Alcohol and Cardiovascular Disease

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ABSTRACT

Louise M. Henderson: Alcohol and Cardiovascular Disease
(Under the direction of Wayne D. Rosamond, PhD)

The relationship between alcohol consumption and three cardiovascular diseases (ischemic stroke, hemorrhagic stroke, and heart failure) was examined in a population sample of middle-aged U.S. adults who were participants in the Atherosclerosis Risk in Communities (ARIC) cohort. Alcohol intake was self-reported at two time periods. Stroke events were ascertained by contacting study participants and reviewing hospitalization and death certificate data. Heart failure (HF) events were identified from hospital discharge diagnoses and death certificates.

To assess the association between alcohol consumption and each cardiovascular disease outcome separately, age-adjusted incidence rates by level of alcohol intake were calculated. Alcohol intake was categorized based on American Heart Association guidelines. Poisson regression was used to estimate incidence rate ratios (RRs) comparing levels of alcohol intake with never drinkers. Results were stratified by race.

The crude RRs for all stroke showed an inverse association for occasional drinkers (RR=0.57, 95%CI:0.42-0.77) and light/moderate drinkers (RR=0.74, 95%CI:0.59-0.94) as compared with never drinkers. After adjustment for age, race, sex, and socioeconomic status the RRs were attenuated (comparing occasional with never drinkers RR=0.91, 95%CI:0.67-1.25 and light/moderate with never drinkers

(RR=0.99, 95%CI:0.77-1.28). Results for ischemic stroke were similar to those for all stroke. The crude RRs for hemorrhagic stroke were 1.16 (95%CI:0.51-2.63) for former drinkers, 1.13 (95%CI:0.48-2.69) for occasional drinkers, 0.74 (95%CI:0.32-1.71) for light/moderate drinkers, and 1.67 (95%CI:0.66-4.25) for heavy drinkers, as compared with never drinkers. Adjustment for age, race, sex, and socioeconomic status resulted in an increase in RRs. The RRs comparing each level of alcohol intake with never drinkers for HF incidence were 1.12 (95%CI:0.95-1.31) for former drinkers, 0.67 (95%CI:0.54-0.82) for occasional drinkers, 0.65 (95%CI:0.54-0.78) for light/moderate drinkers, and 0.75 (95%CI:0.59-0.95) for heavy drinkers. Similar patterns were seen for blacks and whites.

We found no compelling evidence that occasional or light/moderate alcohol intake reduces stroke incidence rates. Adjusted RRs suggest that any level of alcohol intake increases hemorrhagic stroke incidence rates. We found a positive association for former drinking and an inverse association for current drinking for HF incidence. While the association between former drinkers and HF incidence was evident for whites, the evidence among blacks was less strong.

DEDICATION

For Jonathan, Fiona, Cadbury, and Sasha

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LIST OF ABBREVIATIONS

AA	Age adjusted
AHA	American Heart Association
ARIC	Atherosclerosis Risk in Communities
BAL	Blood alcohol level
BMI	Body mass index
BP	Blood pressure
BRFSS	Behavioral Risk Factor Surveillance System
CAD	Coronary artery disease
CDT	Carbohydrate-deficient transferrin
CHD	Coronary heart disease
CHF	Congestive heart failure
CI	Confidence interval
CVD	Cardiovascular disease
DAG	Directed acyclic graph
DBP	Diastolic blood pressure
DR	Diet records
ECG	Electrocardiogram
EPESE	Establishment Populations for the Epidemiologic Study of the Elderly Program
FFQ	Food frequency questionnaire
FHS	Framingham Heart Study
GF	Graduated frequency

GGT	gamma-glutamyl transferase
HBP	High blood pressure
HDL	High-density lipoprotein
HF	Heart failure
HS	High school
ICD-9-CM	International Classification of Diseases, 9th revision, Clinical Modification
ICH	Intracranial hemorrhage
IR	Incidence rate
IS	Ischemic stroke
LDL	Low density lipoprotein
LVH	Left ventricular hypertrophy
MCV	mean corpuscular volume
MI	Myocardial infarction
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart Lung and Blood Institute
NHIS	National Health Interview Survey
NSA	National Stroke Association
PND	Paroxysmal nocturnal dyspnea
P-Y	Person year
QF	Quantity frequency
RCT	Randomized controlled trial
RR	Rate ratio

SAH	Subarachnoid hemorrhage
SBP	Systolic blood pressure
SOLVD	Studies of Left Ventricular Dysfunction
TIA	Transient ischemic attack
USDA	United States Department of Agriculture
USDHHS	United States Department of Health and Human Services
WD	Weekly drinking

CHAPTER 1
STATEMENT OF HYPOTHESES

1.1 Study Objective

The primary objective of the proposed research is to better understand the role of alcohol consumption on the development of cardiovascular diseases, in particular stroke and heart failure, among African-American and white men and women of middle-age in the U.S.

1.2 Specific Aims and Hypotheses

Specific Aim 1: Examine the association between alcohol consumption and stroke incidence among African-American and white men and women ages 45-64 years at baseline (the ARIC study participants) during an average follow-up of 11 years.

Hypothesis 1: The association between alcohol intake and ischemic stroke incidence varies according to the level of alcohol consumed. Using never drinkers as the referent group, there is an inverse association between alcohol intake and ischemic stroke incidence among light to moderate drinkers and there is a positive association between heavy consumption and ischemic stroke incidence.

Hypothesis 2: There is a positive association between alcohol intake and hemorrhagic stroke incidence. Compared with those who do not drink

alcohol, those consuming light to moderate amounts will have increased rates of hemorrhagic stroke and those consuming heavy amounts will have even higher hemorrhagic stroke rates.

Hypothesis 3: The alcohol and stroke relations found in hypotheses 1 and 2 above do not differ by race.

Specific Aim 2: Describe and evaluate the association between alcohol consumption and heart failure (HF) incidence among African-American and white men and women ages 45-64 years at baseline (the ARIC study participants) during an average follow-up of 11 years.

Hypothesis 1: Compared with never drinkers, there is an inverse association between alcohol intake and HF incidence among those who consume light to moderate amounts of alcohol and there is a positive association for those who consume heavy amounts of alcohol.

Hypothesis 2: The association between alcohol intake and HF incidence does not differ by race.

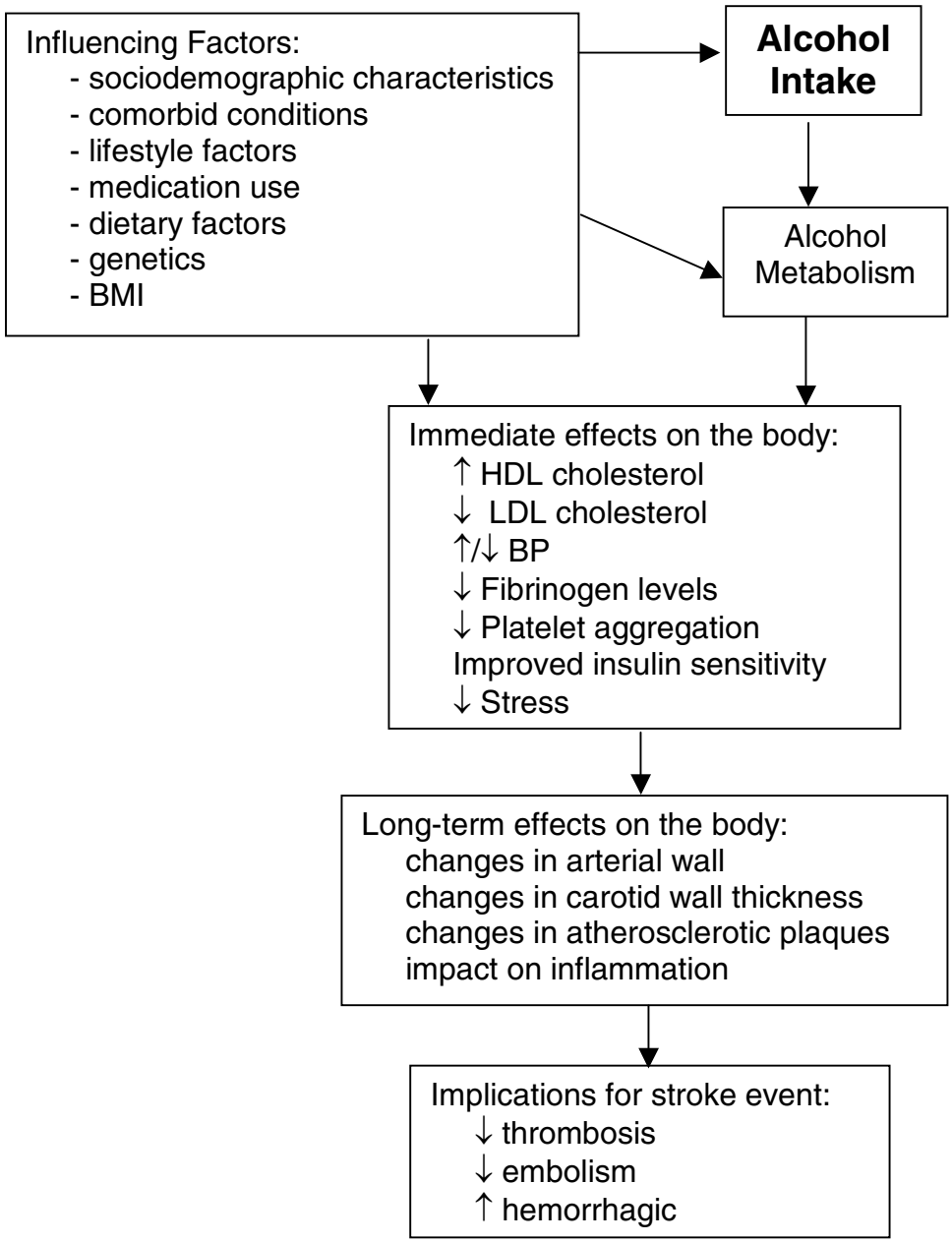
1.3 Rationale

Previous studies have shown light to moderate alcohol consumption to be cardio-protective, with national guidelines and recommendations supporting the consumption of one to two alcoholic drinks per day among those who drink (1, 2). Although the benefits of light to moderate alcohol intake on the cardiovascular system have been well established for reducing the risk of coronary heart disease and myocardial infarction, the impact of alcohol consumption on other cardiovascular diseases is less well understood. Given the heterogeneity of cardiovascular disease

and the numerous pathways through which alcohol may afect the cardiovascular system, an in-depth look at how alcohol consumption is associated with individual cardiovascular diseases is warranted.

The role that alcohol plays within the cardiovascular system is complex, probably involving multiple factors acting together to create potentially beneficial or harmful effects. The relationship between light to moderate alcohol consumption and stroke incidence, for example, has been previously studied and is thought to be protective against ischemic stroke but detrimental for hemorrhagic stroke (Figure 1.1). However (as detailed below), the findings are inconsistent and more diverse populations need to be studied. As another example, the harmful effects of chronic heavy alcohol use on the development of heart failure (termed alcoholic cardiomyopathy) are well documented, but the extent to which light to moderate alcohol intake may be beneficial in preventing HF from other etiologies (for example ischemic cardiomyopathy) remains unclear (Figure 1.2). The few studies that have examined the relationship between HF and moderate alcohol intake focused on white populations in the northeastern portion of the U.S., leaving a gap in the current literature. The proposed research is needed to support the recommendations that light to moderate intake is protective of cardiovascular disease, especially in the areas of stroke and HF.

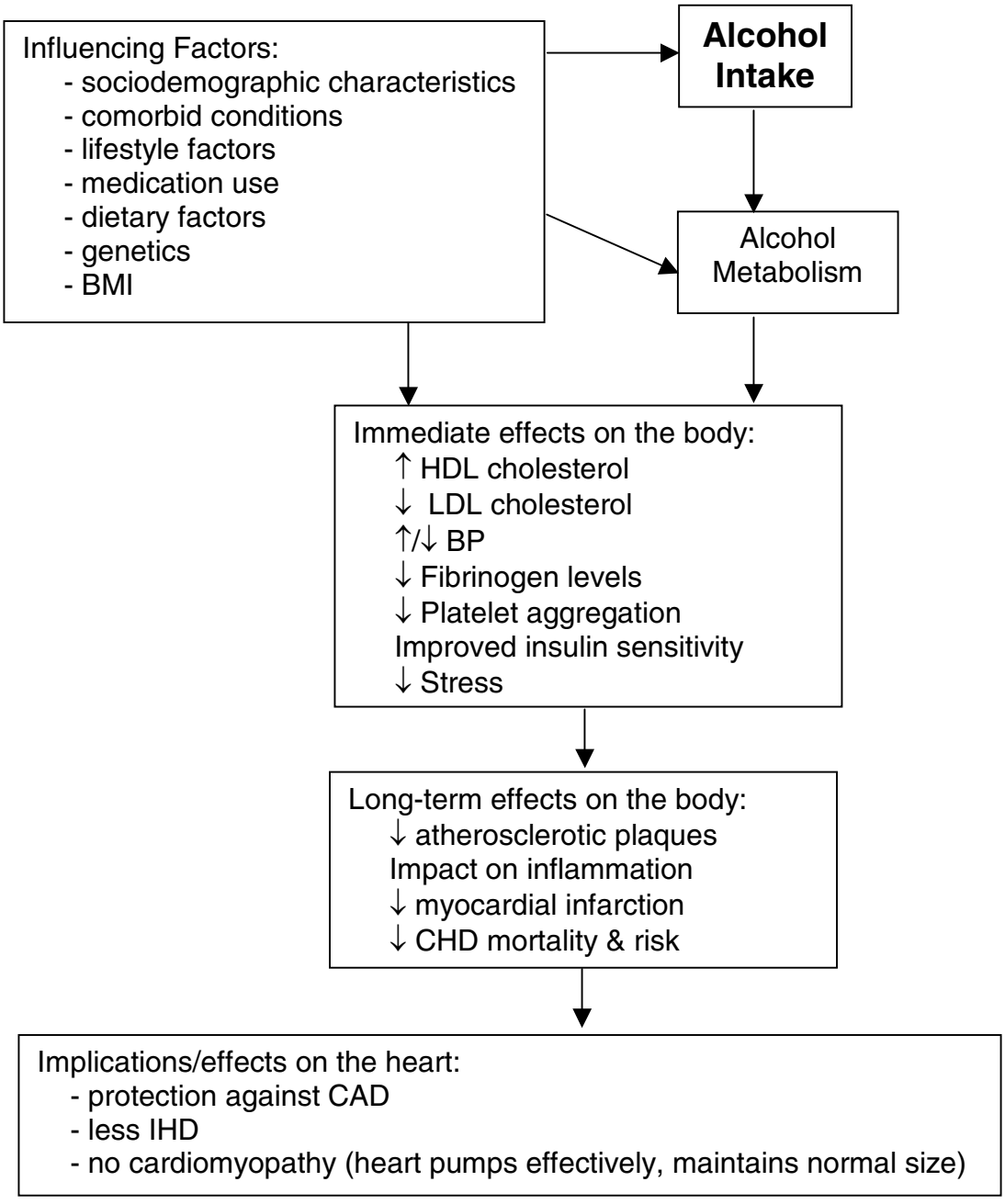
Figure 1.1: Theoretical Framework for Light/Moderate Alcohol Consumption and Stroke Incidence



Legend: The effect of alcohol intake on the body is a complex process with many factors influencing alcohol intake, alcohol metabolism, and other biologic responses. Alcohol leads to immediate and long-term effects on the body, some of which are beneficial (increased HDL cholesterol, decreased LDL cholesterol, and decreased stress) and some of which are harmful (increased blood pressure) to the cardiovascular system. Atherosclerotic plaques may decrease in size and become less likely to rupture. In contrast, the increased blood pressure may result in increased risk of bleeding and thus hemorrhagic stroke.

* Sociodemographic characteristics include age, race, gender, and socioeconomic status; Dietary factors include intake of cholesterol, saturated fat, and antioxidants; Lifestyle factors include smoking, stress, physical activity; Comorbid conditions include diabetes, hypertension, and previous myocardial infarction.

Figure 1.2: Theoretical Framework for Light/Moderate Alcohol Consumption and Heart Failure Hospitalization



Legend: The effect of alcohol intake on the body is a complex process with many factors influencing alcohol intake, alcohol metabolism, and other biologic responses. Alcohol leads to immediate and long-term effects on the body, some of which are beneficial (increased HDL cholesterol, decreased LDL cholesterol, and decreased stress) and some of which are harmful (increased blood pressure) to the cardiovascular system. Light to moderate intake may reduce the rates of coronary heart disease and lessen the risk of myocardial infarction. These changes are beneficial and thought to protect against the development of heart disease, decreasing the incidence of heart failure.

* Sociodemographic characteristics include age, race, gender, and socioeconomic status; Dietary factors include intake of cholesterol, saturated fat, and antioxidants; Lifestyle factors include smoking, stress, physical activity; Comorbid conditions include diabetes, hypertension, and previous myocardial infarction.

1.4 References

1. Pearson TA, Blair SN, Daniels SR, et al. AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update: Consensus Panel Guide to Comprehensive Risk Reduction for Adult Patients Without Coronary or Other Atherosclerotic Vascular Diseases. American Heart Association Science Advisory and Coordinating Committee. Circulation 2002;106:388-91.

2. Goldstein LB, Adams R, Becker K, et al. Primary prevention of ischemic stroke: A statement for healthcare professionals from the Stroke Council of the American Heart Association. Stroke 2001;32:280-99.

CHAPTER 2
BACKGROUND

2.1 Introduction

The burden of cardiovascular diseases in the U.S. is staggering. An estimated 62 million U.S. adults have some type of cardiovascular disease and during 2000, cardiovascular diseases accounted for 950,000 deaths (1). The National Heart Lung and Blood Institute (NHLBI) estimates the cost of cardiovascular diseases (including stroke) during 2003 will be $351.8 billion. The term cardiovascular diseases is heterogeneous and encompasses diseases of the heart and the arterial circulation supplying the heart, brain and peripheral tissues(2). The most common cardiovascular diseases are high blood pressure (HBP), coronary heart disease (CHD), congestive heart failure (CHF), and stroke (Table 2.1).

Established risk factors for cardiovascular disease include smoking, high blood cholesterol, hypertension, physical inactivity, overweight/obesity, and diabetes(1). In a study which combined data from the Multiple Risk Factor Intervention Trial (MRFIT) and the Chicago Heart Association Detection Project in Industry (CHA), researchers compared cardiovascular disease mortality rates of those with a favorable risk profile (cholesterol <200mg/dl, SBP/DBP of 120/80mmHg, and not a current smoker) to others who did not have a low-risk profile (i.e. they had elevated cholesterol, elevated BP, or were a current smoker).

The researchers found cardiovascular disease mortality was 72 85% lower among those non-smokers with normal blood pressure and normal serum cholesterol levels(3).

In addition to the established (traditional) cardiovascular disease risk factors, emerging risk factors have been identified (Table 2.2) (2, 4, 5). For example, light to moderate alcohol consumption has been proposed to play a beneficial role in the prevention of cardiovascular disease, in particular in the reduction of CHD risk and mortality. The findings of several prospective cohort studies indicate a positive, strong, consistent, dose-response relation between moderate alcohol consumption and decreased CHD incidence(6-8). In contrast, epidemiology studies examining the relation between alcohol consumption and stroke or alcohol consumption and CHF, two of the leading causes of death and hospitalization in the U.S., are less consistent and warrant further research.

Although the role of alcohol consumption on cardiovascular disease incidence and mortality has been explored, most studies focused specifically on CHD or the endpoint of all cardiovascular diseases combined. Since the biologic mechanisms through which alcohol impacts disease occurrence is likely to vary from disease to disease, examination of specific cardiovascular diseases, such as CHF, systemic hypertension, or stroke will lead to a more detailed and comprehensive understanding of the role of alcohol on the cardiovascular system. The proposed dissertation work will explore the relationship of alcohol and three cardiovascular diseases, namely hemorrhagic stroke, ischemic stroke, and CHF.

2.2 Stroke

2.2.1 Definition and Pathophysiology

While cerebrovascular diseases typically have an abrupt onset with loss of neurologic function due to an acute interruption of the blood supply to the brain, the underlying disease process of atherosclerosis usually begins in early adulthood(9). Over time atherosclerosis, thought to be caused by inflammation, weakens the arterial wall with lesions protruding into the lumen resulting in restricted or obstructed blood flow or possibly rupturing of the plaque(10). Atherosclerotic plaques occur in large and medium sized vessels of the arterial tree and thus may affect multiple areas of the circulation, including the heart, brain, or aorta(2). Damage to the atherosclerotic plaques is a precursor of ischemic stroke(11) and hence the major etiology of strokes is attributed to atherosclerosis(9).

Since 1975, a loss of functioning lasting less than 24 hours with subsequent return of normal functioning has been termed a transient ischemic attack (TIA). If loss of function remains for more than 24 hours, the event is termed a stroke(12, 13). Recently, a new definition for TIA has been proposed which focuses on if an injury to the brain has occurred rather than on the amount of time until normal functioning returns (14, 15). The proposed TIA definition change has caused debate over the practicality of implementing the new definition (in terms of available imaging resources) and the possibility of using a shorter time period from symptom onset to resolution (one hour instead of 24 hours) (16-18).

Strokes can be classified into two broad groups: ischemic and hemorrhagic (Figure 2.1). Ischemic strokes are caused by an obstruction of a major artery either

by local blood clot formation (thrombosis) or lodging of a clot from elsewhere in the body (embolism)(2). Within this category, the major disease subsets include large artery stenosis occlusion, lacunar infarction, embolisms attributed to cardiac sources, and those with an undetermined cause(19, 20). Large artery stenosis occlusions occur when atherosclerotic narrowing of the major arteries causes an acute occlusion. Lacunar infarctions, thought to account for approximately 15-20% of all strokes, refer to small, deep infarcts which occur in the basal ganglia(19). Cardioembolisms, which occur when a thrombus develops in the heart and lodges in the brain, are usually the result of atrial fibrillation, mural thrombus, dilated cardiomyopathy, valvular disease, or ventricular akinesis following myocardial infarction.(20) Although classification of ischemic strokes into subtypes has improved with the use of CT scans, MRI, and angiography, the exact mechanism of cerebral infarction is often unknown(19).

In contrast to ischemic strokes, those termed hemorrhagic strokes are the result of ruptured blood vessels in the brain and are subdivided into intracranial hemorrhages (ICH) and subarachnoid hemorrhages (SAH) based on the location of the bleeding. ICH occur in the deep portions of the cerebral hemispheres such as the putamen or cerebellum(21). Hypertension and cigarette smoking are important risk factors for ICH and hypertension may play a causative role in the development of ICH(21). SAH results from bleeding into the subarachnoid space surrounding the brain, usually caused by an aneurysm (balloon like swelling in an artery wall) in the circle of Willis(20). Risk factors for SAH are similar to those for ICH, including hypertension and cigarette smoking.

2.2.2 Epidemiology of Stroke in the U.S.

Stroke ranks as the third leading cause of death in the U.S. with an estimated 700,000 new or recurrent strokes each year(1). Stroke incidence rates are higher for males than females, are higher for African-Americans compared with whites (Table 2.3)(1, 22) and increase with age. Similarly, disparities in stroke mortality rates exist with African Americans experiencing higher death rates than whites (23, 24). In 1998, the age-adjusted stroke mortality rate among those ages 35 and older was 156 per 100,000 for African-Americans, and 113 per 100,000 for whites (23). Intriguingly, stroke mortality rates appear to vary by geographic region, with increased rates in the southeastern portion of the country, although the patterns appear to be shifting westward(23-26). Despite the decline of stroke mortality rates during the 20th century(2, 24), stroke continues to be a leading cause of death and disability. In 1999, an estimated 1.1 million Americans reported functional limitations and difficulties carrying out everyday activities as a result of suffering a stroke(27).

Risk factors for stroke include high blood pressure, diabetes, existing/prior cardiovascular conditions, atrial fibrillation, older age, lower educational attainment, physical inactivity, obesity, and smoking(1, 2, 4). While many of the risk factors for stroke are similar to those for CHD, not all of the risk factors apply to both disease processes. A meta-analysis of 45 cohort studies examining the relation of blood cholesterol and blood pressure to stroke risk (predominately deaths) found total cholesterol was not predictive of stroke outcomes but that higher diastolic blood pressure was predictive, especially among those at younger ages(28). Additionally,

data from the Atherosclerosis Risk in Communities (ARIC) cohort study found that increased blood cholesterol levels, which are known to be associated with CHD, were not associated with increased stroke risk(29). In contrast to the findings of no association between blood cholesterol levels and stroke risk, results from a meta-analysis of 13 randomized placebo-controlled double blind trials reported a reduction in stroke risk (but not in fatal stroke occurrence) among those receiving lipid lowering drugs (statins) compared to those in the placebo group (30).

2.3 Congestive Heart Failure

2.3.1 Definition and Pathophysiology

CHF is the inability of the heart to pump blood effectively from the left ventricle throughout the body, resulting in reduced blood flow to the aorta and to the peripheral arterial circulation(2). The initiation of CHF begins when an index event (such as a myocardial infarction) either damages the heart muscle or disrupts the myocardium from being able to generate force(31). Once the event has occurred, the heart pumps less effectively, impairing the ability of the left ventricle to fill with blood or to eject blood(32). In an attempt to make up for the decreased pumping capacity, the heart enlarges, develops more muscle mass, and pumps faster (33). "Chronic CHF either reflects its persistence following an acute onset and partial recovery or indicates gradual ventricular decomposition occurring over weeks, months or years"(2), p.106. Symptoms of heart failure include shortness of breath (dyspnea), persistent coughing or wheezing, edema, fatigue, loss of appetite or

nausea, confusion, and increased heart rate (34). The New York Heart Association developed a classification scheme for CHF based on patient symptoms: class I (~ 35% of patients) consists of those with no symptoms and no limitations in physical activity; class II (~ 35% of patients) consists of those with mild symptoms and slight limitations during ordinary activity; class III (~ 25% of patients) consists of those with marked limitations in activity due to symptoms and comfortable only at rest; and class IV (~ 5% of patients) consists of those with severe limitations who experience symptoms while at rest(35). The symptoms mentioned above (dyspnea, edema, fatigue) comprise a syndrome which is referred to as CHF.

CHF is identified using several diagnostic tests, including electrocardiogram (ECG), echocardiography, or radionuclide ventriculography/ multiple-gated acquisition scanning. Causes of CHF can be classified into several groups based on pathophysiology, including dilated, hypertrophic, restrictive, and valvular(36). Dilated cardiomyopathy is often caused by ischemic heart disease, aortic regurgitation, toxins (such as alcohol), or viral infections of the heart. Hypertrophic cardiomyopathy is usually a result of hypertension, aortic stenosis, or genetic disorders of the cardiac muscle. Aortic regurgitation may result in increased left ventricular size through dilation and hypertrophy. Restrictive cardiomyopathy can result from amyloidosis or pericarditis (i.e. cardiac tamponade and chronic constrictive pericardial disease)(36). Thus, it is evident that CHF is a heterogeneous entity with many different possible causes.

In the United States, CHF is usually a consequence of coronary heart disease, hypertension, or myocardial infarction(2, 37). Based on data from the

Framingham Heart Study, 7% of women and 19% of men who developed CHF had coronary heart disease alone, 40% had hypertension alone, and the remaining had both CHD and hypertension(38). Population attributable risk estimates indicate that hypertension accounts for 39% and 59% of the CHF burden in men and women, respectively and that MI accounts for 34% and 13% of the CHF burden in men and women, respectively(39). While treatment can improve function and prolong life, progressive decompensation and complications lead to a high mortality rate(2). Thus, the most cost-effective approach is to focus on modifiable risk factors, including the reduction of hypertension, dyslipidemia, obesity, and smoking(40).

The Framingham Study, the first prospective population-based study designed to investigate the epidemiology of cardiovascular disease in the U.S., has monitored cohort members through active surveillance for the development of CHF(41). Based on Framingham Study data from clinic examinations and hospital records, criteria for identifying cases of CHF were established (Table 2.4)(42) (38). According to these criteria, to be classified as a CHF case two major and one minor or one major and two minor criteria must be present. The use of these criteria is based on clinical criteria that have been validated(38) (43).

2.3.2 Epidemiology of Congestive Heart Failure in the U.S.

Over the past two decades, CHF incidence and mortality rates have been increasing. It is estimated that almost 5 million U.S. adults ages 20 and older suffer from CHF, with 550,000 new cases each year and 51,000 deaths. The number of hospital discharges for CHF increased by over 260% from 377,000 in 1979 to

999,000 in 2000 and in 1998 approximately $3.6 billion was paid for CHF hospitalizations among those ages 65 and older(1). Clearly, CHF hospitalizations impact the health care system and the growing costs associated with health care as the population continues to age.

Few epidemiologic studies have been designed to study the prevalence, incidence, and long-term prognosis of CHF, probably due to the fact that heart failure is difficult to study(2). Since heart failure develops gradually it is difficult to know at what point to label CHF a disease and thus it is often thought of more as a constellation of symptoms. Also, heart failure often develops after the occurrence of other conditions such as a myocardial infarction or the development of CHD, leading to difficulties in the identification of CHF in hospital and mortality statistics. CHF that is mild may not require hospitalization and since CHF symptoms are nonspecific, diagnosis can be difficult(2). Adding to the difficulty, co-morbid conditions such as emphysema have similar symptoms.

Despite the challenges of studying CHF, the Framingham Heart Study provides national estimates of CHF prevalence and mortality in a cohort of white U.S. adults living in the northeastern portion of the country. For white men, the prevalence of heart failure increased from 8 per 1000 among those 50-59 years to 66 per 1000 among those 80-89 years and for white women from 8 per 1000 to 79 per 1000 (40). It has been estimated that the prevalence of CHF in the black population is approximately 25% higher than for whites (40). According to data from the Framingham Study, the lifetime risk of developing CHF is similar for men and women and is approximately 1 in 5 (20%). However, the lifetime risk of developing

CHF among those without a previous MI is much lower, ranging from 11 to 14% for men and 15 to 16% for women (44). Additionally, Framingham study data report low survival times following CHF diagnosis with a mean of 1.7 years for men and 2.3 years for females and 5-year survival rates of 25% for men and 38% for women (40). In another study which examined survival after CHF hospitalization among Medicare participants, 6-year survival rates were 19% for black males, 16% for white males, 25% for black females and 23% for white females (45).

Although the number of CHF hospitalizations increased by 260% from 1979 to 2000 (1), this rise does not necessarily indicate an increase in the actual number of cases of CHF. Many factors (eg. new diagnostic technologies and treatments, increased patient and physician awareness, changing coding and reimbursement practices) may lead to an apparent increase in CHF. While hospitalization data do not capture the incidence of disease in the population, hospitalization data do facilitate in estimating the burden of disease (on the medical system and society) and probably represent the most severe CHF cases.

Risk factors for heart failure have been identified from several population based epidemiologic studies and include male sex, lower education, physical inactivity, cigarette smoking, diabetes, obesity, hypertension, valvular heart disease, and coronary heart disease (summarized in Table 2.5)(39, 42, 46-48). In three of the four studies, coronary heart disease, valvular heart disease, and diabetes were identified as CHF risk factors. In two of the four studies, hypertension, obesity/overweight, and elevated pulse pressure were reported as risk factors. The role of alcohol as a risk factor for development of CHF was evaluated in two of these

studies(47, 48) and was found to be associated with CHF in one of the two. He et al. found regular alcohol intake at least twice per week reduced the risk of CHF among women but not among men(48).

2.4 Alcohol Consumption

2.4.1 Physiologic Responses to Alcohol Consumption

Once alcohol has been consumed, it passes into the stomach and intestines where it is absorbed into the blood. From the bloodstream, alcohol passes into the liver where it is metabolized by enzymes, including alcohol dehydrogenase (ADH) and cytochrome P450IIE1. The rate of alcohol absorption and metabolism depends on several factors including gender, body weight, food intake, sex hormones, and some medications(49). The effects of alcohol intake on the body are most evident in the liver and nervous system. Consumption of alcoholic beverages leads to physiologic changes including altered membrane fluidity, dose dependent effects on neurotransmitters, and at high concentrations, a slowing of central nervous system functions(50). Chronic heavy alcohol intake causes injury to the liver, resulting in cirrhosis, fatty infiltration of the liver, and hepatitis(51).

One way to determine how alcohol consumption affects the body and protects against CHD would be to conduct a randomized controlled trial (RCT). Because of ethical concerns that study participants assigned to drink alcohol may become dependent as well as the high cost involved and the difficulty in finding participants, no long-term RCT of alcohol use has been conducted. However, several short-term

RCT have been conducted to study physiological changes related to alcohol consumption(52). Since the majority of the RCTs have small sample sizes, the results of a meta-analysis of 42 published RCTs conducted to assess the effect of alcohol consumption on biological markers of cardiovascular risk was conducted and will be discussed(7). Among non-alcohol dependent men and women without chronic disease, 30g of ethanol per day (2.5 drinks/day) increased HDL cholesterol by 4mg/dl, increased apolipoprotein AI by 8.8mg/dl, and increased triglycerides by 5.7mg/dl. Despite the mixed effects of alcohol on cardiovascular risk factors, the findings predict that 30g of alcohol per day would result in a 25% decrease in CHD risk(7).

Although many possible biologic mechanisms have been proposed in the alcohol – CVD relationship, the exact role of alcohol in the pathophysiology of CVD is not fully understood. It is currently hypothesized that light to moderate alcohol consumption has a beneficial effect on atherosclerosis by affecting blood pressure, cholesterol levels, plasma apolipoprotein (a) levels, platelet aggregation, fibrinolytic activity, insulin sensitivity, and stress (see Table 2.6)(53-57). Each of these will be discussed in detail below.

The effect of alcohol consumption on<u>blood pressure</u> depends on the length of use and the amount of intake, with both a “J” shaped relationship(58, 59) and a strictly monotonic dose-response relationship between the two proposed to exist(55). In the Chicago Western Electric Company study, male workers who consumed six or more drinks per day had mean systolic blood pressure of 146.5 mmHg and mean diastolic BP of 94.3 mmHg as compared with workers who

consumed no alcohol or occasional alcohol, who had SBP of 132.9 mmHg and mean DBP of 95.8 mmHg(60). Data from the Honolulu Heart Program indicate a "J" shaped relation between SBP and alcohol intake and a linear relationship for DBP and alcohol intake among males of Japanese ancestry(61). The Kaiser-Permanente Study examined SBP and DBP for men and women(62). Interestingly, SBP for women who drank but limited intake to two or fewer drinks per day was lower than for women who were non-drinkers. For men there was no difference between non-drinkers and those consuming 2 or less drinks per day. Among both men and women, consumption of three or more drinks per day as compared with non-drinkers increased SBP and DBP(62). The effects of alcohol on blood pressure are evident in days to weeks following consumption. Although no biologic mechanism has been identified, a link between alcohol and hypertension clearly exists with heavy alcohol intake a risk factor for hypertension (63).

Alcohol consumption also has effects on high density lipoprotein (HDL) cholesterol levels(64, 65), although these effects are probably modified by factors such as gender, drinking pattern and beverage type, diet, smoking, and exercise(66). Those who consume at least three drinks per day typically have higher mean HDL cholesterol levels (about 10mg/dL higher)(67) than those who consume less than three drinks per day. The Collaborative Lipoprotein Phenotyping Study found increased levels of HDL cholesterol with higher alcohol consumption(68). For the Framingham study, the Albany center study, and the San Francisco cohort study, as alcohol intake increased so did HDL cholesterol levels (Figure 2.2). In the Honolulu Heart Program, mean HDL cholesterol levels increased from 42.2 mg/dl in

nondrinkers to 56.7 mg/dl in those who reported consuming ≥20 ounces of alcohol per week(61). Alcohol intake may increase HDL cholesterol levels via several possible mechanisms. Alcohol consumption may increase the production of apolipoproteins and lipids, slow the catabolism of HDL particles resulting in increased HDL cholesterol, or cause alcohol-induced changes in proteins influencing HDL metabolism, leading to an increase in HDL concentrations(66).

In addition to affecting HDL cholesterol levels, alcohol may play a role in the oxidation of low density lipoprotein (LDL) cholesterol. In particular, the consumption of red wine, which contains antioxidant phenolic compounds, is thought to reduce oxidation of LDL(69). Observational studies have shown that oxidation of LDL cholesterol is important in the progression of atherosclerotic vascular disease(70). Hence, the antioxidant effect of drinking red wine probably affects the oxidation of LDL cholesterol, working to impede atherosclerotic plaque formation(57, 71).

As well as the role of lipids on the cardiovascular system, alcohol drinking is thought to affect several hemostatic factors including fibrinogen levels, platelet aggregation, and fibrinolytic factors. Alcohol consumption decreases platelet aggregation, lowers fibrinogen levels, and increases fibrinolytic activity(67, 72, 73), which decrease the risk of myocardial infarction but increase the risk of bleeding and hemorrhage(67, 72). Several studies, including ARIC, have found fibrinogen levels to be inversely related to alcohol consumption(74, 75).

Positive psychological benefits associated with moderate alcohol consumption may include improved subjective health, perceived stress reduction, mood enhancement, and lowered levels of depression (reviewed in (76), (77)). A

cross-sectional survey conducted in Finland found alcohol intake of 3.3-9 drinks per week was associated with optimum levels of self-reported god health (78). The majority of respondents to U.S. surveys regarding perceptions of drinking report positive reactions to alcohol consumption (reviewed in (77)). While the notion that alcohol drinking reduces stress is documented in self-reported surveys, the results of studies examining the alcohol-stress reduction association have been inconclusive and a mechanism for this effect is unknown (reviewed in (77, 79)). With regard to depression, one study reported that those who consume large amounts of alcohol and those who abstain have higher rates of clinical depression as compared with moderate consumers(76).

Studies have shown that regular, low to moderate alcohol intake improves insulin sensitivity, which can lead to decreased diabetic tendency(80-85). In the Health Professionals' follow-up study, incident diabetes was diagnosed at a lower rate among those who consumed moderate amounts of alcohol as compared with abstainers or with heavy drinkers, even after controlling for other risk factors(82). During 1998-1999, a randomized controlled cross-over trial of 51 healthy postmenopausal women was conducted to assess if low to moderate alcohol intake effected insulin resistance(81). Consumption of two drinks per day (compared with 0 drinks/day) was associated with an increased insulin sensitivity of 7.2% and decreased fasting triglyceride concentrations by 10.3%(81). A case-control study examining the effects of light to moderate alcohol intake on insulin sensitivity among 40 healthy volunteers (20 male and 20 female) used history of alcohol intake to categorize participants into nondrinkers and light/moderate drinkers (10-30g/day).

The study found light/moderate drinkers had lower insulin responses to the glucose challenge and higher HDL-cholesterol concentrations, independent of age, BMI, waist:hip girth, and physical activity levels(85).

Harmful Effects of Heavy Drinking on the Cardiovascular System:

In contrast, the damaging effects of heavy alcohol intake on the body are better understood. The first association between heavy alcohol intake and hypertension was documented in middle-aged French servicemen in 1915 but it was not until the 1970s that the relationship was further explored(63). Despite the fact that many prospective studies have established a link between heavy alcohol intake and hypertension(86-90) and that clinical experiments have confirmed the association(91), a biologic mechanism has not been established(63). Since hypertension is an important risk factor for stroke, it is possible that an effect of heavy alcohol consumption on hypertension might be responsible for the observed relationship between heavy drinking and stroke. The relation between alcohol intake and hypertension is thought to develop in days to weeks(63, 92).

Large quantities of alcohol ingestion have toxic effects on the heart that can lead to alcoholic cardiomyopathy (heart muscle disease)(93). Three main categories of cardiomyopathy include hypertrophic (heart chambers thickened but not dilated), restrictive (heart chambers infiltrated by abnormal tissue), and dilated (heart chambers enlarged with weakened contractions)(63). The relation between chronic alcohol use and heart disease was first recognized by several 19th century physicians and in 1902 MacKenzie first used the term “alcoholic heart disease” to

describe cases of heart failure attributed to alcohol(63). Today, the existence of alcoholic cardiomyopathy is well established with chronic heavy alcohol intake thought to be a cause of dilated cardiomyopathy(94); however, lack of good diagnostic tests makes distinguishing types of dilated cardiomyopathy problematic and the proportion of heavy drinkers who develop cardiomyopathy is unknown(63).

Since the calorie content of alcohol is fairly high (7.1kcal/g), alcohol intake may affect body weight(95). Light to moderate alcohol consumers typically add alcoholic beverages to their usual food intake patterns, leading to more caloric intake than expenditure, which in turn may result in increased weight gain. In contrast, heavy alcohol consumers are more apt to substitute alcoholic beverages for regular food intake, resulting in malnutrition and not overweight/obesity(96). Epidemiologic studies examining the relation between alcohol intake and body weight have reported inconsistent results(97). One possible explanation for the conflicting results is that alcohol is metabolized differently among different populations and is based on factors such as the amount of alcohol consumed, the frequency of consumption, the drinking pattern, family history of obesity and the genotypes of alcohol-metabolizing enzymes which were not controlled for in some of the studies(95, 98). Future epidemiologic studies addressing the relation between alcohol and body weight should consider if alcohol is added to the diet or is substituted for normal food intake since these behavior patterns can produce different effects on body weight and health in the long-term(95).

Despite the positive psychological benefits of light to moderate alcohol consumption (76), the chronic use of heavy alcohol intake to reduce stress may play

an important role in the development of acute stroke events. High stress intensity and weekly stress have been reported as risk factors for fatal stroke, and those who reported being stressed more frequently also reported higher levels of mean alcohol intake(99).

2.4.2 Measurements of Alcohol Consumption

Although alcohol consumption is considered a component of diet, it has unique implications because of the known adverse health and social problems related to heavy intake. Categorization of alcohol intake can be based on the amount of alcohol and the type of beverage consumed. Those who have abstained from alcohol throughout their entire lives are often termed “abstainers” or “teetotalers”. Classification of those who have used alcohol at some point is typically grouped into past or current, both of which can be further categorized by the amount. Beverage type determines the ethanol content (Table 2.7), with a 12oz serving of beer and a 4oz serving of wine containing 0.42 ounces of ethanol and a 1.5oz serving of spirits containing 0.40 ounces of ethanol(67). In addition to the type of and frequency of alcohol consumption, the number of drinks over a time period is also of interest to help in identifying patterns of binge drinking and chronic alcohol abuse.

Accurately assessing alcohol consumption is difficult because of recall bias, changes in behaviors over time, and social stigmas attached to certain patterns of drinking. Measurements of the amount of alcohol consumed are obtained via self-report, surrogate measures (biochemical markers or proxy respondents), or

measurement of blood alcohol level (BAL – the amount of alcohol in the blood stream). Self-reported alcohol consumption data is collected by mailed questionnaires, daily food journals, telephone interviews or in-person interviews. Surrogate measures of alcohol consumption are often used as a means of comparison to try and determine the accuracy of self-reported information. For example, measurements of serum gamma-glutamyl transferase (GGT), carbohydrate-deficient transferrin (CDT), and mean corpuscular volume (MCV) have been used as biological markers of alcohol drinking(100, 101). These markers (GGT and MCV) are not measures of the quantity of alcohol consumed but rather of organ response to alcohol intake which may also be affected by factors other than alcohol (102). Collecting alcohol intake by measuring the BAL is difficult in epidemiologic studies because ethanol is rapidly cleared from the body(103). As stated by Doll, correctly assessing alcohol consumption is challenging.

> "Reliable quantitative evidence is … difficult to obtain. Information about drinking habits has to be obtained not from direct measurement but from answers provided by individual people about themselves or their close relatives and friends. Unless the amount usually drunk is close to zero it is intrinsically difficult to describe, and the description is peculiarly liable to bias".(104)

In an attempt to verify self-reported alcohol consumption, many validation studies have been conducted(105-124) (summarized in Table 2.8). While issues related to the validity of self-reported alcohol consumption need to be addressed, no gold standard for measuring alcohol intake currently exists. In 1987, the director of the National Institute on Alcohol Abuse and Alcoholism defined the ideal marker for monitoring alcohol intake to be a test reflecting the mean blood alcohol level over a

period of weeks, not dependent on the presence of organ damage, and remaining positive even when the drinker is briefly abstinent(109). To date, no such marker exists making the study of the effects of alcohol subject to potential biases.

Methods to validate self-reported alcohol use include comparisons of (1) collateral reports (reports by family members or significant others), official records and biochemical tests, (2) population level self-report and alcohol sales data, and (3) various self-reported alcohol consumption measures. During the 1980s, Midanik published two literature reviews of the validity of self-reported alcohol consumption(107, 110). A review of collateral reports (reports by significant others) used to validate self-reported data indicates that agreement on the frequency of drinking between the two sources ranges from poor to excellent, and probably depends on the population being studied(107, 110). Among the general population, the agreement on the frequency of alcohol intake ranges from 49-91% but information related to ever intoxicated in the past year probably has lower agreement(107, 110). It should be noted that many of these studies were conducted several decades ago, in the 1960s and 1970s, and social attitudes regarding alcohol intake have changed, making the generalizability of these findings a concern. Although studies have shown that alcohol intake recorded by observers was correlated with subsequent self-reported intake(110) , the study design raises concern since the participants knew they were being monitored, which may have influenced their behaviors.

Biochemical markers such as CDT, GGT, and MCV (mean corpuscular volume) have also been used in an attempt to validate self-reported alcohol

consumption(117, 121). Poikolainen et al. found GGT but not CDT to have good correlation with self-reported questionnaire data and diary methods (GGT: r=0.57 to 0.67 for questionnaire reports and r=0.55 for diary vs. CDT: r=-0.16 to –0.12 for questionnaire reports and r-0.13 for diary) (121). A study using data from 76 male twin pairs compared self-reported alcohol consumption from a mailed questionnaire to biochemical markers of alcohol intake and to a dietary history interview (101). Self-reported alcohol intake via the mailed questionnaire had correlations of 0.46 with CDT, 0.32 with GGT, and 0.36 with MCV. The correlations between alcohol intake assessed by the dietary interview and biochemical markers were similar (0.44 for CDT, 0.30 for CDT, and 0.38 for MCV) (101). Interestingly, those who reported higher levels of alcohol intake via either self-report method also had higher levels of biochemical markers as compared with those reporting lower alcohol intake levels. This finding suggests that self-reports of alcohol consumption are a useful tool in distinguishing between levels of drinkers (101). Another study assessed the feasibility of using biologic markers in conjunction with clinical information to identify heavy drinkers (>6 drinks/day for men and >3 drinks/day for women) and found that levels of MCV and GGT were higher among the heavy drinker group (125).

A comparison of alcohol sales data and self-reported alcohol intake estimates finds self-reports are typically underestimates of intake(116, 121-123). Survey results from a study conducted among US Air Force personnel indicate that self-reported alcohol estimates were approximately 20% less than alcoholic beverage sales(122). The Svalbard Study also found self-reported alcohol intake to account for only 40% of reported alcohol sales data(116).

Differences in reporting may occur based on interview mode with in-person interviews reducing concerns about confidentiality and telephone interviews increasing perceptions of anonymity(126). Greenfield and colleagues compared face-to-face with telephone interviews of reported alcohol consumption and found no differences between the two methods(105). Another method frequently used to assess alcohol intake is to use prospective diaries. Comparison of diary methods with questionnaires have also been evaluated(112, 118, 119, 121). Several studies - one of volunteers from the San Francisco Bay(112) area, another of college students(119), and one of volunteers(121) - found prospective diaries and recall techniques gave similar results, although issues related to the study participants and selection raise concerns regarding the generalizability of the findings.

In addition to assessing the validity of alcohol intake measurements, many studies have examined the reliability of alcohol consumption measures. In a study of the general population, reliability of alcohol intake was assessed using a test-retest method (the 2nd survey was conducted 5-7days following the 1st survey) with alcohol information obtained via telephone interviews among ~80 adults in Greensboro, Baltimore, and Chicago(127). The telephone interviews consisted of quantity-frequency questions about the intake of beer, wine and liquor with some asking about consumption in the previous 14 days and some asking about consumption in the previous 28 days. The correlations between the test and re-test surveys ranged from 0.84 to 0.99 for 14-day recall and from 0.92 to 0.99 for 28-day recall(127). Although not directly reporting estimates for alcohol, Willett et al studied the reproducibility of nutritional data obtained from two semiquantitative food

frequency questionnaires and dietary records among women participating in the Nurses' Health Study and found good correlation (range: Pearson r=0.54 to 0.71) between the two questionnaires (128). Several years later, the reproducibility of alcohol intake was assessed in the Nurse's Health Study (n=176) and the Health Professionals Follow-up Study (n=136) (114). The correlation between alcohol intake assessment on the two questionnaires (approx 1 year apart) was high, ranging from 0.78 to 0.90 for women and 0.85 to 0.92 for men, depending on the type of alcoholic beverage(114). Overall, the reliability of alcohol assessment among the general U.S. population appears to be high.

To determine the influence of various methods of alcohol consumption measurements on categorization of drinking status, Rehm and colleagues conducted a sensitivity analysis that compared three standard assessments of alcohol intake: quantity frequency (QF), graduated frequency (GF), and weekly drinking (WD) (113). Measurement of QF involves asking two questions and is a measure of average consumption over a set period of time, usually a year. The GF asks for the highest number of drinks consumed on any occasion within the previous year and based on this response, asks questions regarding the frequency of times a certain number of drinks were consumed. The final assessment, WD, asks for alcohol use during the seven days prior to the survey, which could be none for occasional drinkers. Using random digit dialing, U.S. adults ages 18 and older were interviewed and alcohol information was collected using all three methods outlined above. Results, as shown in Table 2.9, indicate that the WD assessment method categorized most (80%) respondents into the abstainers/light drinker group. In contrast, the GF

categorization classified 8% as hazardous or harmful, the largest proportion of the three methods. This result was probably due to the fact that the GF method captures periods of high intake. This analysis clearly demonstrates that different methods of alcohol assessment can impact the categorization of individuals into particular groups and reinforces the need for measurement techniques to be specific to the objectives of the study and thus relevant to the current public health recommendations/guidelines. As will be discussed later, the ARIC study incorporates alcohol consumption measurements in terms of usual weekly intake, most similar to the WD method.

Measurement of alcohol consumption using self-reported information or biochemical markers almost certainly introduces misclassification since no method of alcohol ascertainment is 100% sensitive or specific. While measurement of alcohol intake by self-report is typically thought to underestimate intake levels, the assumption that all participants underestimate their alcohol intake proportionally allows researchers to adequately rank individuals' according to intake (129, 130)). This assumption of similar underreporting across alcohol intake levels allows for associations to be examined, but safe levels of drinking are impossible to estimate. Instead, researchers are limited to "reported drinking levels" which are underestimates of true intake. Underreporting that is not consistent across groups (heavier drinkers vs. lighter drinkers) may lead to differential misclassification of alcohol intake. If, for example, heavy drinkers systematically underestimate their levels of alcohol intake compared with other drinkers, the study findings may be

biased (101, 131). This issue is major concern for all epidemiologic studies examining alcohol consumption.

Differential reporting of alcohol consumed by gender, behavioral characteristics, or other factors may vary according to the method of alcohol ascertainment. Data from the Whitehall II longitudinal study compared a seven-day diet diary and a food frequency questionnaire and found quartile agreement between the two methods for alcohol to be 57% among males and females (132).

2.4.3 Alcohol Consumption Data Sources

Estimates of alcohol consumption in the general U.S. population are available from several different national surveillance systems and surveys. The National Health Interview Survey (NHIS) is a large, population-based survey of the noninstutionalized U.S. population. The NHIS began in 1957 and continues today with redesigns approximately every 10 years based on data needs. In 1977 the NHIS began including questions on alcohol use in supplemental questionnaires, and collected alcohol use data in 1983, 1985, 1988, 1990, and 1991(133). With the 1997 redesign, alcohol use questions were incorporated into the basic core questionnaire for one sample adult per family. The alcohol related questions in the NHIS are intended to measure alcohol consumption among the general U.S. population ages 18 and older(134). Data from the NHIS allow estimates of lifetime prevalence and current drinking levels for the US adult population by using alcohol consumption questions which inquire about consumption in the past 12 months. According to data from the 1999 NHIS, the majority (48.4%) of U.S. adults 18 and older report

being current drinkers (having at least 12 drinks in the preceding year) and 22% report being lifetime abstainers(135). Women were less likely to be current drinkers than men and current drinking status was inversely associated with age (as age increased the percentage of current drinkers decreased)(135).

The National Health and Nutrition Examination Survey (NHANES) is another data source for obtaining estimates of alcohol consumption among the US population age 20 and older. Respondents are asked the number of drinks they have had in the past year, how often they drank in the preceding 12 months, the number of days they usually drink alcohol per week, month and year, and the average number of alcoholic drinks per day over the past 12 months (136). The 1999-2000 NHANES data report that 62% of respondents had at least 12 alcoholic drinks in the previous year.

The Institute for Survey Research of Temple University conducted the National Alcohol Surveys in 1984, 1990, and 1995. Data were collected from in-person interviews conducted in the 48 contiguous states with adults' ages 18 and older. Participants were asked about current drinking, weekly drinking and consumption of 5 or more drinks on one occasion(137). In 1995 approximately 65% of respondents reported current drinking (drinking at least 1 drink per year), 29% reported weekly drinking, and 4.5% reported drinking 5 or more drinks one a single occasion(137).

The Behavioral Risk Factor Surveillance System also asks questions related to alcohol consumption (138). Among participants aged 18 and older, several questions are asked, with the number of questions differing by year. Alcohol intake

questions from 1991 to 2000 included questions related to beer, wine and liquor consumption in the past month, the number of days during which alcohol was consumed in the previous month, the number of drinks consumed in the previous month, and the number of times 5 or more drinks were had during a single occasion. In 2001 the questionnaire was modified and asked three questions: How many times at least 1 drink was consumed in the previous 30 days, on days when alcohol was consumed how many drinks per day were had on average, and how many times were 5 or more drinks consumed during a single occasion. From these questionnaires, a measure of binge drinking (have you had five or more drinks on an occasion one or more times in the past month) and a measure of chronic drinking (do you have an average of two or more drinks per day) are calculated. Binge drinking ranged from 14.1-15.3% from 1990 to 2001 and was higher among males than females and decreased with age. Less than 1% of females reported chronic drinking (2 or more drinks per day) from 1990 to 1999 and approximately 6% of males reported chronic drinking (Figure 2.3). The apparent increase in chronic drinking levels among females may be due to the fact that the definition for chronic drinking for females changed in 2001, from $\geq$2 drinks/day to >1 drink/day. Similar to binge drinking, there was a decline in reported chronic consumption with age (data not shown).

2.4.4 Epidemiology of Alcohol Consumption in the U.S.

Alcohol consumption patterns in the US vary among demographic groups, across geographic locations, and over time. Data from the US National Alcohol

Survey show rates of 12-month abstinence increased during the 1980s after being stable for approximately 50 years(139, 140). In an analysis of the National Alcohol Survey data, Greenfield et al found that levels of consumption decreased from 1984 to 1990 but remained stable from 1990 to 1995(137). In 1995, the proportion of US adults who reported being current drinkers (consumption of more than 1 drink per year) was 65% and those who reported weekly drinking was 29%(137). Data on the proportion of US adults who consumed at least 12 drinks in the previous year range from the 1999 NHIS estimate of 48% to the 1999-2000 NHANES estimate of 62%.

Findings from the National Health Interview Survey indicate the proportion of self-reported current drinkers was higher among males than females, was higher for younger than older adults, and was positively associated with higher levels of income and education (Table 2.10)(135, 137). These results are similar to those from the U.S. National Alcohol Survey data(137). However, results examining the proportion of current drinkers by race were inconsistent; one study reported higher consumption among African-Americans compared with whites(137) while another study reported higher intake among whites compared with African-Americans(135).

Since no standard method of classifying alcohol consumption exists, comparisons of how frequently alcohol is consumed are problematic. As noted from the NHIS, the NHANES, the National Alcohol Survey, and the BRFSS, current and weekly drinking definitions and estimates vary widely. Despite these limitations, a best estimate of the proportion of current drinkers is somewhere between 48% and 65% with striking differences among demographic groups.

2.4.5 Recommendations / Guidelines

Every five years, the U.S. Department of Health and Human Services (USDHHS) and the U.S. Department of Agriculture (USDA) publish dietary guidelines for the U.S. public, with the goal of promoting health and preventing disease. In 2005, the dietary guidelines related to alcohol consumption stated that those who drink alcoholic beverages should do so in moderation, with moderation defined as up to 1 drink per day for women and up to two drinks per day for men(141) (142). Specific guidelines relevant to alcohol consumption and cardiovascular disease risk have also been published by the American Heart Association (AHA) and the National Stroke Association (NSA)(143-146). The 2002 update to the AHA guidelines for the primary prevention of CVD and stroke is in agreement with the 2005 USDA publication, both recommend that among those who currently drink alcohol intake be limited to $\leq$ 2 drinks/day for men and $\leq$ 1 drink/day for women (147).

In 1996, the AHA examined the relation of alcohol consumption and CHD by taking an in-depth look at the current evidence. Based on their review of the scientific literature, the AHA recommended consulting a physician periodically to assess the benefits and risks of consuming alcohol and that those who drink do so in moderation(146). Another AHA science advisory, published in 2001, focused specifically on wine consumption and heart disease(143) probably due to the "French paradox" (CHD mortality rates in France are much lower than in the U.S. despite similar consumption of animal fats(148)) and the fact that several studies suggested red wine as more beneficial than beer or liquor in the alcohol-CHD

relation(149-151). In reviewing the current literature, the AHA states that no clear evidence exists to support the hypothesis that wine is more beneficial than other forms of alcohol in protecting against coronary heart disease and that more research is needed to address this topic(143).

In an effort to aid primary care physicians on the prevention of a first stroke, two consensus statements establishing guidelines and recommendations have been published, one from the NSA in 1999(144) and one from the AHA in 2001 (4). For both the NSA and AHA, advisory boards reviewed the current literature related to stroke risk factors including hypertension, myocardial infarction, atrial fibrillation, diabetes, asymptomatic carotid artery stenosis, and lifestyle factors (cigarette smoking, alcohol use, physical activity, and diet) and put forth recommendations. For alcohol use, the NSA is in agreement with the AHA, recommending the elimination of heavy drinking and the reduction to moderate drinking (up to 2 drinks per day) for those who drink alcohol and have no contraindications. For those who do not currently drink alcohol, physicians should not recommend alcohol as a means of preventing stroke occurrence(4, 144). Among patients who have had a stroke or TIA, the AHA recommends cessation of excessive drinking, with the goal of reducing consumption to $\leq$ 2 drinks/day for both men and women (152).

Guidelines specific to the prevention, evaluation and management of chronic HF include the recommendation that patients at high risk of developing HF avoid behavior that may increase the risk of HF, including alcohol consumption. Patients at high risk include those with systemic hypertension, CAD, diabetes, history of alcohol abuse, and family history of cardiomyopathy. The guidelines do not address

patients with low to moderate risk and do not discuss light to moderate alcohol intake(32).

2.5 Summary of the Stroke and Alcohol Consumption Literature

Numerous studies have previously examined the relationship between alcohol consumption and stroke risk (Tables 2.11 and 2.12). For ischemic stroke, the evidence for increased risk among heavy drinkers has been fairly consistent; however, the data for stroke risk among those consuming light to moderate amounts of alcohol have been inconclusive. The results of studies examining stroke risk and light to moderate amounts of consumption report either no association or a protective effect (a "J" shaped relationship). In contrast, studies of hemorrhagic stroke have found either an increase in risk with increasing amounts of alcohol consumption or no association between the two.

In early 2003, a meta-analysis of cohort and case-control studies examining the relation between alcohol consumption and stroke was published(153). The authors reviewed 122 abstracts and manuscripts and included those which met the following criteria: (1) observational cohort or case-control studies which used stroke (ischemic, hemorrhagic, or all) as an end point; (2) those that reported relative risk or odds and the variance for the stroke and alcohol relation; (3) those that quantified alcohol intake; and (4) those which used abstainers as the reference group. Of the originally identified abstracts and manuscripts, 35 met the above criteria (19 cohort studies and 16 case-control studies) and were examined for the meta-analysis. The findings support a J-shaped relationship between alcohol intake and the relative risk

of ischemic stroke and a strictly monotonic, positive relation between alcohol intake and relative risk of hemorrhagic stroke. Light to moderate alcohol intake (up to 24g/day or 2 drinks/day) appeared protective for ischemic stroke but heavy intake ($\geq$60/day or 5+ drinks/day) increased the relative risk of both ischemic and hemorrhagic stroke. Although the meta-analysis has the advantage of a larger number of stroke cases than the individual studies (resulting in a gain of statistical power and precision of the estimates), combining studies that measure outcomes by different methods (CT scan, death certificates, and hospital discharge codes) raises issues of outcome misclassification. Additionally, the meta-analysis combines heterogeneous population groups, yet fails to discuss how this factor may impact the findings. The lack of studies assessing the association between alcohol intake and stroke risk among African-Americans is evident from the meta-analysis.

2.5.1 Cohort Studies

Numerous cohort studies have examined the relation between alcohol consumption and stroke in the U.S., Japan, and Western Europe (summarized in Table 2.11). These studies have sample sizes ranging from 1,621 with 26 years of follow-up for a study of Japanese men and women(154) to 107,137 with 6 years of follow-up in a study of men and women enrolled in the Kaiser Health Plan in California(155). Although the study populations represent several diverse geographic regions (Japan, the United Kingdom, Sweden, Finland, and the U.S.), data on the relationship between stroke and alcohol consumption among African-Americans is lacking.

In these published cohort studies alcohol intake was assessed using self-administered questionnaires (9 studies), in-person interviews (12 studies), biologic markers (1 study), or some combination of these methods (2 studies). Outcomes for the cohort studies varied and included all stroke occurrence, all stroke hospitalization, all stroke mortality, ischemic stroke event, hemorrhagic stroke event (ICH and SAH both separately and combined), and cerebral infarction. Several of the cohort studies did not validate the stroke diagnosis and relied solely on death certificate data or hospital discharge codes(156-161), which can result in systematic errors of selection bias and misclassification. Additionally, some of the cohort studies did not specify the type of stroke and included various subtypes together(156, 160-165). Since the categorization of "all strokes" includes a heterogeneous mixture and ischemic and hemorrhagic strokes have very different etiologies, the classification of stroke subtype is important in trying to elucidate the role of alcohol consumption. The cohort studies reported inconsistent results, ranging from no association to increased ischemic and hemorrhagic stroke risk for heavy drinkers to decreased ischemic stroke risk for light/moderate alcohol intake.

Among those cohort studies examining the relation between hemorrhagic stroke and self-reported alcohol consumption, four reported no association(157-159, 166) and six reported increased risk with increased alcohol consumption(8, 154, 155, 167-169). None of the studies found alcohol intake to reduce the risk of hemorrhagic stroke. Differences in study methods and populations could account for some of the contradictory findings. For example, three of the four Japanese studies reported increased hemorrhagic stroke risk with alcohol intake. The study by

Kioyhara et al. found increased hemorrhagic stroke risk for those with hypertension(154), the study conducted among rural Japanese men found increased hemorrhagic stroke risk with heavy intake (≥ 5.8 drinks/d)(168), and another study by Sankai et al. found increased risk for males but not females(170). The gender differences in risk are interesting and warrant further evaluation.

Hemorrhagic stoke and alcohol consumption studies among U.S. populations include the Physicians Health Study, the Honolulu Heart Study, the Kaiser Health Plan study, and the Nurses' Health study. The Physicians Health study found no association between alcohol and hemorrhagic stroke risk among men(166) whereas the Kaiser Health Plan found hemorrhagic stroke risk increased with ≥3 drinks/day among both men and women(155). Both the Honolulu Heart study(167) and the Nurses' Health study(8) reported increases in stroke risk with increased alcohol intake.

The Nurses' Health Study allows evaluation of the SAH and alcohol relationship among women in a well-designed setting because of the prospective study design, the large sample size, and the appropriate assessment of outcomes via clinical diagnosis rather than death certificate data. The Nurses' Health Study found that risk of hemorrhagic stroke increased with reported alcohol intake, but the number of cases was small, leading to imprecise estimates(8). Given that this study was published in 1988, it would be interesting to re-analyze the data with an additional 10-15 years of follow-up data and re-examine the association.

Cohort studies assessing the relationship between ischemic stroke risk and self-reported alcohol consumption also report inconsistent results, ranging from no

association(158, 171) to decreased risk among those consuming light to moderate amounts of alcohol(8, 166) to increased risk among those consuming heavy amounts(168). Of the cohort studies examining the ischemic stroke and alcohol relationship, study populations include white American males and females, western European populations, and Japanese populations; few cohort studies included African-Americans.

Several cohort studies examining the relation between ischemic stroke and alcohol consumption that warrant discussion include the Physicians' Health Study, the Framingham Heart Study, and the Nurses Health Study(8, 166, 171). These cohort studies are prospective, have large sample sizes, ascertained cases using clinical diagnoses (rather than relying on ICD-9 codes or death certificates), and specified ischemic stroke as an outcome (as compared with all strokes). Alcohol information was collected by mailed questionnaires, in person interviews, and self-administered questionnaires. While the Physicians' Health Study and the Nurses' Health Study used alcohol intake at baseline in their analyses, the Framingham Study measured alcohol intake at multiple points in time and used this data to update alcohol exposure for study participants every 10 years(171). The majority of studies assessing the alcohol and stroke relation incorporate one measurement of alcohol in the analyses. In cohort studies, alcohol exposure is typically defined as the reported level at baseline and while this allows for prospective follow-up, it is also a concern because people change their patterns of alcohol consumption over time. In particular, alcohol has both short- and long-term effects on the body (reviewed in Figures 1.1 and 1.2 above) so changes in alcohol drinking may be

related to risk of disease. The ARIC study is able to improve upon previous cohort studies by incorporating two measures of alcohol intake, approximately six years apart. For those who have not had a stroke by the time of the second alcohol measurement, alcohol intake will be updated to reflect changes in drinking patterns.

2.5.2 Case-Control Studies

Several case-control studies have also reported on the association between stroke occurrence and alcohol intake (Table 2.12). Poorly designed case-control studies have inherent limitations including recall bias, misclassification of exposure, and selection of appropriate controls. Of the 16 case-control studies, 14 used in-person or proxy interviews to obtain information on alcohol exposure. Of the other 2 studies, one measured alcohol exposure by interviewing the patient, relative or physician by telephone(172) and the other study used an alcohol diary method(173). Studies have reported that measuring alcohol intake using a proxy does not lead to biased estimates of consumption(174) and the diary method has been found to produce similar results to alcohol consumption recall methods(112, 121).

The control groups in case-control studies should be selected from the source population (the population from which the cases arise)(131). In the case-control studies examining the alcohol and stroke relationship, the control groups were comprised of hospital/clinic based controls(172, 175-179), community controls(173, 180-186), or a combination of the two(187, 188). Identifying the source population when hospital-based controls are used may be difficult because controls are not based on a geographic area but rather on characteristics of those patients who

attend a specific hospital(189). Using community controls (such as neighborhood or population) requires a register or a method of matching cases with controls based on location. The selection of controls from the community may introduce bias into the study depending on the method of community case ascertainment. Random-digit dialing for control recruitment is troublesome since not all households have telephone access (especially those of lower income) and certain groups of individuals are more likely to be home during the day (unemployed, women, and elderly) and thus have a higher probability of being recruited to serve as controls compared with the actual population of the area(131, 189).

The majority of cases in the stroke/alcohol intake case-control studies were identified based on hospital admissions. Ascertaining cases in this manner will exclude those with the more severe strokes because they may die prior to hospital admission. Cases admitted to the hospital were confirmed and classified with the use of clinical exam and/or CT scan. Identification of stroke cases by clinical exam and imaging is important because these are currently the best methods available to validate and confirm the diagnosis. In contrast, those cases identified by ICD codes or death certificates alone will lead to incomplete case ascertainment.

Several studies reported an increased risk for hemorrhagic stroke with heavy alcohol intake(179, 180, 186). Since long-term alcohol use increases blood pressure and one of the major risk factors for hemorrhagic stroke is hypertension, this finding is as expected based on known biologic mechanisms.

2.6 Summary of the Heart Failure and Alcohol Consumption Literature

Although the harmful effects of heavy alcohol intake on the development of cardiomyopathy are well documented, few studies have examined the association between light to moderate alcohol consumption on the development of heart failure in the general population (table 2.13). Two prospective cohort studies of men and women in the northeastern U.S. measured alcohol consumption by conducting in-person interviews. Although both identified incident heart failure based on annual follow-up and medical/hospital record review, the study findings were different. Results from the Framingham Heart Study by Walsh et al. reported a protective effect of light to moderate alcohol intake but no increased HF risk with heavy intake ($\geq$15 drinks/week in men and $\geq$8 drinks/week in women)(190). In contrast, the Establishment Populations for the Epidemiologic Study of the Elderly Program (EPESE) found that heavy intake ($\geq$1.5 drinks/day) decreased heart failure risk(191). The analysis of the EPESE study did not stratify on history of MI while the Framingham Study attempted to take this into account. Finally, it is important to note the differences in definitions of heavy drinking between the two studies.

To understand the effect of light to moderate alcohol intake on the prognosis of patients with left ventricular dysfunction, Cooper et al examined data from the Studies of Left Ventricular Dysfunction (SOLVD). Alcohol consumption was assessed at baseline by asking for the average number of drinks consumed per week over the previous two years. Participants were then followed for an average of 33 months. Among those with ischemic LV dysfunction, light to moderate alcohol consumption (1-14 drinks/week) was associated with a decreased risk of

cardiovascular mortality and HF hospitalization as compared with non-drinkers. However, in patients with non-ischemic LV dysfunction, light to moderate alcohol intake (vs. never intake) was unrelated to cardiovascular mortality or HF hospitalization(192). This study emphasizes the importance of separating those with ischemic and non-ischemic disease since progression to HF is different in these two groups.

Given the findings from these cohort studies, more data on the effects of light to moderate alcohol intake on the risk of HF are needed, especially for diverse populations including African-Americans and other geographic locations.

2.7 Conclusions and Questions

The role of alcohol consumption on the cardiovascular system is complex, involving behavioral as well as biologic mechanisms. While previous studies have found light to moderate consumption to be beneficial with respect to HD, the role alcohol plays on other components of CVD remain unclear.

The previous work examining ischemic and hemorrhagic stroke have produced conflicting results. Issues related to study design, outcome measurements, and generalizability leave room for improvement in future studies. Although heavy alcohol intake has been established as a risk factor in the development of alcoholic cardiomyopathy, the role of light to moderate alcohol in the progression from CAD to HF warrants further study. As the U.S. population increases in age and survival following acute myocardial infarctions improves, the incidence and prevalence of HF is expected to increase.

Specific concerns regarding the use of alcohol as a means of protecting against disease still warrant consideration. Despite the fact that the true benefit of alcohol intake at any level is unknown, current guidelines do not discourage the use of alcohol among current drinkers as long as the amount consumed is in moderation. With an estimated 48-62% of the U.S. population being current drinkers, the role alcohol plays in the development of cardiovascular diseases needs attention, as it is likely to have an impact on public health.

A well-designed long-term prospective cohort study, such as the ARIC cohort, will help to better understand this complex relationship. The ARIC study improves upon previous studies and is well suited to evaluate the association between alcohol and CVD because:

- The ARIC study population is racially and geographically diverse, including both whites and African-Americans from MD, MN, MS, and NC.
- The ARIC study has complete case ascertainment with validated stroke occurrence and complete data on CHF hospitalizations.
- The ARIC study is prospective in nature with alcohol exposure measured prior to disease occurrence. Additionally, alcohol intake was measured at visits one and three, allowing for alcohol exposure to be updated in the analyses. If no event has occurred by visit three, both measures of alcohol intake will be used to obtain a more accurate exposure history than is available with only baseline information.
- The ARIC study uses in-person interviews to obtain extensive information on alcohol consumption. The method of alcohol assessment uses questions that

allow a distinction to be made between former drinkers and abstainers, an important distinction since these two groups are likely to be heterogeneous.

- The ARIC study measures numerous demographic, clinical, and behavioral characteristics of the study participants which will allow for the control of potential confounding factors.

Table 2.1: Prevalence and Incidence of Specific Cardiovascular Diseases in the U.S.

	Prevalence (millions)*	Incidence (new cases/ year in US)
All CVD	61.8	
High Blood Pressure	58.4	
Coronary Heart Disease	12.9	1,100,000**
Congestive Heart Failure	4.9	550,000^
Stroke	4.7	500,000^^

*Source: National Health and Nutrition Examination Survey (NHANES) III 1988-94 and NHANES 1999-2000 for high blood pressure prevalence estimates(193).
** Source: Atherosclerosis Risk in Communities, NHLBI
^ Source: Framingham Heart Study, NHLBI
^^ Source: Various studies, NINDS

Table 2.2: Traditional and Emerging Risk Factors for Cardiovascular Disease (2)

Established / Traditional	**Emerging**
Atrial fibrillation	Alcohol intake
Diabetes	Fibrinogen
High blood cholesterol	Homocysteine
High blood pressure	Inflammation markers (CRP)
Increased Age	Lipoprotein(a)
Male gender	Metabolic syndrome
Overweight/Obesity	Nutrition
Physical inactivity	
Smoking	

Table 2.3: Age-Adjusted Stroke Incidence Rates per 1000 person-years and 95% Confidence Intervals (22)

	Ischemic Stroke		Hemorrhagic Stroke		All Stroke	
	Rate	95% CI	Rate	95% CI	Rate	95% CI
Black Males	4.44	3.31, 5.97	0.77	0.38, 1.57	5.32	4.10, 6.93
White Males	1.78	1.35, 2.34	0.12	0.05, 0.28	2.00	1.56, 2.57
Black Females	3.10	2.34, 4.10	0.58	0.30, 1.10	3.96	3.10, 5.06
White Females	1.24	0.93, 1.65	0.09	0.04, 0.22	1.49	1.16, 1.92

Table 2.4: Framingham Study Congestive Heart Failure Criteria(38)

Major Criteria Paroxysmal nocturnal dyspnea Neck vein distention Rales Radiographic cardiomegaly (increasing heart size on chest x-ray) Acute pulmonary edema Third sound gallop Increased central venous pressure (>16cm water at the right atrium) Circulation time ≥25 seconds Hepatojugular reflux Pulmonary edema, visceral congestion, or cardiomegaly at autopsy Weight loss ≥4.5kg in 5 days in response to treatment of CHF
Minor Criteria Bilateral ankle edema Nocturnal cough Dyspnea on ordinary exertion Hepatomegaly Pleural effusion Decrease in vital capacity by 33% from maximal value recorded Tachycardia (rate ≥120 beat/min)

Table 2.5: Identified Risk Factors for Congestive Heart Failure

	Framingham Heart Study(39, 42)	Established Population for Epidemiologic Study of the Elderly program(46)	East Boston Senior Health Project(47)	NHANES I(48)
Coronary heart disease	√	√		√
Hypertension	√			√
LVH	√			
Valvular heart disease	√		√	√
Obesity/overweight		√		√
Diabetes	√	√	√	√
Elevated pulse pressure		√	√	
Use of antihypertensive medication			√	
Atrial Fibrillation			√	
Male sex				√
Less education				√
Physical inactivity				√
Cigarette smoking				√

LVH=left ventricular hypertrophy

Table 2.6: Putative biological mechanisms underlying cardioprotection by low-moderate alcohol consumption

Parameter	Cardioprotective effect of low-moderate alcohol intake
Lipid & lipoprotein profile	Increases HDL-cholesterol
	Inhibits oxidation of LDL-cholesterol
Thrombosis	Reduces platelet aggregation
	Reduces fibrinogen levels
	Increases fibrinolysis (the process by which clots dissolve)
Cardiovascular system	Increases coronary blood flow
	Reduces blood pressure (<1-2 drinks/day)
Lifestyle	Reduces stress
Other effects	Decreases plasma homocysteine levels

HDL = high density lipoprotein; LDL = low density lipoprotein
Adapted from: Agarwal, DP.(57)

Table 2.7: Quantities of Alcohol (Ethanol) Consumption(67)

Type of Beverage	Ethanol Content (%)	Unit of Measure	Ethanol Amount in oz (ml)
Beer (US)	3.5	12-oz bottle, 355 ml	0.42 (12.43)
Wine	12.1	3.5-oz glass, 104ml	0.42 (12.58)
Distilled spirits, 80 proof	40.0	1-oz shot, 30ml	0.40 (12.00)

Ethanol in grams = 23 x (ethanol in oz).
Ethanol in spirits = 0.411 x (oz of spirits), not x (volume of mixed drink).
1 gram = 0.035 ounces

Table 2.8 Summary of Alcohol Reliability and Validation Studies

Author & Year	Population	Comparison	Methods	Outcome	Results
Giovannucci E(114) 1991	144 women from Nurses' Health Study & 136 men from Health Professionals Follow-up Study	Alcohol consumption measured by self-administered questionnaire with detailed diet records (DR)	Completed FFQ1; 2-4 months later recorded food intake for 4 weeks during 3 month intervals; then completed FFQ2	Spearman rank correlation coefficients, Fisher's method test differences, & linear regression for covariate control	FFQ1 & FFQ2 high correlation ($r \geq 0.9$); FFQ & DR $r \geq 0.86$
Greenfield TK(105) 2000	1990 Alcohol Survey (face to face data) & 1990 Warning Labels Survey (telephone data)	Alcohol consumption measured by random digit dialing with face to face interview survey in 48 states	Drinking measured with graduated frequency approach in each of the two samples	Comparison of mean drinks/day by age, race, gender, income & educational levels	No difference b/t telephone & face to face
Gronbaek(115) 1996	493 Danish men & women from the Danish MONICA Study	Alcohol consumption measured by frequency questionnaire & dietary interview	Completed general health questionnaire & 1 week later interviewed by dietician	Average daily intakes calculated & compared using multiple linear regression	Mod correlation b/t 2 methods ($r \geq 0.72$)
Hilton ME(112) 1989	83 volunteer subjects from the San Francisco Bay area who drank at least twice/week	Alcohol consumption measured by prospective food diary & two recall series	30-day recall series, 2-week recall series, & 10-week diary	Diary assumed to be gold standard & recall measures assessed against diary	Both recall measures gave high correlation w/ diary ($r \geq .88$)
Hoyer G(116) 1995	818 men & women participating in the Svalbard Study on the Norwegian island	Alcohol consumption measured by recorded alcohol sales & self-administered questionnaire	Alcohol sales data were obtained from all agencies selling alcohol & questionnaire data was self-report at study baseline	Comparison of mean annual liters of alcohol by self-report & sales data	Self-reported intake was 40% of reported sales data
Laatikainen T(117) 2002	North Karelia, Finland & Republic of Karelia, Russia	Alcohol consumption measured by self-reported questionnaire & biological markers, GGT & CDT	At study baseline, self-admin. questionnaire re: alcohol intake & blood specimen for GGT & CDT measures	Comparison of questionnaire responses with GGT and CDT separately	Both bologic markers gave higher estimates
Lemmens P(118) 1988	Dutch population sample	Alcohol intake measured by in-person interview of previous 7 days & diary for 2 week period	In-person interview conducted first and then kept diary for 2 weeks	Comparison of the two methods	Diary estimates higher than weekly estimate; rank order same
Midanik LT(106) 1992	112 men & women volunteers who drank alcohol $\geq$ monthly	Alcohol consumption measured via telephone interview before & after December	Comparison of 2 self-reported recalls of drinking during 12-month period	Correlations between the two measures	Reported alcohol intake lower after December
Midanik LT(108) 1989	535 men & women who were members of Northern Kaiser Permanente Medical Care Program during 1st 4 months of 1986	Interview of alcohol intake during previous 7 days and two alcohol use questionnaires: quantity/ frequency index and overall summary measure	During clinic exams, participants completed questionnaires – 2 at beginning of exam & 7-day recall at the end of exam	Spearman rank correlations between (1) 7-day recall & quantity/frequency index and (2) 7-day recall & overall summary measure	Correlation b/t 7-day & QF = 0.66 and b/t 7-day & overall summary = 0.74

Table 2.8 Summary of Alcohol Reliability and Validation Studies (con't)

Author & Year	Population	Comparison	Methods	Outcome	Results
Midanik LT(111) 1982	65 adult alcoholics admitted to a treatment program/clinic	Alcohol intake measured by interviewer administered question & breath test to obtain blood alcohol concentration (BAC)	During clinic visit participants were interviewed re: recent alcohol intake (prev 24hr) & given breath test	Calculated estimated blood alcohol concentration from questionnaire & compared with BAC from breath test	Self-reported estimates higher than breath test
O'Callaghan F(119) 1992	122 college students	Alcohol intake assessed using questionnaire & 2-week diary		Correlation between the 2 measurements	High correlation b/t 2 measures
Poikolainen K(121) 2002	34 volunteer subjects (men & women) from workplaces recruited via advertisements	Alcohol consumption measured by self-admin questionnaire, daily diary, & biomarkers	At study baseline & follow-up participants completed two questionnaires (GF & QF), blood samples taken at baseline & daily diary kept for 31 days	Pearson correlation coefficients between diary, QF & GF and biomarkers & QF, GF, diary	Correlation b/t QF and GF with daily intake r=0.9 Correlation b/t biomarkers & self report was good
Poikolainen K(120) 1983	49 male volunteer subjects	Alcohol intake assessed by questionnaire and two diary time points	At baseline questionnaire given followed by diary measurements	Correlation coefficients	Correlation b/t two measures was good
Rehm J(113) 1999	3961 adult men & women from Ontario, Canada	Alcohol consumption measured by QF, GF, and WD for each subject	Data from 4 probability surveys using telephone interviewing	Cross-tabulation, spearman correlation coefficients	QF highest drink estimates, WD lowest; QF & GF r=0.76-.73
Smith PF(123) 1990	Data from 21 states participating in 1985 BRFSS	Alcohol intake assessed via self-report and through alcohol sales records	Data for alcohol sales from state-specific per capita sales	Correlation coefficients to compare estimates of alcohol intake	Correlation for 21 states r=.81
Townshend J(124) 2002	55 university students recruited by advertisement for social drinkers	Alcohol consumption measured by initial questionnaire (Alcohol Use Questionnaire – AUQ) & then 4 week daily diary	After initial AUQ, participants completed daily diary for 4 weeks, returning diary each week	Differences b/t AUQ & diary examined with paired-sample t-tests; Pearson correlation coefficient comparing AUQ & diary	Correlation b/t 2 sources r=0.975; Low drinkers underestimate & high drinkers overestimate

FFQ=food frequency questionnaire; QF=quantity frequency; GF=graduated frequency; WD=weekly drinking

Table 2.9: Proportion of respondents according to drinking categories by assessment method and gender (113)

	Abstainers/light drinkers			Low Risk			Hazardous			Harmful		
	QF	GF	WD	QF	GF	WD	QF	GF	WD	QF	GF	WD
Male	41.3	48.3	74.3	52.3	40.6	22.5	3.6	3.8	1.6	2.8	7.3	1.6
Female	70.7	72.9	85.6	26.5	21.7	12.3	2.5	3.7	1.9	0.3	1.7	0.2
Total	56.3	61.0	80.0	39.2	30.8	17.3	3.0	3.8	1.7	1.5	4.4	0.9

Abstainers/light drinkers = 0-2.5g pure alcohol per day, Low risk = males: 2.6-40.0g/day & females:2.6-20.0g/day, Hazardous = males:40.1-60.0g/day & females: 20.1-40.0g/day, Harmful= males $\geq$60.1g/day & females $\geq$40.1g/day.

Table 2.10: Proportion (in %) of US population ages 18 and older by alcohol drinking status, NHIS 1999(135)

	Lifetime Abstainer*	Former Infrequent*	Former Regular*	Current Infrequent*	Current Regular*
Total	22.4	8.1	6.7	14.3	48.4
Male	14.7	6.9	8.4	11.0	59.0
Female	29.4	9.3	5.2	17.3	38.8
18-44 yrs	20.7	5.6	4.4	14.3	55.0
45-64 yrs	19.6	10.3	8.1	15.4	46.6
65+ yrs	33.1	12.8	12.1	12.1	29.8
< $20,000	33.3	10.2	8.4	12.5	35.6
$20,000-34,999	23.2	10.6	7.8	14.9	43.6
$35,000-54,999	18.9	8.0	6.7	15.7	50.5
$55,000-74,999	15.4	7.0	5.7	14.7	57.2
> $75,000	11.8	4.6	4.4	13.8	65.3

* Lifetime abstainer had fewer than 12 drinks in lifetime; Former infrequent had at least 12 drinks in their lifetime but fewer than 12 drinks in any year and no drinks in the previous year; Former regular drinkers had at least 12 drinks in any one year and no drinks in the previous year; Current infrequent had as least 12 drinks in their lifetime and fewer than 12 drinks in the previous year; Current regular has at least 12 drinks in the previous year.

Table 2.11 Stroke and Alcohol Consumption Cohort Studies

Author & Year	Setting	Population	Alcohol Exposure	Outcome	Outcome Assessment	events	Follow-up (years)	Results
Berger K(166) 1999	Physicians' Health Study	21,870 male physicians aged 40-84 yrs	Self-administered mailed questionnaire at baseline & 84 months	Ischemic & hemorrhagic stroke incidence	Self-report & verified w/ med. record review	isch=557 hem=88 unk=34	12.2	no association b/t alco & hem stroke; for isch, >1drink/wk RR=0.8
Djousse L(171) 2002	Framingham Heart Study	5,209 males & females in Massachusetts	In-person interview at several exams	Ischemic stroke incidence	Clinical dx or radio images	441	30	No sign association but among 60-69yr olds, drinking ↓ risk
Donahue RP(167) 1986	Honolulu Heart Study	7,878 males aged 45-69yrs in Hawaii	In-person interview	hemorrhagic stroke	Hospital disch, death certificate, or autopsy	76	12	mod alco RR=3.5 & heavy alco RR=3.8 vs. never drinkers
Elkind (194) 2006	Northern Manhattan Study	3176 males & females, including Hispanics, blacks and whites	In-person interview	hemorrhagic & ischemic stroke	Telephone interview & hospital surveillance	IS=172 SAH=4	5.9	↓ IS risk with one drink/mo to 2 drink/ day
Gaziano JM(156) 2000	Physicians' Health Study Enrollment	89,299 US males aged 40-84 yrs	Self-administered mailed questionnaire	all stroke death by ICD-9 430-438	Death certificate	150	5.5	No association b/t alco consumption & stroke mortality
Goldberg RJ(161) 1994	Honolulu Heart Study	6069 males in Hawaii	In-person interview at baseline & year 6	all stroke death & event by ICD-9	Death certificate, hospital discharge	70	15	↑ stroke mortality w/ ↑ alcohol intake
Hansagi H(157) 1995	Swedish pop-based twin registry	15,077 twin males & females aged ≥40yrs in Sweden	Self-administered questionnaire	all, hem & isch stroke death by ICD-8 430-438	Death certificate	769	20	No association b/t alco & hem stroke; mixed results for IS
Hart CL(165) 1999	Scottish cohort	5,766 males aged 35-64yrs in Scotland	In-person interview	all stroke death by ICD-9 430-438	NHS register in Edinburgh	133	21	No association b/y alco & all stroke mortality
Iso H(168) 1995	Rural Japan	2,890 males aged 40-69 yrs in Japan	In-person interview	Hemorrhagic & ischemic stroke incidence	Physician report, claims, medical records & death certificate	hem=58 isch=104	10.5	Increased hem & isch stroke risk for heavy (≥70g/d) drinkers
Iso H (195) 2004	Japan Public Health Center Study	19,544 middle-aged Japanese males	Self-administered questionnaire	Hemorrhagic & ischemic stroke	Hosp surveillance & death certificates	SAH=73 IS=319	11.0	↑ hem stroke risk with ↑ alco intake; ↓ IS risk 1-149g/wk

Table 2.11 (continued) Stroke and Alcohol Consumption Cohort Studies

Author & Year	Setting	Population	Alcohol Exposure	Outcome	Outcome Assessment	events	Follow-up (years)	Results
Jousilahti P(158) 2000	Eastern & Southwestern Finland	14,874 males & females aged 25-64 yrs in Finland	Self-administered mailed questionnaire & from GGT obtained from blood samples	Hemorrhagic & ischemic stroke incidence	Hospital disch registry or death certificate	hem=79 isch=345	10	No association b/t self-report alco drinking & stroke; ↑ stroke risk w/ ↑ GGT levels
Kiyohara Y(154) 1995	Hisayama Study	1,621 males & females aged ≥40yrs in Japan	In-person interview	Hemorrhagic & cerebral infarct	Clinical dx, CT scan, or autopsy	hem=60 cer=244	26	For pts w/ HTN, ↑ hem & cereb stroke risk in heavy drnkrs
Klatsky AL(155) 1989	Kaiser Health Plan, CA	107,137 males & females aged <50yrs	Self-administered questionnaire	Hemorrhagic & occlusive stroke	Hospital disch codes	hem=69 occ=292	6	↑ hem stroke risk with ≥3drk/d; ↓ occ strk risk w/ alco use
Kono S(159) 1986	Japanese physicians	5,135 males	Self-administered questionnaire	Hem stroke & all other stroke by ICD-8 codes	Death certificate	230	19	No association
Leppala JM(196) 1999	Finland	26,556 male smokers aged 50-69yrs	Self-administered questionnaire	Incident stroke identified by linking to ICD codes	Clinical dx or death certificate	isch=733 SAH=83 ICH=95	6.1	SAH & ischemic stroke risk ↑ NS w/ ↑ alcohol intake
Maskarinec G(160) 1998	Hawaii	27,678 males & females aged ≥30yrs	In-person interview	All stroke death by ICD codes	Death certificate	433	20	No association
Mukamal (197) 2005	Cardiovascular Health Study	4,410 US adults aged 65 and older	Annual self-report	Incident ischemic stroke	Hospital surveillance	IS=434	9.2	Slight ↓ in IS risk among 1-6 drink/wk
Palmer AJ(198) 1995	England	6369 males & females aged 18-90y	In-person interview & self-admin questionnaire	All stroke death by ICD codes	Death certificate	159	11	Among males, ↓ stroke mortality for light drinkers
Romelsjo A(162) 1999	Swedish conscripts	49,618 males aged 17-45 yrs	Self-administered questionnaire	All stroke incidence	Clinical dx or death certificate	223	25	No association
Sankai T(169) 2000	6 communities in Japan	12,372 males & females aged 40 to 69 yrs	In-person interview	Incident SAH stroke	Clinical diagnosis & CT scan	71	9.4	Among males, ↑ SAH risk; no assoc. for females
Shaper AG(163) 1991	General practice offices in UK	7,735 British men aged 40-59 yrs	In-person interview	All stroke incid & mortality	NHS registry	110	8	heavy alco intake >42dk/wk, RR=3.8

Table 2.11 (continued) Stroke and Alcohol Consumption Cohort Studies

Author & Year	Setting	Population	Alcohol Exposure	Outcome	Outcome Assessment	events	Follow-up (years)	Results
Stampfer MJ(8) 1988	Nurses' Health Study	87,526 female nurses aged 34-59 yrs	Self-administered questionnaire	Hemorrhagic & ischemic stroke	Participant questionnaire & medical record	hem=35 isch=141	4	↓ ischemic risk for light/mod drinking; ↑ hem stroke risk
Truelsen T(199) 1998	Copenhagen City Heart Study	13,329 males & females aged 45-84 yrs	In-person interview	Incident ischemic & hemorrhagic hospitalization	Clinical dx or death certificate	all=833 hem=81 isch=310	16	↓ stroke risk for wine drinkers
Wannamethee(164) 1996	British Regional Heart Study	7,273 males aged 40-59 yrs	In-person interview at year 1 & year 5	Stroke event & mortality	Clinical dx, self report, med rec. or death certif.	fatal=59 nonfatal=191	13.5	No association for mortality or event

alco=alcohol, dx = diagnosis, yrs=years

Table 2.12 Stroke and Alcohol Consumption Case Control Studies

Author	Setting	Cases	Controls	Alcohol Exposure	Outcome Assessment	Results
Beghi E(187) 1995	Hospitals in Italy	200 males & females aged ≥20 yrs with any stroke diagnosis	170 hospitalized controls & 202 community controls	In-person or proxy interview	clinical or neurological exam, or CT scan	↑ stroke risk among moderate & heavy drinkers using either control group
Ben-Shlomo Y(188) 1992	3 Hospitals in UK	115 males & females aged 15 to 69 yrs with isch or hem stroke	119 hospital controls & 717 community controls	In-person or proxy interview	Clinical exam, CT scan, or lumbar puncture	No association
Caicoya M(180) 1999	Spain	467 males & females aged 40 to 85 yrs with isch or hem stroke	477 community controls	In-person or proxy interview	Clinical exam or CT scan	Moderate drinking ↓ isch stroke risk; heavy drinking ↑ hem & isch strk risk
Gill JS(175) 1986	District hospital England	230 males & females aged 20 to 70 yrs with any stroke diagnosis	230 hospital controls	In-person or proxy interview	Clinical exam, CT scan, angiography, or autopsy	Heavy drinking in men ↑ all stroke risk
Gill JS(181) 1988	District hospital England	230 males & females aged 20 to 70 yrs with any stroke diagnosis	577 community controls	In-person or proxy interview	Clinical exam, CT scan, angiography, or autopsy	No association
Gill JS(182) 1991	2 hospitals in England	621 males & females aged 20 to 70 yrs w/ hem stroke or cerebral infarct	573 community controls	In-person or proxy interview	Clinical exam, CT scan, angiography, or autopsy	Moderate drinking ↓ SAH in women; NS J-shape association
Gorelick PB(176) 1989	3 medical centers in Chicago	201 males & females aged ≥ 44 yrs with incident ischemic stroke	405 outpatient clinic patients	In-person interview	Clinical diagnosis & CT scan	No association
Henrich JB(172) 1989	Connecticut	89 males & females aged 15 to 65 yrs with ischemic stroke	178 hospital based controls	Telephone interview with patient, relative, or physician	Clinical exam & CT scan	No association
Herman B(177) 1983	2 hospitals in the Netherlands	132 males & females aged 40-74 yrs with any stroke dx	239 hospital based controls	In-person or proxy interview	Clinical exam	No association
Jamrozik K(183) 1994	Western Australia	501 males & females aged ≥ 18yrs with isch or hem stroke diagnosis	931 community based controls from electoral roles	In-person or proxy interview	Clinical exam, CT scan, MRI, or autopsy	No association

Table 2.12 (continued) Stroke and Alcohol Consumption Case Control Studies

Author	Setting	Cases	Controls	Alcohol Exposure	Outcome Assessment	Results
Malarcher AM(184) 2001	59 hospitals in Baltimore, Washington	224 females aged 15 to 44 yrs with incident cerebral infarct	392 community based female controls	In-person or proxy interview	Hospital discharge dx, clinical dx, neuroimaging or autopsy	Up to 24g/d in past yr, ↓ stroke risk; wine consumption protective
Palomaki H(178) 1993	Hospital in Finland	156 males with ischemic stroke dx	153 hospital based controls	In-person or proxy interview	Clinical diagnosis, neuroradiological methods	Heavy alco intake ↑ ischemic stroke risk
Sacco RL(200) 1999	New York area community	677 males & females aged > 39 yrs with incident cerebral infarct	1139 community based controls identified via RDD	In-person or proxy interview	Brain imaging & clinical diagnosis	Up to 2 drinks/day ↓ stroke risk & ≥7 drinks/day ↑ risk
Shinton R(173) 1993	Physician offices in England	125 males & females aged 35 to 74 yrs with incident stroke	198 community based controls	Alcohol diary	Clinical exam, CT scan, or autopsy	No association
Thrift A(186) 1999	13 Hospitals in Melbourne, Australia	331 males & females aged 18 to 80 yrs with hemorrhagic stroke	331 neighborhood matched controls	In-person or proxy interview	CT scan, MRI, or autopsy	↑ hem stroke risk for heavy drinkers & ↓ hem stroke risk for wine drinkers
Zodpey SP(179) 2000	Hospital in India	166 males & females with hemorrhagic stroke	166 hospital matched controls	In-person interview	CT scan	↑ hem stroke risk for heavy drinkers

alco=alcohol, CT=computed topography, dx = diagnosis, hem=hemorrhagic, isch=ischemic, yrs=years
* adapted from Reynolds K(153)

Table 2.13 Heart Failure and Alcohol Consumption Studies

Author	Setting	Population	Alcohol Exposure	Outcome	Outcome Assessment	events	Follow-up (years)	Results
Abramson JL(191) 2001	New Haven, CT EPESE study	2235 males & females aged ≥65 yrs free of HF	In-person interview	incident HF (fatal or nonfatal)	Identified via ICD codes; medical record review	281	14	lt drink HR=0.8 (0.6-1.0) & heavy drink HR=0.5 (0.3-0.9) – vs. none
Cooper HA(192) 2000	SOLVD	6609 males & females aged 21 to 80 yrs with an LVEF≤0.35	In-person interview	all cause & CVD specific mortality including HF	by PI at each site	622HF	3	Alcohol consumpt. not associated with worse prognosis in pts w/ LVEF
He J(48) 2001	NHANES I	13643 males & females aged 24-74 years free of HF at baseline	In-person interview	incident HF (fatal or nonfatal)	Interview, medical records, death certificate by ICD-9 codes	741(M) 641(F)	19	Reg alc intake in women, RR=0.71 (0.52-0.96). No association in men
Klatsky (201) 2005	Kaiser Health Plan Study	126,235 males and females enrolled in Kaiser Plan in CA	Self-administered questionnaire	Hospitalized HF	Identified via ICD codes; medical record review	2594	?	Heavy alcohol intake increased non-CAD-HF
Walsh CR(190) 2002	Framingham Heart Study	2796 males & 3493 females aged 28-62 yrs at baseline & free of HF	In-person interview	incident CHF	Medical history, physical exam, & hosp. records	99(M) 120 (F)	10	No association b/t alcohol consumpt. & CHF; moderate consumpt. appears protective

alc=alcohol, dx = diagnosis, yrs=years
EPESE = Establishment Populations for the Epidemiologic Study of the Elderly program
HF = heart failure
SOLVD = Studies of Left Ventricular Dysfunction

Figure 2.1: Classification of stroke based on data from the NINDS Stroke Data Bank, 1983-1986 (adapted from Sacco, et al)(19)

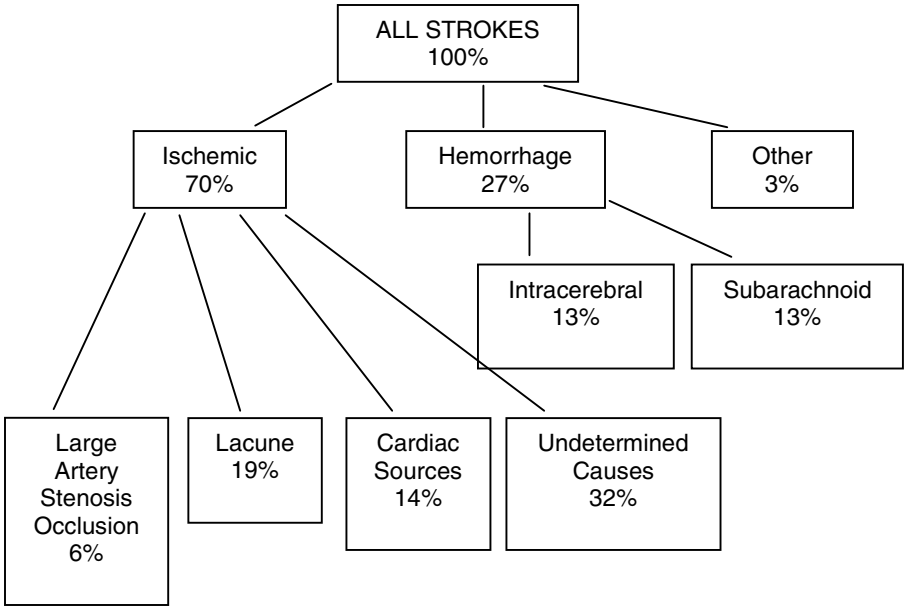
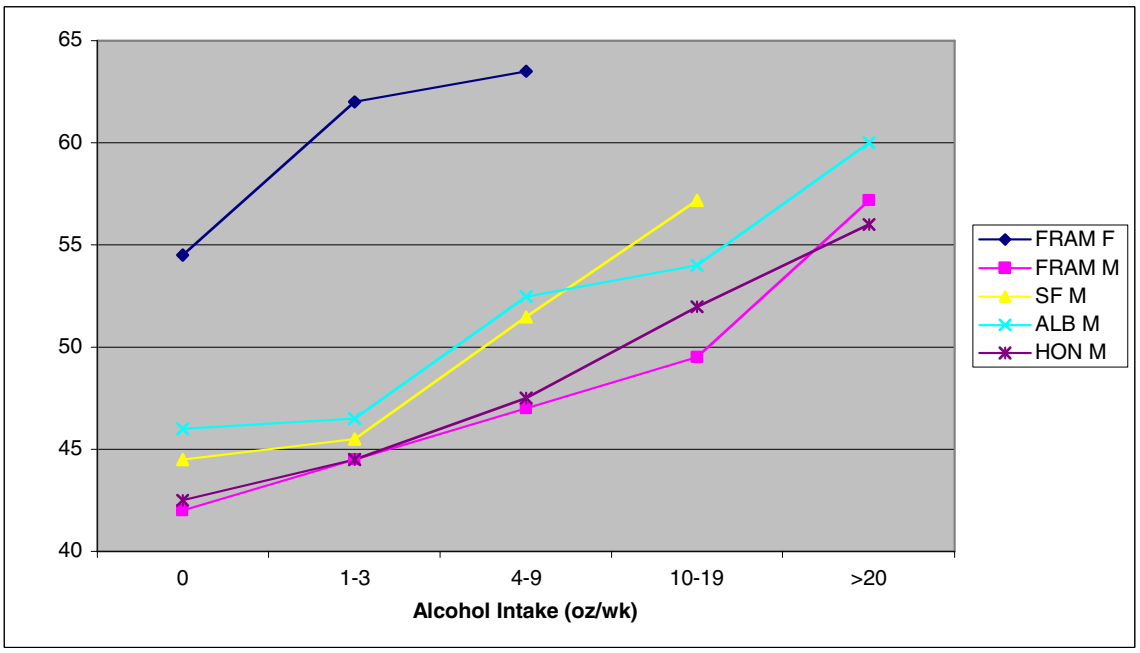
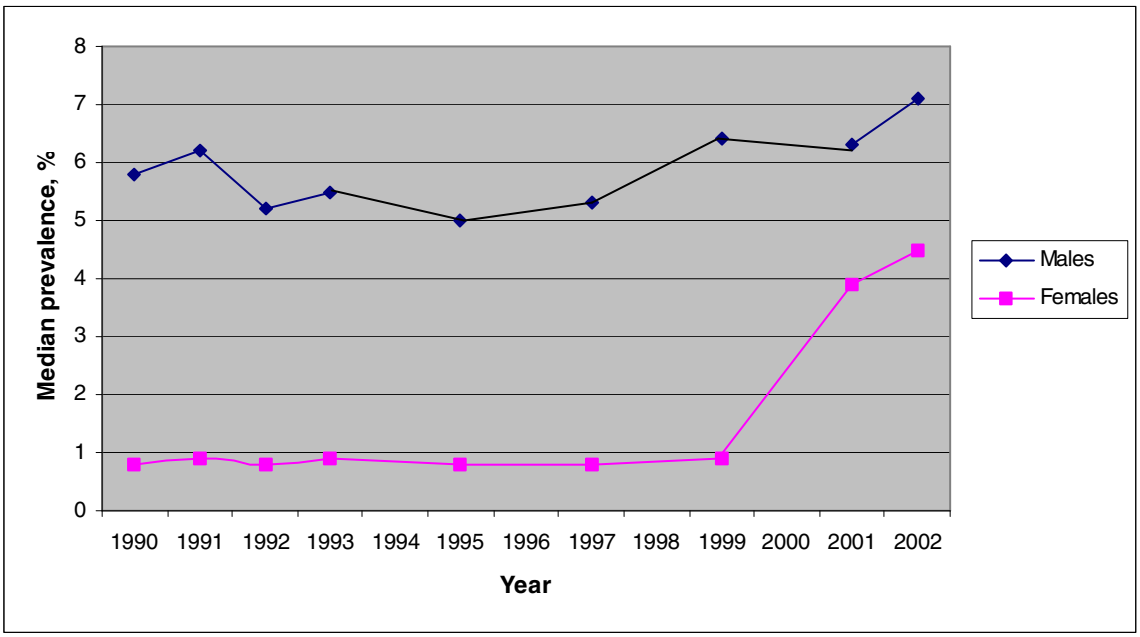


Figure 2.2: Mean High Density Lipoprotein (HDL) Cholesterol Levels(68)



FRAM = Framingham, SF = San Francisco, ALB = Albany, HON = Honolulu, F = female, M = male

Figure 2.3: Chronic Drinking Levels among US Adults ages 18+ by Gender, BRFSS 1990-2001



* No national data for years 1994, 1996, 1998, and 2000.
1990-2000: All respondents ages 18+ who reported an average of ≥ 2 drinks/day.
2001-2002: All male respondents ages 18+ who reported an average of > 2 drinks/day and female respondents ages 18+ who reported an average of > 1 drink/day.

2.8 References

1. Heart Disease and Stroke Statistics - 2003 Update. Dallas, TX: American Heart Association, 2002.

2. Labarthe D. Epidemiology and Prevention of Cardiovascular Diseases: A Global Challenge: Aspen Publishers, 1998.

3. Stamler J, Stamler R, Neaton JD, et al. Low risk-factor profile and long-term cardiovascular and noncardiovascular mortality and life expectancy: findings for 5 large cohorts of young adult and middle-aged men and women. Jama 1999;282:2012-8.

4. Goldstein LB, Adams R, Becker K, et al. Primary prevention of ischemic stroke: A statement for healthcare professionals from the Stroke Council of the American Heart Association. Stroke 2001;32:280-99.

5. Nieto FJ. Cardiovascular disease and risk factor epidemiology: a look back at the epidemic of the 20th century. Am J Public Health 1999;89:292-4.

6. Gaziano JM, Buring JE, Breslow JL, et al. Moderate alcohol intake, increased levels of high-density lipoprotein and its subfractions, and decreased risk of myocardial infarction. N Engl J Med 1993;329:1829-34.

7. Rimm EB, Williams P, Fosher K, Criqui M, Stampfer MJ. Moderate alcohol intake and lower risk of coronary heart disease: meta-analysis of effects on lipids and haemostatic factors. Bmj 1999;319:1523-8.

8. Stampfer MJ, Colditz GA, Willett WC, Speizer FE, Hennekens CH. A prospective study of moderate alcohol consumption and the risk of coronary disease and stroke in women. N Engl J Med 1988;319:267-73.

9. Yatsu F.M. V-CC. Atherosclerosis. In: Barnett H.J.M. MJP, Stein B.M., Yatsu F.M., ed. Stroke Pathophysiology, Diagnosis, and Management, 3rd Edition. Philadelphia: Churchill Livingstone, 1998:29-39.

10. Ross R. Atherosclerosis--an inflammatory disease. N Engl J Med 1999;340:115-26.

11. Gorelick PB. Stroke prevention therapy beyond antithrombotics: unifying mechanisms in ischemic stroke pathogenesis and implications for therapy: an invited review. Stroke 2002;33:862-75.

12. Stern BJ, Johnson, C.J., and Preziosi, T.J. Cerebrovascular Disorders. In: Stobo JD, Hellmann, D.B., Ladenson, P.W., Petty, B.G., and Traill, T.A., ed.

The Principles and Practice of Medicine. Stamford, Connecticut: Appleton & Lange, 1996:845-851.

13. Fisher CM. Transient ischemic attacks. N Engl J Med 2002;347:1642-3.

14. Albers GW, Caplan LR, Easton JD, et al. Transient ischemic attack--proposal for a new definition. N Engl J Med 2002;347:1713-6.

15. Saver JL. A comparison of risk factors for recurrent TIA and stroke in patients diagnosed with TIA. Neurology 2003;60:1871; author reply 1871.

16. Brown MM, Rudd A, McGovern R. Transient ischemic attack--proposed new definition. N Engl J Med 2003;348:1607-9; author reply 1607-9.

17. Ballotta E, Toniato A, Baracchini C. Transient ischemic attack--proposed new definition. N Engl J Med 2003;348:1607-9; author reply 1607-9.

18. Bernstein RA, Alberts MJ. Transient ischemic attack--proposed new definition. N Engl J Med 2003;348:1607-9; author reply 1607-9.

19. Sacco R.L. TD, Mohr J.P. Classification of Ischemic Stroke. In: Barnett H.J.M. MJP, Stein B.M., Yatsu F.M., ed. Stroke Pathophysiology, Diagnosis, and Management, 3rd Edition. Philadelphia: Churchill Livingstone, 1998:341-354.

20. Morgenstern L.B. KSE. Cerebrovascular Disorders. Scientific American Medicine: Neurology: Scientific American, 2002:1-15.

21. Kase C.S. MJP, Caplan L.R. Intracerebral Hemorrhage. In: Barnett H.J.M. MJP, Stein B.M., Yatsu F.M., ed. Stroke Pathophysiology, Diagnosis, and Management, 3rd Edition. Philadelphia: Churchill Livingstone, 1998:649-700.

22. Rosamond WD, Folsom AR, Chambless LE, et al. Stroke incidence and survival among middle-aged adults: 9-year follow-up of the Atherosclerosis Risk in Communities (ARIC) cohort. Stroke 1999;30:736-43.

23. Casper ML BE, Williams GI Jr, Halverson JA, Braham VE, Greenlund KJ. Atlas of Stroke Mortality: Racial, Ethnic, and Geographic Disparities in the United States. Atlanta: Department of Health and Human Services, Centers for Disease Control and Prevention, 2003.

24. Howard G, Howard VJ, Katholi C, Oli MK, Huston S. Decline in US stroke mortality: an analysis of temporal patterns by sex, race, and geographic region. Stroke 2001;32:2213-20.

25. Lanska DJ, Kuller LH. The geography of stroke mortality in the United States and the concept of a stroke belt. Stroke 1995;26:1145-9.

26. Casper ML, Wing S, Anda RF, Knowles M, Pollard RA. The shifting stroke belt. Changes in the geographic pattern of stroke mortality in the United States, 1962 to 1988. Stroke 1995;26:755-60.

27. Prevalence of disabilities and associated health conditions among adults--United States, 1999. MMWR Morb Mortal Wkly Rep 2001;50:120-5.

28. Collaboration PS. Cholesterol, diastolic blood pressure, and stroke: 13,000 strokes in 450,000 people in 45 prospective cohorts. Lancet 1995;346:1647-53.

29. Shahar E, Chambless LE, Rosamond WD, et al. Plasma lipid profile and incident ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) study. Stroke 2003;34:623-31.

30. Blauw GJ, Lagaay AM, Smelt AH, Westendorp RG. Stroke, statins, and cholesterol. A meta-analysis of randomized, placebo-controlled, double-blind trials with HMG-CoA reductase inhibitors. Stroke 1997;28:946-50.

31. Mann DL. Mechanisms and models in heart failure: A combinatorial approach. Circulation 1999;100:999-1008.

32. Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). J Am Coll Cardiol 2001;38:2101-13.

33. American Heart Association Web Site: Learning about Heart Failure (www.americanheart.org/presenter.jhtml?identifier=337). Accessed May 21, 2006.

34. American Heart Association Web Site: Signs and Symptoms of Heart Failure (www.americanheart.org/presenter.jhtml?identifier=339). Accessed May 21, 2006.

35. The Criteria Committee of the New York Heart Association: Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. Boston: Little, Brown, and Company, 1994.

36. Traill TA. Left Ventricular Dysfunction: Mechanisms and Symptoms. In: Stobo JD, Hellmann, D.B., Ladenson, P.W., Petty, B.G., and Traill, T.A., ed. The Principles and Practice of Medicine. Stamford, Connecticut: Appleton & Lange, 1996:33-41.

37. Kannel WB. Current status of the epidemiology of heart failure. Curr Cardiol Rep 1999;1:11-9.

38. Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. J Am Coll Cardiol 1993;22:6A-13A.

39. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. Jama 1996;275:1557-62.

40. Kannel WB. Vital epidemiologic clues in heart failure. J Clin Epidemiol 2000;53:229-35.

41. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. N Engl J Med 1971;285:1441-6.

42. Kannel WB, D'Agostino RB, Silbershatz H, Belanger AJ, Wilson PW, Levy D. Profile for estimating risk of heart failure. Arch Intern Med 1999;159:1197-204.

43. Marantz PR, Tobin JN, Wassertheil-Smoller S, et al. The relationship between left ventricular systolic function and congestive heart failure diagnosed by clinical criteria. Circulation 1988;77:607-12.

44. Lloyd Jones DM, Larson MG, Leip EP, et al. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. Circulation 2002;106:3068-72.

45. Croft JB, Giles WH, Pollard RA, Keenan NL, Casper ML, Anda RF. Heart failure survival among older adults in the United States: a poor prognosis for an emerging epidemic in the Medicare population. Arch Intern Med 1999;159:505-10.

46. Chen YT, Vaccarino V, Williams CS, Butler J, Berkman LF, Krumholz HM. Risk factors for heart failure in the elderly: a prospective community-based study. Am J Med 1999;106:605-12.

47. Chae CU, Pfeffer MA, Glynn RJ, Mitchell GF, Taylor JO, Hennekens CH. Increased pulse pressure and risk of heart failure in the elderly. Jama 1999;281:634-9.

48. He J, Ogden LG, Bazzano LA, Vupputuri S, Loria C, Whelton PK. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. Arch Intern Med 2001;161:996-1002.

49. Alcohol Alert: Alcohol Metabolism: National Institute on Alcohol Abuse and Alcoholism, 1997.

50. Romanoski AJ. Alcohol and Drug Dependence. In: Stobo JD, Hellmann, D.B., Ladenson, P.W., Petty, B.G., and Traill, T.A., ed. The Principles and Practice of Medicine. Stamford, CT: Appleton and Lange, 1996:927-936.

51. Mitchell MC. Acute Hepatitis. In: Stobo JD, Hellmann, D.B., Ladenson, P.W., Petty, B.G., and Traill, T.A., ed. The Principles and Practive of medicine. Stamford, CT: Appleton and Lange, 1996:516-525.

52. Mukamal KJ, Rimm EB. Alcohol's effects on the risk for coronary heart disease. Alcohol Res Health 2001;25:255-61.

53. Rotondo S, Di Castelnuovo A, de Gaetano G. The relationship between wine consumption and cardiovascular risk: from epidemiological evidence to biological plausibility. Ital Heart J 2001;2:1-8.

54. Goldberg DMaS, G.J. Beverage alcohol consumption as a negative risk factor for coronary heart disease, biochemical mechanisms. In: Agarwal DPaS, H. K., ed. Alcohol in Health and Disease. NewYork: Marcel Dekker, 2001:547-572.

55. Grobee DE, Rimm, E. B., Keil, U., and Renaud S. Alcohol and the cardiovascular system. In: Macdonald I, ed. Health Issues Related to Alcohol Consumption. London: Blackwell Science, 1999:127-179.

56. Srivastava LM, Vasisht S, Agarwal DP, Goedde HW. Relation between alcohol intake, lipoproteins and coronary heart disease: the interest continues. Alcohol Alcohol 1994;29:11 24.

57. Agarwal DP. Cardioprotective effects of light-moderate consumption of alcohol: a review of putative mechanisms. Alcohol Alcohol 2002;37:409-15.

58. Gillman MW, Cook NR, Evans DA, Rosner B, Hennekens CH. Relationship of alcohol intake with blood pressure in young adults. Hypertension 1995;25:1106-10.

59. Beilin LJ, Puddey IB, Burke V. Alcohol and hypertension--kill or cure? J Hum Hypertens 1996;10 Suppl 2:S1-5.

60. Dyer AR, Stamler J, Paul O, et al. Alcohol, cardiovascular risk factors and mortality: the Chicago experience. Circulation 1981;64:III 20-7.

61. Kagan A, Yano K, Rhoads GG, McGee DL. Alcohol and cardiovascular disease: the Hawaiian experience. Circulation 1981;64:III 27-31.

62. Klatsky AL, Friedman GD, Siegelaub AB. Alcohol use and cardiovascular disease: the Kaiser-Permanente experience. Circulation 1981;64:III 32-41.

63. Klatsky AL. Alcohol and Cardiovascular Diseases. In: Agarwal DP, and Seitz, H.K., ed. Alcohol in Health and Disease. New York: Marcel Dekker, 2001:517-546.

64. Gordon T, Ernst N, Fisher M, Rifkind BM. Alcohol and high-density lipoprotein cholesterol. Circulation 1981;64:III 63-7.

65. Miller GJ, Miller NE. Plasma-high density-lipoprotein concentration and development of ischaemic heart-disease. Lancet 1975;1:16-9.

66. Hannuksela ML, and Savolainen, M.J. Regulation of the Quantity and Quality of High-Density Lipoproteins by Alcohol: A Review. In: Agarwal D.P. SHK, ed. Alcohol in Health and Disease. New York: Marcel Dekker, Inc., 2001:573-595.

67. Kuller L. Alcohol and Cardiovascular Disease, Data from Committee on Diet and Health. Primer in Preventive Cardiology. Dallas: American Heart Association, 1994.

68. Hulley SB, Gordon S. Alcohol and high-density lipoprotein cholesterol: causal inference from diverse study designs. Circulation 1981;64:III 57-63.

69. Frankel EN, Kanner J, German JB, Parks E, Kinsella JE. Inhibition of oxidation of human low-density lipoprotein by phenolic substances in red wine. Lancet 1993;341:454-7.

70. Griffin BA. Lipoprotein atherogenicity: an overview of current mechanisms. Proc Nutr Soc 1999;58:163-9.

71. Serafini M, Laranjinha JA, Almeida LM, Maiani G. Inhibition of human LDL lipid peroxidation by phenol-rich beverages and their impact on plasma total antioxidant capacity in humans. J Nutr Biochem 2000;11:585-590.

72. Meade TW, Imeson J, Stirling Y. Effects of changes in smoking and other characteristics on clotting factors and the risk of ischaemic heart disease. Lancet 1987;2:986-8.

73. Mukamal KJ, Jadhav PP, D'Agostino RB, et al. Alcohol consumption and hemostatic factors: analysis of the Framingham Offspring cohort. Circulation 2001;104:1367-73.

74. Folsom AR, Qamhieh HT, Flack JM, et al. Plasma fibrinogen: levels and correlates in young adults. The Coronary Artery Risk Development in Young Adults (CARDIA) Study. Am J Epidemiol 1993;138:1023-36.

75. Folsom AR, Wu KK, Davis CE, Conlan MG, Sorlie PD, Szklo M. Population correlates of plasma fibrinogen and factor VII, putative cardiovascular risk factors. Atherosclerosis 1991;91:191-205.

76. Baum-Baicker C. The psychological benefits of moderate alcohol consumption: a review of the literature. Drug Alcohol Depend 1985;15:305-22.

77. Peele S, Brodsky A. Exploring psychological benefits associated with moderate alcohol use: a necessary corrective to assessments of drinking outcomes? Drug Alcohol Depend 2000;60:221-47.

78. Poikolainen K, Vartiainen E, Korhonen HJ. Alcohol intake and subjective health. Am J Epidemiol 1996;144:346-50.

79. Goldberg DM, Soleas GJ. Beverage Alcohol Consumption as a Negative Risk Factor for Coronary Heart Disease. In: Agarwal DP, Seitz HK, eds. Alcohol in Health and Disease. New York: Marcel Dekker, Inc., 2001:547-572.

80. Chick J. Alcohol, health, and the heart: implications for clinicians. Alcohol Alcohol 1998;33:576-91.

81. Davies MJ, Baer DJ, Judd JT, Brown ED, Campbell WS, Taylor PR. Effects of moderate alcohol intake on fasting insulin and glucose concentrations and insulin sensitivity in postmenopausal women: a randomized controlled trial. Jama 2002;287:2559-62.

82. Rimm EB, Chan J, Stampfer MJ, Colditz GA, Willett WC. Prospective study of cigarette smoking, alcohol use, and the risk of diabetes in men. Bmj 1995;310:555-9.

83. Kiechl S, Willeit J, Poewe W, et al. Insulin sensitivity and regular alcohol consumption: large, prospective, cross sectional population study (Bruneck study). Bmj 1996;313:1040-4.

84. Baum-Baicker C. The health benefits of moderate alcohol consumption: a review of the literature. Drug Alcohol Depend 1985;15:207-27.

85. Facchini F, Chen YD, Reaven GM. Light-to-moderate alcohol intake is associated with enhanced insulin sensitivity. Diabetes Care 1994;17:115-9.

86. Witteman JC, Willett WC, Stampfer MJ, et al. Relation of moderate alcohol consumption and risk of systemic hypertension in women. Am J Cardiol 1990;65:633-7.

87. Ascherio A, Rimm EB, Giovannucci EL, et al. A prospective study of nutritional factors and hypertension among US men. Circulation 1992;86:1475-84.

88. Gordon T, Kannel WB. Drinking and its relation to smoking, BP, blood lipids, and uric acid. The Framingham study. Arch Intern Med 1983;143:1366-74.

89. Friedman GD, Selby JV, Quesenberry CP, Jr., Armstrong MA, Klatsky AL. Precursors of essential hypertension: body weight, alcohol and salt use, and parental history of hypertension. Prev Med 1988;17:387-402.

90. Marmot MG, Elliott P, Shipley MJ, et al. Alcohol and blood pressure: the INTERSALT study. Bmj 1994;308:1263-7.

91. MacMahon S. Alcohol consumption and hypertension. Hypertension 1987;9:111-21.

92. Puddey IB, Beilin LJ, Vandongen R. Regular alcohol use raises blood pressure in treated hypertensive subjects. A randomised controlled trial. Lancet 1987;1:647-51.

93. Regan TJ. Alcohol and the cardiovascular system. Jama 1990;264:377-81.

94. Kasper EK, Agema WR, Hutchins GM, Deckers JW, Hare JM, Baughman KL. The causes of dilated cardiomyopathy: a clinicopathologic review of 673 consecutive patients. J Am Coll Cardiol 1994;23:586-90.

95. Suter PM. Alcohol and the Energy Balance: Is Alcohol a Risk Factor for Obesity? In: Agarwal DP, and Seitz, H.K., ed. Alcohol in Health and Disease. New York: Marcel Dekker, 2001:275-301.

96. Rose D, Murphy SP, Hudes M, Viteri FE. Food energy remains constant with increasing alcohol intake. J Am Diet Assoc 1995;95:698-700.

97. Suter PM, Hasler E, Vetter W. Effects of alcohol on energy metabolism and body weight regulation: is alcohol a risk factor for obesity? Nutr Rev 1997;55:157-71.

98. Li TK. Pharmacogenetics of responses to alcohol and genes that influence alcohol drinking. J Stud Alcohol 2000;61:5-12.

99. Truelsen T, Nielsen N, Boysen G, Gronbaek M. Self-reported stress and risk of stroke: the Copenhagen City Heart Study. Stroke 2003;34:856-62.

100. Hoeksema HL, de Bock GH. The value of laboratory tests for the screening and recognition of alcohol abuse in primary care patients. J Fam Pract 1993;37:268-76.

101. Carlsson S, Hammar N, Hakala P, Kaprio J, Marniemi J, Ronnemaa T. Assessment of alcohol consumption by mailed questionnaire in epidemiological studies: evaluation of misclassification using a dietary history interview and biochemical markers. Eur J Epidemiol 2003;18:493-501.

102. Duckert F, Johnsen J, Amundsen A, Stromme J, Morland J. Co-variation between biological markers and self-reported alcohol consumption. A two-year study of the relationship between changes in consumption and changes in the biological markers gamma-glutamyl transpeptidase (GGT) and average volume per erythrocyte (MCV) among problem drinkers. Alcohol Alcohol 1992;27:545-55.

103. Helander A. Biological Markers of Alcohol Use and Abuse in Theory and Practice. In: Agarwal D.P. SHK, ed. Alcohol in Health and Disease. New York: Marcel Dekker, Inc., 2001:177-205.

104. Doll R, Peto R, Hall E, Wheatley K, Gray R. Mortality in relation to consumption of alcohol: 13 years' observations on male British doctors. Bmj 1994;309:911-8.

105. Greenfield TK, Midanik LT, Rogers JD. Effects of telephone versus face-to-face interview modes on reports of alcohol consumption. Addiction 2000;95:277-84.

106. Midanik LT. Reliability of self-reported alcohol consumption before and after December. Addict Behav 1992;17:179-84.

107. Midanik LT. Validity of self-reported alcohol use: a literature review and assessment. Br J Addict 1988;83:1019-30.

108. Midanik LT, Klatsky AL, Armstrong MA. A comparison of 7-day recall with two summary measures of alcohol use. Drug Alcohol Depend 1989;24:127-34.

109. Midanik LT. Perspectives on the validity of self-reported alcohol use. Br J Addict 1989;84:1419-23.

110. Midanik L. The validity of self-reported alcohol consumption and alcohol problems: a literature review. Br J Addict 1982;77:357-82.

111. Midanik L. Over-reports of recent alcohol consumption in a clinical population: a validity study. Drug Alcohol Depend 1982;9:101-10.

112. Hilton ME. A comparison of a prospective diary and two summary recall techniques for recording alcohol consumption. Br J Addict 1989;84:1085-92.

113. Rehm J, Greenfield TK, Walsh G, Xie X, Robson L, Single E. Assessment methods for alcohol consumption, prevalence of high risk drinking and harm: a sensitivity analysis. Int J Epidemiol 1999;28:219-24.

114. Giovannucci E, Colditz G, Stampfer MJ, et al. The assessment of alcohol consumption by a simple self-administered questionnaire. Am J Epidemiol 1991;133:810-7.

115. Gronbaek M, Heitmann BL. Validity of self-reported intakes of wine, beer and spirits in population studies. Eur J Clin Nutr 1996;50:487-90.

116. Hoyer G, Nilssen O, Brenn T, Schirmer H. The Svalbard study 1988-89: a unique setting for validation of self-reported alcohol consumption. Addiction 1995;90:539-44.

117. Laatikainen T, Alho H, Vartiainen E, Jousilahti P, Sillanaukee P, Puska P. Self-reported alcohol consumption and association to carbohydrate-deficient transferrin and gamma-glutamyltransferase in a random sample of the general population in the Republic of Karelia, Russia and in North Karelia, Finland. Alcohol Alcohol 2002;37:282-8.

118. Lemmens P, Knibbe RA, Tan F. Weekly recall and dairy estimates of alcohol consumption in a general population survey. J Stud Alcohol 1988;49:131-5.

119. O'Callaghan FV, Callan VJ. Young adult drinking behaviour: a comparison of diary and quantity-frequency measures. Br J Addict 1992;87:723-32.

120. Poikolainen K, Karkkainen P. Diary gives more accurate information about alcohol consumption than questionnaire. Drug Alcohol Depend 1983;11:209-16.

121. Poikolainen K, Podkletnova I, Alho H. Accuracy of quantity-frequency and graduated frequency questionnaires in measuring alcohol intake: comparison with daily diary and commonly used laboratory markers. Alcohol Alcohol 2002;37:573-6.

122. Polich JM. Epidemiology of alcohol abuse in military and civilian populations. Am J Public Health 1981;71:1125-32.

123. Smith PF, Remington PL, Williamson DF, Anda RF. A comparison of alcohol sales data with survey data on self-reported alcohol use in 21 states. Am J Public Health 1990;80:309-12.

124. Townshend JM, Duka T. Patterns of alcohol drinking in a population of young social drinkers: a comparison of questionnaire and diary measures. Alcohol Alcohol 2002;37:187-92.

125. Bataille V, Ruidavets JB, Arveiler D, et al. Joint use of clinical parameters, biological markers and CAGE questionnaire for the identification of heavy drinkers in a large population-based sample. Alcohol Alcohol 2003;38:121-7.

126. Babor TF. Epidemiology, advocacy and ideology in alcohol studies. J Stud Alcohol 1990;51:293-5.

127. Williams GD, Aitken SS, Malin H. Reliability of self-reported alcohol consumption in a general population survey. J Stud Alcohol 1985;46:223-7.

128. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol 1985;122:51-65.

129. Camargo CA, Jr. Moderate alcohol consumption and stroke. The epidemiologic evidence. Stroke 1989;20:1611-26.

130. Feunekes GI, van 't Veer P, van Staveren WA, Kok FJ. Alcohol intake assessment: the sober facts. Am J Epidemiol 1999;150:105-12.

131. Rothman KJaG, S. Modern Epidemiology. Philadelphia: Lippincott Williams & Wilkins, 1998.

132. Brunner E, Stallone D, Juneja M, Bingham S, Marmot M. Dietary assessment in Whitehall II: comparison of 7 d diet diary and food-frequency questionnaire and validity against biomarkers. Br J Nutr 2001;86:405-14.

133. National Center for Health Statistics. Data File Documentation, National Health Interview Survey, 1997. Hyattsville, Maryland: National Center for Health Statistics.

134. Schoenborn CA AP. Alcohol use among adults: United States, 1997-98. Advance data from vital and health statistics; no. 324. Hyattsville, Maryland: National Center for Health Statistics, 2001.

135. Pleis JR CR. Summary Health Statistics for U.S. adults: National Health Interview Survey, 1999: National Center for Health Statistics, 2003.

136. National Health and Nutrition Examination Survey. In: Statistics NCHS, ed.

137. Greenfield TK, Midanik LT, Rogers JD. A 10-year national trend study of alcohol consumption, 1984-1995: is the period of declining drinking over? Am J Public Health 2000;90:47-52.

138. Behavioral Risk Factor Surveillance System. In: Prevention CfDCa, ed.

139. Midanik LT, Clark WB. The demographic distribution of US drinking patterns in 1990: description and trends from 1984. Am J Public Health 1994;84:1218-22.

140. Hilton ME. Abstention in the general population of the U.S.A. Br J Addict 1986;81:95-112.

141. (USDA) USDoHaHSaUSDoA. Nutrition and Your Health: Dietary Guidelines for Americans, 5th ed. Washington D.C., 2000.

142. Dietary Guidelines for Americans, 2005. Washington, DC: US Department of Health and Human Services and US Department of Agriculture, 2005.

143. Goldberg IJ, Mosca L, Piano MR, Fisher EA. AHA Science Advisory: Wine and your heart: a science advisory for healthcare professionals from the Nutrition Committee, Council on Epidemiology and Prevention, and Council on Cardiovascular Nursing of the American Heart Association. Circulation 2001;103:472-5.

144. Gorelick PB, Sacco RL, Smith DB, et al. Prevention of a first stroke: a review of guidelines and a multidisciplinary consensus statement from the National Stroke Association. Jama 1999;281:1112-20.

145. Pearson TA. AHA Science Advisory. Alcohol and heart disease. Nutrition Committee of the American Heart Association. Am J Clin Nutr 1997;65:1567-9.

146. Pearson TA. Alcohol and heart disease. Circulation 1996;94:3023-5.

147. Pearson TA, Blair SN, Daniels SR, et al. AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update: Consensus Panel Guide to Comprehensive Risk Reduction for Adult Patients Without Coronary or Other Atherosclerotic Vascular Diseases. American Heart Association Science Advisory and Coordinating Committee. Circulation 2002;106:388-91.

148. Renaud S, de Lorgeril M. Wine, alcohol, platelets, and the French paradox for coronary heart disease. Lancet 1992;339:1523-6.

149. Gronbaek M, Deis A, Sorensen TI, Becker U, Schnohr P, Jensen G. Mortality associated with moderate intakes of wine, beer, or spirits. Bmj 1995;310:1165-9.

150. Klatsky AL, Armstrong MA, Friedman GD. Red wine, white wine, liquor, beer, and risk for coronary artery disease hospitalization. Am J Cardiol 1997;80:416-20.

151. Klatsky AL, Armstrong MA. Alcoholic beverage choice and risk of coronary artery disease mortality: do red wine drinkers fare best? Am J Cardiol 1993;71:467-9.

152. Wolf PA, Clagett GP, Easton JD, et al. Preventing ischemic stroke in patients with prior stroke and transient ischemic attack : a statement for healthcare professionals from the Stroke Council of the American Heart Association. Stroke 1999;30:1991-4.

153. Reynolds K, Lewis LB, Nolen JD, Kinney GL, Sathya B, He J. Alcohol consumption and risk of stroke: a meta-analysis. Jama 2003;289:579-88.

154. Kiyohara Y, Kato I, Iwamoto H, Nakayama K, Fujishima M. The impact of alcohol and hypertension on stroke incidence in a general Japanese population. The Hisayama Study. Stroke 1995;26:368-72.

155. Klatsky AL, Armstrong MA, Friedman GD. Alcohol use and subsequent cerebrovascular disease hospitalizations. Stroke 1989;20:741-6.

156. Gaziano JM, Gaziano TA, Glynn RJ, et al. Light-to-moderate alcohol consumption and mortality in the Physicians' Health Study enrollment cohort. J Am Coll Cardiol 2000;35:96-105.

157. Hansagi H, Romelsjo A, Gerhardsson de Verdier M, Andreasson S, Leifman A. Alcohol consumption and stroke mortality. 20-year follow-up of 15,077 men and women. Stroke 1995;26:1768-73.

158. Jousilahti P, Rastenyte D, Tuomilehto J. Serum gamma-glutamyl transferase, self-reported alcohol drinking, and the risk of stroke. Stroke 2000;31:1851-5.

159. Kono S, Ikeda M, Tokudome S, Nishizumi M, Kuratsune M. Alcohol and mortality: a cohort study of male Japanese physicians. Int J Epidemiol 1986;15:527-32.

160. Maskarinec G, Meng L, Kolonel LN. Alcohol intake, body weight, and mortality in a multiethnic prospective cohort. Epidemiology 1998;9:654-61.

161. Goldberg RJ, Burchfiel CM, Reed DM, Wergowske G, Chiu D. A prospective study of the health effects of alcohol consumption in middle-aged and elderly men. The Honolulu Heart Program. Circulation 1994;89:651-9.

162. Romelsjo A, Leifman A. Association between alcohol consumption and mortality, myocardial infarction, and stroke in 25 year follow up of 49 618 young Swedish men. Bmj 1999;319:821-2.

163. Shaper AG, Phillips AN, Pocock SJ, Walker M, Macfarlane PW. Risk factors for stroke in middle aged British men. Bmj 1991;302:1111-5.

164. Wannamethee SG, Shaper AG. Patterns of alcohol intake and risk of stroke in middle-aged British men. Stroke 1996;27:1033-9.

165. Hart CL, Smith GD, Hole DJ, Hawthorne VM. Alcohol consumption and mortality from all causes, coronary heart disease, and stroke: results from a prospective cohort study of scottish men with 21 years of follow up. Bmj 1999;318:1725-9.

166. Berger K, Ajani UA, Kase CS, et al. Light-to-moderate alcohol consumption and risk of stroke among U.S. male physicians. N Engl J Med 1999;341:1557-64.

167. Donahue RP, Abbott RD, Reed DM, Yano K. Alcohol and hemorrhagic stroke. The Honolulu Heart Program. Jama 1986;255:2311-4.

168. Iso H, Kitamura A, Shimamoto T, et al. Alcohol intake and the risk of cardiovascular disease in middle-aged Japanese men. Stroke 1995;26:767-73.

169. Sankai T, Iso H, Shimamoto T, et al. Prospective study on alcohol intake and risk of subarachnoid hemorrhage among Japanese men and women. Alcohol Clin Exp Res 2000;24:386-9.

170. Sasaki S. Alcohol and its relation to all-cause and cardiovascular mortality. Acta Cardiol 2000;55:151-6.

171. Djousse L, Ellison RC, Beiser A, Scaramucci A, D'Agostino RB, Wolf PA. Alcohol consumption and risk of ischemic stroke: The Framingham Study. Stroke 2002;33:907-12.

172. Henrich JB, Horwitz RI. Evidence against the association between alcohol use and ischemic stroke risk. Arch Intern Med 1989;149:1413-6.

173. Shinton R, Sagar G, Beevers G. The relation of alcohol consumption to cardiovascular risk factors and stroke. The west Birmingham stroke project. J Neurol Neurosurg Psychiatry 1993;56:458-62.

174. Graham P, Jackson R. Primary versus proxy respondents: comparability of questionnaire data on alcohol consumption. Am J Epidemiol 1993;138:443-52.

175. Gill JS, Zezulka AV, Shipley MJ, Gill SK, Beevers DG. Stroke and alcohol consumption. N Engl J Med 1986;315:1041-6.

176. Gorelick PB, Rodin MB, Langenberg P, Hier DB, Costigan J. Weekly alcohol consumption, cigarette smoking, and the risk of ischemic stroke: results of a case-control study at three urban medical centers in Chicago, Illinois. Neurology 1989;39:339-43.

177. Herman B, Schmitz PI, Leyten AC, et al. Multivariate logistic analysis of risk factors for stroke in Tilburg, The Netherlands. Am J Epidemiol 1983;118:514-25.

178. Palomaki H, Kaste M. Regular light-to-moderate intake of alcohol and the risk of ischemic stroke. Is there a beneficial effect? Stroke 1993;24:1828-32.

179. Zodpey SP, Tiwari RR, Kulkarni HR. Risk factors for haemorrhagic stroke: a case-control study. Public Health 2000;114:177 82.

180. Caicoya M, Rodriguez T, Corrales C, Cuello R, Lasheras C. Alcohol and stroke: a community case-control study in Asturias, Spain. J Clin Epidemiol 1999;52:677-84.

181. Gill JS, Shipley MJ, Hornby RH, Gill SK, Beevers DG. A community case-control study of alcohol consumption in stroke. Int J Epidemiol 1988;17:542-7.

182. Gill JS, Shipley MJ, Tsementzis SA, et al. Alcohol consumption--a risk factor for hemorrhagic and non-hemorrhagic stroke. Am J Med 1991;90:489-97.

183. Jamrozik K, Broadhurst RJ, Anderson CS, Stewart-Wynne EG. The role of lifestyle factors in the etiology of stroke. A population-based case-control study in Perth, Western Australia. Stroke 1994;25:51-9.

184. Malarcher AM, Giles WH, Croft JB, et al. Alcohol intake, type of beverage, and the risk of cerebral infarction in young women. Stroke 2001;32:77-83.

185. Rodgers H, Aitken PD, French JM, Curless RH, Bates D, James OF. Alcohol and stroke. A case-control study of drinking habits past and present. Stroke 1993;24:1473-7.

186. Thrift AG, Donnan GA, McNeil JJ. Heavy drinking, but not moderate or intermediate drinking, increases the risk of intracerebral hemorrhage. Epidemiology 1999;10:307-12.

187. Beghi E, Boglium G, Cosso P, et al. Stroke and alcohol intake in a hospital population. A case-control study. Stroke 1995;26:1691-6.

188. Ben-Shlomo Y, Markowe H, Shipley M, Marmot MG. Stroke risk from alcohol consumption using different control groups. Stroke 1992;23:1093-8.

189. Rothman KJ. Epidemiology: An Introduction. New York: Oxford University Press, 2002.

190. Walsh CR, Larson MG, Evans JC, et al. Alcohol consumption and risk for congestive heart failure in the Framingham Heart Study. Ann Intern Med 2002;136:181-91.

191. Abramson JL, Williams SA, Krumholz HM, Vaccarino V. Moderate alcohol consumption and risk of heart failure among older persons. Jama 2001;285:1971-7.

192. Cooper HA, Exner DV, Domanski MJ. Light-to-moderate alcohol consumption and prognosis in patients with left ventricular systolic dysfunction. J Am Coll Cardiol 2000;35:1753-9.

193. Hajjar I, Kotchen T. Regional variations of blood pressure in the United States are associated with regional variations in dietary intakes: the NHANES-III data. J Nutr 2003;133:211-4.

194. Elkind MS, Sciacca R, Boden-Albala B, Rundek T, Paik MC, Sacco RL. Moderate alcohol consumption reduces risk of ischemic stroke: the Northern Manhattan Study. Stroke 2006;37:13-9.

195. Iso H, Baba S, Mannami T, et al. Alcohol consumption and risk of stroke among middle-aged men: the JPHC Study Cohort I. Stroke 2004;35:1124-9.

196. Leppala JM, Paunio M, Virtamo J, et al. Alcohol consumption and stroke incidence in male smokers. Circulation 1999;100:1209-14.

197. Mukamal KJ, Chung H, Jenny NS, et al. Alcohol use and risk of ischemic stroke among older adults: the cardiovascular health study. Stroke 2005;36:1830-4.

198. Palmer AJ, Fletcher AE, Bulpitt CJ, et al. Alcohol intake and cardiovascular mortality in hypertensive patients: report from the Department of Health Hypertension Care Computing Project. J Hypertens 1995;13:957-64.

199. Truelsen T, Gronbaek M, Schnohr P, Boysen G. Intake of beer, wine, and spirits and risk of stroke : the copenhagen city heart study. Stroke 1998;29:2467-72.

200. Sacco RL, Elkind M, Boden-Albala B, et al. The protective effect of moderate alcohol consumption on ischemic stroke. Jama 1999;281:53-60.

201. Klatsky AL, Chartier D, Udaltsova N, et al. Alcohol drinking and risk of hospitalization for heart failure with and without associated coronary artery disease. Am J Cardiol 2005;96:346-51.

CHAPTER 3
METHODS

3.1 Data Sources

Data to address the specific aims described in section 1 come from the ARIC cohort study. In brief, the ARIC study is an ongoing prospective cohort study funded by the NHLBI with 3 objectives: "1) to investigate the etiology and natural history of atherosclerosis, 2) to investigate the etiology of clinical atherosclerotic diseases and 3) to measure variation in cardiovascular risk factors, medical care, and disease by race, sex, place and time" (1).

3.2 Study Population

The study population consists of the ARIC participants. As part of the ARIC study, 15,792 study participants aged 45 to 64 years were sampled from 4 sites throughout the United States, including Forsyth County, North Carolina; Jackson Mississippi; Suburban Minneapolis, Minnesota; and Washington County, Maryland. At the Jackson site, only African-Americans were sampled. The study began enrolling participants in November 1986 and completed enrollment in late 1989. Probability sampling was used in determining the cohorts at each of the four sites. In Forsyth County, households were identified by area sampling, in Jackson and Washington County those with drivers' licenses or state identification cards were sampled, and in Minneapolis those eligible for jury duty were sampled (1).

3.3 Data Collection

ARIC cohort baseline data were collected from 1987 to 1989. At baseline, participants underwent a home interview and a clinic examination with participation rates of 46% for Jackson, and 65-67% for Forsyth County, Minneapolis, and Washington County. The baseline home interview included questions on cardiovascular risk factors, family medical history, employment, and education. Eligible participants who decided to participate were scheduled for a clinical exam. During the clinical exam, informed consent was obtained prior to data collection. The clinical exam consisted of an interview and physical exam. During the interview portion, trained ARIC interviewers asked participants questions related to medical history and a detailed food frequency questionnaire. As part of the physical exam, anthropometric measurements (weight, height) were taken, blood pressure was measured, blood samples were drawn, an electrocardiogram (ECG) was performed, pulmonary function was assessed, and a B-mode ultrasound for wall measurements in carotids was conducted. At the end of the exam, the results were shared with the participant and any abnormal results were verified and if necessary participants were referred elsewhere for diagnosis or treatment(1 -3).

During annual telephone follow-up, interviewers obtained information about hospitalizations and medical events within the preceding year. If the participant had been hospitalized, the medical record was obtained and abstracted for information related to coronary or cerebrovascular diseases. If the patient died, the death certificate was obtained and reviewed. Every 3 years participants underwent a

clinical exam, which was similar in content to the first exam described above. Currently, follow-up data has been collected, processed and made available through 2002. Hence, follow-up for this study is through December 31, 2002.

3.3.1 Alcohol Consumption Measurements

Alcohol consumption in the ARIC cohort was measured at visit 1 (baseline) and visit 3 (approximately 6 years later, 1993-1995). As part of the dietary questionnaire, participants were asked if they drank alcoholic beverages and if so, the type and amount. A total of five questions related to alcohol consumption were asked and included:

1. Do you presently drink alcoholic beverages?
2. Have you ever consumed alcoholic beverages?
3. How many glasses of wine do you usually have per week? (4oz glasses)
4. How many bottles or cans of beer do you usually have per week? (12oz bottles or cans)
5. How many drinks of hard liquor do you usually have per week? (1.5oz shots)

Alcohol intake is then calculated as the reported grams of alcohol consumed per week and is a continuous variable. Since alcohol intake data is available at two points in time, both sources of information will be utilized when appropriate. For example, among those who have an event (stroke, hospitalization, death, or loss to follow-up) before the third visit, only alcohol intake from visit 1 will be considered. Among those who reach visit 3 without having an event, alcohol information will be

updated. Previous work has examined the change in alcohol consumption among the ARIC participants between visit 1 and 3 and found that alcohol intake levels declined (4).

Based on findings from the literature, alcohol intake estimates are known to be underestimates, with self- reports only accounting for 40-60% of alcohol purchases (5). For our analyses we will assume that alcohol underreporting is similar among all levels of alcohol consumption. There is the possibility of doing a sensitivity analysis if good estimates of how much underreporting there is by differing levels of reported intake are available.

3.3.2 Measurement of Stroke Events

Clinical stroke events were determined by annually contacting all ARIC study participants and identifying all stroke hospitalizations and deaths. Details of stroke case ascertainment in the ARIC cohort have been previously published(6) and are summarized in Figure 3.1. Briefly, medical records from hospitalizations with an ICD-9 code of 430-438 (cerbrovascular disease) and/or a stroke related keyword in the discharge summary or nurses notes were identified and reviewed by a trained nurse. Abstracted data from the medical record included information on neurological symptoms, medical history, treatments and therapies, procedures performed, and, if deceased, autopsy information. Based on criteria from the National Survey of Stroke, strokes were classified by a computer algorithm into four categories: subarachnoid hemorrhage, intracerebral hemorrhage, thrombotic brain infarction, or

embolic brain infarction. Additionally, a physician independently reviewed the abstracted data and classified the stroke cases, with disagreements between the computer and physician adjudicated by a second physician-reviewer(6).

Validation of stroke events in the ARIC data from 1987 to 1995 indicates that of the 1187 identified stroke hospitalizations, 538 of the medical records had documentation of neurologic symptoms lasting more than 24 hours. Of these 538 hospitalizations, 329 were determined to be definite or probable strokes by the physician reviewer and computer algorithm (agreed on 78% of cases, kappa=0.71)(6).

The occurrence of a stroke event is defined as a definite or probable hospitalized stroke among those with no history of stroke at the time of baseline interview. Those with a previous stroke or an unknown history of stroke will be excluded from the analyses. Although out of hospital fatal strokes are recorded, these events are not validated (6), and will also be excluded from the analyses (in 1995, 4 fatal strokes).

3.3.3 Measurement of Heart Failure

CHF occurrence in the ARIC cohort study was determined by identifying and reviewing all hospital discharges with an ICD-9-CM code of 428.xx during annual follow-up. We will exclude those with prevalent heart failure at baseline. Prevalent HF will be defined as either taking HF medication in the two weeks before baseline, as having at least 2 of 3 HF symptoms (edema, PND, or orthopnea), or taking diuretics or digoxin. Similar to the method of heart failure ascertainment used by He

et al(7), “incident CHF was based on 1 or more hospital or nursing home stays in which the participant had a discharge diagnosis with an ICD-9 code of 428.0 to 428.9 or a death certificate report in which the underlying cause of death was recorded using an ICD-9 code of 428.0 to 428.9”. Currently a paper examining CHF ascertainment in the ARIC cohort is under development.

3.3.4 Measurement of Covariates

For the proposed analyses, potential covariates include socio-demographic characteristics, behavioral characteristics, clinical measurements, and comorbid conditions. Socio-demographic characteristics include age, race, gender, and education. Age is calculated as age at first clinic visit. Race is self-reported as African-American, Asian, Native American, white or other. Highest level of educational attainment was collected at the home interview which occurred prior to the first clinic visit. Participants were asked for the highest level of school completed which was grouped into grade school, high school but no degree, high school graduate, vocational school, college, or graduate/professional school. From these groups, educational status will be further categorized into less than high school, high school graduate, some college, or college graduate.

Data on behavioral characteristics of the study participants includes smoking, diet, and physical activity. Smoking and diet information was collected by self-report through interview questions. Participants were asked detailed questions regarding use of cigarettes, pipes, and cigars. The questions asked about ever smoking, how old when regular smoking began, current use, average number smoked per day, and

if smoke was inhaled (not at all, slightly, moderately, or deeply). In addition, one question asked about use of chewing tobacco, snuff, and nicotine gum (current, never, or past user). In an attempt to ascertain second-hand smoke exposure, non-smokers were asked to provide the number of hours per week they were in close contact with people who were smoking. The detailed tobacco use questions in the ARIC study are invaluable to the proposed study because tobacco use is more common among those who drink (8) and smoking is likely a confounder of the alcohol and CVD relation.

To obtain estimates of usual dietary intake, study participants were asked about their intake of a variety of food items and specified how often they consumed each item (number of times per day, number of times per week, number of times per month, or almost never). This interviewer-administered questionnaire obtained information on intake of dairy foods (8 questions), fruits (6 questions), vegetables (11 questions), meats (13 questions), sweets/baked goods and cereals (13 questions), non-alcoholic beverages (5 questions), other frequently eaten food, products used in cooking activities, and alcoholic beverages. The questionnaire, a modified version of the semiquantitative food frequency questionnaire and developed by Willett, was used because it has demonstrated reproducibility and validity (9), is brief, and is thought to characterize individual dietary patterns better than some other brief questionnaires.

Physical activity data was also collected through participant interviews and was composed of questions regarding leisure time, sport and work related activities during the past year. Participants were asked if they played sports or exercised

during their time away from work (leisure time) and also about other activities done during leisure time (walking, bicycling, watching television). Interviewers asked about sport and exercise activities, asking for the type and frequency (days per week and months per year) of activity. Work related questions asked participants if they sit, stand, walk, or lift during work (never, seldom, sometimes, often, very often) and if they are physically tired after work. Also, participants are asked if they sweat at work (due to physical exertion) and how they think their work compares physically to the work of others at a similar age (much lighter, lighter, as heavy, heavier, or much heavier) (3).

Clinical measurements were obtained from study participants at the initial clinic visit. Participants were requested to fast for 12 hours before the initial clinic visit, at which point blood was drawn to obtain data on blood lipids and hemostatic factors. Blood lipid measures included total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, lipoprotein(a), HDL_2 and HDL_3. Data from the ARIC Intraindividual Variability Study found the measures of total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, and lipoprotein(a) to have high reliability ($R>0.85$)(10). Hemostatic factors such as fibrinogen, plasma factor VII, plasma factor VIII, and von Willebrand factor were also included in the ARIC Intraindividual Study and were found to have high to intermediate reliability(11). Blood pressure was measured three times following an initial 5-minute rest period. The last two measures were averaged to obtain the blood pressure measurement used for this study. From the blood pressure, hypertension was defined as SBP $\geq$ 140 mmHg, DBP $\geq$ 90 mmHg, and/or self-report of antihypertensive medication use. This

definition of hypertension is in agreement with the JNC 6 guidelines for hypertension(12). Participant weight and height were measured during the first clinic examination and body mass index was calculated as weight (kg) divided by height in meters squared.

Comorbid conditions of the participants were obtained at the baseline interview through questions regarding history of illnesses, including diabetes, hypertension, valvular heart disease, history of CHD or MI.

3.4 Data Quality

The ARIC study developed detailed policies and procedures to ensure standardization of data collection, and staff were trained and certified in data collection procedures. Using a computer-assisted data collection system, data was directly entered into computers at each field center by staff while the participant was present in order to prevent transcription errors and to correct implausible values(13). Selected ultrasound and anthropometric measures were repeated during the exam for quality checks. In addition, duplicate blood samples were drawn and duplicate ECGs were transmitted for validation purposes(1).

Issues of data quality related to alcohol intake in the ARIC cohort can be divided into: 1) validity and reliability of responses from the participants and 2) accuracy of recording information by the ARIC study staff. How well the respondents' answers correspond to actual alcohol intake in the ARIC cohort has not been validated, probably due to the lack of a gold standard for alcohol assessment

and no availability of biologic markers to use as proxies for alcohol intake in the ARIC cohort. Also, the reliability of reported alcohol consumption in this cohort has not been evaluated. Numerous other studies have assessed methods for collecting data on alcohol consumption (see section 2.4.2 above for a review) and have found that ascertainment of alcohol intake via trained interviewer administered questionnaire is reliable (14) and that although self- reported alcohol consumption is probably an underestimate, this method does a fairly good job of rank ordering levels of drinkers.

To lessen the variation in question interpretation and allow for those less literate to better understand the questions, interviewers were trained on research interviewing methods and how to complete the form. In ARIC, the alcohol intake questions are close-ended with the interviewer directly entering the responses into the computer. To reduce inter and intra- rater reliability, approximately 5% of the interviews done by each interviewer are monitored by supervisory level staff.

Identification of outcomes occurring during follow-up in the ARIC cohort is via three sources of data: death certificates, hospital discharge indexes, and annual follow-up telephone interviews with the study participants. The term 'outcomes' refers to hospitalized MI or stroke, death from CHD, stroke, or any cause, and all hospitalizations. Hospital discharge diagnoses are recorded for all hospitalizations that occur among the ARIC participants. These hospitalizations are identified by either review of hospital discharge indexes or by annual participant interviews. If a study participant were hospitalized outside of the study area and did not inform the interviewer of this event, the hospitalization may not be captured in the ARIC study.

Once hospitalizations are identified, medical records are abstracted for those hospitalizations with ICD-9 codes of 402, 410-414, 427, 428, 518.4, and stroke (430-438). Participants are followed annually from the baseline interview until death or loss to follow-up.

3.5 Power Calculations

Since the ARIC study data has already been collected and follow up is available through December 31, 2002, the power to detect a specific difference is addressed rather than the question of sample size. In the ARIC cohort, there were a total of 15,792 participants at baseline and with follow-up through December 2002, a total of 564 incident stroke events (57 hemorrhagic and 507 ischemic) and approximately 1000 CHF hospitalizations. Based on previously published papers from the ARIC dataset which examined alcohol intake(4, 15)and preliminary calculations of alcohol intake from the dataset, categorization of study participants into never, light/moderate (up to 2 drinks/day formen and up to 1 drink/day for women), and heavy (>2 drinks/day for men and >1 drink/day for women) drinkers gives estimates of the proportion in each of these groups to be 39.5%, 48.7%, and 11.7%, respectively.

Table 3.1 shows the magnitude of the risk ratios that can be detected for the comparisons of light/moderate with never drinkers and of heavy with never drinkers. The significance level for the power calculations in these two tables is set at 95% (α=0.05). Using estimates of risk among the unexposed for each of the three outcomes (ischemic stroke, hemorrhagic stroke, and HF), the unexposed to exposed

ratio, and the maximum number exposed, risk ratios for varying levels of power (ranging from 0.7 to 0.9) are calculated. Table 3.1, for example, indicates that the study has 70% power to detect a risk ratio of 1.31 or 0.71 in the comparison of ischemic stroke risk among light/moderate versus never drinkers.

3.6 Plan of Analysis

The ARIC Coordinating Center cleaned and edited the data prior to release. As part of this project, each variable was examined for missing values, implausible values, and other inconsistencies. Prior to data analysis for this project, additional data checks will be implemented and will include examination of the distributions of analytic variables using tables and graphs.

The analyses will be limited to study participants who are African-American or white (>99% of the ARIC population) because of the small number of events occurring in the other race groups. Additionally, those participants with missing information on alcohol consumption will be excluded from the analysis since this variable is the main exposure of interest. While imputation methods reduce the loss of power associated with deleting those with missing information, imputation techniques require assumptions about the data and can be difficult to implement. Currently, no analytic ARIC dataset with imputed values for missing data exists and the proportion of data missing in the ARIC cohort is minimal. Thus, complete case analysis is an appropriate choice (16) and will be used in this project.

3.6.1 Alcohol Consumption and Stroke Incidence

Specific Aim 1: Examine the relation and association between alcohol consumption and stroke incidence among African-American and white men and women ages 45-64 years at baseline (the ARIC study participants) during an average follow-up of 11 years.

Hypothesis 1: The association between alcohol consumption and ischemic stroke incidence varies according to the level of alcohol consumed. Using never drinkers as the referent group, there is an inverse association between alcohol intake and ischemic stroke incidence among light to moderate drinkers and there is a positive association between heavy consumption and ischemic stroke incidence.

- To assess the association of varying levels of alcohol intake and ischemic stroke risk, alcohol intake will be categorized. Although there are numerous ways in which alcohol intake could be categorized (percentiles, predetermined cut points, dichotomized), we will base our categorization on the AHA recommendations/ guidelines. The guidelines categorize alcohol intake into never, former, light/moderate ($\leq$2 drinks/day for men and $\leq$1 drink/day for women), and heavy drinkers (>2 drinks/day for men and >1 drink/day for women). Since alcohol consumption levels may change over time, both alcohol measurements (obtained at visit 1 and visit 3) will be incorporated in the analyses. A pooled method similar to that used by Djousse et al. (17) will be used to create two 6-year nonoverlapping follow-up periods (from visit 1 to visit 3 and from visit 3

onwards). Alcohol intake at the beginning of each period will be used as the exposure. Thus, each subject can contribute 1 or 2 observations, depending on if and when a stroke occurred. Follow-up time will be calculated as the time from the beginning of each follow-up period to stroke occurrence, death, loss to follow-up, or the end of the 6-year period.

- Descriptive statistics of the population (sociodemographic characteristics) by categories of alcohol intake will be calculated to ascertain if the groups of alcohol consumers are different.
- Crude and adjusted ischemic stroke incidence rates by level of alcohol consumption will be calculated using Poisson regression. Poisson regression is used for modeling incidence rates for rare outcomes and is thus preferred over survival analysis which is more appropriate when the disease is more common (16). From the Poisson regression models, we will calculate incidence rate ratios (IRR) with 95% confidence intervals, using the never drinkers as the reference category.
- The identification and evaluation of potential confounding factors will involve several steps. To be a confounder the covariate should be 1) associated with stroke incidence, 2) be associated with alcohol consumption, and 3) not be affected by alcohol(16). A directed acyclic graph (DAG) has been drawn to represent the relations between exposure, disease, and covariates (Figure 3.2) and this drawing will be used to identify potential confounding factors (18). DAGs are graphical

representations of subject matter knowledge and indicate how the variables are related (19). Arrows in the diagram indicate possible causal relations and missing arrows indicate no causal relation (19). Creating DAGs is useful for helping to determine which variables are potential confounders and should be included in the analysis (18). In DAGs, unblocked backdoor paths represent confounding. To identify unblocked paths between alcohol (E) and stroke (D), arrows that originate from E are removed and all remaining paths between E and D are documented. Paths that are not blocked by a collider are identified and the variables on unblocked paths are candidates for adjustment. In Figure 3.2 (the DAG of the alcohol-stroke risk relation), adjustment for A will block all paths between E and D. Thus age, race, gender, and socioeconomic status should be considered as potential confounding factors.

Hypothesis 2: There is a positive association between alcohol intake and hemorrhagic stroke incidence. Compared with never drinkers, those consuming light to moderate amounts will have increased rates of hemorrhagic stroke and those consuming heavy amounts will have even higher hemorrhagic stroke rates.

- Alcohol intake will be categorized according to the methods outlined in hypothesis 1.1 above.
- Descriptive statistics of the population (sociodemographic characteristics) by categories of alcohol intake will be calculated to ascertain if the groups of alcohol consumers are different.

- Crude and adjusted hemorrhagic stroke incidence rates by level of alcohol consumption will be calculated using Poisson regression. Follow-up time is measured as detailed above. From the Poisson regression models, incidence rate ratios (IRR) will be calculated and precision will be estimated with 95% confidence intervals.
- Evaluation of confounding will be conducted using DAGs, similar to that described for ischemic stroke in hypothesis 1.1.

Hypothesis 3: The alcohol and stroke relations found in hypotheses 1 and 2 above do not differ by race.

- The crude and age-adjusted rates, as well as the Poisson regression models will be stratified by race. This will generate estimates of the incidence rates and incidence rate ratios separately for blacks and whites.

3.6.2 Alcohol Consumption and Heart Failure Incidence

Specific Aim 2: Describe and evaluate the association between alcohol consumption and heart failure (HF) hospitalizations among African-American and white men and women ages 45-64 years at baseline (the ARIC study participants) during an average follow-up of 11 years.

Hypothesis 1: Compared with never drinkers, there is an inverse association between alcohol intake and HF incidence among those who consume light to moderate amounts of alcohol and there is a positive association for those who consume heavy amounts of alcohol.

- To compare these results with the AHA alcohol consumption guidelines, alcohol will be categorized using the categories outlined in the guidelines and described above. Although the induction time for alcohol to cause HF hospitalization is unknown, we hypothesize that changes in alcohol intake during the study are sufficient to effect HF hospitalization rates. Hence, alcohol measured at baseline and visit 3 will be incorporated as exposures.
- Descriptive statistics of the population (sociodemographic characteristics) by categories of alcohol intake and time period will be calculated to ascertain if the groups of alcohol consumers are different.
- Crude and age-adjusted HF incidence rates by level of alcohol consumption will be calculated using Poisson regression.
- From the Poisson regression models, we will calculate incidence rate ratios (IRR) with 95% confidence intervals, using the never drinkers as the reference category.
- A directed acyclic graph approach will be will be used to identify potential confounding factors. The DAG representing the relation between alcohol and HF hospitalization can be found in Figure 3.3. According to this graph, the variables which should be included as potential confounders are age, race, gender and socioeconomic status.

Hypothesis 2: The association between alcohol intake and HF incidence does not differ by race.

- The crude and age-adjusted rates, as well as the Poisson regression models will be stratified by race. This will albw for comparisons of the incidence rates and incidence rate ratios separately for blacks and whites.

Table 3.1: Estimated power to detect risk ratios comparing drinking groups with never drinkers with alpha=0.05*

Group (vs. never)	Ischemic stroke risk among unexp	Hemorrhagic stroke risk among unexp.	HF risk among un-exposed	Unexposed: Exposed Ratio	Maximum Number Exposed	RR	Power
Light/mod.	3 per 100	n/a	n/a	0.81	7305	0.77	0.70
Light/mod.	3 per 100	n/a	n/a	0.81	7305	0.74	0.80
Light/mod.	3 per 100	n/a	n/a	0.81	7305	0.70	0.90
Light/mod.	n/a	4 per 1000	n/a	0.81	7305	1.81	0.70
Light/mod.	n/a	4 per 1000	n/a	0.81	7305	1.93	0.80
Light/mod.	n/a	4 per 1000	n/a	0.81	7305	2.09	0.90
Light/mod.	n/a	n/a	7 per 100	0.81	7305	0.84	0.73
Light/mod.	n/a	n/a	7 per 100	0.81	7305	0.83	0.83
Light/mod.	n/a	n/a	7 per 100	0.81	7305	0.80	0.91
Heavy	3 per 100	n/a	n/a	3.4	1755	1.41	0.70
Heavy	3 per 100	n/a	n/a	3.4	1755	1.48	0.81
Heavy	3 per 100	n/a	n/a	3.4	1755	1.56	0.91
Heavy	n/a	4 per 1000	n/a	3.4	1755	2.25	0.70
Heavy	n/a	4 per 1000	n/a	3.4	1755	2.46	0.80
Heavy	n/a	4 per 1000	n/a	3.4	1755	2.76	0.90
Heavy	n/a	n/a	7 per 100	3.4	1755	1.26	0.71
Heavy	n/a	n/a	7 per 100	3.4	1755	1.30	0.82
Heavy	n/a	n/a	7 per 100	3.4	1755	1.34	0.90

* Based on calculations from EpiSheet, available at http://members.aol.com/krothman/episheet.xls
Calculations assume 15000 participants, with 39.5% never drinkers, 48.7% light/moderate drinkers, and 11.7% heavy drinkers. For females, estimate that 45% are never, 50% are light/moderate, and 5% are heavy alcohol consumers. For males, estimate that 35% are never, 45% are light/moderate, and 20% are heavy alcohol drinkers.

Figure 3.1: Stroke Case Ascertainment Diagram

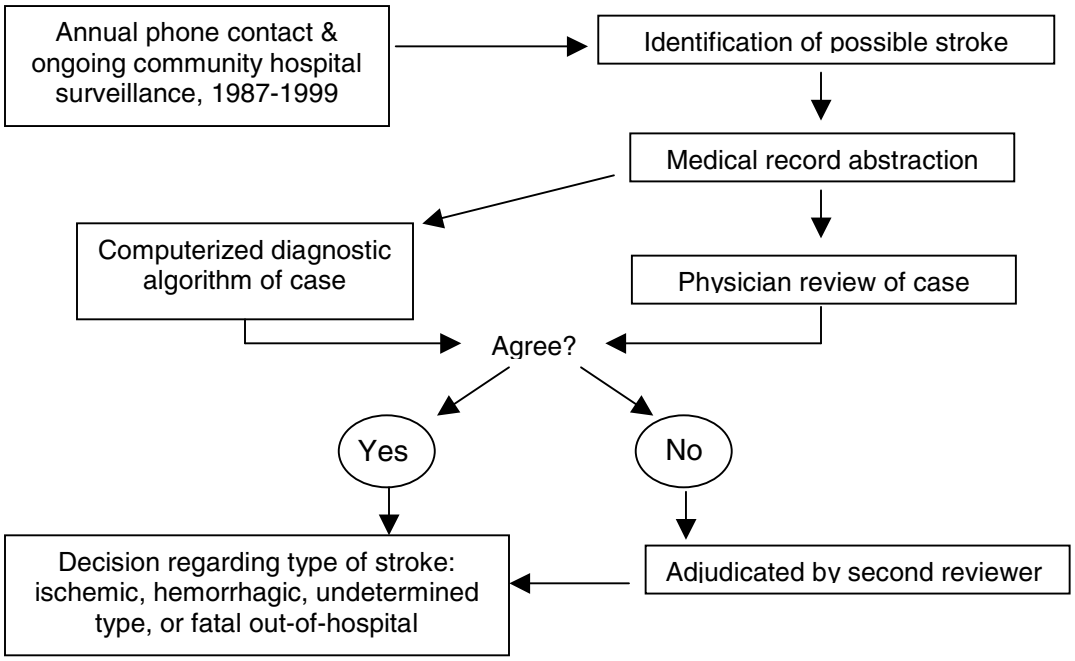
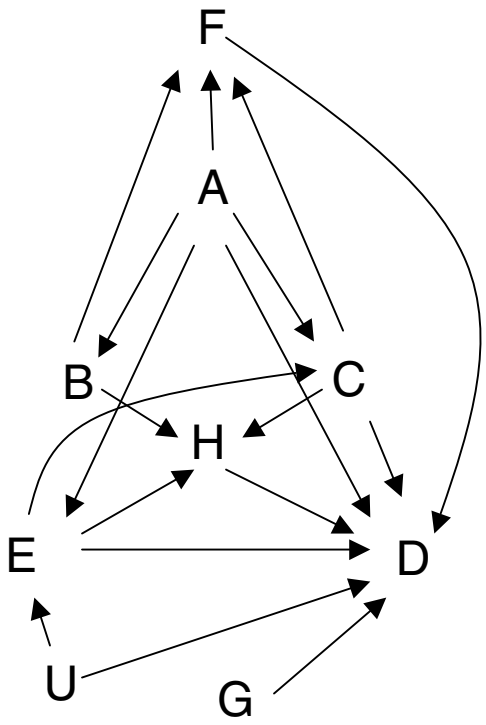
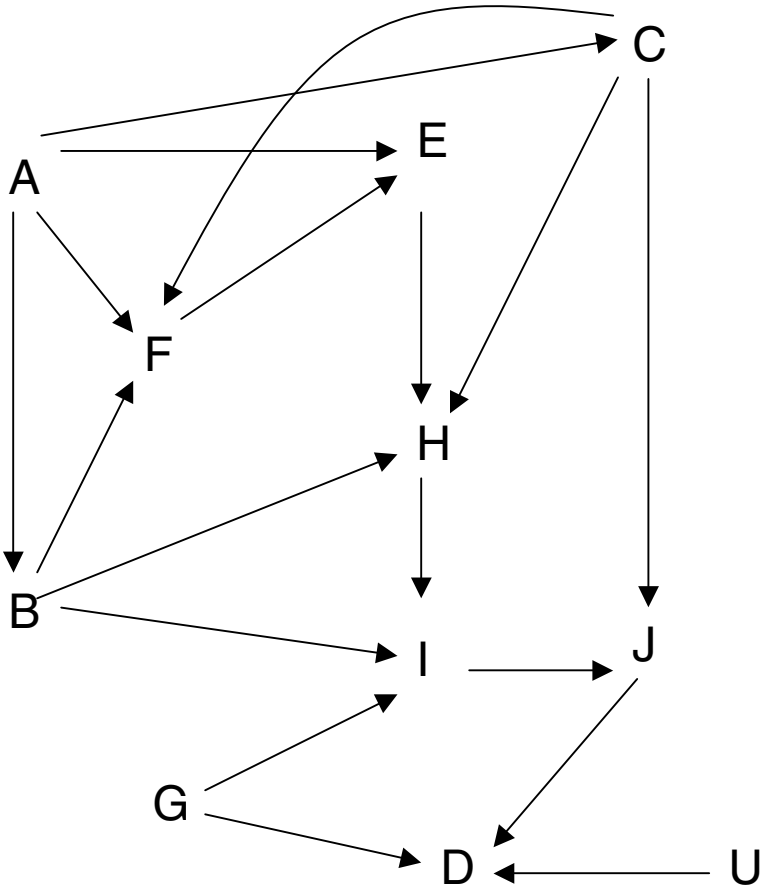


Figure 3.2: Directed Acyclic Graph (DAG): Alcohol Consumption and Cerebrovascular Disease



A: Sociodemographic characteristics including age, race, gender, and socioeconomic status.
B: Dietary factors including intake of cholesterol, saturated fat, and antioxidants.
C: Lifestyle factors including smoking and physical activity, stress.
D: Disease – ischemic or hemorrhagic stroke.
E: Exposure – alcohol intake.
F: Comorbid conditions including diabetes, hypertension, atrial fibrillation, and TIA.
G: Genetic factors.
H: Biologic measures including HDL, LDL, blood pressure, fibrinogen, insulin sensitivity, etc.
U: Unidentified factors.

Figure 3.3: Directed Acyclic Graph (DAG): Alcohol and Heart Failure



A: Sociodemographic characteristics including age, race, gender, and socioeconomic status.
B: Dietary factors including intake of cholesterol, saturated fat, and antioxidants.
C: Lifestyle factors including smoking and physical activity, stress.
D: Disease – hospitalization for congestive heart failure (CHF).
E: Exposure – alcohol intake.
F: Comorbid conditions including diabetes, hypertension, atrial fibrillation, and TIA.
G: Genetic factors.
H: Biologic measures including HDL, LDL, blood pressure, fibrinogen, insulin sensitivity, etc.
I: Previous myocardial infarction
J: Heart disease
U: Unidentified factors.

3.7 References

1. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. Am J Epidemiol 1989;129:687-702.

2. ARIC Manual 1: General Description and Study Management. Chapel Hill, NC: ARIC Coordinating Center, Department of Biostatistics, 1987.

3. ARIC Visit 1 Manual 2 Appendix IX: Study Forms. Chapel Hill, NC: ARIC Coordinating Center, Department of Biostatistics, 1987.

4. Eigenbrodt ML, Mosley TH, Jr., Hutchinson RG, Watson RL, Chambless LE, Szklo M. Alcohol consumption with age: a cross-sectional and longitudinal study of the Atherosclerosis Risk in Communities (ARIC) study, 1987-1995. Am J Epidemiol 2001;153:1102-11.

5. Midanik L. The validity of self-reported alcohol consumption and alcohol problems: a literature review. Br J Addict 1982;77:357-82.

6. Rosamond WD, Folsom AR, Chambless LE, et al. Stroke incidence and survival among middle-aged adults: 9-year follow-up of the Atherosclerosis Risk in Communities (ARIC) cohort. Stroke 1999;30:736-43.

7. He J, Ogden LG, Bazzano LA, Vupputuri S, Loria C, Whelton PK. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. Arch Intern Med 2001;161:996-1002.

8. Friedman GD, Tekawa I, Klatsky AL, Sidney S, Armstrong MA. Alcohol drinking and cigarette smoking: an exploration of the association in middle-aged men and women. Drug Alcohol Depend 1991;27:283-90.

9. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol 1985;122:51-65.

10. Chambless LE, McMahon RP, Brown SA, Patsch W, Heiss G, Shen YL. Short-term intraindividual variability in lipoprotein measurements: the Atherosclerosis Risk in Communities (ARIC) Study. Am J Epidemiol 1992;136:1069-81.

11. Chambless LE, McMahon R, Wu K, Folsom A, Finch A, Shen YL. Short-term intraindividual variability in hemostasis factors. The ARIC Study. Atherosclerosis Risk in Communities Intraindividual Variability Study. Ann Epidemiol 1992;2:723-33.

12. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. Arch Intern Med 1997;157:2413-46.

13. Christiansen DH, Hosking JD, Dannenberg AL, Williams OD. Computer-assisted data collection in multicenter epidemiologic research. The Atherosclerosis Risk in Communities Study. Control Clin Trials 1990;11:101-15.

14. Giovannucci E, Colditz G, Stampfer MJ, et al. The assessment of alcohol consumption by a simple self-administered questionnaire. Am J Epidemiol 1991;133:810-7.

15. Eigenbrodt ML, Fuchs FD, Hutchinson RG, Paton CC, Goff DC, Jr., Couper DJ. Health-associated changes in drinking: a period prevalence study of the Atherosclerosis Risk In Communities (ARIC) cohort (1987-1995). Prev Med 2000;31:81-9.

16. Rothman KJaG, S. Modern Epidemiology. Philadelphia: Lippincott Williams & Wilkins, 1998.

17. Djousse L, Ellison RC, Beiser A, Scaramucci A, D'Agostino RB, Wolf PA. Alcohol consumption and risk of ischemic stroke: The Framingham Study. Stroke 2002;33:907-12.

18. Robins JM. Data, design, and background knowledge in etiologic inference. Epidemiology 2001;12:313-20.

19. Pearl J. Causal Inference in the Health Sciences: A Conceptual Introduction. Health Services and Outcomes Research Methodology 2001;2:189-220.

CHAPTER 4
Alcohol Consumption and Stroke Incidence in the Atherosclerosis Risk in Communities (ARIC) Study, 1987-2002

4.1 Introduction

In the U.S., an estimated 500,000 new strokes occur every year and the expected cost of stroke in 2006 is $57.9 billion (1). Risk factors for stroke include transient ischemic attack, smoking, hypertension, diabetes, female gender, and non-white race (1-4). While controversial, alcohol has been identified as a possible risk factor for stroke. The relationship between alcohol consumption and stroke occurrence has been under investigation for decades although no clear association has been established. Previous studies have found differing results for ischemic and hemorrhagic strokes (reviewed in Reynolds et al (5)). For ischemic stroke, the evidence for increased stroke rates among heavy drinkers has been fairly consistent (6-9) but the data for light to moderate drinkers has been inconclusive, reporting either no association (10-14) or a protective effect (8, 15, 16). In contrast, studies of hemorrhagic stroke incidence have found either an increase in stroke rates with increasing amounts of alcohol consumption (6, 16-20) or no association between the two (11, 15, 21).

Stroke incidence rates are twice as high for blacks as for whites (1). The majority of previous U.S. studies examining the alcohol and stroke association have focused on white populations (10, 15, 16). Few studies have examined the

alcohol/stroke relationship among blacks (22). The Atherosclerosis Risk in Communities (ARIC) study is a large prospective cohort study that includes significant numbers of blacks and can therefore be utilized to study the effect of alcohol intake on stroke incidence among racial groups. The aim of this study is to evaluate the role of alcohol intake on ischemic and hemorrhagic stroke incidence among a middle-aged cohort of black and white men and women in the U.S.

4.2 Methods

Study Population and Design

The ARIC study is a prospective cohort study of 15,792 men and women ages 45 to 64 years of age from 4 U.S. communities. Details of the ARIC study have been previously published (23). At the initial visit (from 1987-1989), participants were interviewed at home and underwent a physical examination. During annual telephone follow-up, interviewers obtained information about hospitalizations and medical events within the preceding year. Additionally, more in-depth visits were conducted every 3 years when participants underwent a clinical exam consisting of an interview and physical exam (**Figure 4.1**). Information collected at visit 1 is from 1987-1989, visit 2 is from 1990-1992, and visit 3 is from 1993-1995. Follow-up data is available through 2002.

Of the 15,792 study participants, we excluded those who were non-white and non-black (n=48) and those who had prevalent coronary heart disease or a history of stroke at the initial visit (n=1,352). Participants who did not provide information on

alcohol intake at a specific visit were excluded from the analysis for that visit (78 at visit 1 and 120 at visit 3) as were participants who had missing covariate information at the time of the study visit (347 at visit 1 and 355 at visit 3). The covariates considered were age, race, sex, education, smoking, diabetes, hypertension, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, physical activity, and body mass index. For the visit 3+ data, we excluded an additional 2,554 participants who either had a stroke event, died, or were lost to follow-up before the visit 3 date. A total of 13,967 participants were included in the visit 1-visit 3 time period and 11,363 participants were included in the visit 3+ time period.

Alcohol Consumption

Alcohol consumption in the ARIC cohort was measured at visit 1 (1986-1989) and at visit 3 (1993-1995). As part of the dietary questionnaire, participants were asked if they drank alcoholic beverages and if so, the type and amount. A total of five questions related to alcohol consumption were asked and included: Do you presently drink alcoholic beverages? Have you ever consumed alcoholic beverages? How many 4-ounce glasses of wine do you usually have per week? How many 12-ounce bottles or cans of beer do you usually have per week? How many drinks of hard liquor (1.5-ounce shots) do you usually have per week?

We calculated the amount of ethanol consumed using the following: one glass of wine = 10.8 g alcohol, one bottle/can of beer = 13.2 g alcohol and one 1.5 ounce

shot of liquor = 15.1 g alcohol. The amount reported on a weekly basis was summed and divided by seven to obtain a daily estimate of alcohol consumed in grams. One drink was defined as 13 grams/day (the average alcohol contents of one glass of wine, one can of beer, and one 1.5oz shot of liquor). We then categorized alcohol consumption into never drinkers (reported never consuming alcoholic beverages), former drinkers (reported previously drinking alcoholic beverages, but not currently drinking), occasional drinkers (reported presently drinking alcohol but the usual amount consumed per week was zero), light to moderate drinkers (reported presently drinking up to 1 drink per day for women and up to 2 drinks per day for men), and heavy drinkers (reported presently drinking more than 1 drink per day for women and more than 2 drinks per day for men). These categories of alcohol consumption were chosen in an attempt to create groups of participants with similar levels of exposure. Specifically, former drinkers are likely to be different than never drinkers in that former drinkers may have stopped drinking for health reasons and may thus be sicker than never drinkers. Also, the group of occasional drinkers consists of those who drink but do not do so on a regular basis which is likely to be a different pattern of alcohol consumption than that of light/moderate drinkers.

Stroke Occurrence

Clinical stroke events were identified by annually contacting all ARIC study participants and by reviewing hospitalization discharge summaries and death records in the geographic locations surrounding the study areas. Details of stroke

case ascertainment in the ARIC cohort have been previously published (24). Briefly, medical records from hospitalizations with an ICD-9 code of 430-438 (cerebrovascular disease) and/or a stroke related keyword in the discharge summary or nurses notes were identified and reviewed by a trained nurse. Data from medical records were then abstracted. The abstracted data included information on neurological symptoms, medical history, treatments and therapies, procedures performed, and, if deceased, autopsy information. Based on criteria from the National Survey of Stroke, strokes were classified by a computer algorithm into four categories: subarachnoid hemorrhage, intracerebral hemorrhage, thrombotic brain infarction, or embolic brain infarction. In addition, a physician independently reviewed the abstracted data and classified the stroke cases, with disagreements between the computer and physician adjudicated by a second physician-reviewer.

Covariate Assessment

Covariate information for each participant was assessed at visit 1 and updated at visit 3 if the participant was still involved in the study. Participant age was defined as the age at the visit date. Race was based on self- reported information and was either black or white. Gender was male or female. Study center was defined as 1 of the 4 study sites: Forsyth County NC, Jackson MS, Minneapolis MN, or Washington County MD. Socioeconomic status was based on the highest self-reported educational level achieved and was categorized into less than high school graduate, high school graduate, or greater than high school graduate. Smoking was classified

as current, previous or never as reported by the participant at the time of the visit. Body mass index was calculated by dividing weight (in kg) by height (in meters squared) and was categorized into normal (<25.0), overweight (25.0 – 29.9), and obese (30.0+). Physical activity was assessed using the modified Baecke leisure time index which includes measures of walking and biking either as a leisure activity or as a mode of transportation to work or shopping, along with time spent watching television (25, 26). Physical activity was categorized into quartiles. Diabetes was dichotomized into a yes/no variable, with participants whose fasting blood glucose level was $\geq$ 126mg/dL at the time of the visit classified as having diabetes. Hypertension was also dichotomized, with those patients who had systolic blood pressure $\geq$ 140 at the study visit or diastolic blood pressure $\geq$ 90 at the study visit or who had taken blood pressure medication in the last 2 weeks classified as being hypertensive. Cholesterol measures included LDL-cholesterol (mg/dL), HDL-cholesterol (mg/dL), and triglycerides (mg/dL) as measured at the time of the visit. Participants with LDL-cholesterol levels $\geq$ 100mg/dL were determined to have high LDL-cholesterol, participants with HDL-cholesterol levels <40 mg/dL were classified as having low HDL-cholesterol, and participants with triglyceride levels $\geq$ 150 mg/dL were classified as having high triglycerides. To account for the fact that these covariates change over time, we incorporated data from visit 1 and visit 3.

Statistical Analyses

Stroke incidence rates were calculated as the number of stroke events divided by the person-time of follow-up. Since participants could contribute 1 or 2 observations

to the study, each person-visit combination was treated as an observation. For participants with visit 1 data, the follow-up time was calculated as the number of days from visit 1 until first stroke occurrence, death, loss to follow-up, or visit 3 date (whichever came first). For participants with visit 3 data who did not have a stroke before visit 3, follow-up time was calculated as the number of days from visit 3 until stroke occurrence, death, loss to follow-up, or December 31, 2002. Because time at risk stopped accruing once a stroke occurred (regardless of the type), the follow-up time is the same for all strokes, ischemic strokes, and hemorrhagic strokes. If a participant experienced more than one event, only the first event was included in the analysis. For example, if a participant had an ischemic stroke on 1/1/1995 and subsequently had a hemorrhagic stroke on 1/1/1997, only the ischemic stroke event is considered. Incidence rates by alcohol intake levels and visit were calculated for all, ischemic, and hemorrhagic strokes separately for the entire cohort and separately for blacks and whites.

Poisson regression multivariate rate ratios (RRs) were estimated to compare differing levels of alcohol consumption on stroke incidence. The outcomes of all stroke, ischemic stroke, and hemorrhagic stroke were examined separately. We stratified the results by race to assess if differences existed. Never drinkers were the reference group in all models. Potential confounders included age, gender, race, study center, educational level, body mass index, physical activity, smoking status, lipid measurements, and comorbid conditions (diabetes, hypertension). We determined which covariates to include in the models using a directed acyclic graph

(DAG) approach (27) (see Appendix for DAG). The covariates in the minimally adjusted models include age, race, sex, and socioeconomic status. The fully adjusted models include covariates in the minimally adjusted model plus smoking, physical activity, ARIC study center, body mass index, and diabetes.

All analyses were performed using SAS v8 software (SAS Institute, Cary NC).

4.3 Results

The person-time contributions by covariates and alcohol intake levels for visit 1-3 and visit 3+ are shown in Table 4.1. During the visit 1-3 time period, the 13,967 participants contributed 94,859 person-years (P-Y) of observation, of which 25% (24,138P-Y) were among never drinkers, 19% (17,587P-Y) were among former drinkers, 17% (16,507P-Y) were among occasional drinkers, 29% (27,506P-Y) were among light/moderate drinkers, and 10% (9,121P-Y) were among heavy drinkers. A similar distribution of person-time is evident for the visit 3+ time period.

During the time period from visit 1 to visit 3, the proportion of person-time contributed to the never drinking category was similar for blacks and whites (11,720 person-years for blacks and 12,418 person-years for whites). Within each of the other 4 alcohol consumption categories, the proportion of person-time was higher for whites than it was for blacks. Females contributed more person-time to the never and occasional groups and less time to the light/moderate or heavy group as compared with males. Those participants with more than a high school education contributed more person-time to the occasional, light/moderate, and heavy drinking categories than did those with a high school degree or less. Participants from

Minneapolis MN had higher proportions of person-time in the categories of current drinkers (occasional, light/moderate, and heavy) versus participants from the other 3 study centers.

In looking at smoking status, the largest proportion of person-time for never drinkers was among never smokers during visit 1 to 3 and after visit 3 (never smokers made up 68% of the never drinkers between visit1 and 3 and 71% following visit 3). During the time between visit 1 and 3, 48% of person-time for heavy drinkers was among current smokers but after visit 3 that percentage was 34%.

The mean HDL-cholesterol levels ranged from 49.5mg/dL to 60.6mg/dL during the visit1 to visit 3 time period and from 49.2mg/dL to 58.3 mg/dL during the visit 3+ time period. The highest HDL-cholesterol levels were seen among the heavy drinkers.

There were 226 strokes of all kinds between visits 1 and 3 and 313 strokes after visit 3 (Table 4.2). From visit 1 to 3, 190 ischemic strokes occurred and after visit 3 there were 270 ischemic strokes. The crude incidence rates (IR) per 100,000 P-Y for all strokes were 238 from visit 1 to 3 and 342 after visit 3. After adjusting for age, the incidence rates per 100,000 P-Y for all strokes were 228 between visit 1 and 3 and 370 after visit 3. From visit 1 to 3 the age-adjusted all stroke incidence rates by level of alcohol intake were highest for former drinkers (IR=311 per 100,000 P-Y) and lowest for occasional drinkers (IR=152 per 100,000 P-Y). After the 3rd visit, the age-adjusted IR were highest for heavy drinkers (IR=542 per 100,000 P-Y) and lowest for occasional drinkers (IR=244 per 100,000 P-Y). The incidence rates for ischemic stroke were lower than those for all stroke, with crude ischemic rates of

200 per 100,000 P-Y between visit 1 and 3 and 295 per 100,000 P-Y following visit 3. Similar patterns of incidence rates by levels of alcohol intake were observed for ischemic stroke as for all stroke.

There were 19 cases of hemorrhagic stroke between visits 1 and 3 and 30 cases after visit 3. The age adjusted incidence rates for hemorrhagic stroke were 20 per 100,000 P-Y between visits 1 and 3 and 32 per 100,000 P-Y after visit 3. The age-adjusted hemorrhagic stroke incidence rates by level of alcohol intake ranged from 12 per 100,000 P-Y among occasional drinkers to 34 per 100,000 P-Y among heavy drinkers during the visit 1 to 3 time period. Age-adjusted hemorrhagic stroke incidence rates after visit 3 ranged from 19 per 100,000 P-Y for light/moderate drinkers to 90 per 100,000 P-Y among heavy drinkers.

Table 4.3 shows the results of stratifying the crude and age-adjusted all and ischemic stroke incidence rates by race. The age-adjusted all stroke incidence rates among whites are lowest for light/moderate drinkers (IR=123 per 100,000P-Y) and highest for former drinkers (IR=188 per 100,000 P-Y) during the time period from visit 1 to visit 3. After visit 3, the age-adjusted all stroke incidence rates among whites are lowest for occasional drinkers (IR=198 per 100,000 P-Y) and highest for heavy drinkers (IR=479 per 100,000 P-Y). Among blacks in the visit 1 to 3 time period, the all stroke age-adjusted incidence rates are lowest among never drinkers (IR=342 per 100,000 P-Y) and the highest among heavy drinkers (IR=717 per 100,000 P-Y). Following visit 3, the age-adjusted IR was highest among occasional drinkers (IR=944 per 100,000 P-Y) and lowest among heavy drinkers (IR=506 per 100,000 P-Y).

Crude and adjusted rate ratios (RRs) with 95% confidence intervals for all, ischemic, and hemorrhagic strokes are shown in Table 4.4. The crude RRs for all stroke showed an inverse association for occasional drinkers (RR=0.57, 95%CI: 0.42-0.77) and light/moderate drinkers (RR=0.74, 95%CI: 0.59-0.94) as compared with never drinkers. After adjustment for age, race, sex, and socioeconomic status the RRs were attenuated (comparing occasional with never drinkers RR=0.91, 95%CI: 0.67-1.25 and light/moderate with never drinkers RR=0.99, 95%CI: 0.77-1.28). Further adjustment for study center, smoking status, diabetes, and leisure activity did not have much impact on the RRs. Results for ischemic stroke were similar to those found for all stroke. The crude RRs for ischemic stroke comparing occasional drinkers with never drinkers and light/moderate drinkers with never drinkers showed an inverse association (RR=0.50 95%CI: 0.36-0.70 and RR=0.74, 95%CI: 0.58-0.95, respectively). Adjusting the models for potential confounders attenuated the RRs. The crude RRs for hemorrhagic stroke were 1.16 (95%CI: 0.51, 2.63) for former drinkers, 1.13 (95%CI: 0.48, 2.69) for occasional drinkers, 0.74 (95%CI: 0.32, 1.71) for light/moderate drinkers, and 1.67 (95%CI: 0.66, 4.25) for heavy drinkers, as compared with never drinkers. Adjustment for age, race, sex, and socioeconomic status resulted in an increase in the RRs.

The results of stratifying the Poisson regression models by race are presented in Table 4.5. The minimally adjusted RRs for whites and all stroke are 1.15 for former drinkers, 1.03 for occasional drinkers, 0.86 for light/moderate drinkers, and 1.37 for heavy drinkers compared with never drinkers. The minimally adjusted RRs for blacks and all stroke are 1.07 for former drinkers, 0.54 for

occasional drinkers, 1.29 for light/moderate drinkers, and 1.35 for heavy drinkers compared with never drinkers. The results for ischemic stroke are similar to those for all stroke. Results for hemorrhagic stroke by race are not shown because of the small number of hemorrhagic stroke events.

4.4 Discussion

In this study of the ARIC cohort, we found no compelling evidence that occasional or light to moderate alcohol intake reduces stroke incidence rates. The unadjusted RRs suggest an inverse association between occasional drinking and all stroke or ischemic stroke and between light/moderate drinking and all stroke or ischemic stroke among the entire cohort. However, adjustment for confounding factors attenuates the association, suggesting that the underlying distribution of covariates varies across levels of alcohol intake. The minimally adjusted stratified results indicate a positive association for whites between heavy alcohol intake and all stroke incidence as well as between heavy alcohol intake and ischemic stroke incidence. Among blacks, light to moderate alcohol intake is associated with increased all stroke incidence. These results indicate that light/moderate alcohol consumption may have different effects on all and/or ischemic stroke incidence among blacks and whites. The adjusted RRs examining alcohol intake and hemorrhagic stroke incidence suggest that any level of alcohol intake increases hemorrhagic stroke incidence rates.

Our results agree with previous studies that found that heavyalcohol intake increases ischemic stroke incidence rates among whites (6-9) and that

light/moderate alcohol intake is not associated with ischemic stroke in whites (10-14, 28, 29). Both the Framingham Heart Study (10) and the Health Professionals Follow-up Study (28) reported no reduction in ischemic stroke incidence among light to moderate drinkers.

Our findings differ from studies that found a reduction in stroke incidence for light/moderate drinkers compared with non-drinkers. In the Nurses' Health Study, a prospective cohort study of white females, alcohol intake of up to 1.2 drinks per day lowered ischemic stroke incidence (16). Several case-control studies have also reported moderate alcohol consumption to be beneficial in ischemic stroke occurrence (9, 30). A meta-analysis of 35 studies found that consumption of 1 drink (12 g) per day as compared with no drinks per day had an inverse association with all stroke (RR=0.80, 95%CI:0.67-0.96) and with ischemic stroke (RR=0.83, 95%CI: 0.75-0.91) (5).

It is not surprising that study results vary, given the differences in study designs, method of alcohol ascertainment, definitions for levels of alcohol intake, definitions for stroke occurrence, selection of study participants, characteristics of study populations, and adjustment for confounding factors. Cohort and case-control study designs have been used to examine the association between alcohol and stroke occurrence. While prospective cohort studies have the advantage of allowing for exposures to be assessed prior to disease occurrence, case-control studies are valuable when the outcome is rare, as is the case with hemorrhagic stroke. The methods of alcohol intake ascertainment and the categorization of alcohol intake between studies make comparisons highly problematic. Alcohol can be assessed by

self-report or proxy respondent and can be obtained by interview or questionnaire. No gold standard for measuring alcohol intake exists. Additionally, categorization of alcohol intake is not standardized with values for light, moderate, and heavy alcohol intake fluctuating across studies. Methods for determining stroke occurrence also vary by study, with some studies relying solely on ICD-9 codes and other studies using abstracted medical records or contacting study participants. Studies also differ in terms of the method of selection for the study population with some studies following participants over time and others selecting participants based on stroke occurrence. The study population for each study is unique and thus comparisons across studies and generalizations to larger populations may be challenging if there are gender, racial, or geographic differences.

This study has several strengths. The ARIC study is prospective with alcohol consumption information was collected prior to stroke occurrence, eliminating the possibility of recall bias. Also, strokes were ascertained by annually contacting participants and by searching hospital discharge files and death certificates. We did not rely solely on administrative data sources. Instead, possible stroke cases were reviewed by a physician for validation and were classified into stroke subtypes. Another strength of the study is our ability to incorporate changes in alcohol intake over time. Alcohol consumption patterns are known to change over time (31), so updating alcohol information is important. Other studies have used a referent group of current non-drinkers, which consists of both never drinkers and former drinkers. Since former drinkers may have stopped drinking for health reasons (32), selecting a

referent group of never drinkers allows for a more homogeneous referent group and is thus preferred.

A limitation of the study is the method of alcohol assessment. Alcohol intake was measured by self-report and studies examining the validity and reliability of alcohol consumption reports have shown that it is typically an underestimate (33-37). Since alcohol intake was measured before the event, any misclassification of alcohol is likely nondifferential (38). Also, HDL-cholesterol, which has been shown to increase with alcohol intake, was highest among the heavy drinkers and lowest among the former drinkers suggesting that our measure of alcohol consumption is valid.

A major advantage of the ARIC cohort is the inclusion of a large number of minority participants. In the entire ARIC cohort, 72.7% are white, 27.0% are black, and 0.3% are other races. The Northern Manhattan Study examined ischemic stroke and alcohol intake among whites, blacks and Hispanics. This study found an inverse association between recent moderate alcohol consumption (at least 1 drink per month and no more than two drinks per day) and ischemic stroke incidence among Hispanics but not among blacks (22). Few studies have addressed the black population, despite the fact that this group has stroke incidence rates that are twice that of whites(1). Our results suggest that compared with no alcohol intake, light/moderate alcohol consumption may increase stroke incidence rates among blacks.

Additional studies examining the role of alcohol intake on stroke incidence among blacks are warranted. Current AHA guidelines state that for those who drink

alcohol, to do so in moderation (up to one drink/day for women and up to two drinks/day for men) and that drinking more than this may increase stroke risk (2). While heavy alcohol intake appears to increase overall stroke incidence, the perceived benefit of light to moderate alcohol intake may not apply to all populations. Since the AHA recommendations are based on results of studies with few minority groups, the guidelines should be reconsidered or at least conveyed with caution.

Figure 4.1: Timeline of the ARIC Cohort Participant Evaluations

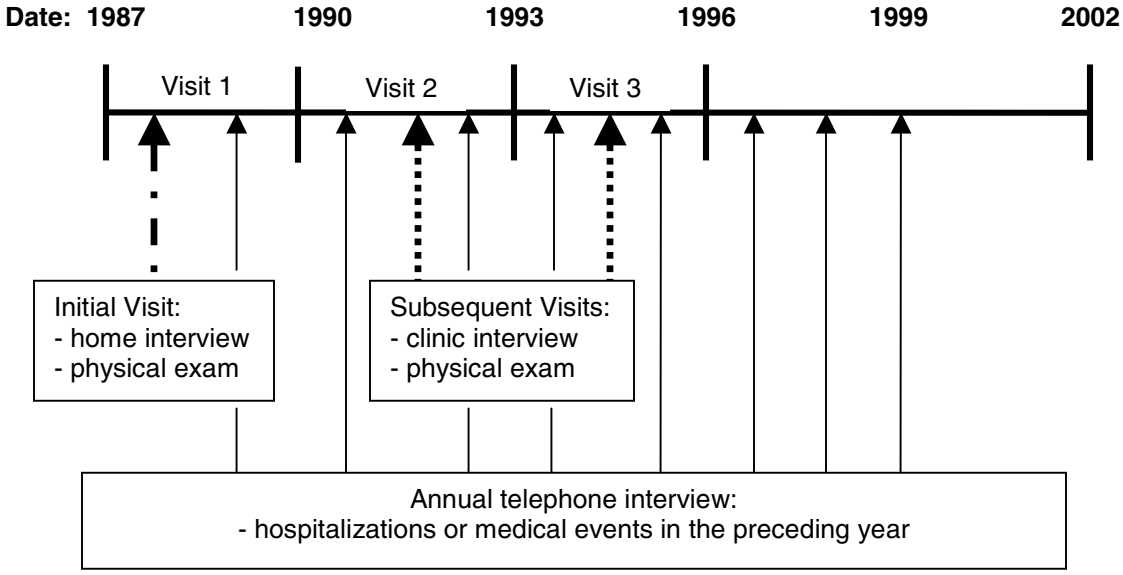


Figure Legend: ARIC participants were enrolled from 1987-1989 and had an initial visit which consisted of a home interview and a physical exam (represented by the single broken arrow). Participants were then contacted annually by telephone and asked about any hospital visits or medical events in the prior year (represented by the solid arrows). Approximately every three years, participants underwent a subsequent visit at which point they underwent an in-clinic interview and a physical exam (represented by the two dotted arrows). The last point of follow-up for the study is the end of 2002.

Table 4.1: Person-time contributions in years (%) by covariates, alcohol intake levels*, and visit

	Visit 1-3					
	Total 94,859 P-Y	Never 24,138 P-Y	Former 17,587 P-Y	Occasional 16,507 P-Y	Light/Mod 27,506 P-Y	Heavy 9,121 P-Y
Race						
Black	26,088 (28)	11,720 (49)	5,972 (34)	1,406 (9)	5,296 (19)	1,694 (19)
White	68,769 (72)	12,418 (51)	11,614 (66)	15,101 (91)	22,210 (81)	7,426 (81)
Gender						
Female	54299 (57)	18,926 (78)	8,774 (50)	11,293 (68)	11,420 (42)	3,886 (43)
Male	40,560 (43)	5,212 (22)	8,813 (50)	5,214 (32)	16,086 (58)	5,235 (57)
Education						
<HS	22,570 (24)	7,920 (33)	6,539 (37)	2,291 (14)	4,209 (15)	1,611 (18)
HS graduate	30,788 (32)	8,216 (34)	5,215 (30)	6,033 (37)	8,272 (30)	3,052 (33)
>HS	41,503 (44)	8,003 (33)	5,833 (33)	8,184 (50)	15,025 (55)	4,458 (49)
Center						
NC	24,523 (26)	6,571 (27)	4,384 (25)	5,119 (31)	6,218 (23)	2,231 (24)
MS	22,620 (24)	10,935 (45)	4,902 (28)	857 (5)	4,553 (17)	1,373 (15)
MN	24,543 (26)	1,078 (4)	3,034 (17)	6,399 (39)	10,626 (39)	3,406 (37)
MD	23,174 (24)	5,554 (23)	5,267 (30)	4,133 (25)	6,110 (22)	2,110 (23)
Smoking						
Never	39,582 (42)	16,457 (68)	5,251 (30)	7,406 (45)	8,924 (32)	1,544 (17)
Former	29,484 (31)	3,936 (16)	6,885 (39)	4,942 (30)	10,513 (38)	3,208 (35)
Current	25,794 (27)	3,745 (16)	5,451 (31)	4,159 (25)	8,070 (29)	4,369 (48)
Diabetes						
No	84,733 (89)	20,497 (85)	14,873 (85)	15,348 (93)	25,459 (93)	8,556 (94)
Yes	10,126 (11)	3,641 (15)	2,713 (15)	1,159 (7)	2,048 (7)	565 (6)
Hypertension						
No	63,280 (67)	14,160 (59)	11,212 (64)	12,240 (74)	19,706 (72)	5,962 (65)
Yes	31,580 (33)	9,978 (41)	6,375 (36)	4,268 (26)	7,800 (28)	3,159 (35)
Body Mass Index						
<25	31,757 (33)	6,564 (28)	5,151 (29)	6,248 (38)	9,847 (36)	3,947 (43)
25 - <30	37,152 (39)	8,579 (36)	6,860 (39)	6,084 (37)	12,106 (44)	3,523 (39)
≥30	25,951 (27)	8,995 (37)	5,576 (32)	4,176 (25)	5,553 (20)	1,651 (18)
Mean (SD)	27.6 (5.3)	28.9 (6.0)	28.3 (5.7)	27.1 (5.1)	26.8 (4.4)	26.3 (4.7)
Range	14.2-65.9	14.2-60.6	14.4-65.9	16.0-54.7	15.4-54.4	15.5-56.3
HDŁ cholesterol						
>=40	74,747 (79)	19,850 (82)	12,759 (73)	12,818 (78)	21,504 (78)	7,816 (86)
<40	20,113 (21)	4,287 (18)	4,828 (27)	3,690 (22)	6,003 (22)	1,305 (14)
Mean (SD)	53.8 (17.6)	54.7 (16.9)	49.5 (15.4)	53.0 (16.8)	53.8 (17.9)	60.6 (21.2)
Range	10-163	12-140	11-147	17-148	10-141	18-163
LDL-cholesterol						
<100	17,178 (18)	4,218 (17)	2,832 (16)	2,958 (18)	5,090 (19)	2,080 (23)
>=100	77,682 (82)	19,920 (83)	14,755 (84)	13,550 (82)	22,416 (81)	7,041 (77)
Mean (SD)	134.5 (39.2)	136.5 (40.7)	137.3 (39.3)	133.0 (37.6)	133.4 (37.8)	129.9 (41.9)
Range	1-395	5-395	6-368	8-370	1-380	19-315
Triglycerides						
<150	69,620 (73)	18,100 (75)	12,829 (73)	11,811 (72)	20,493 (75)	6,387 (70)
>=150	25,239 (27)	6,038 (25)	4,758 (27)	4,696 (28)	7,013 (25)	2,734 (30)
Mean (SD)	128.6 (80.8)	126.0 (78.8)	131.4 (82.4)	131.8 (88.1)	125.5 (75.5)	133.6 (84.0)
Range	24-1277	27-1088	31-1093	29-1277	24-897	34-745
Leisure Activity						
1st Quartile	19,110 (20)	5,669 (23)	4,439 (25)	2,450 (15)	4,617 (17)	1,935 (21)
2nd Quartile	30,540 (32)	7,721 (32)	5,541 (32)	5,390 (33)	8,673 (32)	3,215 (35)
3rd Quartile	15,579 (16)	3,656 (15)	2,667 (15)	2,911 (18)	4,839 (18)	1,506 (17)
4th Quartile	29,581 (31)	7,092 (29)	4,939 (28)	5,707 (35)	9,378 (34)	2,465 (27)
Mean (SD)	2.4 (0.6)	2.3 (0.6)	2.3 (0.61)	2.4 (0.5)	2.4 (0.6)	2.3 (0.5)
Range	1.0-4.5	1.0-4.5	1.0-4.5	1.0-4.25	1.0-4.25	1.0-4.0

* Alcohol intake was categorized into never, former, occasional (current drinkers but no alcohol in last week), light/mod (up to 1 drink/day for women and up to 2 drinks/day for men), and heavy (more than 1 drink/day for women and more than 2 drinks/day for men); P-Y = person-years; HS=high school; HDL-cholesterol=high density lipoprotein cholesterol; LDL-cholesterol = low density lipoprotein cholesterol; Leisure Activity=physical activity level divided into quartiles.

Table 4.1 (continued): Person-time contributions in years (%) by covariates, alcohol intake levels, and visit

	Visit 3+					
	Total 91,601 P-Y	Never 23,362 P-Y	Former 19,936 P-Y	Occasional 14,940 P-Y	Light/Mod 25,919 P-Y	Heavy 7,444 P-Y
Race						
Black	20,725 (23)	8,288 (35)	6,477 (32)	1,690 (11)	2,727 (11)	1,543 (21)
White	70,876 (77)	15,074 (65)	13,459 (68)	13,250 (89)	23,192 (89)	5,901 (79)
Gender						
Female	53,173 (58)	18,225 (78)	10,131 (51)	10,205 (68)	11,397 (44)	3,215 (43)
Male	38,427 (42)	5,137 (22)	9,805 (49)	4,735 (32)	14,521 (56)	4,229 (57)
Education						
<HS	17,280 (19)	6,294 (27)	5,918 (30)	1,302 (9)	2,446 (9)	1,320 (18)
HS graduate	30,665 (33)	8,585 (37)	6,209 (31)	5,303 (35)	8,223 (32)	2,345 (32)
>HS	43,656 (48)	8,482 (36)	7,809 (39)	8,336 (56)	15,250 (59)	3,779 (51)
Center						
NC	23,815 (26)	8,058 (34)	5,102 (26)	3,142 (21)	5,938 (23)	1,575 (21)
MS	18,145 (20)	7,509 (32)	5,505 (28)	1,505 (10)	2,276 (9)	1,350 (18)
MN	25,767 (28)	1,591 (7)	3,733 (19)	6,000 (40)	11,648 (45)	2,795 (38)
MD	23,876 (26)	6,204 (27)	5,597 (28)	4,294 (29)	6,057 (23)	1,724 (23)
Smoking						
Never	39,472 (43)	16,503 (71)	6,205 (31)	7,508 (50)	8,160 (31)	1,096 (15)
Former	36,822 (40)	4,583 (20)	9,863 (49)	5,443 (36)	13,125 (51)	3,808 (51)
Current	15,307 (17)	2,275 (10)	3,868 (19)	1,990 (13)	4,634 (18)	2,540 (34)
Diabetes						
No	79,229 (86)	19,540 (84)	16,131 (81)	13,564 (91)	23,474 (91)	6,520 (88)
Yes	12,373 (14)	3,822 (16)	3,806 (19)	1,377 (9)	2,445 (9)	923 (12)
Hypertension						
No	56,213 (61)	12,769 (55)	11,152 (56)	10,264 (69)	17,564 (68)	4,464 (60)
Yes	35,388 (39)	10,593 (45)	8,785 (44)	4,676 (31)	8,355 (32)	2,979 (40)
Body Mass Index						
<25	25,531 (28)	5,881 (25)	4,618 (23)	4,625 (31)	8,111 (32)	2,296 (30)
25 - <30	36,281 (40)	8,337 (36)	7,895 (40)	5,668 (38)	11,289 (44)	3,092 (42)
≥30	29,788 (33)	9,143 (39)	7,424 (37)	4,647 (31)	6,519 (25)	2,055 (28)
Mean (SD)	28.5 (5.6)	29.3 (6.2)	29.1 (5.8)	28.2 (5.3)	27.6 (4.8)	27.7 (5.2)
Range	14.2-62.0	16.4-60.2	14.7-62.0	14.2-56.6	14.5-59.1	16.1-50.6)
HDŁ cholesterol						
>=40	70,933 (77)	18,609 (80)	14,097 (71)	11,828 (79)	20,274 (78)	6,125 (82)
<40	20,669 (23)	4,753 (20)	5,840 (29)	3,112 (21)	5,645 (22)	1,319 (18)
Mean (SD)	53.1 (18.1)	53.4 (17.2)	49.2 (16.4)	53.8 (17.6)	53.7 (18.6)	58.3 (21.9)
Range	11-195	16-147	17-146	18-119	11-149	18-195
LDL-cholesterol						
<100	19,047 (21)	4,857 (21)	3,935 (20)	3,007 (20)	5,356 (21)	1,892 (25)
>=100	72,555 (79)	18,504 (79)	16,002 (80)	11,934 (80)	20,563 (79)	5,552 (75)
Mean (SD)	127.0 (34.4)	128.0 (34.9)	128.7 (34.6)	126.8 (33.3)	126.2 (33.3)	122.4 (37.6)
Range	7.6-347	7.6-279	10-290	28-317	21-279	20.6-347
Triglycerides						
<150	62,073 (68)	15,989 (68)	13,351 (67)	10,130 (68)	17,455 (67)	5,148 (69)
>=150	29,528 (32)	7,373 (32)	6,586 (33)	4,810 (32)	8,464 (33)	2,295 (31)
Mean (SD)	134.8 (66.7)	134.1 (67.0)	136.4 (67.2)	136.8 (66.7)	134.2 (66.2)	130.5 (66.9)
Range	22-399	28-399	33-399	29-398	22-396	33-397
Leisure Activity						
1st Quartile	17,345 (19)	4,961 (21)	4,567 (23)	2,230 (15)	3,768 (15)	1,819 (24)
2nd Quartile	31,102 (34)	7,924 (34)	6,769 (34)	5,410 (36)	8,634 (33)	2,365 (32)
3rd Quartile	15,543 (17)	3,635 (16)	3,088 (15)	2,669 (18)	4,994 (19)	1,157 (16)
4th Quartile	27,609 (30)	6,841 (29)	5,512 (28)	4,631 (31)	8,522 (33)	2,103 (28)
Mean (SD)	2.4 (0.6)	2.3 (0.6)	2.3 (0.6)	2.4 (0.5)	2.4 (0.5)	2.3 (0.6)
Range	1.0-4.5	1.0-4.5	1.0-4.5	1.0-4.5	1.0-4.5	1.0-4.5

* Alcohol intake was categorized into never, former, occasional (current drinkers but no alcohol in last week), light/mod (up to 1 drink/day for women and up to 2 drinks/day for men), and heavy (more than 1 drink/day for women and more than 2 drinks/day for men); P-Y = person-years; HS=high school; HDL-cholesterol=high density lipoprotein cholesterol; LDL-cholesterol = low density lipoprotein cholesterol; Leisure Activity=physical activity level divided into quartiles.

Table 4.2: Crude and Age Adjusted Incidence Rates for All, Ischemic, and Hemorrhagic Stroke by Level of Alcohol Intake and Visit among ARIC Study Participants, 1987-2002

	# of Cases Visit 1-3	P-Y of Follow-up Visit 1-3	Crude IR per 100,000 P-Y Visit 1-3	AA IR per 100.000 P-Y Visit 1-3	# of Cases Visit 3+	P-Y of Follow-up Visit 3+	Crude IR per 100,000 P-Y Visit 3+	AA IR per 100.000 P-Y Visit 3+
All Stroke								
All	226	94859	238 (207, 269)	228 (215, 241)	313	91601	342 (304, 380)	370 (357, 383)
Never	63	24138	261 (196, 325)	242 (215, 270)	90	23362	385 (306, 465)	403 (373, 434)
Former	58	17587	330 (245, 415)	311 (273, 349)	83	19936	416 (327, 506)	410 (378, 441)
Occasional	26	16508	157 (97, 218)	152 (127, 176)	32	14940	214 (140, 288)	244 (222, 265)
Light/Moderate	55	27506	200 (147, 253)	194 (173, 216)	73	25919	282 (217, 346)	336 (315, 357)
Heavy	24	9121	263 (158, 368)	259 (214, 305)	35	7444	470 (314, 626)	542 (494, 590)
Ischemic Stroke								
All	190	94859	200 (172, 229)	191 (179, 203)	270	91601	295 (260, 330)	327 (315, 338)
Never	54	24138	224 (164, 283)	211 (184, 237)	79	23362	338 (264, 413)	366 (337, 394)
Former	50	17587	284 (205, 363)	269 (234, 304)	73	19936	366 (282, 450)	364 (335, 392)
Occasional	20	16508	121 (68, 174)	115 (95, 136)	24	14940	161 (96, 225)	198 (178, 217)
Light/Moderate	47	27506	171 (122, 220)	165 (146, 184)	64	25919	247 (186, 307)	304 (285, 322)
Heavy	19	9121	208 (115, 302)	204 (165, 244)	30	7444	403 (259, 547)	452 (408, 496)
Hemorrhagic Stroke								
All	19	94859	20 (11, 29)	19 (16, 24)	30	91601	33 (21, 44)	32 (27, 36)
Never	5	24138	21 (3, 39)	17 (12, 23)	7	23362	30 (8, 52)	25 (16, 34)
Former	4	17587	23 (0, 45)	22 (11, 32)	7	19936	35 (9, 61)	35 (22, 48)
Occasional	2	16508	12 (-5, 29)	12 (5, 19)	7	14940	47 (12, 82)	41 (34, 48)
Light/Moderate	5	27506	18 (2, 34)	19 (11, 26)	5	25919	19 (2, 36)	19 (11, 26)
Heavy	3	9121	33 (-4, 70)	34 (15, 54)	4	7444	54 (1, 106)	90 (71, 108)

ARIC=Atherosclerosis Risk in Communities Cohort; P-Y = person-years; IR=incidence rate; AA = age adjusted.

Table 4.3: Crude and Age Adjusted Incidence Rates for All and Ischemic Stroke by Race, Level of Alcohol Intake and Visit among ARIC Study Participants, 1987-2002

	Visit 1-3				Visit 3+			
	Cases n	Follow-up P-Y	Crude IR* (95% CI)	AA IR* (95%CI)	Cases n	Follow-up P-Y	Crude IR* (95%CI)	AA IR* (95%CI)
All Stroke, White								
All	112	68769	163 (133, 193)	150 (138, 162)	187	70876	264 (226, 302)	291 (280, 303)
Never	22	12418	177 (103, 251)	142 (116, 167)	37	15074	245 (166, 325)	256 (228, 283)
Former	23	11614	198 (117, 279)	188 (151, 226)	45	13459	334 (237, 432)	338 (308, 368)
Occasional	25	15101	166 (101, 230)	159 (134, 185)	26	13250	196 (121, 272)	198 (176, 220)
Light/Moderate	29	22210	131 (83, 178)	123 (106, 140)	53	23192	229 (167, 290)	286 (267, 304)
Heavy	13	7426	175 (80, 270)	163 (127, 200)	26	5901	441 (271, 610)	479 (437, 520)
All Stroke, Black								
All	114	26089	437 (357, 517)	440 (403, 477)	126	20725	608 (502, 714)	643 (605, 682)
Never	41	11720	350 (243, 457)	342 (294, 391)	53	8288	639 (467, 812)	679 (615, 742)
Former	35	5972	586 (392, 780)	565 (479, 651)	38	6477	587 (400, 773)	551 (480, 623)
Occasional	1	1407	71 (-68, 210)	658 (0, 1316)	6	1690	355 (71, 639)	944 (870, 1018)
Light/Moderate	26	5296	491 (302, 680)	524 (434, 614)	20	2727	733 (412, 1055)	812 (690, 934)
Heavy	11	1694	649 (266, 1033)	717 (515, 919)	9	1543	583 (202, 964)	506 (364, 649)
Ischemic Stroke, White								
All	96	68769	140 (112, 168)	128 (117, 139)	165	70876	233 (197, 268)	261 (251, 272)
Never	18	12418	145 (78, 212)	115 (93, 138)	33	15074	219 (144, 294)	237 (211, 263)
Former	21	11614	181 (103, 258)	174 (138, 210)	42	13459	312 (218, 406)	310 (285, 335)
Occasional	20	15101	132 (74, 190)	126 (104, 148)	18	13250	136 (73, 199)	147 (127, 167)
Light/Moderate	26	22210	117 (72, 162)	110 (94, 126)	48	23192	207 (148, 266)	267 (250, 284)
Heavy	11	7426	148 (61, 236)	138 (106, 170)	24	5901	407 (244, 569)	418 (377, 459)
Ischemic Stroke, Black								
All	94	26089	360 (287, 433)	363 (329, 397)	105	20725	507 (410, 604)	555 (520, 590)
Never	36	11720	307 (207, 408)	304 (257, 351)	46	8288	555 (395, 715)	608 (549, 668)
Former	29	5972	486 (309, 662)	469 (393, 546)	31	6477	479 (310, 647)	458 (393, 523)
Occasional	0	1407	0	0	6	1690	355 (71, 639)	944 (870, 1018)
Light/Moderate	21	5296	397 (227, 566)	434 (354, 514)	16	2727	587 (299, 874)	677 (564, 789)
Heavy	8	1694	472 (145, 800)	534 (339, 729)	6	1543	389 (78, 700)	357 (244, 471)

* Crude IR = crude incidence rate per 100,000 person-years; ARIC=Atherosclerosis Risk in Communities Cohort; P-Y = person-years; IR=incidence rate; AA = age adjusted.

Table 4.4: Rate Ratios with 95% Confidence Intervals Comparing Alcohol Intake and Stroke Incidence, ARIC 1987-2002

	Alcohol Intake^				
	Never	Former	Occasional	Light/Moderate	Heavy
All Stroke:					
crude RR (95%CI)	reference	1.17 (0.93, 1.47)	0.57 (0.42, 0.77)	0.74 (0.59, 0.94)	1.11 (0.82, 1.49)
min adjusted* RR (95%CI)	reference	1.09 (0.86, 1.38)	0.91 (0.67, 1.25)	0.99 (0.77, 1.28)	1.36 (0.99, 1.86)
fully adjusted** RR (95%CI)	reference	0.97 (0.76, 1.24)	0.89 (0.65, 1.23)	0.94 (0.72, 1.23)	1.14 (0.82, 1.59)
Ischemic Stroke:					
crude RR (95%CI)	reference	1.17 (0.92, 1.50)	0.50 (0.36, 0.70)	0.74 (0.58, 0.95)	1.06 (0.76, 1.47)
min adjusted* RR (95%CI)	reference	1.06 (0.82, 1.36)	0.78 (0.55, 1.10)	0.95 (0.72, 1.24)	1.25 (0.88, 1.75)
fully adjusted** RR (95%CI)	reference	0.94 (0.72, 1.22)	0.75 (0.53, 1.08)	0.89 (0.67, 1.20)	1.04 (0.73, 1.50)
Hemorrhagic Stroke:					
crude RR (95%CI)	reference	1.16 (0.51, 2.63)	1.13 (0.48, 2.69)	0.74 (0.32, 1.71)	1.67 (0.66, 4.25)
min adjusted* RR (95%CI)	reference	1.23 (0.53, 2.84)	2.33 (0.94, 5.80)	1.29 (0.52, 3.16)	2.57 (0.96, 6.84)
fully adjusted** RR (95%CI)	reference	1.12 (0.47, 2.66)	2.30 (0.91, 5.83)	1.21 (0.47, 3.10)	2.08 (0.74, 5.86)

^Alcohol intake was categorized into never, former, occasional (reported being a current drinker but no alcohol in the last week), light/moderate (up to 1 drink/day for women and up to 2 drinks/day for men), and heavy (more than 1 drink/day for women and more than 2 drinks/day for men).
RD = rate difference, RR = rate ratio, CI = confidence interval
* Adjusted for age, race, sex, and socioeconomic status.
** Adjusted for age, race, gender, socioeconomic status, smoking, physical activity, ARIC study center, body mass index, and diabetes.

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Table 4.5: Rate Ratios with 95% Confidence Intervals Comparing Alcohol Intake and Stroke Incidence by Race, ARIC 1987-2002

	Alcohol Intake^				
	Never	Former	Occasional	Light/Moderate	Heavy
All Stroke, Whites:					
crude RR (95%CI)	reference	1.26 (0.89, 1.79)	0.84 (0.58, 1.22)	0.84 (0.60, 1.18)	1.36 (0.91, 2.04)
min adjusted* RR (95%CI)	reference	1.15 (0.80, 1.64)	1.03 (0.70, 1.51)	0.86 (0.61, 1.23)	1.37 (0.90, 2.07)
fully adjusted** RR (95%CI)	reference	0.96 (0.66, 1.40)	0.95 (0.64, 1.41)	0.77 (0.53, 1.12)	1.06 (0.68, 1.67)
All Stroke, Blacks:					
crude RR (95%CI)	reference	1.25 (0.92, 1.69)	0.48 (0.22, 1.04)	1.22 (0.86, 1.74)	1.31 (0.81, 2.13)
min adjusted* RR (95%CI)	reference	1.07 (0.78, 1.47)	0.54 (0.25, 1.17)	1.29 (0.88, 1.88)	1.35 (0.81, 2.22)
fully adjusted** RR (95%CI)	reference	0.98 (0.70, 1.36)	0.57 (0.26, 1.25)	1.28 (0.86, 1.90)	1.20 (0.71, 2.02)
Ischemic Stroke, Whites:					
crude RR (95%CI)	reference	1.35 (0.94, 1.96)	0.72 (0.47, 1.10)	0.88 (0.62, 1.26)	1.42 (0.92, 2.18)
min adjusted* RR (95%CI)	reference	1.20 (0.82, 1.75)	0.88 (0.58, 1.35)	0.88 (0.61, 1.28)	1.39 (0.89, 2.16)
fully adjusted** RR (95%CI)	reference	1.03 (0.69, 1.72)	0.81 (0.52, 1.27)	0.79 (0.53, 1.19)	1.10 (0.68, 1.77)
Ischemic Stroke, Blacks:					
crude RR (95%CI)	reference	1.18 (0.84, 1.64)	0.47 (0.21, 1.08)	1.13 (0.76, 1.66)	1.06 (0.60, 1.86)
min adjusted* RR (95%CI)	reference	0.97 (0.69, 1.38)	0.53 (0.23, 1.23)	1.16 (0.76, 1.76)	1.05 (0.59, 1.89)
fully adjusted** RR (95%CI)	reference	0.87 (0.61, 1.24)	0.56 (0.24, 1.30)	1.15 (0.74, 1.77)	0.94 (0.51, 1.77)

^Alcohol intake was categorized into never, former, occasional (reported being a current drinker but no alcohol in the last week), light/moderate (up to 1 drink/day for women and up to 2 drinks/day for men), and heavy (more than 1 drink/day for women and more than 2 drinks/day for men).
RD = rate difference, RR = rate ratio, CI = confidence interval
* Adjusted for age, sex, and socioeconomic status.
** Adjusted for age, gender, socioeconomic status, smoking, physical activity, ARIC study center, body mass index, and diabetes.

4.5 References

1. Thom T, Haase N, Rosamond W, et al. Heart Disease and Stroke Statistics--2006 Update. A Report From the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2006.

2. Goldstein LB, Adams R, Becker K, et al. Primary prevention of ischemic stroke: A statement for healthcare professionals from the Stroke Council of the American Heart Association. Stroke 2001;32:280-99.

3. Labarthe D. Epidemiology and Prevention of Cardiovascular Diseases: A Global Challenge: Aspen Publishers, 1998.

4. Heart Disease and Stroke Statistics - 2003 Update. Dallas, TX: American Heart Association, 2002.

5. Reynolds K, Lewis LB, Nolen JD, Kinney GL, Sathya B, He J. Alcohol consumption and risk of stroke: a meta-analysis. Jama 2003;289:579-88.

6. Iso H, Kitamura A, Shimamoto T, et al. Alcohol intake and the risk of cardiovascular disease in middle aged Japanese men. Stroke 1995;26:767-73.

7. Beghi E, Boglium G, Cosso P, et al. Stroke and alcohol intake in a hospital population. A case-control study. Stroke 1995;26:1691-6.

8. Caicoya M, Rodriguez T, Corrales C, Cuello R, Lasheras C. Alcohol and stroke: a community case-control study in Asturias, Spain. J Clin Epidemiol 1999;52:677-84.

9. Palomaki H, Kaste M. Regular light-to-moderate intake of alcohol and the risk of ischemic stroke. Is there a beneficial effect? Stroke 1993;24:1828-32.

10. Djousse L, Ellison RC, Beiser A, Scaramucci A, D'Agostino RB, Wolf PA. Alcohol consumption and risk of ischemic stroke: The Framingham Study. Stroke 2002;33:907-12.

11. Jousilahti P, Rastenyte D, Tuomilehto J. Serum gamma-glutamyl transferase, self-reported alcohol drinking, and the risk of stroke. Stroke 2000;31:1851-5.

12. Leppala JM, Paunio M, Virtamo J, et al. Alcohol consumption and stroke incidence in male smokers. Circulation 1999;100:1209-14.

13. Gorelick PB. The status of alcohol as a risk factor for stroke. Stroke 1989;20:1607-10.

14. Henrich JB, Horwitz RI. Evidence against the association between alcohol use and ischemic stroke risk. Arch Intern Med 1989;149:1413-6.

15. Berger K, Ajani UA, Kase CS, et al. Light-to-moderate alcohol consumption and risk of stroke among U.S. male physicians. N Engl J Med 1999;341:1557-64.

16. Stampfer MJ, Colditz GA, Willett WC, Speizer FE, Hennekens CH. A prospective study of moderate alcohol consumption and the risk of coronary disease and stroke in women. N Engl J Med 1988;319:267-73.

17. Donahue RP, Abbott RD, Reed DM, Yano K. Alcohol and hemorrhagic stroke. The Honolulu Heart Program. Jama 1986;255:2311-4.

18. Kiyohara Y, Kato I, Iwamoto H, Nakayama K, Fujishima M. The impact of alcohol and hypertension on stroke incidence in a general Japanese population. The Hisayama Study. Stroke 1995;26:368-72.

19. Klatsky AL, Armstrong MA, Friedman GD. Alcohol use and subsequent cerebrovascular disease hospitalizations. Stroke 1989;20:741-6.

20. Zodpey SP, Tiwari RR, Kulkarni HR. Risk factors for haemorrhagic stroke: a case-control study. Public Health 2000;114:177 82.

21. Hansagi H, Romelsjo A, Gerhardsson de Verdier M, Andreasson S, Leifman A. Alcohol consumption and stroke mortality. 20-year follow-up of 15,077 men and women. Stroke 1995;26:1768-73.

22. Elkind MS, Sciacca R, Boden-Albala B, Rundek T, Paik MC, Sacco RL. Moderate alcohol consumption reduces risk of ischemic stroke: the Northern Manhattan Study. Stroke 2006;37:13-9.

23. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. Am J Epidemiol 1989;129:687-702.

24. Rosamond WD, Folsom AR, Chambless LE, et al. Stroke incidence and survival among middle-aged adults: 9-year follow-up of the Atherosclerosis Risk in Communities (ARIC) cohort. Stroke 1999;30:736-43.

25. Baecke JA, Burema J, Frijters JE. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. Am J Clin Nutr 1982;36:936-42.

26. Evenson KR, Rosamond WD, Cai J, et al. Physical activity and ischemic stroke risk. The atherosclerosis risk in communities study. Stroke 1999;30:1333-9.

27. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology 1999;10:37-48.

28. Mukamal KJ, Ascherio A, Mittleman MA, et al. Alcohol and risk for ischemic stroke in men: the role of drinking patterns and usual beverage. Ann Intern Med 2005;142:11-9.

29. Mukamal KJ, Chung H, Jenny NS, et al. Alcohol use and risk of ischemic stroke among older adults: the cardiovascular health study. Stroke 2005;36:1830-4.

30. Sacco RL, Elkind M, Boden-Albala B, et al. The protective effect of moderate alcohol consumption on ischemic stroke. Jama 1999;281:53-60.

31. Eigenbrodt ML, Mosley TH, Jr., Hutchinson RG, Watson RL, Chambless LE, Szklo M. Alcohol consumption with age: a cross-sectional and longitudinal study of the Atherosclerosis Risk in Communities (ARIC) study, 1987-1995. Am J Epidemiol 2001;153:1102-11.

32. Eigenbrodt ML, Fuchs FD, Hutchinson RG, Paton CC, Goff DC, Jr., Couper DJ. Health-associated changes in drinking: a period prevalence study of the Atherosclerosis Risk In Communities (ARIC) cohort (1987-1995). Prev Med 2000;31:81-9.

33. Midanik LT. Validity of self-reported alcohol use: a literature review and assessment. Br J Addict 1988;83:1019-30.

34. Hoyer G, Nilssen O, Brenn T, Schirmer H. The Svalbard study 1988-89: a unique setting for validation of self-reported alcohol consumption. Addiction 1995;90:539-44.

35. Poikolainen K, Podkletnova I, Alho H. Accuracy of quantity-frequency and graduated frequency questionnaires in measuring alcohol intake: comparison with daily diary and commonly used laboratory markers. Alcohol Alcohol 2002;37:573-6.

36. Polich JM. Epidemiology of alcohol abuse in military and civilian populations. Am J Public Health 1981;71:1125-32.

37. Smith PF, Remington PL, Williamson DF, Anda RF. A comparison of alcohol sales data with survey data on self-reported alcohol use in 21 states. Am J Public Health 1990;80:309-12.

38. Rothman KJaG, S. Modern Epidemiology. Philadelphia: Lippincott Williams & Wilkins, 1998.

CHAPTER 5
Alcohol Consumption and Heart Failure Incidence in the Atherosclerosis Risk in Communities (ARIC) Study, 1987-2002

5.1 Introduction

The burden of heart failure (HF) in the U.S. is staggering. During 2003, an estimated 5 million US adults had HF with 550,000 new cases diagnosed each year (1). Hospital discharges for HF are on the rise, increasing by 174% from 1979 to 2003. The estimated direct and indirect cost of HF in the U.S. for 2006 is $29.6 billion (1).

Despite the importance of studying HF, few prospective cohort studies have been designed to do so. The lack of information on HF is due at least in part to the complex nature of the disease. The underlying causes of HF are complex and include ischemic heart disease, hypertension, aortic regurgitation/increased left ventricular size, toxins (such as alcohol), or viral infections of the heart (2). Determining the biologic mechanisms that cause HF is problematic because it depends on the risk factors, underlying conditions, and type of HF. Risk factors may have opposing effects. For example, coronary artery disease predisposes one to MI, which predisposes one to ischemic HF. While the harmful effects of chronic heavy alcohol use on the development of alcoholic cardiomyopathy have been well documented (3-5), the role of light to moderate alcohol intake is unclear. Prospective observational studies have shown alcohol to be beneficial in protecting

against coronary artery disease and myocardial infarction (6), both of which may lead to HF. A beneficial effect of alcohol on HF is hypothesized to be due, at least in part, to this association. The net effect of alcohol intake on the development of HF warrants investigation because while current guidelines state that light/moderate consumption is beneficial for CAD/MI, the long-term effects of alcohol on other CV outcomes has little supporting data.

Few community based studies have examined the association between light to moderate alcohol intake and HF in the general population (5, 7). The aim of this study is to examine the relationship between alcohol consumption and heart failure incidence in a cohort of black and white men and women in four communities in the US. In this paper we will estimate the total, net effect of alcohol on HF through all causal pathways regardless of if they are causative or preventive.

5.2 Methods

Study Population and Design

The ARIC study is a prospective cohort study of 15,792 men and women ages 45 to 64 years of age from four U.S. communities. Details of the ARIC study have been previously published (8). At the initial visit (from 1987-1989), participants were interviewed at home and underwent a physical examination. During annual telephone follow-up, interviewers obtained information about hospitalizations and medical events within the preceding year. Every three years participants underwent a clinical exam consisting of an interview and physical exam. The first visit took

place between 1987-1989, the second visit was from 1990-1992, and the third visit was from 1993-1995. Follow-up data is available through December 31, 2002.

We considered observations from study participants who participated in the initial visit or the third visit. This was done because alcohol intake was measured at visit 1 and visit 3 and this would allow for alcohol consumption to change over time. Thus, a single participant could contribute more than one follow-up interval to the analysis. **Figure 5.1** summarizes the exclusion criteria by study visit. Of the 15,792 study participants at visit one, we excluded those who were non-white and non-black (n=48). We also excluded those who had prevalent heart failure measured by participants reporting that they had taken HF medication in the prior 2 weeks, or participants reporting they had at least 2 HF symptoms (edema, paroxysmal nocturnal dyspnea, or orthopnea), or participants reporting they were taking diuretics or digoxin (n=600). We further excluded 99 participants who did not provide information on alcohol intake and 383 participants who had one or more missing covariates (body mass index, cholesterol measures, diabetes, education, hypertension, physical activity, or smoking) at visit one. A total of 12,887 participants had data available from visit 3. Of these, we excluded non-whites and non-blacks (n=38) and those who had been hospitalized for HF or who had reported HF medication use in the two weeks before baseline (n=565). We also excluded 139 participants who had missing alcohol information and another 361 who had at least one covariate missing. Thus, 14,662 participants were included in the visit 1-visit 3 time period and 11,784 participants were included in the visit 3+ time period.

Alcohol Consumption

Alcohol consumption in the ARIC cohort was measured at visit 1 (1986-1989) and at visit 3 (1993-1995) using a dietary questionnaire. Participants were asked if they drank alcoholic beverages and if so, the type and amount. We calculated the amount of ethanol consumed using the following: one glass of wine = 10.8 g alcohol, one bottle/can of beer = 13.2 g alcohol, and one 1.5 ounce shot of liquor = 15.1 g alcohol. The amount reported on a weekly basis was summed and divided by seven to obtain a daily estimate of alcohol consumed in grams. We then categorized alcohol consumption into never drinkers (reported never consuming alcoholic beverages), former drinkers (reported previously drinking alcoholic beverages, but not currently drinking), occasional drinkers (reported presently drinking alcohol but the usual amount consumed per week was zero), light to moderate drinkers (reported presently drinking up to 1 drink per day for women and up to 2 drinks per day for men), and heavy drinkers (reported presently drinking more than 1 drink per day for women and more than 2 drinks per day for men). These categories of alcohol consumption were chosen in an attempt to create groups of participants with similar levels of exposure. Specifically, former drinkers are likely to be different than never drinkers in that former drinkers may have stopped drinking for health reasons (9) and may thus be sicker than never drinkers. Also, the group of occasional drinkers consists of those who drink but do not do so on a regular basis whereas the light/moderate drinkers report regular intake.

Incident HF

Incident HF cases were ascertained through hospitalization discharge records and death certificates. Hospitalization discharge records with a primary or secondary ICD-9-CM code of 428.xx and death certificates with an underlying cause of death of HF or with a primary ICD-9 code of 428.xx or ICD-10 code of I50 were identified. To eliminate prevalent HF, we excluded participants who reported any of the following: taking HF medication in the 2 weeks before the initial visit, having at least 2 HF related symptoms (edema, PND, or orthopnea), or taking diuretics or digoxin. Person-time was calculated as time from the visit until HF hospitalization, death, loss to follow-up, visit 3 (for participants enrolled at visit 1), or the end of the study period (December 31, 2002).

Covariates

Covariate information for each participant was assessed at visit 1 and updated at visit 3 if the participant was still involved in the study. This allowed for us to account for changes in covariates over time. Race was based on self -reported information and was either black or white. Study center was defined as 1 of the 4 study sites: Forsyth County NC, Jackson MS, Minneapolis MN, or Washington County MD. Socioeconomic status was based on the highest self-reported educational level achieved and was categorized into less than high school graduate, high school graduate, or greater than high school graduate. Smoking was classified as current, previous or never as reported by the participant at the time of the visit. Body mass index was calculated by dividing weight (in kg) by height (in meters squared) and

was categorized into normal (<25.0), overweight (25.0 – 29.9), and obese (30.0+). Physical activity was assessed using the modified Baecke leisure time index which includes measures of walking and biking either as a leisure activity or as a mode of transportation to work or shopping, along with time spent watching television (10, 11). Physical activity was categorized into quartiles. Diabetes was dichotomized into a yes/no variable, with participants whose fasting blood glucose level was $\geq$ 126mg/dL at the time of the visit classified as having diabetes. Hypertension was also dichotomized, with those patients who had systolic blood pressure $\geq$ 140 at the study visit or diastolic blood pressure $\geq$ 90 at the study visit or who had taken blood pressure medication in the last 2 weeks classified as being hypertensive. Cholesterol measures included LDL-cholesterol (mg/dL), HDL-cholesterol (mg/dL), and triglycerides (mg/dL) as measured at the time of the visit. Participants with LDL-cholesterol levels $\geq$ 100mg/dL were determined to have high LDL-cholesterol, participants with HDL-cholesterol levels <40 mg/dL were classified as having low HDL-cholesterol, and participants with triglyceride levels $\geq$ 150 mg/dL were classified as having high triglycerides.

Statistical Analyses

HF incidence rates were calculated as the number of HF cases divided by the person-time of follow-up. Since participants could contribute 1 or 2 observations to the study, each person-visit combination was treated as an observation. For participants with visit 1 data, the follow-up time was calculated as the number of days from visit 1 until first HF hospitalization, death, loss to follow-up, or visit 3 date

(whichever came first). For participants with visit 3 data who did nothave a HF hospitalization before visit 3, follow-up time was calculated as the number of days from visit 3 until HF occurrence, death, loss to follow-up, or December 31, 2002. If a participant was hospitalized for HF multiple times, only the first hospitalization was included in the analysis.

Using Poisson regression multivariate rate ratios (RRs) were estimated to compare differing levels of alcohol consumption on HF incidence. Never drinkers were the reference group in all models. Potential confounders included age, gender, race, study center, educational level, physical activity, and smoking status. We stratified the results on race to determine if the relationship between alcohol and HF varies for whites and blacks.

All analyses were performed using SAS v8 software (SAS Institute, Cary NC).

5.3 Results

HF incidence rates by sociodemographic characteristics and visit are presented in Table 5.1. During the time period from visit 1 to 3, a total of 514 HF cases were identified and the crude incidence rate was 520 per 100,000 person-years. In the time after visit 3, there were 675 HF cases and the crude incidence rate was 718 per 100,000 person-years. The crude HF incidence rates increased with age, were higher for blacks than whites, were higher for males than females, and decreased with increasing education. The crude HF IRs were higher for hypertensives (904 per 100,000P-Y vs. 331 per 100,000P-Y during the visit 1-3 time period) and diabetics (1843 per 100,000P-Y vs. 362 per 100,000P-Y during the visit 1 to 3 time period).

Additionally, the HF IRs were highest among current smokers and lowest among never smokers, and were higher among those with a MI. Occasional drinkers had the lowest crude HF incidence rates (339 per 100,000P-Y from visit 1 to 3) and former drinkers had the highest rates (877 per 100,000 per 100,000P-Y from visit 1 to 3).

The proportion of person-time contributions and number of HF cases by covariates, alcohol intake levels, and visit are shown in Table 5.2. Over the time period from visit 1 to 3, there were 98813 P-Y and 514 HF cases. Of the person-years, 25% (24247P-Y) were among never drinkers, 19% (18,778P-Y) were among former drinkers, 17% (17,119P-Y) were among occasional drinkers, 29% (29,026P-Y) were among light/moderate drinkers, and 10% (9,643P Y) were among heavy drinkers. The number of HF cases in each category of alcohol intake was 137 among never drinkers, 165 among former drinkers, 58 among occasional drinkers, 108 among light/moderate drinkers, and 46 among heavy drinkers. Following visit 3, there were 94,060P-Y of observation and 675 HF cases. The distribution of person-time and HF cases by alcohol intake categories was similar to that seen between visits 1 and 3.

Table 5.3 provides crude and age adjusted HF incidence rates by level of alcohol intake and visit. During the time period from visit 1 to visit 3 the crude HF incidence rate (cIR) was 5.2 per 1,000P-Y and after adjustment for age was 4.8 per 1,000P-Y. The age adjusted IRs during the time between visit 1 and visit 3 were highest for the former drinkers (aIR=8.0) and lowest for the occasional and light/moderate drinkers (aIR=3.2 and aIR=3.6, respectively). After visit 3, the age-

adjusted IRs were highest among the heavy drinkers (aIR=10.6) and lowest among the occasional drinkers (aIR=4.8). Among both blacks and whites, the age-adjusted IRs between visit 1 and 3 were highest for former drinkers; however, the age-adjusted HF IRs were lowest for occasional blacks drinkers and for never white drinkers. Following visit 3, age-adjusted HF IRs among blacks were lowest for occasional and light/moderate drinkers and highest for former drinkers. During the same time period, whites had the highest aIRs for former drinkers and the lowest rates among occasional drinkers.

Rate ratios with 95% confidence intervals comparing alcohol intake and HF incidence are shown in Table 5.4. Data are presented overall and by visit for the entire cohort as well as for blacks and whites separately. Among the entire cohort during the entire study period, the crude rate ratios comparing alcohol intake with never drinkers are 1.58 for former drinkers, 0.60 for occasional drinkers, 0.72 for light/moderate drinkers, and 1.00 for heavy drinkers. Adjusting the models for age, race, gender, socioeconomic status, smoking, physical activity, and study center modified the RRs. The RRs (95%CIs) comparing each level of alcohol intake with never drinkers are 1.12 (0.95, 1.31) for former drinkers, 0.67 (0.54, 0.82) for occasional drinkers, 0.65 (0.54, 0.78) for light/moderate drinkers, and 0.75 (0.59, 0.95) for heavy drinkers. Similar patterns were seen for blacks and whites during the entire time period. During the time from visit 1 to visit 3, the fully adjusted RRs for the entire cohort were 1.07 (0.84, 1.37) for former drinkers, 0.63 (0.46, 0.87) for occasional drinkers, 0.55 (0.42, 0.72) for light/moderate drinkers, and 0.61 (0.43, 0.87) for heavy drinkers.

5.4 Discussion

In this study we found a positive association between former drinking and HF incidence and an inverse association between current alcohol consumption and HF incidence. While the association between former drinkers and HF incidence is evident for whites, the evidence among blacks is less strong. The strength of the inverse association between current alcohol intake levels and HF incidence varies with race and time period, but in all of the fully adjusted models comparing those who currently drink alcohol (either occasional, light/moderate, or heavy) to the never drinkers, the RRs are consistently less than one.

The Framingham Heart Study examined the association between alcohol and all cause HF as well as HF without a prior MI (5). The referent group was never drinkers and the former drinkers were classified separately. The results of this study indicate that for males, alcohol intake at any level as compared with nondrinkers reduced heart failure incidence. Among women, alcohol consumption of 3-7 drinks per week (approximately the same amount as our measure of light/moderate intake) as compared with non-drinkers reduced heart failure incidence (age-adjusted HR=0.49, 95%CI: 0.25-0.96). In contrast to our study findings in which former drinkers had increased rates of HF incidence, the Framingham study failed to find any level of alcohol intake which was positively associated with HF incidence. The Framingham results comparing former drinkers to never drinkers found age-adjusted HR of 0.72 (0.38-1.37) among males and 1.06 (0.66-1.70) among females.

The Established Populations for the Epidemiologic Study of the Elderly program (EPESE) also examined the association between moderate alcohol intake and heart failure incidence (7). The referent group for this study included current non-drinkers, a combination of never drinkers and former drinkers. The EPESE study found that compared with non drinkers, those who consumed up to 1.5 drinks/day had age/sex adjusted RR=0.71 (0.56-0.92) and those who consumed 2-4 drinks/day had age/sex adjusted RR=0.47 (0.29-0.76). The study also found an inverse association between alcohol intake and mortality. Comparisons with our findings are somewhat problematic given the differences in reference group and the differences in study populations.

It has been hypothesized that the mechanism by which alcohol consumption may reduce the incidence of HF is via the reduction in coronary artery disease and MI rates. Several previous studies have attempted to discern this by stratifying based on MI occurrence. The Framingham Heart Study reported results separately for those without an MI, apparently in an attempt to explain the observed inverse association between moderate alcohol intake and HF incidence (5). The EPESE study by Abramson et al (7) controlled for history of MI as well as MI occurrence during follow-up because of concern that a reduction in MI risk was the reason for the findings of an inverse association between alcohol intake and lower HF incidence. Since the occurrence of MI is affected by alcohol intake (i.e. MI is on the causal pathway between alcohol and HF), MI should not be an adjustment factor nor should it be used for stratification. Ideally we would be able to separate the causative and preventive effects; however the net, total effect of alcohol on HF is not

decomposable (12). In order to determine causative from preventive effects we would need to identify covariates that are hyper-modifiers (covariates creating strata within which the net effect goes in opposite directions) but that are not confounders. It is impossible to say whether the benefits of alcohol on the prevention of MI are offset by the development of HF later on and currently no analytic techniques are available to discern these effects.

Our definition of heavy alcohol intake is based on the AHA guidelines and corresponds to more than 1 drink per day for women and more than 2 drinks per day for men. Studies examining cardiomyopathy and its association with heavy alcohol intake typically consider alcohol intake of 6 or more drinks/day (90-100g/day) to be heavy consumption (13). The ARIC study has few participants with alcohol intake greater than 2 drinks per day which limits our ability to examine categories of heavier alcohol intake.

This study has several strengths. The ARIC study is prospective with alcohol consumption information collected prior to HF occurrence, eliminating the possibility of recall bias. Additionally, we were able to incorporate changes in alcohol consumption over time. Other studies have used a referent group of current non-drinkers, which consists of both never drinkers and former drinkers. Since former drinkers may have stopped drinking for health reasons (9), selecting a referent group of never drinkers allows for a more homogeneous referent group and is thus preferred.

Two limitations of the study include alcohol assessment and ascertainment of HF events. Alcohol intake was measured by self-report and studies examining the

validity and reliability of alcohol consumption reports have shown that it is typically an underestimate (14-18). Since alcohol intake was measured before the event, any misclassification of alcohol is likely nondifferential (19). Also, HDL-cholesterol, which has been shown to increase with alcohol intake, was highest among the heavy drinkers and lowest among the former drinkers suggesting that our measure of alcohol consumption is valid (see Table 5.2). Second, we used hospital discharge records to ascertain HF events so we could have incomplete case ascertainment or some of our HF cases may not be incident in nature.

Our study suggests an inverse association between alcohol intake and heart failure incidence in a community of black and white Americans. Given that approximately 60% of US adults consume light to moderate amounts of alcohol (20), that there are known negative consequences of excessive alcohol intake, and that HF incidence and hospitalization rates are high, additional research examining the role of alcohol on the development of HF is warranted.

Figure 5.1: Study Population by Visit

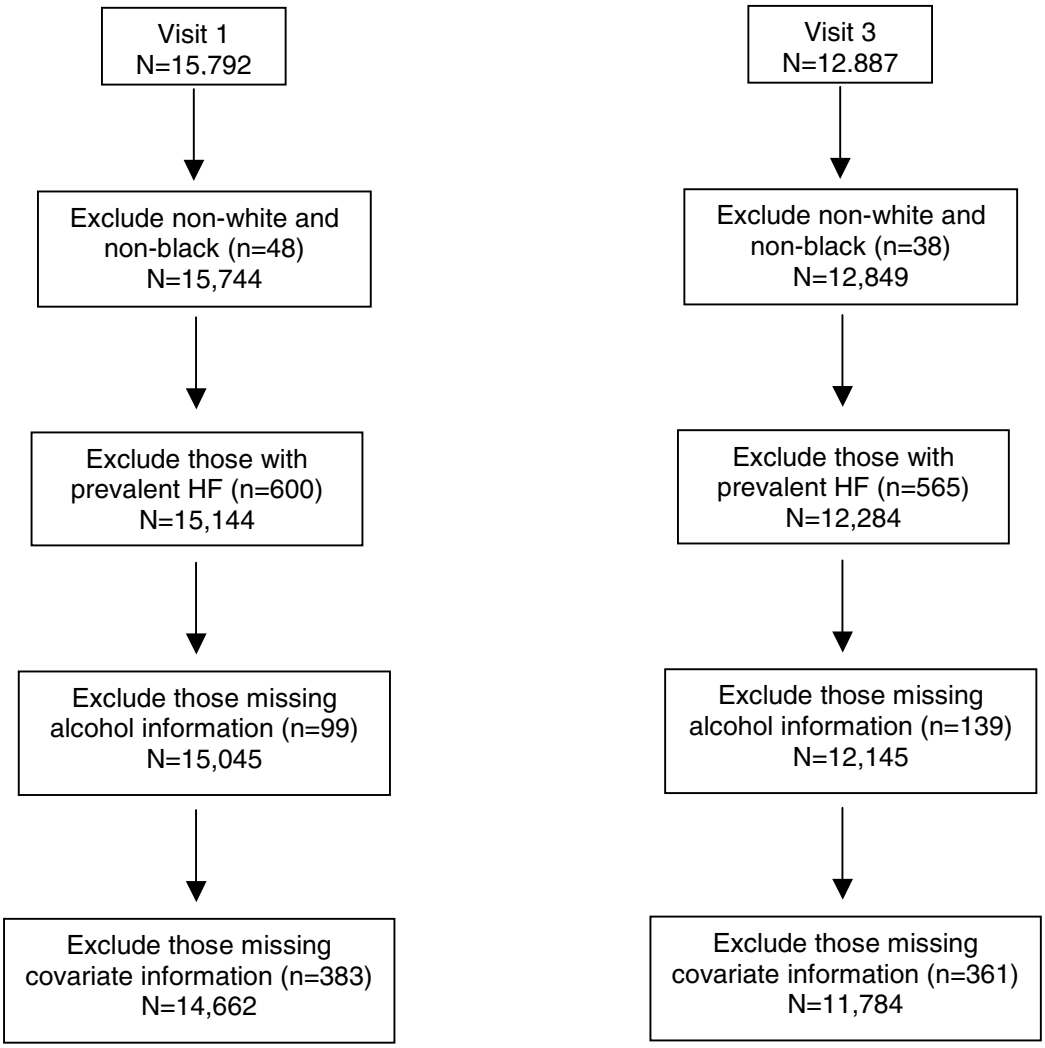

Table 5.1: Heart Failure Incidence Rates per 100,000 person-years by Sociodemographic Characteristics, ARIC population 1987-2002

	Visit 1 Any dx = 428.xx or HF death			Visit 3 Any dx = 428.xx or HF death		
	# cases (n=514)	Person-time (years)	Incidence Rate per 100,000P-Y	# cases (n=675)	Person-time (years)	Incidence Rate per 100,000P-Y
Overall	514	98813	520	675	94060	718
Age						
<55	160	54168	295	54	21295	254
55-59	136	23417	581	122	26036	469
60+	218	21226	1027	499	46727	1068
Race						
Black	196	26383	743	188	20679	909
White	318	72429	439	487	73381	664
Gender						
Female	286	54383	526	308	52958	582
Male	228	44430	513	367	41102	893
Education						
< HS	226	23587	958	239	17624	1356
HS grad	151	32096	470	219	31610	693
> HS	137	43129	318	217	44824	484
Center						
MD	102	24961	409	164	25004	656
MN	172	25402	677	167	26505	630
MS	101	22838	442	122	18127	673
NC	139	25611	543	222	24421	909
Hypertension						
Yes	295	32632	904	427	35970	1187
No	219	66181	331	248	58089	427
Diabetes						
Yes	194	10528	1843	240	12360	1942
No	320	88283	362	435	81699	532
Smoking						
Never	131	40162	326	188	39850	472
Former	160	31266	512	302	38312	788
Current	223	27384	814	185	15895	1164
MI						
Yes	159	3285	4840	131	2464	5317
No	355	95526	372	544	91594	594
Alcohol						
Never	137	24247	565	166	23313	712
Former	165	18778	877	231	20589	1122
Occasional	58	17119	339	65	15301	425
L/M	108	29026	372	148	27024	544
Heavy	46	9643	477	65	7833	830

* HF=heart failure, dx=diagnosis, HS=high school, MD=Washington County MD, MN=Minneapolis MN, MS=Jackson MS, NC=Forsyth County NC, MI=myocardial infarction, Alcohol refers to level of alcohol intake.

Table 5.2: Person-time contributions in years and the number of heart failure cases by covariates, alcohol intake levels, and visit, ARIC 1987-2002

	Visit 1-3					
	ALL P-Y (cases) 98,813 (514)	Never P-Y (cases) 24,247 (137)	Former P-Y (cases) 18,778 (165)	Occasional P-Y (cases) 17,119 (58)	Light/Mod P-Y (cases) 29,026 (108)	Heavy P-Y (cases) 9,643 (46)
Race						
Black	26,383 (196)	11522 (92)	6141 (67)	1421 (5)	5531 (26)	1768 (6)
White	72429 (318)	12725 (45)	12636 (98)	15698 (53)	23495 (82)	7875 (40)
Gender						
Female	54383 (228)	18708 (104)	8774 (68)	11359 (23)	11604 (24)	3938 (9)
Male	44430 (286)	5539 (33)	10004 (97)	5760 (35)	17422 (84)	5705 (37)
Education						
<HS	23587 (226)	7739 (73)	7132 (93)	2388 (16)	4605 (33)	1723 (11)
HS grad	32096 (151)	8369 (40)	5550 (41)	6348 (21)	8626 (32)	3203 (17)
>HS	43129 (137)	8139 (24)	6096 (31)	8382 (21)	15795 (43)	4717 (18)
Center						
NC	25611 (102)	6562 (22)	4748 (37)	5330 (10)	6598 (23)	2373 (10)
MS	22838 (172)	10819 (88)	5004 (54)	865 (3)	4720 (23)	1430 (4)
MN	25402 (101)	1104 (5)	3222 (21)	6489 (21)	11052 (37)	3535 (17)
MD	24961 (139)	5762 (22)	5804 (53)	4434 (24)	6656 (25)	2305 (15)
Smoking						
Never	40162 (131)	16520 (68)	5410 (27)	7539 (12)	9127 (18)	1566 (6)
Former	31266 (160)	3895 (31)	7449 (56)	5192 (18)	11288 (44)	3442 (11)
Current	27384 (223)	3832 (38)	5918 (82)	4388 (28)	8611 (46)	4635 (29)
Diabetes						
No	88283 (320)	20637 (63)	15916 (98)	15894 (43)	26819 (77)	9017 (39)
Yes	10528 (194)	3610 (74)	2862 (67)	1224 (15)	2207 (31)	625 (7)
HTN						
No	66181 (219)	14504 (42)	12065 (67)	12723 (32)	20634 (54)	6255 (24)
Yes	32632 (295)	9743 (95)	6713 (98)	4396 (26)	8392 (54)	3388 (22)
BMI						
<25	33500 (124)	6725 (30)	5600 (39)	6521 (12)	10489 (28)	4165 (15)
25 - <30	39154 (189)	8832 (36)	7479 (63)	6335 (26)	12771 (46)	3737 (18)
≥30	26159 (201)	8690 (71)	5699 (63)	4263 (20)	5766 (34)	1741 (13)
mean (SD)	27.5 (5.2)	28.7 (5.9)	28.1 (5.5)	27.1 (5.0)	26.8 (4.4)	26.3 (4.6)
range	14.2-60.6	14.2-60.6	14.4-53.9	16.0-54.7	15.4-54.4	15.5-56.3
HDL chol						
>=40	76814 (319)	19716 (98)	13295 (94)	13099 (29)	22492 (70)	8212 (28)
<40	21998 (195)	4531 (39)	5482 (71)	4020 (29)	6534 (38)	1431 (18)
mean (SD)	53.3 (17.7)	54.5 (17.0)	48.8 (15.2)	52.6 (16.9)	53.4 (17.9)	60.0 (21.3)
range	10.0-168.0	12.0-168.0	11.0-147.0	16.0-148.0	10.0-141.0	12.0-163.0
LDL-chol						
<100	17483 (80)	4133 (29)	2847 (25)	3033 (8)	5337 (14)	2133 (4)
>=100	81328 (434)	20114 (108)	15930 (140)	14085 (50)	23689 (94)	7510 (42)
mean (SD)	135.2 (39.4)	137.3 (41.1)	138.4 (39.2)	133.8 (37.9)	133.8 (37.9)	130.8 (42.2)
range	1.0-395.0	5.0-395.0	6.0-368.0	8.0-370.0	1.0-380.0	17.0-315.0
Trigly						
<150	72085 (297)	18136 (83)	13530 (89)	12198 (36)	21515 (61)	6706 (28)
>=150	26726 (217)	6111 (54)	5247 (76)	4921 (22)	7511 (47)	2936 (18)
mean (SD)	129.6 (81.1)	125.9 (77.0)	133.7 (84.9)	132.9 (88.9)	126.5 (75.5)	134.7 (84.3)
range	24.0-1277.0	27.0-1088.0	29.0-1218.0	29.0-1277.0	24.0-897.0	34.0-745.0
Leisure						
Q1	19777 (163)	5576 (52)	4656 (55)	2622 (16)	4852 (29)	2071 (11)
Q2	31951 (169)	8006 (41)	5885 (60)	5520 (17)	9187 (32)	3353 (19)
Q3	29241 (125)	6697 (29)	5029 (36)	5534 (18)	9279 (32)	2702 (10)
Q4	17843 (57)	3969 (15)	3208 (14)	3443 (7)	5707 (15)	1516 (6)
mean (SD)	2.4 (0.6)	2.3 (0.6)	2.3 (0.6)	2.4 (0.5)	2.4 (0.6)	2.3 (0.6)
range	1.0-4.5	1.0-4.5	1.0-4.50	1.0-4.25	1.0-4.50	1.0-4.0

* P-Y = person-years; HS=high school; HTN=hypertension; BMI=body mass index; HDL-chol=high density lipoprotein cholesterol; LDL-chol = low density lipoprotein cholesterol; Trigly = triglycerides; Leisure=physical activity level divided into quartiles.

Table 5.2 (continued): Person-time contributions in years and the number of heart failure cases by covariates, alcohol intake levels, and visit, ARIC 1987-2002

	Visit 3+					
	ALL P-Y (cases) 94060 (675)	Never P-Y (cases) 23313 (166)	Former P-Y (cases) 20589 (231)	Occasional P-Y (cases) 15301 (65)	Light/Mod P-Y (cases) 27024 (148)	Heavy P-Y (cases) 7833 (65)
Race						
Black	20679 (188)	8042 (72)	6469 (73)	1723 (9)	2826 (16)	1619 (18)
White	73381 (487)	15271 (94)	14120 (158)	13578 (56)	24198 (132)	6214 (47)
Gender						
Female	52958 (308)	17861 (124)	10005 (90)	10248 (35)	11612 (42)	3232 (17)
Male	41102 (367)	5452 (42)	10584 (141)	5053 (30)	15412 (106)	4601 (48)
Education						
<HS	17624 (239)	6056 (78)	6197 (104)	1319 (13)	2673 (23)	1379 (21)
HS grad	31610 (219)	8697 (53)	6446 (69)	5448 (25)	8510 (55)	2509 (17)
>HS	44824 (217)	8560 (35)	7945 (58)	8534 (27)	15841 (70)	3944 (27)
Center						
NC	24421 (164)	8035 (59)	5303 (50)	3227 (13)	6209 (27)	1647 (15)
MS	18127 (167)	7318 (64)	5511 (63)	1512 (9)	2364 (15)	1422 (16)
MN	26505 (122)	1659 (1)	3848 (32)	6063 (19)	12018 (56)	2917 (14)
MD	25004 (222)	6300 (42)	5926 (86)	4499 (24)	6432 (50)	1847 (20)
Smoking						
Never	39850 (188)	16432 (87)	6319 (49)	7625 (15)	8343 (32)	1131 (5)
Former	38312 (302)	4669 (48)	10195 (125)	5664 (31)	13775 (68)	4009 (30)
Current	15895 (185)	2211 (31)	4074 (57)	2012 (19)	4906 (48)	2692 (30)
Diabetes						
No	81699 (435)	19766 (84)	16749 (146)	13831 (48)	24456 (112)	6897 (45)
Yes	12360 (240)	3546 (82)	3840 (85)	1470 (17)	2568 (36)	936 (20)
HTN						
No	58089 (248)	13048 (51)	11696 (81)	10541 (28)	18234 (66)	4570 (22)
Yes	35970 (427)	10265 (115)	8892 (150)	4761 (37)	8790 (82)	3262 (43)
BMI						
<25	26678 (143)	6043 (33)	4879 (44)	4785 (14)	8577 (38)	2394 (14)
25 - <30	37753 (223)	8507 (42)	8376 (75)	5919 (20)	11717 (61)	3234 (25)
≥30	26628 (309)	5762 (91)	7333 (112)	4598 (31)	6730 (49)	2205 (26)
mean (SD)	28.3 (5.4)	29.1 (5.9)	28.9 (5.6)	28.1 (5.2)	27.5 (4.8)	27.7 (5.0)
range	14.2-62.0	16.4-60.2	14.7-62.0	14.2-56.6	14.5-59.1	16.1-50.6
HDL chol						
>=40	59228 (431)	18384 (120)	1448 (136)	12013 (38)	21003 (92)	6380 (45)
<40	21831 (244)	4928 (46)	6141 (95)	3288 (27)	6021 (56)	1453 (20)
mean (SD)	52.7 (18.1)	53.2 (17.3)	48.7 (16.1)	53.5 (17.6)	53.4 (18.6)	57.5 (21.7)
range	11.0-195.0	16.0-147.0	15.0-146.0	18.0-121.0	11.0-177.0	18.0-195.0
LDL-chol						
<100	19333 (150)	4772 (32)	3915 (52)	3147 (14)	5588 (34)	1911 (18)
>=100	77426 (525)	18541 (134)	16674 (179)	12154 (51)	24136 (114)	5921 (47)
mean (SD)	127.3 (34.3)	128.4 (34.9)	129.1 (34.1)	126.5 (33.0)	126.6 (33.6)	123.6 (37.2)
range	7.6-347.0	7.6-279.0	10.0-289.6	28.2-291.2	21.4-317.8	20.6-347.0
Trigly						
<150	63701 (408)	15948 (99)	13732 (148)	10447 (34)	18198 (82)	5376 (45)
>=150	30357 (267)	7364 (67)	6856 (83)	4854 (31)	8826 (66)	2457 (20)
mean (SD)	135.0 (66.7)	134.4 (66.5)	136.5 (67.3)	136.5 (66.6)	134.4 (66.2)	131.9 (67.3)
range	22.0-399.0	28.0-399.0	33.0-399.0	29.0-398.0	22.0-396.0	33.0-397.0
Leisure						
Q1	17764 (200)	4788 (54)	4679 (67)	2323 (23)	4002 (30)	1972 (26)
Q2	31840 (204)	7913 (49)	7034 (69)	5516 (16)	8947 (57)	2430 (13)
Q3	27572 (188)	6553 (45)	5534 (62)	4546 (14)	8827 (46)	2112 (21)
Q4	16882 (83)	4059 (18)	3342 (33)	2916 (12)	5247 (15)	1318 (5)
mean (SD)	2.4 (0.6)	2.3 (0.6)	2.3 (0.6)	2.4 (0.5)	2.4 (0.5)	2.3 (0.6)
range	1.0-4.5	1.0-4.50	1.0-4.50	1.0-4.50	1.0-4.50	1.0-4.50

* P-Y = person-years; HS=high school; HTN=hypertension; BMI=body mass index; HDL-chol=high density lipoprotein cholesterol; LDL-chol = low density lipoprotein cholesterol; Trigly = triglycerides; Leisure=physical activity level divided into quartiles.

Table 5.3: Crude and Age Adjusted Heart Failure Incidence Rates by Level of Alcohol Intake and Visit among ARIC Study Participants, 1987-2002

	Visit 1-3				Visit 3+			
	Cases n	Follow-up person-years	Crude IR* (95% CI)	AA IR* (95%CI)	Cases n	Follow-up person-years	Crude IR* (95%CI)	AA IR* (95%CI)
Drinking Status**								
All drinkers	514	98812	520 (475, 565)	484 (466, 502)	675	94058	718 (664, 772)	747 (730, 765)
Never	137	24247	565 (470, 660)	495 (460, 530)	166	23312	712 (604, 820)	668 (630, 706)
Former	165	18777	879 (745, 1013)	802 (747, 856)	231	20588	1122 (977,1267)	1060(1013,1108)
Occasional	58	17119	339 (252, 426)	323 (289, 358)	65	15301	425 (322, 528)	477 (444, 511)
Light/Moderate	108	29026	372 (302, 442)	355 (327, 383)	148	27024	548 (459, 636)	657 (630, 684)
Heavy	46	9643	477 (339, 615)	464 (405, 524)	65	7833	830 (628, 1032)	1009(940,1077)
Blacks								
All drinkers	196	26383	743 (639, 847)	735 (692, 778)	188	20679	909 (779, 1039)	887 (839, 935)
Never	92	11522	798 (365, 962)	749 (687, 812)	72	8042	895 (688, 1102)	805 (729, 881)
Former	67	6141	1091 (830, 1352)	1043 (935, 1152)	73	6469	1128(870,1387)	1117(1024,1211)
Occasional	5	1421	352 (434, 660)	350 (220, 480)	9	1723	522 (181, 864)	493 (379, 606)
Light/Moderate	26	5531	470 (289, 651)	467 (388, 546)	16	2826	566 (289, 844)	492 (384, 600)
Heavy	6	1768	339 (68, 611)	382 (249, 516)	18	1619	1112 (598, 1625)	948 (721,1174)
Whites								
All drinkers	318	72428	439 (391, 487)	401 (382, 419)	487	73379	664 (605, 723)	694 (676,711)
Never	45	12725	354 (250, 457)	297 (258, 336)	94	15271	616 (491, 740)	570 (531, 608)
Former	98	12636	776 (622, 929)	690 (629, 751)	158	14120	1119 (944, 1293)	1016(964,1068)
Occasional	53	15698	338 (247, 429)	321 (285, 357)	56	13578	412 (304, 520)	466 (431, 500)
Light/Moderate	82	23495	349 (273, 425)	328 (299, 357)	132	24198	545 (452, 639)	644 (617, 670)
Heavy	40	7875	508 (351, 665)	474 (407, 451)	47	6214	756 (540, 973)	903 (837, 968)

* IR = incidence rate per 1000 person-years
** Drinking status: Never=lifetime abstainers, Former=previous drinkers but not current drinkers, Occasional=report currently drink but not on a regular basis, light/moderate=drink up to 1 drink per day for women and up to 2 drinks per day for men, heavy=drink more than 1 drink per day for women and more than 2 drinks per day for men.
ARIC=Atherosclerosis Risk in Communities Cohort; P-Y = person-years; IR=incidence rate; AA = age adjusted

Table 5.4: Rate Ratios with 95% Confidence Intervals Comparing Alcohol Intake and Heart Failure Incidence, ARIC 1987-2002

	Alcohol Intake^				
	Never	Former	Occasional	Light/Moderate	Heavy
All, Visit 1-3					
Crude RR (95%CI)	reference	1.56 (1.24, 1.95)	0.60 (0.44, 0.81)	0.66 (0.51, 0.85)	0.84 (0.61, 1.17)
Min adjusted* RR (95%CI)	reference	1.39 (1.11, 1.76)	0.81 (0.59, 1.09)	0.75 (0.58, 0.96)	0.97 (0.70, 1.35)
Fully adjusted** RR (95%CI)	reference	1.07 (0.84, 1.37)	0.63 (0.46, 0.87)	0.55 (0.42, 0.72)	0.61 (0.43, 0.87)
Blacks, Visit 1-3					
Crude RR (95%CI)	reference	1.37 (1.00, 1.86)	0.44 (0.18, 1.09)	0.59 (0.38, 0.90)	0.43 (0.19, 0.96)
Min adjusted* RR (95%CI)	reference	1.29 (0.93, 1.79)	0.52 (0.21, 1.28)	0.63 (0.39, 0.99)	0.50 (0.22, 1.14)
Fully adjusted** RR (95%CI)	reference	1.04 (0.74, 1.48)	0.45 (0.18, 1.12)	0.47 (0.29, 0.76)	0.28 (0.14, 0.77)
Whites, Visit 1-3					
Crude RR (95%CI)	reference	2.19 (1.54, 3.11)	0.95 (0.64, 1.42)	0.99 (0.69, 1.42)	1.44 (0.94, 2.19)
Min adjusted* RR (95%CI)	reference	1.76 (1.23, 2.51)	1.13 (0.77, 1.70)	1.02 (0.71, 1.46)	1.45 (0.95, 2.21)
Fully adjusted** RR (95%CI)	reference	1.26 (0.87, 1.82)	0.85 (0.57, 1.27)	0.72 (0.49, 1.07)	0.87 (0.55, 1.37)
All, Visit 3+					
Crude RR (95%CI)	reference	1.58 (1.29, 1.92)	0.60 (0.45, 0.79)	0.77 (0.62, 0.96)	1.17 (0.87, 1.55)
Min adjusted* RR (95%CI)	reference	1.41 (1.15, 1.73)	0.77 (0.58, 1.03)	0.88 (0.70, 1.11)	1.20 (0.90, 1.61)
Fully adjusted** RR (95%CI)	reference	1.16 (0.94, 1.44)	0.70 (0.53, 0.94)	0.75 (0.59, 0.96)	0.88 (0.64, 1.20)
Blacks, Visit 3+					
Crude RR (95%CI)	reference	1.26 (0.91, 1.74)	0.58 (0.29, 1.16)	0.63 (0.37, 1.08)	1.24 (0.74, 2.09)
Min adjusted* RR (95%CI)	reference	1.11 (0.79, 1.55)	0.69 (0.35, 1.36)	0.69 (0.40, 1.18)	1.25 (0.74, 2.12)
Fully adjusted** RR (95%CI)	reference	0.97 (0.68, 1.39)	0.60 (0.30, 1.22)	0.58 (0.32, 1.03)	0.93 (0.53, 1.65)
Whites, Visit 3+					
Crude RR (95%CI)	reference	1.82 (1.41, 2.34)	0.67 (0.48, 0.93)	0.89 (0.68, 1.15)	1.23 (0.87, 1.74)
Min adjusted* RR (95%CI)	reference	1.65 (1.28, 2.14)	0.86 (0.62, 1.20)	0.99 (0.76, 1.30)	1.23 (0.86, 1.76)
Fully adjusted** RR (95%CI)	reference	1.34 (1.02, 1.76)	0.81 (0.58, 1.13)	0.85 (0.64, 1.14)	0.91 (0.62, 1.03)

Table 5.4 (continued): Rate Ratios with 95% Confidence Intervals Comparing Alcohol Intake and Heart Failure Incidence, ARIC 1987-2002

	Alcohol Intake^				
	Never	Former	Occasional	Light/Moderate	Heavy
All					
Crude RR (95%CI)	reference	1.58 (1.36, 1.83)	0.60 (0.48, 0.73)	0.72 (0.61, 0.85)	1.00 (0.80, 1.24)
Min adjusted* RR (95%CI)	reference	1.40 (1.20, 1.63)	0.78 (0.63, 0.96)	0.82 (0.69, 0.97)	1.09 (0.87, 1.35)
Fully adjusted** RR (95%CI)	reference	1.12 (0.95, 1.31)	0.67 (0.54, 0.82)	0.65 (0.54, 0.78)	0.75 (0.59, 0.95)
Blacks					
Crude RR (95%CI)	reference	1.32 (1.06, 1.66)	0.53 (0.31, 0.92)	0.60 (0.43, 0.84)	0.85 (0.55, 1.30)
Min adjusted* RR (95%CI)	reference	1.18 (0.94, 1.49)	0.61 (0.35, 1.05)	0.64 (0.45, 0.91)	0.90 (0.58, 1.38)
Fully adjusted** RR (95%CI)	reference	1.01 (0.79, 1.29)	0.55 (0.31, 0.95)	0.51 (0.35, 0.74)	0.64 (0.40, 1.01)
Whites					
Crude RR (95%CI)	reference	1.93 (1.57, 2.37)	0.75 (0.58, 0.96)	0.90 (0.73, 1.12)	1.24 (0.95, 1.62)
Min adjusted* RR (95%CI)	reference	1.68 (1.37, 2.08)	0.96 (0.75, 1.23)	0.99 (0.80, 1.23)	1.31 (1.00, 1.71)
Fully adjusted** RR (95%CI)	reference	1.29 (1.04, 1.61)	0.81 (0.63, 1.04)	0.79 (0.63, 0.99)	0.88 (0.66, 1.17)

^Alcohol intake was defined as: Never drinkers=lifetime abstainers, former drinkers=previous intake but no current intake, occasional drinkers=report alcohol intake but none in the previous month, light/moderate drinkers=up to 1 drink per day for women and up to 2 drinks per day for men, heavy drinkers=more than 1 drink per day for women and more than 2 drinks per day for men.
RR = rate ratio, CI = confidence interval
* Adjusted for age, race, gender, and socioeconomic status.
** Adjusted for age, race, gender, socioeconomic status, smoking, physical activity, and ARIC study center.

5.5 References

1. Thom T, Haase N, Rosamond W, et al. Heart Disease and Stroke Statistics--2006 Update. A Report From the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2006.

2. Labarthe D. Epidemiology and Prevention of Cardiovascular Diseases: A Global Challenge: Aspen Publishers, 1998.

3. Regan TJ. Alcohol and the cardiovascular system. Jama 1990;264:377-81.

4. Kasper EK, Agema WR, Hutchins GM, Deckers JW, Hare JM, Baughman KL. The causes of dilated cardiomyopathy: a clinicopathologic review of 673 consecutive patients. J Am Coll Cardiol 1994;23:586-90.

5. Walsh CR, Larson MG, Evans JC, et al. Alcohol consumption and risk for congestive heart failure in the Framingham Heart Study. Ann Intern Med 2002;136:181-91.

6. Rimm EB, Williams P, Fosher K, Criqui M, Stampfer MJ. Moderate alcohol intake and lower risk of coronary heart disease: meta-analysis of effects on lipids and haemostatic factors. Bmj 1999;319:1523-8.

7. Abramson JL, Williams SA, Krumholz HM, Vaccarino V. Moderate alcohol consumption and risk of heart failure among older persons. Jama 2001;285:1971-7.

8. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. Am J Epidemiol 1989;129:687-702.

9. Eigenbrodt ML, Fuchs FD, Hutchinson RG, Paton CC, Goff DC, Jr., Couper DJ. Health-associated changes in drinking: a period prevalence study of the Atherosclerosis Risk In Communities (ARIC) cohort (1987-1995). Prev Med 2000;31:81-9.

10. Evenson KR, Rosamond WD, Cai J, et al. Physical activity and ischemic stroke risk. The atherosclerosis risk in communities study. Stroke 1999;30:1333-9.

11. Baecke JA, Burema J, Frijters JE. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. Am J Clin Nutr 1982;36:936-42.

12. Kaufman JS, Maclehose RF, Kaufman S. A further critique of the analytic strategy of adjusting for covariates to identify biologic mediation. Epidemiol Perspect Innov 2004;1:4.
13. Lucas DL, Brown RA, Wassef M, Giles TD. Alcohol and the cardiovascular system research challenges and opportunities. J Am Coll Cardiol 2005;45:1916-24.

14. Midanik LT. Validity of self-reported alcohol use: a literature review and assessment. Br J Addict 1988;83:1019-30.

15. Hoyer G, Nilssen O, Brenn T, Schirmer H. The Svalbard study 1988-89: a unique setting for validation of self-reported alcohol consumption. Addiction 1995;90:539-44.

16. Smith PF, Remington PL, Williamson DF, Anda RF. A comparison of alcohol sales data with survey data on self-reported alcohol use in 21 states. Am J Public Health 1990;80:309-12.

17. Poikolainen K, Podkletnova I, Alho H. Accuracy of quantity-frequency and graduated frequency questionnaires in measuring alcohol intake: comparison with daily diary and commonly used laboratory markers. Alcohol Alcohol 2002;37:573-6.

18. Polich JM. Epidemiology of alcohol abuse in military and civilian populations. Am J Public Health 1981;71:1125-32.

19. Rothman KJaG, S. Modern Epidemiology. Philadelphia: Lippincott Williams & Wilkins, 1998.

20. Gunzerath L, Faden V, Zakhari S, Warren K. National Institute on Alcohol Abuse and Alcoholism report on moderate drinking. Alcohol Clin Exp Res 2004;28:829-47.

CHAPTER 6
DISCUSSION

6.1 Summary of Findings

The aims of this study were to evaluate (1) the association between alcohol consumption and stroke (all, ischemic, and hemorrhagic) incidence and (2) the association between alcohol intake and HF incidence in a cohort of U.S. adults. To assess these relationships, data from the ARIC Cohort Study were analyzed using Poisson regression.

The results provide no compelling evidence that occasional or light to moderate alcohol intake reduces stroke incidence rates. The unadjusted RRs suggest an inverse association between occasional drinking and all stroke or ischemic stroke, and an inverse association between light/moderate drinking and all stroke or ischemic stroke. Adjustment for confounding factors attenuated the association, suggesting that the underlying distribution of covariates varied across levels of alcohol intake. The minimally adjusted race-stratified results indicate a positive association for whites between heavy alcohol intake and all stroke incidence as well as between heavy alcohol intake and ischemic stroke incidence. Among blacks, light to moderate alcohol intake is associated with increased all stroke incidence. These results indicate that light/moderate alcohol consumption may have different effects on all and/or ischemic stroke incidence among blacks and whites.

The adjusted RRs examining alcohol intake and hemorrhagic stroke incidence suggest that any level of alcohol intake increases hemorrhagic stroke incidence rates.

Additionally, the results suggest a positive association between former drinking and HF incidence and an inverse association between current alcohol consumption and HF incidence. While the association between former drinkers and HF incidence was evident for whites, the evidence among blacks was less strong. The strength of the inverse association between current alcohol intake levels and HF incidence varies with race and time period, but in all of the fully adjusted models comparing those who currently drink alcohol (either occasional, light/moderate, or heavy) to the never drinkers, the RRs are consistently less than one.

These study results add to the current knowledge of alcohol and cardiovascular disease in several ways. Previous study results examining the association between light to moderate alcohol intake and stroke occurrence are conflicting. A meta-analysis attempting to summarize the alcohol and stroke relationship, reported a reduction in ischemic stroke rates for light to moderate intake (up to 2 drinks/day) and an increase in both ischemic and hemorrhagic stroke rates with heavy intake (5+ drinks/day) versus never drinkers (1). Using a well-designed prospective cohort study I found all stroke and ischemic stroke incidence rates are not reduced among those consuming light to moderate amounts of alcohol. We did find that alcohol intake is positively associated with hemorrhagic stroke incidence rates. These results should be considered in re-evaluating the current AHA and USDHHS dietary guidelines which state that current light to moderate drinkers may

have a cardiovascular health benefit from their alcohol intake behavior (2-4). On the other hand, our results agree with the few studies that have examined the relationship between HF incidence and moderatealcohol intake and our results extend to a wider population (blacks and those from the southern US). These apparent contradictory effects of alcohol on the different types of cardiovascular disease highlight the importance of having alcohol consumption recommendations that take into account the many facets of cardiovascular disease.

6.2 Issues with Alcohol

There are a myriad of problems associated with studying alcohol consumption. These include the untangling of the causative and preventive effects of alcohol on the cardiovascular system as well as general health, the availability of methods to alcohol measurement, and the fact that patterns of alcohol intake change over time.

The potential biologic mechanisms through which alcohol may affect the cardiovascular system are complex due to the fact that some mechanisms suggest a preventive effect while others suggest a causative effect. Current evidence suggests that moderate alcohol intake (up to 1 drink/day for women and up to 2 drinks/day for men) increases HDL-cholesterol, reduces LDL-cholesterol oxidation, increases insulin sensitivity, and decreases clotting and platelet aggregation (5). In contrast, heavy alcohol intake (more than 1 drink/day for women and more than 2 drinks/day for men) increases oxidative stress, increase triglycerides, increases blood pressure, and decreases HDL-cholesterol (5). Teasing out the opposing

beneficial and preventive effects of alcohol is difficult at best making the analysis of alcohol problematic.

The health effects of alcohol are numerous, with alcohol consumption estimated to cause 100,000 deaths each year in the US (6). Those who drink alcohol have higher mortality rates from injuries, violence, suicide, and cirrhosis as compared with abstainers. Despite these negative health effects, a meta-analysis of approximately 50 studies found an inverse association between light to moderate drinking (up to 1 drink/day for women and up to 2 drinks/day for men) and all cause-mortality (7). It is thought that this relationship is due to the protective effects of alcohol intake on CHD. One way to determine how alcohol consumption affects the body and reduces or increases stroke or HF rates would be to conduct a RCT. Because of ethical concerns that study participants assigned to drink alcohol may become dependent as well as the high cost involved and the difficulty in finding participants, no long-term RCT of alcohol use is feasible.

Measuring alcohol intake is another area in the alcohol research field which needs attention. Current methods to obtain alcohol data rely on self-report, proxy report or biomarkers. None of these methods are reliable or valid, and each varies according to the specific study. Improvements in methods to obtain valid and reliable alcohol consumption estimates are needed. Thirty years ago, there was no good test to monitor blood glucose levels in diabetic patients over time. In the last decade it was discovered that the amount of glycosylated hemoglobin (HgbA1C) in the blood reflects blood glucose control for the past 120 days (the lifespan of the red blood cell). Today, diabetic patients are able to get an accurate and valid measure

of their average blood glucose level with the HgbA1c test. A biomarker/test that could provide an estimate of the amount of alcohol consumed over the past few months would be a major step forward in the research arena of alcohol consumption.

Another problem with studying alcohol is that alcohol consumption patterns are known to change over time. In the ARIC data, for example, alcohol intake tended to decrease during a six-year follow-up period (8). The majority of studies examining the stroke and alcohol association measured alcohol at baseline, not updating drinking levels during the study period. Determining the impact that this has on the associations between alcohol and outcomes is difficult because the impact will depend on the amount of change in alcohol drinking over time as well as the induction time (i.e. the time it takes for the disease to develop following an exposure). If none of the study participants change their drinking patterns over the course of the study and the induction time were short, measurement of alcohol at baseline alone would be sufficient. If however, a large proportion of participants changed their behaviors or the induction time were not short, updating alcohol information might help to reduce the misclassification of alcohol consumption. Another concern regarding the patterns of alcohol drinking relate to the differing effects of binge drinking versus steady alcohol intake. Questions that ask about the frequency of alcohol intake need to be able to discern between these two distinct types of behaviors.

6.3 Future Research/Public Health Implications

According to the National Institute on Alcohol Abuse and Alcoholism, approximately 35% of US adults are abstainers, 60% are occasional to moderate alcohol drinkers, and 5% have alcohol dependence (6). Given that the US population is approximately 300 million, this equates with 180 million occasional to moderate alcohol drinkers in the US. Each year an estimated 500,000 new strokes and 550,000 new HF cases occur. To what extent alcohol contributes to this morbidity and mortality is unknown.

The AHA guidelines regarding alcohol intake state that for those who drink, doing so in moderation is good for your heart (2). This recommendation is based on the large number of studies (mostly observational) that found moderate alcohol intake (up to 30g/day or approximately 2.3 drinks/day) is cardioprotective against MI/CHD (9). Studies examining the association between stroke incidence and alcohol have found conflicting results. Few studies have examined HF incidence and alcohol intake in the community. Our data suggest that there is no benefit in terms of stroke prevention but that alcohol intake may be inversely associated with HF occurrence.

Additional studies examining the role of alcohol intake on stroke incidence among blacks are warranted. Current AHA guidelines state that for those who drink alcohol, to do so in moderation (up to one drink/day for women and up to two drinks/day for men) and that drinking more than this may increase stroke risk (2, 3). While heavy alcohol intake appears to increase overall stroke incidence, the perceived benefit of light to moderate alcohol intake may not apply to all populations.

Since the AHA recommendations are based on results of studies with few minority groups, the guidelines should be reconsidered or at least conveyed with caution. In terms of HF, few studies have examined the association between alcohol intake and HF incidence. Analysis of the ARIC study population and the Framingham Heart Study suggest a protective effect of alcohol on heart failure incidence. Although the findings appear to be similar, more studies in this area should be conducted. The mechanisms of the association are unclear and the other health risks associated with alcohol intake are not trivial. While the AHA guidelines do not recommend abstainers start drinking alcohol, the benefit of light/moderate intake needs to be obvious if the guidelines are going to imply that drinking has benefits. Given the uncertainty of data derived from observational studies and the varied results from previous studies, strong consideration should be given to revising or completely abandoning guidelines that imply a health benefit to alcohol use.

6.4 References

1. Reynolds K, Lewis LB, Nolen JD, Kinney GL, Sathya B, He J. Alcohol consumption and risk of stroke: a meta-analysis. Jama 2003;289:579-88.

2. Pearson TA, Blair SN, Daniels SR, et al. AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update: Consensus Panel Guide to Comprehensive Risk Reduction for Adult Patients Without Coronary or Other Atherosclerotic Vascular Diseases. American Heart Association Science Advisory and Coordinating Committee. Circulation 2002;106:388-91.

3. Goldstein LB, Adams R, Becker K, et al. Primary prevention of ischemic stroke: A statement for healthcare professionals from the Stroke Council of the American Heart Association. Stroke 2001;32:280-99.

4. Dietary Guidelines for Americans, 2005. Washington, DC: US Department of Health and Human Services and US Department of Agriculture, 2005.

5. Lucas DL, Brown RA, Wassef M, Giles TD. Alcohol and the cardiovascular system research challenges and opportunities. J Am Coll Cardiol 2005;45:1916-24.

6. Gunzerath L, Faden V, Zakhari S, Warren K. National Institute on Alcohol Abuse and Alcoholism report on moderate drinking. Alcohol Clin Exp Res 2004;28:829-47.

7. Gmel G, Gutjahr E, Rehm J. How stable is the risk curve between alcohol and all-cause mortality and what factors influence the shape? A precision-weighted hierarchical meta-analysis. Eur J Epidemiol 2003;18:631-42.

8. Eigenbrodt ML, Mosley TH, Jr., Hutchinson RG, Watson RL, Chambless LE, Szklo M. Alcohol consumption with age: a cross-sectional and longitudinal study of the Atherosclerosis Risk in Communities (ARIC) study, 1987-1995. Am J Epidemiol 2001;153:1102-11.

9. Rimm EB, Williams P, Fosher K, Criqui M, Stampfer MJ. Moderate alcohol intake and lower risk of coronary heart disease: meta-analysis of effects on lipids and haemostatic factors. Bmj 1999;319:1523 8.