Biological And Psychosocial Risk Factors Of Stroke In African Americans Enrolled In The Jackson Heart Study (Jhs)

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A Thesis
presented in partial fulfillment of requirements
for the degree of Master of Science
in the Department of Pharmacy Administration
The University of Mississippi

By
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ABSTRACT

Objectives: The objective of this study is to estimate the impact of biological, psychosocial and other risk factors on stroke in African Americans enrolled in the JHS and determine the population attributable risk of risk factors.

Methods: This study used a nested case control design. Cases were patients with stroke during the follow up period. Corresponding controls were selected from subjects who are alive at that time period and who are at risk of stroke by matching on the person-years spent in the cohort. Odds ratios (OR) and population attributable risks (PAR) were calculated to understand the association of risk factors with incident stroke.

Results: A total of 129 cases of incident stroke were identified during the follow-up and 590 controls were identified. Hypertension and diabetes were the two strongest risk factors of stroke, with an OR of 1.8 (95% CI 1.1 - 3.1) for hypertension and an OR of 1.7 (95% CI 1.1 - 2.7) for diabetes, followed by the Framingham stroke risk score. The risk of stroke increased by 4% for every 1% increase in the Framingham stroke risk score (OR 1.04, 95% CI 1.01 - 1.08). Family history of stroke and alcohol consumption increased the risk of stroke, but the association was not significant. We found that psychosocial risk factors including depression, stress and major life events were not significantly associated with incident stroke in this study. The overall PAR including both biological and psychosocial risk factors accounted for 77.5% of incident stroke in our study.

Conclusions: In conclusion, the six biological risk factors together accounted for 76.5% of PAR in the African Americans in the JHS. The association of psychosocial risk factors and incident stroke is unclear and further studies are necessary.
TABLE OF CONTENTS

ABSTRACT ........................................................................................................................ II

TABLE OF CONTENTS .................................................................................................. III

CHAPTER 1: BACKGROUND ......................................................................................... 1

Introduction ......................................................................................................................... 2

Study Objectives ................................................................................................................. 5

Literature Review ................................................................................................................ 6

Overview of Stroke ............................................................................................................. 6

  Stroke Prevalence ............................................................................................................ 8

  Risk Factors of Stroke ..................................................................................................... 10

  Biological risk factors of stroke.................................................................................... 12

  Psychosocial risk factors of stroke .............................................................................. 15

  Theoretical Framework ................................................................................................. 17

  Racial Disparities in Stroke ............................................................................................ 17

  The Jackson Heart Study (JHS) ...................................................................................... 18

CHAPTER II: METHODOLOGY ................................................................................... 20

Methodology ...................................................................................................................... 21

  Data Source and Study Design .................................................................................... 21

  Cases and Controls ........................................................................................................ 22

  Operationalization of Risk Factors ............................................................................ 23

Statistical Analysis ........................................................................................................... 25
Missing data management ........................................................................................................ 25
Descriptive statistics ............................................................................................................ 25
Objectives 1 to 3 .................................................................................................................... 25
Objective 4 ............................................................................................................................ 26
CHAPTER III: RESULTS ........................................................................................................ 27
Results ..................................................................................................................................... 28
Discussion ............................................................................................................................. 31
Limitations ............................................................................................................................... 36
CHAPTER IV: CONCLUSIONS ............................................................................................ 38
Conclusions ............................................................................................................................. 39
Bibliography ........................................................................................................................... 40
LIST OF APPENDICES ........................................................................................................ 52
A: TABLES ............................................................................................................................ 53
   Table 1: Operationalization of risk factors ........................................................................... 54
   Table 2: Baseline characteristics of cases and controls ....................................................... 56
   Table 3: Risk of stroke associated with biological, psychosocial and socioeconomic risk factors in the study population ................................................................................... 58
   Table 4: Population attributable risk (PAR) and 95% CI for biological and psychosocial risk factors ......................................................................................................................... 59
B: FIGURES ............................................................................................................................ 60
   Table 1: Theoretical framework on stroke risk factors ......................................................... 61
   Table 2: Odds ratios (95% CI) for stroke risk factors ......................................................... 62
CURRICULUM VITAE ........................................................................................................... 63
CHAPTER I: BACKGROUND
Introduction

Stroke is a cerebrovascular accident which occurs due to loss of brain functioning when lack of blood supply leads to the death of brain cells. Stroke can be classified into four major types: ischemic, primary intracerebral hemorrhage (ICH), subarachnoid hemorrhage and undetermined stroke. Ischemic stroke is the most common type of stroke followed by primary ICH. Ischemic stroke is caused by the contraction of arteries which leads to restricted blood flow to the brain while intracerebral and subarachnoid hemorrhage are caused by the rupture of blood vessels in the brain due to high blood pressure or weak blood vessel walls.\(^1\) Ischemic stroke is the most common type of stroke followed by primary ICH. About 87% of all strokes are ischemic stroke, followed by 10% of ICH and 3% of subarachnoid hemorrhage strokes.\(^2\) Compared to ischemic stroke, ICH leads to higher case-fatality and poorer functional outcomes.\(^3,4\)

Stroke is one of the leading causes of death and neurological disabilities across the world. The global burden of disease study (GBD) reported stroke to be the second most common cause of death. This study also projected that cerebrovascular diseases would remain the second leading cause of death in 2020 if current trend continues.\(^5\) In 2010, stroke was the fourth leading cause of death in the United States (US) and the overall death rate due to stroke was 41.9 per 100,000 population.\(^6\) Despite that the death rate due to stroke in the US declined by 35.8% from 2000 to 2010, the number of new or recurrent strokes remains very high; around 795,000 episodes of new or recurrent strokes were recorded in the US in 2010.\(^2\) In 2010, the overall prevalence of stroke in the US adults aged 20 and above was an estimated 2.8%.\(^7\)
Stroke disproportionately affects minorities and people living in the southern states of the US. In 1996, stroke was the third and sixth leading cause of death among black women and black men, accounting for 7.9% and 5.3% of all deaths among African American women and men, respectively. The stroke mortality rate of African Americans is higher than whites in 45 to 84 year olds. The black-to-white stroke mortality ratio in the southern states is estimated to be 6% to 21% higher compared to the rest of the US which indicates higher stroke mortality among blacks in southern states. However, the mortality due to stroke could be reduced by various primary and secondary interventions. Strategies such as use of a combination of drugs including statin, blood pressure lowering medications, folic acid and aspirin to manage the risk factors of stroke could reduce the mortality of stroke by 80%.

Apart from the clinical implications, stroke is also associated with significant economic costs in the US. The economic burden of stroke has been increasing along with the increasing costs of healthcare and is a significant contributor to the healthcare expenditures in the US. In 2010, the total cost of stroke was estimated to be $36.5 billion, of which $20.6 billion were attributable to direct medical cost. The average per patient costs of direct medical care is estimated to be $5,455. The American Heart Association/American Stroke Association forecasted that the total direct medical costs related to stroke will reach $184.1 billion and the projected indirect cost of stroke due to loss of productivity will be $56.5 billion in the US in 2030.

Epidemiological studies have identified risk factors of stroke which are generally categorized as modifiable risk factors (risk factors that can be treated or controlled), non-modifiable risk factors and other risk factors. Population attributable risk (PAR) is a measure used to reflect the proportion of disease risk which can be attributed to the causal effects of a set of risk factors or an individual risk factor. Risk factors including hypertension, current smoking, abdominal
obesity, diet and physical activity account for more than 80% of the PAR for stroke in the general population.\textsuperscript{13}

African Americans are at an increased risk of stroke and stroke mortality due to high prevalence of several stroke risk factors along with low socioeconomic status and inadequate access to care. While the biological risk factors of stroke have been studied extensively in non-Hispanic whites and Hispanics, very few studies have assessed the biological risk factors in the African American population and the psychosocial risk factors are inadequately studied in all populations. There is a need to further understand the reasons of higher risk of stroke and stroke-related mortality in the African American population. Such an investigation is made possible through the Jackson Heart Study (JHS) which is conducted in the African American population in Jackson, Mississippi. Mississippi is located in the southeastern part of the US which has been called the “Stroke Belt” due to the significantly higher prevalence of stroke in this region compared to the other parts of the nation. Mississippi also has the highest proportion of African Americans in the US (37.6% in 2010).\textsuperscript{14} The JHS was initiated in 2000 and currently has a follow up period of 12 years. The JHS cohort consists of 5,302 African American adults living in three counties in the Jackson metropolitan statistical area. Overall 17% of the JHS participants were randomly recruited through a commercial listing which provides contact details of residents in the Jackson MSA, 30% of participants volunteered and 22% were from Atherosclerosis Risk in Communities (ARIC) study, which is a prospective epidemiologic study conducted in four US communities. The JHS family cohort contains families of relatives of the JHS participants. This family cohort contributes to 31% of the JHS cohort. Data pertaining to traditional and nontraditional risk factors of cardiovascular diseases are collected in the JHS, along with extensive personal and family medical history, diet and physical activity, physical measures and biomarkers. Non-
biologic variables such as general stress, work-related stress, financial stress, religious practices, and food habits along with many social and cultural measures are also collected.\textsuperscript{15} The JHS is the largest study that collects information on factors affecting the occurrence of cardiovascular and other illnesses in the African American population. Its vast amount of data provides us a great opportunity to understand the occurrence of stroke and investigate the risk factors of stroke in the African American population.

\textbf{Study Objectives}

1) To estimate the impact of biological risk factors on stroke in African Americans enrolled in JHS;

2) To estimate the impact of psychosocial risk factors on stroke in African Americans enrolled in JHS;

3) To estimate the impact of other risk factors on stroke in African Americans enrolled in JHS; and

4) To determine the population attributable risk of risk factors of stroke in African Americans enrolled in JHS.
Literature Review

Overview of Stroke

Stroke is a cerebrovascular accident which occurs due to loss of brain functioning when lack of blood supply leads to the death of brain cells. The World Health Organization (WHO) defined stroke as “rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin.” Stroke is classified into four major types: ischemic, primary intracerebral hemorrhage (ICH), subarachnoid hemorrhage and undetermined stroke. Ischemic stroke is the most frequent stroke followed by primary ICH and subarachnoid hemorrhage.

Ischemic stroke is caused by the contraction of arteries which leads to restricted blood flow to the brain. Ischemic stroke is the most frequent type of stroke. Causes of ischemic stroke include atherosclerosis with stenosis, cardioembolic, lacuna, uncertain cause and other causes. Hemorrhagic stroke is caused by the rupture of blood vessels in the brain due to high blood pressure or weak blood vessel walls. Hemorrhagic stroke is further classified into intracerebral and subarachnoid hemorrhage. Compared to ischemic stroke, ICH is less frequent but has higher case-fatality and leads to poorer patient functional outcome.

Stroke is associated with significant clinical and economic burden worldwide. By 2020, stroke will be the fourth most costly illness in the world. Stroke related expenditures in the US
increased considerably from the past few decades and are projected to increase in the future. The healthcare expenses due to all kinds of strokes in the US was estimated to be $6.5 billion in 1975 ($2.4 billion direct costs and $4.1 billion indirect costs)\textsuperscript{20} and $7.4 billion in 1976 (half the costs were direct costs).\textsuperscript{21} The life time costs of stroke in the US were $40.6 billion in 1990 of which direct costs were 42% of the total costs.\textsuperscript{22} In 2010, the total stroke-related expenses in the US estimated using the medical expenditure panel survey (MEPS) data was $36.5 billion of which the direct medical costs due to stroke was $20.6 billion and the mean expense per patient for direct medical care was estimated at $5,455.\textsuperscript{23} The American Heart Association/American Stroke Association forecasted the total direct medical stroke related costs in the US in 2030 to $184.1 billion. The projected indirect cost of stroke due to the loss of productivity is $56.5 billion.\textsuperscript{11}

The economic and clinical burden of stroke is significantly high in the African American population. A population-based epidemiological study conducted in the Greater Cincinnati/Northern Kentucky region found that incidence of stroke is higher in all age groups of African Americans compared to whites. The case fatality was however similar in both the races. The study found that the greater burden of stroke in African Americans is due to higher stroke incidence rates.\textsuperscript{24} In 1996, stroke was the third leading cause of death among black women and sixth leading cause of death in black men and also accounted for 7.9% and 5.3% deaths respectively. The mortality rates of African Americans is higher than whites in ages 45 to 84.\textsuperscript{8} Howard et al. (2007) assessed the costs of stroke in African Americans with a focus on regional differences in the expenditures of stroke by calculating the age- and sex-specific black-to-white stroke mortality rate for 26 states in the US. They found that the black-to-white stroke mortality ratio in the southern states is 6% to 21% higher compared to the rest of the US which indicates
higher mortality due to stroke of blacks in the southern states. The black-to-white mortality rates decreased with increasing age which indicated a declining ethnic disparities with age.\textsuperscript{9}

Men have higher age-specific stroke rates, but women have more stroke events due to their longer life expectancy and older age at the time of stroke onset. Stroke mortality is similar in both men and women less than 45 years of age whereas the risk of stroke mortality in women is significantly lower than men in the age groups 45 to 74 years (20\% to 35\% lower). In age groups above 85 years and older, stroke-related mortality is higher by 12\% to 14\% in women than men. After stroke, women have poorer functional outcomes, lower quality of life and higher likelihood of depression compared to men.\textsuperscript{25}

\textbf{Stroke Prevalence}

Stroke is a highly prevalent cerebrovascular disease in the US. Estimates using 2007 to 2010 data of the National Health and Nutrition Examination Survey (NHANES) extrapolated that 6.8 million Americans aged 20 years and above had experienced a stroke in 2010. The overall stroke prevalence in this period was 2.8\%.\textsuperscript{11, 26} Studies using the 2010 Behavioral Risk Factor Surveillance (BRFSS) data estimated that the prevalence of stroke was 2.6\% in adults aged 18 years and above.\textsuperscript{7} Stroke prevalence varies by race and ethnicity. The BRFSS data show that stroke prevalence is 3.7\% in non-Hispanic blacks, 2.7\% in non-Hispanic whites, 1.8\% in Hispanics, 3.5\% in multiracial population and 2.1\% in others. Although the annual prevalence of stroke in the general population from 2006 to 2010 did not change, prevalence of stroke was found to be higher in older adults, blacks, American Indians/Alaska Natives, low educated people and in the southeastern United States. The American Heart Association/American Stroke Association projected that the prevalence of stroke in US population 18 years and older will
reach 3.8% in 2030. The projected prevalence of stroke in 2030 is highest in African American females (5.7%), followed by white non-Hispanic females (4.7%). The prevalence of stroke is projected to be 3.7% in white non-Hispanic men and 4.2% in African American men. The relative increase in the prevalence of stroke is projected to be higher in white Hispanic men, black men and black women compared to white non-Hispanics. Ageing population is considered a major driver of increase in stroke prevalence.11

A study using the Rochester Epidemiology Project medical records linkage system reported that the age- and sex- adjusted incidence rate of ischemic stroke in the white population enrolled in the study was 147 per 100,000 population.27 A similar study in the African American population residing in the 5-county region of greater Cincinnati and Northern Kentucky reported the overall age- and sex-adjusted incidence of ischemic stroke as 246 per 100,000 population.28

The prevalence of stroke also differs for different subtypes of stroke. Intracerebral hemorrhage (ICH) is less frequent compared to ischemic stroke but has higher case-fatality and leads to worse functional outcomes.3 Donnan et al. (2010) conducted a meta-analysis of data from 36 studies and reported the overall incidence of ICH as 24 cases per 100,000 person-years. The study found that the incidence of ICH increases with age and is higher in men than women. The study also observed that the incidence of ICH did not decrease significantly in the recent decades unlike the incidence of ischemic stroke.4 Subarachnoid hemorrhage is less frequent than ischemic stroke and ICH. An epidemiologic study conducted by Broderick et al. (1993) showed that the incidence of ICH in Greater Cincinnati area was 15 per 100,000 population while the incidence of subarachnoid hemorrhage was six per 100,000 population (less than half).30
Howard et al. (2006) assessed the prevalence of stroke symptoms in a stroke-free population randomly sampled from a national cohort with greater sample of people from the southeast and the African American population. The study found 17.8% prevalence of one or more symptoms of stroke in people who had no prior diagnosis of stroke or Transient ischemic attack (TIA). The prevalence of stroke symptoms was higher in the African American population compared to whites and higher in people with lower levels of education, income and those with fair to poor perceived health.31

**Risk Factors of Stroke**

Risk factors are characteristics which increase the likelihood of a disease in an individual compared to one without the characteristic. Epidemiological studies have identified numerous risk factors of stroke and some of the risk factors are well established. Risk factors are considered to be established if they have high prevalence in many populations, have significant independent impact on the risk of stroke and the control of such risk factors resulted in reduced risk. Odds ratio and relative risk are the frequently used measures for the association of a risk factor with a disease. Population attributable risk (PAR) is a measure used to reflect the proportion of disease risk which can be attributed to the causal effects of a set of risk factors or an individual risk factor. PAR is defined as “the proportional reduction in average disease risk over a specified time interval that would be achieved by eliminating the exposure(s) of interest from the population while distributions of other risk factors in the population remain unchanged.”32

Stroke risk factors increase the likelihood of stroke by altering the vascular structure through atherosclerosis, which leads to hardening and narrowing of the arteries thereby reducing the
cerebral blood flow (CBF). Risk factors such as hypertension, ageing, diabetes and hypercholesterolemia increase the risk of stroke through this mechanism.\textsuperscript{33-35} Risk factors like hypertension and diabetes also impair protective mechanisms which maintain the cerebral blood flow during reduced blood pressure which could lead to stroke in case of reduced intravascular pressure.\textsuperscript{36} Risk factors such as ageing and diabetes could also enhance the tissue damage due to ischemic stroke.\textsuperscript{37} Although the effect of some of the risk factors is known the effects of interaction of these risk factors is less known.\textsuperscript{38} There are multiple schemes in classifying the risk factors of stroke. The World Health Organization (WHO) has identified over 300 various risk factors for coronary artery diseases and stroke but only few have been established. The risk factors of stroke are identified and classified into four categories, they are: major modifiable risk factors, other modifiable risk factors, non-modifiable risk factors and novel risk factors.\textsuperscript{39} Risk factors are considered to be major risk factors if they had high prevalence in many populations, have significant independent impact on the risk of stroke and the treatment and control of these risk factors reduce the risk of stroke. Major modifiable risk factors are the risk factors which have significant impact on the risk of stroke and can be treated or controlled; non-modifiable risk factors are risk factors which cannot be controlled or treated. The other two categories including other modifiable risk factors and the novel risk factors.

The American Stroke Association has classified the risk factors of stroke into three different categories. Risk factors which can’t be changed (non-modifiable risk factors), risk factors which can be controlled, changed or treated (modifiable risk factors) and other less well-documented risk factors.\textsuperscript{40} Non-modifiable risk factors include biological factors such as age, family history, race, sex and prior stroke, TIA or heart attack which are non-modifiable. Modifiable risk factors include various biological risk factors such as high blood pressure, cigarette smoking, diabetes,
carotid or other artery disease, peripheral artery disease, atrial fibrillation, coronary heart disease, sickle cell anemia, high blood cholesterol, poor diet, physical inactivity and obesity. Other less well documented risk factors include geographic location, socioeconomic factors, alcohol abuse or drug abuse. Some studies have suggested that certain psychosocial factors such as stress and depression could also be significant risk factors for stroke.13

Many studies have assessed the effect of either biological or psychosocial risk factors on the risk of stroke. Biological risk factors would include several known biological modifiable and non-modifiable risk factors of stroke, such as hypertension, smoking and atrial fibrillation. Psychosocial risk factors include risk factors such as stress, mental ill-health and other risk factors include various novel and emerging risk factors such as low socioeconomic status (SES), alcohol use, use of certain medications, lipoprotein(a) etc.

**Biological risk factors of stroke.** The biological risk factors of stroke have been studied extensively. The risk factors of acute myocardial infarction and stroke are studied in two global studies, INTERHEART and INTERSTROKE, respectively.13, 41-43 The INTERSTROKE study was conducted in 22 countries and the association of traditional and emerging risk factors of stroke is assessed in this study. The INTERSTROKE study was aimed at studying the contribution of risk factors to the burden of stroke across low, middle and high income countries. Risk factors of subtypes of stroke such as ischemic stroke and ICH were also studied. The study also assessed differences between risk factors of stroke and myocardial infarction. The major risk factors of stroke which accounted for more than 80% of PAR are hypertension, current smoking, abdominal obesity, diet and physical activity. Risk factors such as diabetes, alcohol, psychosocial stress, depression, cardiac causes and ratio of apolipoproteins B to A1 along with the others risk factors together account for approximately 90% of the stroke PAR.13 The INTERHEART study
was conducted in 52 countries across continents. The effect of potentially modifiable risk factors and psychosocial risk factors on the risk of acute myocardial infarctions is studied in this study. Comparisons between the INTERHEART and the INTERSTROKE studies revealed similar risk factors for both myocardial infarction and stroke. However, the relative importance of the risk factors of stroke seem to be different compared to myocardial infraction. The difference is notable for hypertension, apolipoproteins, physical activity and alcohol intake. Psychosocial stress in the INTERSTROKE study was a combined measure of stress at workplace and general stress at home. Whereas the INTERHEART study used a composite measure of general stress, financial stress, locus of control, life events. While the INTERSTROKE study had participants from many low, middle income countries and some high income countries, the study did not contain any population from the US. The INTERSTROKE study did not assess the differences in risk factors of stroke across many races and also had no representation of the African American population.

The Dubbo study is a longitudinal cohort study of elderly population in Australia to assess the patterns and predictors of mortality, hospitalization and need for residential care. Simons et al. (1998) reported findings from the Dubbo study about the prediction of ischemic stroke by potential risk factors using cox proportional hazards model. The results of the Dubbo study show that advancing age, prior history of stroke, hypertension, atrial fibrillation, impaired peak expiratory flow, physical disability, and depression significantly increased the risk of stroke while factors such as female sex, being married, higher HDL cholesterol lowered the risk of stroke. The study was unable to find significant association between cardiovascular risk factors such as cigarette smoking, diabetes, coronary heart disease (CHD), left ventricular hypertrophy, total cholesterol or triglycerides, lipoprotein (a) and alcohol intake and ischemic stroke.
Harmsen et al. (1990) evaluated the cardiovascular risk factors of stroke in a cohort containing general population in Goteborg, Sweden. The mean follow-up period was 11.8 years. Multivariate analysis found that high blood pressure, smoking, severe psychological stress, atrial fibrillation, previous transient ischemic attacks and intermittent claudication are independently associated with non-hemorrhagic stroke. The study also found that risk factors such as serum cholesterol concentration, occupational and leisure time physical activity, BMI, alcohol abuse, low occupational class are not significantly associated with the risk of stroke.45

Risk factors such as increased blood pressure, increased blood cholesterol, carotid stenosis, and atrial fibrillation were strongly associated with increased risk of ischemic stroke. The causality of these risk factors was determined by various randomized controlled trials (RCTs) which showed that treating these risk factors is associated with reduced incidence of ischemic stroke.46-50 Whisnant et al. (1996) conducted a case control study in the Rochester Epidemiology Project to estimate the risk of ischemic stroke for various risk factors. The study identified seven independently significant risk factors of stroke: hypertension, transient ischemic attack, cigarette smoking, ischemic heart disease, atrial fibrillation, diabetes mellitus, and mitral valve disease. The PAR of ischemic stroke due to these seven major risk factors is estimated to be 57%.51-52 Studies have found significant association of increased apoB/apoA1 ratio, obesity, physical inactivity, psychosocial stress and low fruit and vegetable intake with ischemic heart disease and these risk factors could be potential risk factors for ischemic stroke considering the association of these risk factors to ischemic heart disease.46 Risk factors such as ratio of apolipoproteins and physical activity were identified to be significant by the INTERSTROKE study as well. Hankey et al. (2006) also proposed several potential risk factors of stroke such as inherited susceptibility, inflammatory markers, and hemostatic factors.
Psychosocial risk factors of stroke. Psychosocial risk factors of stroke are understudied in African Americans and very few studies have examined the impact of psychosocial risk factors such as stress. Ebrahim et al. (2002) studied whether psychological distress leads to increased risk of ischemic stroke and transient ischemic attack (TIA) through the association between 30-item General Health Questionnaire (GHQ) and the incidence of stroke. The study found a significant association between psychological distress and fatal stroke. No evidence of association was found for psychological distress measured by GHQ and non-fatal stroke or TIA.

Salaycik et al. (2007) conducted a prospective study on Framingham Heart Study (FHS) participants. The study had up to 8 years of follow-up and the association between stroke and depression was analyzed with a cox proportional hazards model after adjusting for traditional risk factors of stroke. In participants less than 65 years of age the study found that risk of stroke in those with depression symptoms is 4.21 times greater as compared to those without symptoms of depression. In participants aged 65 years and above the depressive symptoms were not associated with an increased risk of stroke. The study also found that use of anti-depressant medications did not alter the risk of stroke associated with depression.

Mussolino et al. (1999) conducted a study using a population-based cohort of stroke-free white and black population enrolled in the NHANES I epidemiologic follow up study. Participants were followed for an average of 16 years. The study assessed the association between stroke and baseline self-reported depressive symptoms after adjusting for covariates such as baseline age, race, sex, education, smoking status, BMI, use of alcohol, physical activity, serum cholesterol level, diabetes history, history of heart disease and systolic blood pressure. The study found that depression is a significant predictor of stroke and the association was significant in white men,
and black men and women, while in white women the association reached borderline significance. Individuals with advanced depressive symptoms had a 50% to 160% increased risk of stroke compared to individuals with lower level of depressive symptoms.\textsuperscript{55}

The association of depression and stroke-related mortality was studied by Everson et al. (1998) in a prospective study in a community sample of initially stroke-free adults from Alameda County, California. The follow up period was 29 years and various confounders are adjusted. The study found that individuals who reported 5 or more depressive symptoms had 50% increased risk of stroke mortality.\textsuperscript{56} Another study with a 13-year follow up conducted by Larson et al. (2001) in the Baltimore epidemiologic catchment area also found that depression is a risk factor for stroke and it appears to be independent of traditional cardiovascular risk factors.\textsuperscript{57} A similar study in older Japanese population has reported that depression is associated with increased risk of ischemic stroke but not hemorrhagic stroke.\textsuperscript{58} The relative risk is also significant for total stroke, but the relative risk is much higher for ischemic stroke.

While the association of depression and stroke has been assessed in some studies, very few have assessed the impact of other psychosocial risk factors such as stress on the risk of stroke. Colantonio et al. (1992) assessed the influence of various psychosocial factors as predictors of stroke incidence in non-institutionalized elderly patients based in New Haven, Connecticut. Factors such as depression, marital status, social support, social networks and religiousness were assessed. Depression was measured by the Center for Epidemiologic Studies Depression Scale (CES-D). Higher scores on depression scale were associated with greater incidence of stroke, whereas frequent attendance at religious service was associated with lesser lower incidence of stroke.\textsuperscript{59}
Theoretical Framework

Based on the review of the literature, the current study will employ a theoretical framework (Figure 1) where risk factors of stroke are classified as biological risk factors, psychosocial risk factors and other risk factors.

Racial Disparities in Stroke

Racial and ethnic variations in the prevalence and mortality of stroke in the US have been documented in the literature. Mortality due to stroke across races and ethnicities were studied using national detailed mortality database file which contains National Vital Statistics data. Mortality rate for all stroke subtypes was the highest in African Americans compared to other ethnic groups. Stroke mortality rates increased with age among all racial groups, however stroke mortality rates were significantly higher in African Americans and American Indians/Alaska Natives compared to whites in the age group 25-44. The relative risk of ischemic stroke mortality is found to be 2.5 times higher in African Americans compared to non-Hispanic whites and 80% higher in American Indian/Alaska Native compared to non-Hispanic whites whereas the relative risk of ICH mortality is 4.2 times higher in African Americans compared to non-Hispanic whites and 60% higher in American Indians/Alaska Natives compared to non-Hispanic whites. Stroke mortality rates were similar to non-Hispanic whites in both Asian/Pacific Islanders and Hispanics.

The Atherosclerosis Risk in Communities (ARIC) study is a population-based cohort study with samples from adults aged 45 to 64 years in four different states in the US. Of all the strokes identified in the study, 83% strokes were categorized as ischemic strokes, 10% intracerebral hemorrhage and 7% subarachnoid strokes. The study found that the age-adjusted incidence rate
of total strokes was the highest in black men and women (4.4 and 3.1 per 1000 person-years) as compared to white men and women (1.8 and 1.2 per 1000 person-years). The unadjusted black versus white age-adjusted rate ratio for ischemic stroke was 2.4. After adjusting for baseline hypertension and various other covariates including diabetes, education level, smoking status, and prevalent coronary heart disease, the rate ratio was 1.38 which indicates a 38% greater risk of incident ischemic stroke in African Americans compared to whites. The study stressed on the need to investigate new individual and community level risk factors which could account for the increased risk of stroke in African Americans.  

The Jackson Heart Study (JHS)

The JHS is the largest study that collects information on factors affecting the occurrence of cardiovascular and other illnesses in the African American population. The study was initiated due to the observed ethnic and regional disparities in cardiovascular disease morbidity and mortality as well as overall healthcare access. The study was grown out of the ARIC study which found a relation between ethnic disparities in care and observed mortality. The JHS was designed to identify the factors leading to high prevalence and worsening of cardiovascular diseases in African Americans. The study is conducted in a cohort of 5,302 adult African American participants from three counties (Hinds, Madison and Rankin) in Jackson, Mississippi metropolitan statistical area (MSA). Overall 17% of the JHS participants were randomly recruited through a commercial listing which provides contact details of residents in the Jackson MSA, 30% of participants volunteered and 22% were from ARIC study, which is a prospective epidemiologic study conducted in four US communities. A nested cohort, which has family members among the relatives of JHS participants contributed 31% of the JHS cohort.
Data pertaining to traditional and nontraditional risk factors of cardiovascular diseases are collected along with extensive personal and family medical history, information on diet and physical activity, physical measures, biomarkers. Non-biologic variables such as general stress, work related stress, financial stress, religious practices, food habits along with many social and cultural measures are also collected. JHS has a large proportion of participants between 45 and 64 years old which has higher incidence of stroke and other cardiovascular diseases. The study was initiated in 2000 and the Exam 1 of the study has data for four years (2000 to 2004), Exam 2 has data from 2005 to 2008 and Exam 3 has data from 2009 to 2012. The JHS data also has annual follow up questionnaires which contains questions related to health-related events which occurred after each visit. The JHS data contain a component with anthropometric details, interview component which includes details about personal and family history, psychosocial variables, information related to various diseases and medications used as well as a genetic information component. Until now the study has a follow up period of 12 years.\textsuperscript{22}

The African American population has higher incidence of various subtypes of stroke and also have higher prevalence of some of the known risk factors such as hypertension, diabetes and cardiovascular diseases. Although the risk factors of stroke in the non-Hispanic white and Hispanic population was studied extensively, very few studies have looked into the biological risk factors of stroke in African Americans and no study has assessed the association between psychosocial risk factors on the risk of stroke in African Americans. The review of available literature indicates the need to further examine the risk factors of stroke in African Americans as well as to estimate the impact of these risk factors on stroke. The proposed study will estimate the impact of biological and psychosocial risk factors on stroke and estimate the PAR of these risk factors in African Americans enrolled in the JHS.
CHAPTER II: METHODOLOGY
Methodology

Data Source and Study Design
In the proposed study, subjects were be selected based on the presence or absence of incident stroke (outcome), but not on the presence or absence of risk factors (exposure). A cohort study is considered suitable when exposure is rare, while a case-control study is considered suitable when the outcome is rare. The potential risk factors hypothesized to be related to stroke (e.g., cardiovascular disease, hypertension, smoking) are not rare. Hence, the study employed a prospective case-control design using the JHS data. The designs and methods of JHS were reported previously by Taylor et al. (2005) and a brief summary is provided here. Participants in the JHS are African Americans and were recruited from three counties which make up Jackson MSA. The JHS baseline data (Visit 1) was collected from 2000 to 2004. Visit 2 data was collected from 2005 to 2008 and Visit 3 was collected from 2009 to 2012. Annual followup data was collected at each year. The JHS currently has data of 5,302 participants and the proposed study utilized the data of all the participants upto 12 years of follow up period (All annual follow up data and Visits 1-3). The following files were used in the study: COHORT, ALLEVTSTROKE, INCEVTSTROKE, DERIVE, PDSA, PFHA, RHXA, STSA, MHXA, FRTVEG, AFODCOMB, CENA. A brief description of each file is reported below.

1. COHORT file: Event level file with clinical visit and annual follow up visit information
2. ALLEVTSTROKE file: Event level file with information about stroke events and the indicators of type of stroke
3. DERIVE file: Derived variable dataset with participant level data
4. PDSA file: Participant level dataset with personal level data – socioeconomic status
5. PFHA file: Participant level dataset with personal and family history
6. RHXA file: Participant level dataset with reproductive history
7. STSA file: Participant level dataset with stress variables
8. MHXA file: Participant level dataset with medical history variables
9. FRTVEG: Participant level dataset with fruit and vegetable consumption variables
10. CENA file: Central laboratory dataset which contains variables including cholesterol and fat consumption variables

All JHS participants with complete baseline information and who had at least one follow up visit were included in the study. Participants with stroke at the baseline were excluded from the study. The proposed study was approved by the Institutional Review Board (IRB) of the University of Mississippi.

Cases and Controls

Participants of JHS who had incident stroke during the JHS follow up period are considered as cases. Cases of stroke were identified based on variable “Stroke” from the dataset INCEVTSTROKE. This dataset contains the adjudicated incident stroke events in the JHS cohort. All stroke events are pooled irrespective of the subtype of stroke. For each case, upto five corresponding controls were selected from the JHS cohort through incidence density sampling method. Variable “date” of stroke event from the dataset INCEVTSTROKE to identify the time
from the baseline exam to the event. Controls were selected from subjects who are alive at that time period and who are at risk of stroke. Cases and controls were matched on the time spent in the cohort. Incidence density sampling program for nested case control studies by Richardson DB (2004) was used for control selection.65

**Operationalization of Risk Factors**

Based on the theoretical framework the association of biological, psychosocial and other risk factors with stroke was studied. Biological risk factors that studied include the following: history of cardiovascular diseases (personal and family history of CVD), comorbidities and medical history (obesity, atrial fibrillation, hypertension, diabetes, cholesterol intake), lifestyle factors such as alcohol intake, tobacco use, physical activity.

Obesity was measured as BMI >= 30 or WHtR >=0.53 in men and WHtR>=0.50 in women.66 Hypertension was classified based on JNC 7 BP classification. Smokers were categorized into non smokers, current and former smokers. Participants were classified as drinkers and non drinkers based on alcohol consumption in the past 12 months. In order to accommodate the model, few risk factors are grouped together. Framingham stroke risk score was calculated based on variables: age, gender, systolic blood pressure (SBP), use of antihypertensive medications, diabetes mellitus, cigarettes, cardiovascular disease, atrial fibrillation and left ventricular hypertrophy (LVH). Cornell voltage criteria (sensitivity 42% and specificity 95%) was used to diagnose LVH since ECG data was collected at the baseline.67 Variables age, systolic blood pressure (SBP), use of antihypertensive medication, diabetes status, smoking status, cardiovascular disease (CVD), atrial fibrillation (AF), left ventricular hypertrophy (LVH) were grouped by Framingham stroke risk score. Framingham stroke risk score was calculated at
baseline for all the participants using the health risk appraisal function developed by Wolf et al. (1990).  

Psychosocial risk factors including stress, depression and major life events were examined. Questions from CES-D scale (Center for Epidemiologic Studies Depression (CES-D)) were used to measure depression in the JHS. In the proposed study, variable “Total Depressive Symptoms Score” would be used to measure depression. “Total Depressive Symptoms Score” ranges from 0 to 48 and was calculated for each participant based on their responses to the questions on depressive symptoms. Stress was measured by an eight-item global stress form developed for the JHS and the questionnaire measures global perceptions of chronic stress. Stress was measured at an interval level as “Not Stressful”, “Mildly Stressful”, “Moderately Stressful”, “Very Stressful”. Stress is measured through the questions “Stress in your job”, “Stress in your relationships”, “Stress living in neighbourhood”, “Stress caring for others”, “Stress related to legal problems”, “Stress from medical problems”, “Stress from racism/discrimination”, “Stress meeting basic needs”. “Global Stress Total Score” was calculated for each participant based on the responses from the above eight questions and has a range of 0-24. Major life events were measured through 11-item events inventory developed for the Eastside Village Survey. Variable “Major Life Events” was calculated based on the occurrence of the events and has a range of 0 – 9.

Other risk factors such as socioeconomic factors including education level, income status, occupation were also explored. Education level was categorized into less than high school, high school or college and college/associate degree or higher. Income status was classified as lower-middle income and below, upper-middle and above. Occupation was categorized into working and unemployed. Operationalization of the variables is provided in table 1.
Statistical Analyses

**Missing data management.** Logistic regression procedures in SAS delete observations with missing values. In case of the excluded observations being systematically different from the retained observations the results could be biased. It could also lead to loss of information and reduced statistical power.\(^1\) Multiple Imputation (MI) technique was used to impute the missing values in the dataset. The imputation method was determined by the pattern of missingness in the data (monotone or arbitrary) and the type of variable (continuous or categorical).\(^2\) Variables with skewed distribution were fifth-root transformed to near normality before they are imputed. PROC MI and PROC MIANALYZE procedures in SAS was used to analyze the data. Risk factors with more than 10% of missing data were not be examined.

**Descriptive statistics.** Descriptive measures were used to describe the characteristics of study sample. Cases and controls were compared for demographic, lifestyle and clinical variables. Standardized differences were calculated for continuous and categorical variables. Period prevalence of stroke in the population was computed.

**Objectives 1 to 3.** Conditional logistic regression was performed on matched cases and controls to determine the association between biological, psychosocial and other risk factors and stroke. Odds ratios (OR) and 95% confidence intervals (CI) were computed for each risk factor. Unmatched odds ratio can be biased if there is high variation of the proportion of exposed over the study period. Hence matched odds ratios were estimated to avoid the potential bias. PROC LOGISTIC procedure in SAS was used to conduct logistic regressions. All analysis were conducted using Statistical Analysis System (SAS) version 9.4 (SAS Institute Inc., Cary, NC).
Objective 4. PARs were computed for risk factors with adjustment for confounders using a method based on conditional logistic regression to calculate PARs in a case control study described by Bruzzi et al. (1985). Odds ratios and the distribution of risk in cases was used to compute PAR for each risk factor as well as combination of various risk factors. While the overall PAR estimates measure the impact of any exposure to the risk factor, level-specific PAR estimates could measure the impact of the level of exposure. Variance calculations and 95% CIs of PAR were calculated using the bootstrap procedure outlined by Efron and Tibshirani (1993). The interactive risk attributable program (IRAP) software (US National Cancer Institute, 2002) was used to perform all PAR analysis.
CHAPTER III: RESULTS
Results

A total of 129 cases of incident stroke were identified during follow-up, 36 were identified in follow-up period after the visit 1, 70 in visit 2, 23 in visit 3 and 590 corresponding controls were selected. Control selection was done using incidence density sampling where cases and controls were matched on person-years spent in the cohort. The characteristics of cases and controls are presented in Table 1. The mean age of cases is significantly higher than controls (64.8 ±10.2 vs 56.5 ±11.7, p<0.0001). The percentage of women is higher in the cases (63.6%) than controls (61.0%). As determined by a composite of WHtR and BMI in ascertaining obesity status, we found very high prevalence of obesity in both cases and controls (69.8% in cases and 72.0% in controls). The mean BMI of cases was lower than controls (31.0 ± 6.1 vs 32.0 ± 7.1, p=0.02) but the mean waist to height ratio (WHtR) is slightly higher in cases (0.61 ± 0.1 vs 0.60 ± 0.1, p=0.01). Prevalence of diabetes and hypertension was generally high in the study sample of both cases and controls, for example, 87.6% of cases and 64.4% of controls had hypertension, 41.1% of cases and 22.7% of controls had diabetes and 14.7% of cases and 7.1% of controls had coronary heart disease. Around 41.9% of cases and 31.9% of controls had a family history of stroke. The mean Framingham stroke risk score in the cases was 13.8% and 7.9% in the controls.

Regarding psychosocial risk factors, 16.3% of the cases and 14.4% of controls had depression, as measured by having a CES-D score greater than 23 and/or use of any antidepressant medication. The mean global stress score for cases is significantly lower than controls (3.6 ± 3.8 in cases vs.
4.9 ± 4.2, \( p < 0.0001 \). Further, the mean number of major life events is significantly lower in cases as compared to controls (2.5 ± 1.8 vs 2.8 ± 2.0, \( p = 0.0005 \)).

The proportion of cases who had a college education or degree was lower compared to controls (44.2% vs 57.3%, \( p = 0.05 \)). The majority of the study sample were having some type of health insurance (91% in cases vs. 87% in controls, \( p = 0.03 \)) while the percentage of cases currently employed is lower as compared to the controls (27.1% vs. 53.9%, \( p < 0.0001 \)).

Logistic regression results estimating odds ratios and 95% CI for stroke risk factors are provided in Table 2 and graphically presented in Figure 1. Hypertension and diabetes were the two strongest risk factors of stroke, with an OR of 1.8 (95% CI 1.1 - 3.1) for hypertension and an OR of 1.7 (95% CI 1.1 - 2.7) for diabetes, followed by the Framingham stroke risk score. The risk of stroke increased by 4% for every 1% increase in the Framingham stroke risk score (OR 1.04, 95% CI 1.01 - 1.08). Compared to those without a family history of stroke, participants with a family history of stroke were 43% more likely to have an incident stroke, however the association was not significant (OR 1.4, 95% CI 0.9 - 2.2). Alcohol consumption increased the risk of stroke by 33% (OR 1.3, 95% CI 0.8 – 2.1).

We found that psychosocial risk factors including depression, stress and major life events were not significantly associated with incident stroke in this study. Study participants who were employed (OR 0.5, 95% CI 0.3 - 0.7) were significantly less likely to have stroke.

PAR estimates along with 95% CI are provided in Table 3. Biological risk factors together accounted for 76.5% of PAR of stroke in this study sample. The overall PAR including both biological and psychosocial risk factors accounted for 77.5% of incident stroke in our study. When the PAR of individual risk factors was evaluated, we found that hypertension was a major
contributor to the risk of stroke in the study sample with a PAR of 57.2% followed by diabetes with a 22.8% PAR. Obesity and family history of stroke contributed to around 11.8% and 12.0% of PAR respectively.
Discussion

In this study we used data from the JHS to assess the association of biological, psychosocial and socioeconomic risk factors on the incidence of stroke. We estimated odds ratios of each individual risk factor and their respective PARs. The study found that hypertension and diabetes are the most significant risk factors of stroke, followed by Framingham stroke risk score, family history of stroke, and unemployment.

The results of the current study indicate that hypertension is the most significant risk factor of stroke in the African American population. Hypertension is associated with an 80% excess risk and also contributed to 57% of PAR for stroke in this population. These findings are consistent with previous studies which showed that hypertension is the most important risk factor of stroke and underlies the importance of hypertension control in African Americans. The PAR of hypertension of 57% is slightly higher than the PAR reported in the INTERSTROKE study (52%). The proportion of participants with hypertension in this study is 68.6%, which is higher than that reported in the INTERSTROKE study population (53.5%). The higher prevalence of hypertension in African Americans is attributable to several genetic, environmental and treatment factors. For example, studies have found that certain genetic mutations are more prevalent in the African American population, which in turn, may have an effect on the pathophysiology of hypertension, leading to a higher prevalence of hypertension in African Americans. African Americans are also less likely to respond to certain antihypertensive drugs,
however, we were unable to assess the effect of hypertension control on the risk of stroke due to data limitation.

Consistent with studies such as the INTERSTROKE and the Northern Manhattan Stroke Study (NOMASS), we found that diabetes was a significant risk factor for stroke with 73% excess risk and 22% PAR. The PAR of diabetes in this population is much higher than the 5% PAR reported in the INTERSTROKE study. The higher PAR in African Americans could be due to the high prevalence of diabetes in this population.

Unlike several other studies including INTERSTROKE and NOMASS, physical activity was not found to be significantly associated with stroke in our study. This finding could be due to the difference in ways physical activity was measured in various studies. In the JHS, physical activity was measured using the Active Living Index which measures leisure time physical activity only. The INTERSTROKE study classified participants as physically active if they were involved in moderate or strenuous exercise for at least four hours per week, whereas the NOMASS used a questionnaire adapted from the National Health Interview Survey (NHIS) which assessed the frequency and duration of 14 activities to measure physical activity. We found that alcohol consumption is associated with 33% excess risk of stroke, but the relationship is not statistically significant. Results from several studies indicated that heavy alcohol consumption increases the relative risk of stroke while moderate or low alcohol consumption may be a protective factor. A meta-analysis of pooled data from several studies has shown that heavy alcohol consumption increases the risk of stroke by 64%. The JHS examinations ask questions about alcohol consumption in the past 12 months and the number of drinks per week. However 56.5% of study participants did not answer the alcohol consumption question, leaving us unable to distinguish between heavy and moderate/low alcohol consumption.
In our study, we found that the Framingham stroke risk score was significantly associated with the risk of stroke and each 1% increase in the Framingham risk score could lead to a 4% increase in the risk of stroke. Framingham stroke risk score was developed using the Framingham Heart Study cohort and it has been used in other studies to evaluate the risk of stroke. The Framingham stroke risk score is easy to calculate and has practical significances. Healthcare professionals could assess individual’s Framingham stroke risk score, identify those who are at higher risk, and prescribe lifestyle modifications and medical managements to reduce the risk of stroke.

The current study did not find a significant association between obesity and stroke. Although BMI is the most frequently used measure of obesity, anthropometric studies have shown that body composition differs between African Americans and Caucasians in that African Americans have denser muscle and skeletal mass. Measures of abdominal obesity such as WHR or WHtR are better measures of obesity in African Americans. In this study, we did not find significant relationships between obesity and stroke when obesity was measured by BMI, WHtR or a composite of BMI and WHtR. The association of obesity and stroke has been conflicting in the literature. While some studies found a significant independent association between obesity and stroke, others did not find a similar association. Such inconsistent results have been reported across the gender of participants and the subtype of stroke. For example, results from the INTERSTROKE study show that there was no association of BMI and stroke, however, abdominal obesity, measured by WHR was significantly associated with the risk of stroke. Research has shown that obesity is strongly associated with hypertension and diabetes, which are highly prevalent conditions in our study population. Due to this reason, the independent
association between obesity and stroke may not be as evident as other traditional risk factors such as hypertension and diabetes in the African American population.

Our study did not find any significant associations between psychosocial risk factors such as depression, stress and major life events and stroke. Although depression after the incidence of stroke has been widely studied, very few studies have looked at depression as a prospective risk factor of stroke. Only one study reported that the relative risk of stroke is significantly higher in African Americans with depression (RR 2.60) than non-Hispanic whites. In this study, depression was measured using a composite of CES-D scores of greater than 23 or the use of antidepressant medications, because CES-D score was not available for 44.8% of the participants. The percentage of missing data for CES-D is significantly different in cases and controls (53.5% in cases and 42.9% in controls; p<0.001). Also, only 22.5% of participants who were on depression medications had responded to the CES-D scale; the low response rate indicates that the study participants with depression were less likely to answer the CES-D scale leading to non-response bias in the measurement of depression. The INTERSTROKE study reported that self-perceived psychosocial stress significantly increased the risk of ischemic stroke but not ICH. Jood et al. found that permanent self-perceived stress was significantly associated with ischemic stroke. Our study did not find that psychosocial stress was associated with an increased risk of stroke. Since both ischemic stroke and ICH are pooled together in our study, the association between stress and stroke could have been biased towards the null. Similarly, major life events were not found to be significantly associated with incident stroke in the current study. Major life events are dramatic events which have a cumulative effect over time on the psychological well-being of the participant, increasing the risk of ischemic stroke. The study found that employed participants were less likely to have stroke, which could be due to better
living standards as a consequence of employment. Unlike findings from the NOMASS, our study did not find a significant association between education level and the risk of stroke. Level of education is a frequently used surrogate measure for SES since higher education level is correlated with high income leading to better healthcare access. However, studies have shown that the correlation between education and income is low in African Americans compared to Caucasians, which might explain the insignificant association between education level and the risk of stroke in our study.

In summary, the results of the current nested case-control study indicate that biological risk factors contribute significantly to the risk of incident stroke in African Americans. The combination of hypertension, diabetes, obesity, family history of stroke, alcohol consumption, and the Framingham stroke risk score accounted for 76.5% of the risk of stroke. With the addition of psychosocial risk factors the PAR of stroke increased to 77.5%. PAR for the combination of risk factors is generally smaller than the sum of individual risk factor PARs since PAR calculations were based on logistic models which assume multiplicative effect on the odds ratio scale. Although previous studies had evaluated the risk factors of stroke, ours is the first study to consider biological, psychosocial and socioeconomic risk factors in the African American population and compute their corresponding PARs. The aim of the JHS was to investigate the causes of high incidence of CVDs in African Americans and provide a basis for efforts aimed at improving the overall health in the African American population in the US. Our study findings shed lights on the risk factors of stroke and their respective PARs in African Americans, which could be used to guide the design and assessment of effective strategies for stroke prevention in the African American population.
Our study has several strengths. First, we studied the biological, psychosocial and socioeconomic risk factors in the African American population in one study and estimated their individual and collective impact on the risk of stroke using PARs. PAR provides information on the percentage of stroke cases that could be prevented by eliminating the risk factor(s) and is an important measure to assess the potential impact of stroke prevention programs. Second, great care has been taken to minimize the risk of biases in the design of our study. For example, the chance of diagnostic misclassification bias of stroke is minimal since we only selected stroke cases that had been adjudicated against participants’ hospital records; also, the effect of recall bias in case control studies is also minimized by measuring risk factor exposure at baseline, prior to the incidence of stroke. In addition, although mortality is high in the JHS cohort, selection bias in our study is minimized due to the use of incidence density sampling, which allows us to select controls from the pool of JHS participants who were alive at the time of incidence stroke cases and thereby only controls with similar person-years as their corresponding cases in the cohort were selected. This approach leads to selection of cases and controls with the same length of exposure mitigating the selection bias. And lastly, the use of Framingham stroke risk score in our stroke risk models and our findings related to the association between Framingham stroke risk score and incident stroke provide quantitative evidence for stroke risk factor modification in African Americans with increased risk of stroke.

Limitations

The results of the current study should be interpreted in light of certain limitations. First, in order to obtain a sufficient sample for analysis, we combined ischemic stroke and hemorrhagic stroke events in analysis; previous studies have indicated that there are minor differences in the risk factors of ischemic stroke and hemorrhagic stroke. While risk factors such as diabetes, low
physical activity, stress and depression have been shown to be associated with ischemic stroke in a few studies, their associations with hemorrhagic stroke are unclear.\textsuperscript{13, 99} The findings of the associations between certain risk factors and stroke could have been affected due to the pooling of ischemic and hemorrhagic stroke events. Nevertheless, our study is the first one to report the risk biological, psychosocial and socioeconomic risk factors of stroke in the African American population. Second, the JHS data does not contain information on TIA and carotid bruit which were biologically linked to stroke and were found to be significant risk factors of stroke in previous studies.\textsuperscript{100, 101} TIAs have very similar biological mechanisms as ischemic stroke and are often labeled as mini strokes. The inclusion of these risk factors could have accounted for a higher PAR of stroke. Finally, the JHS is a single-site multicenter epidemiologic study of African Americans in the Jackson area in Mississippi. Caution should be exerted when extrapolating the results of this study to African American populations in general.
CHAPTER IV: CONCLUSIONS
Conclusions

In conclusion, the six biological risk factors together accounted for 76.5% of PAR in the African Americans in the JHS. The association of psychosocial risk factors and incident stroke is unclear and further studies are necessary. The PARs of stroke risk factors can be used to guide the design and evaluation of health promotion programs targeted to reduce the risk factors of stroke in the African American population.
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6) National vital statistics report. Available at website

7) Behavioral Risk Factor Surveillance System: prevalence and trends data. Available at Centers for Disease Control and Prevention website.


14) The percent of the total population is calculated by using the total population of all races. The totals for each geography can be found in Table 11, page 18 of the 2010 Census Brief, Overview of Race and Hispanic Origin: 2010 available at www.census.gov/prod/cen2010/briefs/c2010br-02.pdf


26) NHANES, NHLBI


71) Peng C-YJ, Harwell M, Liou S-M, Ehman LH. Advances in missing data methods and implications for educational research. Real data analysis. 2006;31-78.


LIST OF APPENDICES
APPENDIX A: TABLES
Table 1: Operationalization of risk factors

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Variable name in JHS data</th>
<th>Operationalization of variable</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Age</td>
<td>Measured as a continuous variable</td>
</tr>
<tr>
<td>Gender</td>
<td>Gender</td>
<td>Male/Female/Other</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>Body Mass Index Grouping Visit 1</td>
<td>BMI &lt;25 was categorized into normal, BMI 25 – 30 as overweight and BMI ≥ 30 as obese</td>
</tr>
<tr>
<td>WHtR</td>
<td>Waist to Height Ratio</td>
<td>WHtR &gt;=0.53 in men or WHtR&gt;=0.50 in women</td>
</tr>
<tr>
<td>Smoking</td>
<td>Cigarette Smoking Only</td>
<td>Smoking was categorized into non smokers, former smokers and current smokers</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td>Alcohol drinking classification I</td>
<td>Alcohol intake was classified as having consumed alcohol in the past 12 months and no alcohol intake</td>
</tr>
<tr>
<td><strong>Exercise</strong></td>
<td>Active Living Index (leisure time physical activity variable)</td>
<td>Measured as a continuous variable</td>
</tr>
<tr>
<td><strong>Family history</strong></td>
<td>Have mother had stroke, Doctor said father had stroke, Has siblings had stroke</td>
<td>Yes or No</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>JNC 7 BP Classification</td>
<td>Categorized into hypertension and normal based on JNC 7 BP classification</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>Diabetes Status (Type I or II)</td>
<td>Categorized into diabetes and no diabetes</td>
</tr>
<tr>
<td><strong>Myocardial infarction</strong></td>
<td>History of MD diagnosed MI</td>
<td>Yes or No</td>
</tr>
<tr>
<td><strong>Coronary Heart Disease</strong></td>
<td>Coronary Heart Disease</td>
<td>Yes or No</td>
</tr>
<tr>
<td><strong>Atrial Fibrillation</strong></td>
<td>Atrial Fibrillation</td>
<td>Yes or No</td>
</tr>
</tbody>
</table>

*Psychosocial risk factors*
<table>
<thead>
<tr>
<th><strong>Life events</strong></th>
<th><strong>Major Life Events: Occurrence (0 - 9)</strong></th>
<th><strong>Measured as a continuous variable</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress</td>
<td>Global Stress Total Score</td>
<td>Measured as a continuous variable</td>
</tr>
<tr>
<td></td>
<td>1: Stress in your job</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2: Stress in your relationships</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3: Stress living in neighborhood</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4: Stress caring for other</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5: Stress related to legal problems</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6: Stress from medical problems</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7: Stress from racism/discrimination</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8: Stress meeting basic needs</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>Total Depressive Symptoms Score</td>
<td>Measured as a continuous variable</td>
</tr>
<tr>
<td>Depression Rx</td>
<td></td>
<td>Categorized as users of antidepressants and non users</td>
</tr>
<tr>
<td>Occupation</td>
<td>Kind of work you do</td>
<td>Categorized as working or unemployed</td>
</tr>
<tr>
<td>Income status</td>
<td>Income Status</td>
<td>Categorized into lower-middle and below, upper-middle and above</td>
</tr>
<tr>
<td>Education level</td>
<td>Education Level Group 3</td>
<td>Grouped as less than high school, high school/GED or some college or higher</td>
</tr>
</tbody>
</table>
TABLE 2 – Baseline characteristics of cases and controls

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Cases (N = 129)</th>
<th>Controls (N = 590)</th>
<th>P-value</th>
<th>Standardized Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biological Factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age in years, Mean (SD)</td>
<td>64.8 (10.2)</td>
<td>56.5 (11.7)</td>
<td>&lt;.0001</td>
<td>74.1%</td>
</tr>
<tr>
<td>Body Mass Index (BMI), Mean (SD)</td>
<td>31.0 (6.1)</td>
<td>32.0 (7.1)</td>
<td>0.0266</td>
<td>14.6%</td>
</tr>
<tr>
<td>Waist to Height Ratio (WHtR), Mean (SD)</td>
<td>0.61 (0.1)</td>
<td>0.60 (0.1)</td>
<td>0.0156</td>
<td>11.0%</td>
</tr>
<tr>
<td>Obesity, n (%)</td>
<td>90 (69.8%)</td>
<td>425 (72.0%)</td>
<td>0.5008</td>
<td>20.8%</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>47 (36.4%)</td>
<td>230 (39.0%)</td>
<td>0.2735</td>
<td>5.3%</td>
</tr>
<tr>
<td>Female</td>
<td>82 (63.6%)</td>
<td>360 (61.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol, n (%)</td>
<td>48 (37.2%)</td>
<td>252 (42.7%)</td>
<td>0.0817</td>
<td>9.9%</td>
</tr>
<tr>
<td>Smoking status, n (%)</td>
<td></td>
<td></td>
<td>0.0722</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>26 (20.2%)</td>
<td>70 (11.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous smoker</td>
<td>29 (22.5%)</td>
<td>130 (22.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non smoker</td>
<td>74 (57.4%)</td>
<td>384 (65.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>53 (41.1%)</td>
<td>134 (22.7%)</td>
<td>&lt;.0001</td>
<td>41.8%</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>113 (87.6%)</td>
<td>380 (64.4%)</td>
<td>&lt;.0001</td>
<td>56.3%</td>
</tr>
<tr>
<td>Antihypertensive Medication, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial Infarction, n (%)</td>
<td>4 (3.1%)</td>
<td>9 (1.5%)</td>
<td>0.0833</td>
<td>10.5%</td>
</tr>
<tr>
<td>Coronary Heart Disease, n (%)</td>
<td>19 (14.7%)</td>
<td>42 (7.1%)</td>
<td>&lt;.0001</td>
<td>24.6%</td>
</tr>
<tr>
<td>Cardiovascular Disease, n (%)</td>
<td>19 (14.7%)</td>
<td>61 (10.3%)</td>
<td>0.0096</td>
<td>13.1%</td>
</tr>
<tr>
<td>Left Ventricular Hypertrophy (LVH), n (%)</td>
<td>34 (26.4%)</td>
<td>74 (12.5%)</td>
<td>&lt;.0001</td>
<td>35.4%</td>
</tr>
<tr>
<td>Family history of stroke, n (%)</td>
<td>54 (41.9%)</td>
<td>188 (31.9%)</td>
<td>&lt;.0001</td>
<td>20.8%</td>
</tr>
<tr>
<td>Active living index, Mean (SD)</td>
<td>2.0 (0.8)</td>
<td>2.1 (0.8)</td>
<td>0.222</td>
<td>7.3%</td>
</tr>
<tr>
<td><strong>Psychosocial Factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression, n (%)</td>
<td>21 (16.3%)</td>
<td>85 (14.4%)</td>
<td>0.2371</td>
<td>5.2%</td>
</tr>
<tr>
<td>Global stress score, Mean (SD)</td>
<td>3.6 (3.8)</td>
<td>4.9 (4.2)</td>
<td>&lt;.0001</td>
<td>33.1%</td>
</tr>
<tr>
<td>Life Events, Mean (SD)</td>
<td>2.5 (1.8)</td>
<td>2.8 (2.0)</td>
<td>0.0005</td>
<td>17.4%</td>
</tr>
<tr>
<td><strong>Socioeconomic Factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education, n (%)</td>
<td></td>
<td></td>
<td>0.0503</td>
<td></td>
</tr>
<tr>
<td>High school and less</td>
<td>70 (54.3%)</td>
<td>248 (42.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>College education and degree</td>
<td>57 (44.2%)</td>
<td>338 (57.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insurance, n (%)</td>
<td>118 (91.5%)</td>
<td>515 (87.3%)</td>
<td>0.0365</td>
<td>12.3%</td>
</tr>
<tr>
<td>Employment Status, n (%)</td>
<td>35 (27.1%)</td>
<td>318 (53.9%)</td>
<td>&lt;.0001</td>
<td>56.7%</td>
</tr>
<tr>
<td>Income Status, n (%)</td>
<td></td>
<td></td>
<td>0.0022</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>-------</td>
<td>-------</td>
<td>------------</td>
<td></td>
</tr>
<tr>
<td>Lower - Middle</td>
<td>63</td>
<td>48.8%</td>
<td>200</td>
<td>(33.9%)</td>
</tr>
<tr>
<td>Middle - Upper</td>
<td>46</td>
<td>35.7%</td>
<td>296</td>
<td>(50.2%)</td>
</tr>
</tbody>
</table>

1 Values < 0.05 are BOLDED; Paired t-test for continuous variables, McNemar's test for dichotomous variables, and univariate Conditional logistic regression for categorical variables

2 Standardized difference >= 10% considered to be significant. Standardized difference = \( 100 \times \frac{(x_1-x_2)}{\sqrt{\frac{s_1^2+s_2^2}{2}}} \), where \( x_1 = \text{mean of group 1}, \ x_2 = \text{mean of group 2}, \ s_1 = \text{standard deviation of group 1}, \ \text{and} \ s_2 = \text{standard deviation of group 2.} \)
<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biological factors</strong></td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>0.9 (0.5 - 1.4)</td>
</tr>
<tr>
<td>Framingham stroke risk score</td>
<td>1.05 (1.02 - 1.08)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>1.3 (0.8 - 2.1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.8 (1.1 - 3.1)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.7 (1.1 - 2.7)</td>
</tr>
<tr>
<td>Family History</td>
<td>1.4 (0.9 - 2.2)</td>
</tr>
<tr>
<td>Active Living Index</td>
<td>1.03 (0.8 - 1.3)</td>
</tr>
<tr>
<td><strong>Psychosocial factors</strong></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>0.7 (0.4 - 1.2)</td>
</tr>
<tr>
<td>Major life events</td>
<td>1.02 (0.9 - 1.1)</td>
</tr>
<tr>
<td>Stress</td>
<td>0.9 (0.9 - 1.0)</td>
</tr>
<tr>
<td><strong>Socioeconomic factors</strong></td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>0.9 (0.6 - 1.4)</td>
</tr>
<tr>
<td>Employed</td>
<td>0.4 (0.3 - 0.7)</td>
</tr>
<tr>
<td>Risk factors</td>
<td>PAR</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>------</td>
</tr>
<tr>
<td><strong>Biological factors</strong></td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>11.8%</td>
</tr>
<tr>
<td>Framingham stroke risk score</td>
<td>50.9%</td>
</tr>
<tr>
<td>Alcohol</td>
<td>-6.8%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>57.2%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>22.8%</td>
</tr>
<tr>
<td>Family History</td>
<td>12.0%</td>
</tr>
<tr>
<td><strong>Psychosocial factors</strong></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>2.3%</td>
</tr>
<tr>
<td>Stress</td>
<td>-42.3%</td>
</tr>
<tr>
<td><strong>All biological risk factors</strong></td>
<td>76.5%</td>
</tr>
<tr>
<td><strong>All biological and psychosocial risk factors</strong></td>
<td>77.5%</td>
</tr>
</tbody>
</table>
APPENDIX B: FIGURES
FIGURE 1: Theoretical framework of stroke risk factors

[Diagram showing the relationship between biological risk factors, psychosocial risk factors, other risk factors, blockage/bursting of blood vessel, and stroke.]
FIGURE 2: Odds ratios (95% CI) for stroke risk factors: Results of logistic regression
CURRICULUM VITAE
CURRICULUM VITAE

SASIKIRAN NUNNA
sasikiran545@gmail.com 662-801-9284 | 101 Creekmore Dr Apt 2123, Oxford, MS 38655.

EDUCATION:

• The University of Mississippi
  Aug 2012 – May 2017
  Currently pursuing PhD. in Pharmacy Administration (with specialization in Health Economics and Outcomes Research)

• Birla Institute of Technology and Science, Pilani, India
  Aug 2006 – May 2010
  Bachelor of Pharmacy (Hons.)

TECHNICAL SKILLS:

• Advanced MS Excel skills and SAS skills
• Administrative claims data management and analysis using SAS, SQL, STATA and SPSS
• Drug level forecasting, market size forecasting and econometric modelling in STATA
• Understanding and applying appropriate statistical techniques to research
• Decision modeling using TreeAge

WORK EXPERIENCE:

• Applied Data Analytics – HEOR Intern at Xcenda LLC
  Jun 2015 – Aug 2015
  o End of life costs and resource use associated with advanced melanoma
    ▪ Assess the incremental all-cause/melanoma related costs and health care utilization
  o Worked on electronic medical records (EMR)
• Analyst – Center for Pharmaceutical Marketing and Management (CPMM) at the University of Mississippi
Jan 2013 – Present
  o Worked on Ad hoc analyses using SAS for Mississippi Medicaid utilizing the fee for service and managed care claims data as a part of research assistantship (RA)
  o Projects related medication adherence, opioid abuse monitoring exceptions monitoring and access to care
  o Worked on various PQA/NCINQ measures in Mississippi Medicaid data and also worked on a PQA measure update panel

• Analyst - IMS Health
  o Worked as a full time employee in the analytic services team, a part of the Commercial Effectiveness Services (CES) segment of IMS Health at India Delivery Center (IDC), Bangalore
  o Worked extensively on IMS prescription data using to assess prescription and payer activity across various therapeutic areas; Performed post-launch brand performance tracking in US, using prescription, sales data as well longitudinal data of IMS
  o Projects utilizing anonymous patient level data (APLD): Compliance and persistence studies, patient and physician segmentation projects, sales force segmentation projects using SAS
  o IMS datasets: NPA, NSP, Xponent, MIDAS, Lifelink

• Associate Analyst – Global Data
  Jun 2010 to Jul 2011
  o Developed patient based models to forecast market size and drug sales in US, EU-5 and Japan
  o Responsibilities include analysis of prescription and claims data for inputs to the models and building forecasting models for market size forecasting and drug sales

SELECTED POSTER PRESENTATIONS:

• Nunna S, D’Souza AO, Eaddy M, Landsman-Blumberg PB. Use of Joinpoint Regression to define phases of care in patients with advanced melanoma: An evaluation from metastatic diagnosis until death (ISPOR 2016)
• D’Souza AO, Okoro T, Shah M, Nunna S, Eaddy M. End-of-life Costs in Advanced Melanoma (NCCN annual conference 2016)
• Nunna S, Banahan III B, Hardwick SP, Noble S. Oral anticoagulant use: Resource utilization and the occurrence of bleeding events (ISPOR 2016)
• Nunna S, Shah R, Banahan III B, Hardwick SP, Clark JP. Prevalence of mental health disorders and access to care among children enrolled in the Mississippi Medicaid (ISPOR 2015)

• Nunna S, McCaffrey D. Assessing current attitudes and perceptions of the University of Mississippi employees regarding healthcare services provided by Employee Health Service (Southern Pharmacy Administration conference 2014)

RELEVANT COURSEWORK:

• Research methods, primary data techniques, secondary data techniques, data management (SAS)
• Quantitative methods in psychology, general linear models, applied multivariate analysis, econometrics, applied quantitative analysis (panel data estimation techniques), applied longitudinal data techniques
• Drug development and marketing, pharmacoepidemiology
• Pharmacoeconomics, health economics, pharmaceutical and healthcare policy

EXTRA-CURRICULAR ACTIVITIES AND HONOR SOCIETIES:

• Recipient of William E. Farlow fellowship for the year 2015
• Member of Rho Chi Academic Honors Society in Pharmacy, Chi Chapter
• International student representative on two Chancellor’s standing committees (International Student Programs and Recruitment Admissions Orientation and Advising), 2013-15
• Secretary, Graduate Student Council, 2013-14