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Cardiovascular Health Index and Risk of Stroke

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2013

Abstract

Cardiovascular Health Index and Risk of Stroke

Ambar Kulshreshtha, MD, MPH

Stroke is a leading cause of death and disability in the United States, with an estimated 600,000 incident strokes annually. Despite the advent of promising treatments, prevention is still the best approach in reducing the burden of stroke. A healthy lifestyle and achieving low risk factor levels can reduce the risk of stroke by about 80%. The American Heart/Stroke Association proposed a definition of cardiovascular health and developed a new public health metric, the "cardiovascular health index" (CVHI), which incorporates several traditional cardiovascular risk factors and lifestyle behaviors and can be evaluated over time. The concept emphasizes primordial prevention by defining goals for health factors and behaviors and is meant to be simple in order to facilitate dissemination and implementation in the community. The new cardiovascular health metric has not been specifically evaluated in relation to stroke risk. This dissertation aims at bridging the gaps in public health and clinical knowledge on the utility of the new cardiovascular health metric in relation to stroke prevention. It contributes novel insight on the utility of the new metric of cardiovascular health for stroke prediction, and the impact of family history, familial and environmental factors. Knowledge gained from this dissertation will be useful for implementation of public health and individualized approaches that would increase the prevalence of a better cardiovascular health profile for stroke prevention.

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CHAPTER 1: Background

1.1 Stroke: Magnitude of Problem

Global

According to World Health Organization (WHO) estimates, cardiovascular diseases are the leading causes of mortality worldwide and account for over 20% of all deaths.[1] Stroke causes 9% of all deaths around the world and is the second most common cause of death after coronary heart disease.[2] Stroke incidence has increased by more than 100% over the past four decades leading to a global stroke epidemic.[3] [4,5] Rates of stroke mortality and burden vary greatly among countries and low and middle income countries are the most affected with 85% of stroke burden.[6] The proportion of deaths caused by stroke is 10–12% in developed countries and 12% of these deaths are in people less than 65 years of age. Stroke also results in substantial long-term morbidity and is responsible for a major proportion of overall disease burden (as measured in disability-adjusted life-years (DALYs) lost.

United States

Stroke is the fourth leading cause of death in the United States, with an estimated 600,000 incident strokes annually and 6.8 million stroke survivors. [7-9] From 1999 to 2009, the relative rate of stroke deaths fell by 36.9% and the actual number of stroke deaths declined by 23%. Still every year, approx. 800, 000

people continue to experience a new or recurrent stroke (ischemic or hemorrhagic).

Approximately 610 000 of these are first attacks, 185 000 are recurrent attacks. Analysis of data from the Framingham Heart Study indicates that stroke incidence is declining over time. Data from 1950 to 1977, 1978 to 1989, and 1990 to 2004, showed that the age-adjusted incidence of first stroke per 1000 person-years in each of the 3 periods was 7.6, 6.2, and 5.3 in men and 6.2, 5.8, and 5.1 in women, respectively.[10] Evidence from other studies, however, indicates that there may be a leveling off of prior declines and a possible increase.[11,12] Overall stroke prevalence in 2008 is estimated to be 2.8%. Stroke represents not only an enormous public health problem, but it is a serious financial burden on the United States economy.[13] The direct and indirect cost of stroke in 2009 was $38.6 billion and will exceed $2.2 trillion dollars by 2050 with the highest per capita contributors being Blacks and Hispanics.[14] Despite the larger burden of stroke both in terms of mortality and disability, the study of stroke has not received enough attention.

1.2 Definition and Types of Stroke

Episodes of stroke have been reported from the 2nd millennium BC onward in ancient Mesopotamia and Persia.[15] The word ‘stroke’ is derived from a Greek word meaning ‘struck down with violence’ and it appeared first in Hippocrates writings where he described it as a phenomenon of sudden paralysis. In current medical terminology, stroke is described as a condition caused by rapidly

developing loss of brain function due to disturbance in the blood supply to the brain. This can be due to ischemia (lack of blood flow) caused by blockage (thrombosis**,** arterial embolism), or a hemorrhage (leakage of blood). The recommended standard World Health Organization stroke definition is as follows: 'A focal (or at times global) neurological impairment of sudden onset, and lasting more than 24 hours (or leading to death), and of presumed vascular origin.' This standard definition excludes transient ischemic attack (TIA), which is defined as focal neurological symptoms, but lasting less than 24 hours, subdural hemorrhage, epidural hemorrhage, poisoning, and symptoms caused by trauma. A diagnosis of stroke depends on the thoroughness of the evaluation but some patients might not come to the attention of medical personnel because of sudden death or no access to medical assessment.

Strokes can be classified into two major categories: ischemic and hemorrhagic (Table-1). Ischemic strokes are those that are caused by interruption of the blood supply, while hemorrhagic strokes are the ones which result from rupture of a blood vessel or an abnormal vascular structure. In United States, about 87% of strokes are caused by ischemia and the remainder by hemorrhage.[16] The symptoms of a stroke may begin suddenly or develop over hours or days, depending upon the type of stroke and the area of the brain that is damaged. Depending upon the area affected, a person may lose the ability to move one side of the body, the ability to speak, or a number of other functions. The damage from a stroke may be temporary or permanent and can cause long-lasting disability or even death. Stroke is a medical emergency and immediate

treatment (e.g. clot-busting drugs) can save lives and reduce disability. A person's long term outcome depends upon how much of the brain is damaged, how quickly treatment begins, and several other factors. Early treatment and preventive measures can reduce the brain damage that occurs because of stroke.

Table 1: Types of stroke and their mechanism

Types of Stroke	Subtypes and Mechanism	Diagnosis
A) Ischemic stroke	• Thrombotic Ischemic Stroke: Sudden occlusion of arteries supplying the brain due to thrombus formed directly at the site of occlusion • Embolic Ischemic Stroke: Thrombus in another part of the circulation, which follows the blood stream until it obstructs arteries in the brain. • Other causes including venous thrombosis systemic hypoperfusion (eg. Shock), cryptogenic (unknown origin)	• Neuro-imaging
B) Hemorrhagic stroke	• Intra-cerebral hemorrhage: Bleeding from one of the brain's arteries into the brain tissue. • Subarachnoid hemorrhage: Arterial bleeding on the surface of the brain (between the two meninges)	Neuro-imaging or Lumbar puncture.

1.3 Pathophysiology of Stroke

Stroke occurs most often against a background of advanced atherosclerotic lesions in the cerebral arteries. Atherosclerosis is characterized by the accumulation of lipids, calcium, and other substances in the inner arterial lining. (Figure :1) Plaque formation occurs by the passive diffusion of lipids (low density lipoprotein [LDL]) into the subendothelial space. As lipid accumulates, plaques can become unstable leading to their rupture. When atherosclerotic plaques rupture, a thrombus forms, which can interrupt blood flow or break off and embolize to another part of the body. Recent evidence affirms the mechanism of platelet activation to atherogenesis and the crucial role of this process in the pathogenesis of thrombotic stroke. Inflammation in plaques also plays an important role, and C-reactive protein seems to be an independent risk factor for stroke. [17] [18] When the atherosclerotic plaque is disrupted, platelets adhere to the damaged endothelium and undergo activation and aggregation into a platelet-rich thrombus. Increased levels of surrogate platelet activation markers are present after ischemic stroke, indicating increased platelet reactivity. Although the platelet plays a role in the occlusive event over an activated plaque, artery-to-artery embolism is more often the causative event in stroke, rather than local occlusion.

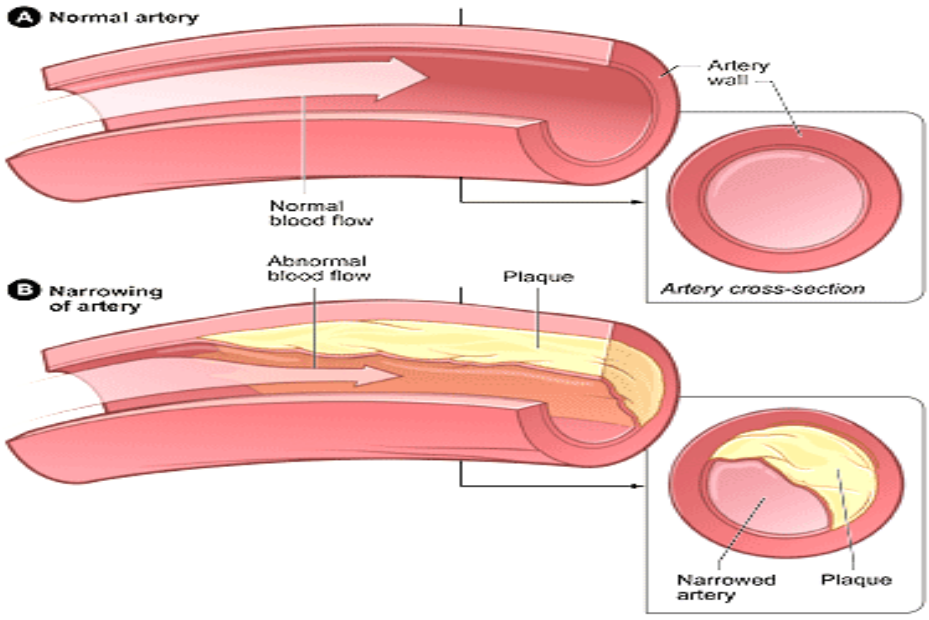


Figure 1: Atherosclerosis

(Reformatted from NLHBI website: public domain)

Signs and symptoms of a stroke may diminish and disappear in minutes or hours without residual clinical abnormalities or may persist and progress ending in permanent disability or death (Figure-2). Episodes that resolve completely within 24 hours are designated Transient Ischemic Attacks (TIA) while those that persist longer than 24 hours are termed completed strokes.

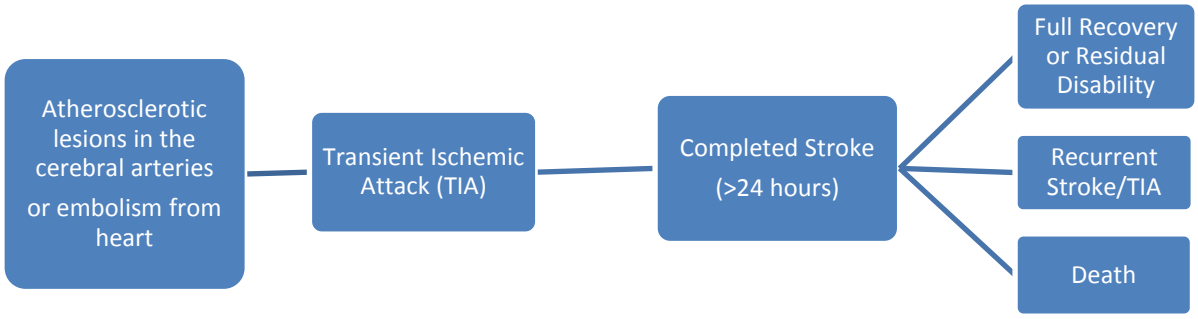


Figure 2: Pathophysiology and outcomes after stroke

1.4 Risk Factors for Stroke

Stroke is a multi-factorial disease where a combination of risk factors influences a person's likelihood of having a stroke. Observational studies have shown that the risk factors for cardiovascular disease are the same in different populations.[19-21] (Table-2) The recent INTERSTROKE case-control study identified risk factors for stroke and their prevalence and contribution to stroke burden in 22 countries between 2007 and 2010.[22] Ten modifiable risk factors (hypertension, smoking status, abdominal obesity, diet with low intake of fish and fruit, physical inactivity, self-reported diabetes mellitus, excessive alcohol intake, psychosocial stress, apolipoproteins (a high ratio of apolipoprotein B to apolipoprotein A1), and cardiac causes (especially atrial fibrillation for ischemic stroke) account for more than 90% of ischemic stroke and intracerebral hemorrhage. However, the relative importance of these individual risk factors and the absolute risk of stroke may vary across populations. [23]

Table 2: Risk factors for stroke[24,25]

Category	Risk Factor	Relative Risk
Non-modifiable	• Age • Male sex • Family history; genetics • Low birth weight (<2500g) • Black Race	 2.4 2.0 4.6
Modifiable	• Hypertension • Atrial fibrillation • Previous history of TIA • Physical inactivity • Tobacco use/Smoking • Diabetes Mellitus • Other cardiac diseases • Migraine with Aura • Heavy alcohol consumption • Dyslipidemia • Obesity • HRT • Sleep Disordered Breathing • Diet (low fruit and vegetables) • Psychosocial stress and Depression	8.0 4.0 (at age of 50 yrs) 3.0 (within 2 days) 2.7 1.9 1.8 1.8 1.7 1.6 1.5 1.4 per inc. of 5kg/m2 1.4

Non-modifiable Risk factors

There is considerable overlap between the risk-factors for stroke and coronary artery disease. Non-modifiable risk factors for stroke are similar to those of coronary artery disease. The most important risk factor is age and the risk of stroke doubles for each successive decade after age 55 years.[26] Stroke is also more prevalent in men than in women although stroke –related fatalities are higher in women than men. [27] Factors such as oral contraceptive use and pregnancy contribute to the increased risk of stroke in women.[28-30] Blacks and some Hispanic Americans have higher stroke incidence and mortality rates

compared with whites. [31,32] Also both paternal and maternal history of stroke has also been associated with an increased stroke risk.[33,34]

Modifiable Risk factors

There are several important modifiable risk factors for stroke. One in three United States adults has hypertension which is a major risk factor for both ischemic and hemorrhagic stroke. [35-37]

It has been shown that the treatment and lowering of blood pressure among hypertensive individuals is associated with a significant reduction in stroke risk. [38,39] Despite the efficacy of antihypertensive therapy, however, a significant proportion of the population have undiagnosed or inadequately treated hypertension and thus are at increased risk for stroke. [40,41]Lack of diagnosis and inadequate treatment are particularly evident in minority populations and in the elderly. [42] Another important risk for stroke is smoking. The risk of ischemic stroke associated with current cigarette smoking has been shown to be approximately double that of nonsmokers after adjustment for other risk factors.[43] Almost 90% of non-smokers have been shown to have detectable levels of serum cotinine because of presence of environmental tobacco smoke. Thus, because of the high population prevalence of passive smoking, even a small increase in relative risk of stroke will have a substantial population attributable risk.[44] Stroke risk associated with former smoking has however been shown to substantially decrease with increasing time since cessation. [45-47]

Diabetes patients have both an increased susceptibility to atherosclerosis and an increase prevalence of risk factors like hypertension, dyslipidemia and obesity.[48,49] Studies have shown that impaired glucose tolerance nearly doubles the stroke risk and patients with diabetes mellitus nearly triple the stroke risk as compared with patients with normal glucose levels. [50] [51] Other major risk factors include atrial fibrillation, prior cardiac disease and sickle cell. Atrial fibrillation is a powerful risk factor for stroke, independently increasing risk almost 3 to 4 -fold throughout all ages.[52,53] The presence of stroke is also strongly associated with the presence of symptomatic and asymptomatic cardiac disease.[54-56] The prevalence of stroke in sickle cell patients is more than 11% and a substantial number of these patients also have 'silent' strokes on brain MRI. [57] An important risk factor for coronary artery disease which has not shown a similar consistent relationship with stoke is dyslipidemia. Prior epidemiological studies had found no association between cholesterol levels and overall stroke rates but these studies were likely confounded by the inclusion of both hemorrhagic and ischemic stroke.[58] Recent studies show a weak association between serum cholesterol and an increasing risk of ischemic stroke. [59] [60] [61]

Other well documented risk factors include obesity, physical inactivity, poor diet and alcohol and drug abuse. Recent evidence supports abdominal obesity in men and obesity and weight gain in women as independent risk factors for stroke. [62]. The beneficial effects of physical activity and increased fruit and

vegetable consumption have also been consistently demonstrated in both cohort and case-control studies of stroke.[63-65] However, it has been controversial if the effect is specifically due to diet or a reflection of a generally healthier lifestyle in these individuals.[66] Strong evidence indicates that alcoholism and heavy drinking are risk factors for all stroke subtypes and majority of studies have suggested a J-shaped relationship between alcohol consumption and ischemic stroke risk, with a protective effect in light or moderate drinkers and an elevated risk with heavy alcohol consumption.[67-72] Few other important risk factors include habitual snoring and migraine headaches. [73,74] Migraine has been more consistently associated with stroke in women.[75,76] Most of the perceived increased stroke risk associated with the use of OCs is based on early studies with high-dose preparations but studies of later-generation of OCs containing lower doses of estrogens did not find an increased risk of stroke.[77-79] Illicit drug abuse, hyperhomocystemia and lipoprotein (a) are other known risk factors.[25]

1.5 Differences in Stroke Incidence

Socioeconomic and Geographic Differences

Previous studies indicate that lower socioeconomic status is associated with higher stroke risk in many developed countries[80] [81-83]Socioeconomically disadvantaged populations are susceptible to under-diagnosis of hypertension, diabetes, and other risk factors and also likely to receive suboptimal care for interventions to reduce risk. Stroke mortality in the United States is strongly related to the income of the county of residence and geographic area. [84] The

southeastern region has documented an excess mortality from stroke since the 1940s although it was first documented in 1965. [85-88] Definitions of the "stroke belt" frequently include the entire Southeastern region of the United States excluding the state of Florida (i.e., North Carolina, South Carolina, Georgia, Tennessee, Arkansas, Mississippi, Alabama, and Louisiana) (Figure 3).[89] Within the stroke belt, a “buckle” region along the coastal plain of North Carolina, South Carolina, and Georgia has been identified with an even a higher stroke mortality rate than the remainder of the stroke belt. [90] The overall average stroke mortality is >20% higher in the stroke belt than in the rest of the nation and >40% higher in the stroke buckle. Despite the persistence of the stroke belt and buckle over the past half-century and the excess stroke mortality, the contributing causes remain unclear. [91]

Figure 3: Stroke Belt in United States

Racial Differences

National statistics have shown an increase in deaths attributed to stroke for blacks because of a higher stroke incidence compared with whites.[92] [93] Possible reasons for the higher incidence and mortality rate of strokes in blacks include a higher prevalence of hypertension, obesity, and diabetes within the black population although it still does not explain all of the excess risk.[94] [95] Among people > 18 years of age, the estimated prevalence of stroke based on the 2009 National Health Interview Survey was 3.8% among blacks; it was 2.5% among whites and it was 1.3% among Asians[96] The per capita cost of stroke estimates is highest in blacks ($25,782) and the economic burden will be enormous over the next several decades. Further efforts to improve stroke prevention and treatment in these high stroke risk groups are therefore necessary.

1.6 Primary Prevention of Stroke

While many treatment options exist for prevention of stroke, primary preventive strategies could greatly reduce the need for secondary prevention in the first place. In stroke, like other chronic diseases, the clinician's first contact with the patient comes late in the natural history of the disease, usually after a major event or complication (e.g. TIA) and when much of the irreversible pathological damage has already occurred. It follows that primary prevention is more important. Primary prevention can be defined as ‘action taken prior to the onset of disease which removes the possibility that a disease will ever occur’. The concept of primary prevention is more holistic and includes the concept of

'positive health' that enables every individual to have an acceptable level of health to lead a socially and economically productive life. There are two common approaches that have been proposed as a way of reducing burden of stroke and other chronic diseases in the community.[97] The first preventive strategy seeks to identify the 'causes of cases' and is targeted to high-risk susceptible individuals offering them protection. The second approach seeks the 'causes of incidence' by using population strategies to identify the determinants of incidence in the population as a whole. As these approaches are complementary, to have an adequate impact on the population, these approaches should be implemented together.

Table 3: Levels of prevention

Level	Definition
Primordial prevention	Primordial prevention is prevention of risk factors themselves, beginning with change in social and environmental conditions in which these factors are observed to develop, and continuing across lifespan.
Primary prevention	Primary prevention strategies intend to avoid the development of diseases. Most population-based health promotions are primary preventive measures.
Secondary prevention	Secondary prevention strategies attempt to diagnose and treat an existing disease in its early stages before it results in significant morbidity.
Tertiary prevention	These treatments aim to reduce the negative impact of established disease by restoring function and reducing disease-related complications

The 'High-Risk' Strategy

The prevention of stroke relies on the reduction of the overall absolute risk of disease rather than management of individual risk factors. The strategy for primary prevention in people with no history of stroke is to estimate the absolute risk of a vascular event and to take appropriate action according to that level of risk. This 'high-risk' approach to reducing stroke incidence involves identifying those at highest risk (e.g. using tools such as risk factor scoring) and then treating them aggressively. Thus, in this 'high risk' preventive strategy, those at the top end of the distribution are identified and preventive care is given (e.g. control of hypertension).[98] Although this focus on 'high-risk' strategy could be successful for individuals and maybe an efficient use of limited resources, it does not influence the large proportion of deaths occurring in the population with for example a slightly raised blood pressure and thus at small risk. Recent evidence also suggests that high-risk approach could also widen socioeconomic inequalities.[99]

The Population Strategy

'Population Strategy' is preventive approach directed at the whole population irrespective of individual risk levels. More than three decades ago, Geoffrey Rose suggested that a small reduction in risk in a large number of people may prevent many more cases than treating a small number at higher risk. [100] This 'population-based' approach aims to shift the distribution of risk factors across a

population in a beneficial direction with the goal of reducing stroke in the whole population (Table-4). This is an attempt to control the determinants of incidence to lower the mean level of risk factors for the entire population. Thus rather than by changing risk factors on a person-by-person basis, using a whole-population approach could change everyone's exposure level and work directly on the 'underlying causes of disease' (Figure 4). Population strategies work better when risk is widely diffused throughout the whole population as in the case of CVD. For example, modest reduction in salt intake in population can result in dramatic reductions in stroke.[101] Population based strategies are directed towards socio-economic, behavioral and lifestyle changes and therefore require firm political commitment and effective policies. Few common successful examples include seat belt-use, immunizations, folic acid fortification, fluoridation, and anti-smoking efforts. [102-104]

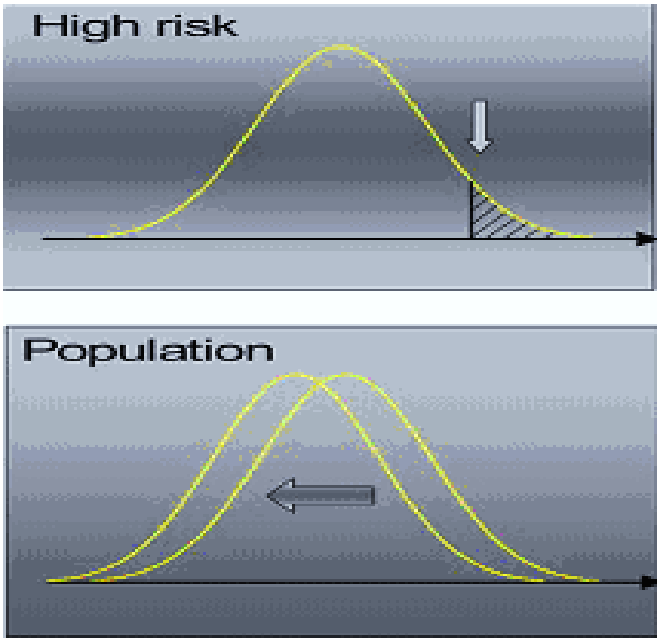


Figure 4: The high risk versus the population approach to prevention (From: Makover ME, Ebrahim S, 2005)

The 'Prevention Paradox' in population-strategies

In the population approach, many people need to participate in making the population healthy but only relatively few will benefit .i.e. 'a measure that brings large benefits to the community offers little to each participating individual'- the 'prevention paradox'. Rose extrapolates from Framingham data to suggest that if all men <55 years reduced their cholesterol level by 10% only 1 in 50 could expect to avoid a heart attack on average. The rest (49 out of 50) would eat a modified diet for 40 years and perhaps gain little from it. Even though one should not expect too much from individual health education, measures like social motivation, peer-pressure and societal policy changes can still bring about more pervasive changes in the population. For example, a clinician's counseling to quit smoking may help few individuals but a social pressure that makes smoking unacceptable along with market forces (e.g. high prices) is likely to make a larger number of individuals adopt a bigger change. Thus, to influence mass behavior, one must look at mass determinants which are largely social and economic.

Importance of Primordial Prevention

In primary prevention, efforts are directed towards individuals who already have adverse levels of known risk factors with the aim of preventing the first occurrence of a disease event. For example,use of antihypertensives in people with hypertension to prevent the first occurrence of stroke. However, once

adverse levels of risk factors are present, the development of subclinical atherosclerosis and vascular changes leading to elevations in long-term risk for CVD and stroke are largely unavoidable. The association of risk factor levels with CVD risk is continuous and graded across all levels; it is therefore of paramount importance to focus on prevention at all levels of risk (see Chapter-2). Primordial prevention deals with the underlying conditions leading to exposure and consists of actions and measures that inhibit the emergence of risk-factors.[105] It aims to modify the conditions that generate the unequal distribution of exposures in the whole population. Given the substantial burden of risk factors in the United States like obesity and adverse lifestyle beginning in childhood, primordial prevention has both relevancy and urgency.

Table 4: **Comparison of population vs high-risk strategy for reducing stroke**

Population Strategy	High-Risk Strategy
• Radical. Potentially large benefits(community wide interventions to modify behavior and social norms)	• Benefits large in high prevalence population in (targeted behavioral or pharmacological interventions)
• Seeks to alter the underlying causes of disease.	• Seeks to protect individuals who are susceptible to the causes.
• Targets unaware population also with reduction in the cumulative population risk of heart disease	• Interventions appropriate for individuals. Easier to understand, motivates individuals and physicians for greater risk reduction
• Restoration of 'biological normality' to which one is genetically adapted. (E.g. lower intake of saturated fat).	• End result maybe an increased 'biological abnormality' away from one is genetically adapted. (e.g. statin intake for high cholesterol)
• Risk ratio is not beneficial	• Risk ratio is favorable
Limitations	***Limitations***

• Mass changes hard to communicate and implement	• Impact on total burden may be small. Could be behaviorally or culturally unsustainable
• Individual benefits small with poor motivation	• Expensive and costs likely to be governed by screening modalities used.
• Interventions could challenge vested interests /societal norms	• Palliative and temporary, requires personal co-operation
• These normalizing measures are presumed to be safer but if a preventive measure exposes many people to even a small risk, then the harm may outweigh the benefits. (e.g. long-term preventive medicines like polypill)	• Required level of evidence both of benefit and (especially) safety should be very stringent. Could increase health disparities.
Implementation	***Implementation***
• Culturally and linguistically appropriate and effective community health promotion and prevention needs to be encouraged and integrated with primary health care.	• Cost-effective and customized diagnostic and management algorithms and guidelines should be developed to be made widely available for all health care settings.
• Infrastructure, capacity building for research should be prioritized. Policy changes to enable the environment essential for healthy behavior	• Availability of effective and affordable drugs, devices and procedures along with a proper referral chain has to be ensured.

1.7 Concepts of Health and Disease

Disease

Characteristics of populations influence our definitions of health and disease. Consideration of what is 'normal' is influenced by what is prevalent.[106] Since the late 1960s, the definition of illness has been considered using the concept of the triad of disease, illness, and sickness. [107] According to this concept (i) 'disease' can be defined as a physiological or psychological dysfunction due to a

pathological process which is generally empirical in its character (and is a subject of cognition through human senses); (ii) 'illness' is understood as a subjective experience of a feeling to be unhealthy and which reduces the capacity of the 'ill' person; and (iii) 'sickness' is a state of social dysfunction i.e. a role that the individual assumes when ill and society is expected to release the 'sick' person from all or some part of his/her obligations.(Figure-5)

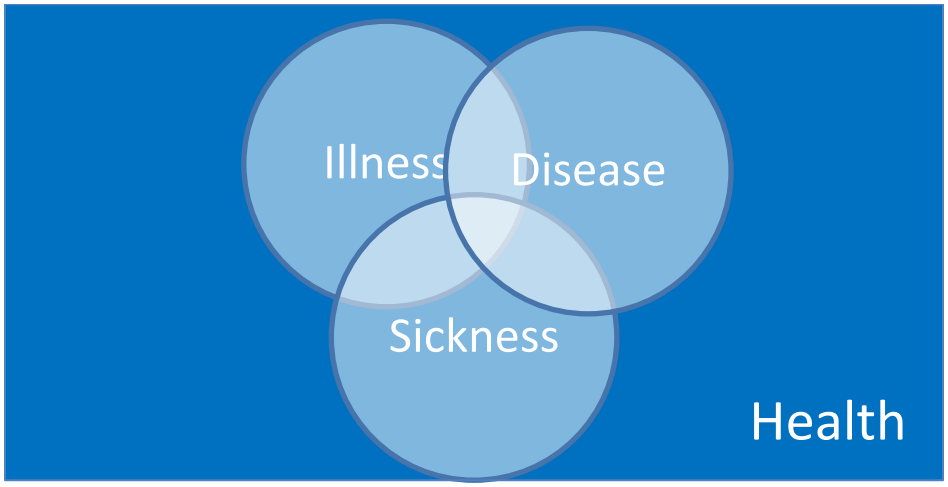


Figure 5: Concept of health and disease

Health

An understanding of health is the basis of all health care. Modern medicine is often preoccupied with the study of disease and neglects the study of health.[108] During the past few decades, there has been a reawakening that health is a fundamental human right and social goal that is to be attained by all people. An example is '*Health for All',* a global health movement undertaken by the World Health Organization (WHO) in the late 20th century. There were several attempts to define health.[109] A positive definition of health that supports a holistic approach

is the famous WHO's definition which says that: '*Health is a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity*'. It is further useful to see health and disease along a continuum, with the lowest point on the health-disease spectrum being death and the highest point corresponds to the WHO definition of health. This spectral concept emphasizes that health and disease in an individual is not static but a dynamic phenomenon that is subject to continuous changes. (Figure-6)

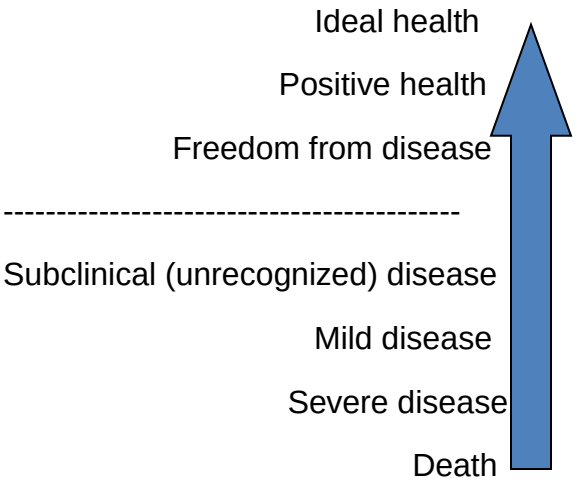


Figure 6: Health-disease spectrum

Even though it is the most widely accepted, the WHO definition of health has often been criticized for being too broad and an idealistic goal than a practical proposition.[110] It is also difficult to see 'health' as a population issue and not merely as a problem for individuals. More recently, *Ideal health* in a population framework was defined by the Global Burden of Disease investigators and it has been characterized as 'optimal levels of functioning or capacity in all the important domains of health and freedom from any type of illness or disease.'[111] The 'optimal' levels of functioning are defined as those levels above which further

gains would not (in general) be regarded as improvements in health. Thus states of exceptional functioning above these levels are considered to be talents or exceptional abilities, not higher states of health. The distinction between 'ideals' and 'goals' seems to be of the particular importance in this context. 'Ideals' are the subjects of cognition, while goals are the subjects of will. [112] Achievable goals are able to stimulate the willingness to go in the direction which is indicated by ideals. Therefore, inspite of its limitations, the concept of *ideal health* sets out the standard that should symbolize our aspirations and represent an overall objective or goal towards which people and nations should strive.

1.8 Measuring Cardiovascular Health

Towards an Operational Definition of Health

It is well known that the majority of stroke events occur in individuals with average or only mildly adverse levels of risk factors, as this is where the majority of the population lies.[113] Similarly, data from national surveys suggested that one tenth of events still occurred even when most of these risk factors were borderline and people with optimal risk factor profile had negligible events. [114] This illustrates that greater absolute reductions in stroke would come through measures such as a modest lowering of blood pressure among the far larger proportion of the population with blood pressure near or slightly above the mean. In many other countries, population shifts in risk factor levels (not due to medications but through primordial prevention) have explained up to two thirds to three fourths of the dramatic reductions in CHD mortality rates.[115-118] Thus, such

growing literature support the Rose hypothesis discussed earlier that small reductions in population risk factors (e.g. cholesterol concentrations, blood pressure, or smoking) can translate into substantial reductions in cardiovascular events and deaths. [119-121]

The ultimate goal of any healthcare system is to improve population health. As few diseases or healthcare interventions have a single effect more meaningful summary measures of health are thus needed. Studies of epidemiology of health, however, have been hampered because of the inability to measure health directly. The WHO and GBD definition of health is also not an 'operational' definition because it does not lend itself to direct measurement. Other individual indicators about health conditions like life expectancy, mortality rates or incidence of particular conditions are useful but insufficient to understand the real impact of a given condition on a population. There are a range of conceptual and methodological issues regarding the inputs of other proposed summary measures of health and only few of them have desirable properties. More recent developments address the need for practical and credible indices that combine information on different aspects of an individual's health.

AHA's Ideal Cardiovascular Health

The American Heart Association (AHA) is a non-profit organization in the United States that promotes appropriate care in an effort to reduce disability and deaths caused by heart disease and stroke. In 2010, the AHA defined 'ideal

cardiovascular health,' identifying seven health factors and lifestyle behaviors that support overall cardiovascular health.[122] The association created the definition as part of its effort to achieve its new national goal: '*By 2020, improve the cardiovascular health of all Americans by 20 percent while reducing deaths from cardiovascular diseases and stroke by 20 percent.*' This will be the first time the AHA has adopted better health as a principal goal and the novel focus of the new goal will be preventing heart disease and stroke most notably by helping people identify and adopt healthier lifestyle choices.

The construct of cardiovascular health index (CVHI) as defined by AHA is (1) the simultaneous presence of 4 favorable health behaviors (abstinence from smoking within the last year, ideal body mass index, physical activity at goal, and consumption of a dietary pattern that promotes cardiovascular health); (2) the simultaneous presence of favorable health factors (untreated total cholesterol <200 mg/dL, untreated blood pressure <120/<80 mm Hg, and absence of diabetes mellitus); and (3) the absence of clinical CVD (including CHD, stroke, heart failure, etc). The health-promoting benefits of each of the component metrics of health behaviors and health factors have been well established and there are consistent associations with regards to CVD-free survival, quality of life, compression of morbidity, overall longevity and reduction in healthcare costs. [123,124] The simultaneous combination of many ideal health factors and healthy behaviors is also associated with longevity and also with healthy aging without disability as has been shown in some studies. The AHA's definition of

cardiovascular health has received much attention in the public health and scientific community. Several recent studies have reinforced the relevance of the new metric in reduction of CVD rates. [125,126] [127,128] The new CVHI has not been specifically evaluated in relation to stroke risk. This dissertation aims at bridging the gaps in public health and clinical knowledge on the utility of the new cardiovascular health metric in relation to stroke prevention.

CHAPTER 2: Hypothesis and Rationale

Current clinical guidelines often specify risk factor thresholds that are redefined as 'action levels' but they deny treatment below these specified values. This view regards extreme values as indicating a disease state (e.g. hypertension) and average values as being 'normal' (e.g. normotensive). In 2002, Law and Wald demonstrated that proportional treatment benefits are similar over a continuous range of risk factor values.[129] This implies the lower the risk factor, lower the risk of disease even below the currently established 'average' values. The shift in the distributions makes the current 'averages' high in relation to the prehistoric values attributed to differences in lifestyle, such as diet and exercise that underlie the differences in these physiological variables.[130,131] Thus according to Wald, present 'average' values of certain risk factors in populations should not be regarded as 'normal'. Several national guidelines are opting for a sequential lowering of thresholds defining 'elevated' risk factors and what was considered average a decade ago has been reclassified as elevated recently.

Table 5: Comparison of pre-historic and current values of physiological variables *(from: Wald BMJ 2002;324:1570–6)*

Physiological Variables[132,133]	**Prehistoric Value**	**Current Value**	**Population below Prehistoric Average (%)**
Syst. Blood Pressure (mm Hg)	110	145	<1
Dias. Blood Pressure (mm Hg)	70	80	<5
Serum Cholesterol (mmol/l)	3.2	6.0	<1

Body Mass Index (Kg/m2)	22	27	<10

Interventions that improve risk factor control and reduce the risk of CVD including stroke, do so regardless of initial levels. Therefore understanding the dose-response relationship between risk factors and the diseases they cause is important to realize the full potential of prevention. The goal here is not to 'normalize' risk factors but to reduce them as much as possible by lowering all reversible risk factors and not just those labeled 'abnormal' by established guidelines (as long as no harm arises).[129] [134] Wald and Law, however, propose a radical approach to address this by suggesting that the entire adult population should receive mass treatment with a combination multidrug treatment (called the 'polypill') without any risk factor screening and that such treatment would lower average levels of several risk factors simultaneously to prevent CVD events.[135] Their novel idea of mass drug treatment to reduce the absolute risk of CVD by controlling multiple risk factors has been viewed as a very promising public health strategy. At the same time several critics have expressed concerns about side-effects and interaction between different drug components and more importantly that the pharmacological 'one size fits-all' solution would be unethical and divert resources from health-promotion efforts.[136]

While the principles and relevance of a population-curing polypill can be debated in the United States, there is urgency for similar drastic approaches to address the growing risk factor burden in the American population. Most Americans older

than age 35 years have one or more CVD risk factors, with more than a third having dyslipidemia, one fifth of them smoke, one third have high blood pressure, more than 30% are obese, and nearly 10% have diabetes.[8,137] Age-standardized prevalence estimates for poor, intermediate, and ideal cardiovascular health for each of the 7 metrics of

CVHI in the American Heart Association 2020 goals, among US adults aged ≥20 years, National Health and Nutrition Examination Survey (NHANES) 2009-2010 is presented in Figure 7. About 60% of the men and 50% of the women age 35 to 74 years in the NHANES III had at least one elevated CVD risk factors. CVD risk develops over the entire life course of an individual as a result of the combined influences of lifestyle, environment and genetic susceptibility. This time course of evolution provides a window of opportunity for prevention and intervention. In contrast with a proposal of using drug treatment for primary prevention where issues of safety will inevitably remain, an appropriate preventive strategy would be to reduce the risk of disease by reducing the average levels of risk factors in the population through promotion of better and optimal health (healthy diet, exercise, smoking cessation etc). AHA's new public health metric expands focus on CVD prevention and promotion of positive "cardiovascular health" throughout the lifespan. It is hoped that a refocus on overall cardiovascular health will motivate Americans to improve their risk factor levels and thus reduce outcomes such as stroke and cardiac events.

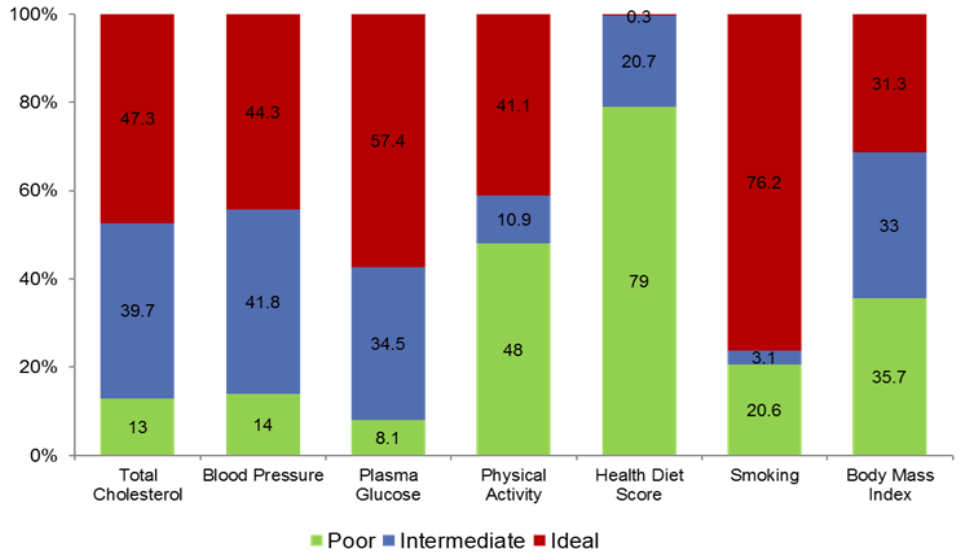


Figure 7: Age-standardized prevalence of CVHI metrics : NHANES 2009-2010 (data from Circulation 127(1): e6-e245)

This dissertation will contribute novel insight on whether this new metric of cardiovascular health is useful for stroke prediction, and the impact of race and familial factors. In our first study, we will examine the relationship between the cardiovascular health index and incident stroke in a prospective cohort study, the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. REGARDS is an ongoing large, population-based cohort of Americans designed to study regional and racial stroke disparities. In our second study we will examine the relationship between family history of stroke and the CVHI in REGARDS. Family history represents the influence of genetic factors and family environment that affect the metabolic profile, health behaviors and overall risk of disease. Examination of whether family history of stroke relates to the CVHI and its individual components will provide important information for risk factor modification. In our final study, we will evaluate in more detail the role of familial

factors on the CVHI using the twin sample of the Emory Twins Study. The twin study design will also be useful in clarifying whether familial factors play a role in the association between CVHI and carotid intima-media thickness (CIMT), a surrogate marker of atherosclerosis and a risk factor for stroke.

2.1 Study-1

As discussed in the previous section, the American Heart Association (AHA) recently proposed a definition of cardiovascular health and developed a new metric which can be followed over time. [122,138] The concept emphasizes primordial prevention by defining goals for health factors and behaviors to define 'ideal' cardiovascular health (CVHI). The metric defines seven components, which include three health factors (blood sugar, serum cholesterol, blood pressure) and four health behaviors (BMI, physical activity, diet and cigarette smoking) into ideal, intermediate and poor levels. Previous studies have shown that most CVD events are preventable by achieving few parameters of cardiovascular health.[114,139-141] The current prevalence of ideal cardiovascular health in the United States population is very low (2%) as it includes only those without treatment and manifest CVD, who have ideal levels of all seven cardiovascular health factors and health behaviors.[142] The prevalence of ideal cardiovascular health incidence rates of CVD was recently reported.[125,143] These studies found that the number of ideal factors by the AHA metric shows a graded

relationship to CVD incidence, although very few individuals had ideal cardiovascular health in the population.

The INTERSTROKE study, a case control study of 3000 cases in 22 countries showed that ten risk factors explained 90% of the attributable risk of stroke.[22] Some of these risk factors are also included in the AHA metric including high blood pressure,[144,145] high blood cholesterol[146], diabetes [147], smoking[148] [47], BMI, lack of physical activity and unhealthy diet[149,150]. The new AHA health metric has not been specifically evaluated in relation to stroke outcomes. Therefore, our first objective is to determine the prevalence of ideal CVHI in a population cohort and examine the relationship between CVHI and incident stroke. Our analyses will demonstrate the potential of using population-level strategies[100] to bring about a significant reduction in population levels of risk of stroke.

Study-1: Hypothesis: We hypothesize that people with poor levels of cardiovascular health have higher risk of incident stroke.

Variables

Outcome: Incident stroke

Confounders: Age, race, sex, socioeconomic status, geographic region, family history of stroke

Exposure: Cardiovascular health index

Model:

$$h(t X_i) = h_0 t \exp[\beta_1 CVH + \beta_2 Age + \beta_3 Race + \beta_3 Sex + \beta_4 SES + \beta_5 GEO + \beta_6 FAM + \Upsilon_1 CVH*Age + \Upsilon_2 CVH*Race + \Upsilon_3 CVH*Sex + \Upsilon_4 CVH*SES + \Upsilon_5 CVH*GEO + \Upsilon_6 CVH*FAM]$$

X_i= (0,1) stroke status

2.2 Study-2

Despite significant advances in the last few decades in the understanding of genetics, there are substantial limitations in epidemiological approaches to studying the effects of genetic determinants on diseases. Family history represents the integration of shared genetic and environmental risk factors and could be used as a screening tool for individuals with increased disease risk.[151] Increased risk is associated with more number of affected relatives and earlier ages of disease onset.[151] First degree relatives share half their genetic information and their disease experience may offer a clue to disease susceptibilities and other familial factors which affect risk such as shared behaviors and lifestyles. Family history of a disease can thus be viewed as a cost-effective way of using integrated disease information.[152]

For cardiovascular diseases the impact of a positive family history has been well recognized.[153-157] Family history of stroke is often considered to be a predictor of stroke but findings published by few studies have been inconsistent.[158] [33,34,159,160] The conflicting results from these studies may be a consequence of differences in study design, the methods used to identify stroke events in the family members and small sample size. It is also possible that, because of the

heterogeneous nature of stroke, these studies did not account for the various stroke subgroups and assumed that the same genetic factors would influence all kinds of stroke. For example, a study reported that ischemic stroke, particularly large and small-artery disease strokes, had significantly stronger family history of stroke while cardio-embolic and undetermined stroke subtypes did not.[161] In the ARIC study, parental history of stroke did not confer an increased risk of clinical stroke although an increased risk with subclinical stroke was observed.[162] There is however limited data on blacks, a group characterized by a higher stroke risk than whites.

Pathophysiological mechanism

A positive parental history of stroke may lead to an increased risk of stroke events through several mechanisms. First, genetic heritability of stroke risk factors, such as elevated blood pressure, elevated serum cholesterol, and diabetes. Secondly, inheritance of susceptibility to the effects of such risk factor. Thirdly, familial sharing of cultural/environmental and lifestyle factors, such as unhealthy diet, higher-fat diet and lower physical activity. And finally, interaction between genetic and environmental factors

Thus family history represents the contributions and interactions of unique genetic and environmental factors that affect the metabolic profile and life course of individuals..[163] Family history of stroke is associated with a higher proportion of conventional risk factors but people with a family history are also more likely to practice risk-reducing behaviors. [163,164] [138] How family history of stroke affects health behaviors and CVD risk factors has not been comprehensively evaluated in populations. Our objective is to examine the relationship of family history of stroke with cardiovascular health factors and behaviors.

Study-2 Hypothesis: We hypothesize that people with family history of stroke have a lower prevalence of ideal CVHI factors but higher prevalence of ideal health behaviors than those without family history of stroke.

Variables

Exposure: Family history of stroke

Confounders: Age, race, sex, socioeconomic status, geographic region

Outcome: Cardiovascular health index

Methods: Ordinal logistic regression after verifying proportional odds assumption

$$\ln\left[\frac{P(CVH \geq g|X)}{P(CVH < g|X)}\right] = \alpha_g + \beta_1 FAM + \beta_2 AGE + \beta_3 SEX + \beta_4 RACE + \beta_5 SES + \beta_6 GEO$$

$$g = 1,2$$

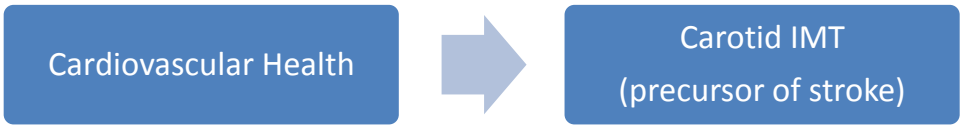
Family history is used as a tool to educate people about their risk and encourage behaviors that can reduce their risk of diseases. If our hypotheses are confirmed, these data may provide support to the potential benefits of screening for family history of stroke, to improve cardiovascular health and reduce stroke events in diverse patient groups. Greater understanding of the relationship between family history and stroke risk factors may lead to early recognition of and intervention to prevent stroke events.

2.3 Study-3

Atherosclerosis is a multifactorial systemic disease that underlies various cardiovascular diseases such as coronary heart disease and stroke. Epidemiologic studies and intervention trials based on the incidence of end points like myocardial infarction and stroke require years of follow-up and the participation of large population is time-intensive and costly. The use of surrogate marker is therefore of great value because it potentially allows researchers to have reliable data in less time and from smaller populations.[165] This has implications for identifying and tracking subclinical disease earlier. Carotid intima-media thickness (CIMT) has been related to CVD including incidence of both myocardial infarction and stroke. [166-172] In a population-based study, CIMT was associated with a higher incidence of stroke and the relation was independent of presence of carotid plaque.[173] Epidemiological studies have also reported associations of CIMT with several CVD risk factors including smoking, blood pressure and high blood cholesterol [174-177] Carotid IMT is increasingly being used as a quantitative index for evaluating the progression of atherosclerosis and as a surrogate end point in clinical trials.

Carotid IMT relies on its ability to predict future clinical cardiovascular end points.[172] Its values range from 0.25 to 1.5 mm in healthy adults [178] and values >1.0 mm are often regarded as abnormal. [179] For an absolute CIMT difference of 0.1 mm, the future risk of a coronary event increases by 10% to 15%, and the stroke risk increases by 13% to 18%.[172] The validity of CIMT for these purposes has been assessed by making comparisons of mean CIMT in people with and

without clinical evidence of CVD and discriminatory ability is well demonstrated.[180-182] For example, CIMT and Framingham Risk Score for Stroke correlate well and it may help in discriminating between subjects at low or high 10-year risk.[183] For CIMT measurement, the thickness of artery walls is measured by a high resolution ultrasound that detects the presence and progression of atherosclerosis disease. It is a convenient, safe, painless and non-invasive procedure that is a direct measurement of vascular disease even in its early stages, before it causes symptoms. Thus, CIMT can be measured relatively simply and noninvasively and it is well suited for use in large-scale population studies, for risk stratification in individuals and as an end point in intervention studies.[179]



Given the heterogeneous nature of stroke and the complexity of its risk factors contributing to its incidence, evaluation of intermediate phenotypes may be more advantageous than hard clinical events. Our objective is to separate the role of familial factors and genetic factors in the association between the cardiovascular health index, and CIMT in a twin sample. Analysis of monozygotic and dizygotic twin pairs discordant for cardiovascular health factors will help disentangle the role of genetic and other familial factors involved in the association cardiovascular health factors and CIMT

Study Hypothesis-3: We hypothesize that people with lower levels of cardiovascular health have increased CIMT and this relationship is continuous and graded across all levels of cardiovascular health. This relationship is not confounded by shared familial and genetic factors.

Variables

Outcome: Carotid IMT (continuous)

Confounders: Age, SES, education, comorbidities

Exposure: Cardiovascular health index

Linear Mixed Model

$$IMT_{ij} = \beta_0 + \beta_1(CVH) + \beta_2(AGE) + \beta_3(SES) + \beta_3(EDU) + \beta_3(DEP) + \alpha_i + \varepsilon_{ij}$$

α_i = random effect of the pair
ε_{ij} = random effect of the individual

Within-pair differences = differences between a twin with a higher CVH score and his twin brother with a lower score

2.4 Description of Study and Data Set – REGARDS

REGARDS is a population-based study of adults 45 and older in the United States that seeks to determine causes of racial and geographic differences in stroke mortality. The cohort includes 30 000 subjects, (proposed) half from stroke-belt regions and half from other regions of the country, half white and half black, half men and half women, each of whom will have up to 4 years of follow-up data. REGARDS is approved by the Institutional Review Boards of all participating institutions. Subjects are recruited from commercially available lists of U.S. residents using mail and telephone contacts. . Exclusion criterion include race other than African American or white, active treatment for cancer, medical conditions that would prevent long-term participation, cognitive impairment judged by the telephone interviewer, residence in or inclusion on a waiting list for a nursing home, or inability to communicate in English. Demographic characteristics, health behaviors, medical history information, stroke symptom history using the Questionnaire for Verifying Stroke-free Status (QVSS), are collected through a computer-assisted telephone interview (CATI). CATI is used to collect these data in order to provide a higher level of quality control and standardization by the use of trained, certified and monitored staff. It also allows for the assessment of differences in the characteristics of participants completing and not completing the in-home exam. During a home visit, written informed consent, blood and urine samples, electrocardiogram, and blood pressure and body mass index measures are obtained. During scheduling the

participant is reminded to fast over night for 10-12 hours before the visit and is asked to have medications available for recording at the time of the visit. Technicians who are trained on methods for REGARDS protocol complete the in-home visits and ship samples to the central laboratory. If the participant changes his/her mind for some reason the in-home visit is not completed and he/she is classified as a partial participant. Physical measurements, a resting ECG, medication inventory, phlebotomy, and urine collection are performed using standardized methods. The personnel take two blood pressure measurements utilizing a standard aneroid sphygmanometer. Height is obtained utilizing an 8-feet metal tape measure and a square, weigh (without shoes) is obtained using a standard 300 lbs calibrated scale. Venipuncture is performed using standardized methods. The examiner records prescription and nonprescription medications taken within the previous 2 weeks. Self-administered questionnaires (on additional demographic and risk factor characteristics) are left with the participant to be completed and returned by prepaid envelopes.

Follow-Up for Stroke Events

The study conducts active surveillance of cohort members to ascertain, validate and classify fatal and non-fatal stroke outcomes. Participants are followed via telephone at 6-month intervals for identification of stroke events over the follow-up period extending up to 4 years. Data are collected on suspected events that

require hospitalization, as well as on physician evaluations for stroke-like symptoms detected using the Questionnaire for Verifying Stroke-Free Status. If the participant is unable to respond to follow-up telephone calls for medical reasons, a proxy respondent is identified by the participant at baseline will be interviewed. If a participant is hospitalized or sees a physician for stroke-like symptoms, contact information for the hospital and or physician is obtained from the participant and pertinent in and outpatient medical records are sought. Medical records retrieval is initiated by having the participant sign a permission form for release of records. If a death is reported, the death certificate and associated hospital or physician records are collected, including medical records for the 28-day period preceding death. If death occurred within a month following a procedure, information on the procedure is collected. If medical records are unavailable or judged insufficient by the Events Committee, a physician questionnaire for descendants or an informant interview will be completed using methods developed and used in other studies. Committee members review the records independently (information on geographic region and race is masked) using criterion for stroke and stroke subtypes similar to the GNCKSS and TOAST. The adjudication process validates stroke occurrence, and also classifies events by stroke ‘subtype’ and severity using the NIH stroke scale. For every potential event reviewed, each adjudicator completes an Events Form and submits it to the Operations Office. No further action is needed if the two reviewers agree on the occurrence of stroke and stroke subtype. In cases of disagreement, a third adjudicator reviews the potential

event. For all deaths, the underlying and contributing causes will also be classified by the Events Committee.

Sources of Funding for REGARDS

REGARDS is supported by a cooperative agreement U01 NS041588 from the National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH), Department of Health and Human Service. A full list of participating REGARDS investigators and institutions can be found at http://www.regardsstudy.org

2.5 Description of Study and Data Set - Emory Twins Studies

The Emory Twin Studies includes samples recruited in two companion studies: the Twins Heart Study (THS) and the Stress and Vascular Evaluation in Twins (SAVEIT). The purpose of these studies was to elucidate the role of psychological, behavioral, and biologic risk factors for subclinical cardiovascular disease in twins. Both studies recruited white, middle-aged male MZ and DZ twin pairs (who were raised in the same household) from the Vietnam Era Twin (VET) Registry, one of the largest twin registries in the United States, which includes 7369 male-male twin pairs—both of whom served in the US military during the time of the Vietnam War. Both studies followed identical procedures, measurements, and protocols. THS enrolled 180 twin pairs between 2002 and

2006 and SAVEIT included 127 twin pairs enrolled between 2005 and 2010. After excluding the second visit of a few pairs who participated in both studies, the combined sample included 281 pairs. Twins included in the Emory Twin Studies were randomly selected from the VET Registry among those born between 1946 and 1956. In addition, a random sample of twin pairs discordant for major depression was included in THS, and a random sample of twin pairs discordant for PTSD was included in SAVEIT. Pairs of twins were examined at the same time at the Emory University General Clinical Research Center, and all data collection, occurred during a 24-hour admission under controlled conditions. Both studies were approved by the Emory Institutional Review Board, and all twins signed an informed consent. The two twins maintained an identical schedule while in the study. Activity was limited to leisurely ambulation within the Emory facilities, and all assessment, including the ambulatory ECG monitoring, began and ended at the same time. Zygosity information by means of deoxyribonucleic acid typing was available for all twin pairs. All subjects signed an informed consent to participate in the study.

Cardiovascular Risk Assessment

All measurements were performed in the morning after an overnight fast, and both twins in a pair were tested at the same time. A medical history and a physical examination were obtained on all twins. Weight and height were used to calculate body mass index, and waist and hip circumference were used to calculate the waist-hip ratio (WHR). Systolic blood pressure and diastolic blood

pressure were measured by mercury sphygmomanometer on the right arm with the subject in sitting position after 10 minutes of rest. The average of two measurements 5 minutes apart was used in the statistical analyses. Venous blood samples were drawn for the measurement of glucose and lipid profile after an overnight fast. The Emory Lipid Research Laboratory, a participant in the Centers for Disease Control/National Heart, Lung and Blood Institute Lipid Standardization Program, performed all analyses from freshly isolated ethylenediaminetetraacetic acid (EDTA) plasma. Direct high-densitylipoprotein (HDL) and direct low-density lipoprotein (LDL) cholesterol were obtained using homogeneous assays (Equal Diagnostics, Exton, Pennsylvania). Glucose was measured (CX7 chemistry autoanalyzer, Beckman Coulter Diagnostics, Fullerton, California). Physical activity was assessed by means of a modified version of the Baecke Questionnaire of Habitual Physical Activity used in the Atherosclerosis Risk in Communities Study, a 16-question instrument documenting the level of physical activity at work, during sports and nonsports activities. Cigarette smoking was classified into current smoker (any number of cigarettes) versus never or past smoker. Pack-years of smoking were calculated as the number of packs of cigarettes smoked per day times the number of years smoked. Diabetes mellitus was defined as having a fasting glucose level of >126 mg/dl or being treated with antidiabetic medications. Food frequency Questionnaire data was collected dietary data over the past 12 months. The questionnaire classifies average food intake according to 9 frequency categories ranging from “almost never or less than once per month” to “<6

times/d" using standardized portion sizes for each dietary item, including beverages and nutritional supplements. Questionnaires were scored by the Nutrition Questionnaire Service Center, Channing Laboratory, Harvard University, and nutrient intake data were derived following the nutrient database of the US Department of Agriculture. Daily food intake in grams was calculated from food intake frequency and portion sizes.

Source of Funding for Emory Twins Studies

This study was supported by K24HL077506, R01 HL68630 and R01 AG026255 to VV, and by K24 MH076955 to JDB from the National Institutes of Health; by the Emory University General Clinical Research Center MO1-RR00039 and by grant 0245115N from the American Heart Association. The United States Department of Veterans Affairs has provided financial support for the development and maintenance of the Vietnam Era Twin (VET) Registry. Numerous organizations have provided invaluable assistance, including: VA Cooperative Study Program; Department of Defense; National Personnel Records Center, National Archives and Records Administration; the Internal Revenue Service; National Opinion Research Center; National Research Council, National Academy of Sciences; and the Institute for Survey Research, Temple University.

CHAPTER 3: Cardiovascular Health Index and Risk of Incident Stroke

Study 1

Cardiovascular Health Index and Risk of Incident Stroke in Black and White Americans: REasons for Geographic And Racial Differences in Stroke Study

3.1 Abstract

Background: The American Heart Association developed Cardiovascular Health Index (CVHI) as a metric defining cardiovascular health. We investigated the association between CVHI and incident stroke in black and white Americans.

Methods: REGARDS is a national population-based cohort of 30,239 blacks and whites, aged ≥ 45 years, sampled from the US population in 2003 - 2007. Data were collected by telephone, self-administered questionnaires and an in-home exams. Incident strokes were identified through bi-annual participant contact followed by adjudication of medical records. Levels of the CVHI components (blood pressure, cholesterol, glucose, body mass index, smoking, physical activity, and diet) were each coded as poor (0 points), intermediate (1 point) or ideal (2 points) health. An overall CVHI score was categorized as inadequate (0-4), average (5-9) or optimum (10-14) cardiovascular health.

Results: Among 22,914 subjects with CVHI data and no previous cardiovascular disease, there were 432 incident strokes over 4.9 years of follow-up. After adjusting for demographic, socioeconomic, and region of residence, each better health category of overall CVHI score was associated with a 25% lower risk of stroke (HR=0.75, 95% CI = 0.63, 0.90). The association was similar for blacks and whites (interaction p-value = 0.55). A one point higher CVHI score was associated with an 8% lower risk of stroke (HR=0.92, 95% CI=0.88, 0.95).

Conclusion: In both blacks and whites better cardiovascular health, based on the CVHI score, is associated with lower risk of stroke, and a small difference in scores was an important stroke determinant.

3.2 Introduction

Stroke is the fourth leading cause of death in the United States, and the leading cause of adult disability with direct and indirect costs exceeding $50 billion annually.[184] Although some studies have suggested a decline in stroke incidence, other studies suggest a recent reversal and possible increases in national stroke rates.[10-12] Thus, sustained focus on prevention is critical to reducing the stroke burden.

Previous studies demonstrated that most cardiovascular disease (CVD) events including stroke are preventable by optimizing a few key indicators of cardiovascular health.[114,139-141] In 2010, the American Heart/Stroke Association (AHA/ASA) proposed a population metric to define and track the nation's cardiovascular health through time. [122] This metric was released to the public in the form of a score called Cardiovascular Health Index (CVHI). The CVHI metric emphasizes primordial prevention and includes seven modifiable components, including three health factors (glucose, cholesterol and blood pressure) and four health behaviors (body mass index, physical activity, diet and cigarette smoking), categorizing each of these seven factors into ideal, intermediate, and poor levels.

Recent evidence suggested that presence of more ideal cardiovascular health factors from the CVHI metric is associated with lower CVD and all-cause mortality. [125,126,185] There are limited data available yet pertaining to stroke.[186] More broadly, there are scarce data on the utility of a composite measure of biological and behavioral risk factors in predicting stroke. Using data from the

Reasons for Geographic And Racial Differences in Stroke (REGARDS) study, we sought to determine the association between CVHI and incident stroke, and examined differences by race.[100]

3.3 Methods

Study Participants

The REGARDS study is a population-based investigation of stroke incidence and cognitive function among US adults ≥ 45 years of age.[187] The study was designed to sample an equal proportion of women and men, but to oversample blacks, as well as people living in the Southeastern US states where mortality rates of stroke are highest in the US (commonly referred to as the “stroke belt” and “stroke buckle” of the US). Potential participants were identified from commercially available lists of US residents and recruited through a mailing followed by telephone calls. Overall, 30,239 participants were enrolled between January 2003 and October 2007. For this analysis, we included participants with baseline data on blood pressure, cholesterol, glucose, body mass index (BMI), smoking, diet and physical activity. We excluded participants with a self-reported history of stroke, peripheral vascular disease, or coronary heart disease. Diet information was missing for 6,086 (27%) participants, and we imputed information on diet for these participants. Our final sample size was 22,914 for all analyses. The REGARDS study protocol was approved by the Institutional Review Boards at the collaborating centers and all participants provided informed consent.

Data Collection

Socio-demographic and clinical data were collected at baseline through a telephone interview, an in-home examination and self-administered questionnaires left in the home. Trained interviewers conducted computer-assisted telephone interviews to obtain information on participants' demographics, cigarette smoking, physical activity, and use of medications. Trained health professionals conducted an in-home visit that included a physical examination and collection of fasting blood samples, which were shipped overnight to the University of Vermont for analysis. During the in-home visit, the self-administered Block 98 Food Frequency Questionnaire (FFQ) was left with the participant to be returned by self-addressed prepaid envelopes. [188] The FFQ documented dietary intake patterns for the one year preceding their in-home visit. Nutrient analysis was conducted by NutritionQuest.

Cardiovascular Health Index

Components of the CVHI metric include cigarette smoking, BMI, blood pressure, cholesterol, blood glucose, physical activity and diet (Appendix). Current and former smoking and time since smoking cessation for former smokers was determined by three questions "Have you smoked at least 100 cigarettes in your lifetime?", "Do you smoke cigarettes now, even occasionally?" and "How old were you when you stopped smoking?"were ascertained as previously described. Height and weight were measured using calibrated equipment. Blood pressure

was the average of two measurements taken using aneroid sphygmomanometers. Total cholesterol was measured using an enzymatic reaction and glucose by colorimetric reflectance spectrophotometry. Physical activity and diet classification were modified from the original CVHI definitions as follows. Physical activity was assessed through a single question "How many times per week do you engage in intense physical activity, enough to work up a sweat?" We defined ideal physical activity as 4 or more times per week, intermediate as 1-3 times per week, and poor as none. The diet score was based on responses to the Block FFQ, and the 'healthy diet score' was calculated based on how many of each of the following five dietary goals were met: fruits and vegetables ≥ 4.5 cups/day; fish, 3.5 ounces, ≥ 2 servings/week; sodium <1500 mg/day; sweets/sugar-sweetened beverages ≤ 450 kcal/week; and whole grains (1.1g of fiber in 10 gms of carbohydrates), 1-oz equivalent servings, ≥ 3 servings/day.

Each CVHI component was given a point score of 0, 1 or 2 to represent poor, intermediate, or ideal health, respectively (Appendix). Based on the sum of all 7 CVHI components, an overall CVHI score was categorized as: inadequate (0-4), average (5-9) or optimum (10-14) cardiovascular health.

Study Outcome

Participants or their proxies were contacted every 6 months by telephone to identify hospitalizations, emergency department visits, overnight stays in nursing homes or rehabilitation centers, or death during the previous 6 months. [189]

Reasons for medical encounters were requested and medical records were obtained to confirm the diagnosis of stroke, transient ischemic attack (TIA), causes of death, and verify any reported stroke symptoms. For proxy-reported deaths an interview was conducted with next of kin. After initial review by a stroke nurse to exclude obvious non-cases, medical records were reviewed by at least two physicians of a committee of stroke experts to validate and classify potential strokes.

Stroke events were defined according to the World Health Organization (WHO) as ‘‘rapidly developing clinical signs of focal, at times global, disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin.’’[190] Events not meeting this definition but characterized by symptoms lasting <24 hours, with neuroimaging consistent with acute ischemia or hemorrhage were also classified as stroke events.’ Time to a stroke event was recorded as the number of days between the baseline examination and the date of stroke event. Participants who did not develop a stroke were censored on their date of death or last follow-up contact, whichever occurred first.

Statistical Analyses

Baseline characteristics were calculated and compared for REGARDS participants by race and CVHI health categories using chi-square statistics. We calculated the distribution of each CVHI component as poor, intermediate, and

ideal. We also compared the distribution of number of ideal health factors by race and sex. Next, for each CVHI component stroke incidence rates and adjusted hazard ratios for stroke were calculated separately for blacks and whites. Crude and multivariable-adjusted hazard ratios across overall CVHI categories (optimum and average vs inadequate) were calculated. CVHI score was also examined as a continuous variable. Additionally, adjusted hazard ratios for stroke were calculated for increasing number of ideal health factors with the reference group defined as having no ideal factors. All hazard ratios were calculated using Cox proportional hazards models adjusting for age, race, sex, geographic region of residence (stroke belt or other), income and education. Tests for interaction by age, sex, race, geographic region and income were performed by including multiplicative interaction terms with these variables and CVHI categories. Finally, the crude and multivariable hazard ratio for stroke associated with a one point higher overall CVHI score was calculated. All analyses were conducted using SAS 9.2 (SAS Institute, Cary, NC).

3.4 Results

There were 22,914 participants with data on CVHI and no previous CVD. The mean age was 65 years, 40% were black, and 58% female. Baseline socio-demographic factors for CVHI categories by race are presented in Table 6. Male sex, low income and less education and current alcohol use were associated with cardiovascular health in both blacks and whites. The distribution of CVHI categories differed significantly between blacks and whites. Whites had a higher

proportion of people in the optimum cardiovascular health category (17%) as compared to blacks (6%) irrespective of age, sex, income, education and geographic region. The distribution of ideal status varied widely across CVHI factors (Figure 8), ranging from 84% of participants having ideal status for smoking, to 0% of participants having an ideal diet. For those missing information on diet, scores were imputed and scores were similar when individuals missing diet were assumed to have a poor diet or an intermediate diet.

The mean (SD) for overall CVHI score was 7.2 (2.2) points. Adjusting for age and sex, the mean (± SD) overall CVHI score was lower for blacks (6.5 ± 2.0) than whites (7.6 ± 2.1). Blacks had fewer ideal factors compared with whites. Only 3% of the blacks and 8% of whites had five or more ideal factors (Figure 9).

Over 4.9 years of follow-up, there were 432 incident strokes (232 in whites and 200 in blacks). For many CVHI components, the incidence of stroke was lowest in those with ideal status and highest in those with poor levels (Table 7). For example, for blood pressure the annual incidence rates per 10,000 persons for poor, intermediate and ideal status were 3.2, 1.8 and 1.1, respectively, for blacks and 2.4, 1.9 and 0.8, respectively, for whites. The hazard ratios for some of CVHI components (total cholesterol, blood pressure, blood glucose and smoking), adjusted for age, sex, income, education, alcohol use and geographic region also showed a graded relationship particularly among white participants (Table 7).

However, a gradation was not observed for all CVHI components (such as cholesterol, healthy diet score, and BMI).

The overall CVHI score categories of cardiovascular health were inversely associated with incident stroke in a graded fashion with the optimum health category having lower stroke rates compared with average and inadequate categories (Figure 10). Stroke incidence rates were highest in the inadequate health category (2.4 per 10,000 person-years) and lowest in optimum health category (1.3 per 10,000 person-years). After multivariable adjustment, with CVHI score category modeled as an ordinal variable, each better health category was associated with a 25% lower risk of incident stroke (HR=0.75, 95% CI = 0.63, 0.90). Compared with the inadequate health category, the average (HR=0.72, 95% CI= 0.55, 0.96) and optimum (HR=0.52, 95% CI= 0.35, 0.76) cardiovascular health categories were both associated with lower stroke risk. Although the association of CVHI category and stroke was not statistically significant among blacks (Table 8), the crude and adjusted hazard ratios were similar for blacks and whites (p-value for interaction = 0.55). The association of overall CVHI score and stroke was similar when individuals missing diet information were excluded from the analyses (data not shown).

For the total CVHI score on a continuous scale from 0 (all 7 poor) to 14 (all 7 ideal), a one point higher CVHI score was associated with an 8% lower risk of stroke (HR=0.92, 95% CI=0.88, 0.95) and this was similar in both blacks and

whites (Table 8). Finally, increasing number of ideal factors was inversely associated with risk of stroke in a graded fashion. Even those with only 1 ideal factor compared with those with 0 ideal factors had a lower stroke risk (HR 0.70 (0.42, 1.19)). Hazard ratios were lower with a higher number of ideal factors. For example, those with 6 versus 0 ideal factors had a multivariable adjusted hazard ratio of 0.34 (0.08. 1.52) (Table 9). The graded relationship was similar for blacks and whites.

3.5 Discussion

The stroke epidemic can be curtailed with a multidisciplinary strategy that identifies and manages stroke risk factors.[191] The AHA developed the CVHI metric as part of its strategic impact goal to improve the cardiovascular health of all Americans by 20%, by 2020. Our study shows that the CVHI metric is a useful tool to describe the risk of incident stroke and has the potential to help refine population interventions to reduce stroke incidence rates in the US population. Using a simple point system to represent the CVHI metric, an incremental increase in the overall CVHI score (inadequate to average to optimum) was associated with a 25% lower risk of incident stroke. However, there were important differences in population levels of CVHI, as blacks had lower levels of cardiovascular health factors than whites. These findings suggest that comprehensive population-based interventions targeting risk factors included in the CVHI will be critical to support the attainment of the AHA's 2020 impact goal

for cardiovascular health, reduce the incidence and prevalence of stroke, and also help eliminate disparities.

The prevalence of *ideal* cardiovascular health is extremely low in the United States as measured in national studies and other cohorts including REGARDS.[125,143] [128,186] The distribution of ideal factors in REGARDS was similar to the NHANES and *Atherosclerosis Risk in Communities Study* (ARIC) studies.[128,185] The ARIC study also showed that the number of ideal CVHI factors in 1988-89 was associated with 20-year CVD incidence, and that blacks had fewer ideal health factors compared to whites, although analysis of stroke was not presented. [125] Our study from a more contemporary cohort similarly demonstrates that blacks have lower levels of ideal factors compared with whites. We also found that the association of CVHI and stroke was weaker in blacks than whites, although this difference was not statistically significant. This finding needs confirmation from other studies or further follow-up in REGARDS. National statistics demonstrate higher stroke incidence and stroke mortality rates for blacks compared with whites, [192] possibly due to the higher prevalence of hypertension, obesity, and diabetes among blacks, although the higher risk factor levels only explain about 50% of the excess risk.[193] Understanding the basis for these differences will be important to design and effectively implement stroke prevention programs among blacks.

Observational studies have shown that stroke is a multifactorial disease and that the risk factors are similar across different populations. [19-21] The INTERSTROKE case-control study showed that ten risk factors explained 90% of the attributable risk of stroke.[22] Some of these risk factors are also part of the CVHI metric and each component is predictive of incident stroke, including high blood pressure, high blood cholesterol, diabetes , smoking , obesity (BMI >30) , lack of physical activity and unhealthy diet.[25] The incorporation of only modifiable risk factors in the CVHI metric was intentional because of its potential translation into prevention programs, particularly lifestyle change which remains primary potent weapon in the battle against the stroke epidemic.

Our findings regarding small differences in CVHI score related to lower stroke risk supports the hypothesis that modest shifts in the population distribution of risk factors can have a dramatic impact on reducing the disease burden in populations.[97] Improvements in a single health behavior (e.g. a healthier diet) could result in not only a reduction of CVD, but also improvements of other cardiovascular health factors (e.g. BMI, cholesterol). Indeed, these components are interrelated and do not operate in silos. Our study showed that a one-point increase in overall CVHI score, which corresponds to improvement of one component of the CVHI score by one level(e.g. from poor to intermediate or from intermediate to ideal) was associated with an 8% lower risk of stroke. The Nurses' Health Study showed that women with ideal levels of all five risk factors included in that study had an 80% reduction in the risk of ischemic stroke

compared with women with no ideal risk factor levels.[194] These and other studies [140,195] [127] demonstrate the real potential of using population-based strategies targeting multiple risk factors simultaneously to achieve reductions in stroke and CVD rates in communities.

Our study has several strengths including the large national sample, with over-sampling of blacks to allow examination of racial differences. Data collection used standardized questionnaires and measured risk factor levels. REGARDS has a rigorous ascertainment of stroke outcomes including adjudication of stroke events by neurologists. There are also some limitations to our study. Health factors and behaviors were measured only once and thus we cannot assess whether changes in CVHI score affects stroke incidence, and we expect some misclassification. The cooperation rate for participation in REGARDS was 49%. Although, this is similar to other large national cohorts, this may limit generalizability of the findings.[192] [193] Approximately one-third of REGARDS participants did not return a FFQ and we used multiple imputation of data for these missing data. However, the results were similar when these individuals were excluded in a sensitivity analysis. We also used a modified definition for physical activity and diet for computation of the CVHI score.

In conclusion, in this large population-based sample of US adults, a healthier cardiovascular disease risk factor profile as defined by the CVHI score was associated with a substantially reduced risk of stroke. Based on our findings,

differences in CVHI score corresponding to an improvement of one level of one component of the CVHI metric may result in substantial reductions in stroke risk. This provides confidence of the translation of meeting the AHA goals to reduction in stroke incidence.[127] Future studies are needed to determine the actual risk reduction benefit that can be achieved through an intervention approach to improve health behaviors and risk factors in the CVHI metric

CHAPTER 4: Family History of Stroke and Cardiovascular Health Index

Study 2

Association of Family History of Stroke and Cardiovascular Health Index

4.1 Abstract

Background: Family history of stroke (FHS) is perceived to be a risk factor for stroke, but few studies have comprehensively examined its association with cardiovascular risk factors and behaviors. We investigated the association between FHS and Cardiovascular Health Index (CVHI), a new metric defined by the American Heart Association.

Methods: REGARDS is a national population-based cohort of 30,239 blacks and whites, aged ≥ 45 years, sampled from the US population in 2003 - 2007. Data were collected by telephone, mail questionnaires, and in-home exams. FHS was ascertained by a questionnaire. Levels of the CVHI components (blood pressure, cholesterol, glucose, body mass index, smoking, physical activity, and diet) were each coded as poor (0 points), intermediate (1 point) or ideal (2 points) health. An overall CVHI was categorized as inadequate (0-4), average (5-9) or optimum (10-14) cardiovascular health. Ordinal logistic regression was used to model the data.

Results: Among 20,567 subjects with CVHI data and no previous history of stroke or heart disease, there were 7702 (37.4%) participants with FHS. FHS was associated with poorer levels of health factors, particularly blood pressure (OR=1.13, 95% CI = 1.07, 1.19) and was inversely associated with health behaviors. The overall association of FHS and CVHI was not significant. Sibling history of stroke was the only family history subtype that was associated with CVHI (OR=1.06, 95% CI=1.01, 1.18). **Conclusion:** The increased risk of stroke

associated with FHS maybe mediated by its association with poorly controlled blood pressure

4.2 Introduction

Effectiveness of health programs can be increased by targeted interventions aimed at individuals with an increased risk of developing disease.[194 196] An important and easily accessible source of risk information is family history. Family history represents the integration of shared genetic and environmental risk factors and could be used as a screening tool for individuals with increased disease risk including cardiovascular diseases. [151],[153-157] Familial history of stroke (FHS) is a recognized risk factor for stroke events although its importance has not been conclusively confirmed by epidemiological studies. [33,126,158,197,198] Familial aggregation of stroke appears to be caused by a strong association of conventional stroke risk factors such as hypertension, diabetes, and dyslipidemia between parents and offspring, but this has not been systematically examined.

The American Heart and Stroke Association (AHA/ASA) has proposed a new public health metric, Cardiovascular Health Index (CVHI), that consists of seven prevention components, including three health factors (blood sugar, serum cholesterol, blood pressure) and four health behaviors (BMI, physical activity, diet and cigarette smoking), and categorizes them into ideal, intermediate, and poor levels.[138] The relationship between FHS and an overall intermediate phenotype like the AHA's ideal cardiovascular health index (CVHI) has not been

comprehensively evaluated. Many risk factors for stroke are under genetic influence and a considerable degree of heritability appears to be conferred by intermediate phenotypes. Further, there are few studies that address this issue in Blacks, a group characterized by a higher stroke risk than White Americans. In this study, we examined the association of FHS with individual cardiovascular health factors and behaviors and an overall phenotype (CVHI) in a large population- based cohort study. We hypothesize that people with FHS have a lower prevalence of ideal CVD health factors but higher prevalence of ideal health behaviors than those without FHS.

4.3 Methods

Study Participants

The REGARDS study is a population-based investigation of stroke incidence among US adults ≥ 45 years of age.[187] The study was designed to oversample blacks and to provide approximate equal representation of men and women. Residents from the Southern US states, commonly referred to as the “stroke buckle” (coastal North Carolina, South Carolina, and Georgia) and “stroke belt” (remainder of North Carolina, South Carolina, and Georgia as well as Alabama, Mississippi, Tennessee, Arkansas and Louisiana) were over-sampled and represent 56% of the cohort with the remaining 44% of participants recruited from the rest of the United States. Potential participants were identified from commercially available lists of US residents and recruited through an initial

mailing followed by telephone contacts. Overall, 30,239 black and white US adults were enrolled between January 2003 and October 2007. We included participants who have data on hypertension, cholesterol, diabetes, BMI, smoking, diet, physical activity and FHS, all ascertained at baseline (at the time of study enrollment). Participants were excluded if they had stroke symptoms (n=1930), coronary artery disease (n=5314), peripheral arterial disease (n=602) or if they lacked any family history data (n=3785). We excluded participants who had coronary artery disease, peripheral arterial disease or stroke as they may have already changed their behavior or may be on medications that affect CVHI components (BP, lipids, glucose). To preserve an adequate sample size for the present analyses, we imputed information on diet (20%) for these participants. Our final sample size was 20,567 for all analyses. The REGARDS study protocol was approved by the Institutional Review Boards governing research in human subjects at the participating centers and all participants provided informed consent.

Data Collection

Socio-demographic and clinical data were collected at baseline through a telephone interview, a self-administered questionnaire and an in-home examination. Trained interviewers conducted computer-assisted telephone interviews to obtain information on participants' demographics, cigarette smoking, physical activity, and use of antihypertensive, blood sugar lowering, and cholesterol lowering medications. Trained health professionals conducted

in-home study visits that included a physical examination and the collection of a blood sample. At the end of the in-home examination, the Block 98 Food Frequency Questionnaire (FFQ) was left with the participants for self-administration. [188,199] Using the FFQ, each participant recorded food intake for one year prior to their in-home visit. This form was mailed back to the REGARDS coordinating center for entry into a database by study personnel. Nutrient analysis was conducted by NutritionQuest. FHS was ascertained by a family history questionnaire that had questions on whether first-degree relatives (biological parents and siblings) ever had a stroke. FHS was considered positive if at least one parent or one sibling had a stroke. Ischemic and hemorrhagic stroke were not identified separately.

Cardiovascular Health Index

Components of CVHI include cigarette smoking, physical activity, diet, BMI, blood pressure, cholesterol and diabetes. These components are categorized as being poor, intermediate or ideal (Appendix). Current and former smoking and time since smoking cessation for former smokers was determined by three questions “Have you smoked at least 100 cigarettes in your lifetime?”, “Do you smoke cigarettes now, even occasionally?” and “How old were you when you stopped smoking?” Physical activity was assessed through a single question “How many times per week do you engage in intense physical activity, enough to work up a sweat?” Height and weight were measured using calibrated equipment and body mass index was calculated. The diet score for the

Cardiovascular Health Index was based on fish, fruit and vegetable consumption and sodium, sugar, and fiber/carbohydrate ratio intake. An ideal diet was defined by the following 5 factors: fish consumption ≥ 2 servings/week, fruit/vegetables ≥ 4.5 cups/day, sodium intake < 1500 mg/day, sugar < 450 kcal/week, and fiber/carbohydrate ratio >0.1 as per recommendations of the new metric. Systolic and diastolic blood pressure was measured two times using aneroid sphygmomanometers following a standardized protocol. The two BP measurements were averaged for the current analyses. Total cholesterol was measured using an enzymatic reaction. Glucose was measured in serum using colorimetric reflectance spectrophotometry. In addition to using all 7 components for a composite CVHI score, the components were grouped into two domains: health behaviors (cigarette smoking, physical activity, diet, and body mass index); and biological risk factors (blood pressure, cholesterol and diabetes). The CVHI does not integrate these seven components into an overall score so we classified each component equally into a sum score assigning 2, 1 and 0 points respectively to ideal, intermediate or poor status. An overall LS-7 score pooled the individual component scores and was categorized as: optimum (10-14), average (5-9) and inadequate (0-4) cardiovascular health. Those with the highest number of points are therefore in better cardiovascular health.

Statistical Methods

The goal of our study was to examine the contribution of FHS to cardiovascular health status in adults. Our primary predictor variable was FHS measured as a dichotomous variable using the family history questionnaire in REGARDS. Ordinal groupings of the cardiovascular health index (optimum, average and inadequate) were used as the dependent variable in the analyses. Individual components of the CVHI categories were treated as a 3-point ordinal scale (0,1,2) , as defined by AHA (see appendix) for testing in ordinal logistic regression. The seven metrics were then summed to obtain a score that ranged between 0 and 14. Baseline characteristics were calculated and compared for REGARDS participants by CVHI categories using t-tests (or nonparametric equivalent) for continuous variables and chi-square for dichotomous variables. Next, for FHS, odds ratios for CVHI health factors and behaviors were calculated (ideal and intermediate compared with the reference group of poor). The odds ratios were adjusted for demographic and other confounders. The analyses of health behavior and health factor data were further stratified by specific FHS (paternal history, maternal history and sibling history).

To further evaluate the association between FHS and overall CVHI, we used multivariable ordinal logistic regression, a method that allows the outcome variable to have more than 2 categories. Ordinal logistic regression calculates a single odds ratio (OR) for the association between the predictor variable (FHS) and levels of higher (better) versus lower (poorer) cardiovascular health categories. Crude and multivariable adjusted odds ratios were calculated before and after adjustment for confounders. We obtained the final model using

backward elimination of variables and applying statistical and epidemiological criteria for assessment of interaction and confounding. Interaction terms for age, race and gender were considered significant if the *P* value for the term was less than .05 by the Wald test. Confounding was assessed by the impact of the potential confounder on the parameter estimate for the main effect (of FHS). If removal of a confounding variable caused a change of 10% or more in the value of the parameter estimate, that variable was considered to be a confounder and was left in the model. Additionally, we also examined the relationship of FHS and CVHI as a continuous score and as a summary measure of behavioral and health factors separately. The proportional odds assumption of ordinal logistic regression, using the score test, was verified for our models. Results are reported as ORs with 95% CI. Statistical analysis was performed with SAS version 9.2 (SAS Institute Inc, Cary, NC).

4.4 Results

For the 20,567 participants included in the present analyses, the mean age was 63.9 +/- 9.3 (SD) years, 59.2 % were women, 39.2 % blacks, and 7702 (37.4%) had any FHS. Among the included participants, 19% had maternal history of stroke, 15% had paternal history of stroke, and 11% had a sibling history of stroke. More whites than blacks reported a FHS (22.1% vs 15.4%).

Overall, 15% of participants had optimum, 74% had average, and 11% had inadequate cardiovascular health. Age, sex, race, income, education, geographic

region and alcohol consumption were significantly associated with CVHI categories (Table 10). However, FHS was not associated with CVHI categories. Examining by individual CVHI factors, blood pressure was associated with FHS and all its subtypes (Table 11). Participants with FHS had 13% (OR=1.13, 95% CI = 1.07, 1.19) higher odds to have poorer BP levels versus ideal or intermediate levels (p-value <0.01). Participants with maternal or sibling history of stroke also had higher odds of poor levels of BP. Similarly, participants with FHS had 8% (OR=1.08, 95% CI= 1.03, 1.15) higher odds to have poorer cholesterol levels versus ideal or intermediate (p-value 0.002). For glucose, participants with family history were more likely to have poorer levels of these factors although the association was not significant. A composite score which included the sum of three CVHI factors (blood pressure, cholesterol and glucose) was significantly associated with FHS (OR=1.04, 95% CI =1.02, 1.07). Individual CVHI behaviors, particularly diet, were inversely associated with FHS and any of its subtypes (Table 12). For example, participants with FHS had 11% (OR=0.89, 95% CI = 0.82, 0.96) lower odds to have poorer diet score versus ideal or intermediate (p-value <0.006). Similarly, participants with FHS had 8% (OR=0.92, 95%CI= 0.85, 0.99) lower odds to have poorer levels of smoking versus ideal or intermediate (p-value=0.03). Other behavioral factors like physical activity and BMI were not significantly associated with family history. A composite score which included the sum of all four CVHI behaviors was, however, not significantly associated with FHS (OR=0.98, 95% CI= 0.97, 1.00).

In our final model, after adjustment for appropriate confounders (age, gender, race, income, education, alcohol use, geographic region), there was no significant association between CVHI and FHS (OR=1.00, 95% CI=0.94, 1.07) (Table 13). However, the subtype of sibling history of stroke was associated with CVHI (OR=1.06, 95% CI=1.01, 1.18, p-value =0.01). Next, we examined interaction of CVHI with age, race and gender. Interaction with age was significant ($P_{interaction}$ <0.001) but not with race ($P_{interaction}$ 0.90) and gender ($P_{interaction}$ 0.89). When we stratified by age, among older individuals, people with FHS had a 12% lower odds (OR=0.88, 0.79, 0.97) to have inadequate CVHI versus optimum and average. Younger participants with FHS had higher odds to have inadequate CVHI versus optimum and inadequate, but the association was not significant. Our results were unchanged when we kept cardiovascular health as continuous variable.

4.5 Discussion

Although a modest association of stroke and FHS is well recognized, the role of cardiovascular risk factors as intermediate phenotypes in this relationship is not as clear. [34,163] Several mechanisms have been postulated including genetic heritability of risk factors and familial sharing of environmental and lifestyle factors, lower socioeconomic status; and/or the interaction between genetic and environmental factors. In our study, FHS was associated with poorer CVD health factors but better health behaviors. There was no association with the overall CVHI score. Many of the components of CVHI including blood pressure,

cholesterol are intermediate phenotypes and have a substantial genetic component themselves and thus an overall CVHI may have limited utility in understanding this relationship. Among the CVHI health factors, blood pressure was significantly associated with FHS and all its subtypes. FHS was also associated with poorer levels of other CVHI health factors (cholesterol, blood sugar). Among health behaviors, healthy diet and smoking were inversely associated with FHS. We also found a modest association of CVHI and sibling history of stroke, suggesting the importance of environmental factors in a shared household.

In our study, participants with FHS including paternal, maternal or sibling history of stroke had a poorer level of blood pressure. These data suggest that people with FHS are more likely to have poorly controlled hypertension. Genetic susceptibility to hypertension may account for a significant proportion of the heritability of stroke.[164] Our results are consistent with previous studies demonstrating that heritability of stroke is mediated through the heritability of risk factors, particularly hypertension. [200,201] [202] People with family history are also more likely to practice risk-reducing behaviors.[203] [204] [152] [205] FHS may motivate individuals for improvement in health behaviors and our data suggest that there is an association of FHS with healthier diet and smoking, although this relationship is not consistently observed across all FHS subtypes.

In our study, sibling history of stroke was the only FHS subtype that was related to CVHI (maternal and paternal FHS was not). Previous studies have shown that a positive sibling history of stroke is indeed strongly correlated with incidence of stroke. [206-208] Meschia et al also showed that the severity of stroke was also more closely correlated with a history of stroke in the siblings than that in the parents. [207] Cardiovascular risk factors are more closely correlated with sibling-sibling relations than with parental-sibling relations and this may explain our finding. [209] This suggests that environmental factors in a shared household among siblings may be an important determinant in the familial aggregation of cardiovascular risk factors. Family history of stroke has been associated with a young age at onset, with the highest rates in patients aged 60 years or younger.[200] In our study, the association of FHS and CVHI appeared to be modified by age. Younger individuals with FHS had higher odds of inadequate CVHI but the opposite was true in older individuals. It is possible that the relative importance of family history and genetic factors may diminish with increasing age as other acquired factors become more dominant. This finding needs further exploration.

A positive family history could be the result of shared genes, shared environment, or both, but these factors are difficult to disentangle. Compared to individual risk factors, the utility of CVHI as a summary measure of cardiovascular health appears less evident in understanding this relationship. The observed association between hypertension and FHS in our study suggests

that familial susceptibility to stroke is partially attributable to familial predisposition to hypertension.

Our study has several strengths including the large national sample, with over-sampling of blacks and use of standardized questionnaires and measured risk factor levels. REGARDS is the largest study of FHS among blacks– a subgroup of population with the highest incidence of stroke. FHS does not appear to confer increased risk among this population any differently than whites.We excluded participants with history of stroke or heart disease and thus there is limited potential for reverse causation—i.e., people changing behaviors or treating risk factors due to a clinical event. Our study has a few important limitations. FHS was assessed by informant interview and not by examination or medical record review of family members. Further, we have no details on the classification of stroke (ischemic or hemorrhagic) and the diagnosis of stroke may have been inaccurate due to poorer diagnostic tools used in the past. Recall bias is also possible due to use of self-reported data, but previous studies have found self-reported history to be reliable for stroke data. [210] Because of early case fatality, sicker individuals could have been excluded because they died before reaching age of inclusion eligibility of REGARDS and thus survivorship bias could have diluted our study findings. Our study uses family history as a dichotomous variable and this may cause misclassification or otherwise limit information, as shown in recent studies which have used a continuous measure. [211,212]

In conclusion, FHS is associated with poorer levels of CVHI health factors, particularly hypertension but more optimum level of CVHI behaviors like healthy diet. [213] In the presence of FHS, earlier detection and treatment of modifiable risk factors, particularly hypertension, maybe valuable in reducing the burden of stroke.

CHAPTER 5: Cardiovascular Health Index and Carotid Intima Media Thickness in a Twins Study

Study 3

Association Between Ideal Cardiovascular Health and Carotid Intima-media Thickness: A Twin Study

5.1 Abstract

Background and Objective: The American Heart Association recently developed the Cardiovascular Health Index (CVHI), a new public health metric consisting of seven modifiable risk factors. The CVHI has been shown to predict the risk of several diseases but its relationship with preclinical markers such as Carotid Intima-media Thickness (CIMT) has not yet been assessed. This study assessed the relationship between CVHI and CIMT, and whether this association is independent of genetic and early environment factors in a twin sample.

Methods: We examined 245 male monozygotic and dizygotic twin pairs (total 490 subjects) free of overt cardiovascular disease. CIMT was measured using high resolution B-mode ultrasonography. Each of the seven CVHI components was given a point score of 0, 1 or 2 to represent poor, intermediate, or ideal health, respectively. The sum of all seven CVHI component scores, an overall CVHI score (range 0 to 14), was categorized as inadequate (0-4), average (5-9) or optimum (10-14) cardiovascular health. Mixed-model regression was used for analysis.

Results: The mean age of participants was 55.4 years (± 3.12), 96% whites, and 61% monozygotic and 39% dizygotic twins. The mean CIMT was 0.75 (± 0.11) and the mean CVHI score was 7.7 (± 2.06). Overall, 18% of participants had optimum, 77% had average and 5% had poor cardiovascular health. There was an inverse correlation between CVHI and CIMT (Spearman r = - 0.22, p <0.001). For every unit increase in overall CVHI score (indicating better cardiovascular health), CIMT decreased by 0.009 (p-value = 0.0002). Among monozygotic twins

discordant for CVHI, for each unit increase in CVHI score, CIMT was significantly decreased by 0.01 (p-value=0.0004). However, among dizygotic twins discordant for CVHI, CIMT was not significantly associated with CVHI (p-value=0.18).

Conclusions: The CVHI is independently associated with CIMT, a preclinical marker of atherosclerosis burden and an established risk factor of cardiovascular disease. This association is not confounded by shared genetic and other familial factors.

5.2 Introduction

Epidemiological studies have suggested the importance of a global risk profile in the prediction and prevention of stroke. [214] Most cardiovascular disease events including stroke are preventable by optimizing one or more cardiovascular risk factors.[114,139-141] The American Heart Association and the American Stroke Association (AHA/ASA) proposed a new public health metric, the cardiovascular health index (CVHI), which can be followed over time. [122,138] This index emphasizes primordial prevention by defining goals for health factors and behaviors that comprise the definition of 'ideal' cardiovascular health. The CVHI has seven components which include three health factors (blood sugar, serum cholesterol, blood pressure) and four health behaviors (body mass index (BMI), physical activity, diet and cigarette smoking) and classifies each of them into ideal, intermediate and poor levels. For disease prevention and improving

cardiovascular health in the population, early detection of CVD must be emphasized as a goal.

Given the heterogeneous nature of stroke and the complexity of its risk factors, evaluation of intermediate phenotypes may be useful in the prevention of hard clinical events. Carotid intima-media thickness (CIMT), a preclinical marker for cardiovascular disease, has been extensively used as a quantitative index for evaluating the severity and progression of atherosclerosis and for the prediction of coronary heart disease and stroke [165-172]. Carotid intima-media thickness is also associated with several cardiovascular risk factors including blood pressure, dyslipidemia and health behaviors such as smoking and physical activity, but its relation with an overall cardiovascular health phenotype has not been shown. [174-177,179,183,196] Furthermore, as most health behaviors in adult life are influenced by the familial environment, studies on CIMT and cardiovascular risk factors may be confounded by other exposures or behaviors shared by members of the same family.[34,163,207] Our objective was to assess the relationship between CVHI and CIMT and to separate the role of familial factors (including genetic and early environment factors) in a twin sample. We hypothesized that people with lower CVHI have increased CIMT and this relationship is continuous and graded across all levels of CVHI and is not confounded by shared genetic and other familial factors.

5.3 Methods

Study population

The Emory Twin Studies includes samples recruited in two companion studies: the Twins Heart Study (THS) and the Stress and Vascular Evaluation in Twins (SAVEIT). The purpose of these studies was to elucidate the role of psychological, behavioral, and biologic risk factors for subclinical cardiovascular disease in twins. Both studies recruited randomly selected samples of middle-aged male monozygotic (MZ) and dizygotic (DZ) twin pairs (who were raised in the same household) from the Vietnam Era Twin (VET) Registry, which includes 7369 male-male twin pairs both of whom served in the US military during the time of the Vietnam War. [215] Both studies followed identical procedures, measurements, and protocols. THS enrolled 180 twin pairs between 2002 and 2006 and SAVEIT enrolled 127 twin pairs between 2005 and 2010 as previously described. [216-218] We excluded participants with a history of coronary artery disease and stroke. We also excluded a few duplicate twin pairs who participated in both studies or twins missing information on CIMT. Each twin in a recruited pair was examined at the same time at the Emory University General Clinical Research Center, and all data collection including medical history, and physical examination and blood tests, occurred during a 24-hour admission under controlled conditions. Depressive symptoms were ascertained by using the Beck Depression Inventory-II which has satisfactory test-retest reliability and internal consistency.[219,220] Information on current use of medications was also collected. Both studies were approved by the Emory Institutional Review Board,

and all twins gave informed consent. Zygosity information by means of DNA typing was available for all twin pairs.

Cardiovascular Health Index (CVHI)

Components of the CVHI metric include blood pressure, cigarette smoking, BMI, cholesterol, blood glucose, physical activity and diet (Appendix). Systolic blood pressure and diastolic blood pressure were measured by mercury sphygmomanometer on the right arm with the subject in sitting position after 10 minutes of rest. The average of two measurements 5 minutes apart was used in the statistical analyses. Venous blood samples were drawn for the measurement of glucose and lipid profile (total cholesterol) after an overnight fast. Cigarette smoking was classified into current smoker (poor); quit in the past year (intermediate) and never smoker or quit more than one year ago (ideal). Glucose levels were measured on the Beckman CX7 chemistry autoanalyzer. Physical activity was determined by means of a modified version of the Baecke Questionnaire of habitual physical activity.[201] We used tertiles of the cumulative score to classify individuals into poor, intermediate and ideal levels of physical activity. Each CVHI component was given a point score of 0, 1 or 2 to represent poor, intermediate, or ideal health, respectively, based on pre-defined categories (Appendix). Based on the sum of all 7 CVHI components, an overall CVHI score, ranging from 0 to 14, was categorized as inadequate (0-4), average (5-9) or optimum (10-14) cardiovascular health.

To measure the specific score for diet we used the DASH (Dietary Approaches to Stop Hypertension) diet score which is endorsed by AHA and has been linked to diminished risk of CHD and stroke.[208 210] We constructed the DASH score according to the method proposed by Fung et al that has been utilized in several epidemiological studies.[221] The DASH score is calculated based on eight food items (fruits, vegetables, nuts and legumes, low fat dairy products, whole grains, sodium, sweetened beverages, red and processed meats) and on the following principles: 1) high intake of fruits, vegetables, nuts and legumes, low-fat dairy products, and whole grains are beneficial for human health and receive high scores; 2) high intake of sodium, sweetened beverages, and red and processed meats are harmful and deserve lower scores. For each of the above eight food groups, we categorized study subjects into quintiles (assigned 1-5 points) according to their individual food intake component scores. Scoring by quintile helped to reduce the potential for misclassification. The scores for each food group were then summed to yield an overall score ranging from 8 to 40, where higher scores represent greater adherence to the DASH diet. The cumulative score was grouped into tertiles to classify individuals with ideal, intermediate and poor diets.

Carotid Intima Media Thickness (CIMT)

CIMT was measured using high resolution B-mode ultrasonography with standard techniques.[200,222,223] Briefly, CIMT was quantified both on the near and far wall at the distal 1.0 cm of both the left and right common carotid arteries

proximal to the bifurcation. For each segment, the sonographer used multiple different scanning angles to identify the longitudinal image of CIMT showing the maximum CIMT. At least 10 pictures for each segment were stored digitally, and measurements were made off-line using semi-automated computerized analytical software (Carotid Tools, MIA Inc., Iowa City, Iowa) by one observer blinded to other twin data. Of the stored images, the one with maximum thickness was selected, and CIMT measured, for each segment. Average values of the CIMT of each of the four segments (right near and far walls, and left near and far walls) were used as the CIMT values for each twin in the analysis (total mean of maximum CIMT). In order to minimize variability, the same technician did CIMT measurements throughout the study, and the same equipment and analytical software was used to measure CIMT for all the twin participants. In our lab, the mean absolute difference in CIMT measured in seven subjects in whom two carotid artery examinations were performed three days apart, was 0.03 (±0.02) mm. The mean difference in two successive readings of the same 10 segments of CIMT was 0.02 (±0.02) mm with a Pearson correlation coefficient of 0.93.

Statistical Analyses

Continuous variables were described as mean ± SD and categorical variables as frequencies (percent). We compared baseline demographic characteristics, cardiovascular health factors and behaviors, inflammatory markers and medications across CVHI categories, treating the twins as individuals. We also

compared individual CVHI components across CIMT categories (greater or less than the median of 0.75) and with CIMT as a continuous score while accounting for correlated data using mixed models or generalized estimating equation (GEE) models. In additional analyses, we examined the Spearman correlation between CVHI and CIMT and the relation between CIMT and number of ideal health factors. Next, we analyzed the relationship between CIMT and CVHI categories using mixed model regression analysis adapted for twin studies. [224] We fitted mixed models for twins which allowed for partitioning within and between pair differences in the dependent variable as a function of the independent variables. Potential multicollinearity was investigated using condition indices and variance decomposition proportions using a condition index of > 20 and at least two non-intercept variables with variable decomposition proportions values of >0.05.

We next analyzed twin pairs discordant for CVHI, defined as two twin brothers differing in their individual CVHI scores by atleast 1 point. We defined “within-pair differences” as the differences between a twin’s with a higher CVHI score and his twin brother’s lower CVHI score. This within-pair analysis by design takes into account shared genetic and many early environmental factors. Within-pair analysis was further stratified by zygosity to determine whether the relationship between CVHI and CIMT was different between MZ and DZ twins. Monozygotic twins share 100% of their genetic material, and therefore differences between MZ twins are controlled for genetic factors. Dizygotic twins share on average 50% of genes and differences between the twins are only partially controlled for

shared genetic factors. Shared genetic factors would be implicated if the within-pair difference in CIMT in CVHI-discordant pairs were smaller in MZ than in DZ pairs. All statistical analyses were conducted using SAS software, version 9.3 (SAS Institute Inc, NC). Significance level was set at 0.05, two- sided.

5.4 Results

From the initial sample of 307 twin pairs, 40 twin pairs were excluded because of history of coronary artery disease and 9 twin pairs because of history of stroke. We also excluded a few duplicate twin pairs who participated in both studies and twins missing information on CIMT (13 twin pairs). The combined sample for analysis included 245 twin pairs or 490 twins. The mean age of participants was 55.4 years (± 3.12), 96% whites, 61% MZ and 39% DZ twins, a distribution that reflects that of the entire Vietnam Era Twin Registry. The mean CIMT was 0.75 (± 0.11) and the mean CVHI score was 7.7 (± 2.06). Overall, 18% of participants had optimum, 77% had average and 5% had poor cardiovascular health. Age-adjusted prevalence of ideal CVHI components ranged from 15% for BMI to 75% for smoking (Figure 11). There were no significant differences in demographic variables between MZ and DZ twins. Besides adverse levels of CVHI components (systolic blood pressure, glucose, smoking), lower education and being unemployed were associated with poorer cardiovascular health (Table 14).

CIMT was normally distributed with a median of 0.75 mm. The distribution of the seven CVHI components, including health behaviors and health factors, by CIMT

dichotomous categories (greater or less than the median of 0.75) is presented in Table 15. Using mixed model regression adapted for twin studies, all health factors (total cholesterol, blood pressure, blood glucose) were significantly associated with CIMT categories with a higher proportion of subjects in the poor category of each component showing high vs low CIMT. Among the health behaviors, only BMI was significantly different comparing high and low CIMT categories (p-value=0.006). For the overall CVHI, more than twice participants in the inadequate CVHI category had high vs low CIMT (7.8% vs 3.1%). Conversely, fewer participants in the optimum CVHI category had high vs low CIMT (12.6% vs 23.0%), p-value=0.004. When CIMT was analyzed as a continuous variable, results were overall similar (Table 15). For a unit change in CVHI category, from inadequate to average or average to optimum, CIMT decreased by 0.03 mm (p-value = 0.0003). When CVHI was treated as a continuous score, with higher score indicative of better cardiovascular health, the score was negatively correlated with CIMT (Spearman r = - 0.22, p <0.001) (Figure 12). Also, as the number of ideal health factors and health behaviors in participants increased, CIMT declined in a graded manner (Figure 13).

In the unadjusted model, for every unit increase in overall CVHI score (indicating better cardiovascular health), CIMT decreased by 0.009 mm (p-value = 0.0002). This association was mildly diminished after adjusting for age, college education, employment and further adjusting for other comorbid conditions like , depression (p-value = 0.001). Cardiovascular health categories were also similarly significantly associated with CIMT in the crude and adjusted models (Table 16).

Our final analyses focused on twin pairs who were discordant for CVHI, that is, where one member of the twin pair had higher CVHI score than the other. The CVHI score was continuous for this analysis and the results were stratified by zygosity. There were a total of 197 discordant twin pairs, 76 were DZ discordant and 121 were MZ discordant. Among MZ twins discordant for CVHI, for each unit increase in CVHI score, CIMT was significantly decreased by 0.01 (p-value=0.0004). However, among DZ twins discordant for CVHI, CIMT was not significantly associated with CVHI (p-value=0.18). Further adjustment for potential confounders, did not alter the results (Table 17).

5.5 Discussion

Carotid Intima-Media Thickness is an important preclinical marker and has been shown to predict future clinical cardiovascular end points including coronary heart disease and stroke.[172] Our study in a twin sample shows that a new metric developed by AHA, the cardiovascular health index, is inversely associated with CIMT and this association is independent of shared genetic and familial factors. We also found that this association is more robust for CVHI health factors (blood pressure, plasma cholesterol, plasma glucose) compared with CVHI behavioral factors (diet, physical activity and smoking), except BMI, which was strongly related to CVHI. Furthermore, the association of CVHI with CIMT was not substantially diminished when examined within pairs, suggesting that familial factors do not play a role in this association. [111] Importantly, the association remained strong within MZ pairs, who are also matched for genetic factors.

These results suggest a causal relationship between health factors and CIMT. Our study confirms the utility of measuring CVHI and expands it towards prevention of preclinical atherosclerosis, as measured by CIMT. Combination of health factors and behaviors is a powerful negative predictor of plaque burden and it appears to play a role in CVD prevention in the preclinical phase.

CVHI was defined and created by AHA as part of a national effort to improve cardiovascular health of all Americans by 20% by 2020.[122] The prevalence of ideal cardiovascular health is very low in the United States as measured in several studies.[125,143] [128,186] The distribution of ideal factors in our sample of middle-aged male Vietnam era veterans was comparable to what was reported in National Health and Nutrition Examination Survey, but health behaviors such as diet, physical activity and smoking were more favorable than the United Sates general population. Veterans are more likely to have health insurance as compared to non-veterans and it is possible that they are more motivated to practice healthier behaviors. Their cardiovascular risk factors are, however, comparable to the non-veteran population. [225,226]. Several nationally representative studies have found that veterans are more likely than civilians to participate in recommended preventive care but may not always have better health outcomes.[227,228]

Our study shows that CIMT was inversely associated with optimum CVHI and the association was independent of shared genetic and familial factors. Furthermore,

as the number of ideal health factors increased, the CIMT showed a gradient decline. Poorer levels of CVHI have shown to be associated with several chronic diseases and mortality.[125,225,226,229] Thus, measurement of CIMT in asymptomatic people with less than optimum health could potentially inform more aggressive management approaches and help in the global prevention of many diseases. CIMT has been used as a quantitative index for evaluating the progression of atherosclerosis and as a surrogate end point in clinical trials. For an absolute CIMT difference of 0.1 mm, the future risk of a coronary event increases by 10% to 15%, and the stroke risk increases by 13% to 18%.[172] CIMT and Framingham Risk Score for Stroke also correlate well and CIMT is useful in discriminating between subjects at low or high 10-year risk.[183] Epidemiological studies have shown associations of CIMT with several CVD risk factors including smoking, BMI, blood pressure, and high blood cholesterol. [174-177,230] However, there are limited data on the effect of diet and physical activity on CIMT.[227,228] Our study shows that the overall association of CVHI and CIMT was primarily driven by health factors such as blood pressure, cholesterol and blood glucose instead of health behaviors.

Previous studies have indicated that genetic factors have a substantial influence on the variation of CIMT[231,232] In our study, the association of CIMT and CVHI was stronger in MZ than DZ twins indicating that CVHI is causal To our knowledge, ours is the first study to demonstrate a link between CVHI, a new public health metric and CIMT- a marker of “vascular health”. Furthermore, using a co-twin design, we were able to control for many unmeasured risk factors

including maternal factors, early familial environment, and genetic influences in assessing the relationship of overall CVHI with CIMT.

Our study has notable strengths. Twins provide naturally matched pairs of individuals who, in addition to demographics, share parental factors and upbringing environment. Therefore, potential confounding effects of a large number of unmeasured factors may be removed by comparisons between twins who share them. Our study had the advantage of having standardized measurements of several cardiovascular risk factors and health behaviors which we were able to use for ascertainment of the CVHI score. There are also a few limitations with our study. Our study sample is restricted to healthy middle-aged male Vietnam era veterans, and therefore our results may not be generalizable to women or younger subjects. We controlled for many known lifestyle factors and compared twins raised in the same family; and it is unlikely that other behavioral factors substantially confound the association between CVHI and CIMT. However, despite the strengths of a twin design, unmeasured confounding still cannot be completely ruled out.

In summary, our study shows that CIMT, a convenient, inexpensive, safe and non-invasive modality to measure vascular health correlates with the global cardiovascular health (CVHI) of the individual. The association of CVHI and CIMT is driven by health factors (blood pressure, cholesterol, blood sugar) and is independent of maternal factors and early familial environment. Thus the

conveniently measured CVHI metric provides a powerful indicator of subclinical CVD. Further understanding of the CVHI and CIMT relationship may enhance prevention and intervention efforts to assist in more effective ways to target people with less than optimum levels of cardiovascular health.

CHAPTER 6: Summary of Findings and Future Directions:

6.1 Summary

More than 75% of health care costs in United States are due to chronic conditions, but some of these conditions are also the most preventable.[233] A few modifiable risk factors such as smoking, inadequate physical activity and poor diet are responsible for a majority of chronic illnesses, disability and premature death. In setting the national goals for 2020, the American Heart Association has shifted focus from preventing cardiovascular diseases to improving national cardiovascular health.[122] The new CVHI metric was proposed as rates of nonfatal CVD remained unchanged and because of national trends of increasing prevalence of poor risk factors such as diet, physical inactivity, diabetes, obesity and continuing increases in healthcare costs due to post-event survival. Thus, we are preventing deaths by means of costly and procedure-based interventions. If current trends continue, the burdens of adverse health behaviors could reverse mortality gains achieved in recent decades.

The prevalence of ideal cardiovascular health is very low among Americans as measured in several studies.[125,143] [128,186] From NHANES (1988–2010), a low prevalence of ideal cardiovascular health is present across the United States: 2.0% (95% CI, 1.5%–2.5%) in 1988–1994 and 1.2% (95% CI, 0.8%–1.9%) in 2005–2010. A stepwise association is present between the number of ideal CVHI metrics and risk of all-cause mortality, CVD mortality, and heart disease mortality

after 14.5 years of follow-up in the United States. [126] The metrics with the greatest potential for improvement are health behaviors, including diet, physical activity and BMI.

Poorer levels of CVHI have recently been shown to be associated with several other chronic diseases and mortality.[125,225,226,229] As yet, the association had not been examined for stroke, family history and pre-clinical markers of stroke. In our first study, we examined the relationship between the CVHI and incident stroke in a prospective cohort study, the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. Our study showed that a one point higher CVHI score was associated with an adjusted 8% lower risk of stroke (HR=0.92, 95% CI=0.88, 0.95). We concluded that, in both blacks and whites, better cardiovascular health, based on the CVHI score, is associated with lower risk of stroke, and a small difference in scores was an important stroke determinant.

Family history represents the influence of genetic factors and family environment that affect the metabolic profile, health behaviors and overall risk of disease. In our second study we examined the relationship between family history of stroke and the CVHI in REGARDS. In our study, family history of stroke was associated with poorer levels of health factors, particularly blood pressure (OR=1.13, 95% CI = 1.07, 1.19) but better health behaviors, particularly smoking and healthy diet. Thus our results show that the increased risk of stroke associated with family

history of stroke maybe mediated by its association with poorly controlled blood pressure. In our final study, we evaluated in more detail the role of familial and early environmental factors on the CVHI using a twin sample as part of the Emory Twins Studies. Our outcome was carotid intima-media thickness (CIMT), a preclinical marker of atherosclerosis burden and an established risk factor of stroke. The CVHI was found to be independently associated with CIMT. This association was not confounded by shared genetic and other familial factors.

Our results provide strong support for use of the new CVHI, as a powerful tool for quantifying and monitoring the cardiovascular health of the U.S. population for stroke prevention. These data suggest that a majority of stroke events are preventable by achieving optimum levels of few, readily measurable, physiological risk factors and behaviors of cardiovascular health. Some of the key strengths of our studies are their public health relevance, timeliness of our research questions, the rigorous assessment of exposures, outcomes and variables.

Perspective on Cardiovascular Health Index

The CVHI was proposed by AHA to reorient approach towards CVD epidemiology and emphasizing primordial prevention and a life-course approach to prevent risk factor development. A combination of primordial, primary and secondary prevention approaches through medical and public health policy interventions (e.g. restructuring food policy to reduce trans-fats and sodium) will be critical to reduce the prevalence of poor CVHI components. Several recent

studies reinforce the relevance of using CVHI for primordial prevention and targeting risk factors.[127,234] As we mentioned in the introductory chapters that pharmacological approaches, such as combination pills, can have a big impact and maybe cost-effective when administered for primary prevention. However, findings from our studies emphasize that similar or greater achievements can be achieved by effective translation of policies that improve these health behaviors and physiological factors at population-level. The CVHI components are based on data that suggest excellent prognosis with respect to CVD-free survival, healthy longevity and quality of life. Further, the metric is designed to be simple and accessible to practitioners so they can provide guidance in promoting cardiovascular health in their patients. It also makes it possible to have clear and actionable items for policy makers and thus allow all subsets of the population to make improvements in their cardiovascular health. Other strengths of the CVHI are presented in Table 18.

The CVHI metric also has some important limitations. First, components are not weighted. In our studies we found blood pressure to be associated more strongly with stroke, family history and CIMT compared with other components. The CVHI score weighs the ideal, intermediate and poor levels of the 7 metrics equally (0,1,2). The CVHI score is not intended as a prediction score; rather, it serves as a means for monitoring the distribution (poor, intermediate, or ideal) of all seven metrics across the population. Folsom et al demonstrated that there were roughly equal stepwise decreases in hazards for cardiovascular events for each additional single health behavior or health factor present at ideal levels,

which supports the notion of simple and equal scoring without weighting the different factors.[125] We indeed did present the main analyses for CVHI in all our papers as both categorical and continuous (CVHI as 0-14). Second, there are some components that are important for cardiovascular health that have been left out of the metric. An example is psychosocial stress. This was primarily done because of lack of consensus for a clear definition and limitations of data-collection in national data sets. Third, it is possible that the true effects of health behaviors are underestimated in our analysis as measurement error is more likely compared to physiological factors. Thus probably the true impact of suboptimal levels of health behaviors is probably even greater. Fourth, it is unclear if combination of CVHI factors into a total score adds anything to examining the risk factors independently. The definition of CVHI emphasizes both individual components and the combination index for populations surveillance and monitoring. Finally, at present there is limited evidence to suggest if CVHI has any clinical utility and its use as a prediction score. We have proposed to conduct a pilot study to investigate the utility of CVHI in a primary care patient population.

Table 18: Strengths and Limitations of CVHI

Strengths of the CVHI metric

- Clear and measurable definition of cardiovascular health.
- Emphasis on modifiable health factors and behaviors
- Evidence-based with respect to CVD-free survival
- Simple and accessible to practitioners and individuals
- Allow for all subsets of the population to benefit
- Readily measured using nationally-representative data
- Allow for assessment and monitoring changes over time

Limitations of the CVHI metric

- Risk factors and behaviors are not weighted
- Excludes other modifiable risk factors like alcohol intake
- Uncertain clinical utility as a prediction score
- Unclear if combination of CVHI factors into a total score adds anything to examining the risk factors independently

In conclusion, this dissertation contributes novel insights on the utility of the new metric of cardiovascular health for stroke prediction, and the impact of family history and familial factors. Knowledge from this dissertation could be used for improvements in population level strategies and healthcare systems for better and more efficient monitoring of health behaviors such as physical activity, diet quality, obesity, and smoking for stroke prevention. Even modest improvements in cardiovascular health profile should result in substantial reductions in stroke risk and thus are critical in the nationwide efforts to achieve American Heart Association goals.

6.2 Future Directions

We have proposed and are conducting several other studies that will contribute to the growing literature on CVHI. Some of these studies are outlined below.

Project 1: Association of Prevalent Stroke and All-cause mortality with CVHI

Individuals who suffer a stroke are at increased risk of recurrent disease as well as other cardiovascular events like myocardial infarction.[235] In view of this it is reasonable to hypothesize that individuals who report having had a stroke would adopt a lifestyle aimed at reducing this risk. Recently, a prospective cohort study among 71,243 women from the Nurses' Health Study showed that adherence to a low-risk lifestyle (e.g. not smoking, BMI<25kg/m^2) had a relative risk of 0.21 for primary stroke compared with women who did not meet the criteria for low-risk lifestyle.[194] Another prospective cohort study showed that at one year after stroke, 36% of 169 stroke survivors who smoked before had given up smoking completely and another 26% reported having reduced the amount smoked; 72% of 140 of those who drank heavily before their stroke, no longer drank more than the weekly limit. This suggests that stroke patients are more willing to make lifestyle changes to reduce the risk of subsequent events.[236] Towfighi et al found out that regular exercise (>12 times/month) and abstinence from smoking were independently associated with lower all-cause mortality after stroke. Combinations of health lifestyle factors were associated with lower all-cause and cardiovascular mortality in a dose dependent fashion.[237] Thus, to lower the incidence of subsequent stroke events, reduce stroke deaths and eliminate

health disparities, public health programs need to focus on risk factors prevention and education targeting on different population.

The extent to which modification of self-reported risk behaviors and factors differs among stroke survivors from that of the general population is unclear and the degree to which a higher prevalence of adverse self-reported risk factors are associated with greater all-cause mortality is unclear. One of our future projects is to determine whether CVHI scores differ among those with and without self-reported prevalent stroke. We seek to further determine if the association between self-reported stroke and CVHI score varies by race. We have proposed to do this study in REGARDS cohort.

Project 2: Flow-mediated Dilation and CVHI

Endothelial dysfunction refers to impairment of endothelium-dependent vasodilation due to abnormalities in endothelial integrity and homeostasis.[238,239] Several studies have shown that endothelial dysfunction plays an important role in the pathogenesis of coronary artery disease (CAD) and is also an early manifestation of atherosclerosis.[240-243] Endothelial dysfunction is both spatially and temporally linked to atherosclerosis, demonstrable before the appearance of structural atherosclerotic disease and predisposing to clinical events in late obstructive disease.[244] Endothelial dysfunction can be measured in the coronary arteries by intra-arterial infusion of substances that promote release of nitric oxide, such as acetylcholine, but this method is limited by its invasive nature

which affects its widespread use in asymptomatic subjects.[245] One of the most widely used non-invasive tests is flow-mediated dilation (FMD), an ultrasound-based method in which arterial diameter is measured in response to an increase in shear stress causing endothelium-dependent dilatation.[246] FMD has been shown to correlate with invasive measures of endothelial function and also with major traditional vascular risk factors. [247-250] Whether a favorable CVD risk profile is associated with a higher FMD has not evaluated. Our objective is to evaluate the association between FMD and CVHI in a twin sample. This study will further highlight the utility of CVHI metric and its relationship with pre-clinical biomarkers of cardiovascular dieseases.

Project 3: Psychosocial Stress and CVHI

Psychosocial stress has also been implicated in the development and prognosis of cardiovascular disease. The biological definition of stress suggests that it is ‘a state of threatened homeostasis provoked by a psychological, environmental, or physiologic stressor’. A number of psychosocial stressors are prospectively associated with incidence and progression of CVD. Most of these studies have examined chronic stressors in the form of work stress and produced fairly consistent results.[251,252] However, these studies have generally included white population and thus more research is needed to determine whether associations between psychosocial stressors and CVD outcomes vary by race. Psychosocial stress can contribute to stroke risk or survival following a stroke through a variety

of mechanisms. Psychosocial stress have known neuroendocrine and immunological effects both of which could influence stroke risk.[253] They are well-recognized risk factors that appear to contribute to all recognized mechanisms underlying cardiovascular events, specifically, endothelial dysfunction, myocardial ischemia, plaque rupture, thrombosis, and arrhythmias. Studies have also found an association with progression of carotid atherosclerosis,[254,255]

Other potential underlying pathophysiological mechanisms that have been proposed include increases in sympathetic nervous system activity as evidenced by changes in heart rate variability, increased inflammation indicated by higher C -reactive protein, and increased platelet aggregation. [256] Moreover, psychosocial stress may negatively impact stroke risk factors. For example, previous research has shown that high levels of stress are associated with decreased physical activity, higher prevalence of smoking, hypertension and altered lipid metabolism [257-262] Subjects who have higher levels of stress expresses symptoms such as low mood, changes in eating habits, decreased adherence to recommended lifestyle and treatment, and increased suicidal ideation, all of which may manifest in a subsequent stroke event.[263,264]

Thus psychosocial stress may affect changes in an individual's health status that may influence the risk of stroke through non-compliance with medical recommendations as well as presence of elevated CVD risk factors such as smoking and hypertension. The extent and degree to which these psychosocial risk factors varies by race, gender and socio-economic status and how it affects

overall cardiovascular health has not been well characterized in the United States population. Another of our proposal is to compare the prevalence of cardiovascular health, and the frequency of risk factor treatment among eligible people with and without adverse psychosocial factors. We hypothesize that people with adverse psychosocial factors are less likely to be compliant to medical recommendations and are less likely to be at ideal cardiovascular health predisposing them to more stroke events compared with people without these factors.

Project 4: Utility of CVHI in Primary Care

Interventions selected for use in prevention must lead to favorable changes in risk factors and outcomes, be cost effective, and be financially and logistically feasible. There is a well-documented gap between guidelines for management of risk factors and the care delivered in primary care settings for chronic illnesses.[265] There have also been a few attempts to improve delivery of preventive services at primary care offices, but their success has been limited because of provider barriers including limited amount of time with patients, provider motivation and competing demands faced by providers.[266-268] Despite this, improving the delivery of preventive services at primary care offices remains an important goal. The United States Preventive Services Task Force data suggest that among the most effective interventions available to physicians for reducing the incidence and severity of disease and disability are those that address the personal health practices of patients.[269] Preventive intervention is

most appropriate in a setting where early contact is available, as in the primary care setting.

Multiple-behavior interventions are likely to have much greater impact on public health than single-behavior interventions.[270] Previous studies have shown that most cardiovascular disease events are preventable by achieving few parameters of cardiovascular health though multifactorial interventions.[114,139-141,271] The American Heart Association (AHA) new metric, Cardiovascular Health Index (CVHI) emphasizes goals for seven most important modifiable health factors and behaviors in achieving ideal cardiovascular health. Although there has been enormous interest in the new AHA metric as a measure to improve public health, its effectiveness as a multi-factorial intervention, has not been formally evaluated in a clinical trial and especially in a primary care setting. We hypothesize that people with at least one heart disease risk factor who participated in an online/paper-based CVHI self-monitoring intervention, compared with usual-care control subjects would demonstrate improvements in health behaviors and factors. We propose to conduct a single center pilot randomized controlled trial in which 120 patients will be assigned to either a CVHI intervention or a usual care group. Patients will be randomized to the intervention or control groups and evaluated on improvement in CVHI score (primary outcome). Effectiveness of both approaches will be evaluated after 6 months in a primary care clinic population in Atlanta. The pilot project will also test the feasibility of implementing such a project, identifying barriers to care

among patients and providers. Our goal is to publish results from our pilot study in a manuscript and identify key strategies leading to implementation of a larger project focused on improved patient education and health goals within the Emory Healthcare system in Atlanta. The need to address multiple risk factors in primary care via effective and efficient practical approaches is increasingly urgent**.** Scaling-up such interventions in primary care will empower the physician-patient relationship to promote healthy behaviors and achieve the full potential of primary care.

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Tables and Figures

Table 6: Baseline characteristics of 22, 914 REGARDS study participants by race and CVHI health categories

Characteristic	Overall (%)	Cardiovascular Health Categories							
		Blacks (n=9,553)				Whites (n=13,361)			
		Optimum n=692	Average n=7302	Inadequate n=1559	P-value	Optimum n=2589	Average n=9756	Inadequate n=1016	P-value
Age	45.2	7.4	75.7	16.9	0.13	20.5	71.2	8.3	<0.001
<65 years %									
>65 years %		7.0	77.4	15.5		18.1	75.1	6.8	
Sex	58.6	8.6	78.4	12.9	<0.001	18.5	74.9	6.6	<0.001
Male %									
Female%		6.5	75.3	18.2		20.1	71.4	8.4	
Income	16.3	8.1	77.2	14.7	<0.001	20.2	72.9	6.8	<0.001
>$20,000k %									
< $20,000k %		4.6	74.1	21.3		12.4	73.5	14.1	
Education	10.8	7.9	77.1	14.9	<0.001	20.1	72.7	7.2	<0.001
>12 years %									
<12 years %		4.1	73.2	22.7		8.3	78.8	13.1	
Geographic Region	21.0	7.3	76.1	16.6	0.18	19.6	72.7	7.7	0.24
Belt %									
Non-belt %		7.0	78.1	14.9		18.5	74.2	7.3	
Alcohol Consumption	53.5	7.8	75.9	16.2	0.008	21.3	72.0	6.7	<0.001
Current %									
Former %		6.9	75.5	17.6		14.9	74.8	10.2	

Table 7: Incidence rates and adjusted HR of stroke for CVHI components among REGARDS participants by race

		Overall		Blacks		Whites	
		IR†	HR* (95% CI)	IR	HR (95% CI)	IR	HR (95% CI)
Total Cholesterol (n=22,106)	Ideal	1.9	0.8 (0.6, 1.1)	2.3	0.7 (0.4, 1.0)	1.6	0.7 (0.5, 1.2)
	Intermediate	1.8	0.8 (0.6, 1.0)	1.8	0.8 (0.5, 1.3)	1.8	0.8 (0.6, 1.3)
	Poor	2.1	Ref	2.5	Ref	1.8	Ref
Blood Pressure (n=22,864)	Ideal	0.9	0.4 (0.3,0.6)	1.1	0.4(0.2, 0.7)	0.8	0.5 (0.3, 0.8)
	Intermediate	1.8	0.7(0.6, 0.9)	1.8	0.6(0.4, 0.8)	1.9	0.9 (0.6, 1.3)
	Poor	2.8	Ref	3.2	Ref	2.4	Ref
Blood Glucose (n=22,551)	Ideal	1.6	0.6 (0.5, 0.9)	1.7	0.7 (0.4, 1.1)	1.5	0.6 (0.4, 1.0)
	Intermediate	2.3	0.9 (0.6, 1.2)	2.5	1.0 (0.6, 1.6)	2.2	0.8 (0.5, 1.4)
	Poor	2.5	Ref	2.4	Ref	2.6	Ref
Physical Activity (n=22,585)	Ideal	1.8	0.9 (0.7, 1.1)	1.8	0.8 (0.6,1.2)	1.8	0.9 (0.6, 1.3)
	Intermediate	1.8	0.9 (0.6, 1.1)	2.0	0.9 (0.7, 1.3)	1.6	0.9 (0.6, 1.2)
	Poor	2.0	Ref	2.2	Ref	1.9	Ref
Healthy Diet Score (n=16,829)	Ideal**			-		-	
	Intermediate	1.8	1.0 (0.7, 1.3)	2.2	1.1 (0.7,1.8)	1.5	0.9 (0.6, 1.3)
	Poor	1.9	Ref	2.0	Ref	1.7	Ref

Smoking (n=22,914)	Ideal	2.2	0.6 (0.5, 0.8)	2.9	0.3 (0.1, 1.2)	1.6	0.5 (0.4, 0.7)
	Intermediate	2.3	0.5 (0.2, 1.1)	1.9	0.7 (0.5, 1.0)	2.5	0.7 (0.3, 1.8)
	Poor	2.4	Ref	2.3	Ref	2.4	Ref
Body mass index (n=22,771)	Ideal	2.1	1.0 (0.8, 1.3)	2.2	1.1 (0.7,1.6)	1.9	1.0 (0.7, 1.4)
	Intermediate	1.9	1.1 (0.9, 1.4)	2.1	1.1(0.8,1.6)	1.7	1.1 (0.8, 1.6)
	Poor	2.0	Ref	2.3	Ref	1.9	Ref

*adjusted for age, gender, income, education, alcohol use, geographic region

**category had no data

† Incident rate per 10,000 person-years

Table 8: Incidence rate and adjusted hazard ratio (95% CI) of incident stroke for categories of overall CVHI score by race

	Overall (n=22, 914)		Blacks (n=9,553)		Whites (n=13,361)	
	IR†	HR* (95% CI)	IR	HR* (95% CI)	IR	HR* (95% CI)
Cardiovascular Health Categories						
Optimum	1.3	0.52 (0.35, 0.76)	1.6	0.63 (0.33, 1.22)	1.2	0.49 (0.29, 0.89)
Average	1.9	0.73 (0.55, 0.96)	1.9	0.76 (0.53, 1.10)	1.7	0.71 (0.46, 1.10)
Inadequate	2.4	1.0	2.4	1.0	2.2	1.0
P for Trend		≤0.001		0.22		0.04
CV Health Score Per Unit Increase		0.92 (0.88, 0.95)		0.93 (0.87, 0.98)		0.91 (0.86, 0.96)

*adjusted for age, sex, income, alcohol use, education, geographic region

† Incident rate per 10,000 person-years

Table 9: Adjusted hazard ratios for incident stroke associated with number of CVHI components

No. of Ideal Health Metrics	Overall		Blacks		Whites	
	Stroke (n)	HR* (95% CI)	Stroke (n)	HR (95% CI)	Stroke (n)	HR (95% CI)
0 (n=576)	16	Ref	8	Ref	8	Ref
1 (n=4465)	99	0.70 (0.42, 1.19)	56	0.86 (0.41, 1.81)	43	0.51 (0.24, 1.20)
2 (n=7249)	155	0.67 (0.40, 1.13)	74	0.81 (0.39, 1.69)	81	0.49 (0.24, 1.02)
3 (n=6105)	104	0.53 (0.31, 0.90)	43	0.66 (0.31, 1.41)	61	0.38 (0.18, 0.80)
4 (n=3187)	40	0.4 (0.23, 0.73)	15	0.58 (0.25, 1.38)	25	0.27 (0.12, 0.60)
5 (n=1117)	16	0.5 (0.25, 1.0)	3	0.51 (0.14, 1.96)	13	0.38 (0.16, 0.92)
6 (n=216)	2	0.34 (0.08, 1.52)	1	0.50 (0.56, 1.07)	1	0.15 (0.02, 1.19)

* adjusted for age, sex, socioeconomic, alcohol use, education, geographic region

Table 10: Baseline characteristics of 20, 567 REGARDS study participants and LS7 health categories

	Overall (%)	Cardiovascular Health Categories (n= 20,567)			
Characteristic		**Optimum n=3064**	**Average n=15273**	**Inadequate n=2230**	**P-value**
Age > 65 years %	45.3	14.3	75.8	9.9	<0.001
Female%	59.2	14.4	73.5	12.5	<0.001
African American Race %	39.2	7.3	76.6	16.2	<0.001
Income < $20,000k %	15.6	7.7	73.6	18.7	<0.001
Education < 12 years %	9.9	5.8	75.0	19.3	<0.001
Geographic Region Stroke Belt %	21.5	15.0	75.4	9.6	0.01
Alcohol consumption Current %	54.1	17.4	72.8	9.7	<0.001

Table 11: Family history of stroke for CVHI components of health factors among REGARDS participants

Health Factors (Poor vs Intermediate and Ideal)	Family History of Stroke (n=7702) OR (95% CI)	P-Value	Paternal History of Stroke (n=3141) OR (95% CI)	P-value	Maternal History of Stroke (n=3983) OR (95% CI)	P-value	Sibling History of Stroke (n=2180) OR (95% CI)	P-value
Total Cholesterol (n=19848)	1.08 (1.03, 1.15)	0.002	1.02 (0.95, 1.1)	0.55	1.1 (1.03, 1.2)	<0.01	1.07 (0.98, 1.17)	0.09
Blood Pressure (n=20504)	1.13 (1.07, 1.19)	<0.01	1.08 (1.0, 1.16)	0.04	1.01 (1.01, 1.16)	0.01	1.17 (1.07, 1.28)	<0.01
Blood Glucose (n=17387)	1.06 (0.99, 1.13)	0.07	1.01 (0.93, 1.10)	0.69	1.05 (0.97, 1.14)	0.16	1.105 (1.0, 1.2)	0.04

*adjusted for age, gender, race, income, education, alcohol use, geographic region

Table 12: Family history of stroke for CVHI components of health behaviors among REGARDS participants

Health Behaviors (Poor vs Intermediate and Ideal)	Family History of Stroke (n=7702) OR (95% CI)	P-value	Paternal History of Stroke (n=3141) OR (95% CI)	P-value	Maternal History of Stroke (n=3983) OR (95% CI)	P-value	Sibling History of Stroke (n=2180) OR (95% CI)	P-value
Physical Activity (n=15355)	0.95 (0.91, 1.07)	0.08	0.97 (0.9, 1.04)	0.50	0.94 (0.88, 1.01)	0.06	0.94 (0.86, 1.02)	0.16
Healthy Diet Score (n=16451)	0.89 (0.82, 0.96)	0.006	0.98 (0.88, 1.09)	0.79	0.85 (0.77, 0.93)	<0.01	0.97 (0.85, 1.1)	0.66
Smoking (n=20557)	0.92 (0.85, 0.99)	0.03	0.87 (0.78, 0.97)	0.01	0.98 (0.88, 1.08)	0.69	0.95 (0.84, 1.08)	0.49

Body Mass Index (n= 20426)	1.01 (0.94, 1.05)	0.90	0.98 (0.91, 1.05)	0.65	0.96 (0.9, 1.03)	0.28	1.09 (1.0, 1.19)	0.03

*adjusted for age, gender, race, income, education, alcohol use, geographic region

Table 13: Odds ratio (95% CI) for family history of stroke and CVHI overall categories by age-group

	Overall* **(n=20, 567)**		**Age < 65 years (n=11255)**		**Age ≥ 65 years (n=9312)**	
	Inadequate vs Optimum and Average	**P-value**	**Inadequate vs Optimum and Average**		**Inadequate vs Optimum and Average**	**P-value**
Family History of Stroke (n=7702)	1.00 (0.94, 1.07)	0.85	1.05 (0.95, 1.17)	0.28	0.88 (0.79, 0.97)	0.009
Paternal History of Stroke (n=3141)	0.99 (0.91, 1.08)	0.84	1.01 (0.90, 1.13	0.79	0.94 (0.82, 1.08)	0.41
Maternal History of Stroke (n=3983)	0.96 (0.89, 1.04)	0.42	1.09 (0.98, 1.21)	0.09	0.89 (1.80, 1.02)	0.09
Sibling History of Stroke (n=2180)	1.06 (1.01, 1.18)	0.01	1.18 (1.02, 1.38)	0.02	0.95 (0.83, 1.10)	0.55

* adjusted for age, sex, socioeconomic status, education and geographic region

Table 14: Distribution of covariates of Emory Twins Study participants (n=490) by cardiovascular health categories

	Cardiovascular Health Index Category			
	Optimum (CVHI= 10-14) N=94	**Average** (CVHI=5-9) N=380	**Inadequate** (CVHI=0-4) N=27	**P-value**
Age (years)	54.9	55.4	55.5	0.29
Systolic Blood Pressure mmHg)	121.6	131.4	140.0	<.001
Low Density Lipoprotein – Cholesterol	116.4	123.4	131.5	0.07
Body Mass Index (Kg/m2)	26.7	30.0	32.3	<0.001
Plasma glucose (mg/dl)	93.5	103.5	119.8	<0.001
Currently Employment (%)	95.7	82.4	62.9	<0.001
No. of alcoholic drinks/week	4.8	5.2	4.9	0.68
College education (%)	82.9	67.6	61.5	0.008
Current Smoking (%)	0	40	75	<0.001
Depression (%)	20.2	26.7	28.0	0.4
Meds- thiazide (%)	1.2	7.2	7.7	0.09
Meds- Beta blocker (%)	4.5	10.6	7.7	0.19
Meds- Aspirin (%)	18.7	75.8	5.4	0.08
Meds- Statin (%)	9.0	23.2	1.6	0.08
Meds- Anti-depressant (%)	1.2	3.5	0	0.3
Meds- Diabetes (%)	2.3	5.1	5.9	0.64

Table 15: Distribution of CVHI components in Emory Twins Study by CIMT categories (n=490)

CVHI Components	*Categories*	Low CIMT ≤ 0.75 n (%)	High CIMT > 0.75 n (%)	P-value	CIMT Continuous (Coefficient in mm)	P-value
Total Cholesterol (n=490)	*Ideal*	124 (47.5)	93 (40.6)	0.05	-0.003	0.62
	Intermediate	119 (45.6)	111 (48.5)			
	Poor	18 (6.9)	25 (10.9)			
Blood Pressure (n=490)	*Ideal*	51 (19.5)	32 (13.9)	0.04	-0.02	0.008
	Intermediate	133 (50.9)	113 (49.3)			
	Poor	77 (29.5)	84 (36.7)			
Blood Glucose (n=490)	*Ideal*	145 (55.6)	104 (45.4)	0.01	-0.02	0.02
	Intermediate	102 (39.1)	103 (44.9)			
	Poor	14 (5.4)	22 (9.6))			
Physical Activity (n=412)	*Ideal*	57 (25.7)	50 (26.3)	0.72	0.003	0.72
	Intermediate	135 (60.8)	109 (57.4)			
	Poor	30 (13.5)	31 (16.3)			
Healthy Diet Score (n=462)	*Ideal*	47 (19.1)	44 (20.4)	0.42	0.006	0.39
	Intermediate	127 (51.6)	117 (54.1)			
	Poor	72 (29.3)	55 (25.5)			

CVHI Components	***Categories***	**Low CIMT ≤ 0.75 n (%)**	**High CIMT > 0.75 n (%)**	**P-value**	**CIMT Continuous** (Coefficient in mm)	**P-value**
Smoking (n=490)	*Ideal*	202 (77.4)	165 (72.0)	0.22	-0.01	0.06
	Intermediate	1 (1.0)	2 (1.3)			
	Poor	59 (22.6)	61 (26.6)			
Body Mass Index (n=490)	*Ideal*	48 (18.4)	26 (11.3)	0.006	-0.024	0.007
	Intermediate	125 (47.9)	92 (40.2)			
	Poor	88 (33.7)	111 (48.5)			
Cardiovascular Health (n= 490)	*Optimum*	60 (23.0)	29 (12.6)	0.004	-0.03	0.0003
	Average	193 (73.9)	182 (79.5)			
	Inadequate	8 (3.1)	18 (7.8)			

Table 16: Unadjusted and adjusted association between CIMT (mean estimate and 95% CI) and overall CVHI and cardiovascular health categories (n=490).

	Overall CVHI Score	P-value	Cardiovascular Health Category Mean Estimate of CIMT (in mm)			P-value
			Optimum	Average	Inadequate	
Model- 1 (Unadjusted)	-0.009	0.0002	0.73 (0.71, 0.75)	0.75 (0.74, 0.77)	0.83 (0.78, 0.87)	0.0003
Model-2 (Adjusted for age, college education, employment)	-0.003	0.001	0.72 (0.69, 0.75)	0.74 (0.73, 0.76)	0.81 (0.79, 0.87)	0.0002
Model-3 (Further adjusted for, depression, medications)	-0.01	0.001	0.69 (0.64, 0.74)	0.71 (0.70, 0.77)	0.83 (0.77, 0.89)	0.0074

Table 17: Unadjusted and adjusted within pair differences in CIMT comparing MZ and DZ twin pairs discordant for cardiovascular health.

			Twins discordant for CVHI (n=394)			
	MZ+DZ		MZ (n=242)		DZ (n=152)	
	Mean est.	P-value	Mean est.	P-value	Mean est.	P-value
Model-1 (Unadjusted)	-0.009	0.0002	-0.01	0.0004	-0.006	0.18
Model-2 (Adjusted for age, college education, employment)	-0.008	0.0002	-0.01	0.0003	-0.005	0.26
Model-3 (Further adjusted for depression, medications)	-0.008	0.0001	-0.01	0.0002	-0.008	0.11

Figure 8: Distribution of CVHI components among REGARDS participants (Overall)

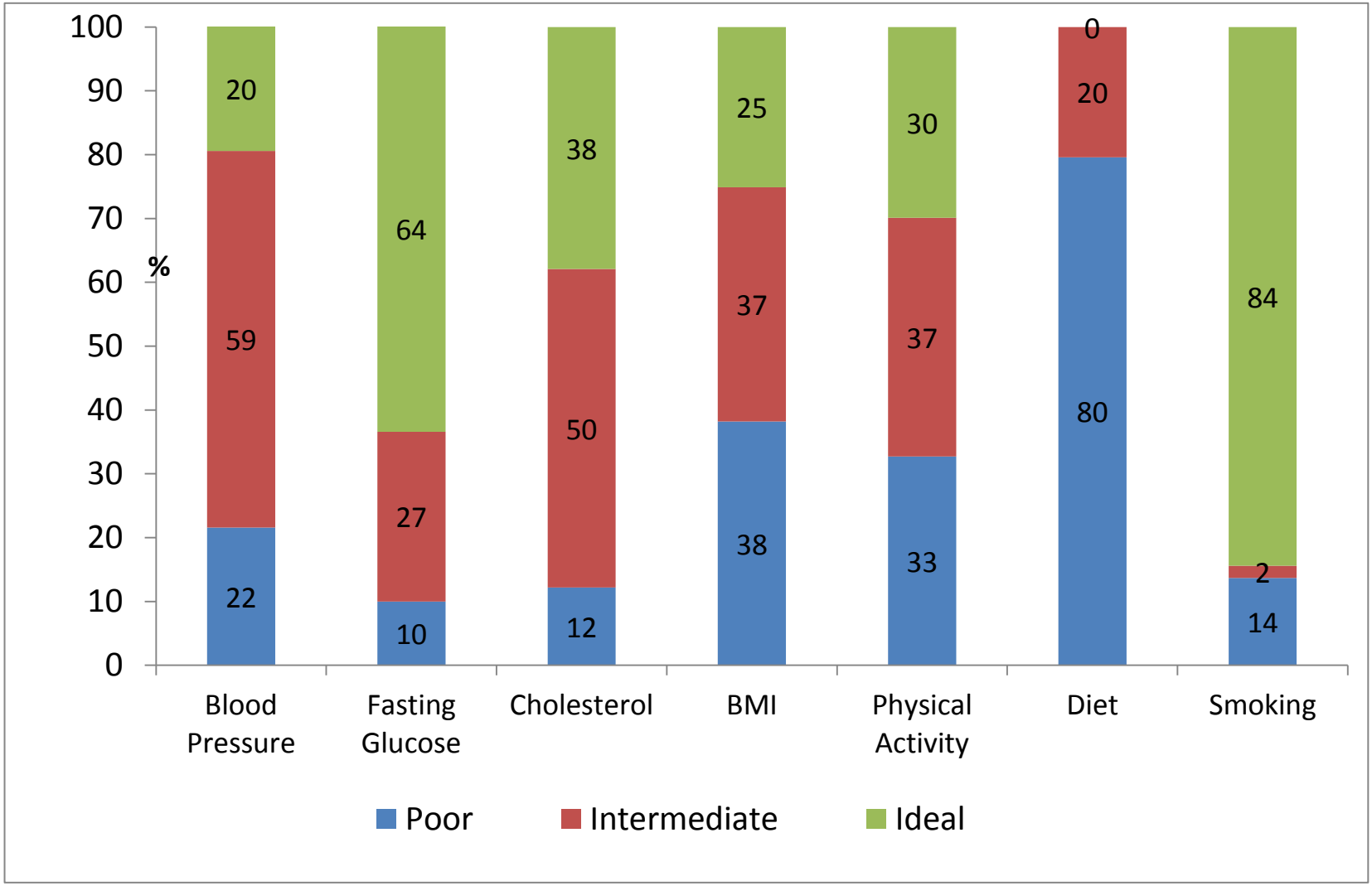


Figure 9: Distribution of the number of ideal health factors in the REGARDS cohort by race and gender

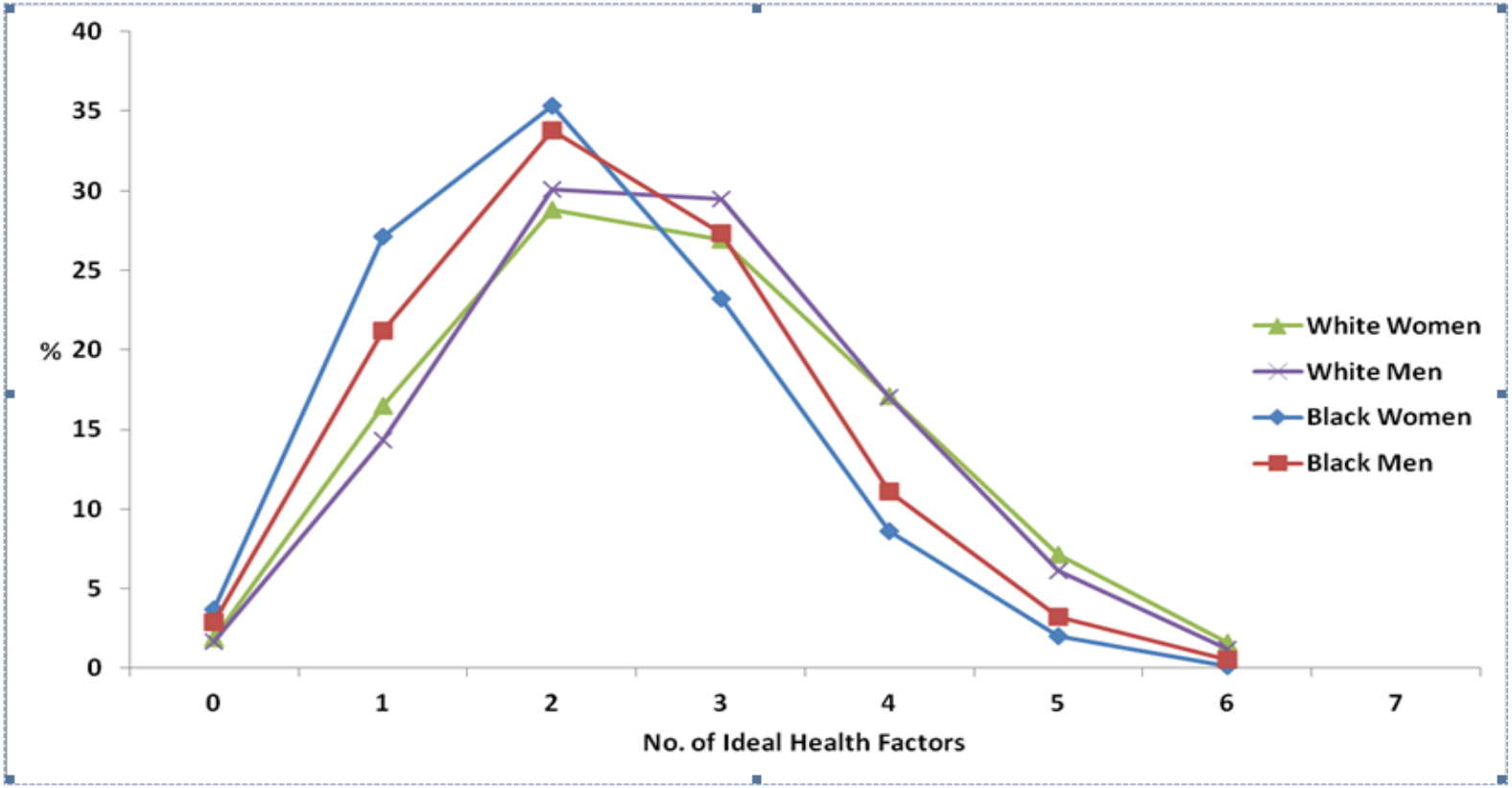


Figure 10: Survival free from stroke by cardiovascular health categories

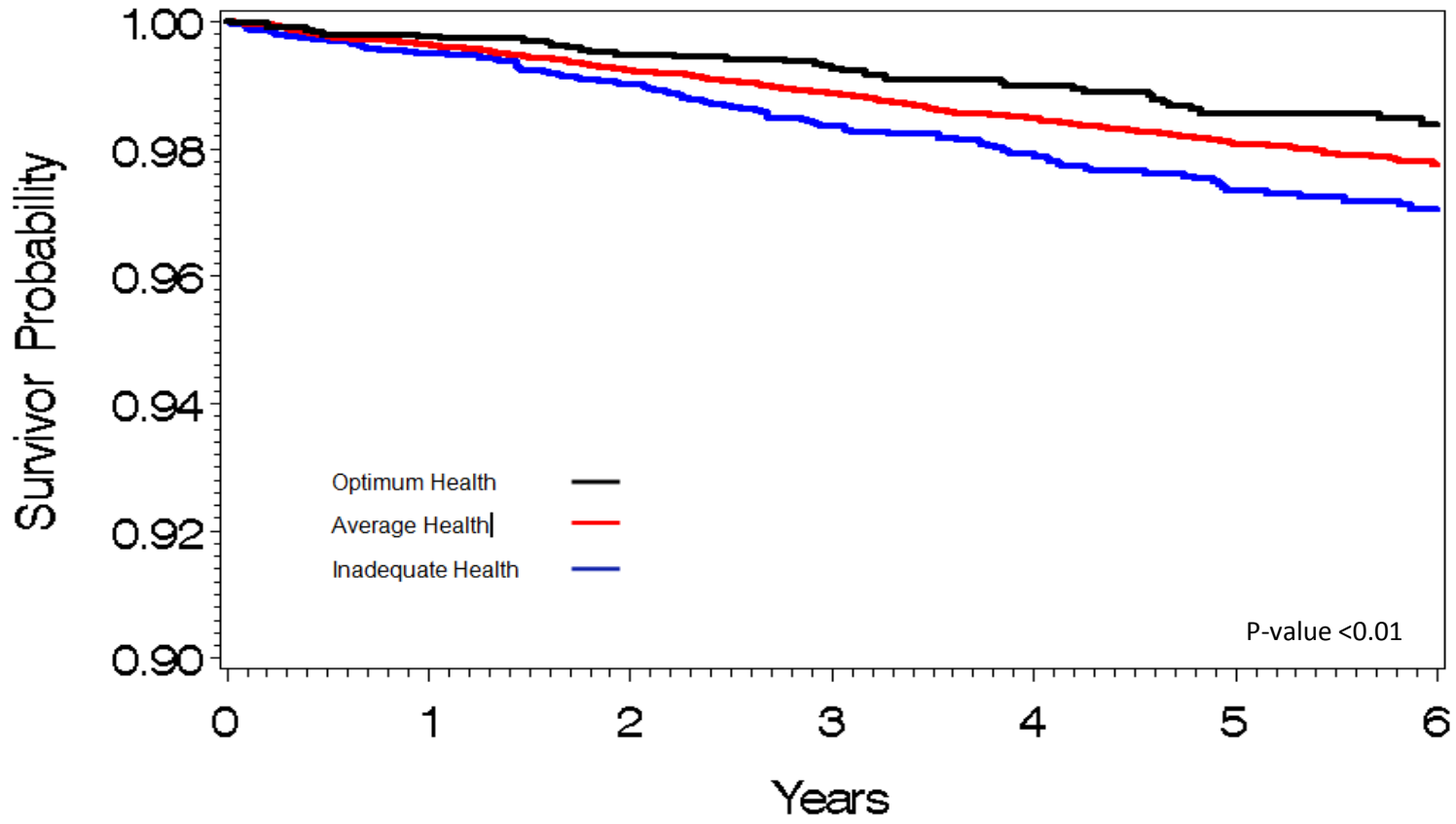


Figure 11: Cardiovascular health profile of Emory Twins Study participants (n=490)

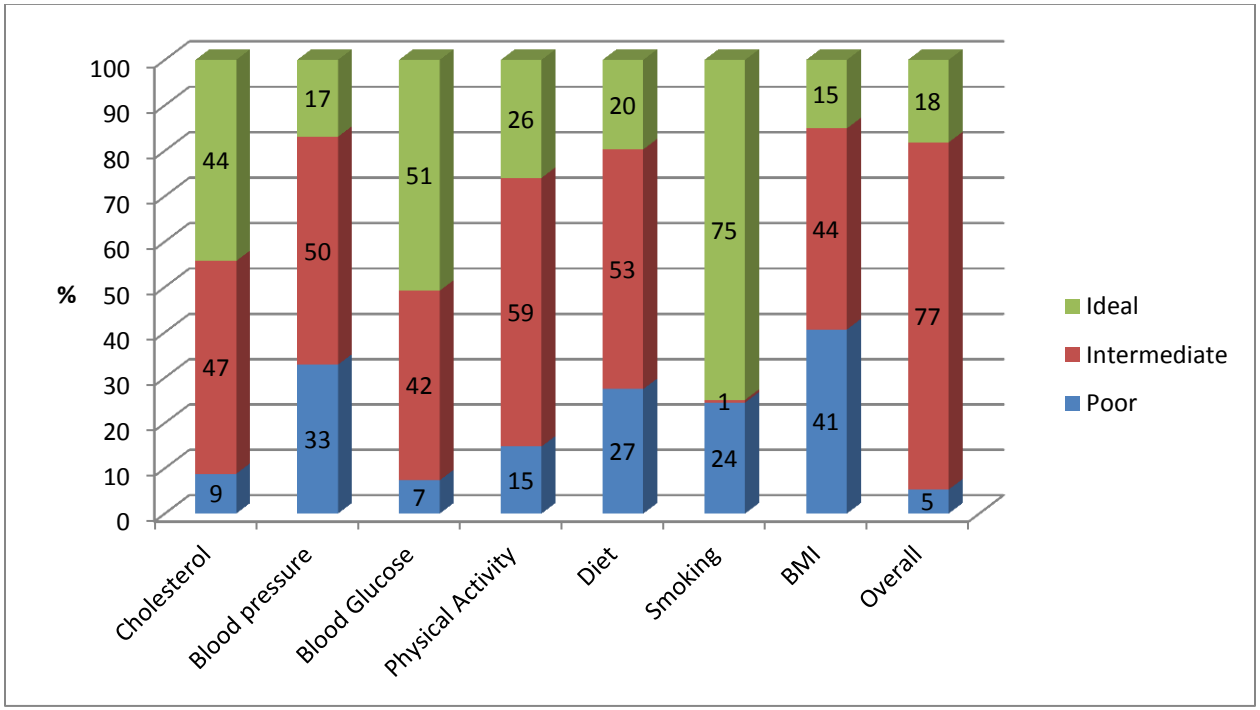


Figure 12: Correlation between CVHI and CIMT

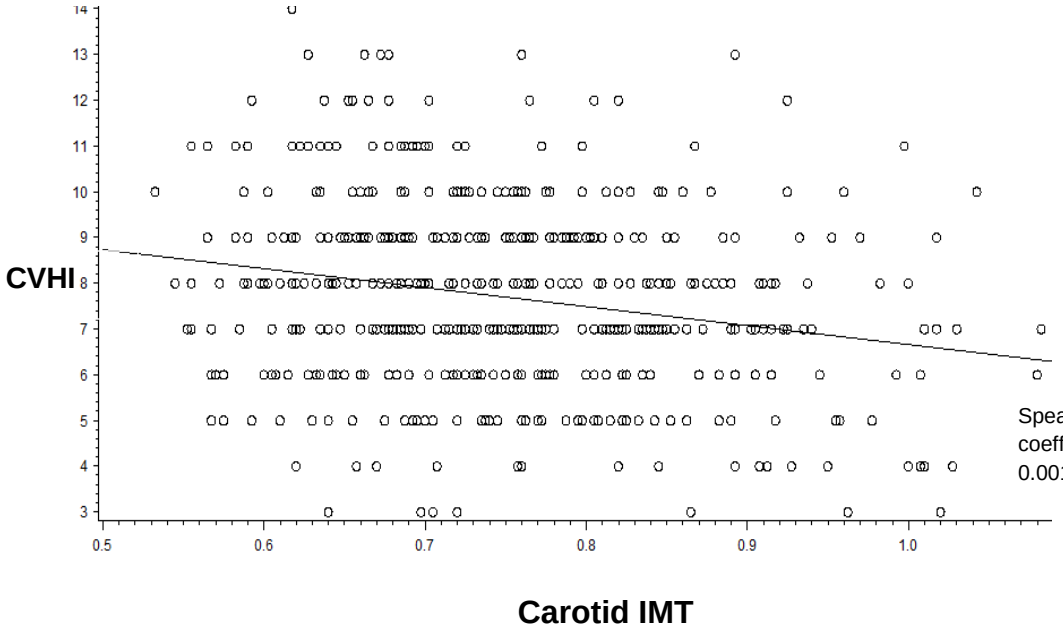
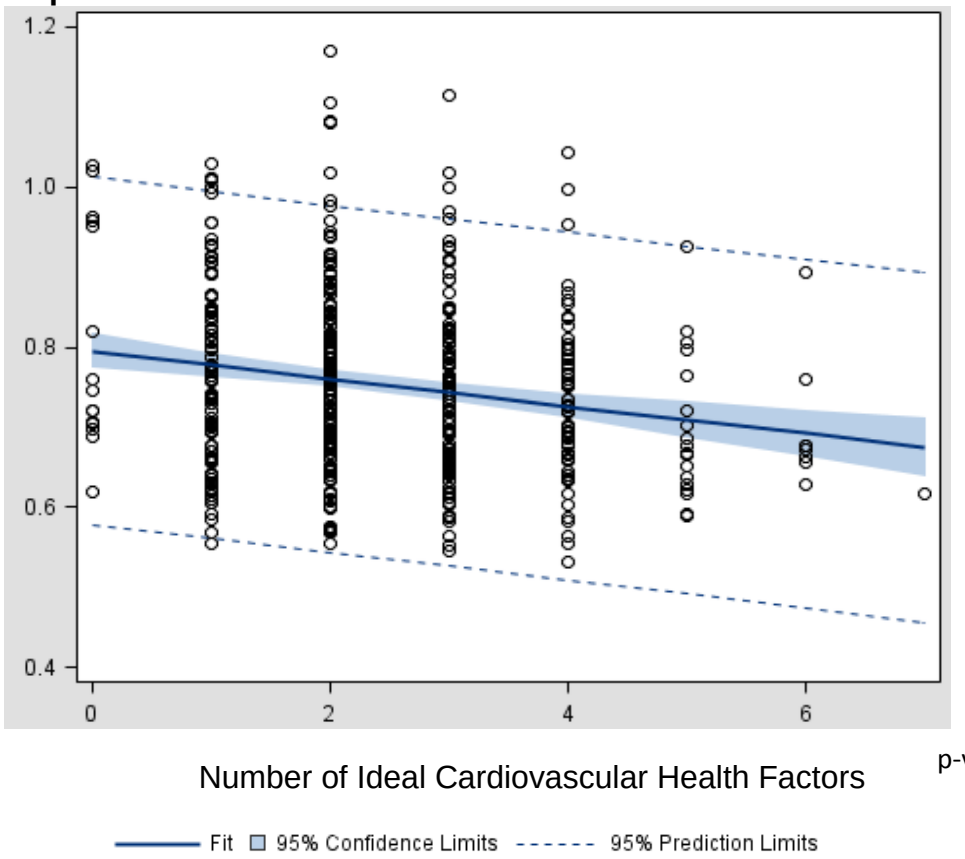


Figure 13: Bar plot of number of ideal health factors and behaviors and CIMT



p-value <0.001

APPENDIX TABLE

Health Metric	Levels	Score	Definition
Total cholesterol	Ideal	2	<200 mg/dl, without lipid lowering medication
	Intermediate	1	200-239 mg/dl or treated to <200 mg/dl
	Poor	0	≥240 mg/dl
Blood pressure	Ideal	2	<120/<80 mm Hg, without antihypertensive medication
	Intermediate	1	SBP 120–139 or DBP 80–89 mm Hg or treated with antihypertensive to <120/<80 mm Hg
	Poor	0	SBP ≥140 or DBP ≥90 mm Hg
Blood glucose	Ideal	2	<100 mg/dl, without antidiabetes medication
	Intermediate	1	100–125 mg/dl or treated with antidiabetes to <100 mg/dl
	Poor	0	≥126 mg/dl
Physical activity*	Ideal	2	4 or more times per week of intense physical activity
	Intermediate	1	1-3 times per week of intense physical activity
	Poor	0	No physical activity
Healthy diet score†	Ideal	2	4–5 components

	Intermediate	1	2–3 components
	Poor	0	0–1 components
Smoking	Ideal	2	Never or quit >12 months
	Intermediate	1	Former, quit ≤12 months
	Poor	0	Current
Body mass index	Ideal	2	<25 kg/m^2
	Intermediate	1	25–29.99 kg/m^2
	Poor	0	≥30 kg/m^2

* modified for REGARDS. Participants in REGARDS were asked "How many times per week do you engage in intense physical activity, enough to work up a sweat?" We defined ideal physical activity as a frequency of 4 or more times per week, intermediate as 1-3 times per week, and poor as none.

†modified for REGARDS. Responses to the Block FFQ were used for the 'healthy diet score' that is based on how many components of the 5 diet goals are met. Fruits and vegetables ≥ 4.5 cups/day; Fish 3.5 ounces ≥ 2 servings/week; Sodium <1500 mg/day; Sweets/sugar-sweetened beverages ≤ 450 kcal/week; Whole grains (1.1g of fiber in 10 gms of carbohydrates), 1-oz equivalent servings ≥ 3 servings/day.