 9.6 (95% CI 7.7, 11.5) than Forsyth County, North Carolina 19.2 (95% CI 15.6, 22.8), Sacramento County, California 20.7 (95% CI 16.9, 24.5), and Washington County, Maryland 19.8 (95% CI 16.1, 23.5) (Table 3). The rates were significantly lower in Allegheny County for the original cohort, females, and whites. The rates were insignificant but still lower in Allegheny County for the new cohort, males, and blacks. Blacks in all sites together had a slightly higher incidence rate per 1000 person-years than whites (18.2 versus 17.3 per 1000, p= 0.651). Similarly, the new cohort had a slightly higher incidence rate than original cohort (19.7 versus 17.0 per 1000, p=0.846). Women had a slightly higher incidence rate than men (18.1 versus 16.4 per 1000, p=0.887) (Table 3).

2.4.4. Age specific incidence rates:

Allegheny County had a lower total stroke incidence rate than the other three sites for all age groups. For those aged 65-74 years, the difference was statistically significant. For those aged 75-84 years, Allegheny County had a significantly lower rate than Forsyth County and Sacramento County. For those aged 85 and older, the differences were not statistically significant (Figure 1). The incidence rate steadily increased with increasing age groups at all four sites. For all CHS participants, the incidence rates were 10.6 per 1000 person-years for those aged 65-74 (95% CI 9.5, 11.7), 22.0 for those aged 75-84 (95% CI 19.5, 24.7), and 32.7 (95% CI 23.8, 44.9) for those aged 85 and older (Figure 1).

2.4.5. Stroke type-specific incidence:

The distribution of incident stroke types was similar among the four sites (p= 0.681). For all CHS participants, this was 85% ischemic, 10% hemorrhagic and 5% undefined stroke type (Figure 2). Most of the difference in sites for stroke incidence was due to a difference in ischemic stroke. For ischemic but not hemorrhagic stroke there were statistically significant differences among the four sites (Figure 3).

2.4.6. Mortality and case fatality:

Though not significant, age and sex standardized total stroke mortality rates per 1000 person-years were lower in Allegheny County (1.55; 95% CI 0.77, 2.43) than Forsyth County (2.79; 95% CI 1.34, 4.26), Sacramento County (2.67; 95% CI 1.16, 4.24), and Washington County (3.07; 95% CI 1.37, 4.83) (Figure 4). The one month case fatality percentages were similar in the four sites for all strokes (p=0.947) and stroke types (p=0.871 for ischemic and p=0.234 for hemorrhagic). For all CHS participants, case fatality was 12.6% for all strokes, 8.1% for ischemic strokes, and 44.6% for hemorrhagic strokes (Figure 5).

2.4.7. Cumulative incidence and mortality:

The cumulative total stroke incidence rates per 1000, through June 30 2000, adjusted for age, gender, race, and cohort were significantly different among the four sites (p <0.001). The cumulative total stroke incidence was lower in Allegheny County; 156 per 1000 (95% CI 144.2, 167.8) compared to Forsyth County; 172 (95% CI 148.5, 195.5), Sacramento County; 175 (95% CI 153.4, 196.6), and Washington County; 176 (95% CI 150.5, 201.5) (Figure 6). The cumulative total stroke mortality rates per 1000, through June 30 2000, were lower, but not statistically significantly, in Allegheny County after adjusting for age, gender, race, and cohort (p=0.467) (Figure 6). For all CHS participants, the cumulative total stroke mortality was 19 deaths per 1000 (95% CI 15.1, 22.9)

Table 1: CHS participants at baseline by cohort and demographic characteristics by site

	Forsyth County, NC N %	Sacramento County, CA N %	Washington County, MD N %	Allegheny County, PA N %	Total N %
Total number of those at stroke risk at baseline	**1488** 100.0%	**1471** 100.0%	**1251** 100.0%	**1429** 100.0%	**5639** 100.0%
Cohort:					
Original cohort	**1266** 85.1%	**1267** 86.1%	**1251** 100.0%	**1218** 85.2%	**5002** 88.7%
New cohort	**222** 14.9%	**204** 13.9%	**NA** NA	**211** 14.8%	**637** 11.3%
Age groups at baseline:					
65-74 years	**997** 67.0%	**989** 67.2%	**801** 64.0%	**972** 68.0%	**3759** 66.7%
75-84 years	**443** 29.8%	**420** 28.6%	**394** 31.5%	**411** 28.8%	**1668** 29.6%
85+ years	**48** 3.2%	**62** 4.2%	**56** 4.5%	**46** 3.2%	**212** 3.8%
Gender:					
Males	**900** 60.5%	**850** 57.8%	**726** 58.0%	**811** 56.8%	**3287** 58.3%
Females	**588** 39.5%	**621** 42.2%	**525** 42.0%	**618** 43.2%	**2352** 41.7%
Race:					
Whites	**1154** 78.0%	**1228** 84.6%	**1238** 99.1%	**1123** 79.0%	**4743** 84.7%
Blacks	**326** 22.0%	**224** 15.4%	**11** 0.9%	**299** 21.0%	**860** 15.3%

Table 2: Incident total stroke events, stroke follow up period (person-years), and crude rates of CHS participants at baseline by cohort and demographic characteristics by site

	Forsyth County, NC Events P-Y Crude rate	Sacramento County, CA Events P-Y Crude rate	Washington County, MD Events P-Y Crude rate	Allegheny County, PA Events P-Y Crude rate	Total Events P-Y Crude rate
Total number of those at stroke risk at baseline	**185** 12221.9 **15.1**	**200** 12324.5 **16.2**	**170** 10389.7 **16.4**	**110** 12039.4 **9.1**	**665** 46975.7 **14.2**
Cohort:					
Original cohort	**159** 10843.1 **14.7**	**175** 11016.9 **15.9**	**170** 10389.7 **16.4**	**101** 10697.4 **9.4**	**605** 42947.3 **14.1**
New cohort	**26** 1378.8 **18.9**	**25** 1307.5 **19.1**	**NA** NA **NA**	**9** 1342.0 **6.7**	**60** 4028.3 **14.9**
Age groups at baseline:					
65-74 years	**94** 8695.8 **10.8**	**109** 8811.9 **12.4**	**90** 7164.6 **12.6**	**60** 8650.8 **6.9**	**353** 33323.2 **10.6**
75-84 years	**81** 3264.4 **24.8**	**79** 3162.2 **25.0**	**68** 2925.2 **23.2**	**46** 3138.0 **14.7**	**274** 12489.7 **21.9**
85+ years	**10** 261.8 **38.2**	**12** 350.4 **34.2**	**12** 300.0 **40.0**	**4** 250.8 **15.9**	**38** 1162.9 **32.7**
Gender:					
Males	**71** 4583.5 **15.5**	**79** 4998.9 **15.8**	**74** 4015.4 **18.4**	**50** 4925.7 **10.2**	**274** 18523.6 **14.8**
Females	**114** 7638.4 **14.9**	**121** 7325.5 **16.5**	**96** 6374.2 **15.1**	**60** 7113.7 **8.4**	**391** 28452.0 **13.7**
Race:					
Whites	**143** 9930.8 **14.4**	**172** 10667.5 **16.1**	**168** 10292.1 **16.3**	**91** 9905.9 **9.2**	**574** 40796.4 **14.1**
Blacks	**41** 2233.3 **18.4**	**27** 1491.4 **18.1**	**2** 84.7 **23.6**	**19** 2084.3 **9.1**	**89** 5893.8 **15.1**

Table 3: Age standardized total stroke incidence rates and 95% confidence intervals per 1000 person-years of CHS participants by cohort, gender, and race by site

	Forsyth County, NC Rate 95% CI	Sacramento County, CA Rate 95% CI	Washington County, MD Rate 95% CI	Allegheny County, PA Rate 95% CI	Total Rate 95% CI
All CHS participants*	**19.2** 15.6, 22.8	**20.7** 16.9, 24.5	**19.8** 16.1, 23.5	**9.6** 7.7, 11.5	**17.7** 15.9, 19.5
Cohort:					
Original cohort	**17.9** 14.2, 21.6	**19.1** 15.7, 22.5	**19.7** 16.1, 23.3	**10.7** 8.1, 13.5	**17.0** 15.3, 18.7
New cohort	**23.6** 13.3, 34.1	**23.1** 12.3, 34.1	**NA** NA	**10.4** 1.4, 19.6	**19.7** 13.6, 25.8
Gender:					
Males	**17.8** 11.6, 24.0	**16.0** 12.1, 19.9	**21.1** 15.4, 26.8	**12.2** 8.3, 16.1	**16.4** 14.1, 18.8
Females	**19.7** 15.2, 24.2	**22.8** 17.5, 28.0	**18.8** 14.1, 23.5	**8.4** 6.1, 10.6	**18.1** 15.7, 20.5
Race:					
Whites	**18.4** 14.3, 22.5	**19.8** 16.1, 23.4	**19.4** 15.8, 23.0	**10.7** 7.7, 13.6	**17.3** 15.4, 19.1
Blacks	**21.4** 13.7, 29.1	**20.2** 11.1, 29.4	**24.4** 0, 59.4	**12.0** 5.6, 18.4	**18.2** 13.7, 22.8

* Age and sex standardized

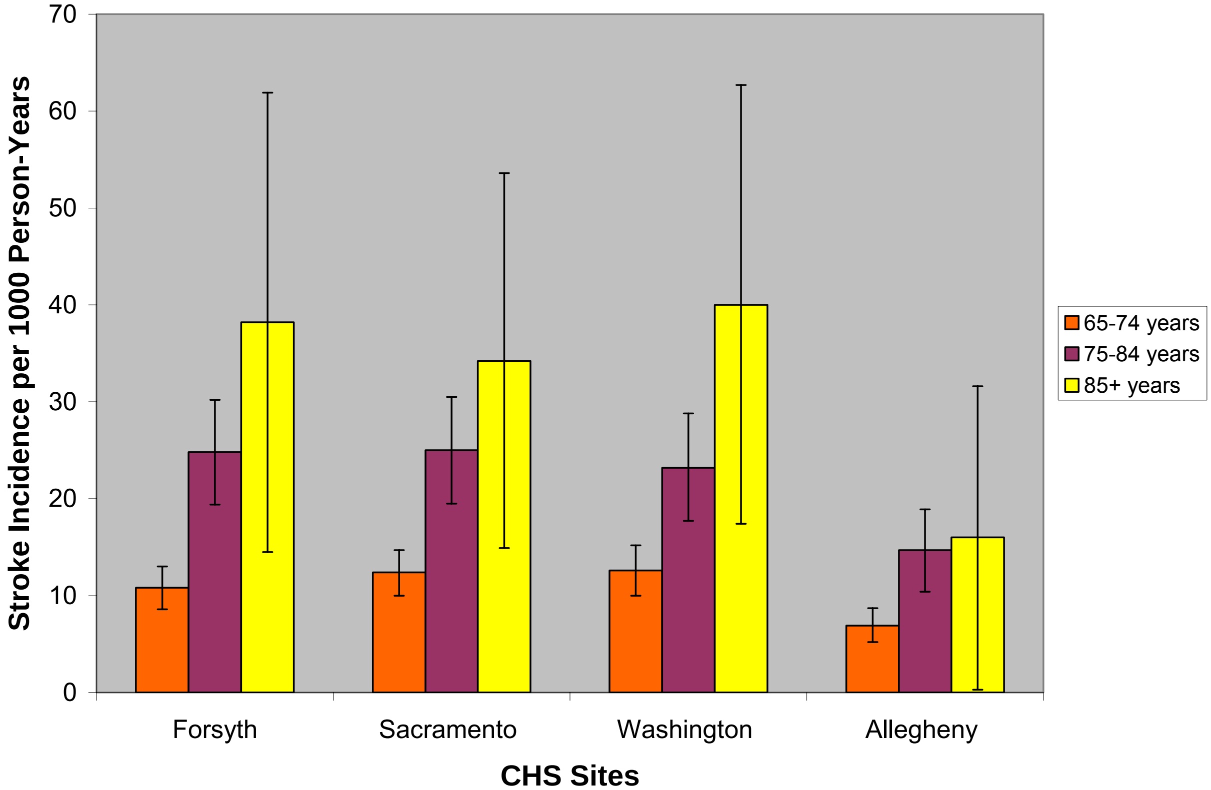


Figure 1: Age specific total stroke incidence rates per 1000 person-years of CHS participants by site

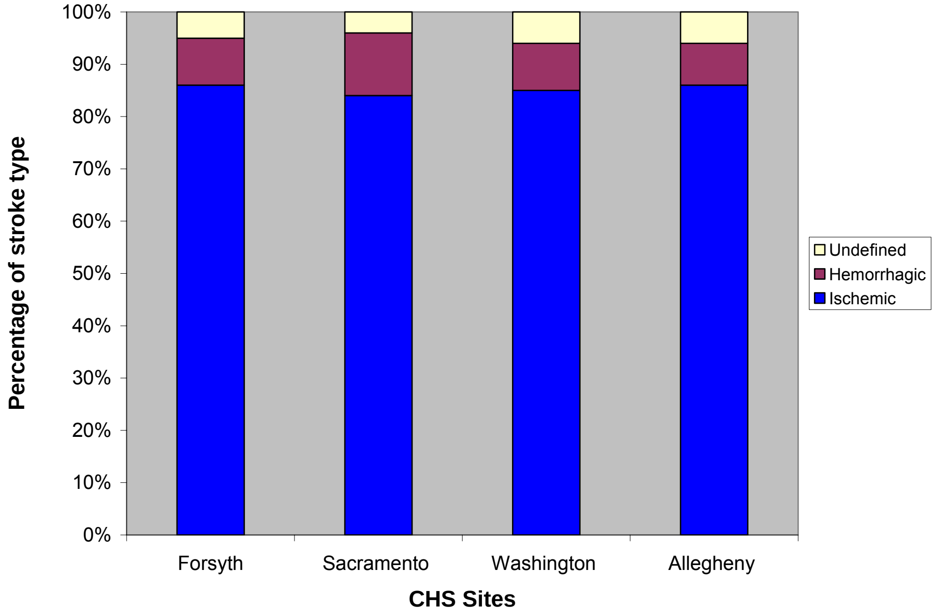


Figure 2: Proportionate frequency of incident stroke types of stroke type of CHS participants by site

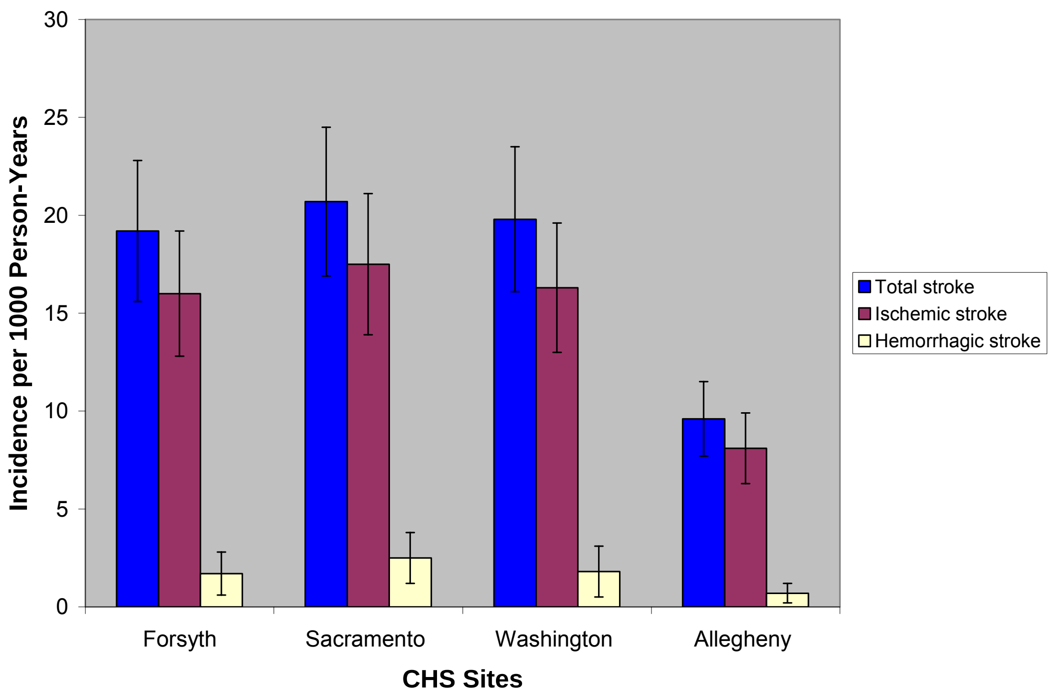


Figure 3: Age and sex standardized stroke type-specific incidence rates per 1000 person-years of CHS participants by site

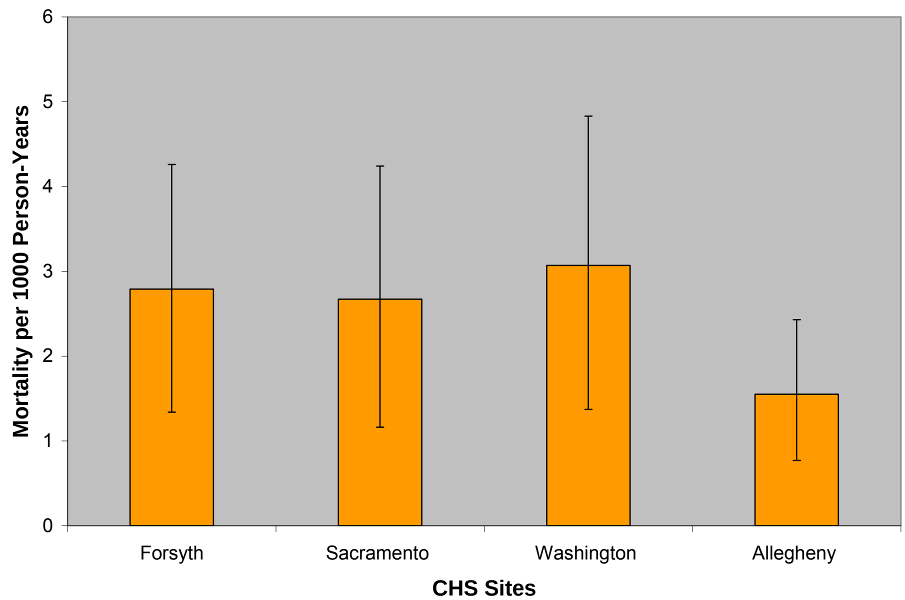


Figure 4 Age and sex standardized stroke mortality rates and 95% confidence intervals per 1000 person-years of CHS participants by site

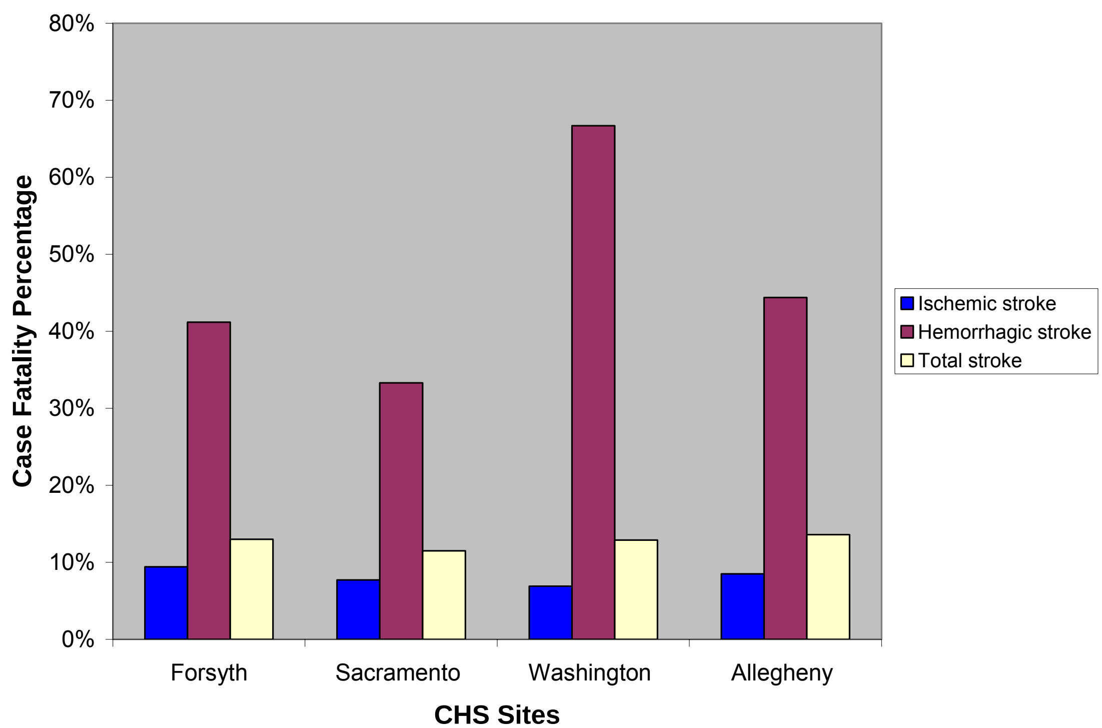
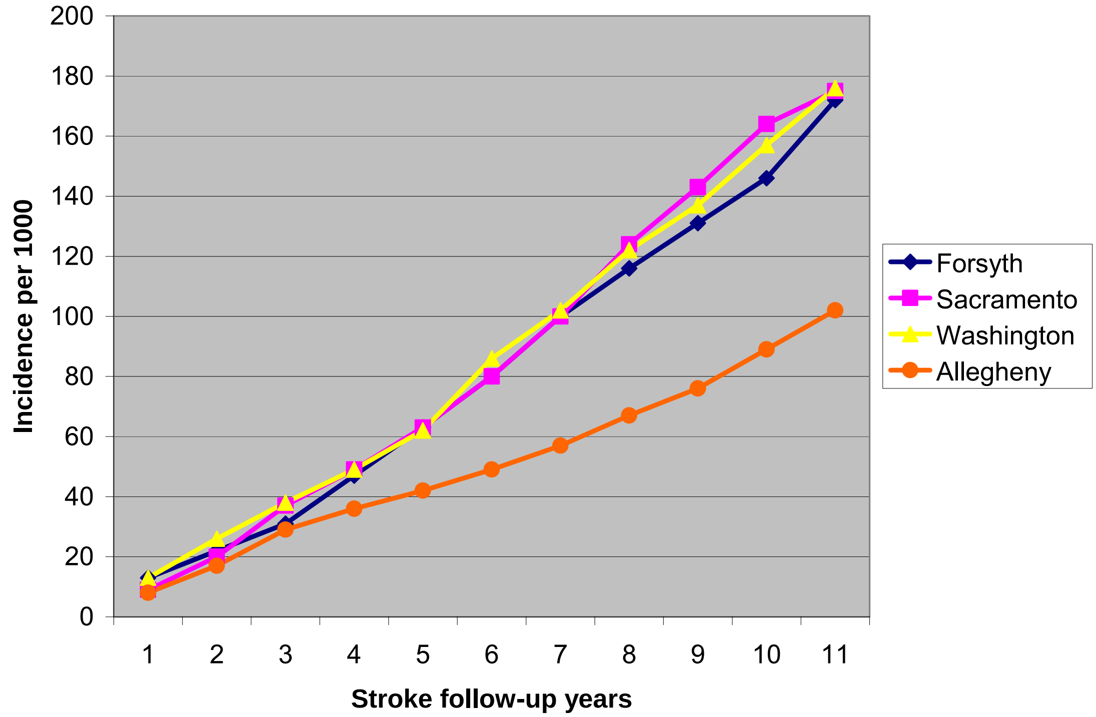


Figure 5: Stroke type-specific one-month case fatality of CHS participants by site



Cummulative total stroke mortality

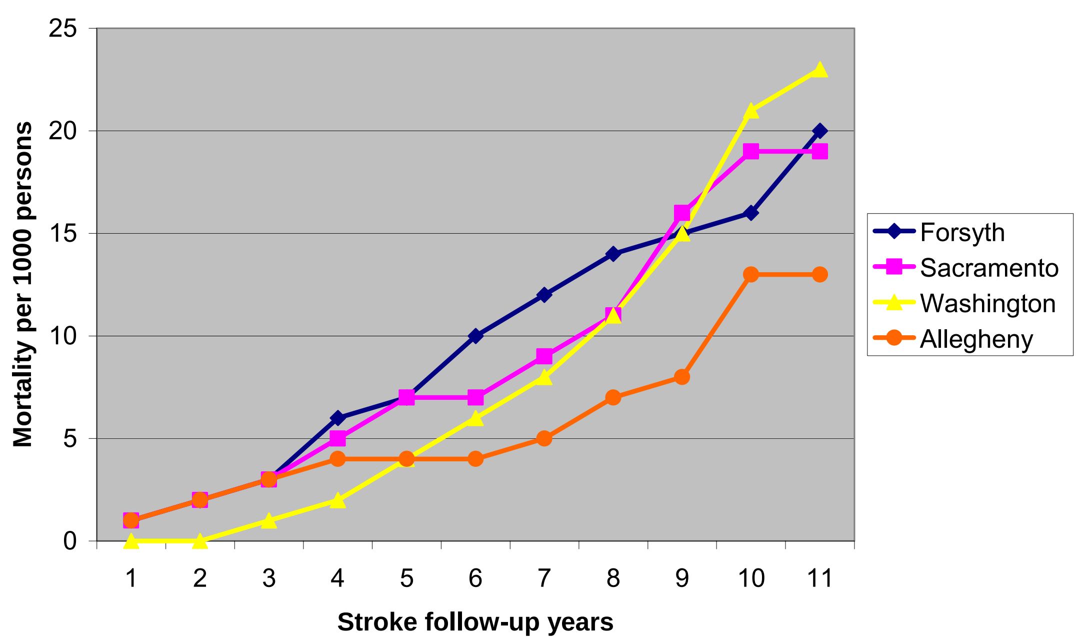


Figure 6: Adjusted* cumulative total stroke incidence (above) and mortality (below) per 1000 CHS participants over follow up years by site

* Adjusted for age, gender, race.

2.5. DISCUSSION

2.5.1. Overall total stroke Incidence:

Comparing rates of disease on national or international levels, and attempting to determine factors that explain any geographic differences have often led to important knowledge about etiology and prevention. Comparing stroke incidence rates reported in different studies is not without risk because of definition criteria, methodology of case ascertainment, population, age range, and time period covered. The overall total (all stroke types) stroke incidence reported in this report was substantial at 17.7 per 1000 person years and many-fold higher than that reported in other population based studies estimating stroke incidence in the United States [6-15] and worldwide [5, 24, 25] because of the older age of CHS population. The overall annual stroke incidence rates in United States studies [6-15] per 100,000 populations, approximately ranged between 93 and 293. In all these studies, the populations used were either all age groups, adults 35 years and over, or the older population excluded. This may resulted in dilution of the rates by including (into the denominator) the younger population who had a very low stroke risk. In ARIC study [8] which used a similar design to CHS study in people aged 45 to 64 years in 4 US communities, the age-adjusted total stroke incidence rates per 1000 person-years were 4.45 for blacks and 1.72 for whites. The current CHS rates per 1000 person-years were 18.2 for blacks and 17.3 for whites.

When age-specific rates for older people were compared between this study and other stroke incidence population studies in United States, CHS rates were generally higher. [6, 7, 9, 12, 14] The more through case ascertainment and validation of the CHS population using different overlapping techniques probably yielded more stroke cases than might be discovered using the registry-based methodology applied in these studies. In the Lehigh Valley, a region in

Pennsylvania and New Jersey, in 1982-1983,[14] the age specific stroke incidence per 100,000 populations were estimated to be 652 for those 65-74 years, 1408 for those 75-84 years and 2243 for those 85 years and more. These rates compare with CHS rates of 1060, 2200, and 3270 in these age groups respectively. In Northern Manhattan, New York City, between 1993 and 1996,[7] the average annual stroke incidence rates per 100,000 for those 65-74 years were 650 for males and 468 for females, those 75-84 years were 688 for males and 629 for females, and those 85 years and more were 857 for males and 931 for females.

The rates in CHS were comparable to those reported in many westernized countries. For example, comparing the current stroke incidence rates in those aged 85 years or older (32.7 per 1000 person-years) to other studies showed that the annual stroke incidence per 1000 population were either higher than in France (18.2)[26], The United Kingdom (18.9)[27], and Germany (21.2)[28], similar to Greece (26.6)[29], Italy(28.8)[30] and Norway(30.4)[31], and lower than in Japan (38.5 in females and 49.2 in males).[32]

Our age standardized results showed a non-significant slightly higher incidence rate per 1000 person-years for blacks than whites (18.2 and 17.3 respectively). Although racial differences in stroke incidence and mortality with more blacks affected than whites was well documented in United States,[7, 8, 12, 13, 33-35] it was also reported that older age groups have a smaller racial difference in stroke incidence as compared to younger population.[7, 8, 12, 34, 36] Broderick and colleagues [12] reported that blacks under age 65 in Greater Cincinnati had a two to four times greater stroke incidence rate compared to whites of similar age in the Rochester, Minnesota. Above 65 years, however, the differences disappeared and the age-specific stroke incidence rates were similar for elderly blacks and whites. Absence of racial difference in stroke risk in people 65 years or older was also documented in a nationally representative data.[36]

The crude incidence rates we observed were slightly higher in males than females (14.8 and 13.7). After age standardization, females had slightly higher rates than males (18.1 and 16.4). None of these differences in incidence were statistically significant. Older populations may have less gender differences in stroke incidence. The data reported for age specific stroke incidence rates in males and females in the Northern Manhattan Stroke Study [7] showed that male/female risk decrease steadily from 2.5 times in those aged 45-54 years until it reversed in those aged 85 years or older, when females had slightly higher stroke incidence than males. Similar observations were noted in Rochester, Minnesota [9] and the French West Indies. [26]

2.5.2. Site specific total stroke incidence:

Our results showed significantly lower stroke incidence rates in Allegheny County field center than the other three study sites in Forsyth County, Sacramento County, and Washington County. The lower stroke incidence rate in Allegheny County was consistent over time and began as early as the fourth year of follow up. The lower stroke incidence rate in Allegheny County was consistent by cohort, gender, race, and age groups. Differences between Allegheny County and the other three sites were statistically significant for the original cohort, females, whites, and those aged 65-74 and 75-84. Lack of statistical significance for differences in rates for the Allegheny County new cohort, blacks and those aged 85 years or older, can be explained by the small total number of events in these three groups (60, 89, and 38 respectively).

In ARIC study [8] which used a similar design to CHS in people aged 45 to 64 years in 4 US communities, there were noticeably higher rates for stroke incidence per 1000 person-years in the Jackson, Mississippi site (4.47) than the other 3 sites (Forsyth County, NC; (1.72) Washington County, MD; (1.92) and Minneapolis, MN (1.80)). This may be explained by the fact that all participants at the Jackson site were blacks and blacks in this study had higher rates than whites (4.45 and 1.72 respectively). In the current study, however, the racial differences between sites did not account for site-differences in stroke rates for two reasons; blacks did not have a significantly higher stroke incidence than whites, and also Washington County, the site with a significantly lower percentage of blacks percentage, had significantly higher rates than Allegheny County and similar rates to Forsyth County and Sacramento County.

The lower stroke incidence in Allegheny County, both incidence rates and cumulative incidence, may be due to lower prevalence of stroke risk factors in Allegheny County at baseline, better control of these factors at baseline and over the years, or both together. These two hypothesis will be discussed in the next articles. The degree of urbanization has been linked with stroke risk, with higher rates in non-metropolitan areas.[37-39] Allegheny County was entirely urban while the other sites were mixed urban/rural communities.

2.5.3. Type-specific stroke incidence:

The significantly lower incidence rates in Allegheny County for total strokes were replicated for ischemic strokes but not hemorrhagic strokes. This was not surprising giving the fact that 85% of incident strokes were ischemic (566 events) and only 10% were hemorrhagic (65 events). The frequency of ischemic strokes in the CHS population (85%) was either similar to other US studies (84%)[8, 12] or slightly higher (77%). [7] The hemorrhagic strokes were less frequent in the CHS population (10%) than other American populations of younger age (14.5% and 23%).[7, 8, 12]. MRI use was noticeably higher in this study (62%) than the other recent studies like the Greater Cincinnati (22%) or ARIC (27%) studies. One advantage of this study was the use of validated events rather than reliance on the less accurate discharge diagnosis coding or death certificate.[40, 41] For example, in Framingham study, analysis of death certificate validity disclosed marked over-reporting of cerebral hemorrhage and under-reporting of cerebral embolus.[41]

2.5.4. Stroke mortality and case fatality:

The overall one month case fatality rates reported for all CHS participants were comparable to other US studies (10% -15%) [6, 7] but lower than that reported in Europe, Russia, and Japan (17% to 33%) [25-32, 42-44] probably due to better health care. The stroke mortality rate per 1000 person-years was also lower in Allegheny County (1.55) than the other three sites (2.79, 2.67, 3.07). However, the differences were not significant probably due to the small number of fatal strokes (84 events). The same observation was obtained after plotting the cumulative total stroke mortality rates over time, adjusted for age, gender, race, and cohort. The lower mortality rate in Allegheny County than the other three sites might be explained by the lower incidence and similar case fatality and proportional frequencies of incident stroke types in Allegheny County compared to the other three sites. Though much higher due to older population, the current study findings were consistent with national data (1999) that showed lower age-adjusted stroke mortality rates per 100,000 American of all ages in Pennsylvania (58.0) compared to North Carolina (78.1), California (63.3), and Maryland (63.1).[45] The similar one month case fatality across sites might be due to similar stroke management or stroke severity across sites, for example, there were no significant differences between sites for total mortality or incident CHD (Appendix C) also those who had incident CHD before stroke were similar across sites. In addition, longer time period (for example one year case fatality) might be needed to delineate between sites differences in case fatality.

2.5.5. Conclusions:

This report was unique in examining geographic differences in stroke incidence in older populations in United States. Stroke incidence rates steadily increased with increasing age at all four CHS sites. There were little or no race and sex differences in incidence. Total stroke incidence rates were significantly lower in Allegheny County than other three sites. Though not statistically significant, the total stroke mortality rates were also lower in Allegheny County than other three sites. The differences could not be explained by age or race differences between sites. Case fatality rates and proportional frequencies of incident stroke types were not significantly different between the four sites. Further studies are needed to investigate the cause of lower stroke incidence in Allegheny County. This may provide insight into stroke etiology, prevention, and treatment differences among these four communities.

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3. SECOND ARTICLE: Variations in stroke risk factors at baseline relative to variations in stroke incidence among four US communities: The Cardiovascular Health Study (CHS)

3.1. ABSTRACT

BACKGROUND: Geographic variation in stroke incidence and mortality remain unexplained in United States. In older adults (≥65 years) recruited from Medicare eligibility lists in four US communities, stroke but not CHD incidence rates were significantly lower in Allegheny County, PA than the other three Counties.

OBJECTIVES: To compare the prevalence of baseline potential stroke risk factors relative to incident stroke events in four US communities.

METHODS: Participants in the Cardiovascular Health Study (CHS) who had no history of stroke at baseline (n=5639) were followed for about 10 years for the development of stroke. Extensive historical, physical and laboratory evaluations were performed at baseline to identify possible stroke risk factors. The prevalence of baseline potential risk factors was compared among the four CHS sites. Hazard ratios for stroke incidence were calculated with Cox regression models.

RESULTS: Total stroke incidence unadjusted hazards in Forsyth County, North Carolina; Sacramento County, California; and Washington County, Maryland combined compared to Allegheny County, Pennsylvania was 1.74 (95% CI= 1.42, 2.14; p< 0.001). Although Allegheny County had the lowest stroke hazard among the four sites, risk factor distributions were relatively similar. After adjustment for age, hypertension, diabetes, education, BMI, LDL

cholesterol and previous coronary heart disease, transient ischemic attack, and atrial fibrillation, there was modest reduction of the excess hazard in the other three sites compared to Allegheny County (HR=1.52, CI 1.17, 1.98 compared to 1.74 CI 1.42, 2.14). White matter grade (WMG) $\geq$ 3 on the baseline brain MRI was less common in Allegheny County than the other 3 sites (25.8%and 36.3% respectively, $p< 0.001$) and accounted for 25% of the excess hazard in the other three sites compared to Allegheny County (HR=1.65, CI 1.20-2.26 compared to 1.87 CI 1.36-2.55)

CONCLUSION: Site-differences in stroke risk factors at baseline only partially explain site-differences in stroke incidence. White matter grade might be more helpful in explaining these differences. Further study is needed to delineate the causes of geographic differences in stroke incidence.

3.2. BACKGROUND

The Southeast regions of United States have consistently excess stroke mortality and incidence (the "stroke belt"). This pattern has, at times, been attributed to less favorable stroke risk factors profiles. For example, hypertension prevalence,[1] less desirable response to antihypertensive medications,[2] and hypertension related mortality and morbidity [3-5] were all reported to be high among southeastern states. In another report,[6] however**,** high hypertension prevalence among southeastern states was confirmed only in black females. Although low socioeconomic status (SES)and education levels are common in the Southeast US, [1, 7] these factors did not make a significant contribution to the stroke belt.

Few studies in United States examined the association between geographic variations of multiple stroke risk factors and stroke incidence and/or mortality. Relatively inconsistent patterns of association have been shown in these studies. Recent data are lacking. In addition, prior studies frequently included only one or a few traditional cardiovascular risk factors, typically did not incorporate the effect of many potentially important factors as medication use, education level, or markers of sub-clinical cardiovascular disease such as carotid artery stenosis or MRI findings. For example, NHANES I [1] data show that the prevalence of current smoking and abstinence from alcohol were higher in the southeast than other regions of the United States, but that the highest diabetes prevalence rates were in the northeast in women and midwest in men. In the three-area epidemiological study,[8] only blood pressure in white men and black women and glucose intolerance in both races mirrored a gradient observed for stroke mortality in three US regions: Savannah, Georgia (high stroke rates), Hagerstown, Maryland (intermediate stroke rates) and Pueblo, Colorado (low stroke rates). No consistent pattern was found correlating stroke mortality with other cerebrovascular risk factors, including the prevalence of transient ischemic attacks, angina, cigarette smoking, cholesterol levels, or height and weight.

Among international studies, hypertension emerges as the only factor with a prevalence pattern consistently linked with stroke risk. In the MONICA study,[9, 10] set in a predominantly European population, there were large variations of baseline risk-factor patterns: prevalence of smoking and elevated blood pressure were associated with higher stroke rates, however, high total cholesterol was not. One recent report comparing stroke incidence in Hungary and Japan showed that[11] Hungary had a higher stroke incidence. While hypertension was higher in Hungary; atrial fibrillation, smoking and regular alcohol consumption were more frequent in Japan, there were no differences in diabetes or ischemic heart disease. In China, [12] ecological data showed a north-south gradient, with higher prevalence of hypertension and stroke incidence and mortality in the north compared with the south of the country. In Spain,[13] stroke mortality and cigarette smoking, as well as illiteracy rates, and sedentary lifestyle were substantially higher and wine consumption were substantially lower along the Mediterranean coast than in the rest of the country. Among 22 Scottish health districts, hospital admission rates for stroke were associated with prevalence of hypertension, absence of fruit consumption and alcohol consumption in men and smoking in women.[14]

The current report utilized data from a big prospective study comparing large number of possible stroke risk factors in older people in four geographically separated US communities using standardized methodology. The aim of this report was to determine whether the differences in stroke incidence among the four CHS sites observed in a previous report (First Article) can be explained by site-differences in the prevalence of potential stroke risk factors at baseline relative to incident stroke events.

3.3. METHODS

3.3.1. Study population:

The Cardiovascular Health Study (CHS) design, including recruitment techniques, definitions of risk factors and outcomes, has been described in detail.[15, 16] CHS is a population-based, longitudinal study of coronary heart disease and stroke in older adults. Participants of the CHS were recruited from a random sample of Health Care Financing Administration (HCFA) Medicare eligibility lists in four US communities: Forsyth County, 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 were receiving cancer treatment. The Allegheny County field center population was entirely urban; and the other three sites recruited a mixture of urban, suburban, and rural populations. 5888 men and women, 65 years of age or older at study entry, were recruited in 2 waves. A total of 5,201 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 the racial representativeness of the study. No second wave participants were recruited in Washington County, MD.

3.3.2. Risk factors and outcome assessments:

Extensive historical, physical and laboratory evaluations were performed at baseline examination for each cohort to identify the presence and severity of the conventional cardiovascular risk factors such as hypertension, smoking, hypercholesterolemia and glucose intolerance. Sub-clinical cardiovascular disease, such as carotid artery atherosclerosis and left ventricular enlargement, was also assessed.

Hypertension was defined as SBP ≥140, DBP ≥90, or a history of hypertension plus use of antihypertensive medication.[17] Diabetes was defined according ADA guidelines [18] (fasting glucose ≥ 126 or taking insulin or oral hypoglycemics). Baseline brain MRI examination was done in years 4, 5 and 6. 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. Up to five large infarcts were described for each participant. Smokers were categorized as current or non-smoker including former smokers. Body Mass Index was calculated by dividing weight (kg) by height (m) squared. History of coronary heart disease at baseline was confirmed by a report of angioplasty or bypass surgery prior to study entry. Aspirin use was confirmed by reported using aspirin 3 or more days in past 2 weeks. Any sub-clinical cardiovascular disease variable was a composite measure including any of the following: ankle arm index (AAI) ≤ 0.9, internal or carotid wall thickness > 80^{th} percentile, carotid stenosis > 25%, major ECG abnormalities, claudication from Rose questionnaire, and angina from Rose questionnaire. [19]

Ascertainment methods of stroke and other CHS endpoints, either incident or prevalent have been described.[20-22] 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.[20, 22] Provisional diagnoses of stroke were assigned by the field center principal investigator, and then reviewed and adjudicated at periodic meetings of the cerebrovascular disease endpoint committee. The committee also classified the stroke types as hemorrhagic or ischemic infarction.[20] Participants with pre-baseline stroke were excluded from the analysis.

3.3.3. Statistical analysis:

Potential stroke risk factors at baseline were compared between the four sites for significant differences. Data were checked for normality. ANOVA test was used for continuous variables that were normally distributed. Kruskal-Wallis test was used for continuous variables that were not normally distributed. Pearson Chi square was used for categorical variables. Potential stroke risk factors at baseline were also compared between Allegheny County and the other three sites combined for significant differences using the t-test or Mann-Whitney for continuous variables and Chi square for categorical variables. A five percent level of significance was used for all tests.

Hazard ratios for stroke incidence were calculated using Cox regression models. Hazards in Forsyth County, Sacramento County, Washington County and then these three sites combined were compared to that in Allegheny County. Years of follow up were defined as the time from the baseline visit to occurrence of stroke, or as the time from the baseline visit to censoring or the end of follow up for those who did not have a stroke. All models were adjusted for age, race, gender, and education. The effects conventional cardiovascular risk factors on stroke incidence hazard ratios among sites (including hypertension, diabetes, smoking, BMI, LDL and HDL cholesterol, alcohol drinking, previous coronary heart disease (CHD), atrial fibrillation (AF), or transient ischemic attacks (TIA)) were then evaluated.

Sub-clinical cardiovascular diseases (including Intima-Media Thickness “IMT”, carotid stenosis, abnormal Ankle-Arm blood pressure Index (AAI) measured by ultrasound and major ECG abnormalities), specific MRI findings (including presence of one or more large infarcts and white matter grade), the use of medications (including aspirin, oral anticoagulants, and medications for hypertension, diabetes, or hyperlipidemia) and the availability of supplemental insurance (to Medicare) were all evaluated in age adjusted models. Covariates were entered into the model if their significance level was less than 0.05, and were removed from the model if their significance level was greater than 0.10.

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.

3.4. RESULTS

3.4.1. Socio-demographics:

The total number of participants at risk for incident stroke at baseline in the four sites was 5639. Of these, 5002 (88.7%) were recruited between 1989 and 1990 (original cohort) and 637 (11.3%) were recruited between 1992 and 1993 (new cohort). The mean age at baseline was 72.8 years (median 72 years, range 65-100 years); 3759 (66.7%) participants were aged 65-74 years, 1668 (29.6%) were 75-84 years, and 212 (3.8%) were 85 or more years old. More than half (58%) of the participants were women. There were no significant age or gender differences between sites. Approximately 85% of the participants were white and 15% were black; the Washington County site had a significantly lower percentage of black participants (Table 4). Allegheny County had more higher education (more than 12 years) than the other three sites (49.4% and 41.7% respectively, $p < 0.001$). Allegheny County had lower percentage of additional insurance to Medicare compared to the other three sites (88.4% and 92.1% respectively, $p < 0.001$).

3.4.2. Hypertension:

The prevalence of hypertension was slightly lower in Allegheny County than in the other three sites (56.0% and 58.8% respectively, $p=0.070$). This difference was significant among white participants ($p=0.016$) but not black participants ($p=0.168$). The systolic blood pressure was similar and the diastolic pressure was slightly higher in Allegheny County compared to the other three sites ($p=0.903$ and $p < 0.001$ respectively). Diastolic blood pressure was significantly lower in Washington County than the other three sites ($p < 0.001$) (Table 5). The percentage of hypertensive CHS participants treated by any antihypertensive medication was significantly lower in Allegheny County than the other three sites (65.0% versus 68.7%; $p < 0.048$). This was true for both diuretics and vasodilators ($p<0.001$ and $p=0.006$ respectively).

3.4.3. Diabetes:

There was no significant difference in diabetes prevalence at baseline between Allegheny County and the other three sites (16.6% and 15.6% respectively, p< 0.074). However, diabetes prevalence was significantly lower in Sacramento County than Allegheny County (13.0% and 16.6% respectively, p< 0.001). (Table 5) Among participants with diabetes, there were no significant differences between Allegheny County and the other three sites regarding the use of any diabetic medication, any hypertensive medication, or any lipid lowering medication (p value=0.390, 0.141, and 0.102 respectively)

3.4.4. Blood cholesterol:

Both Allegheny County and the other three sites had similar percentage of those having high LDL cholesterol (100 mg/dl or more) (85.5% and 83% respectively, p=0.085), Low HDL cholesterol (35 mg/dl or less) (6.3% and 6.5% respectively, p=0.759) and high triglycerides (200 mg/dl or more) (13.6% and 14.6% respectively, p=0.372) (Table 5). Among participants with hypertension or diabetes, in both Allegheny County and the other three sites, there were no significant differences in either LDL or HDL levels (In those with hypertension: p=0.831 for high LDL and p= 0.652 for low HDL. In those with diabetes: p=0.375 for high LDL and p=0.123 for low HDL). High triglycerides (200 mg/dl or more) among those with diabetes was observed less frequently in Allegheny County than the other three sites (20.8% and 28.5% respectively, p= 0.020).

3.4.5. Smoking and alcohol drinking:

Current smoking was more common in Allegheny County than the other three sites, the difference however was not significant (13.2% and 11.5% respectively, p value=0.074). The number of cigarettes pack-years smoked in Allegheny County (mean ± SD 20.8 ±29.3) was higher than the other three sites (mean ± SD 16.5 ±25.2, p value=0.015) (Table 5). Those who drank 8 alcohol drinks per week (more than 90th percentile) were more common in Allegheny County than the other three sites, the difference however was not significant (11.2% and 9.7% respectively, p value=0.103) (Table 5).

3.4.6. Medical and family History:

There were no significant differences between Allegheny County and the other three sites as regards previous history of coronary heart disease, atrial fibrillation, or transient ischemic attacks (p value=0.720, 0.191, and 0.879 respectively). Family history of stroke was lower in Allegheny County than the other three sites (28.7% and 32.0% respectively, p< 0.026) (Table 5).

3.4.7. Sub-clinical cardiovascular disease and MRI findings:

Using the composite variable for any sub-clinical disease, there was no significant difference between Allegheny County and the other three sites. However, carotid stenosis (≥25%) in Allegheny County was significantly less frequent than the other three sites (43.2% and 48.2% respectively, p< 0.001) and abnormal Ankle-Arm blood pressure Index (AAI) was more common in Allegheny County than the other three sites (14.6% and 12.0% respectively, p< 0.010). White matter grade ≥ 3 was less common in Allegheny County than the other three sites (25.8%and 36.3% respectively, p< 0.001) (Table 7). After adjustment for age and white matter grade and comparing that to age adjusted model, there was 25% reduction of the excess hazard in the other three sites compared to Allegheny County (Table 7). Those who had two or more large infarct were not significantly different between sites.

3.4.8. Stroke Hazards:

Total stroke incidence unadjusted hazards compared to Allegheny County were 1.66 in Forsyth County (95% CI= 1.31, 2.10; p< 0.001), 1.78 in Sacramento County (95% CI= 1.41, 2.24; p<

0.001), 1.79 in Washington County (95% CI= 1.41, 2.27; $p < 0.001$), and 1.74 in all the three sites combined (95% CI= 1.42, 2.14; $p < 0.001$). In models adjusted for all traditional cardiovascular risk factors, reduced stroke incidence hazard was consistently observed in Allegheny County. There was slight reduction of the excess hazard in the other three sites compared to Allegheny County after adjustment for age, gender, race, and education (1.71, 95% CI= 1.39, 2.11; $p < 0.001$). There was almost 30% reduction of the excess hazard in the other three sites compared to Allegheny County after adjustment for traditional stroke risk factors including age, hypertension, diabetes, education, BMI, LDL cholesterol and previous CHD, TIA and atrial fibrillation (1.52, 95% CI= 1.17-1.98; $p=0.002$) (Table 8).

Table 4: CHS participants by cohort and demographic characteristics by site

	Forsyth County, NC N %	Sacramento County, CA N %	Washington County, MD N %	Allegheny County, PA N %	Total N %
Total number of those at stroke risk at baseline	**1488** 100.0%	**1471** 100.0%	**1251** 100.0%	**1429** 100.0%	**5639** 100.0%
Cohort:					
Original cohort	**1266** 85.1%	**1267** 86.1%	**1251** 100.0%	**1218** 85.2%	**5002** 88.7%
New cohort	**222** 14.9%	**204** 13.9%	**NA** NA	**211** 14.8%	**637** 11.3%
Age groups at baseline:					
65-74 years	**997** 67.0%	**989** 67.2%	**801** 64.0%	**972** 68.0%	**3759** 66.7%
75-84 years	**443** 29.8%	**420** 28.6%	**394** 31.5%	**411** 28.8%	**1668** 29.6%
85+ years	**48** 3.2%	**62** 4.2%	**56** 4.5%	**46** 3.2%	**212** 3.8%
Gender:					
Males	**900** 60.5%	**850** 57.8%	**726** 58.0%	**811** 56.8%	**3287** 58.3%
Females	**588** 39.5%	**621** 42.2%	**525** 42.0%	**618** 43.2%	**2352** 41.7%
Race:					
Whites	**1154** 78.0%	**1228** 84.6%	**1238** 99.1%	**1123** 79.0%	**4743** 84.7%
Blacks	**326** 22.0%	**224** 15.4%	**11** 0.9%	**299** 21.0%	**860** 15.3%

Table 5: Prevalence of potential stroke risk factors at baseline among CHS participants by sites

	Forsyth County, NC	Sacramento County, CA	Washington County, MD	Allegheny County, PA	Other three sites	Total	P-value[1]	P-value[2]
Blood pressure								
Systolic BP mm Hg (Mean±SD)	**136.7** ±21.8	**139.7** ±22.0	**132.1** ±20.6	**136.3** ±21.8	**136.4** ±21.7	**136.4** ±21.7	< 0.001	0.903
Diastolic BP mm Hg (Mean±SD)	**72.6** ±10.9	**72.3** ±11.8	**65.6** ±10.8	**71.6** ±10.5	**70.4** ±11.6	**70.7** ±11.4	< 0.001	< 0.001
Hypertension								
Hypertension	**869** 58.5%	**882** 60.2%	**719** 57.5%	**799** 56.0%	**2470** 58.8%	**3269** 58.1%	0.147	0.070
History of hypertension & its medication	**566** 38.0%	**515** 35.1%	**518** 41.4%	**485** 34.0%	**1599** 38.0%	**2084** 37.0%	< 0.001	0.006
BP ≥140/90 mm Hg	**598** 40.3%	**691** 47.2%	**405** 32.4%	**592** 41.5%	**1694** 40.3%	**2286** 40.6%	< 0.001	0.455
Blood glucose:								
Fasting glucose mg/dl (Mean±SD)	**110.3** ±41.2	**107.5** ±31.2	**113.1** ±35.1	**112.7** ±37.6	**110.2** ±36.1	**110.8** ±36.5	< 0.001 KWT	0.002 MWT
2-hour glucose mg/dl (Mean±SD)	**145.5** ±59.4	**149.9** ±54.2	**149.2** ±58.3	**142.9** ±60.5	**148.1** ±57.3	**147.3** ±57.8	< 0.001 KWT	< 0.001 MWT
Diabetes :								
Diabetes	**234** 16.0%	**188** 13.0%	**228** 18.3%	**237** 16.6%	**650** 15.6%	**887** 15.9%	< 0.001	0.074
Fasting glucose ≥126 mg/dl	**197** 13.6%	**168** 11.6%	**210** 16.8%	**213** 15.0%	**575** 13.9%	**788** 14.2%	< 0.001	.107
History of diabetes & its medication	**129** 8.7%	**94** 6.4%	**112** 9.0%	**119** 8.3%	**335** 8.0%	**454** 8.1%	0.051	0.657
Cholesterol:								
High LDL (≥ 100 mg/dl)	**1172** 80.9%	**1198** 83.4%	**1050** 85.0%	**656** 85.5%	**3420** 83.0%	**4076** 83.4%	0.011	0.085
Low HDL (≤35 mg/dl)	**103** 7.0%	**72** 5.0%	**97** 7.8%	**90** 6.3%	**272** 6.5%	**362** 6.5%	0.021	0.759
High triglycerides (≥200 mg/dl)	**185** 12.6%	**202** 13.9%	**219** 17.5%	**194** 13.6%	**606** 14.6%	**800** 14.3%	0.002	0.372
Smoking:								
Current smoking	**215** 14.5%	**144** 9.8%	**123** 9.8%	**189** 13.2%	**482** 11.5%	**671** 11.9%	< 0.001	0.074
Pack-years smoked (Mean±SD)	**17.5** ±26.4	**16.3** ±24.9	**15.5** ±24.0	**20.8** ±29.3	**16.5** ±25.2	**17.6** ±26.4	< 0.001 KWT	< 0.001 MWT

1= Differences across sites 2= Differences between Allegheny County and the other three sites combined

Table 5 (continued)

	Forsyth County, NC	Sacramento County, CA	Washington County, MD	Allegheny County, PA	Other three sites	Total	P-value[1]	P-value[2]
Alcohol:								
drinks/ week (Mean±SD)	**1.7** ±5.2	**3.7** ±7.9	**1.6** ±4.8	**2.8** ±6.7	**2.4** ±6.3	**2.5** ±6.4	< 0.001 KWT	< 0.001 MWT
≥8 drinks/ week (> 90th)	**103** 6.9%	**228** 15.6%	**74** 5.9%	**159** 11.2%	**405** 9.7%	**564** 10.0%	< 0.001	0.103
Medical history:								
Coronary heart disease (CHD)	**256** 17.2%	**258** 17.5%	**281** 22.5%	**276** 19.3%	**795** 18.9%	**1071** 19.0%	0.002	0.720
Atrial fibrillation (AF)	**29** 2.3%	**40** 3.2%	**38** 3.0%	**26** 2.1%	**107** 2.8%	**133** 2.7%	0.275	0.191
TIA (Transient ischemic attack)	**21** 1.4%	**20** 1.4%	**33** 2.6%	**26** 1.8%	**74** 1.8%	**100** 1.8%	0.047	0.879
Family history of stroke	**451** 32.4%	**355** 27.4%	**425** 36.8%	**377** 28.7%	**1231** 32.0%	**1608** 31.2%	< 0.001	0.026
Education:								
More than12 years	**553** 37.4%	**774** 52.8%	**422** 33.7%	**705** 49.4%	**1749** 41.7%	**2454** 43.6%	< 0.001	< 0.001
College or higher	**421** 28.6%	**604** 41.2%	**300** 24.0%	**603** 42.3%	**1325** 31.6%	**1928** 34.3%	< 0.001	< 0.001
Body mass index (Mean±SD)	**26.2** ±4.8	**26.9** ±4.5	**26.9** ±4.7	**26.8** ±4.8	**26.7** ±4.7	**26.7** ±4.7	< 0.001	0.470
Creatinine level mg/dl (Mean±SD)	**1.05** ±0.30	**1.03** ±0.44	**1.08** ±0.41	**1.08** ±0.38	**1.05** ±0.39	**1.06** ±0.39	0.002	0.026

1= Differences across sites 2= Differences between Allegheny County and the other three sites combined

Table 6: Control of potential stroke risk factors at baseline among CHS participants by sites

	Forsyth County, NC	Sacramento County, CA	Washington County, MD	Allegheny County, PA	Other three sites	Total	P-value[1]	P-value[2]
Hypertension:								
Any hypertension medication	**605** 69.7%	**547** 62.1%	**544** 75.7%	**519** 65.0%	**1696** 68.7%	**2215** 67.8%	< 0.001	0.048
Diuretics	**390** 44.9%	**323** 36.7%	**399** 55.5%	**289** 36.2%	**1112** 45.1%	**1401** 42.9%	< 0.001	< 0.001
Beta blockers	**150** 17.3%	**138** 15.7%	**146** 20.3%	**147** 18.4%	**434** 17.6%	**581** 17.8%	0.103	0.601
Vasodilators	**105** 12.1%	**101** 11.5%	**130** 18.1%	**79** 9.9%	**336** 13.6%	**415** 12.7%	< 0.001	0.006
ACE inhibitors[5]	**104** 12.0%	**123** 14.0%	**71** 9.9%	**109** 13.6%	**298** 12.1%	**407** 12.5%	0.059	0.244
Diabetes:								
Any diabetic medication	**137** 58.5%	**96** 51.3%	**114** 50.0%	**119** 50.2%	**347** 53.5%	**466** 52.6%	0.204	0.390
Insulin intake In diabetics	**44** 18.8%	**19** 10.2%	**34** 14.9%	**28** 11.8%	**97** 14.9%	**125** 14.1%	0.050	0.236
Any oral Hypoglycemic	**95** 40.6%	**81** 43.3%	**83** 36.4%	**92** 38.8%	**259** 39.9%	**351** 39.6%	0.530	0.769
Lipid lowering medication in:								
LDL ≥ 100 mg/dl	**65** 5.6%	**67** 5.6%	**69** 6.6%	**32** 4.9%	**201** 5.9%	**233** 5.7%	0.500	0.310
Hypertension	**40** 4.6%	**57** 6.5%	**49** 6.8%	**44** 5.5%	**146** 5.9%	**190** 5.8%	0.218	0.673
Diabetes	**20** 8.5%	**12** 6.4%	**22** 9.6%	**12** 5.1%	**54** 8.3%	**66** 7.4%	0.235	0.102
Aspirin	**524** 35.2%	**442** 30.1%	**419** 33.5%	**478** 33.4%	**1385** 32.9%	**1863** 33.1%	0.028	0.772
Oral anticoagulants	**13** .9%	**16** 1.1%	**20** 1.6%	**18** 1.3%	**49** 1.2%	**67** 1.2%	0.359	0.775
Surgery:								
Carotid endarterectomy	**16** 1.1%	**12** .8%	**28** 2.2%	**10** 0.7%	**56** 1.3%	**66** 1.2%	0.001	0.055
Coronary bypass or angioplasty	**63** 4.3%	**87** 6.0%	**62** 5.0%	**79** 5.6%	**212** 5.1%	**291** 5.2%	0.182	0.476
Additional insurance	**1103** 91.2%	**1168** 94.0%	**918** 91.0%	**1095** 88.4%	**3189** 92.1%	**4284** 91.1%	< 0.001	< 0.001

1= Differences across sites 2= Differences between Allegheny County and the other three sites combined

Table 7: Sub-clinical cardiovascular disease and multiple risk factors at baseline among CHS participants by sites

	Forsyth County, NC	Sacramento County, CA	Washington County, MD	Allegheny County, PA	Other three sites	Total	P-value[1]	P-value[2]
Ultrasound								
Common carotid IMT (Mean±SD mm)	**1.06** ±0.22	**1.06** ±0.21	**1.06** ±0.21	**1.06** ±0.21	**1.06** ±0.22	**1.06** ±0.21	0.673 KWT	0.729 MWT
Internal carotid IMT (Mean±SD mm)	**1.39** ±0.54	**1.47** ±0.59	**1.45** ±0.57	**1.42** ±0.55	**1.44** ±0.57	**1.43** ±0.56	< 0.001 KWT	0.239 MWT
Carotid stenosis (≥25%)	**634** 43.2%	**720** 49.1%	**659** 53.0%	**617** 43.2%	**2013** 48.2%	**2630** 46.9%	< 0.001	0.001
Carotid stenosis (≥50%)	**64** 4.4%	**41** 2.8%	**74** 5.9%	**63** 4.4%	**179** 4.3%	**242** 4.3%	0.001	0.837
Low Ankle-Arm Index (≤0.9)	**173** 11.9%	**183** 12.7%	**135** 11.1%	**205** 14.6%	**491** 12.0%	**696** 12.6%	0.039	0.010
ECG:								
Left ventricular hypertrophy	**70** 4.8%	**53** 3.7%	**65** 5.3%	**71** 5.4%	**188** 4.6%	**259** 4.8%	0.132	0.247
Atrial fibrillation	**31** 2.1%	**42** 2.9%	**38** 3.0%	**27** 1.9%	**111** 2.6%	**138** 2.5%	0.137	0.115
MRI:								
White matter grade 3 or more	**294** 33.0%	**336** 37.0%	**295** 39.6%	**226** 25.8%	**925** 36.3%	**1151** 33.6%	<0.001	<0.001
One or more large infarct	**239** 26.7%	**266** 29.0%	**192** 25.4%	**284** 32.2%	**697** 27.1%	**981** 28.4%	0.012	0.004
Two or more large infarct	**92** 10.3%	**105** 11.4%	**66** 8.7%	**104** 11.8%	**263** 10.2%	**367** 10.6%	0.184	0.196
Multiple risk								
Any sub-clinical disease (group 1)	**1005** 67.5%	**989** 67.2%	**847** 67.7%	**978** 68.4%	**2841** 67.5%	**3819** 67.7%	0.914	0.504
History of CHD, TIA, AF, or family history of stroke (group 2)	**625** 50.7%	**568** 46.1%	**621** 52.7%	**582** 48.1%	**1814** 49.8%	**2396** 49.4%	0.006	0.299
Groups 1&2	**419** 31.9%	**381** 29.0%	**424** 35.4%	**397** 31.3%	**1224** 32.0%	**1621** 31.8%	0.007	0.655
Hypertension & diabetes (group 3)	**163** 11.1%	**145** 10.0%	**167** 13.4%	**160** 11.2%	**475** 11.4%	**635** 11.4%	0.050	0.839
Groups 1,2 &3	**48** 3.3%	**45** 3.1%	**70** 5.6%	**46** 3.3%	**163** 3.9%	**209** 3.8%	0.002	0.253

1= Differences across sites 2= Differences between Allegheny County and the other three sites combined

Table 8: Total stroke incidence hazard reduction for the other three CHS sites compared to Allegheny County

Models	N	HR	95% CI	P value	Hazard reduction[1]
Traditional risk factors:					
Model-0: Unadjusted	**665**	**1.740**	(1.418-2.135)	<0.001	Reference
Model-1: adjusted for age at baseline	**665**	**1.716**	(1.399-2.106)	<0.001	3.2%
Model-2: adding gender, race, education to Model-1	**660**	**1.712**	(1.392-2.105)	<0.001	3.8%
Model-3: adding hypertension, diabetes to Model-2	**651**	**1.693**	(1.376-2.084)	<0.001	6.4%
Model-4: adding smoking, alcohol drinks, LDL, HDL and BMI to Model-3	**584**	**1.572**	(1.211-2.041)	0.001	22.7%
Model-5: adding previous CHD, TIA and atrial fibrillation to Model-4	**544**	**1.529**	(1.175-1.989)	0.002	28.5%
Adjusted for age, education, hypertension, diabetes, BMI, LDL and previous CHD, TIA and atrial fibrillation	**544**	**1.525**	(1.173-1.982)	0.002	29.1%
Sub-clinical disease and medication use:					
Adjusted for age at baseline	**665**	**1.716**	(1.399-2.106)	<0.001	Reference
Adjusted for age and any sub-clinical disease	**665**	**1.717**	(1.399-2.107)	<0.001	-0.1%
Adjusted for age and treatments	**665**	**1.712**	(1.395-2.101)	<0.001	0.6%
White matter grade:					
Adjusted for age at MRI	**304**	**1.865**	(1.362-2.552)	<0.001	Reference
Adjusted for age and white matter grade	**301**	**1.647**	(1.201-2.257)	0.002	25.2%

1 Taken as the percentage of excess hazard reduction for the model compared to a reference model

3.5. DISCUSSION

The current report was unique in examining multiple possible stroke risk factors, collected using standardized methodology, in four geographically separated US communities, with the aim to explain geographic variations in stroke incidence.

3.5.1. Prevalence of potential risk factors at baseline:

Allegheny County, which had the lowest stroke hazard among the four sites, had relatively similar risk factors distributions to the other three sites. Hypertension prevalence, the most frequently reported single risk factor associated with high stroke incidence/mortality geographic areas both in United States [1, 8] and worldwide [10-12, 14, 23], was generally lower in Allegheny County than the other three sites, though the trend was significant only among white participants. However, better response to hypertension medications in Allegheny County could not be shown in this report as was expected from the stroke belt experience.[2] Despite a strong link with cardiovascular disease, diabetes prevalence did not vary directly with stroke risk – similar to most previous reports. [1, 11, 13] Better education (12 years or more or collage education) were more prevalent in Allegheny County. Similarly, an inverse relationship between education and stroke incidence or mortality was shown in most of the reports from the industrialized countries.[13, 24, 25]

3.5.2. Multiple risk factors at baseline and site-differences in stroke risk:

The current findings indicated that traditional stroke risk factors can explain to certain extent the site differences in stroke risk. A 30% reduction in stroke risk was obtained after adjustment for age, hypertension, diabetes, education, BMI, LDL level and previous CHD, TIA and atrial fibrillation. Similarly, most previous reports show that geographic differences in stroke incidence and/or mortality, at most, can be partially explained by the differences in stroke risk factors. National data [1] showed that baseline risk factors, that including age, sex, race, smoking status, history of diabetes, history of heart disease, education, systolic blood pressure, alcohol use, and physical activity, played a very minor role in the estimated excess stroke risk in the Southeast. In England,[26] the hazard ratio for stroke in the rest of Britain compared with southern England was 1.44 (95% confidence interval =1.16 to 1.78), After adjustment for baseline systolic blood pressure, smoking status, physical activity, social class, and height, the hazard ratio decreased moderately, but was still significant (1.24, 95% CI, 1.00 to 1.54). In different MONICA populations,[10] smoking and elevated blood pressure explained 21% of the variation in stroke incidence among men and 42% in women. In Sweden,[23] cardiovascular score (hypertension, diabetes, smoking, and being overweigh) and socioeconomic status together accounted for 44% of the geographic variation of stroke incidence among men and 63% among women..

3.5.3. White matter grade at baseline and site-differences in stroke risk:

Recently, white matter lesion which is most likely associated with small-vessel pathology [27] was identified as a strong stroke predictor with three or more folds increase in stroke risk.[28-30] One of the most interesting finding in this report was that white matter grade was responsible for 25% of the excess stroke hazard observed in the other three sites compared to Allegheny County. So white matter grade was the most important single risk factor to explain the observed site differences in stroke risk. White matter grade may be a marker of integrated exposure and control of stroke risk factors and may help in explaining geographic variations in stroke incidence. As Allegheny County had a similar stroke history and lower white matter grade at baseline, the current results suggested the importance of white matter lesion to point any future increase or reduction of stroke risk in a given community, probably many years before it happen. The current findings suggested white matter grade progression could be used a marker of the efficacy of the various pharmacologic and non-pharmacologic therapies of stroke on the individual level and as a marker of the efficacy of different stroke prevention strategies on a community level.

3.5.4. Medication use and sub-clinical cardiovascular disease:

Inclusion of medication usage and sub-clinical cardiovascular disease was an important innovation in the current study. Medication usage and sub-clinical cardiovascular disease in this report had very little to do with site differences in stroke risk. The rate for any sub-clinical disease at baseline was similar across sites. With few exceptions, the rates for medication use at baseline were generally similar across sites. However, risk factors investigated in this report and their treatment were limited to baseline data and did not take in consideration the changes over time in controlling conditions like hypertension, diabetes, and high blood lipids.

3.5.5. Alternative explanation of site-differences in stroke risk:

As the site-differences in stroke risk were only partially explained in this report, factors other than traditional stroke risk factors and sub-clinical cardiovascular disease should be investigated further. These factors might be more helpful in explaining regional differences in stroke risk. Limited data have identified several potential factors, including genetic influences on stroke [31-33] – especially compelling as family history of stroke was lower in Allegheny County than in other sites. The degree of urbanization has likewise been linked with stroke risk, with higher rates in non-metropolitan areas.[1, 34, 35] Allegheny County was entirely urban while the other sites were mixed urban/rural communities. Dietary life style including the consumption of fish, fruits and vegetables and dietary calcium and potassium may help in explaining geographic stroke incidence variations.[36, 37] Finally, environmental factors such as the quality of drinking water and environmental exposure to lead and perhaps cadmium may have some role in explaining these stroke variations.[38, 39]

3.5.6. Conclusions:

Site-differences in stroke risk factors only partially explain site-differences in stroke incidence. White matter grade may be a marker of integrated exposure and control of stroke risk factors and may help in explaining geographic variations in stroke incidence. Further study is needed to delineate the causes of geographic differences in stroke incidence.

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4. THIRD ARTICLE: Control of stroke risk factors across visits relative to variations in stroke incidence among four US communities: The Cardiovascular Health Study (CHS)

4.1. ABSTRACT

BACKGROUND: Control of modifiable stroke risk factors specially hypertension, diabetes, blood lipids, smoking, atrial fibrillation, and carotid stenosis have been associated with subsequent reduced risk of stroke. In older adults (≥65 years) recruited from Medicare eligibility lists in four US communities, stroke but not CHD incidence rates were significantly lower in Allegheny County, Pennsylvania than the other three Counties.

OBJECTIVES: To compare the control of stroke risk factors across visits relative to incident stroke events in four US communities.

METHODS: Participants in the Cardiovascular Health Study (CHS) who had no history of stroke at baseline (n=5639) were followed for about 10 years for the development of stroke. Stroke risk factors and their control were compared at baseline, year-5 and year-9 between Allegheny County, Pennsylvania and the other three CHS sites combined (Forsyth County, North Carolina; Sacramento County, California; and Washington County, Maryland).

RESULTS: The total number of participants at risk for incident stroke in the four sites was 5639 at baseline, 4513 at year 5 and 4306 at year 9. After adjustment for age, gender and race, the hazards of stroke incidence in all the three sites combined compared to Allegheny County were 1.75 (95% CI= 1.42, 2.14) at baseline, 2.01 (95% CI= 1.49, 2.71) at year 5, and 2.39 (95% CI= 1.54, 3.73) at year 9. Between baseline and year 9, control of hypertension, diabetes, blood lipids, smoking, atrial fibrillation and transient ischemic attack were generally similar across sites. White matter grade ≥ 3 on brain MRI was lower in Allegheny County than the other three sites in both the first (25.8%, 36.3%, $p<0.001$) and second MRI (37.8%, 44.2%, $p=0.009$). White matter grade was a strong stroke predictor irrespective of site and was responsible for one fifth to one fourth of the reduced risk in Allegheny County.

CONCLUSION: Control of stroke traditional risk factors probably played a minor role in explaining the difference in stroke hazard between CHS sites. White matter grade may be a marker of integrated exposure and control of stroke risk factors and may help in explaining geographic variations in stroke incidence.

4.2. BACKGROUND

There is strong evidence from epidemiological studies and clinical trials that control of modifiable traditional stroke risk factors specially hypertension, diabetes, blood lipids, smoking, atrial fibrillation, and carotid stenosis were associated with subsequent reduced risk of stroke.[1] Data from randomized controlled trials in older population indicated that a 10 mm Hg reduction in systolic BP was associated with a reduction in risk of stroke of approximately one third. [2] Tight control of hypertension in diabetics significantly reduces stroke incidence.[3] Angiotensin-converting-enzyme (ACE) was reported to reduce the risk of stroke in high-risk diabetic patients by one third.[4]

The double stroke risk (RR=1.8) associated with current smoking in Framingham study was shown to disappear about 5 years after cessation.[5] Several meta-analysis of large randomized trials suggests that statins reduce the incidence of stroke by about 20-25% in patients with and without coronary heart disease. [6-8] Carotid endarterectomy was repeatedly reported as a highly effective stroke preventive measure among patients with severe carotid stenosis and recent transient ischemic attack.[9, 10] Warfarin and to a less extent aspirin were reported in clinical trials to be highly effective in reducing stroke in atrial fibrillation patients.[11]

In a recent report from Oxfordshire (United Kingdom),[12] a 29% reduction in stroke incidence over the last 2 decades was associated with substantial reductions in the pre-morbid proportion of smokers, mean total cholesterol, and mean systolic and diastolic blood pressures and well as major increases in pre-morbid treatment with antiplatelet, lipid-lowering, and blood pressure lowering drugs. In a previous report from the Cardiovascular Health Study (First article), it was shown that Forsyth, Sacramento, and Washington Counties had similar stroke risk that was significantly higher than the risk in Allegheny County. In another report from the same study (Second article) , the distribution of stroke risk factors between sites at baseline explained less than one third of the difference in stroke risk between Allegheny County and the other three sites. In this report, we tested the hypothesis that control of potentially modifiable stroke risk factors (traditional and sub-clinical) across visits (baseline, year 5, and year9) was better in Allegheny County compared to the other three CHS site.

4.3. METHODS

4.3.1. Study population:

The Cardiovascular Health Study (CHS) design, including recruitment techniques, definitions of risk factors and outcomes, has been described in detail.[13, 14] CHS is a population-based, longitudinal study of coronary heart disease and stroke in adults aged 65 years and older. Participants of the CHS were recruited from a random sample of Health Care Financing Administration (HCFA) Medicare eligibility lists in four US communities: Forsyth County, 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 were receiving cancer treatment. 5888 men and women 65 years of age or older at study entry, were recruited in 2 waves. A total of 5,201 participants were recruited in 1989 to 1990 in the first wave (original cohort) and additional 687 black participants were recruited in 1992 to 1993 in the second wave (new cohort).

4.3.2. Risk factors and outcome assessments:

Baseline and thereafter annual extensive historical, physical and laboratory evaluations were performed to identify the presence and severity of the conventional cardiovascular risk factors such as hypertension, hypercholesterolemia and glucose intolerance; as well as sub-clinical disease such as carotid artery atherosclerosis and left ventricular enlargement. Ascertainment methods of stroke and other CHS endpoints, either incident or prevalent have been described.[15-17] 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.[15, 17]

Hypertension was defined as SBP ≥140, DBP ≥90, or history of hypertension plus taking antihypertensive medication.[18] Diabetes was defined according ADA guidelines [19] (fasting glucose ≥ 126 or taking insulin or oral hypoglycemics). Carotid ultrasounds were done 3 times at baseline, year 5 and year 11. Brain MRIs were done twice, once in years 4, 5 and 6 and again in years 10 and 11. White matter grade was scored with a value of 0 to 9 with 0 indicating no changes and 9 indicating most pronounced changes. Any MRI lesion with a maximum diameter of at least 3 mm was considered a large infarct. Up to five large infarcts were described for each participant. History of coronary heart disease at baseline was confirmed by a report of angioplasty or bypass surgery prior to study entry. Aspirin use was confirmed by reported using aspirin 3 or more days in past 2 weeks. Smokers were categorized as current or non-smoker including former smokers.

4.3.3. Statistical analysis:

Participants were included in the analyses at baseline (1989-90), year 5 (1992-93), year 9 (1996-97), and at the time of their brain 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 calculated 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 or the end of follow up for those who did not have a stroke.

Control of potential stroke risk factors were compared between Allegheny County and the other three sites combined for significant differences. Data was checked for normality. The t-test was used for continuous variables that were normally distributed. Mann-Whitney test was used for continuous variables that were not normally distributed. Pearson Chi square was used for categorical variables. A five percent level of significance was used for all tests. Stroke incidence hazard ratios at different visits were calculated using a Cox regression model. Hazards in all the three sites combined were compared to that in Allegheny County after adjustment for age, race, and gender. In both MRIs, the effect of white matter grade was evaluated after controlling for age, site, or both. The percentage of excess-hazard reduction in a specific model was calculated by comparing the excess hazard reduction for that model to an age adjusted model.

4.4. RESULTS

4.4.1. Demographics and stroke hazard:

The total number of participants at risk for incident stroke in the four sites was 5639 at baseline, 4513 at year 5 and 4306 at year 9. Baseline and year 9 data included both cohorts while year 5 was entirely original cohort. The mean age was 72.8 years at baseline (SD 5.6 years), 75.4 years at year 5 (SD 5.6 years), and 78.5 at year 9 (SD 5.1 years). Approximately 85% of the participants were white at baseline and year 9 and almost 60% of the participants were females at all the three visits. Allegheny County had a higher percentage of African Americans at all visits compared to the other three sites because Washington County did not recruit African American cohort (Table 9). The number of adjudicated incident stroke events with in almost 10 years of follow-up after baseline was 665 events. A total of 359 incident stroke events developed after year 5 was and 164 developed after year 9. After adjustment for age, gender and race, the hazards of stroke incidence in all the three sites combined (Forsyth, Sacramento, and Washington Counties) compared to Allegheny County were 1.75 (95% CI= 1.42, 2.14; p< 0.001) at baseline, 2.01 (95% CI= 1.49, 2.71; p< 0.001) at year 5, and 2.39 (95% CI= 1.54, 3.73; p< 0.001) at year 9 (Figure 7).

4.4.2. Blood pressure and hypertension:

In both Allegheny County and the other three sites, both systolic and diastolic blood pressure was relatively constant across visits with slight differences (Table 10). The proportion of participants who had systolic blood pressure 140 mmHg or more and/or diastolic blood pressure 90 mmHg or more were 48.2% at baseline and 46.2% at year 9 in Allegheny County, and 46.7% at baseline and 46.3% at year 9 in the other three sites. In both study populations, there was more than a 10% increase in the use of blood pressure medication across visits. Allegheny County had a significantly lower percentage of use of any blood pressure medication at baseline compared to the other three sites (65.0% and 68.7% respectively). The percents of any blood pressure medication use were similar in both Allegheny County and the other three sites in both year 5 (69.4% and 69.2% respectively) and year 9 (78.8% and 78.5% respectively).

4.4.3. Blood glucose and diabetes:

Fasting blood glucose was slightly higher in Allegheny County compared to the other three sites at baseline (112.7 and 110.2 mg/dl respectively, p=0.002) and year 9 (104.7 and 101.7 mg/dl respectively, p=0.020) (Table 11) Both study populations had 8 to 9 mg/dl decrease in fasting blood glucose level between baseline and year 9. The use of insulin and/or oral hypoglycemic was similar and increased across visits in both Allegheny County (50.2% at baseline, 58.2% at year 5 and 72.7% at year9) and the other three sites (53.5% at baseline, 62.9% at year 5 and 76.2% at year9).

4.4.4. Blood cholesterol:

There were no significant differences at baseline and year 5 between Allegheny County and the other three sites in the use of lipid lowering medication for all participants or for those who had LDL≥ 100 (Table 11). No significant differences were observed between Allegheny County and the other three sites at baseline or year 5 for those who had high LDL ≥100 (p=0.085 for baseline and p=0.405 for year 5), low HDL ≤35 mg/dl (p=0.759 for baseline and p=0.291 for year 5) and high triglycerides ≥200 mg/dl (p= 0.372 for baseline and p= 0.821 for year 5).Those who used any lipid lowering medication and had their LDL cholesterol level below 100 mg/dl were increased from 8.6% at baseline to 23.9% at year 5 in Allegheny County and from 12.2% at baseline to 21.9% at year 5 in the other three sites.

4.4.5. Smoking and alcohol drinking:

In both Allegheny County and the other three sites, current smoking rates were relatively similar and decreasing across visits (13.2% and 11.5% respectively at baseline and 8.0% and 7.9% respectively at year 9). The number of alcoholic drinks per week were consistently higher in Allegheny County compared to the other three sites at baseline (Mean± SD 2.8±6.7 and 2.4±6.3 respectively, p<0.001), year 5 (Mean± SD 2.3±5.3 and 1.9±4.9 respectively, p<0.001), and year 9(Mean± SD 2.2±5.3 and 1.7±5.2 respectively, p<0.001) (Table 12).

4.4.6. Medical history:

History of coronary heart disease and atrial fibrillation were relatively similar in Allegheny County and the other three sites at baseline (p=0.720 and p=0.191 respectively), year 5(p=0.439 and p=0.469 respectively), and year 9 (p=0.062 and p=0.804 respectively). History of transient ischemic attacks was lower in Allegheny County than the other three sites at year 5 (1.1% and 2.4%, p=0.008) and year 9 (2.7% and 3.8%, p=0.093) (Table 12).

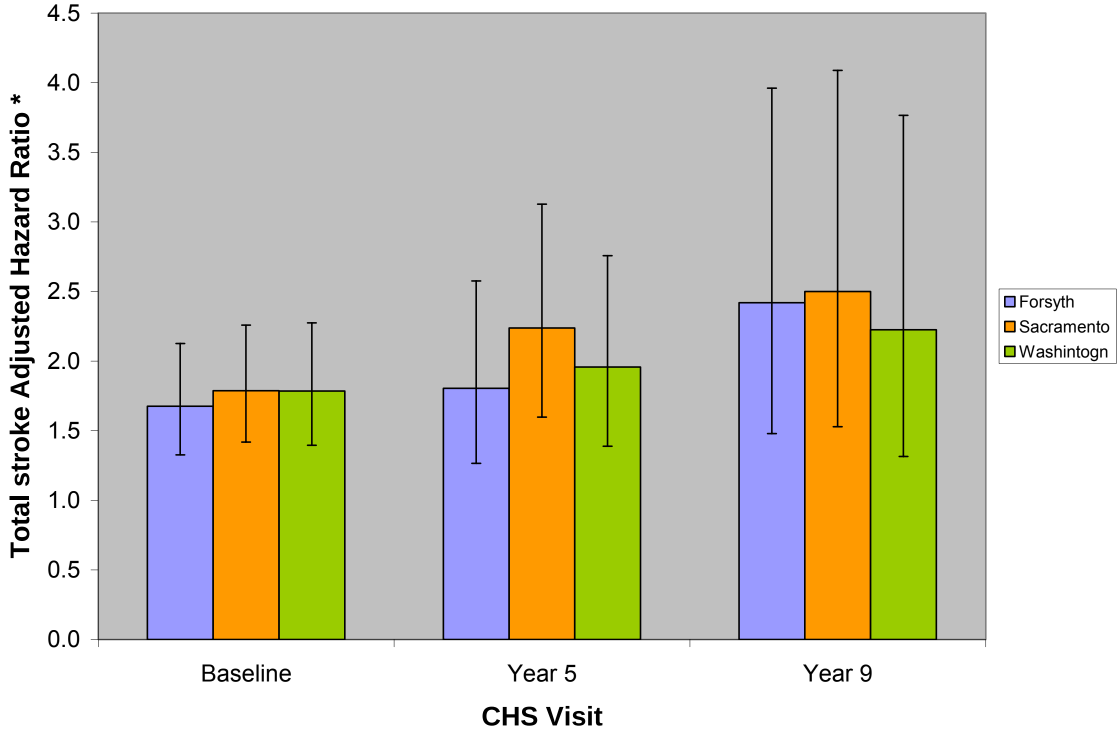
4.4.7. Carotid stenosis:

In all the three visits, common and internal carotid wall thickness were generally similar in both study populations. Those who had carotid stenosis ≥ 25% were lower in Allegheny County than the other three sites at baseline (43.2%, 48.2%, p=0.001) and year 5 (42.0%, 47.7%, p=0.003) but similar at year 9 (29.2%, 28.2%, p=0.638). Those who had carotid stenosis ≥ 50% were not significantly different between Allegheny County and the other three sites at any visit (Table 12).

4.4.8. Brain MRI findings:

White matter grade ≥ 3 was lower in Allegheny County than the other three sites in both the first (25.8%, 36.3%, p<0.001) and second MRI (37.8%, 44.2%, p=0.009) (Table 12). After controlling for center and age, white matter grade was a strong stroke predictor in both the first

(2.61, 95%CI 2.06, 3.31; p<0.001) and second MRI (2.97, 95%CI 1.65, 5.35; p<0.001). After controlling for white matter grade and age, the excess stroke hazard in the other three sites compared to Allegheny County was reduced in both the first (25.2%; p<0.001) (Figure 8) and second MRI (20.1%, p=0.243). Those who had one or more large infarct by MRI was more in Allegheny County compared to the other three sites at the first (32.2%, 27.1% respectively, p= 0.004) but not the second MRI (27.2%, 30.8% respectively, p=0.113) (Table 12).



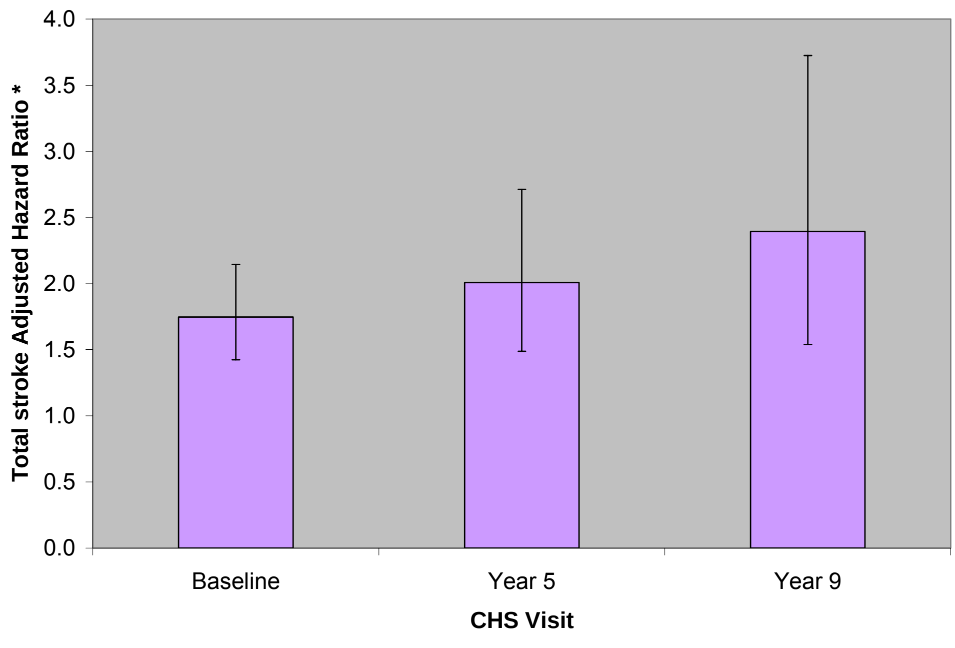


Figure 7: Total stroke adjusted* hazard ratio at different CHS visits in the three CHS sites separately (above) and combined (below) compared to Allegheny County

* Adjusted for age, gender and race

Table 9: Demographic characteristics of CHS participants at baseline, year 5, and year 9 by site

	Baseline (1989-90 for original cohort) (1992-93 for new cohort)			Year 5 (1992-93)			Year 9 (1996-97)		
	Other three sites	**Allegheny County, PA**	**Total**	**Other three sites**	**Allegheny County, PA**	**Total**	**Other three sites**	**Allegheny County, PA**	**Total**
At stroke risk total	**4210** 100.0%	**1429** 100.0%	**5639** 100.0%	**3486** 100.0%	**1027** 100.0%	**4513** 100.0%	**3167** 100.0%	**1139** 100.0%	**4306** 100.0%
Age in years (Mean±SD)	**72.8** ±5.7	**72.8** ±5.3	**72.8** ±5.6	**75.4** ±5.4	**75.5** ±5.4	**75.4** ±5.4	**78.6** ±5.0	**78.2** ±5.1	**78.5** **±5.1**
Males	**1734** 41.2%	**618** 43.2%	**2352** 41.7%	**1378** 39.5%	**440** 42.8%	**1818** 40.3%	**1289** 40.7%	**490** 43.0%	**1779** 41.3%
Females	**2476** 58.8%	**811** 56.8%	**3287** 58.3%	**2108** 60.5%	**587** 57.2%	**2695** 59.7%	**1878** 59.3%	**649** 57.0%	**2527** 58.7%
Whites	**3620** 86.6%	**1123** 79.0%	**4743** 84.7%	**3333** 96.4%	**942** 92.3%	**4275** 95.4%	**2709** 86.1%	**897** 79.2%	**3606** 84.3%
Blacks	**561** 13.4%	**299** 21.0%	**860** 15.3%	**126** 3.6%	**79** 7.7%	**205** 4.6%	**437** 13.9%	**236** 20.8%	**673** 15.7%

Table 10: Hypertension control in CHS participants at baseline, year 5, and year 9 by site

	Baseline (1989-90 for original cohort) (1992-93 for new cohort)			Year 5 (1992-93)			Year 9 (1996-97)		
	Other three sites	**Allegheny County, PA**	**P-value**	**Other three sites**	**Allegheny County, PA**	**P-value**	**Other three sites**	**Allegheny County, PA**	**P-value**
Systolic BP (M±SD mm Hg)	**136.4** ±21.7	**136.3** ±21.8	0.903	**136.1** ±21.2	**134.1** ±21.6	0.018	**136.9** ±20.7	**136.9** ±20.5	0.997
Diastolic BP (M±SD mm Hg)	**70.4** ±11.6	**71.6** ±10.5	<.001	**70.9** ±11.3	**69.7** ±11.3	0.008	**69.6** ±11.3	**70.2** ±11.2	0.164
Hypertension	**2470** 58.8%	**799** 56.0%	0.070	**1626** 55.4%	**483** 54.6%	0.651	**1602** 64.0%	**580** 65.0%	0.576
History of hypertension & its medication	**1599** 38.0%	**485** 34.0%	0.006	**997** 33.1%	**298** 32.5%	0.723	**1166** 42.7%	**427** 44.8%	0.257
BP ≥140/90	**1694** 40.3%	**592** 41.5%	0.455	**1144** 39.5%	**325** 37.4%	0.271	**971** 40.8%	**357** 41.6%	0.666
BP < 140/90 with medication	**1048** 53.3%	**335** 51.8%	0.514	**774** 54.6%	**244** 58.0%	0.227	**727** 53.7%	**273** 53.8%	0.965
BP ≥140/90 with medication	**920** 46.7%	**312** 48.2%		**643** 45.4%	**177** 42.0%		**626** 46.3%	**234** 46.2%	
hypertension & any hypertension medication	**1696** 68.7%	**519** 65.0%	0.048	**1125** 69.2%	**335** 69.4%	0.943	**1257** 78.5%	**457** 78.8%	0.888
hypertension & diuretics	**1112** 45.1%	**289** 36.2%	<.001	**616** 37.9%	**166** 34.4%	0.160	**680** 42.5%	**233** 40.2%	0.336
hypertension & beta blockers	**434** 17.6%	**147** 18.4%	0.601	**272** 16.7%	**72** 14.9%	0.341	**351** 21.9%	**97** 16.7%	0.008
hypertension & vasodilators	**336** 13.6%	**79** 9.9%	0.006	**161** 9.9%	**65** 13.5%	0.027	**191** 11.9%	**53** 9.1%	0.068
hypertension & ACE inhibitors	**298** 12.1%	**109** 13.6%	0.244	**262** 16.1%	**99** 20.5%	0.025	**357** 22.3%	**156** 26.9%	0.025

Table 11: Diabetes and blood lipids control in CHS participants at baseline, year 5, and year 9 by site

	Baseline (1989-90 for original cohort) (1992-93 for new cohort)			**Year 5** (1992-93)			**Year 9** (1996-97)		
	Other three sites	**Allegheny County, PA**	**P-value**	**Other three sites**	**Allegheny County, PA**	**P-value**	**Other three sites**	**Allegheny County, PA**	**P-value**
Fasting glucose (Mean ±SD mg/dl)	**110.2** ±36.1	**112.7** ±37.6	0.002 MWT	**106.7** ±31.8	**107.7** ±32.8	0.643 MWT	**101.7** ±29.4	**104.7** ±37.1	0.020 MWT
2-hour glucose (Mean ±SD mg/dl)	**148.1** ±57.3	**142.9** ±60.5	<.001 MWT	N/A	N/A	N/A	**139.7** ±52.0	**139.7** ±51.8	0.823 MWT
Diabetes	**650** 15.6%	**237** 16.6%	0.074	**411** 14.9%	**134** 16.0%	0.247	**378** 16.5%	**132** 16.0%	0.928
Fasting glucose ≥126 mg/dl	**575** 13.9%	**213** 15.0%	0.107	**328** 12.0%	**114** 13.7%	0.187	**262** 11.7%	**95** 11.8%	0.961
History of diabetes & its medication	**335** 8.0%	**119** 8.3%	0.657	**238** 7.8%	**74** 8.0%	0.890	**273** 9.8%	**91** 9.3%	0.608
Any diabetic medication In diabetics	**347** 53.5%	**119** 50.2%	0.390	**258** 62.9%	**78** 58.2%	0.329	**288** 76.2%	**96** 72.7%	0.427
Insulin intake In diabetics	**97** 14.9%	**28** 11.8%	0.236	**65** 15.9%	**22** 16.4%	0.877	**87** 23.0%	**28** 21.2%	0.669
Any oral Hypoglycemic In diabetics	**259** 39.9%	**92** 38.8%	0.769	**200** 48.8%	**59** 44.0%	0.339	**217** 57.4%	**72** 54.5%	0.568
BP≥130/80 in diabetes	**451** 69.4%	**158** 66.7%	0.440	**259** 64.8%	**84** 64.1%	0.896	**223** 64.3%	**78** 63.9%	0.948
Fasting glucose <126 mg/dl with med	**61** 18.3%	**23** 19.5%	0.778	**55** 23.9%	**13** 18.3%	0.324	**64** 27.1%	**20** 25.3%	0.754
Fasting glucose ≥126 mg/dl with med	**272** 81.7%	**95** 80.5%		**175** 76.1%	**58** 81.7%		**172** 72.9%	**59** 74.7%	
High LDL (≥ 100 mg/dl)	**3420** 83.0%	**656** 85.5%	0.085	**2000** 72.0%	**589** 70.5%	0.405	N/A	N/A	N/A
Low HDL (≤35 mg/dl)	**272** 6.5%	**90** 6.3%	0.759	**218** 7.9%	**75** 9.0%	0.291	N/A	N/A	N/A
High triglycerides (≥200 mg/dl)	**606** 14.6%	**194** 13.6%	0.372	**535** 19.3%	**158** 18.9%	0.821	N/A	N/A	N/A
Any lipid lowering medication	**235** 5.6%	**68** 4.8%	0.231	**214** 7.1%	**72** 7.8%	0.465	N/A	N/A	N/A
Any lipid lowering medication in LDL ≥ 100	**201** 5.9%	**32** 4.9%	0.310	**157** 7.9%	**51** 8.7%	0.526	N/A	N/A	N/A
LDL <100 mg/dl with medication	**28** 12.2%	**3** 8.6%	0.532	**44** 21.9%	**16** 23.9%	0.735	N/A	N/A	N/A
LDL ≥ 100 mg/dl with medication	**201** 87.8%	**32** 91.4%		**157** 78.1%	**51** 76.1%				

Table 12: Control of other potential stroke risk factors in CHS participants at baseline, year 5, and year 9 by site

	Baseline (1989-90 for original cohort) (1992-93 for new cohort)			Year 5 (1992-93)			Year 9 (1996-97)		
	Other three sites	**Allegheny County, PA**	**P-value**	**Other three sites**	**Allegheny County, PA**	**P-value**	**Other three sites**	**Allegheny County, PA**	**P-value**
Current smoking	**482** 11.5%	**189** 13.2%	0.074	**277** 9.4%	**79** 8.9%	0.650	**212** 7.9%	**72** 8.0%	0.900
Alcoholic drinks per week (Mean±SD)	**2.4** ±6.3	**2.8** ±6.7	<.001 MWT	**1.9** ±4.9	**2.3** ±5.3	<.001 MWT	**1.7** ±5.2	**2.2** ±5.3	<.001 MWT
7-8 alcohol drinks per week (> 90th percentile)	**405** 9.7%	**159** 11.2%	0.103	**277** 9.2%	**102** 11.1%	0.087	**239** 8.8%	**109** 11.9%	0.005
History of coronary heart disease	**795** 18.9%	**276** 19.3%	0.720	**768** 22.0%	**238** 23.2%	0.439	**803** 25.4%	**321** 28.2%	0.062
History of Atrial fibrillation	**107** 2.8%	**26** 2.1%	0.191	**85** 2.8%	**22** 2.4%	0.469	**93** 3.9%	**31** 3.7%	0.804
History of transient ischemic attacks	**74** 1.8%	**26** 1.8%	0.879	**85** 2.4%	**11** 1.1%	0.008	**120** 3.8%	**31** 2.7%	0.093
Use of aspirin	**1385** 32.9%	**478** 33.4%	0.772	**1122** 37.3%	**345** 37.4%	0.195	**1056** 88.1%	**339** 84.8%	0.077
Use of oral anticoagulants	**49** 1.2%	**18** 1.3%	0.775	**84** 2.8%	**27** 2.9%	0818	**114** 4.2%	**46** 4.7%	0.510
Coronary angioplasty or angiography	**59** 1.4%	**33** 2.3%	0.019	**77** 2.5%	**22** 2.4%	0.766	**40** 1.5%	**15** 1.6%	0.727
common carotid wall thickness (M±SD mm)	**1.06** ±0.22	**1.06** ±0.21	0.729 MWT	**1.07** ±0.22	**1.07** ±0.24	0.721 MWT	**1.08** ±0.26	**1.10** ±0.27	0.142 MWT
Internal carotid wall thickness (M±SD mm)	**1.44** ±0.57	**1.42** ±0.55	0.239 MWT	**1.42** ±0.54	**1.42** ±0.59	0.181 MWT	**1.71** ±0.78	**1.67** ±0.83	0.092 MWT
Carotid stenosis (≥25%)	**2013** 48.2%	**617** 43.2%	0.001	**1408** 47.7%	**385** 42.0%	0.003	**506** 28.2%	**186** 29.2%	0.638
Low Ankle-Arm Index (≤0.9)	**491** 12.0%	**205** 14.6%	0.010	**329** 12.0%	**106** 12.5%	0.664	**325** 18.3%	**145** 21.7%	0.057
LV hypertrophy by ECG	**188** 4.6%	**71** 5.4%	0.247	**123** 4.4%	**37** 4.4%	0.979	**136** 5.8%	**49** 5.9%	0.960
White matter grade 3 or more	N/A	N/A	N/A	**925** 36.3%	**226** 25.8%	<.001	**718** 44.2%	**204** 37.8%	0.009
One or more large infarct	N/A	N/A	N/A	**697** 27.1%	**284** 32.2%	0.004	**500** 30.8%	**147** 27.2%	0.113
Two or more large infarct	N/A	N/A	N/A	**263** 10.2%	**104** 11.8%	0.196	**191** 11.8%	**54** 10.0%	0.260

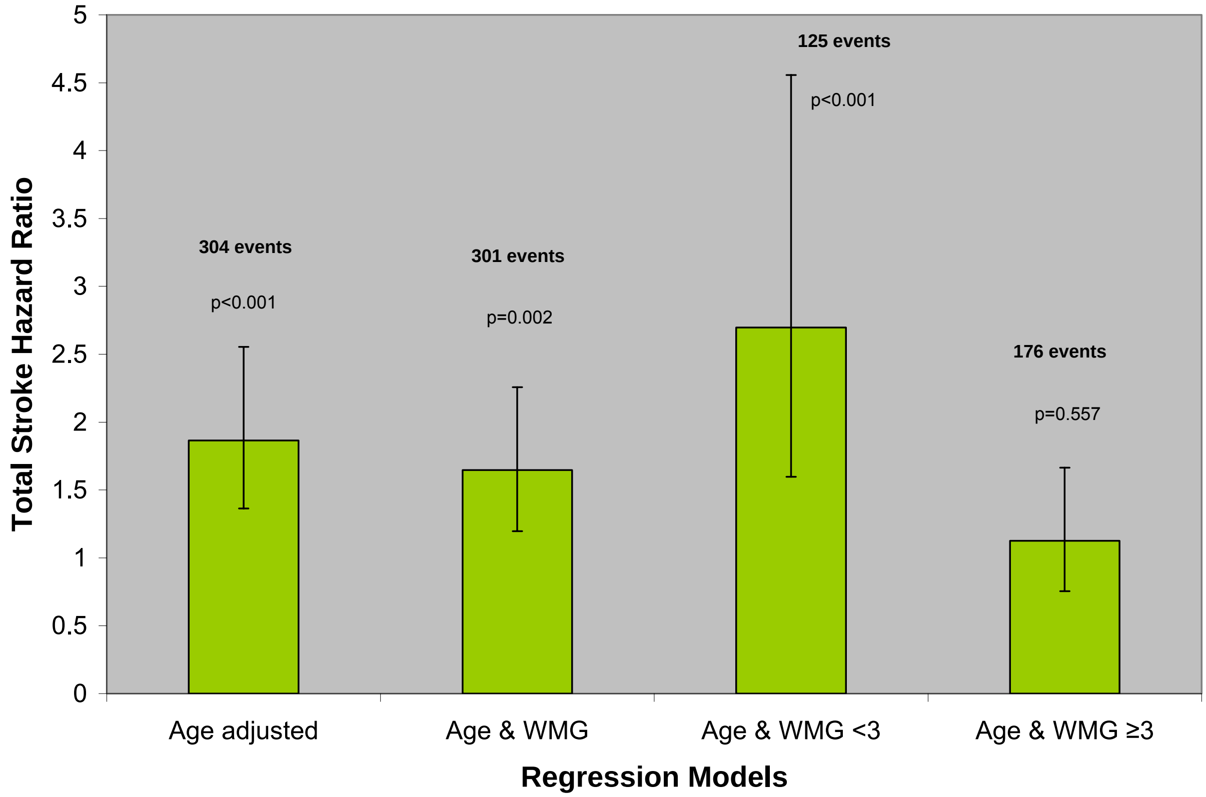


Figure 8: Total stroke hazard ratio at first MRI in the three CHS sites combined compared to Allegheny County

4.5. DISCUSSION

4.5.1. Blood pressure and hypertension:

Several clinical trials suggested a dose-response relationship between blood pressure lowering and reduction of stroke risk. In these trials, regardless the agent used, 30% to 40% reduction in stroke risk was reported [2] The current data showed that both Allegheny County and the other three sites had a relatively constant blood pressure between baseline and year 9 which could be considered as having experienced a relative improvement given the increasing age of the cohort. In meta-analyses of randomized trials, the efficacy of blood pressure medications in reducing stroke risk was dependent on the type and dosage of medication.[20, 21] The data showed reduction in stroke risk by 51% with high dose diuretics,[21] 30% with ACE inhibitors [20]and 29% with beta blockers.[21] By year 9, Allegheny County had a higher use of ACE inhibitors, lower use of beta blockers, and a similar use of diuretics compared to the other three sites.

4.5.2. Blood glucose and diabetes:

In both Allegheny County and the other three sites, a 20% increase in the rate of diabetes medication accompanied by improved glycemic control was shown between baseline and year 9. Although tight glycemic control is recommended to prevent microvascular disease, previous studies failed to demonstrate the benefit of tight glycemic control in stroke risk reduction.[1] In addition, previous studies showed the tight control of hypertension (less than 130/80) in diabetics significantly reduces stroke incidence.[3, 22] Blood pressure less than 130/80 was slightly improved in both study populations between baseline and year 9 without significant differences between study populations.

4.5.3. LDL cholesterol:

Although many clinical trials showed reduced stroke risk after lowering LDL levels,[23] the current data did show any better LDL control in Allegheny County compared to other three sites. The improved LDL control (LDL <100 mg/dl with medication) in both Allegheny County and the other three sites between baseline (8.6% and 12.2% respectively, p=0.532) and year 5 (23.9% and 21.9% respectively, p=0.735) could be explained by the higher percentage of people who use any lipid lowering medication at year 5 compared to baseline.

4.5.4. Alcohol drinking and cigarette smoking:

Results from observational studies indicated that heavy alcohol consumption increases the relative risk for both ischemic and hemorrhagic stroke while light or moderate alcohol consumption may be protective for ischemic stroke. [24, 25]Allegheny County had significantly higher number of alcohol drinks per week, however, the stroke risk due to alcohol drinking should not be considered higher in Allegheny County because in both study populations the amount of alcohol consumed was relatively small (1.7-2.8 drinks per week). Current cigarette smoking has been long recognized as a major risk factor for stroke with almost doubling of relative risk and disappearance of the risk about 5 years after cessation. [5, 26] In the current data, by year 9, Allegheny County had similar smoking rates compared to the other three sites indicating comparable smoking cessation rates.

4.5.5. Carotid stenosis:

Severe symptomatic carotid artery stenosis is responsible for approximately 20 to 30% of ischemic strokes and almost 3 times more than asymptomatic one.[9, 27] Carotid stenosis ≥ 25% was lower while carotid stenosis ≥ 50% was similar in Allegheny County compared to the other three sites at baseline and year 5. Little differences in stroke risk between sites based on carotid stenosis could be expected because symptomatic (with TIA) carotid stenosis ($\geq$ 25% or $\geq$ 50%), a more important stroke risk factor than the asymptomatic stenosis, was not significantly different between study populations at any visits. Large randomized controlled trials have documented that carotid endarterectomy is a highly effective stroke preventive measure among patients with severe carotid stenosis and recent transient ischemic attack. [9, 10] Because carotid endarterectomy was not different between study populations at baseline and data were not available at other visits, we could not verify the differences between study populations in surgical control of carotid stenosis.

4.5.6. History of transient ischemic attack and atrial fibrillation:

In clinical trials, warfarin was highly effective in reducing stroke risk in atrial fibrillation patients while Aspirin, to a less extent, reduced the stroke risk in both transient ischemic attack and atrial fibrillation. [11] The current data did not show any better control of either transient ischemic attack or atrial fibrillation (oral anti-coagulant or aspirin use) in Allegheny County compared to the other three sites. Moreover, atrial fibrillation prevalence was similar in both study populations at all visits. The lower prevalence of transient ischemic attack in Allegehny County at year 5 ($p=0.008$) and year 9 ($p=0.093$) may be explained by the lower prevalence of carotid stenosis (>25%) at baseline and year 5.

4.5.7. Brain MRI white matter grade (WMG):

Several recent reports from prospective studies indicated that higher grade of white matter lesion is a strong predictor of stroke specially lacunar infarction and the risk is independent of traditional risk factors.[28-30] In this report, likewise white matter grade was a strong stroke predictor irrespective of sites. Moreover, the excess hazard in the other three sites compared to Allegheny County was reduced in both the first and second brain MRI explaining almost one fifth to one fourth of the lower risk of stroke in Allegheny County which had significantly lower prevalence of white matter grade ≥ 3 in both MRIs. White matter grade was shown to be strongly related to age [31] which might explain the higher prevalence of those who had white matter grade ≥ 3 in the second MRI irrespective of sites. White matter grade may be a marker of integrated exposure and control of stroke risk factors and may help in explaining geographic variations in stroke incidence. As Allegheny County had a similar stroke history and lower white matter grade at baseline, the current results suggested the importance of white matter lesion to point any future increase or reduction of stroke risk in a given community, probably many years before it happen. The current findings suggested white matter grade progression could be used a marker of the efficacy of the various pharmacologic and non-pharmacologic therapies of stroke on the individual level and as a marker of the efficacy of different stroke prevention strategies on a community level.

4.5.8. Conclusion:

The current report showed some degree of improvement of control of traditional stroke risk factors specially LDL cholesterol, diabetes, smoking, and hypertension between baseline and year 9. However, the improvements were not significantly different between Allegheny County and the other three sites suggesting that these factors did not play a major role in explaining the observed difference in stroke hazard between study populations. The prevalence of coronary heart disease, atrial fibrillation and transient ischemic attack were increased in both study populations across visits with out significant differences with the exception of transient ischemic attack that was significantly lower in Allegheny County at year 5. The use of aspirin and oral anti-coagulants were markedly increased in both study populations across visits with out significant differences. White matter grade which was a strong predictor of stroke irrespective of sites and was lower in Allegheny County in both MRIs may be a marker of integrated exposure and control of stroke risk factors and may help in explaining geographic variations in stroke incidence.

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5. GENERAL DISCUSSION

5.1. Studying stroke incidence in CHS population:

CHS was an ideal study to examine geographic variations in stroke incidence and/or mortality for a number of reasons; CHS was the first study to allow comparisons of stroke incidence and/or mortality in older people (65 years and more) in four United States communities on the same time using a standardized methodology, the stroke incidence reported before in ARIC study's four centers was for younger people (less than 65 years).[1] As stroke is very dependent on age with doubling of stroke incidence for each decade after the age of 55, the older age of the CHS population allowed more events to happen on the study period as well as shedding the light on that stroke high risk group. Another reason to catch more stroke events in the CHS population (665 incident stroke events) was the long follow-up period (10 years in the original cohort and 7 years in the new cohort). The recruitment of additional African American (new) cohort after the beginning of the study allowed racial comparisons of stroke incidence. Unlike most previous stroke incidence studies in United States, CHS had a prospective cohort design that allowed detecting incident stroke events as they happened "what is called hot pursuit". One of the disadvantages of comparing stroke incidence rates obtained from different studies was the different case ascertainment methodology. Also comparing rates from different studies that were obtained at different points of time should be done with caution. CHS sites used the same case ascertainment methodology on the same time. One advantage of this study was the use of validated events rather than reliance on the less accurate discharge diagnosis coding or death certificate.[2, 3] Provisional diagnoses of stroke were assigned by the field center principal investigator, and then reviewed and adjudicated at periodic meetings of the cerebrovascular disease endpoint committee. In addition, collecting and validating information on previous history of stroke allowed calculating rates in only stroke-free participants; this was very difficult or even impossible to achieve in previous registry-based studies. MRI use was noticeably higher in this study (62%) than the other recent studies like the Greater Cincinnati (22%) or ARIC (27%) studies allowing more accurate classification of stroke types and sub-types. Collecting information about a large number of cardiovascular risk factors (at baseline and annually) like hypertension, diabetes, smoking, sub-clinical disease, medication use….etc allowed studying the role these factors played in site-differences in stroke risk. CHS data had some limitations in studying stroke incidence, the old age of participants at baseline resulted in a large number of participants died (28.7%) during the follow-up period. Although the percentage of African Americans (15%) was a little bit higher than the national average (13%), it was difficult to bi-racially compare the rates by age group and gender due to small number of events, one of the sites (Washington County) could not recruit African Americans cohort, also absence of information about the Hispanic origin did not allow more racial comparisons. The complexity of CHS data with thousands of variables and many data files grouped by year, cohort, event type (incident versus prevalent), and diagnostic procedures (like MRI and ultra-sound files) required a lot of extra caution by any researcher to handle these data.

5.2. Overall total stroke Incidence:

Comparing stroke incidence rates reported in different studies is not without risk because of definition criteria, methodology of case ascertainment, population, age range, and time period covered. The overall total (all stroke types) stroke incidence reported in this report was substantial at 17.7 per 1000 person years and many-fold higher than that reported in other population based studies estimating stroke incidence in the United States [1, 4-12] and worldwide [13-15] because of the older age of CHS population. The overall annual stroke incidence rates in United States studies [1, 4-12] per 100,000 populations, approximately ranged between 93 and 293. In all these studies, the populations used were either all age groups, adults 35 years and over, or the older population excluded. This may resulted in dilution of the rates by including (into the denominator) the younger population who had a very low stroke risk. In ARIC study [1] which used a similar design to CHS study in people aged 45 to 64 years in 4 US communities, the age-adjusted total stroke incidence rates per 1000 person-years were 4.45 for blacks and 1.72 for whites. The current CHS rates per 1000 person-years were 18.2 for blacks and 17.3 for whites.

When age-specific rates for older people were compared between this study and other stroke incidence population studies in United States, CHS rates were generally higher. [4-6, 9, 11] The more through case ascertainment and validation of the CHS population using different overlapping techniques probably yielded more stroke cases than might be discovered using the registry-based methodology applied in these studies. In the Lehigh Valley, a region in Pennsylvania and New Jersey, in 1982-1983,[11] the age specific stroke incidence per 100,000 populations were estimated to be 652 for those 65-74 years, 1408 for those 75-84 years and 2243 for those 85 years and more. These rates compare with CHS rates of 1060, 2200, and 3270 in these age groups respectively. In Northern Manhattan, New York City, between 1993 and 1996,[5] the average annual stroke incidence rates per 100,000 for those 65-74 years were 650 for males and 468 for females, those 75-84 years were 688 for males and 629 for females, and those 85 years and more were 857 for males and 931 for females.

The rates in CHS were comparable to those reported in many westernized countries. For example, comparing the current stroke incidence rates in those aged 85 years or older (32.7 per 1000 person-years) to other studies showed that the annual stroke incidence per 1000 population were either higher than in France (18.2)[16], The United Kingdom (18.9)[17], and Germany (21.2)[18], similar to Greece (26.6)[19], Italy(28.8)[20] and Norway(30.4)[21], and lower than in Japan (38.5 in females and 49.2 in males).[22]

Our age standardized results showed a non-significant slightly higher incidence rate per 1000 person-years for blacks than whites (18.2 and 17.3 respectively). Although racial differences in stroke incidence and mortality with more blacks affected than whites was well documented in United States,[1, 5, 9, 10, 23-25] it was also reported that older age groups have a smaller racial difference in stroke incidence as compared to younger population.[1, 5, 9, 24, 26] Broderick and colleagues [9] reported that blacks under age 65 in Greater Cincinnati had a two to four times greater stroke incidence rate compared to whites of similar age in the Rochester, Minnesota. Above 65 years, however, the differences disappeared and the age-specific stroke incidence rates were similar for elderly blacks and whites. Absence of racial difference in stroke risk in people 65 years or older was also documented in a nationally representative data.[26]

The crude incidence rates we observed were slightly higher in males than females (14.8 and 13.7). After age standardization, females had slightly higher rates than males (18.1 and 16.4). None of these differences in incidence were statistically significant. Older populations may have less gender differences in stroke incidence. The data reported for age specific stroke incidence rates in males and females in the Northern Manhattan Stroke Study [5] showed that male/female risk decrease steadily from 2.5 times in those aged 45-54 years until it reversed in those aged 85 years or older, when females had slightly higher stroke incidence than males. Similar observations were noted in Rochester, Minnesota [6] and the French West Indies. [16]

5.3. Site specific total stroke incidence:

Our results showed significantly lower stroke incidence rates in Allegheny County field center than the other three study sites in Forsyth County, Sacramento County, and Washington County. The lower stroke incidence rate in Allegheny County was consistent over time and began as early as the fourth year of follow up. The lower stroke incidence rate in Allegheny County was consistent by cohort, gender, race, and age groups. Differences between Allegheny County and the other three sites were statistically significant for the original cohort, females, whites, and those aged 65-74 and 75-84. Lack of statistical significance for differences in rates for the Allegheny County new cohort, blacks and those aged 85 years or older, can be explained by the small total number of events in these three groups (60, 89, and 38 respectively).

In ARIC study [1] which used a similar design to CHS in people aged 45 to 64 years in 4 US communities, there were noticeably higher rates for stroke incidence per 1000 person-years in the Jackson, Mississippi site (4.47) than the other 3 sites (Forsyth County, NC; (1.72) Washington County, MD; (1.92) and Minneapolis, MN (1.80)). This may be explained by the fact that all participants at the Jackson site were blacks and blacks in this study had higher rates than whites (4.45 and 1.72 respectively). In the current study, however, the racial differences between sites did not account for site-differences in stroke rates for two reasons; blacks did not have a significantly higher stroke incidence than whites, and also Washington County, the site with a significantly lower percentage of blacks percentage, had significantly higher rates than Allegheny County and similar rates to Forsyth County and Sacramento County.

The lower stroke incidence in Allegheny County, both incidence rates and cumulative incidence, may be due to lower prevalence of stroke risk factors in Allegheny County at baseline, better control of these factors at baseline and over the years, or both together. These two hypothesis will be discussed in the next articles. The degree of urbanization has been linked with stroke risk, with higher rates in non-metropolitan areas.[27-29] Allegheny County was entirely urban while the other sites were mixed urban/rural communities.

5.4. Type-specific stroke incidence:

The significantly lower incidence rates in Allegheny County for total strokes were replicated for ischemic strokes but not hemorrhagic strokes. This was not surprising giving the fact that 85% of incident strokes were ischemic (566 events) and only 10% were hemorrhagic (65 events). The frequency of ischemic strokes in the CHS population (85%) was either similar to other US studies (84%)[1, 9] or slightly higher (77%). [5] The hemorrhagic strokes were less frequent in the CHS population (10%) than other American populations of younger age (14.5% and 23%).[1, 5, 9]. MRI use was noticeably higher in this study (62%) than the other recent studies like the Greater Cincinnati (22%) or ARIC (27%) studies. One advantage of this study was the use of validated events rather than reliance mainly on the less accurate discharge diagnosis coding or death certificate.[2, 3] For example, in Framingham study, analysis of death certificate validity disclosed marked over-reporting of cerebral hemorrhage and under-reporting of cerebral embolus.[3]

5.5. Stroke mortality and case fatality:

The overall one month case fatality rates reported for all CHS participants were comparable to other US studies (10% -15%) [4, 5] but lower than that reported in Europe, Russia, and Japan (17% to 33%) [15-22, 30-32] probably due to better health care. The stroke mortality rate per 1000 person-years was also lower in Allegheny County (1.55) than the other three sites (2.79, 2.67, 3.07).

However, the differences were not significant probably due to the small number of fatal strokes (84 events). The same observation was obtained after plotting the cumulative total stroke mortality rates over time, adjusted for age, gender, race, and cohort. The lower mortality rate in Allegheny County than the other three sites might be explained by the lower incidence and similar case fatality and proportional frequencies of incident stroke types in Allegheny County compared to the other three sites. Though much higher due to older population, the current study findings were consistent with national data (1999) that showed lower age-adjusted stroke mortality rates per 100,000 American of all ages in Pennsylvania (58.0) compared to North Carolina (78.1), California (63.3), and Maryland (63.1).[33] The similar one month case fatality across sites might be due to similar stroke management or stroke severity across sites, for example, there were no significant differences between sites for total mortality or incident CHD also those who had incident CHD before stroke were similar across sites. In addition, longer time period (for example one year case fatality) might be needed to delineate between sites differences in case fatality.

5.6. Prevalence of potential risk factors at baseline:

The current report was unique in examining multiple possible stroke risk factors, collected using standardized methodology, in four geographically separated US communities, with the aim to explain geographic variations in stroke incidence. Allegheny County, which had the lowest stroke hazard among the four sites, had relatively similar risk factors distributions to the other three sites.

Allegheny County showed lower prevalence of a number of traditional cardiovascular risk factors and markers of sub-clinical cardiovascular disease than the other sties, partially explaining the geographic discrepancy in stroke incidence. For example, in Allegheny County, higher prevalence of better education and alcohol consumption, and lower prevalence of family history of stroke, hypertension among white participants, carotid stenosis (≥25%), higher white matter grades (≥3), and elevated triglycerides (≥ 200 mg/dl) among diabetic participants; were among the differences of possible stroke risk factors that support the low stroke hazard in Allegheny County compared to the other three sites.

On the other hand, higher proportion of abnormal Ankle-Arm blood pressure Index (≤0.9), lower use of any hypertension medications among hypertensives and lower percentage of people having supplemental insurance were among the possible risk factors profile in Allegheny County that did not support the low stroke hazard compared to the other three sites.

Hypertension prevalence, the most frequently reported single risk factor associated with high stroke incidence/mortality geographic areas both in United States [27, 34] and worldwide [35-39], was generally lower in Allegheny County than the other three sites, though the trend was significant only among white participants. However, better response to hypertension medications in Allegheny County could not be shown in this report as was expected from the stroke belt experience.[40] Despite a strong link with cardiovascular disease, diabetes prevalence did not vary directly with stroke risk – similar to most previous reports. [27, 37, 41] Better education (12 years or more or collage education) were more prevalent in Allegheny County. Similarly, an inverse relationship between education and stroke incidence or mortality was shown in most of the reports from the industrialized countries.[41-43]

5.7. Multiple risk factors at baseline and site-differences in stroke risk:

The current findings indicated that traditional stroke risk factors can explain to certain extent the site differences in stroke risk. A 30% reduction in stroke risk was obtained after adjustment for age, hypertension, diabetes, education, BMI, LDL cholesterol and previous CHD, TIA and atrial fibrillation. Similarly, most previous reports show that geographic differences in stroke incidence and/or mortality, at most, can be partially explained by the differences in stroke risk factors. Data from the First National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study (1971-1987) [27] showed that baseline risk factors, that including age, sex, race, smoking status, history of diabetes, history of heart disease, education, systolic blood pressure, alcohol use, and physical activity, played a very minor role in the estimated excess stroke risk in the Southeast. In England,[44] the hazard ratio for stroke in the rest of Britain compared with southern England was 1.44 (95% confidence interval =1.16 to 1.78), After adjustment for baseline systolic blood pressure, smoking status, physical activity, social class, and height, the hazard ratio decreased moderately, but was still significant (1.24, 95% CI, 1.00 to 1.54). In different MONICA populations,[36] smoking and elevated blood pressure explained 21% of the variation in stroke incidence among men and 42% in women. In Sweden,[39] cardiovascular score (hypertension, diabetes, smoking, and being overweigh) and socioeconomic status together accounted for 44% of the geographic variation of stroke incidence among men and 63% among women..

5.8. Medication use and sub-clinical disease at baseline:

Inclusion of medication usage and sub-clinical cardiovascular disease was an important innovation in the current study. Medication usage and sub-clinical cardiovascular disease at baseline in this report had very little to do with site differences in stroke risk. The rate for any sub-clinical disease at baseline was similar across sites. With few exceptions, the rates for medication use at baseline were generally similar across sites. However, risk factors investigated in this report and their treatment were limited to baseline data and did not take in consideration the changes over time in controlling conditions like hypertension, diabetes, and high blood lipids.

5.9. Blood pressure and hypertension control across visits:

Several clinical trials suggested a dose-response relationship between blood pressure lowering and reduction of stroke risk. In these trials, regardless the agent used, 30% to 40% reduction in stroke risk was reported [45] The current data showed that both Allegheny County and the other three sites had a relatively constant blood pressure between baseline and year 9 which could be considered as having experienced a relative improvement given the increasing age of the cohort. In meta-analyses of randomized trials, the efficacy of blood pressure medications in reducing stroke risk was dependent on the type and dosage of medication.[46, 47] They showed reduction in stroke risk by 51% with high dose diuretics,[47] 30% with ACE inhibitors [46]and 29% with beta blockers.[47] By year 9, Allegheny County had a higher use of ACE inhibitors, lower use of beta blockers, and a similar use of diuretics compared to the other three sites.

5.10. Blood glucose and diabetes control across visits:

In both Alllegheny County and the three sites, a 20% increase in the rate of diabetes medication accompanied by improved glycemic control was shown between baseline and year 9. Although tight glycemic control is recommended to prevent microvascular disease, previous studies failed to demonstrate the benefit of tight glycemic control in stroke risk reduction.[48] In addition, previous studies showed the tight control of hypertension (less than 130/80) in diabetics significantly reduces stroke incidence.[49, 50] Blood pressure less than 130/80 was slightly improved in both study populations between baseline and year 9 without significant differences between study populations.

5.11. LDL cholesterol control across visits:

Although many clinical trials showed reduced stroke risk after lowering LDL levels,[51] the current data did show any better LDL control in Allegheny County compared to other three sites. The improved LDL control (LDL <100 mg/dl with medication) in both Allegheny County and the other three sites between baseline (8.6% and 12.2% respectively, p=0.532) and year 5 (23.9% and 21.9% respectively, p=0.735) could be explained by the higher percentage of people who use any lipid lowering medication at year 5 compared to baseline.

5.12. Alcohol drinking and cigarette smoking control across visits:

Results from observational studies indicated that heavy alcohol consumption increases the relative risk for both ischemic and hemorrhagic stroke while light or moderate alcohol consumption may be protective for ischemic stroke. [52, 53]Allegheny County had significantly higher number of alcohol drinks per week, however, the stroke risk due to alcohol drinking should not be considered higher in Allegheny County because in both study populations the amount of alcohol consumed was relatively small (1.7-2.8 drinks per week). Current cigarette smoking has been long recognized as a major risk factor for stroke with almost doubling of relative risk and disappearance of the risk about 5 years after cessation. [54, 55] In the current data by year 9, Allegheny County had similar smoking rates compared to the other three sites indicating comparable smoking cessation rates.

5.13. Carotid stenosis across visits:

Severe symptomatic carotid artery stenosis is responsible for approximately 20 to 30% of ischemic strokes and almost 3 times more than asymptomatic one.[56, 57] Carotid stenosis ≥ 25%

was lower while carotid stenosis ≥ 50% was similar in Allegheny County compared to the other three sites at baseline and year 5. Little differences in stroke risk between sites based on carotid stenosis could be expected because symptomatic (with TIA) carotid stenosis (≥ 25% or ≥ 50%), a more important stroke risk factor than the asymptomatic stenosis, were not significantly different between study populations at all visits. Large randomized controlled trials have documented that carotid endarterectomy is a highly effective stroke preventive measure among patients with severe carotid stenosis and recent transient ischemic attack. [57, 58] Because carotid endarterectomy was not different between study populations at baseline and data were not available at other visits, we could not verify the differences between study populations in surgical control of carotid stenosis.

5.14. History of transient ischemic attack and atrial fibrillation across visits:

In clinical trials, warfarin was highly effective in reducing stroke risk in atrial fibrillation patients while Aspirin, to a less extent, reduced the stroke risk in both transient ischemic attack and atrial fibrillation. [59] The current data did not show any better control of either transient ischemic attack or atrial fibrillation (oral anti-coagulant or aspirin use) in Allegheny County compared to the other three sites. Moreover, atrial fibrillation prevalence was similar in both study populations at all visits. The lower prevalence of transient ischemic attack in Allegehny County at year 5 (p=0.008) and year 9 (p=0.093) may be explained by the lower prevalence of carotid stenosis (>25%) at baseline and year 5.

5.15. Brain MRI white matter grade and stroke risk:

Several recent reports from prospective studies indicated that higher grade of white matter lesion is a strong predictor of stroke specially lacunar infarction and the risk is independent of traditional risk factors.[60-62] In this report, likewise white matter grade was a strong stroke predictor irrespective of sites. One of the most interesting finding in this report was that white matter grade at baseline was responsible for 25% of the excess stroke hazard observed in the other three sites compared to Allegheny County which had significantly lower prevalence of high white matter grade. So white matter grade was the most important single risk factor to explain the observed site differences in stroke risk. White matter grade was shown to be strongly related to age [63] which might explain the higher prevalence of those who had white matter grade ≥ 3 in the second MRI irrespective of sites. As Allegheny County had a similar stroke history and lower white matter grade at baseline, the current results suggested the importance of white matter lesion to point any future increase or reduction of stroke risk in a given community, probably many years before it happen. White matter grade may be a marker of integrated exposure and control of stroke risk factors and may help in explaining geographic variations in stroke incidence. White matter grade progression could be used a marker of the efficacy of the various pharmacologic and non-pharmacologic therapies of stroke on the individual level and as a marker of the efficacy of different stroke prevention strategies on a community level.

5.16. Alternative explanation of site-differences in stroke

As the site-differences in stroke risk in this report were only partially explained by risk factors distributions at baseline, also the control of major stroke risk factors did not play a major role in explaining the observed difference, factors other than traditional stroke risk factors and sub-clinical cardiovascular disease should be investigated further. These factors might be more helpful in explaining regional differences in stroke risk. Limited data have identified several potential factors, including genetic influences on stroke [64-66] – especially compelling as family history of stroke was lower in Allegheny County than in other sites. The degree of urbanization has likewise been linked with stroke risk, with higher rates in non-metropolitan areas.[27-29] Allegheny County was entirely urban while the other sites were mixed urban/rural communities. Dietary life style including the consumption of fish, fruits and vegetables and dietary calcium and potassium may help in explaining geographic stroke incidence variations.[67, 68] Finally, environmental factors such as the quality of drinking water and environmental exposure to lead and perhaps cadmium may have some role in explaining these stroke variations.[69, 70]

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6. APPLICATION TO PUBLIC HEALTH

Despite the advent in stroke treatment, stroke continues as the third leading cause of death among the US population in 2001, after heart diseases and cancer. 164,000 Americans died in 2001 from stroke (6.8% of all deaths). [1] It is now estimated that there are more than 700, 000 incident strokes annually and 4.8 million stroke survivors.[2, 3] Stroke imposes a substantial economic burden on individuals and society with more than $140,000 estimated mean lifetime cost and 53 $ billion estimated national direct and indirect cost.[3, 4]

6.1. Epidemiological studies and stroke prevention:

Comparing rates of disease on national or international levels, and attempting to determine factors that explain any geographic differences have often led to important knowledge about etiology and prevention. Major reductions in stroke mortality and morbidity may possibly be achieved through more effective prevention strategies. [5] High-risk or stroke-prone individuals should be identified and targeted for specific interventions. Stroke risk is not homogeneous across the country, the so called stroke belt states have a stroke mortality that is 1.3-1.5 times the risk in the remainder of the nation.[6] Epidemiological studies can detect geographical differences in stroke morbidity and mortality. Identifying areas of high and low stroke risk is very essential for stroke prevention for two reasons; in addition to targeting high stroke risk regions for specific interventions to achieve the best outcome, studying risk factors distribution associated with these regions will help in identifying the most important factor/factors that is/are responsible for these regional/geographical variability in stroke risk.

6.2. Stroke risk in older population:

Although United States had one of the lowest stroke incidence and mortality rates in the westernized countries, age-specific incidence rates in this study were higher than those reported for similar age groups in US but were comparable to those reported in many westernized countries suggesting that older Americans are at least less privileged compared to their younger counterparts as regards this lower stroke risk in United States and deserve more effective stroke prevention programs.

6.3. Reducing stroke risk:

After adjustment for age, hypertension, diabetes, education, BMI, LDL level and previous coronary heart disease, transient ischemic attack, and atrial fibrillation, there was almost 30% reduction of the excess hazard in the other three CHS sites compared to Allegheny County. These findings suggested that in a similar population, reducing the prevalence of these factors could lead to a considerable degree of stroke incidence reduction. However, as the site-differences in stroke risk were only partially explained in this report, factors other than traditional stroke risk factors and sub-clinical cardiovascular disease (like genetic, dietary, and environmental factors) should be investigated further.

6.4. White matter grade and stroke prediction:

As Allegheny County had a similar stroke history and lower white matter grade at baseline and significantly lower stroke risk thereafter, the current results suggested the importance of white matter lesion to point any future increase or reduction of stroke risk in a given community, probably many years before it happen. White matter grade progression could be used a marker of the efficacy of the various pharmacologic and non-pharmacologic therapies of stroke on the individual level and as a marker of the efficacy of different stroke prevention strategies on a community level.

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7. SUMMARY

7.1. First article:

The first article examined the site-differences in stroke incidence, mortality and case fatality among CHS participants. Age and sex standardized total stroke incidence rates were significantly lower in Allegheny County than other three sites. The cumulative total stroke incidence rates were also significantly lower in Allegheny County than other three sites. Stroke incidence rates steadily increased with increasing age at all four CHS sites. In this old cohort, there were little or no race and sex differences in stroke incidence. Though not statistically significant, age and sex standardized total stroke mortality rates were also lower in Allegheny County than other three sites. The site-differences in stroke risk could not be explained by age or race differences between sites. Age and sex adjusted incidence and mortality rates for all CHS participant were many fold higher than reported by previous studies because of the older age of CHS participants compared to these studies. Stroke types were similar between sites with lower percentage of hemorrhagic stroke in CHS population compared to previous studies. One month case fatality rates were not significantly different between the four sites and were similar to those previously reported in previous studies.

7.2. Second article:

The second article compared the prevalence of potential stroke risk factors at baseline between CHS sites relative to incident stroke events with aim to explain site-differences in stroke incidence. Stroke hazard ratios for the other three sites compared to Allegheny County were calculated with Cox regression models before and after adjusting to possible stroke risk factors at baseline. Total stroke incidence unadjusted hazards in Forsyth, Sacramento, and Washington Counties combined compared to Allegheny County was 1.74 (95% CI= 1.42, 2.14; $p < 0.001$). Although Allegheny County had the lowest stroke hazard among the four sites, risk factor distributions across sites were relatively similar. After adjustment for age, hypertension, diabetes, education, BMI, LDL cholesterol and previous coronary heart disease, transient ischemic attack, and atrial fibrillation, there was almost 30% reduction of the excess hazard in the other three sites compared to Allegheny County (1.52, 95% CI= 1.17-1.98; $p=0.002$). The results indicated that site-differences in stroke risk can be only partially explained by site-differences in stroke risk factors at baseline. White matter grade ≥ 3 was less common in Allegheny County than the other three sites combined (25.8%and 36.3% respectively, $p < 0.001$). White matter grade was responsible for 25% of the excess hazard in the other three sites compared to Allegheny County. White matter grade may be a marker of integrated exposure and control of stroke risk factors and may help in explaining geographic variations in stroke incidence.

7.3. Third article:

The third article compared potential stroke risk factors and their control relative to incident stroke events across the CHS visits (baseline, year-5 and year-9) between Allegheny County and the other three CHS sites combined. After adjustment for age, gender and race, the hazards of stroke incidence in all the three sites combined compared to Allegheny County were 1.75 (95% CI= 1.42, 2.14) at baseline, 2.01 (95% CI= 1.49, 2.71) at year 5, and 2.39 (95% CI= 1.54, 3.73) at year 9. The current report showed some degree of improvement of control of traditional stroke risk factors specially LDL cholesterol, diabetes, smoking, and hypertension between baseline and year 9. However, the improvements were not significantly different between Allegheny County and the other three sites suggesting that these factors did not play a major role in explaining the observed difference in stroke hazard between study populations. The prevalence of coronary heart disease, atrial fibrillation and transient ischemic attack were increased in both study populations across visits with out significant differences with the exception of transient ischemic attack that was significantly lower in Allegheny County at year 5. The use of aspirin and oral anti-coagulants were markedly increased in both study populations across visits with out significant differences. White matter grade which was a strong predictor of stroke irrespective of sites and was lower in Allegheny County in both MRIs may be a marker of integrated exposure and control of stroke risk factors and may help in explaining geographic variations in stroke incidence.

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APPENDIX A: US census 2000 standard population

Population 65 years and over by Age:

	Number	% of 65 years or over population	% of total population
65-74 years	18,391	52.6	6.5
75-84 years	12,361	35.3	4.4
85+ years	4,240	12.1	1.5
Total	**34,992**	**100.0**	**12.4**

Total 2000 US population is: **281,422, 000**

Population 65 years and over by age and sex:

	Number	% of 65 years or over population	% of total population
Males 65-74 years	8,303	23.7	3.0
Females 65-74 years	10,088	28.8	3.6
Males 75-84 years	4,879	13.9	1.7
Females 75-84 years	7,482	21.4	2.7
Males 85+ years	1,227	3.5	0.4
Females 85+ years	3,013	8.6	1.1
Total	**34,992**	**100.0**	**12.4**

Total 2000 US population is: **281,422, 000**

APPENDIX B: Cumulative stroke incidence and mortality tables

Table 13: Cumulative total stroke incidence and SE per 1000 persons for all CHS participants*

Stroke follow up years	Forsyth County, NC	Sacramento County, CA	Washington County, MD	Allegheny County, PA	Total
	Rate Standard error	**Rate** Standard error	**Rate** Standard error	**Rate** Standard error	**Rate** Standard error
1	**13**	**9**	**13**	**8**	**11**
	3	2	3	2	1
2	**22**	**20**	**26**	**17**	**21**
	4	4	4	3	2
3	**31**	**37**	**38**	**29**	**34**
	4	5	5	4	2
4	**47**	**49**	**49**	**36**	**45**
	5	5	6	5	3
5	**63**	**63**	**62**	**42**	**57**
	6	6	7	5	3
6	**80**	**80**	**86**	**49**	**73**
	7	7	8	6	4
7	**100**	**100**	**102**	**57**	**89**
	8	8	9	6	4
8	**116**	**124**	**122**	**67**	**107**
	9	9	9	7	4
9	**131**	**143**	**137**	**76**	**121**
	9	10	10	7	5
10	**146**	**164**	**157**	**89**	**138**
	10	10	11	8	5
11	**172**	**175**	**176**	**102**	**156**
	12	11	13	10	6
95% lower CI	**148.5**	**153.4**	**150.5**	**82.4**	**144.2**
95% upper CI	**195.5**	**196.6**	**201.5**	**121.6**	**167.8**

*Adjusted for age, gender, and race

Table 14: Cumulative total stroke mortality and SE per 1000 persons for all CHS participants

Stroke follow up years	Forsyth County, NC	Sacramento County, CA	Washington County, MD	Allegheny County, PA	Total
	Rate Standard error	**Rate** Standard error	**Rate** Standard error	**Rate** Standard error	**Rate** Standard error
1	**1**	**1**	**0**	**1**	**1**
	1	1	0	1	0
2	**2**	**2**	**0**	**2**	**2**
	1	1	0	1	1
3	**3**	**3**	**1**	**3**	**3**
	1	1	1	1	1
4	**6**	**5**	**2**	**4**	**4**
	2	2	1	2	1
5	**7**	**7**	**4**	**4**	**6**
	2	2	2	2	1
6	**10**	**7**	**6**	**4**	**7**
	3	2	2	2	1
7	**12**	**9**	**8**	**5**	**9**
	3	2	3	2	1
8	**14**	**11**	**11**	**7**	**11**
	3	3	3	2	2
9	**15**	**16**	**15**	**8**	**14**
	3	4	4	3	2
10	**16**	**19**	**21**	**13**	**18**
	4	4	5	4	2
11	**20**	**19**	**23**	**13**	**19**
	5	4	5	4	2
95% lower CI	**10.2**	**11.2**	**13.2**	**5.2**	**15.1**
95% upper CI	**29.8**	**26.8**	**32.8**	**20.8**	**22.9**

*Adjusted for age, gender, and race

APPENDIX C: Incident CHS end points

Table 15: Adjusted* hazard ratio of CHS cardiovascular end points in the three CHS sites combined compared to Allegheny County

Outcome	N	P value	HR	95% CI
Total mortality	1910	0.267	**1.061**	(0.956, 1.178)
CHD	1026	0.629	**0.966**	(0.838, 1.113)
MI	557	0.428	**1.084**	(0.889, 1.322)
CHF	980	0.703	**0.972**	(0.841, 1.124)
Angina	877	0.083	**0.875**	(0.753, 1.017)
Stroke	663	<0.001	**1.747**	(1.423, 2.145)
TIA	173	0.097	**1.375**	(0.944, 2.002)

*Adjusted for age, gender, and race

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