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OBESITY AND RISK OF STROKE IN NHANES I FOLLOW UP STUDY

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ABSTRACT

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Stroke is the third leading cause of death in the US. Role of obesity as an independent risk factor has been relatively well established for coronary heart diseases but not for stroke. Purpose of this study was to assess long-term risk of stroke due to obesity measured at baseline. The research was conducted using First National Nutritional Health and Examination Survey and its follow ups. Overall, increased risk of stroke was observed in obese individuals (BMI > 30 kg/m^2). Similar association was observed in different subgroups of race, gender, those with or without diabetes and cardiovascular disease.

OBESITY AND RISK OF STROKE IN NHANES-I FOLLOW UP STUDY

THESIS

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CHAPTER 1

INTRODUCTION TO STUDY

Stroke is a leading cause of mortality and morbidity in the Unites States. Stroke killed 167,366 people in 1999 thus becoming the third leading cause of death the US. (The Centers for Disease Control and Prevention, CDC, 2002). According to National Heart Lung and Blood Institute (NHLBI) about 600,000 people suffer a new or recurrent stroke each year. About 500,000 of these are first attacks and 100,000 are recurrent attacks (American Heart Association, 1999). Incidence of stroke was highest in 1968 in the US and then stabilized to 0.5 to 1.0 per 1000 in year 2000. Although incidence of stroke has stabilized over last 2 decades, aging of the US population has contributed to a 3.2% increase in actual number of stroke deaths (American Heart Association, 1997). Hypertension, diabetes mellitus, and smoking are some of the well-established risk factors of stroke. Role of obesity as an independent risk factor has been relatively well established for coronary heart diseases but not for stroke. Recently, the American Heart Association Prevention Conference declared obesity as an independent risk factor based on the results of Honolulu Heart Study. However, not all studies still regard it as an important risk factor (Tegos, Kalodiki, Daskalopoulou, & Nicolaides, 2000). Large population based follow up studies like Nurses Health Study, Honolulu Heart Study, and others have shown increased risk of stroke at higher levels of body mass index (BMI) in men and women. These studies focused on central obesity, using BMI as a parameter of

obesity. (Gillum, Mussolino, & Madans, 2001; Rexrode, et al., 1997). On the other hand, some researchers have given more importance to the pattern of body fat distribution over central obesity (Barrett Connor & Khaw, 1988). Therefore, role of obesity (measured by BMI) ås an independent risk factor of stroke has remained somewhat controversial. Thus, there appear some consistencies among results published over last two decades. In addition to inconsistencies among various studies of obesity and stroke, limited literature is available on whether the association between obesity and stroke changes in presence or absence of associated cardiovascular conditions. Obesity being one of the major risk factors for all chronic diseases, the association between obesity and stroke deserves more attention as recommended by some researchers.

Aim of this study was to explore the association between long-term risk of stroke and baseline obesity using BMI as a measure of obesity. This study analyzed the risk of stroke at different levels of BMI. The study used data collected in the National Health and Nutritional Examination Survey done in 1975 and its follow-up study from 1982 to 1992. This secondary data is available for public use from the CDC.

Problem and Purpose

The purpose of this study was to examine the association between stroke and obesity and to further explore the role of obesity as a risk factor of stroke in the presence of other potential risk factors. Stroke or cerebrovascular diseases are due to abrupt impairment of brain function secondary to focal or multifocal changes in intra or extra cranial blood vessels. These changes refer to ischemia or hemorrhage in brain parenchyma or sub arachnoid space. Ischemia or hemorrhage ceases the blood supply to

brain parenchyma causing cerebral infarction and subsequent focal or generalized neurological deficit. Ischemic strokes are due to atherosclerosis of intra or extra cranial blood vessels and thromoboemolism secondary to it (Cecil, 1998). This mechanism is very similar to thromoboelmolism of coronary artery and subsequent myocardial ischemia. Atherogenic serum lipids and high blood cholesterol levels are key factors in the pathophysiology of thromboembolism. Obesity is associated with higher levels of blood pressure, blood glucose, and atherogenic serum lipids (World Health Organization, 2000). Obesity has been shown to increase the risk of having hypertension and diabetes. These factors if present together can worsen the course of heart disease (American Heart Association, 2002).

Obesity can increase risk of stroke, in the same way as coronary artery diseases. Honolulu Heart Study, Framingham Heart Study, Whitehall Study and others have shown increased risk of stroke at higher levels of BMI (BMI > 27kg/m^2) especially among smokers (Shinton, 1997; Abbott, Donahue, & MacMohan, 1987). Other studies have shown increased risk of stroke due to diabetes, augmented by presence of obesity and hypercholesterolemia. This study hypothesizes that obesity independently increases risk of stroke by accelerating the process of thromboembolism. In addition to increasing the risk of ischemic strokes, arteriosclerosis of cerebral arteries causes non-compliant arterial walls leading to hypertension and subsequent increase in the risk of hemorrhagic strokes.

This study computed hazard ratios for stroke at different levels of BMI. Association between obesity and stroke was further explored in different strata of co morbid conditions diagnosed at baseline. These strata were gender, race, diabetes

mellitus, and cardiovascular disease (presence of at least history of heart attack or diagnosis of heart disease or hypertension). Diabetes is an independent risk factor of stroke. (Noto et al., 1988). The effect of obesity on risk of stroke during the later stages of diabetes is not well established. This relationship may change during later stages as a diabetic individual actually loses weight. This study attempts to analyze the risk of stroke due to obesity among diabetics and non-diabetics to see if their risks are different from their comparison normal weight group. Thus, it will allow assessing long-term risk of stroke due to obesity among diabetics. The risk is also assessed by strata of cardiovascular conditions to explore similar trend in cardiovascular patients who lose some weight after being diagnosed with heart disease. Individuals with and without these conditions are compared to their normal weight counterparts in corresponding category to evaluate independent effect of obesity.

Research Question

Studies have shown increased risk of stroke at BMI levels 27 kg/m^2 and above. To further explore this association, this study will test the hypothesis whether long-term risk of stroke increases at higher levels of BMI and if this association changes significantly in presence or absence of co morbid conditions such as hypertension, diabetes mellitus, and heart disease.

Significance

Consequences of stroke are serious as most survivors are left with long-term serious physical and mental disability. Ten to fifteen percent of ischemic stroke patients die owing to pre existing systemic conditions. Of the survivors, $1/5^{th}$ require long term

institutional care for recovery and nearly a third of population is left with disabilities. In 1992, one million people of age over 15 had disabilities resulting from stroke (American Heart Association, 1997). This makes stroke the second most frequent cause of neurological morbidity in the developed countries.

Economic cost associated with morbidity and mortality due to stroke is very high. Loss of stroke patients from workforce and the extended hospital stay during recovery increases indirect cost associated with this disease to exceedingly high levels. Estimated cost of stroke and cardiovascular diseases in year 1999-2000 together was $329.2 billion of which stroke accounted for $50 billion, direct and indirect cost together (American Heart Association, 2002).

As stroke continues to increase morbidity and mortality in the US population, epidemic of obesity and increasing aging population make control of stroke decisive. Highest increase in obesity has occurred in the last decade in all states and regions of US. This increase was maximum among young adults between 18-29 years of age. Epidemic of obesity has contributed to 300,000 premature deaths each year in US (CDC, 2002). As highest increase in obesity has occurred among young population, burden of chronic diseases is likely to be extremely high in coming years if appropriate prevention strategies are not implemented. Stroke being major cause of morbidity and mortality, it is extremely important to study role of obesity as a modifiable risk factor of stroke.

Etiology of Stroke, as any other chronic disease is multifactorial. Disease outcome and prognosis is determined by complex interplay of co morbid conditions. It is therefore important to identify modifiable risk factors and design appropriate prevention

strategies. Some studies have reported increased risk of stroke with increase in obesity but need to strengthen these findings as advised by researchers remains.

Findings of this study should add to existing literature to better define role of obesity as a risk factor for stroke. This study will elucidate on the change in risk of stroke due to obesity in presence of diabetes and cardiovascular conditions. This should also strengthen or refute findings of previous studies and generate research questions for additional studies. The ultimate goal of this study is to establish obesity as an important independent risk factor for stroke in order to aid designing prevention strategies and reduce burden due to morbidity and mortality.

Definition of Terms

Stroke: Stroke is defined as a neurological deficit lasting more than 24 hours caused by reduced blood flow in a particular artery supplying brain (Cecil, 1998). Eighty three percent of strokes are ischemic and 17% are hemorrhagic. (American Stroke Association, 2002).

Transient Ischemic Attack (TIA): Clinically, precursor of stroke, lasts less than 24 hours and may leave permanent brain injury if not resolved in one-hour period.

Ischemic Stroke: Accounting for 83% of total stroke, these strokes are due to reduced blood supply secondary to thromboembolic occlusion of artery. Reduced blood flow deprives brain of supply of glucose and oxygen critical for normal high energy demand functioning. The degree of occlusion, adequacy of collateral circulation and duration of blood flow determines severity of brain damage. Histopathological outcome

is cerebral infarction characterized by necrosis of neurons, glia and endothelial cells (Cecil, 2000).

Hemorrhagic Stroke: Hemorrhagic strokes account for 17% of total cases (American Heart Association, 1997). Hemorrhage can be intracranial or in the subarachnoid space due to rupture of a blood vessel. Brain damage is extensive in this type of stroke and outcome is frequently fatal. Seventy five percent patients with hemorrhagic stroke die of cerebral edema and herniation.

Obesity: Obesity is defined as a condition of abnormal or excessive body fat distribution in adipose tissue to the extent that health may be impaired (Garrow, 1997).

Body Mass Index (BMI): This is calculated using the formula, body weight in kilograms divided by square of height in meters. The Medline Encyclopedia uses BMI as a parameter to define obesity. According to this definition, an individual is obese when his or her BMI is more than 30 kg/m^2

CHAPTER 2

BACKGROUND AND RATIONALE

Stroke and cerebrovascular diseases have been studied in detail in literature. Over past two decades, many researchers have studied the risk factors of stroke. This chapter includes discussion on non-modifiable and modifiable risks factors of stroke and role of obesity in chronic diseases and stroke with salient literature published on the same.

Non-Modifiable Risk Factors of Stroke

Age

Incidence and mortality due to stroke increase with increasing age. Incidence of stroke doubles in each decade after 55 years of age (American Stroke Association, 2002; Cecil, 1998). In 1995, there were 46 deaths per 100,000 in the age group of 55 to 64 years. This figure rose to 1637 per 100,000 with increase in age group of 85 years and older. Causes of stroke differ within different age groups. Children less than 15 yrs of age have stroke secondary to hematological diseases and vasculopathies. These causes being out of scope of this study are not discussed in detail. Atherogenic causes of stroke dominate after the age of 35 years. Presences of other risk factors like smoking and heavy intake of alcohol are believed to increase the risk of stroke in this age group (Bendixen, Posner, & Lango, 2001). Increasing age and presence of one or more chronic conditions further increase the chances of stroke. Studies have found substantial risk of stroke among elderly people. One in every 40 patients reported suffering from ischemic

stroke within six months after they were discharged with diagnosis of myocardial infarction (Lichtman, Krumholz, Wang, Radford, & Brass, 2002). A study in Italy has reported age as an independent predictor of stroke with different risk factors for stroke changing with age. (Noto et al., 1988).

Gender

Stroke is more common in men than in women. However, mortality due to stroke is higher in women at all ages with more than half of total stroke deaths occurring in women (American Stroke Association, 2002). Women on high estrogen contraceptive pills have a higher risk of stroke. This risk is further increased by presence of other risk factors such as migraine, smoking, and hypertension in women over 35 years of age (Simon et al, 2001). Risk of stroke varies in different ethnic groups in women. Black women less than 45 years of age have death rate three times higher than the death rates of their White counterparts (American Stroke Association, 2002). Mortality in Hispanic women is lower than mortality among White or Black women. Death rates in Hispanic women are 5% less than death rates for Whites (Wyller, 1999).

Ethnicity

Death rates due to stroke are higher in African Americans than Whites, partially due to higher incidence of hypertension and diabetes among Blacks. Risk of fatal stroke is higher in blacks. Age-adjusted stroke mortality rates in blacks are 2 to 4 times higher than Whites. Black men of 65 years or more experience death rates 3 times more than Whites (CDC, 1999). Men of Hispanic origin have 10% lower death rates. Asian Americans and Alaska natives have rates lower than Whites (CDC, 1999). Chinese and

Japanese populations also experience high incidence of stroke. The changing profile of stroke mortality and morbidity across different ethnic populations partially reflects difference in other risk factors of stroke in these populations (Sacco et al., 2001).

Family History of Stroke

Framingham heart study of offsprings revealed increased risk of stroke in individuals with family history of stroke. Proposed reasons for increased incidence of stroke were genetic tendency for stroke and genetic determination of other risk factors of stroke. It is also shown that family history is an independent risk factor for all stroke subtypes except cardio embolic and undetermined type of stroke (Polychronopoulos, 2002). Other study has proposed that family history plays a significant role in sub arachnoid hemorrhage but is not a major player in pathogenesis of ischemic stroke (Kubota et al., 1997).

Modifiable Risk Factors of Stroke

Hypertension

Hypertension is the only risk factor found consistently related with every type of stroke. Individuals with borderline hypertension are at two times higher risk of stroke than normotensive individuals. Risk of stroke increases four times in individuals with blood pressure 160/95 mm of Hg. Hypertension increases risk of thromboemobilic as well as lacunar and hemorrhagic strokes. A study by the Department of Neuroepidemiology, Beijing Neurosurgical Institute, Beijing, showed stronger association for systolic blood pressure than diastolic blood pressure with 25% increase in risk of stroke for every 10 mm of Hg rise in systolic blood pressure (Fang, 2001). Higher

systolic blood pressure is a direct cause of stroke however; elevated diastolic blood pressure and mean pressure are correlated with incidence of stroke. Systolic blood pressure more than 14 mm of Hg of normal is strongly related with stroke (RR > 4) (Chronic Disease Epidemiology and Control, 1998). For every 5 mm of Hg increase in diastolic blood pressure in the range of 70 to 110 mm of Hg, the risk of stroke increases by 50%. It is important to control diastolic hypertension as even 6 mm of Hg reduction in diastolic blood pressure can reduce the risk of stroke in 2 to 3 years (Cecil, 1998). These results suggest importance of control of hypertension in controlling morbidity and mortality due to stroke. According to Framingham Heart Study, it is important to treat hypertension at every age to reduce risk of stroke. Another clinical trial suggests that treating patients with nonsevere hypertension would prevent a larger proportion of the population-wide burden of stroke than treating only those with more severe hypertension (Kaplan, R.C., 2001).

Diabetes Mellitus

Diabetes is an independent risk factor of stroke. Diabetes mellitus is strongly correlated with hypertension and further increases the risk of stroke if obesity and high blood cholesterol levels are present (American Stroke Association, 2002). Forty to sixty percent of adults with type 2 diabetes have hypertension. Researchers have reported that tight blood pressure control (mean, 144/82 mm Hg) can reduce the relative risk of both fatal and nonfatal stroke for diabetic patients by 44%, compared to less stringent control (Chronic Disease Epidemiology and Control, 1998). Studies have also shown diabetes to act independently of hypertension. In a prospective study of stroke, RR of stroke

mortality and morbidity associated with diabetes after adjusting for risk factors like hypertension, smoking, history of heart disease was 1.8 in males and 2.2 in females (Barrett-Connor, 1990). A study in Finland corroborated similar findings. This prospective study followed 8077 men and 8572 women average of 16 years. Part of cohort was free from diabetes at baseline and few developed it over follow up period. Cox modeling of different risk factors showed diabetes to be one of the most important factors contributing to increased risk of death from stroke. The results suggested that risk of stroke due to diabetes is determined by duration of diabetes. Relative risk of stroke in those who developed diabetes during follow up was 1.7. Study participants who reported diabetes at the baseline were at six times higher risk of stroke. Relative risk was 8.2 for women who were diabetics at baseline whereas relative risk for women who developed diabetes over follow up period was 3.2. Thirty three percent of stroke deaths in women in this study were attributable to diabetes compared to only 16% deaths in men. Thus, women were at increased risk of stroke due to diabetes compared to men. (Tuomilehto, Rastenyte, Jousilahti, Sarti, & Vartiainen, 1996). In addition to increasing risk of stroke, diabetes deteriorates recovery and neurological outcome of stroke. High blood glucose levels impair recovery and the ability to return to healthy working life (Chronic Disease Epidemiology and Control, 1998). Mortality from stroke is significantly higher in diabetics than non-diabetics.

A study examined the risk of stroke among diabetics and non-diabetics. Risk among diabetics was two folds than risk of stroke among non-diabetics. However, this study did not find any significant effect of controlling for co morbid conditions like hypertension,

myocardial infarction on risk of stroke. The study also showed that there was no association between hemorrhagic stroke and diabetes (Pulsinelli, Levy, Sigsbee, Scherer, & Plum, 1996).

Heart Disease and Coronary Artery Disease

Heart disease and Carotid artery disease are other chronic conditions, which are significant risk factors of stroke. Risk of stroke in heart disease patients is two folds higher than individuals without heart disease. Carotid artery disease increases the risk due to atherosclerosis, which can lead to thromboembolism (American Stroke Association, 2002)

Smoking

Smoking increases risk of stroke two folds in smokers compared to non-smokers. Heavy smokers are at greater risk that light smokers. (CDC, 199). The mechanisms by which smoking acts are poorly understood. Transdermally administered nicotine has produced stroke in animal models. But role of nicotine remains controversial. It is proposed that nicotine causes alterations in blood brain barrier. Nicotine is also believed to interact with signaling pathways that are independent of acetylcholine receptors, believed to prevent detrimental effects of nicotine (Hawkins, Brown, & Davis, 2002; Boden-Albala & Sacco, 2002). A study was designed in Japan to determine Population Attributable Fraction (PAF) of stroke due to Atrial Fibrillation, hypertension and smoking. This study followed 2302 residents of Shibata who were followed for 20 years through 1977 to 1997. Two hundred and thirteen strokes were reported at the end of study period. PAF for smoking, 14.9 %, was highest among three covariates although

significant results were found only for Atrial Fibrillation (Nakayama et al, 2000). Smoking increases risk of thromboembolic as well as hemorrhagic strokes. Studies have shown that smoking independently increase risk of stroke three times. This risk is dependent on amount of smoking and rapidly decreases after smoking cessation. Risk due to smoking remains the same in males and females and decreases with advancing age. Risk is consistent among all subtypes of strokes. The highest risk is reported for sub arachnoid hemorrhage and ischemic stroke due to atherogenic thromboembolism (Hankey, 1999). An Australian study compared spouses of first time stroke cases with spouses of non-smoking matched neighborhood controls. Risk of stroke among spouses of smoking cases was two folds higher than the spouses of non-smokers (You, Thrift, McNeil, Davis, & Donnan, 1999). Effects of smoking are augmented in presence of excessive body fat and lack of physical activity (Shinton, 1997).

Alcohol

Growing body of research supports increased risk of stroke due to recent heavy alcohol consumption and protective effect of low to moderate alcohol drinking (Suter & Vetter, 1999; Berger et al., 1999). Alcohol has shown to precipitate vasoconstriction and rupture of small cerebral arteries in animal models. Alcohol induced cardiac arrhythmias and embolic brain infarction has been observed in stroke cases (Hillbom, & Numminen, 1998). Studies have also shown that this relationship depends on the dose of alcohol and pathology of stroke. Alcohol ingestion of 30g/day has shown borderline protective effect on deep cerebral infarction. Heavy alcohol drinking, over 140 g/day increased the risk for all stroke types combined (OR = 3.2; 95% CI, 1.1-9.7), intracerebral hemorrhage (OR

= 6.2; 95% CI, 1.3-24.0), and was associated with superficial cerebral infarction (OR = 4.6; 95% CI, 1.0-20.6) (Caicoya, Rodriguez, Corrales, Cuello, & Lasheras, 1999)

Role of Obesity in Chronic Cardiovascular Conditions

The epidemic of obesity is an intimidating problem in the US. According to Surgeon General's Report, 34 percent of US adults aged 20 to 74 years are overweight, and an additional 27 percent are obese. About half of all women aged 20 to 74 are overweight or obese. Percentages of obese women among African American, Native American, and Mexican American are higher than general population. Obesity plays a key role in progression of chronic diseases. (Shaper, 1998). The Department of Medicine, Brigham and Women's Hospital, Boston, MA did a 10-year follow up study from 1986 to 1996 to identify the risk of multiple chronic diseases in obese individuals. Their cohort included men from Health Professionals Study and women from Nurses Health Study. BMI was used to classify obesity among study subjects. Men and women in the same BMI category were compared with each other. Study found dose response relationship between BMI and development of chronic diseases for both men and women. Overweight and obese adults with BMI in higher range were also at significantly increased risk than leaner counterparts. Risk of developing diabetes was 20 times higher among obese individuals compared to non-obese. Findings were consistent for men and women for all chronic disorders like hypertension, stroke, diabetes, and others. Authors recommended adults to maintain BMI between 18.5 and 21.9 to minimize their risk of chronic diseases (Field et al., 2001). Same findings resonate in studies done in other countries thus emphasizing importance of control of obesity to minimize risk of chronic

conditions. A study by Department of Primary Care and Population Sciences, Royal Free Hospital School of Medicine, London was designed to see if BMI was associated with lower morbidity and mortality among British men. This prospective cohort study was conducted over period of 14.8 years. Increased all cause mortality was found in men with higher BMI (BMI $\geq$ 30). Cardiovascular mortality in this group increased progressively for BMI greater then 20 after adjusting for lifestyle risk factor.

The WHO consultation on obesity reviewed epidemiology of obesity recommended a coherent system to classify obesity. This consultation recommended that BMI should be internationally adopted to classify obesity. Epidemic of obesity is replacing traditional health issues like infectious diseases and under nutrition. Obesity results in co morbidities like diabetes, stroke, heart diseases, cancer and others. Although genetic causes of obesity have been documented, such treatment for obesity is unlikely to be available in near future. Therefore this consultation recommended behavioral and lifestyle changes and invasive interventions for extreme cases to control obesity (WHO, 2000). Thus, study of obesity and implementation of appropriate control measures is becoming critical with increasing evidence of detrimental effects of obesity.

Obesity and Stroke

Studies of obesity as a risk factor of stroke have reported somewhat inconsistent results. Study by Gillum et al., was done using NHANES-I and NHEFS data. This study was first longitudinal study to report stroke risk in Black population. Primary exposure variable was ratio of triceps to subscapular skinfold thickness (SFR). Study hypothesized that increased SFR also increased risk of stroke independent of being overweight defined

using BMI. SFR was associated with increased risk of stroke among White males who were former smokers. This association was not strong but was statistically significant. Study reported U- shaped association between SFR and stroke among White males. In White males, stroke risk was elevated only in top quartile of BMI in never smokers. In Black women risk of stroke was higher in lower BMI quartiles compared to top quartiles. Whitehall Study examined risk of death from stroke due to obesity in the British population (Shinton, 1991). This was a prospective cohort study done by the Department of Medicine, University of Birmingham in the United Kingdom. Purpose of this study was to analyze risk of stroke associated with obesity in adult males over 40 yrs of age. Body mass index was used to measure obesity in the study population. Mortality ratio was calculated to assess the risk of death due to stroke. Men aged 40 to 54 who belonged to the highest quintile of BMI had a mortality ratio of 2.01 (95% confidence interval 0.9 to 4.7) compared to the lowest quintile. Mortality ratio was 0.19 (95% CI 0.7 to 2.0) in men aged 55 to 64. Study concluded that 60% deaths from stroke could be prevented with prevention of obesity and stroke. Nurses' Health Study examined the association of weight change and risk of stroke in women (Rexrode et al., 1987). Women with BMI 27 kg/m^2 or greater; had significantly increased risk of ischemic stroke, with relative risks (RRs) of 1.75 (95% CI, 1.17-2.59) for BMI of 27 to 28.9 kg/m2; RR 1.90 (95% CI, 1.28-2.82) for BMI of 29 to 31.9 kg/m^2; and RR 2.37 (95% CI, 1.60-3.50) for BMI of 32 kg/m^2 or more (P for trend<.001), compared to those with BMI less than 21 kg/m^2. This study also found increased risk of ischemic and total stroke among women associated with obesity. However, obesity showed non-significant inverse association with

hemorrhagic stroke. It is clear from the discussion above that risk factors of stroke are very similar to other cardiovascular diseases. Some risk factors are well established but inconsistencies remains on others like obesity. Reducing obesity has prime importance in reducing burden of chronic diseases including stroke. Research studies like this will provide additional evidence to strengthen these facts.

CHAPTER 3

RESEARCH DESIGN AND MATERIALS

This study utilized data from First National Health and Nutrition and Examination Survey (NHANES-I) from 1974 and its Epidemiological Follow-Up study (NHEFS) completed in 1992. These surveys were administered by the Centers for Disease Control and Prevention (CDC) and the National Center for Health Statistics (NCHS) to obtain information on health and nutritional status of US population. Later, NHANES-I Epidemiologic Follow-up Study, NHEFS, was designed to study morbidity and morality in the baseline NHANES-I cohort.

Data Sources

The public use data files of these surveys were obtained from the Center for Disease Control, Hyattsville, Maryland. Baseline NHANES-I files were obtained from FTP (File Transfer Protocol) site of the Center for Disease Control. Data on follow-up study was obtained on a CD-ROM from the Center for Disease Control Office in Maryland. Due to design and sampling of NHANES-I, information on smoking status was asked only to selected individuals at the time of baseline examination. This information is available on a non-public use data file. This file was obtained from NCHS after completing confidentiality agreement. None of these data files (public and non public use) included personal identifiers thus avoiding risk of accidental disclosure of any information that could have revealed identity of any study subject.

NHANES - I Data

Purpose and Scope of NHANES-I: Health examination surveys were designed and conducted by the National Center For Health Statistics to obtain information on health status of the US population. The National Health Survey Act of 1956 facilitated establishment and continuation of surveys and special studies of US population to collect such information. The primary objective of NHANES-I was to obtain information on the nutritional status of sample population with emphasis on women, children and elderly who are considered at increased risk of malnutrition. The survey also used medical and dental examination, to gain information on prevalence of certain medical conditions in most reliable and accurate way. The medical examinations allowed obtaining information on non-symptomatic, undiagnosed and unrecognized conditions in the population and study of their distribution in the population. Any information that allows identification of an individual was held in strict confidence and sent only to authorities engaged in survey for survey purpose.

Sampling

NHANES-I was a cross sectional survey of national probability sample of civilian and non-institutionalized US population of 1-74 yrs of age except those residing on Indian reservations. This was a multistage, stratified, probability sample of loose clusters of person based on land-based segments. The first stage of sample consisted of 65 primary sampling units or PSU, which were counties or group of adjacent small counties. For design and survey purpose, PSUs were divided into 357 strata. One PSU was

selected from each stratum with probability proportional to the size of PSU. These 357 strata were then collapsed into 40 super strata. This grouping was based on geographic region. Each PSU had poverty and non-poverty stratum. Systematic segments were derived from each poverty and non-poverty stratum. After these segments were identified, addresses within boundaries were obtained. Households were then interviewed for age and sex of each household member and sociodemographic and other characteristics.

Target Population

The survey collected data from 1971 to 1974 about health and nutrition status of the NHANES-I sample using standardized medical examination and personal interviews. NHANES-I data was augmented by a sub sample in 1974-1975. This sub set of NHANES-I sample included 20,729 persons 25-74 years of which 14,407 completed more detailed medical examination. This sample was representative of the US. population aged 25-74 yrs of age at the time of examination. This sample was further followed during first epidemiologic follow up study from 1982-92.

Data Collection

NHANES-I data collection was a three-team operation. The first team was team of census staff, second team consisted of trained staff of NHANES-I (also referred to as HER staff) interviewers and third team had examining staff in the examination centers, which included a physician, a nurse, a dermatologist, an ophthalmologist, a dentist, two dietary interviewers, two health technicians, one laboratory technician, and a coordinator.

All of them were public health services officers except for ophthalmologist and dermatologist who were usually senior residents.

Data on NHANES-I participants was obtained by means of interviews and examinations. Interview included 4 sections namely, general household interview, food frequency interview, food program questionnaire and a general medical history questionnaire. First three sections included questions about general household conditions, 24-hour food intake, nutritional composition and additional information about nutritional status of a household. Medical examination included general medical examination, anthropometric examinations, dental, dermatological and ophthalmologic examinations and hand wrist x rays (ages 1-17 only). Medical examination was also supplemented by laboratory testing such as hematological, urological examinations and blood chemistry. Sub sample of individuals between ages 25-74 years received more detailed examination. In addition to parameters mentioned above, the examination included general medical history supplemental questions about arthritis, respiratory and cardiovascular conditions; health care needs questionnaire and a general medical well-being questionnaire. This subset also received extended examination, which included X rays of Chest, hip and knee joints, audiometry, electrocardiography, goniometry, spirometry, pulmonary diffusion and tuberculin tests along with additional laboratory determinations.

Personal Interviews and Examination

HER staff conducted personal interviews of eligible members (1-74 yrs) of each household. HER staff had complete knowledge of survey purpose, sampling techniques and other details about the survey and were in best position to detect any signs of non-

cooperation and overcome them. The staff also obtained written consent for examination of minors and authorization to obtain additional medical records from appropriate health authorities. Interview included medical history questionnaire, food program questionnaire or general medical history supplement appropriate for the age of sample person. Appointments for medical examination were made during this interview. Examinations were carried out in specially constructed mobile examination centers (MEC). All subjects received general medical examination geared towards identifying physical conditions pertinent to nutritional deficiencies and certain chronic diseases. This examination included examination of vital signs and systemic examination with attention to signs of vitamin deficiencies. Subset for more detailed examination received more detailed cardiovascular examination such as auscultation of heart. Additional examination also included musculoskeletal examination, ear, eye examination and tuberculin test. At the end of examination physician administered appropriate supplemental medical history questionnaire based on medical history questionnaire responses at home. Dental, ophthalmologic, dermatological and some other examinations are out of scope of this study and are not discussed in detail here. This was followed by the laboratory examinations. Laboratory technician screened urine samples for glucose, albumin and blood. Nurse drew blood for laboratory testing at the time of examination. Blood analysis was performed in the mobile examination center. Tests were duplicated and any abnormal findings according to CDC guidelines were reported to examining physician immediately. Finally, health technicians took anthropometric measurements such as height, weight, and skin-fold thickness.

The overall non-response examination rate in NHANES-I was 30 %. This increased with age in White females and was least for Black male aged 65 and over. To examine how non-response rates could affect a health variable, linear model was fit and no statistically significant differences found in the odds ratios (OR) of respondents and non-respondents.

NHANES - I Epidemiologic Follow - up Study (NHEFS)

The follow up study started as a joint project between National Center for Health Statistics (NCH) and National Institute of Aging in collaboration with other public health agencies. Unlike NHANES-I, the follow up study relied largely on self-reporting of various conditions. Attempts to obtain death certificates and hospital records were made wherever possible.

Purpose and Scope of NHEFS

NHANES-I provided abundant information on prevalence of health conditions and risk factors. To further explore effects of clinical, environmental and behavioral factors in tracing natural history of disease, this follow up study was designed. This helped investigate association between factors measured at the baseline and development of specific health conditions. NHEFS was comprised of a series of four follow up surveys with the first follow up cycle starting in 1982, second in 1986, third in 1987 and final 4^{th} wave completed in 1992. Three objectives of NHEFS were:

- To study the morbidity and mortality associated with risk factors measured at baseline and outcome variables available from follow up data.
- To study changes in risk factors of a subject between the study period

- To study natural history of disease and chronic disease impairment

Sampling

NHEFS is a longitudinal study of baseline cohort derived from NHANES-I. This used individuals who were 25 to 74 years at their NHANES-I examination as its baseline population. This subset of population was representative of US population at the time of NHANES-I. Follow up data collection followed the same clustering as NHANES-I. Although, not all subjects belonged to the same clusters anymore, the number in original clusters were sufficient to organize fieldwork around same clusters. PSU from the NHANES-I were grouped in to four equal workload regions.

Tracing and Data Collection

As mentioned earlier, the data collection was completed over period of 1982 to 1992 in four follow up cycles (Figure 3). Data was collected by means of personal interviews and physical measurements taken only during early cycles. Personal interviews were administered in person and over the phone. Subjects were traced using all tracing methods such as crisscross and city directories, the US. postal address change service, state department of motor vehicle listings, department of vital statistics and follow up with neighbors at previous address. Subject was considered successfully traced if he or the proxy responded correctly to a set of information such as name, date of birth, and address at the time of NHANES-I interview and household membership at NHANES-I. Subjects who couldn't be traced were considered lost to follow-up. Diseased persons were also considered lost to follow-up unless this information was verified by a death certificate. Statistical analysis of lost to follow-up showed that those

who were lost to follow-up were more likely to have died than those who were successfully traced. Smokers were 86 % more likely to be untraced than non-smokers, which call for cautious interpretation of results of smoking and mortality especially among younger ages.

Interviews

Interviews included a two hour detailed personal interview administered in person about health history of a subject. Interview was administered to subjects, and proxies. Physical measurements were taken on subjects only. Interview addressed occurrence or recurrence of medical events, and various risk factors. Two versions of the questionnaire were used, subject and proxy. The proxy interview was administered to proxies of the subjects who were diseased. Questions related to opinion, feelings or emotions were omitted from the proxy interview. The proxy questionnaire was usually answered over the phone in contrast to the subject questionnaire, which was administered in person. Subjects who were incapacitated or were unable to be present for the interview answered the subject questionnaire via proxy respondent. Both questionnaires were divided into sections based on general topics. Interviews administered in later cycles averaged 30 minutes. These interviews were administered over the phone. Because of this, no physical measurements were taken. A CATI (Computer Assisted Telephone Interviewing) system was used which allowed interviewer to enter information supplied by the subject directly into computer while interviewing. If subject or proxy could not be contacted at the time of main interview, then the abbreviated questionnaire was mailed to them.

First Wave 1982-84

Data for this wave of follow up was collected for all 14,407 subjects 25 to 74 yrs at their NHANES-I examination. Tracing for these subjects began in 1981 and data was collected from 1982 to 1984. Almost 93% (n = 13,383) of cohort was successfully traced by end of survey period. The 1982 survey included tracing subjects to their proxies or current addresses, acquiring death certificates, performing in depth interviews with subjects or their proxies, taking pulse, blood pressure and weight measurements of subjects and obtaining hospital and nursing home records including pathology and electrocardiograms.

Second Wave 1986

This wave of follow-up collected data for oldest members of the NHANES-I cohort, aged 55 or older at the baseline examination (n = 5677). The purpose of this data collection was to assess changes in the health status of oldest members of the NHEFS cohort. Data was collected for 3980 individuals who were not diseased at the time of 1982-84. Remaining 1697 individuals were found diseased at 1982-84 interviews and were excluded from the data collection.

Third Wave 1987

This cycle continued collecting information for NHEFS cohort from the last contact period. Data was collected for 11,750 controls identified non diseased by the end first and second wave of follow up. By beginning of this follow up wave, 2657 individuals were identified diseased.

Fourth Wave 1992

The 1992 follow up cohort included 3212 diseased subjects at the time of 82, 86 and 87 periods and 11,195 non-diseased subjects prior to 1992. Data collection was undertaken for non-diseased individuals irrespective of their prior tracing status. A total of 9282 interviews were conducted for 1992 follow up phase. By the end of 92-interview phase i.e. by July 19th 1993, interviews were collected for 82% (n = 9281) of the 11,195 of 1992 cohort.

CHAPTER 4

METHODS AND ANALYSIS

This was a cohort study done using a secondary data source; NHANES-I and NHEFS surveys. The study included elderly population of NHANES-I as its target population.

Inclusion and Exclusion Criteria

The baseline cohort for this study included individuals between ages of 40 to 75 years, free of stroke at their NHANES-I examination. As the stroke or cerebrovascular diseases due to atherogenic causes are less common in less than forty years of age and risk of stroke doubles in each decade after 55 years of age, this age group was selected. History of stroke at baseline was ascertained from questions asked in the medical history questionnaire. Stroke at baseline was defined as individuals who were told by the doctor about stroke at or before baseline. Two hundred and eighty seven cases of stroke at baseline were excluded from the analysis. Observations with missing values of BMI, missing information on heart disease, hypertension, diabetes mellitus and malignancy at baseline were also excluded from the analysis. Final baseline cohort has 7037 subjects with known information on BMI and satisfying age criteria. Additional information at baseline about history of heart disease, cancer, hypertension and diabetes was obtained from medical history files.

Information Obtained from Baseline Data Files

Baseline data files were used to extract information about anthropometric measurements and history of multiple cardiovascular conditions. The anthropometric measurements file was used to obtain information on age, gender, race, height and weight. Body Mass Index in kg/m^2 was computed by dividing weight in kilograms by square of height in meters. Each participant was asked questions on various medical conditions at the baseline. History of stroke at baseline was determined using question "Ever been told by the doctor whether he/she had stroke?" This was followed by the question on year of occurrence of stroke. Individuals with history of stroke at baseline were defined as those who answered yes to question about the history of stroke or those who reported the year of occurrence of stroke before baseline. Individuals with positive history of stroke at baseline were excluded from analysis. Similar questions were used for history of diabetes, heart disease, and cancer at baseline. Cases of heart disease at baseline were defined as those who were told by the doctor that he/she had heart attack or heart failure. Cases of diabetes at baseline were defined as those with positive history of diabetes or use of medication for diabetes. Similarly, cases of hypertension were determined as those with positive history of hypertension or use of medication for hypertension. For analysis purposes, heart disease and hypertension were combined into one category of cardiovascular diseases. Alcohol drinking was determined using question on frequency of alcohol "how often do you drink?" Alcohol drinking was categorized into 4 categories. Responses, everyday and just about everyday were combined into the category of regular drinkers. Second and third category included those who reported

frequency of 2-3 times a week and 1-4 times a month respectively. 3-12 times a year and not more than 2-3 times a year were combined into the category of less than once a month. Physical activity was defined as amount of exercise derived from non-recreational activity. This was recorded into three categories of very active, moderately active and quite active. Smoking was reported as current, past and never smokers and the same categories were used for analysis.

Exposure variable (BMI as a measure of obesity) was calculated using height and weight measured at the baseline NHANES-I examination. Outcome variable, stroke was derived from the follow up cycles. Unique identity number called as Sample Sequence Number identified each individual during the baseline survey. Same number was used when tracking down individuals for follow up study. This number was used to merging data sets to have complete information about an individual from baseline examination to the end follow up period.

Data from Follow-Up Files

Data from the follow up study was available on interview, health care facility, vital and mortality tapes. Interview and health care facility files were available for each year of follow up and vital status and mortality file included information from all 4 follow up phases on one tape. Information on occurrence of vital events during follow up time was obtained using these files. Each respondent was asked question if "He/She had stroke after the NHANES-I interview?" Same question was repeated in each follow up cycle to obtain information on new or recurrent stroke. Respondent was also asked to provide the year of occurrence of stroke. Additionally, each respondent was asked about

hospitalizations or nursing home admission during follow up period. Information on hospitalizations and nursing home admissions was obtained using health care facility files for each year. Data from interview and health care facility tapes were merged to yield complete follow-up information for each individual.

Exposure Measurement

Body mass index was computed from the weight and height measured at the time of NHANES-I examination. According to the WHO, BMI provides most useful, population level measure of obesity, which can be used to estimate prevalence of obesity within a population. Body mass index was then categorized into three groups according to WHO classification. First category of normal weight people included BMI between 18.0 to 25.0, overweight weight category included BMI 25.1- 30.0 and obese category included BMI > 30. WHO encourages use of this classification over quartiles or tertiles as used in prior studies on NHANES-I population. According to WHO, quintiles or tertiles change with weight gain in a population and can underestimate burden of obesity in a given population. Classification by WHO gives comparison standards, which do not change with the study population and are easy to follow. Following this classification of obesity given by WHO makes it easier for physicians to clinically classify cases of obesity, quantify risk, and evaluate treatment measures.

The waist hip ratio and waist circumference are other popular measure of obesity. These are clinically accepted methods to identify body fat distribution in only last 10 years. As these measurements were not taken at the time of NHANES-I, the study could not consider them as exposure variables.

Case Ascertainment

Cases of stroke were identified using self-reported information as well as the information documented on health care facility abstracts and death certificates from the follow up cycles. All cases of stroke fulfilled following criteria:

1. Self report of first stroke after 1975 in one of the follow up interviews;
2. Or history of admission to health care facility with diagnosis of stroke, defined using ICD 9 CM codes 431, 432, 433, 435-37 and 439;
3. Death certificate with underlying or non-underlying cause of death coded as stroke using ICD 9 CM codes 431, 432, 433, 435-37 and 439;

Statistical Analysis

Stroke and Study Time Determination

Incident stroke included both fatal as well as non-fatal strokes (Fig 1). The date of incident stroke was earliest of self-report or hospital admission for stroke or the date of death due to stroke. Date of self-report of stroke was reported using only year of occurrence. Occurrence of first stroke being self-report, the date and month of occurrence of stroke was not available. Therefore, the time periods calculated in this study are in number of years and do not include days. For each subject the date of entry into study was same as the date of NHANES-I interview and date of end of study was the earliest of date of stroke or date of death or date of last contact. One hundred and eighty six individuals recorded study time or follow up time of zero years. These individuals either experienced stroke after their baseline examination or reported their stroke during first

follow-up examination. These were not included in analysis, as they did not contribute any follow up time to study models.

Exposure variable BMI was calculated and categorized as mentioned above. After complete follow up information for each subject was obtained, descriptive statistics of the study population in various BMI categories were obtained. Crude incidence of stoke per 1000 person years in each category of BMI was calculated as number of stoke in each BMI category divided by person years follow up for that category.

Cox Proportional Hazards Model

Risk of stroke due to obesity was determined using Survival Analysis. Cox Proportional Hazards Models were used to obtain risk ratios. Univariate models were used for gender, race, smoking, alcohol and physical activity. Final model included gender, race, smoking and alcohol as covariates. Physical activity did not show significant effect and was not included in the models. Study models did not adjust for diabetes and cardiovascular conditions as this could undermine effect modification due to these conditions. Obesity is an independent risk factor for both diabetes mellitus and cardiovascular diseases. If the effect of obesity on risk of stroke was being mediated either by diabetes or hypertension adjusting for these variables in the model might obscure this effect. Controlling for the effect of diabetes and cardiovascular conditions will not allow detecting any effect of these variables on the association between obesity and risk of stroke. In other words, adjusting for these variables in multivariate models could mask the effect modification in the association of obesity and stroke.

In Cox Proportional Hazards Models, age at event was used as a dependent variable. Previous studies of similar association done using NHEFS data have used follow-up time as a dependent variable. This study used age at event for multiple of reason. NHANES-I and NHEFS followed study subjects over 22 years. Present study thus examined risk of stroke over relatively long duration of time (22 years follow up). The study also included older individuals in its target population. These subjects were 40-75 years at baseline examination in 1975. Increased mortality and morbidity at the end of study period (22years) could be partly due to the effect of age or long follow up period. To consider this effect into analysis, age at event was used as a dependent variable in the models. Study time or follow up time was used as one of the covariates in the model. Kon et al has shown that this type of model was more appropriate for NHANES-I and NHEFS data although follow up time has been used and advised by National Center for Health Statistics.

Stratified Analysis

Stratified analysis was used to study the effect of obesity on risk of stroke in presence of other potential risk factors. Data was analyzed separately for gender, race, diabetes and cardiovascular conditions. Interaction between BMI and gender, race, diabetes and cardiovascular conditions was tested using additional models, which included interaction term (product term) of the respective variable. (Gender, race, diabetes, and cardiovascular conditions).

Power Calculations

Power reached for this cross sectional study for given sample size was calculated using EpiInfo 2000 software. Table 1 shows power reached for different associations. Power reached for this study was enough to detect relative risk of 1.5 with 80% power given that expected prevalence of stroke among non-exposed was 2.2% (CDC STAT FACTS: Total stroke in < 18 yrs) It is clear from table below that the study had enough power to detect a relative risk of 1.6 with 90% power given that prevalence of stroke among exposed is 3.5 and sample size is 7037.Sample size of this study was 7037 and incidence of stroke among exposed is 11.7%. These figures allow detecting RR of 5.6 with 85% power if sample size is about 400 subjects. From this it is clear that the study has enough power to detect RR of 1.5 in the given population.

TABLE 1

Power Calculations for the Study: 982 Cases and 6055 Non Cases

% Prevalence of Stroke Among Exposed	Relative Risk	Power	Sample Size		
			Exposed	Non Exposed	Total
3.08	1.4	80	5955	4943	10893
3.30	1.5	80	4236	3516	7752
3.52	1.6	90	3840	3187	7027
3.74	1.7	90	2940	2440	5380
3.96	1.8	90	2341	1943	4284
4.18	1.9	90	1922	1595	3517
4.40	2.0	90	1614	1340	2954

Involvement of Human Beings in Research

All the data files except one are public use data files. There is no direct risk involved to study subjects as there is no direct contact with subjects and identifiers have been eliminated from the file.

CHAPTER 5

RESULTS

The results summarize crude incidence and risk of stroke at the end of follow up period in the study population. The study population was followed from 1982 to 1992 to determine long-term risk of stroke due to obesity, measured at baseline examination in 1972. Total 982 strokes (fatal and non-fatal) were reported during 103,986 person follow-up years.

Descriptive Analysis of Study Population

Target population included 7037 individuals, 40-75 years at their baseline examination. This was the population of elderly males and females of all races (Table 2). Forty Four percent of population comprised of males and 56% were females. Only two

major ethnic groups were identified at the time of NHANES-I examination in 1972. Races, other than White or Black were included in the category of "Others". Majority of study population was White (82%), about 16% were Blacks and only 2 % were other races. As mentioned before, this population was older; 45% of study participants being over age of 66 and above at baseline. The population was effectively followed over period of 22 years with mean follow up time of 14 years.

As shown in table 2, about 45% of study population was within normal range of BMI. About one third, (36%) were overweight (BMI 25-30 kg/m^2) and one fifth (18.47%) were obese (BMI > 30 kg/m^2). Large number of obese individuals were 65 years and older (Table 3). Obesity was more prevalent among females than males. Blacks were more obese than whites.

TABLE 2:

Classification of BMI

BMI Categories	Number	Percentage
Normal/ BMI 1 (BMI 18-25 kg/m2)	3190	45.33%
Overweight/ BMI2 (BMI 26-30 kg/m2)	2547	36.19%
Obese/BMI3 (BMI >31 kg/m2)	1300	18.47%
(N = 7037)		

Distribution of Lifestyle Behaviors in Study Population

Smoking

Nearly half of the population reported having never smoked in their lifetime (Table 3). Out of remaining, one third were current smokers and one fifth reported being former smokers. Current and former smokers appeared less obese than never smokers. Among obese individuals, 62% were non-smokers. This percentage reduced to 48% and 45% in overweight and normal weight category respectively. This was consistent with the fact that smokers lose weight over time due to chronic smoking. More former

smokers were overweight where as higher numbers of current smokers were normal weight.

Alcohol

More than 50% of study population reported drinking alcohol less than once a month (Table 3). Among obese people, 66% drank less than once a month and only 8% were everyday drinkers. Among overweight people, 56% reported drinking alcohol less than once a month and 20% reported drinking 1-4 times a month. Everyday drinkers accounted for 15 % of normal weight people compared to 13% and 8% of overweight and normal weight category respectively.

Physical Activity

Physical activity in NHANES-I was measured qualitatively. The categories of physical activities reflected amount of physical activity derived from non-recreational activities. Very active was the highest level of non-recreational physical activity followed by moderately active and quite active, which reflected the lowest category. Only 11 % of study population reported being quite active, 48% were moderately active and remaining 41% were very active in their non-recreational physical activities (Table 3). Very active people were less obese. They made up 43% of normal weight population. Among moderately active, 44% were normal weight, 36% were overweight and 20% were obese.

Quite active individuals made up 14% of obese category compared to only 10% of normal weight.

Chronic Diseases in Study Population

History of heart disease, history of hypertension, history of diabetes mellitus and cancer were the chronic diseases analyzed in this study. Prevalence of diabetes in the study population at baseline was 6% (Table 3). About 7-8% of population reported having heart disease at baseline. Thirty percent of population reported hypertension at baseline. More obese people reported cardiovascular conditions at baseline than normal weight people. Ten percent of obese population reported heart disease compared to only 8% in normal weight and overweight people. Among obese individuals, 46% were hypertensives compared to only 21% among normal weight individuals. Similarly, 10% of obese people were diabetics compared to only 6% in overweight category. Only 6.4% of study population reported cancer at baseline. Cancer was reported by fewer obese and 50% of individuals with cancer were normal weight.

TABLE 3: Descriptive Analysis of Study Population

VARIABLE	NORMAL	OVERWT.	OBESE	TOTAL
Age Group				
< 45	553 (17.86%)	341 (13.39%)	213 (16.38%)	1107
46-55	717 (22.48%)	558 (21.91%)	275 (21.15%)	1550
56-65	500 (15.67%)	453 (17.79%)	241 (18.54%)	1194
66-75	1420 (44.51%)	1195 (46.92%)	571 (43.92%)	3186
Gender				
Males	1375 (43.90%)	1324 (51.99%)	419 (32.44%)	3118
Females	1815 (56.49%)	1223 (48.01%)	881 (67.56%)	3919
Race				
White	2703 (84.73%)	2153 (84.53%)	972 (74.77%)	5828
Black	451 (14.29%)	375 (14.72%)	322 (24.77%)	1148
Other	36 (1.13%)	19 (0.75%)	6 (0.46%)	61
Heart Disease				
Yes	248 (7.77%)	201 (7.89%)	124 (9.54%)	573
No	2942(92.23%)	2346(92.11%)	1176(90.46%)	6464
Hypertension				
Yes	693(21.72%)	791(31.06%)	604(46.46%)	2088
No	2497(78.28%)	1756(68.94%)	696(53.54%)	4949
Diabetes				
Yes	161 (5.05%)	165 (6.48%)	130(10.00%)	456
No	3029(94.95%)	2382(93.52%)	1170(90.00%)	6581
Cancer				
Yes	116 (3.64%)	75 (2.94%)	43 (3.31%)	234
No	3074(96.36%)	2472(97.06%)	1257(96.69%)	6803
History of Alcohol				
Everyday	479(15.02%)	336(13.19%)	104 (8.00%)	919
2-3 /wk	349(10.94%)	258(10.13%)	107 (8.23%)	714
1-4/mn	617(19.34%)	514(20.18%)	235(18.08%)	1366
<1/mn	1745(54.70%)	1439(56.50%)	854(65.69%)	4038
Smoking				
Current	1210(37.93%)	760(29.84%)	274(21.08%)	2244
Former	514(16.11%)	563(22.10%)	221(17.00%)	1298
Never	1466(45.96%)	1224(48.06%)	805(61.92%)	3495
Physical Activity				
Very Active	1365(42.79%)	1069(41.97%)	465(35.77%)	2899
Moderately Active	1481(46.43%)	1229(48.25%)	652(50.15%)	3362
Quite Active	343(10.75%)	249(9.78%)	184(14.08%)	776

Incidence of Stroke in General Population

Further analysis was done to compute incidence of stroke in each category of BMI. Crude incidence of stroke was calculated using number of strokes in each category divided by the person years follow-up in that category. Table 4 shows crude incidence of stroke in each BMI category. Normal weight category (BMI 1) included large proportion of study population. In this category, 426 strokes occurred over 46,682 person years follow up. Crude incidence of stroke in normal weight individuals was 9.1 /1000 person years. Category of overweight people (BMI 2) included 2547 individuals, followed over 38,380 person years. Crude incidence of stroke among overweight individuals was 8.7/1000 person years follow up. In obese category, (BMI 3) 222 strokes occurred over 18,924 person years of follow up. Crude incidence of stroke in this category was 11.7/1000 person years.

Risk ratios were obtained using Cox Proportional Hazards Model. Relative risk of stroke (crude) was 0.86 (95% CI 0.689-0.922) among overweight and 1.28 (95% CI 0.986-1.434) among obese. Univariate analysis showed statistically significant results for gender, race, smoking and history of alcohol. Final multivariate model was adjusted for gender, race, smoking and history of alcohol considering possible confounding due to these variables. Table 4 shows adjusted relative risk for overweight and obese individuals in reference to normal weight individuals. Relative risk of stroke among overweight was detected 1.09. This association was not statistically significant. Relative risk among obese individuals was 1.40, thus they were at 40% increased risk of stroke compared to normal weight individuals.

TABLE 4

Overall Incidence of Stroke in General Population

	NORMAL N = 3190	OVERWT N = 2547	OBESE N = 1300
Number of Strokes	426	334	222
Person Years Follow-Up	46682	38380	18924
Incidence/1000 yr	9.1	8.7	11.7
Relative Risk (Adjusted)	1.00*	1.09	1.40
95% C.I		(0.944-1.261)	(1.191-1.658)

(*Used as a reference category in Cox Models adjusted for gender, race, smoking, history of alcohol, and study time.)

As this study aimed at analyzing risk of stroke in different sub groups of gender, race, diabetes and heart disease, descriptive statistics among these strata were carefully observed. Similar survival analysis models were run in these strata to obtain relative risk of stroke. Distribution of these strata into three the BMI categories is described below in detail.

Stratified Analysis

Descriptive Statistics in Males

Half of the male population was over 65 years of age (Table 5). Larger proportion of this age group was normal weight than obese. Forty six percent of this population was normal weight and only 12% was obese. Among White males, 13% were obese and 43% were normal weight. Among Blacks, 16 % were obese and 51% were normal weight. Prevalence of heart disease did not vary largely among different BMI

categories. Hypertension was reported by about a third of obese male population. Larger proportions of obese population were diabetic (7.40%) or hypertensive (34.8%) at baseline compared to normal or overweight people. Among males, larger proportions of occasional drinkers (<1 / month) were normal weight in contrast to overall study population where larger proportion of same category was obese.

Incidence of Stroke in Males

Two hundred strokes were observed in this category over 17,776 person years follow up in normal weight males (N = 1375). Crude incidence of stroke in normal males was 11.2 per 1000 person years follow-up. In overweight category, 181 strokes were reported over 18,798 person years follow-up and crude incidence of stroke was 9.6/1000 person years. Four hundred and nineteen individuals in the obese category contributed 5685 person years of follow-up. Fewer (74) strokes were reported in this category. Crude incidence of stroke was highest (13.01/1000 person years) among obese males. Risk ratios shown in the table are adjusted for race, smoking, history of alcohol and follow-up time. Obese males were at 62% increased risk of stroke compared to normal weight category. Risk among overweight males was only 20% higher than normal weight people. This finding was not statistically significant.

TABLE 5:

Descriptive Statistics in Males

VARIABLE	NORMAL	OVERWEIGHT	OBESE	TOTAL
Age Group				
< 45	123(8.95)	145(10.95)	49(11.69)	317
46-55	322(23.42)	313(23.64)	107(25.54)	742
56-65	233(16.95)	244(18.43)	81(19.33)	558
66-75	697(50.69)	622(46.98)	182(43.44)	1501
Race				
White	1103(80.22)	1155(87.24)	337(80.43)	2595
Black	252(18.33)	158(11.93)	78(18.62)	488
Other	20(1.45)	11(0.83)	4(0.95)	35
Heart Disease				
Yes	150(10.91)	126(9.52)	46(10.98)	322
No	1225(89.09)	1198(90.48)	373(89.02)	2796
Hypertension				
Yes	258(18.76)	338(25.53)	146(34.84)	742
No	1117(81.24)	986(74.47)	273(65.16)	2376
Diabetes				
Yes	66(4.80)	85(6.42)	31(7.40)	182
No	1309(95.20)	1239(93.58)	388(92.16)	2936
Cancer				
Yes	36(2.62)	29(2.19)	7(1.67)	72
No	1339(97.38)	1295(97.81)	412(98.33)	3046
History of Alcohol				
Everyday	304(22.11)	269(20.32)	77(18.38)	650
2-3 /wk	181(13.16)	179(13.52)	58(13.84)	418
1-4/mn	278(20.22)	311(23.49)	107(25.54)	696
<1/mn	612(44.51)	565(42.67)	177(42.24)	1354

Smoking				
Current	642(46.69)	478(36.10)	134(31.98)	1254
Former	354(25.75)	431(32.55)	134(31.98)	919
Never	379(27.56)	415(31.34)	151(36.04)	945
Physical Activity				
Very Active				
Moderately	589(42.84)	602(45.47)	180(42.98)	1371
Active	609(44.29)	617(46.60)	196(46.78)	1422
Quite Active	177(12.87)	105(7.93)	43(10.26)	325

Incidence of Stroke in Males

TABLE 6:

Incidence of Stroke in Males

	NORMAL N =1375	OVERWT N = 1324	OBESE N = 419
Number of Strokes	200	181	74
Person Years Follow up	17776	18798	5685
Incidence/1000 yr	11.2	9.6	13.01
Relative Risk	1.00*	1.186	1.623
95% C.I		(0.967-1.456)	(1.240-2.125)

(*Used as a reference category in Cox Models adjusted for gender, race, smoking, history of alcohol, and study time.)

Descriptive Statistics in Females

Among females, 43 % of population was over age 65(Table 7). This age group accounted for 44% of obese category, 46% of overweight and 40% of normal weight category. Seventy two percent of obese populations were White females and 27% were Black females. Among normal weight, 88 % were Whites and 11% were Blacks. Half of

the obese female population was hypertensive at baseline. Heart disease, hypertension and diabetes were higher in obese females. Majority (68%) of females reported drinking alcohol less than once per month. These accounted for 77% of obese population. Majority females in the study population reported high to moderate levels of physical activity. In the obese category, 32% were very active compared to 42% in the normal weight category.

Incidence of Stroke in Females

One thousand eight hundred and fifteen normal weight females contributed 28,906-person years follow-up (Table 8). Total 226 strokes were reported during the follow-up period in the normal weight category. Crude incidence of stroke among normal weight females was 7.8/1000 person years. Overweight females (N= 881) experienced 153 strokes over 19,582 years of follow-up. Crude incidence of stroke in this category was 7.8/1000 person years. Crude Incidence of stroke was highest among obese females; 11.1 per 1000 person years. Total 148 strokes were reported in this category over 13,239-person year follow-up. Adjusted relative risk of stroke for obese females was 1.244. Being overweight did not show any association with the risk of stroke in females. (RR 0.981 CI: 0.798-1.206)

TABLE 7

Descriptive Statistics in Females

VARIABLE	NORMAL	OVERWEIGHT	OBESE	TOTAL
Age group				
< 45	430(23.69)	196(16.03)	164(18.82)	790
46-55	395(21.76)	245(20.03)	168(19.07)	808
56-65	267(14.71)	209(17.09)	160(18.16)	636
66-75	723(39.83)	573(46.85)	389(44.15)	1685
Race				
White	1600(88.15)	998(81.60)	635(72.08)	3233
Black	199(10.96)	217(17.74)	244(27.70)	660
Other	16(0.88)	8(0.65)	2(0.23)	26
Heart Disease				
Yes	98(5.40)	75(6.13)	78(8.85)	251
No	1717(94.60)	1148(93.87)	803(91.15)	3668
Hypertension				
Yes	435(23.97)	453(37.04)	458(51.99)	1346
No	1380(76.03)	770(62.96)	423(48.01)	2573
Diabetes				
Yes	95 (5.23)	80 (6.54)	99(11.24)	274
No	1720(94.77)	1143(93.46)	782(88.76)	3645
Cancer				
Yes	80 (4.41)	46 (3.76)	36 (4.09)	162
No	1735(95.59)	1177(96.24)	845(95.91)	3757
History Of Alcohol				
Everyday	175 (9.64)	67(5.48)	27(3.06)	269
2-3 /wk	168 (9.26)	79(6.46)	49(5.56)	296
1-4/mn	339(18.68)	203(16.60)	128(14.53)	670
<1/mn	1133(62.42)	874(71.46)	677(76.84)	2684
Smoking				
Current	568(31.29)	282(23.06)	140(15.89)	990
Former	160(8.82)	132(10.79)	87(9.88)	379
Never	1087(59.89)	809(66.15)	654(74.23)	2550
Physical Activity				
Very Active				
Moderately	776(42.75)	467(38.18)	285(32.35)	1528
Active	872(48.04)	612(50.04)	456(51.76)	1940
Quite Active	166(9.15)	145(11.77)	140(15.89)	451

TABLE 8:

Incidence of Stroke in Females

	NORMAL N =1815	OVERWT N = 1223	OBESE N = 881
Number of Strokes	226	153	148
Person Years Follow up	28906.00	19582.00	13239.00
Incidence/1000 yr	7.8	7.8	11.1
Relative Risk	1.00*	0.981	1.244
95% C.I		(0.798-1.206)	(1.008-1.536)

(*Used as a reference category in Cox Models adjusted for gender, race, smoking, history of alcohol, and study time.)

Descriptive Statistics in White

Among obese Whites, 65% were females and 35% were males (Table 9). Heart disease was reported by 10% of obese White population. Hypertension was reported by 44% of obese compared to 20% of normal weight population. Similarly, diabetes was reported higher in the obesity category than normal weight category. White current smokers accounted for 37% of normal weight group compared to 20% of obese group. Greater percentage of normal weight individuals were very active.

Incidence of Stroke in Whites

Category of obese Whites included 972 individuals. Total 168 strokes were reported in this category over 14,064 person years follow-up. Crude incidence of stroke was highest in this category. (Table 10). Crude incidence of stroke was similar in normal weight and overweight whites. Obese white had 31% increased risk of stroke compared to normal weight whites (Adjusted RR 10315 CI: 1.092-1.584). Obesity did not show any

association with risk of stroke in overweight whites. (Adjusted RR 1.005 CI: 0.857-1.178).

TABLE 9

Descriptive Statistics Among Whites

VARIABLE	NORMAL	OVERWT	OBESE	TOTAL
Age group				
< 45	484(17.91)	272(12.63)	143(14.71)	899
46-55	615(22.75)	481(22.34)	205(21.09)	1301
56-65	438(16.20)	377(17.51)	186(19.14)	1001
66-75	1166(43.14)	1023(47.52)	438(45.06)	2627
Gender				
Female	1600(59.19)	998(46.35)	635(65.33)	3233
Male	1103(40.81)	1155(53.65)	337(34.67)	2595
Heart Disease				
Yes	213(7.88)	179(8.31)	97(9.97)	489
No	2490(92.12)	1974(91.69)	875(90.02)	5339
Hypertension				
Yes	532(19.68)	629(29.22)	427(43.93)	1588
No	2171(80.32)	1524(70.78)	545(56.07)	4220
Diabetes				
Yes	127(4.70)	129(5.99)	92(9.47)	348
No	2576(95.30)	2024(94.01)	880(90.53)	5480
Cancer				
Yes	104(3.85)	71(1.22)	40(4.12)	215
No	2599(96.15)	2082(96.70)	932(95.88)	5613
History of Alcohol				
Everyday	433(16.02)	306(14.21)	87(8.95)	826
2-3 /wk	302(11.17)	223(10.36)	77(7.92)	602
1-4/mn	512(18.94)	430(19.97)	182(18.72)	1124
<1/mn	1456(53.84)	1194(55.46)	626(64.40)	3276
Smoking				
Current	1001(37.03)	626(29.08)	200(20.58)	1827
Former	459(16.98)	505(23.46)	172(17.70)	1136
Never	1243(45.99)	1022(47.47)	600(61.73)	2865
Physical Activity				
Very Active				
Moderately	1166(43.14)	886(41.15)	356(36.63)	2408
Active	1259(46.58)	1060(49.23)	488(50.21)	2807
Quite Active	278(10.28)	207(9.61)	128(13.17)	613

TABLE 10

Incidence of Stroke in Whites

	NORMAL N =2703	OVERWT N = 2153	OBESE N = 972
Number of Strokes	352	274	168
Person Years Follow up	40494	32518	14064
Incidence/1000 yr	8.6	8.4	11.9
Relative Risk	1.00*	1.005	1.315
95% C.I		(0.857-1.178)	(1.092-1.584)

(*Used as a reference category in Cox Models adjusted for gender, race, smoking, history of alcohol, cancer and study time.)

Descriptive Statistics among Blacks

Forty percent of obese Blacks were above 65 years (Table 11). Three fourth of obese population were Black females. Diabetes was reported highest among obese people. Similarly heart disease and hypertension were more prevalent among obese individuals. Majority Black population reported drinking alcohol less than once a month and were normal weight (60% of normal weight population). Half of Black population belonged to the never smokers category. Forty four percent of normal weight Blacks were current smokers compared to never smokers who made up 62% of obese population. Half of obese population was moderately active and 16% quite active.

TABLE 11

Descriptive Statistics in Blacks

VARIABLE	NORMAL	OVERWT	OBESE	TOTAL
Age group				
< 45	61(13.53)	65(17.33)	69(21.43)	195
46-55	96(21.29)	73(19.47)	69(21.43)	238
56-65	58(12.86)	70(18.67)	54(21.43)	182
66-75	236(52.33)	167(44.53)	130(40.37)	533
Gender				
Female	199(44.12)	217(57.87)	244(75.78)	660
Male	252(55.88)	158(42.13)	78(24.22)	488
Heart disease				
Yes	35(7.76)	20(5.33)	26(8.07)	81
No	416(92.24)	355(94.67)	296(91.93)	1067
Hypertension				
Yes	151(33.48)	153(40.80)	173(53.73)	477
No	300(66.52)	222(59.20)	149(46.27)	671
Diabetes				
Yes	32 (7.10)	33(8.80)	36(11.18)	101
No	419(92.90)	342(91.20)	286(88.82)	1047
Cancer				
Yes	12(1.05)	4(1.07)	3 (0.93)	19
No	439(97.34)	371(98.93)	319(99.07)	1129
History of Alcohol				
Everyday	40(8.87)	28(7.47)	15(4.66)	83
2-3 /wk	45(9.98)	33(8.80)	30(9.32)	108
1-4/mn	99(21.95)	80(21.33)	53(16.46)	232
<1/mn	267(59.20)	234(62.40)	224(19.52)	725
Smoking				
Current	199(44.12)	128(34.13)	71(22.05)	398
Former	46(10.20)	55(14.67)	49(15.22)	150
Never	206(45.68)	192(51.20)	202(62.73)	600
Physical Activity				
Very Active	189(41.91)	175(46.67)	107(33.23)	471
Moderately	200(44.35)	160(42.67)	161(50.00)	521
Active	61(13.53)	41(10.67)	54(16.77)	156
Quite Active				

Incidence of Stroke in Blacks (Table 12)

Normal weight Blacks (N=451) contributed 5668 person years of follow up. Seventy-three strokes occurred in normal weight Blacks. Crude incidence of stroke in these individuals was 12.8/1000 person years. Crude incidence of stroke among overweight was 10.2 and 10.8 among obese. Although crude incidence of stroke was highest in normal weight Blacks, their obese counterparts were at three times higher risk of stroke. (Adjusted RR 2.941 CI: 1.182-7.320). Overweight Blacks had 70% increased risk of stroke compared to normal weight population. This finding was not statistically significant.

TABLE 12

Incidence of Stroke in Blacks

	NORMAL N =451	OVERWT N = 375	OBESE N = 322
Number of Strokes	73	57	52
Person Years Follow up	5668	5550	4804
Incidence/1000 yr	12.8	10.2	10.8
Relative Risk	1.00*	1.693	2.941
95% C.I		(0.635-4.517)	(1.182-7.320)

(*Used as a reference category in Cox Models adjusted for gender, race, smoking, history of alcohol, cancer and study time.)

Descriptive Statistics among Diabetics

Among obese diabetics, 57% were over age, 65 (Table 13). Seventy six percent of obese population were females and 23 % males. Approximately one third obese population was White and remaining Black. Two third of obese population reported

hypertension. Similarly, 20% of obese population reported heart disease. Among obese, 83% reported drinking alcohol less than once a month. Seventy percent of obese population were never smokers compared with 56% of normal weight population.

TABLE 13

Descriptive Statistics among Diabetics

VARIABLE	NORMAL	OVERWT	OBESE	TOTAL
Age group				
< 45	10(6.21)	4(2.42)	14(10.77)	28
46-55	20(12.42)	17(10.30)	22(16.92)	59
56-65	28(17.39)	30(18.18)	20(15.38)	78
66-75	103(63.98)	114(69.09)	74(56.92)	291
Gender				
Female	95(59.01)	80(48.48)	99(76.15)	274
Male	66(40.99)	85(51.52)	31(23.85)	182
Race				
White	127(78.88)	129(78.18)	92(70.77)	348
Black	32(19.88)	33(20.00)	36(27.69)	101
Other	2(1.24)	3(1.82)	2(1.54)	7
Heart disease				
Yes	30(18.63)	18(10.91)	26(20.00)	74
No	131(81.37)	147(89.09)	104(80.00)	382
Hypertension				
Yes	63(39.13)	75(45.45)	86(66.15)	224
No	98(60.87)	90(54.55)	44(33.85)	232
Cancer				
Yes	11(6.83)	5(3.03)	6(4.62)	22
No	150(93.17)	160(96.97)	124(95.38)	434
History of Alcohol				
Everyday	16(9.94)	8(4.85)	4(3.08)	28
2-3 /wk	10(6.21)	10(6.06)	2(1.54)	22
1-4/mn	17(10.56)	20(12.12)	16(12.31)	53
<1/mn	118(73.29)	127(76.97)	108(83.05)	353

Smoking				
Current	43(26.71)	45(27.27)	19(14.62)	107
Former	27(16.77)	38(23.03)	21(16.15)	86
Never	91(56.62)	82(49.70)	90(69.23)	90
Physical Activity				
Very Active	44(27.33)	46(27.88)	33(25.38)	123
Mode. Active	85(52.80)	90(54.55)	64(49.23)	239
Quite Active	32(19.88)	29(17.58)	33(25.38)	94

Incidence of Stroke in Diabetics

Crude incidence of stroke among diabetics was almost twice compared to general population (Table 14). Lowest crude incidence was found among obese diabetics (22.7/1000 person years) followed by normal weight and overweight individuals. Relative risk of stroke among overweight diabetics was 1.05. This finding was not statistically significant (CI 0.68-1.60). Obesity did not show any association with the risk of stroke among obese people. (RR 0.981 CI 0.61-1.56)

TABLE 14

Incidence of Stroke in Diabetics

	NORMAL N =161	OVERWT N = 165	OBESE N = 130
Number of Strokes	43	47	32
Person Years Follow up	1775	1860	1408
Incidence/1000 yr	24.2	25.2	22.7
Relative Risk	1.00*	1.053	0.981
95% C.I		(0.68-1.60)	(0.61-1.56)

(*Used as a reference category in Cox Models adjusted for gender, race, smoking, history of alcohol, cancer and study time.)

Descriptive Statistics among Non-Diabetics

Among obese non-diabetics, two third were females compared to males who accounted for only one third of population (Table 15). In obese category, 66% were females and 33% were males. Whites accounted for 75% of obese and 85% of normal weight population. Blacks accounted for 24% of obese population and 13% of normal weight population. More obese people reported hypertension and heart disease than normal weight individuals. Only 9% of obese population was of everyday drinkers compared to 15% of normal weight. Sixty one percent of obese population reported drinking alcohol less than once a month compared to only 45% in the normal weight category. People who were very active appeared less obese than quite active individuals.

TABLE 15

Descriptive Statistics among Non Diabetics

VARIABLE	NORMAL	OVERWT	OBESE	TOTAL
Age group				
< 45	543(17.93)	337(14.15)	199(17.01)	1079
46-55	697(23.01)	541(22.71)	253(21.62)	1491
56-65	472(15.58)	423(17.76)	221(18.89)	1116
66-75	1317(43.48)	1081(45.38)	497(42.48)	2895
Gender				
Female	1720(56.78)	1143(47.98)	782(66.84)	3645
Male	1309(43.22)	1239(52.02)	388(33.16)	2936
Race				
White	2576(85.04)	2024(84.97)	880(75.21)	5480
Black	419(13.83)	342(14.36)	286(24.44)	1047
Other	34(1.12)	16(0.67)	4(0.34)	54
Heart Disease				
Yes	218(7.20)	183(7.86)	98(8.38)	499
No	2811(92.80)	2199(92.32)	1072(91.62)	6082
Hypertension				
Yes	630(20.80)	716(30.06)	518(44.27)	1864
No	2399(79.20)	1666(69.94)	652(55.73)	4717
Cancer				
Yes	105(3.47)	70(2.94)	37(3.16)	212
No	2924(96.53)	2312(97.06)	1133(96.84)	6369
History of Alcohol				
Everyday	463(15.29)	328(13.77)	100(8.55)	891
2-3 /wk	339(11.19)	248(10.41)	105(8.97)	692
1-4/mn	600(19.81)	494(20.74)	219(18.72)	1313
<1/mn	1627(53.71)	1312(55.08)	746(63.76)	3685
Smoking				
Current	1167(38.53)	715(30.02)	255(21.79)	2137
Former	487(16.08)	525(22.04)	200(17.09)	1212
Never	1375(45.39)	1142(47.94)	715(61.11)	3232
Physical Activity				
Very Active	1321(43.61)	1023(42.95)	432(36.92)	2776
Moderately Active	1396(46.09)	1139(47.82)	588(50.26)	3123
Quite Active	311(10.27)	220(9.24)	150(12.82)	681

Incidence of Stroke among Non-Diabetics

Crude incidence of stroke among non-diabetics was similar to the general population in contrast to diabetics where crude incidence was twice the incidence in normal population (Table 16). Crude incidence was found highest among tow extreme categories of BMI. Crude incidence of stroke among obese was 10.8/1000 person years. Relative risk for them was 1.45, which was statistically significant

TABLE 16

Incidence of Stroke in Non-Diabetics

	NORMAL N =3029	OVERWT N = 2382	OBESE N = 1170
Number of Strokes	383	287	190
Person Years Follow up	44907	36520	17516
Incidence/1000 yr	8.5	7.8	10.8
Relative Risk	1.00*	1.067	1.458
95% C.I		(0.914-1.245)	(1.221-1.740)

(*Used as a reference category in Cox Models adjusted for gender, race, smoking, history of alcohol and study time.)

Descriptive Statistics among Individuals with Cardiovascular Conditions

As shown in Table 17, males with cardiovascular conditions appeared more obese (32%) than females with cardiovascular conditions (19%). Among obese individuals, 72 % were Whites and 27% were Blacks. Diabetes was reported by 14% of obese population compared to 10% and 9% by overweight and normal weight people respectively. About 73% of obese population reported drinking alcohol less than once a month and only 6% were everyday drinkers. Among normal weight however, 62%

reported drinking alcohol less than once a month and 14% were everyday drinkers. Sixty eight percent of obese populations were never smokers compared to 49% in the normal weight category. Among obese, 30% reported being very active. This proportion was little higher, 33%, among normal weight individuals.

Incidence of Stroke in Individuals with Cardiovascular Diseases

Crude incidence of stroke (17.7/1000 person years) was highest among normal weight individuals (Table 18). Crude incidence was lowest in the overweight category. Obese individuals with cardiovascular conditions had 31% increased risk of stroke (Adjusted RR 1.31 CI 1.043-1.661), which was significant. Overweight individuals were at 14% increased risk of stroke. This finding however was not statistically significant.

TABLE 17

Descriptive Statistics among Individuals with Cardiovascular diseases

VARIABLE	NORMAL	OVERWT	OBESE	TOTAL
Age group				
< 45	60(7.10)	59(6.52)	78(12.04)	197
46-55	125(14.79)	154(17.02)	103(15.90)	382
56-65	122(14.44)	168(18.56)	129(19.91)	419
66-75	538(63.67)	524(57.90)	338(52.16)	1400
Gender				
Female	360(15.01)	420(46.41)	171(26.39)	951
Male	485(57.40)	485(53.59)	477(73.61)	1447
Race				
White	664(78.58)	736(81.33)	467(72.07)	1867
Black	171(20.24)	159(17.57)	177(27.31)	507
Other	10(1.18)	10(1.10)	4(0.82)	24
Diabetes				
Yes	79(9.35)	86(9.50)	92(14.20)	257
No	766(90.65)	819(90.50)	556(85.80)	2141
Cancer				
Yes	38(4.50)	28(1.17)	28(4.32)	94
No	807(95.50)	877(96.91)	620(95.68)	2304
History of Alcohol				

Everyday	115(13.61)	100(11.05)	41(6.33)	256
2-3 /wk	73(8.64)	67(7.40)	43(6.64)	183
1-4/mn	128(15.15)	151(16.69)	92(14.20)	371
<1/mn	529(62.60)	587(64.86)	472(72.84)	1588
Smoking				
Current	292(34.56)	233(25.75)	115(17.75)	640
Former	143(16.92)	205(22.65)	93(14.35)	441
Never	410(48.52)	467(51.60)	440(67.90)	1317
Physical Activity				
Very Active	281(33.25)	305(33.70)	197(30.40)	783
Moderately Active	435(51.48)	497(54.92)	336(51.85)	1268
Quite Active	129(15.27)	103(11.38)	115(17.75)	347

TABLE 18

Incidence of Stroke in Individuals with Cardiovascular Conditions

	NORMAL N =845	OVERWT N = 905	OBESE N = 648
Number of Strokes	172	170	133
Person Years Follow up	10088	12325	8790
Incidence/1000 yr	17.0	13.7	15.1
Relative Risk	1.00*	1.148	1.316
95% C.I		(0.926-1.416)	(1.043-1.661)

(*Used as a reference category in Cox Models adjusted for gender, race, smoking, history of alcohol, and study time.)

Descriptive Statistics among Individuals without Cardiovascular Conditions

Sixty two percent of obese population of individuals without cardiovascular conditions were females (Table 19). Over three fourth of obese population of individuals without cardiovascular conditions was White. Only 5% of obese individuals in this class reported diabetes at baseline. About 56% of the obese population were never smokers

and 59% drank alcohol less than once per month. In the obese category, 41% were very active and 47 % moderately active.

TABLE 19

Descriptive Statistics among Individuals without Cardiovascular Conditions

VARIABLE	NORMAL	OVERWT	OBESE	TOTAL
Age group				
< 45	493(21.02)	282(17.17)	135(20.71)	910
46-55	592(25.25)	404(24.60)	172(26.38)	1168
56-65	378(16.12)	285(17.36)	112(12.18)	775
66-75	882(37.61)	671(40.86)	233(35.74)	1786
Gender				
Female	1330(56.72)	904(55.05)	404(61.96)	2167
Male	1065(43.28)	738(44.95)	248(38.04)	2472
Race				
White	2039(86.95)	1417(86.30)	505(77.45)	3961
Black	280(11.94)	216(13.15)	145(22.24)	641
Other	26(1.11)	9(0.55)	2(0.31)	37
Diabetes				
Yes	82(3.50)	79(4.81)	38(5.83)	199
No	2263(96.50)	1563(95.91)	614(94.17)	4440
Cancer				
Yes	78(3.33)	47(2.86)	15(2.30)	140
No	2267(96.67)	1595(97.14)	637(97.10)	4499
History of Alcohol				
Everyday	364(15.52)	236(14.37)	63(14.29)	663
2-3 /wk	276(11.77)	191(11.63)	64(9.82)	531
1-4/mn	489(20.85)	363(22.11)	143(21.93)	995
<1/mn	1216(51.86)	852(51.89)	382(58.59)	2450
Smoking				
Current	918(39.15)	527(32.10)	159(24.39)	1604
Former	371(15.82)	358(21.80)	128(19.63)	857
Never	1056(45.03)	757(46.10)	365(55.98)	2178
Physical Activity				
Very Active	1084(46.23)	764(46.53)	268(41.10)	2116
Moderately Active	1046(44.61)	732(44.58)	316(46.81)	2094
Quite Active	214(9.13)	146(8.89)	69(10.43)	429

Incidence of Stroke among Individuals without Cardiovascular Disease

Crude incidence of stroke (8.7/1000 person years) was highest in obese category (Table 20). Crude incidence of stroke among overweight was lower than normal weight individuals. Crude relative risk of stroke among obese individuals without cardiovascular conditions was Obese individuals were at 47% increased risk of stroke (Adjusted RR 1.47 CI 1.15-1.88). This association was statistically significant. Risk of stroke (adjusted) among overweight in this stratum was only 1.09. This finding was not statistically significant.

TABLE 20

Incidence of Stroke in Individuals without Cardiovascular Conditions

	NORMAL N =2345	OVERWT N = 1642	OBESE N = 652
Number of Strokes	254	162	89
Person Years Follow up	36594	26055	10134
Incidence/1000 yr	6.9	6.2	8.7
Relative Risk	1.00*	1.019	1.473
95% C.I		(0.836-1.242)	(1.154-1.881)

(*Used as a reference category in Cox Models adjusted for gender, race, smoking, history of alcohol,and study time.)

CHAPTER 6

DISCUSSION

This study aimed at analyzing association between long-term risk of stroke and obesity measured at baseline. Additionally the study also focused on differences if any, in change of this association among strata of some modifiable and non-modifiable risk factors. Overall, crude incidence of stroke was highest in the obese individuals in general population. Cox Proportional Hazards Models on overall study population showed 40% increased risk of stroke among obese people compared to normal weight people. Being overweight did not increase risk of stroke. Findings remained somewhat similar in stratified analysis.

Risk of Stroke and Gender

Incidence of stroke has always been reported higher among men than women. (Wyller, 1999). Studies have reported incidence of stroke among males, 1.25 times higher than females. (Tegos et al., 1998). Present study showed that crude incidence of stroke in overweight males was 9.6. Crude incidence of stroke in obese males was 13.1. Adjusted risk ratio in overweight males was 1.18 (95% CI 0.96-1.45) and in obese males was 1.6 (95% CI 1.19-1.65). Although overweight males showed slightly higher risk compared to normal weight, this finding was not statistically significant. Results in obese males were significant with wide confidence interval. These results could be due to lack of enough power and fewer number cases, especially in obese category (N=419

and Number of strokes = 7). Crude incidence of stroke in females was 7.8 in the overweight category and 11.1 in obese category. Adjusted relative risk in overweight category was 0.981 with 95% confidence interval 0.79-1.206. Being overweight did not show any association with increased risk of stroke in females. (RR 0.98, 95% CI 0.79-1.20). Relative risk of stroke among obese females was 1.24, which was statistically significant (1.00-1.53). This was somewhat lower than RR of 1.75 reported in the nurse's health study (Rexrode et al., 1988) in the category of BMI $\geq$ 27kg/m2. The estimates in Nurses' health study were adjusted for menopause and hormone use. Both physiological and surgical menopause are known to increase risk of stroke. These factors have not been considered in the analysis of this study. The Nurses' Health Study also included change in BMI over period follow up period. This study could not use this variable due to limitations of the data collection of NHANES-I study.

The study tried to explore if there risk of stroke in males was different from risk of stroke in females. This was evaluated by incorporating an interaction term for gender in the study models. No statistically significant differences were found between risk of stroke in males and risk of stroke in females. Therefore, although relative risk of stroke is 1.40 in males and 1.24 in females, their risks are not very different from each other.

Risk of Stroke and Race

Results among strata by race were consistent with the literature. Risk of stroke among obese Blacks was much higher than the risk of stroke among obese Whites in their respective comparison strata.

Crude incidence of stroke was highest in the obese Whites. Obese Whites were at 31% increased risk of stroke compared to their normal weight reference group. Being overweight did not show any association with risk of stroke among Whites (RR 1.00 95% CI 0.85-1.17).

Previous studies on stroke have shown increased mortality due to stroke among Blacks (Sacco, 1998). Recent study by NIH done in Cincinnati revealed that incidence in Blacks was 1.6 times higher than the incidence in general population. This study also pointed out that younger Blacks (< 65 years) in this area experienced stroke two to three times more than the older Black population. Reasons postulated for higher incidence of stroke were increased prevalence of hypertension, diabetes, and smoking in younger population and their lower socioeconomic status (National Institute of Health, 2002).

The present study found higher incidence of stroke in the lowest BMI category for blacks. Relative risk of stroke in obese Blacks was 2.94 (95% CI 1.18-7.32); three times higher than their normal weight comparison group. In the study population, higher number of Blacks reported hypertension and diabetes at baseline. Increased incidence of stroke and almost three times higher risk of stroke among Blacks could be due to increased prevalence of cardiovascular conditions at baseline in this population.

Race did not show any statistically significant interaction with obesity. Therefore, the risk of stroke among obese black when compared with their normal weight black population was not very different from the risk of Whites in comparison with their normal weight counterparts.

Risk of Stroke and Co-morbid Conditions

This study also explored effect of obesity on stroke in presence or absence of cardiovascular conditions (heart disease and hypertension) and diabetes mellitus reported at the baseline interview. The results did not show any effect modification due to diabetes mellitus and hypertension.

Those who were overweight or obese and reported history of either heart disease or hypertension at their baseline examinations had increased risk of stroke compared to normal weight individuals. Association between stroke and overweight adults without cardiovascular diseases was weak and non-significant. Obese category in the same class was at 47 % increased risk of stroke. This association was statistically significant. Presence of carotid artery disease, hypertension, and diabetes mellitus have shown to increase the risk of stroke in men and women (Tegos et al., 1998). Heart disease and stroke are believed to act as independent risk factors for each other (Pontiroli et al., 1998). Stratified analysis of present study found crude incidence of stroke much higher among people with these co morbid conditions. Incidence of stroke among those who were free from these conditions was much low. Crude incidence of stroke among individuals with cardiovascular conditions was 17.0 in normal weight category and 15.1 in obese individuals. Individuals with cardiovascular conditions who were obese at baseline could have lost weight thus minimizing their risk of stroke due to obesity and other chronic conditions. This could be a reason for lower crude incidence of stroke among obese category. Similarly, crude incidence of stroke among individuals with diabetics was twice higher than non-diabetics. Crude incidence of stroke in individuals

with history of heart disease was twice the incidence of those without heart disease. Being overweight did not increase risk of stroke in individuals without heart disease. However, having heart disease and being overweight increased risk of stroke 41% and 31% in obese adults respectively. Thus, obesity was a significant risk factor for stroke in individuals with or without heart disease. This association did not remain constant among diabetics. Obesity did not show statistically significant association among overweight diabetics (RR = 1.05, 95% C.I 0.68-1.60). It did not show any association among obese diabetics (RR = 0.98, 95% CI= 0.61-1.56). Obese non-diabetics however, had 45% increased risk of stroke (95% CI= 1.22-1.74). Being overweight did not show statistically significant association among non-diabetics. Some studies have postulated that increased risk of stroke due to obesity is mediated via presence or absence of hypertension or diabetes mellitus. It is also suggested that obesity is a predictor of coronary artery disease but not a predictor for stroke (Pontiroli et al., 1987). Obesity is believed to increase risk of stroke by causing hypertension, increasing insulin resistance and diabetes mellitus. In this study incidence of stroke was two folds higher among diabetics than non-diabetics. Therefore, it was evident that the diabetic population was experiencing stroke in much higher numbers than non-diabetic population. However, obesity did not show statistically significant association with the risk of stroke among diabetics. Non-diabetics were at 50% increased risk compared to their normal counterparts. These results suggest effect of obesity as an independent risk factor for stroke. Diabetes is known to increase the risk of stroke two to five times (Manson, 1997; Stamler, 1993). Effect of obesity on risk of stroke in diabetics could have been masked

by the already increased risk of stroke due to diabetes. In non-diabetics this effect is elevated to 50% increased risk of stroke.

No statistically significant interaction was found due to diabetes and cardiovascular conditions. These results again suggest that the risk of stroke due to obesity was not different in the strata of co morbid conditions.

Limitations

This study uses secondary data collected by means of personal interviews and physical examinations. Some bias could have been introduced in the study due to errors in measurement of anthropometric parameters such as weight and height. However, NHANES-I employed rigorous measurement protocols and possibility of such kind of bias is minimal. History of heart disease, hypertension, diabetes mellitus, and stroke was collected at the baseline during personal interviews. Some recall bias or misreporting of information about occurrence of these conditions is another possible source of bias. Misreport of history of stroke at baseline could result in that case being included as incident case of stroke during follow up. For first occurrence of stroke reported during follow up cycles, year of occurrence was reported. For stroke cases that actually occurred at baseline but reported during follow up, study time was less than 1 year. All these cases were excluded from the analysis, as they didn't contribute to the study models. Thus bias due to misreporting of stroke cases at baseline was removed. Some cases may have reported year of occurrence of stroke inaccurate, which leaves some residual bias. Similar errors could have occurred in self-report of other baseline variables. Information on incident case of stroke was derived using hospital discharge; death certificate and self

reported information. Year of occurrence of stroke was taken as earliest of these three indicators. Inaccuracies in coding of death certificates and hospital discharge diagnosis are another source of bias.

Some studies have reported change in weight as more reliable measure of obesity than baseline BMI alone. However, during NHANES-I and NHANES-I follow up study change is weight was not recorded for all subjects at regular interval of times and therefore could not be considered in analysis. Risk of stroke in the middle or overweight category of BMI could not reach the statistical significance due to lack of enough power.

Conclusion

Overall BMI > 26 kg/m2 was found to increase the risk of stroke. Association between risk of stroke and being overweight was somewhat inconsistent among analysis strata. Increased risk due to overweight was found only among individuals with cardiovascular conditions. Hazard ratios in the overweight category failed to reach the statistical significance. Lack of consistency in overweight category of BMI could be due to large number of normal weight individuals than overweight individuals. Some people in this category could have lost weight over follow up period and therefore experienced less mortality and morbidity. Obesity was found consistently associated with risk of stroke except among obese diabetics. Obesity is an important risk factor among non-diabetics. It does not however appear to increase risk on its own among diabetics whose risk of stroke is already elevated due to their diabetic status. Non-significant results among diabetics could also be due to loss of weight over follow up period. Obese diabetics did not show increased risk when compared to their normal weight counterparts.

Increased risk of stroke due to obesity in obese diabetics may become apparent on repeating this analysis within groups, where normal weight non-diabetics will be the comparison population. Association between stroke and obesity was reversed in individuals with heart disease where both overweight and obese cardiovascular patients were at increased risk. The category of cardiovascular diseases included both hypertension and heart disease. Some elevated risk in the overweight category could be due to higher number of hypertensive in this group.

Obese males were at increased risk of stroke compared to non-obese males. In females, being overweight did not show any association with risk of stroke. Ethnicity was a significant predicator of stroke. Being obese and African American increased risk of stroke three times. Although it has shown some protective effect in overweight BMI category in females, risk remains high in obese females. All potential risk factors (gender, race, diabetes and cardiovascular conditions) did not show statistically significant interaction. Therefore, risk due to obesity was not different in due to effect of either of these risk factors (Gender, race, diabetes or cardiovascular conditions). It is therefore important to maintain healthy BMI and emphasis control of obesity in primary prevention of stroke. Further research in the area of stroke and associated cardiovascular conditions is needed.

FIGURE 1
Case Ascertainment

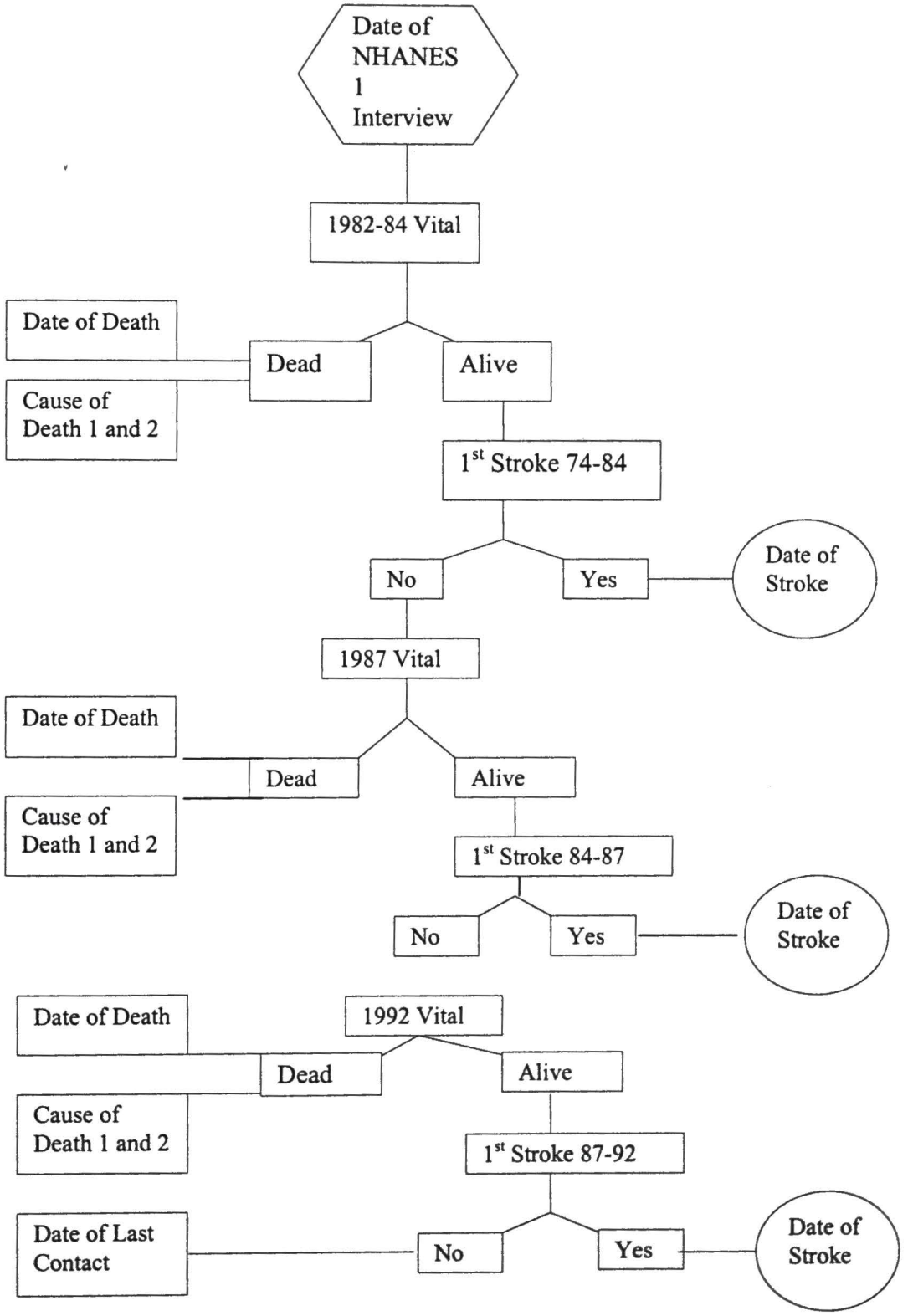


FIGURE 2

Data Collection Summary of NHANES-I and NHEFS Study

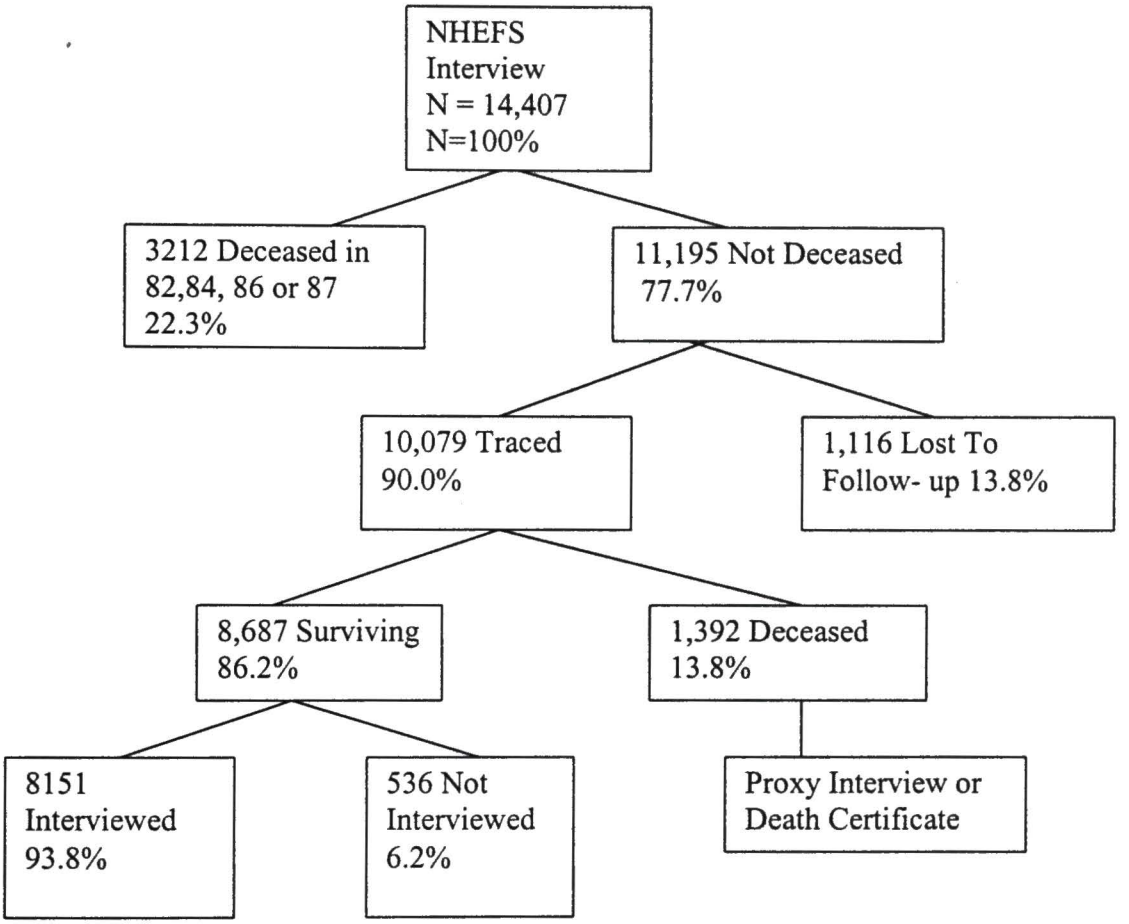
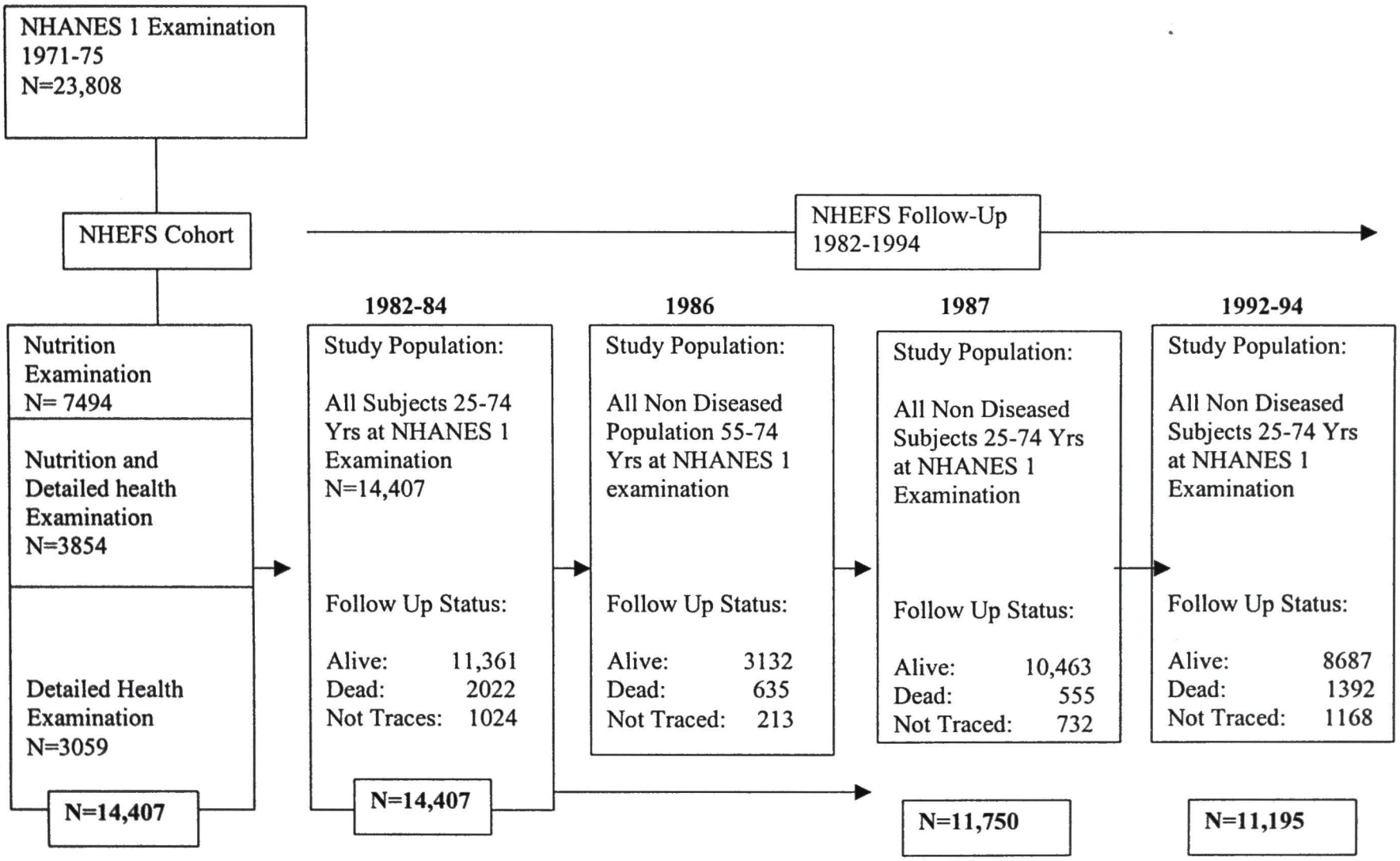


FIGURE 3 Schematic Diagram of NHANES 1 Epidemiologic Follow-Up Study

Ref: Vital And Health Statistics: Plan And Operations Of NHANES 1 Epidemiologic Follow-Up Study



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