ASSOCIATION OF MID-LIFE ALCOHOL CONSUMPTION WITH STROKE AND COGNITIVE DECLINE IN THE ATHEROSCLEROSIS RISK IN COMMUNITIES STUDY

Sara Bingham Jones

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Approved by:

Wayne D. Rosamond

Laura Loehr

Christy L. Avery

Rebecca F. Gottesman

Lisa Wruck

ABSTRACT

Sara Bingham Jones: Association of Mid-Life Alcohol with Stroke and Cognitive Decline in the
Atherosclerosis Risk in Communities Study
(Under the direction of Wayne D. Rosamond)

One in three adults will experience stroke or develop dementia in their lifetime, underscoring

the need to identify modifiable factors to delay or prevent disease. Alcohol, a common exposure in

most populations, may confer cardiovascular benefits at light-to-moderate doses. Its association with

stroke and cognitive function is uncertain.

This dissertation aims to estimate the associations between mid-life alcohol consumption and

incident stroke and rate of cognitive decline using data from the Atherosclerosis Risk in Communities

Study, a biracial population-based cohort of 15,792 adults aged 45-64 at baseline with >20 years of

follow-up. Alcohol consumption was self-reported as usual drinks per week; categorized as never,

former, light (≤3), moderate (4-17), and heavier (≥18). One-third of participants were light drinkers,

roughly one-fifth each were moderate, never and former drinkers and only 4% reported heavier

consumption.

Suspected strokes were obtained through self-report and hospital surveillance, validated using

medical records, and adjudicated by physician experts. Light and moderate consumption were not

strongly associated with ischemic stroke (HR=0.98, 95% CI 0.79-1.21; 1.06, 0.84-1.34) while heavier

drinking was associated with a 31% increased rate relative to abstention in Cox proportional-hazard

regression. Specification of intake with quadratic splines did not support a J-shaped relationship with

stroke; we noted a roughly linear relative increase across intake. Moderate-to-heavy, but not light,

consumption increased hemorrhage rates.

Cognitive status was assessed at visits 2, 4, and 5 using three validated tests. Linear regression with generalized estimating equations estimated the difference in 20-year decline by alcohol intake. We used multiple imputation with chained equations to address informative attrition in sensitivity analysis. Global 20-year cognitive change did not differ between light drinkers and abstainers (0.019 z-score units; 95% CI -0.032, 0.070) and was somewhat faster for heavier drinkers (-0.041; -0.0152, 0.070). No consistent pattern in 20-year change was observed across tests, but effects were somewhat larger on tests of verbal fluency and executive function.

Light-to-moderate consumption at mid-life was not associated with reduced stroke risk or slower cognitive decline compared with abstention over 20 years of follow-up in the ARIC study. Heavier consumption tended to increase the risk for both outcomes.

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CHAPTER 1: INTRODUCTION

Brain-related diseases are important targets for public health prevention, particularly given the ageing population and expected concomitant increases in disease burden. Stroke is a leading cause of mortality and disability, and dementia prevalence is estimated to be as high as 50% among adults aged 85 years and older.[7, 8] Approximately 1 in 3 Americans will have a stroke or develop dementia in their lifetime, underscoring the need for continued examination of modifiable risk factors for these diseases.[9]

The association between alcohol and coronary heart disease has been widely studied, with relatively consistent findings of a J-shaped relationship such that moderate drinkers have the lowest risk of disease.[10-14, 15] Whether similar dose-response relationships exist between alcohol consumption and diseases of the brain, including stroke and cognitive impairment, is less well understood. Previous studies have reported that heavy alcohol consumption is associated with increased ischemic and hemorrhagic stroke risk as well as cognitive decline and dementia.[2, 6, 16-19] However, results are conflicting with regard to whether low-to-moderate intake is associated with reduced risk of stroke and cognitive decline.[1, 14, 18, 20-26] Several of these studies rely on a single baseline measure of alcohol intake that in studies of cognitive decline is often temporally close to outcome measurement,[1, 19-22, 24-35] use few categories of alcohol intake thus limiting assessment of dose response, have mixed reference groups,[19, 21, 22, 21, 28, 29, 31, 32, 35] are limited in availability of potential confounders,[1, 19, 20, 24-26, 28-32, 34-37] adjust for possible mediators including HDL cholesterol and blood pressure,[1, 19, 21, 22, 24-27, 30-32, 34, 35] have short (<5 year) follow-up periods,[20, 21, 23, 25, 1, 21, 27-32, 34] and lack clinician-based diagnosis of stroke or ideal measurement of cognitive decline.[1, 28, 30, 31, 37]

Furthermore, there are few studies of the effects of alcohol in African-American populations despite the fact that African-Americans have a higher incidence of stroke and dementia and higher prevalence of problem drinking.[7, 38] Some evidence suggests that effects on stroke risk may differ by race, but studies are few. [39-41]

Alcohol may exert protective effects for ischemic stroke by increasing high-density lipoprotein, apolipoprotein A, insulin sensitivity, and fibrinogen levels as well as by decreasing inflammation, thrombotic factors, and platelet activity.[6, 42-44] Moderate alcohol consumption may reduce the risk of cognitive decline through similar mechanisms, resulting in preserved brain vasculature, fewer subclinical infarcts and microbleeds, and less white matter degradation. In addition, moderate alcohol may facilitate learning and memory by increasing acetylcholine, a neurotransmitter involved in attention and memory storage, in the hippocampus.[8, 18] In contrast, high doses of alcohol have clear deleterious effects through direct neurotoxic effects on brain structures, elevated blood pressure, reduced cerebral blood flow, and development of atrial fibrillation and cardiomyopathy that increase the risk of stroke and cognitive decline.[18] The anti-thrombotic effects of alcohol that may protect against ischemic stroke may increase hemorrhage risk. Heavy drinking can also lead to Wernicke-Korsakoff syndrome, a thiamine deficiency characterized by cognitive and memory deficits. Chronic alcohol abuse indirectly leads to thiamine deficiency through malnourishment and directly plays a role by decreasing absorption from the gastrointestinal tract, interfering with the conversion of thiamine into its active form.[45] Moderate alcohol intake may have harmful effects as well. There is risk of addiction for certain populations and studies suggest that moderate intake may be associated with increased stomach, esophageal and breast cancer risk.[46] Additional risks include disruption of sleep, medication interaction, and harm to fetal development. Because of these hazards, and the inability to predict those sub-groups at risk for progression to problem drinking, the American Heart Association does not currently

recommend initiation of moderate drinking among abstainers for the purpose of reducing risk of heart disease.[47] Instead, public health messages focus on reduction of heavy drinking and binge drinking episodes and encouragement of current drinkers to consume alcohol in moderation. The risk-benefit tradeoff of moderate drinking versus abstention may differ with age, with benefits outweighing risks beginning in middle age.[48] Currently, the definition of moderate intake is not standardized and U.S. and international guidelines differ.[49] There is some evidence that current recommendations for moderate drinking among older adults by the National Institute on Alcohol Abuse and Alcoholism may be conservative. Continued research will help to better identify harmful and beneficial doses of alcohol.

Public health recommendations regarding alcohol consumption require integration of evidence on many outcomes including injury, cancer, coronary heart disease, and all-cause mortality.[14] Herein, we propose to contribute further understanding through additional research of the association between alcohol consumption and diseases of the brain, conditions for which evidence to date has been inconsistent. There remains a need for further elucidation of the complex relationship between alcohol and stroke and cognitive decline and to report these findings for both White and African-American populations. Finally, obtaining estimates of the effect of changes in population-level drinking patterns on disease burden will be of use to population scientists and policy makers.

CHAPTER 2: STUDY OBJECTIVES AND SPECIFIC AIMS

The proposed study seeks to estimate the association between alcohol consumption and stroke and cognitive decline in a population-based sample of White and Black participants aged 45-64 at baseline in the Atherosclerosis Risk in Communities study. The proposed study will utilize data from the 5 study visits of the ARIC study as well as data collected at annual follow-up and through surveillance of community hospital discharge lists. Manuscript 1 will address Specific Aims 1 and 2 and manuscript 2 will address Specific Aim 3.

Specific Aim 1: Estimate the dose-response relationship between alcohol intake over time and incident total, ischemic, and hemorrhagic stroke among White and Black participants in the Atherosclerosis Risk in Communities (ARIC) Study (Manuscript 1; Chapter 5). Time-to-event analysis will be used to obtain effect estimates for the association of mid-life alcohol consumption with incident total, ischemic, and hemorrhagic stroke. Models will be adjusted for potential confounders, and account for the competing risk of death. We hypothesize that heavy drinking will be associated with the highest rate of all stroke types and that light-to-moderate drinking will be associated with reduced rate of ischemic, and to a lesser degree hemorrhagic, stroke compared with lifetime abstention from drinking. We will assess modification of these relationships by race and sex given the previous findings that effects of alcohol on cardiovascular disease risk may vary by race-ethnicity and that the dose-response relationship may differ by sex.

Specific Aim 2: Investigate the feasibility of estimating the proportional changes in stroke incidence among sex-race groups that could result from population-level shifts in alcohol consumption categories (Manuscript 1). If feasible, the proportional change in total, ischemic, and

hemorrhagic stroke events resulting from changes in the distribution of alcohol intake will be estimated using generalized impact fraction methods. Generalized impact fractions will be estimated within strata of age, sex, and race using effect estimates obtained from Cox regression models in Specific Aim 1. We will estimate the expected change in stroke incidence that corresponds with achievement of the 2020 Healthy People Goals for reductions in heavy drinking.[50] These goals target a ~3% reduction in the prevalence of heavy drinking, defined as consumption of >2 drinks per day for men and >1 drink per day for women.

Specific Aim 3: Estimate the association between alcohol consumption and rate of cognitive decline among the ARIC participants attending Visit 2 (Manuscript 2; Chapter 6). Linear regression with generalized estimating equations will be used to estimate the rates of cognitive decline across levels of alcohol consumption. Inverse-probability weights will be calculated to account for the different mechanisms of attrition (drop-out and death) that may induce selection bias. Alternative methods to address attrition will be considered in the event that inverse-probability weights prove infeasible. We hypothesize that moderate consumption of alcohol will be associated with a slower rate of decline in cognitive function than lifetime abstention. Heavy alcohol intake is hypothesized to result in the steepest decline in cognitive function. We will explore modifications of these relationships by sex, race, and ApoE ε4 allele status.

In summary, by utilizing data from a large, racially-diverse population-based cohort we will contribute further understanding of the effects of alcohol consumption on vascular-related diseases of the brain. The study strengths include a long duration of follow-up, multiple measurements of exposure and confounders, robust stroke ascertainment, and repeated assessment of cognitive function. Results will be interpreted in light of study limitations including possible exposure misclassification, selection bias from competing risks and attrition, and residual confounding. This study will contribute additional data on the effects of alcohol consumption for future meta-analyses

and for clinicians judging risks and benefits of alcohol consumption for their patients. In addition,

results may aid in understanding the thresholds effects of alcohol, and will provide novel estimates

of the population impact of changes in alcohol consumption on disease burden to assist public

health practitioners working in areas of lifestyle modification and policy.

CHAPTER 3: BACKGROUND AND SIGNIFICANCE

3.1 Public Health Burden of Stroke and Cognitive Impairment

Stroke and pathological cognitive decline are important targets for public health prevention. Both are associated with significant morbidity and heath care costs and are estimated to increase in burden over the next few decades due to longer life expectancies and demographic population changes.[51, 52] Worldwide, dementia contributes to 11.2% of total years lived with disability and stroke to 9.5% for adults aged 60 years and older.[53] With approximately 1 in 3 Americans estimated to have a stroke or develop dementia in their lifetime, there is urgent need for continued examination of modifiable risk factors for these diseases. Cardiovascular (CV) risk factors such as high blood pressure, obesity, diabetes, physical inactivity, and smoking have been implicated in disease risk. Identifying additional modifiable factors such as alcohol consumption may provide further avenues for preventing or delaying disease. This is particularly important for cognitive decline, as there are no effective pharmaceutical treatments for dementia.

A. Stroke and its Epidemiology

Stroke has historically been defined using variations of the World Health Organization criteria as a "sudden impairment of brain function resulting from the interruption of circulation to one or other parts of the brain following either an occlusion (ischemic stroke) or hemorrhage (hemorrhagic stroke) of the artery supplying that area".[54] A more recent definition has been established that incorporates both clinical and tissue-based criteria.[55] Under these new definitions, ischemic stroke is defined as "an episode of neurological dysfunction caused by focal cerebral, spinal or retinal infarction" that requires either objective evidence of ischemic injury or clinical evidence of

injury based on symptoms lasting more than 24 hours. Intracerebral hemorrhage is defined as "rapidly developing clinical signs of neurological dysfunction attributable to focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma". Subarachnoid hemorrhage is defined as "rapidly developing signs of neurological dysfunction and/or headache because of bleeding into the subarachnoid space (between the arachnoid membrane and the pia mater)".

Despite its sudden onset, many strokes are the result of an atherosclerotic disease process that begins decades earlier. Atherosclerosis is an inflammatory disease of the arterial wall that can result in weakening of the vessel wall and protrusion of atherosclerotic plaques into the lumen.[56] This narrowing can lead to restriction or cessation of blood flow to the brain (ischemia) and subsequent infarction. In the U.S., strokes of ischemic etiology are common and account for 87% of all strokes.[7] Ischemic events may occur by way of thrombosis, wherein a blood clot forms around an atherosclerotic lesion, or embolism, wherein clots that develop in the heart or break off from a thrombus become lodged in circulation and obstruct blood flow to the brain.[57] Large artery stenoses result from occlusion of one of the large arteries that supplies the brain such as the internal carotids, cerebral, and basilar arteries (Figure 1[58]). Lacunar infarctions occur in the deep penetrating arteries of the brain with resultant lesions often seen in the putamen, thalamus, and pons. Cardioembolic strokes result from arterial occlusions (often in the middle or posterior cerebral artery) from emboli of a cardiac source.
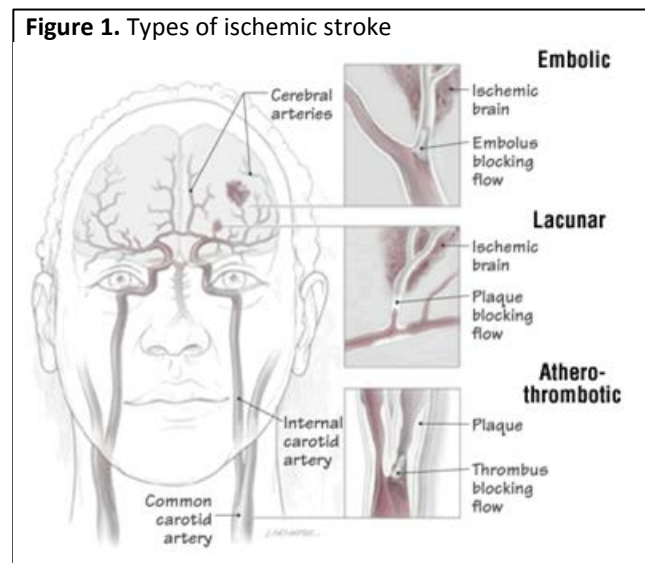
Intracerebral and subarachnoid hemorrhages account for the remaining 10% and 3%,

Figure 1. Types of ischemic stroke

Embolic
Cerebral arteries
Ischemic brain
Embolus blocking flow

Lacunar
Ischemic brain
Plaque blocking flow

Athero-thrombotic
Internal carotid artery
Plaque
Thrombus blocking flow

Common carotid artery

respectively, of strokes in the U.S.[7] Their etiology is not atherosclerotic in nature, but can still result from many years of exposure to CV risk factors, particularly the damaging effects of high blood pressure, cigarette smoking, and other harmful lifestyle habits. Hemorrhagic events result from rupture of a blood vessel and bleeding in the brain, either in the deep portions of the cerebral hemisphere in the case of ICH or in the subarachnoid spaces in the case of SAH.[57] Rupture may result from weakening of the vessel wall, as from sustained elevated blood pressure, or from malformation in the vessel as in arteriovenous malformations. Brain damage from hemorrhagic strokes results from the increased pressure of blood on surrounding tissue and the direct toxic effects of blood on brain tissue.[57]

Stroke is the 4th leading cause of death in the United States, accounting for 1 in 19 deaths, and is a leading cause of disability. There are 610,000 new and 185,000 recurrent strokes each year in the U.S. Since 1950, death rates from stroke have declined.[54] Despite this, the number of deaths attributed to stroke are projected to increase from 5.7 million currently to 7.8 million in 2030 and the number of first-ever strokes will increase from 16 to 23 million worldwide. Overall prevalence is 2.8% in the U.S. and is projected to increase to 3.4% by 2030.[7] Prevalence rates increase with age and reach 13-17% in adults aged ≥80 years.[54] The burden of stroke is higher among African Americans compared with whites (age-adjusted incidence per 100,000 person-years: white men 150, white women 130, black men 300, black women 300).[54] Lifetime risk of stroke at age 65 is 20.6% for women and 16.8% for men, with 5-year survival averaging approximately 40%.[54] Direct and indirect costs exceed $38 billion annually and the lifetime cost of stroke to an individual averages more than $140,000.[7]

Elevated blood pressure is a strong risk factor for both ischemic and hemorrhagic stroke.[7] Other risk factors include diabetes mellitus, atrial fibrillation, physical inactivity, low social support, and family history of stroke.[7] Smokers have 2-4 times the risk of stroke as nonsmokers; however,

data are inconsistent as to whether smoking increases the risk of ICH. High cholesterol levels

increase the risk for stroke in some studies, but effects are smaller than those observed for heart

disease and are absent in some studies. Finally, there are risk factors specific to women that include

pregnancy, hormone use, and age at menopause. Several of these risk factors are also associated

with alcohol intake including low social support, HDL-C, smoking, and physical activity.

B. Cognitive Decline and its Epidemiology

Cognitive function, defined as "the mental processes that are required to receive, analyze,

and act on information from the environment", is classified into cognitive domains including, among

others, reception, memory and learning, attention, visuoperception and visual reasoning, language,

construction, motor ability, decision making, and executive control (Table 1).[51, 59] Declines in

function over time are common with aging, but a complete understanding of 'normal' cognitive

aging is lacking.[60] On average, most aspects of cognition decline with age including working memory

and processing speed.[59] Other functions, for example expert knowledge and vocabulary, remain

stable or even increase with age. Declines exist on a continuum from normal aging to pathological

declines. The latter may hinder independent living, social relationships, and quality of life. The

definition of pathological declines is somewhat arbitrary and studying declines that have yet to

reach the threshold for clinical diagnosis will improve our understanding of modifiable factors that

affect the entire disease process. Cognitive aging is not uniform across the population; some

individuals experience very little decline well into their 80s while others exhibit declines beginning in

their 60s.[59] This variation in degree and rate of decline is of interest to researchers, particularly if it

can be leveraged to identify modifiable risk factors. Alcohol consumption is one such putative factor

with mechanistic support.

Table 1. Description of selected cognitive domains

Cognitive function	Description	Task
Orientation	Awareness of self in relation to one's surroundings, including time, place, and person. Requires integration of attention, perception, and memory	Knowledge of today's date
Attention and concentration	Ability to sustain and focus thoughts and behavior	Symbol substitution
Mental tracking	Hold information in memory while performing a mental operation	Repeat numbers in reverse order
Memory	Capacity to retain information and utilize it for adaptive purposes	Short-term word recall
Language	Ability to comprehend and produce speech	Verbal fluency – name as many words as possible beginning with 'F'
Construction	Combined perception and motor response.	Draw a clock face
Reasoning	Thinking with a conscious intent to reach a conclusion	Arithmetic calculations, organize pictures in logical temporal order
Psychomotor speed	Amount of time it takes to process information, plan a response, and carry out a physical movement; combines decision time and motor components	Digit symbol substitution
Executive function	Ability to respond in an adaptive manner to novel situations. Comprised of several other functions including planning, organization, coordination, implementation, and evaluation.	Route finding task

Cognitive declines that have progressed to a certain degree of severity are defined clinically as mild cognitive impairment (MCI) and dementia. MCI is an intermediate state of cognitive function between normal cognition and dementia that generally does not impair daily life.[51] MCI can be thought of as a sub-clinical impairment and is a risk factor for development of dementia later in life.[60] Not all individuals with MCI appear to develop dementia and some even show improvements in cognitive function. Dementia is a "clinical syndrome caused by neurodegeneration and characterized by inexorably progressive deterioration in cognitive ability and capacity for independent living". Common pathologies include Alzheimer's disease (AD), vascular dementia, and Lewy body dementia.[52] A relatively new definition of vascular cognitive impairment has been developed and includes impairments ranging from mild to severe affecting at least 1 cognitive domain and with evidence of clinical stroke or subclinical vascular brain injury.[61]

Many different disease processes underlie changes in brain structure and function that

manifest themselves as declines in one or more domains of cognition. These include, among others, vascular disease, degenerative diseases, traumatic brain injury, and toxicity. Alcohol has the most direct effects through neurotoxicity and alterations in vascular risk factors, but also can be an upstream contributor to traumatic brain injury. The latter, however, is beyond the scope of this dissertation.

Vascular and neurodegenerative processes occur over the life course, are multi-factorial, and incompletely understood. Neurodegenerative and vascular-related pathologies overlap considerably and share several risk factors including alcohol consumption. Alzheimer's disease, one of the more common neurodegenerative dementias, is characterized by accumulation of amyloid plaques and neurofibrillary tangles as well as neuronal loss. Mixed pathology is seen in 25-80% of dementias and there is some evidence that cerebrovascular and AD lesions may act synergistically in the development of dementia.[62] Vascular dementia is the end result of vascular lesions in the brain that impair its function. Because the brain relies on a constant supply of blood for proper functioning, interruption of blood flow results in tissue death.[61] Important factors in the likelihood of developing dementia are the volume of brain damage, the number of lesions, and their location; however, the types of lesions that result in dementia are quite heterogeneous.

Contributors to vascular-related cognitive impairment include clinical stroke (likely reflecting both tissue damage from the event itself and the presence of CV risk factors such as high blood pressure that contribute to additional brain damage), microbleeds, white matter lesions, and silent brain infarctions. Silent brain infarctions are 5 times as prevalent as clinical strokes in the population, with prevalence estimates ranging from 8-28%.[55, 59] These, along with white matter lesions, are common and may increase the risk of impairment for some individuals. Even transient ischemic attacks, once thought not to result in permanent damage, are associated with mild cognitive deficits.[59] Measures of both atherosclerosis (e.g. carotid intima-media thickness) and

arteriosclerosis are associated with impairment. Atherosclerosis of medium and large arteries

contributes to cognitive impairment through emboli that arise from carotid plaques and thrombotic

occlusion of large vessels that result in cerebral hypoperfusion and subsequent brain damage. Small

vessel disease, similar to atherosclerotic changes but without calcification, can result in

hemorrhages, microinfarcts and microbleeds, white matter hyperintensities, as well as lacunar

infarcts.[62] Finally, cerebral amyloid angiopathy in which amyloid β-protein is deposited in vessel

walls, may lead to disturbances in blood flow, microinfarcts and microbleeds, white matter lesions,

and hemorrhages. Collectively, atherosclerosis, small vessel disease, and cerebral amyloid

angiopathy can lead to cerebrovascular lesions and subsequent cognitive decline.

Cardiovascular risk factors that are associated with cognitive decline include diabetes (via

damaging effects of elevated insulin and glucose) and hypertension, which is associated with MCI

even in the absence of lesions.[59] Randomized controlled trials have largely been unable to show a

beneficial effect of glucose and blood pressure modification on later development of dementia.

However, trials are few in number given the long-term follow-up required, have had somewhat

inconsistent results, and are subject to methodological limitations.[61] In addition to the CV risk

factors discussed above, age, race, education, obesity, hypercholesterolemia, physical inactivity,

smoking, dietary factors, depression, and social isolation have been implicated in cognitive

decline.[35, 51] Alcohol consumption is one of the dietary factors that has received attention from

researchers as both a protective and harmful factor, though its putative causal relationship with

cognitive decline has not been rigorously evaluated and evidence to date is weak.[33, 63] Assessing this

association in a study with long-term follow-up and multiple measures of cognitive function will

contribute to this literature.

Data on the epidemiology of mild cognitive impairment (MCI) and dementia are highly

variable due to large differences in study methods (e.g. diagnostic criteria, measurement tools, and

sampling).[64] The prevalence of MCI is reported at 2-20%, and is thought to be 13% among adults

≥65 years of age representing 5.4 million adults.[64, 65] Data from the Aging, Demographics, and

Memory Study of adults aged over 70 years reported 13.7% prevalence of dementia (10.8% in men

and 15.5% in women), with 70% attributed to AD and 17% to vascular dementia.[66] Prevalence of

non-dementia cognitive impairment was 22%. Global prevalence is estimated to triple within 40

years and in the U.S. prevalence will rise to 11-16 million by 2050.[51] The incidence of AD and

dementia increase with age, doubling roughly every 5 years after age 65. Age-adjusted incidence of

dementia ranges from 2.4 per 1000 person-years in the age group 65-69 to 27.5 per 1000 p-y in the

age group 85-89 and ranges from 9-26 per 1000 person-years for 'pre-dementia syndromes'.[65, 66]

Healthcare costs totaled $183 billion dollars in 2011 and the cost of informal care in the U.S. was an

additional $18 billion per year.[53] Persons with dementia have higher annual health care costs than

similarly-aged persons without dementia ($42,072 versus $13,515). Finally, dementia confers

significant costs to care givers, who can experience high levels of stress, depression, financial

difficulties, and adverse health outcomes. In summary, the prevalence of dementia is high and will

continue to increase over time given the sharp increase in incidence associated with aging coupled

with expected demographic shifts and individuals attaining older ages.

C. Summary

Stroke and cognitive impairment represent a significant health burden nationwide and

globally. The prevalence of these conditions is projected to increase dramatically as the population

demographic shifts to a greater proportion of older adults and people experience increased

longevity. Identifying modifiable risk factors to prevent or delay disease - such as the consumption

of alcoholic beverages - is necessary to reduce disease burden, its high economic cost, and negative

impact on quality of life. Given its plausible mechanisms of effect through reduction of CV risk

factors and vascular disease, alcohol represents a viable target for intervention.

3.2 Alcohol Consumption Patterns in the U.S.

Several national surveys collect data on alcohol consumption including the National Health and Nutrition Examination Survey (NHANES), the Behavioral Risk Factor Surveillance System (BRFSS), the National Health Interview Surveys (NHIS), and the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) conducted by the National Institute on Alcohol Abuse and Alcoholism (NIAAA).

NHANES is a cross-sectional, nationally representative survey of US civilian, non-institutionalized persons and includes an in-person home interview and health examination. Alcohol consumption information was collected on adults aged 20-85 years in two 2-year waves from 1999 to 2002 (Figure 2).[67] Overall, 70% of adults were current drinkers, 17% were former drinkers, and 13% were lifetime abstainers. Binge drinking, defined as consumption of 5 or more

Figure 2. Prevalence of alcohol consumption levels by sex and age, NHANES 1999-2002
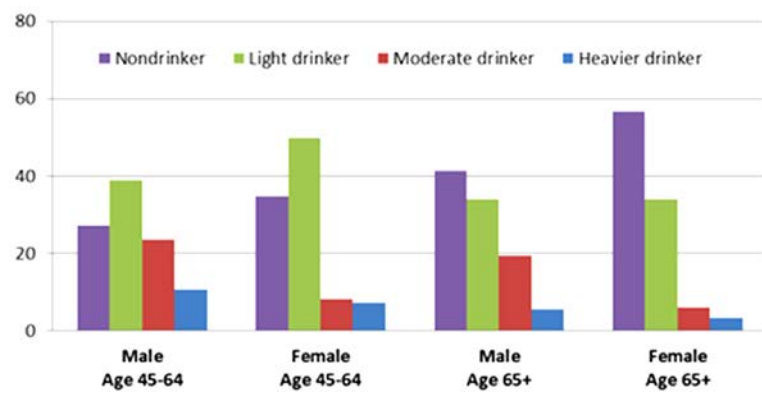
drinks in 1 day at least once in the past year was reported by 42% of white males, 18% of white females, 27% of black males, and 10% of black females.

The BRFSS is a state-based, cross-sectional telephone survey of non-institutionalized, civilian U.S. adults aged 18 years or older. Questions on alcohol in this survey include one on frequency of drinking (days per week), quantity of drinking (average drinks per occasion), and frequency of binge drinking (occasions in the past 30 days during which at least 5 (for men) or 4 (for women) drinks

were consumed). A report from the 2006 survey cross-classified individuals according to average

consumption (calculated by multiplying frequency x quantity) and binge drinking.[68] Nearly 70% of

current drinkers were both non-binge and non-heavy drinkers. Table 2 shows the frequency of the

four drinking patterns according to socio-demographic characteristics. Consistent with other survey

findings, both heavy and binge drinking were more prevalent among younger compared with older

adults, in men compared with women, and among Whites compared with Blacks. Assessment of

drinking patterns is important to the study of alcohol consumption because average consumption

measures may under-represent harmful drinking patterns such as infrequent episodes of excessive

drinking.

Table 2. Prevalence of heavy and binge drinking by sociodemographic characteristics, BRFSS 2006

	Binge/Heavy % (95% CI)		Binge/Non-Heavy % (95% CI)		Non-Binge/Heavy % (95% CI)		Non-Binge/ Non-Heavy % (95% CI)	
Total (N=157,914)	7.6	(7.3–7.9)	21.8	(21.3–22.3)	1.7	(1.6–1.8)	69	(68.4–69.5)
Age (years)								
18–24	15	(13.5–16.7)	35.9	(33.7–38.2)	0.3	(0.2–0.6)	48.8	(46.4–51.1)
25–39	7.6	(7.1–8.2)	29.5	(28.5–30.4)	0.6	(0.5–0.8)	62.2	(61.2–63.2)
40–54	7.4	(6.9–7.8)	19.3	(18.6–20.0)	1.6	(1.4–1.8)	71.8	(71.0–72.5)
55+	4.2	(3.9–4.5)	9.1	(8.6–9.7)	3.5	(3.2–3.8)	83.1	(82.5–83.8)
Race or ethnicity								
White	7.7	(7.4–8.1)	20.9	(20.4–21.4)	1.9	(1.8–2.0)	69.5	(69.0–70.1)
Black	5.7	(4.7–6.8)	19.9	(18.1–21.7)	1.3	(0.9–1.8)	73.1	(71.1–75.0)
Hispanic	8.5	(7.2–10.0)	29.7	(27.3–32.2)	0.5	(0.3–0.8)	61.3	(58.8–63.8)
Other	5.7	(4.4–7.2)	22.3	(19.4–25.5)	0.7	(0.4–1.3)	71.3	(68.0–74.4)
Gender								
Male	8.4	(7.9–8.8)	27.2	(26.4–27.9)	0.8	(0.7–0.9)	63.7	(62.8–64.5)
Female	6.7	(6.3–7.1)	15.5	(14.9–16.0)	2.6	(2.4–2.8)	75.2	(74.6–75.9)
Marital status								
Married	5.5	(5.2–5.8)	18.8	(18.3–19.3)	1.6	(1.5–1.8)	74.1	(73.5–74.6)
Previously married	8.6	(7.8–9.3)	17.8	(16.9–18.8)	2.8	(2.5–3.2)	70.8	(69.7–71.9)
Never married	12.5	(11.6–13.5)	32.4	(31.0–33.8)	0.9	(0.7–1.1)	54.2	(52.8–55.7)
Education								
<High school	13	(11.2–15.0)	31.7	(29.1–34.4)	1	(0.7–1.4)	54.4	(51.6–57.1)
High school graduate	9.2	(8.6–9.9)	25.4	(24.3–26.4)	1.4	(1.2–1.6)	64	(62.8–65.1)

Some college	8.4	(7.7–9.0)	22.3	(21.4–23.3)	1.4	(1.3–1.6)	67.9	(66.8–68.9)
College graduate	5.3	(5.0–5.7)	18	(17.3–18.7)	2	(1.8–2.2)	74.7	(74.0–75.4)
Income, $								
<20,000	10.3	(9.1–11.6)	27.3	(25.3–29.4)	1.4	(1.0–1.7)	61	(58.9–63.1)
20,000–34,999	8.8	(7.9–9.8)	23.2	(21.9–24.7)	1.5	(1.3–1.8)	66.4	(64.9–67.9)
35,000–49,999	7.8	(7.1–8.6)	22.7	(21.5–24.0)	1.8	(1.5–2.1)	67.7	(66.3–69.0)
50,000–75,000	6.9	(6.2–7.5)	22	(20.9–23.0)	1.4	(1.2–1.6)	69.8	(68.7–71.0)
>75,000	7	(6.5–7.6)	19.9	(19.1–20.7)	1.8	(1.6–2.0)	71.2	(70.4–72.1)

* Binge drinking was defined as consuming ≥5 drinks on an occasion for men and ≥4 drinks for women.
Heavy drinking was defined as consuming on average >2 drinks/day for men and >1 drink/ day for women.

Another analysis of the BRFSS assessed time trends in binge drinking according to demographic characteristics from 1993 to 2001.[69] Binge-drinking episodes increased slightly among men from 10.8 per person per year to 12.5 and remained stable among women (2.2 to 2.7). Younger aged adults consistently had higher rates of binge drinking; among 35-54 year-olds binge-drinking episodes increased from 5.4 to 6.7 and among adults 55 and older changed little from 2.5 to 2.7. Finally, Blacks had lower binge drinking rates than Whites, increasing from 4.2 to 5.4, while Whites increased from 6.6 to 7.4. In summary, these data suggest that the heaviest drinking occurs in young white males and that this group has experienced the largest increase in consumption from the early 1990s to 2000s.

The National Health Interview Surveys from 5 years (1997-2001) were pooled to assess drinking patterns in adults over the age of 60.[70] These interviews represented 15,811 men and 24,745 women. Alcohol was measured in terms of quantity (average drinks per occasion), frequency (number of drinking days per year), and episodes of heavy episodic drinking (number of days on which 5 or more drinks were consumed). The majority (57% of men and 77% of women) reported less than 1 drink per day on average. One to two drinks per day was reported by 26% of men and 20% of women. No episodes of heavy episodic drinking were reported by 80% of men and 95% of women. If these results are generalizable to the ARIC population, it would suggest that heavy drinking episodes are not prevalent in our population, reducing concerns for strong confounding of

average volume estimates by different drinking patterns. It also highlights the importance of

studying alcohol exposures in mid-life, which are more variable than in older adults, and that may

reflect relevant exposure window.

Sales data support many of
the conclusions above from self-
reports regarding secular trends in
alcohol consumption. Sales data
have the advantage of being
objective, but may not represent
total alcohol actually consumed
because of waste or home

Figure 3. Per capita ethanol consumption by beverage type, United States, 1977-2009[4]
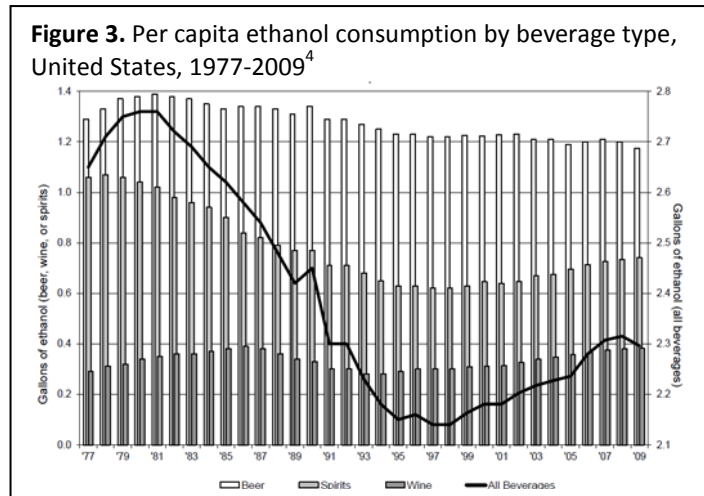
production. A recent analysis from NIAAA reports that while alcohol sales have decreased

substantially from the mid-1970s, there has been a steady increase since the late 1990s (Figure 3).[4]

This increase is largely due to wine and spirits which offset the continued decline in beer sales.

Finally, while longitudinal reports are less common than repeated, cross-sectional surveys, they

support that on average individuals reduce their average consumption over the life-course. Peak

consumption generally occurs in the late teens and early twenties followed by a sharp decline and

stabilization in the 30-50s, with declines again in older age (~60s). Trajectories of alcohol

consumption vary by individual, and according to socioeconomic and demographic factors. [69, 71]

A. Summary

The consumption of alcohol is relatively common in the United States and has increased

over the past decade. Abstention increases with age and is higher in subgroups such as women and

individuals of higher SES. While drinking in excess decreases with age, there remains a significant

portion of adults that consume more than the recommended average intake (e.g. 20% of men aged

60 and older consume 3+ drinks per day according to the NHIS). Given the high prevalence of

alcohol consumption in the US, examining potential health benefits and risks associated with this

exposure may inform population scientists about the extent of disease that is attributable to alcohol

exposure. The persistence of heavy drinking, particularly among certain sub-groups, suggests that

there is potential reduction in disease burden that may be achieved through population

interventions to reduce heavy drinking. Reducing the proportion of persons engaging in binge and

excessive drinking is part of the Healthy People 2020 goals, has been identified as a high priority

health issue, and is a Leading Health Indicator.[50] Estimates from 2008 for the proportion of adults

that engage in binge and excessive drinking are 27.1% and 28.2%, respectively. Targets were set for

each at 24.4% and 25.4%, a reduction of roughly 3% by 2020. These targets will inform Aim 2 and

provide reasonable intervention goals for population shifts in alcohol consumption. We will

estimate what effect achievement of these goals will have on stroke burden. Finally, a greater

understanding of the benefits and risks of alcohol consumption may inform individual and clinician

decision-making regarding risk factor modification.

3.3 Mechanisms Linking Alcohol with Stroke and Cognitive Impairment

The primary component of alcohol is ethanol (C_2H_5OH), which is an energy-yielding

molecule. It may be partially metabolized (~2%) in the stomach by gastric alcohol dehydrogenase

(ADH). Remaining alcohol then diffuses across the stomach and intestine and enters portal

circulation where it is further metabolized in the liver at a rate of roughly 15 grams per hour.

Ethanol can also be biotransformed in Phase I reactions in the smooth endoplasmic reticulum by

way of the microsomal ethanol-oxidizing system (MEOS; Figure 4). The bioavailability of alcohol

varies by sex and age. Men have more gastric ADH and therefore reduced bioavailability of alcohol

than women. In addition, body composition changes as people age and percentage body water declines. This water loss slows ethanol distribution and results in higher blood alcohol content.[49] Women tend to have a lower percentage of water, which is another reason for their greater alcohol bioavailability relative to men. In addition to ethanol, some alcoholic beverages, notably red wine, contain antioxidant polyphenol compounds of the flavonoid and stilbene classes. These components have been hypothesized to confer health benefits in addition to ethanol and may have

Figure 4. Metabolism of ethanol into acetaldehyde by alcohol dehydrogenase and the MEOS pathway

unique cardioprotective properties.[72] Red wine has the highest concentration of polyphenolic compounds, with white wine and beer containing 10-20% the amount in red wine depending on cultivar and age.[73, 74]
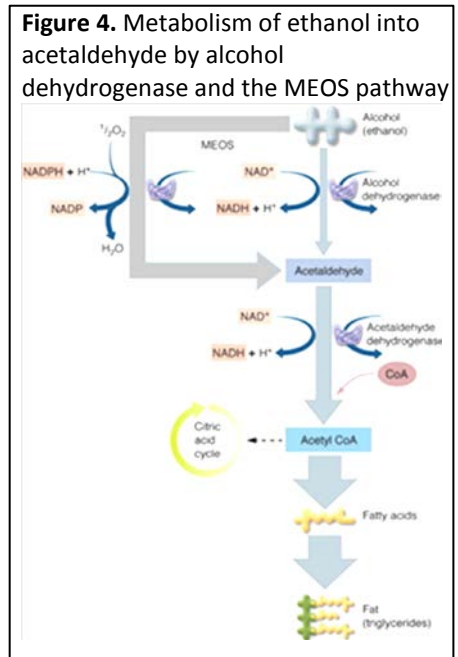
A. Alcohol as a Risk Factor for Stroke and Cognitive Decline- Effects of Heavy Alcohol Consumption

High doses of alcohol have clear deleterious effects on health that accumulate over time. There is a direct neurotoxic effect on brain structures as well as indirect health effects through elevated blood pressure, increased reactive oxygen species, reduced cerebral blood flow, and development of atrial fibrillation and cardiomyopathy.[18, 75] Heavy drinking can also have negative health effects in combination with nutritional deficiencies. One example is Wernicke-Korsakoff syndrome, a thiamine deficiency characterized by cognitive and memory deficits. Chronic alcohol abuse indirectly leads to thiamine deficiency through malnourishment and directly plays a role by interfering with the conversion of thiamine into its active form and decreasing its absorption in the intestines.[45] Other nutrient deficiencies such as pellagra nicotinic acid deficiency can cause memory

impairment and lead to dementia; these symptoms typically reverse upon treatment with nicotinic acid.[76]

Direct neurotoxic effects of chronic heavy alcohol use can lead to cognitive deficits in the absence of nutritional deficiencies, i.e. in uncomplicated alcoholics.[76] Heavy drinking results in structural brain changes including ventricular enlargement and brain shrinkage. There is atrophy of both the white and grey matter, although evidence suggests that white matter is more severely affected.[77] These structural changes are a hallmark of one form of dementia known as alcoholic dementia, a progressive multi-domain cognitive impairment. Human studies have also shown that heavy alcohol intake can result in changes to dendrite receptors, neurotransmitters, and neuronal loss in several brain areas, most commonly the superior frontal association cortex, hypothalamus, and cerebellum.[78] Damage to these areas can result in deficiencies in the areas of planning, organization, problem solving, and disinhibition. The associations of alcohol with brain abnormalities including brain atrophy, subclinical infarcts, and white matter disease were assessed in the Cardiovascular Health Study.[77] Drinking was associated with increased risk of brain atrophy with no apparent threshold, whereas the relationship between alcohol consumption and white matter disease was U-shaped.

Mechanisms underlying alcohol's neurotoxicity are not fully understood, but could occur by several pathways. These include glutamate excitotoxicity (a process through which excessive stimulation of receptors leads to neuronal cell death), oxidative stress, hyperhomocysteinemia, reduced availability of brain-neurotrophic factor and nerve growth factor, and DNA damage. Acute ethanol exposure inhibits N-methyl-D-aspartate (NMDA) receptor activity. However, chronic exposure leads to compensatory upregulation of NMDA glutamate receptors and glutamate binding sites in the frontal cortex.[79, 80] During withdrawal, inhibition of glutamate activity is removed and there is potential for elevated activity and glutamate-mediated excitotoxicity. Excess glutamate

Figure 5. Effect of ethanol on NMDA receptors and excitotoxicity

A. Chronic ethanol exposure with NMDA receptor inhibition and NMDA receptor up-regulation (right)

B. Ethanol withdrawal with increased NMDA receptor activation by glutamate and homocysteine
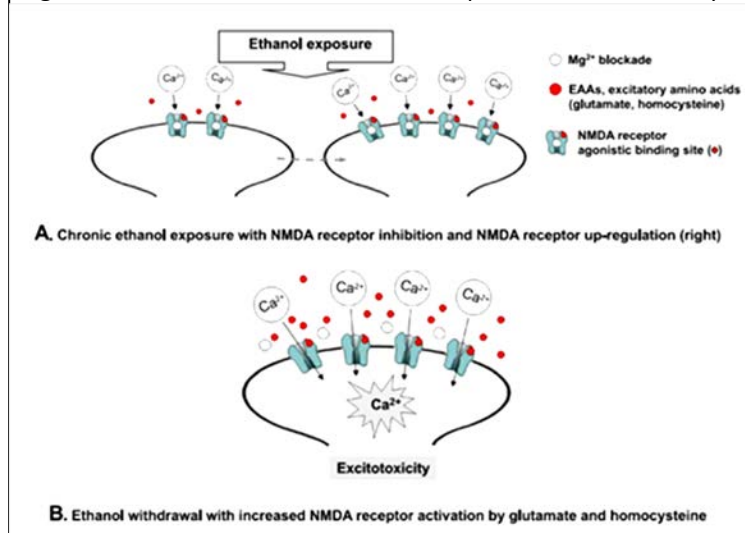
binds to the over-expressed receptors and leads to excitotoxicity.[80] In this way, chronic alcohol exposure results in increased sensitivity of neurons to excitotoxicity. Upregulation of NMDA receptors leads to generation of free radicals that contribute to oxidative damage.

Homocysteine, often present at unusually high concentration in the plasma of heavy drinkers, can also contribute to excitotoxicity. It is an excitatory amino acid and is able to function as an agonist at glutamate binding sites on NMDA receptors. Upon binding of the NDMA receptor, there is a prolonged influx of calcium ions that enter the cell. This leads to a cascade of events that damage cell structures and DNA and ultimately results in neuronal apoptosis (Figure 5).[79]

Other mechanisms may explain the neurotoxic effects of alcohol beyond those mediated through NMDA receptors.[78] First, chronic ethanol exposure reduces the availability of brain-derived neurotrophic factor and receptors for nerve growth factor. These changes can impair intracellular signaling pathways contributing to neuronal cell death and malfunctioning of neural circuits. Second, the oxidative stress brought on by alcohol intake can result in DNA strand breaks and cell death. Third, damaging acetaldehyde protein adduct formation, derived from the highly reactive byproduct of ethanol metabolism, has been observed in white matter and neurons in the frontal cortex. Taken together, the neurotoxicity of alcohol may play a key role in the development of cognitive impairment through direct damage to the brain's structure and function. These effects are likely cumulative, highlighting the importance of understanding long-term, cumulative alcohol

exposure when studying cognitive changes over time.

In addition to the direct neurotoxic effects described above, heavy alcohol intake has indirect effects on the brain through elevated blood pressure, atrial fibrillation and cardiomyopathy, reactive oxygen species, endothelial dysfunction, inflammation, glucose intolerance and insulin insensitivity, and reduced cerebral blood flow. These effects can increase the risk of stroke and dementia and also result in microinfarctions and lesions that contribute to cognitive decline. Alcohol intake has a dose-dependent effect on blood pressure, with consistent findings of increased blood pressure at high doses (usually more than 2 drinks per day,[77, 81] but other studies have found thresholds below and above this level).[82] The blood pressure response to alcohol is biphasic. Within several hours of consumption, blood pressure is lowered due to vasodilation and then 11-13 hours later rises higher than baseline levels.[83] A meta-analysis of randomized controlled trials reported a mean decrease in systolic blood pressure of -3.31 mm/Hg and in diastolic blood pressure of -2.04 mm/Hg associated with interventions to reduce drinking by 67% from a baseline consumption of 3-6 drinks per day.[84] Mechanisms through which alcohol affects blood pressure are not completely understood, but could include stimulation of the sympathetic nervous and the renin-angiotensin-aldosterone systems, increases in endothelin (a potent vasoconstrictor), and changes in cortisol and intracellular calcium.[81, 82] Elevated blood pressure is a well-established and strong risk factor for both ischemic and hemorrhagic stroke and has been shown in some, but not all, randomized controlled trials to reduce risk of dementia.[7, 61]

Alcohol intake is associated with increased risk for atrial fibrillation and cardiomyopathy. Although the precise dose-response relationship between alcohol and atrial fibrillation is debated, findings for increased risk with heavy drinking are relatively consistent. Authors of a recent meta-analysis report a relative risk of 1.22 (95% CI: 1.02-1.46) in consumers of more than 3-4 drinks per day compared with abstainers.[85] Alcohol may alter atrial structure, trigger fibrillation, have

proarrhythmic effects (QT interval elongation, impaired vagal heart rate control, and hyperadrenergic activity), and enhance persistence of otherwise asymptomatic episodes.[85-88] Atrial fibrillation is a known risk factor for stroke and is associated with vascular dementia.[7, 61] Cardiomyopathy may develop as a result of heavy alcohol consumption and is associated with reduced ejection fraction and stroke volume and can lead to heart failure.[89, 90] Cardiomyopathy in turn can increase the risk of embolic stroke and dementia.[91, 92] A common form of cardiomyopathy identified in chronic heavy drinkers is dilated cardiomyopathy in which the heart is enlarged, weakened and contracts poorly.[93] Evidence suggests that even in the absence of clinically manifest cardiomyopathy, heavy alcohol intake has a negative inotropic effect and decreases left ventricular ejection fraction.[90]

Alcohol increases oxidative stress which has been shown to promote endothelial dysfunction and inflammatory responses.[83] Alcohol may negatively impact endothelial function through changes in adhesion molecules, interleukin-6, and C-reactive protein, and also has prothrombotic effects through decreased fibrinolytic ability, elevations in factor VII, fibrinogen, and plasma viscosity.[77, 83, 94] Inflammation and endothelial dysfunction are hallmarks of the atherogenic process[56] and together with impaired hemostatic function contribute to reduced cerebral blood flow and increased susceptibility of the brain to injury.[61] Some studies have demonstrated that binge drinkers have more rapid progression of atherosclerosis in carotid arteries compared with moderate and non-drinkers. Atherosclerosis of the carotid artery can lead to cerebral hypoperfusion or infarction by way of emboli from carotid plaque or thrombotic occlusion of the vessel. Measures of carotid intimal-medial thickness, a marker for atherosclerosis, are associated with both stroke and cognitive decline.[7, 61] Finally, heavy alcohol consumption is associated with insulin resistance, glucose intolerance, and diabetes,[77, 83] which in turn are associated with stroke risk and cognitive decline.[7, 95-97]

B. Alcohol as a Protective Factor for Stroke and Cognitive Decline – Effects of Low-to-Moderate Consumption

There are a number of plausible mechanisms through which alcohol may protect against stroke and cognitive decline.[72] Low-to-moderate alcohol intake modulates several vascular risk factors and is associated with increased high-density lipoprotein cholesterol, decreased fibrinogen and platelet aggregation, and improvements in inflammatory markers and insulin sensitivity.[6, 42-44] These factors contribute to the formation of atherosclerosis and thrombosis, which when present in the carotid or cerebral arteries, contributes to ischemic stroke risk. Moderate alcohol consumption may reduce the risk of cognitive impairment through similar atherothrombotic mechanisms, resulting in preserved brain vasculature and fewer subclinical infarcts. Finally, there is evidence that alcohol consumption increases acetylcholine in the hippocampus, a neurotransmitter that facilitates learning and memory.[8, 18, 98]

Experimental study designs and randomized feeding trials have been used to understand mechanisms of alcohol action. In these studies, participants are randomized to short-term alcohol consumption and their effects on biomarkers can be measured with minimal confounding. However, attributing disease causality to alcohol as mediated through changes in biomarkers requires the assumption that short-term changes in biomarkers reflect a long-term reduction in disease risk assuming these biomarker levels are sustained.[99]

Numerous trials have reported changes in biomarkers according to alcohol consumption. One of the strongest and most consistent findings is an increase in HDL cholesterol. A meta-analysis of trials with mean duration of 4 weeks reported a 4.0 mg/dl increase in HDL-C associated with intake of 30 grams of ethanol per day (the equivalent of roughly 2 standard drinks of beer (12-oz), wine (5-oz), or liquor (1.5oz)).[13] In addition, apolipoprotein A1 increased by 8.8 mg/dl and triglyceride by 5.7 mg/dl (Figure 6). No significant changes in thrombolytic factors were found. The

authors extrapolated the effect of changes in biomarkers on disease risk and report a predicted relative reduction in heart disease risk of 25%.[13]

Figure 6. Percent change in biomarkers associated with intake of 30g (~2 drinks) of alcohol per day

A more recent meta-analysis, published over a decade after the earlier report by Rimm et al., found dose-dependent increases in HDL-C of 2.8, 4.0, and 5.5 mg/dl for 1-2, 2-4, and ≥5 drinks per day, respectively, and no change in LDL.[100] For a similar 30-g dose as assessed in the previous meta-analysis, HDL increased 3.7 mg/dl and apolipoprotein AI increased 8.7 mg/dL, quite similar to the results of Rimm et al. In contrast to the earlier results, the authors reported significant decreases in fibrinogen (-0.2 g/L) and no change in triglyceride levels except at very high doses of alcohol (>60 g/day was associated with a 24.3 mg/dL increase). Finally, adiponectin increased 0.56 mg/L with alcohol consumption, which is hypothesized to result in improved insulin sensitivity. Results were inconsistent with regard to changes in endothelial and hemostatic factors other than fibrinogen, with some studies reporting cardioprotective changes in these factors and others reporting no change. Put in a clinical context, these findings suggest alcohol produces meaningful changes in biomarkers. Moderate alcohol intake appears to increase HDL-C more than single pharmacological interventions, which increase HDL-C levels roughly 2.6 mg/dl.[101] Furthermore, a 1 gram/L increase in fibrinogen may double the risk of heart disease and stroke based on pooled cohort data.[102]

Alcohol is postulated to increase HDL-C through a variety of pathways, but the precise pathways remains unknown. Potential mechanisms include increased lipoprotein transport and lipase activity.[100] HDL-C is responsible for removing LDL particles from vessel walls and therefore
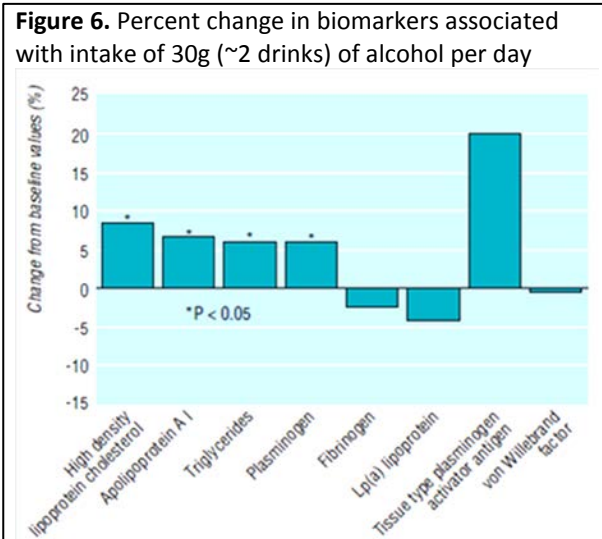
contributes to reduced plaque build-up and atherosclerosis. Apolipoprotein A1 is a component of the HDL complex, helping to clear cholesterol from white blood cells in artery walls, and may be involved in anticlotting activity. Fibrinogen is an important factor in thrombosis, contributing to platelet aggregation, fibrin formation, and plasma viscosity and therefore is a risk factor for atherothrombotic disease.[103] In addition to reducing fibrinogen concentration, alcohol may also affect its conformation and stability.[100] Other studies have reported that ethanol prevents platelet aggregation, opposes thrombin activity, and reduces inflammatory cytokines. These effects have greater inconsistencies across studies than those of HDL-C and fibrinogen, but remain potential mechanisms through which alcohol may impact risk of stroke and cognitive decline.

Elevated blood pressure is a risk factor for stroke and cognitive decline and there is evidence that light-to-moderate alcohol intake may reduce the risk for hypertension.[104] Results are variable, with some suggesting a J-shaped association in women but not men[93] and others findings increased risk in black men with only moderate intake.

Metabolic abnormalities including impaired glucose tolerance, metabolic syndrome, and diabetes have been associated with stroke risk and cognitive decline.[7, 95, 96] Light to moderate drinkers have lower insulin levels, greater insulin sensitivity, and reduced risk of type II diabetes mellitus.[93] Postmenopausal women who were randomized to consume 30 grams of alcohol per day had lower insulin concentrations and higher insulin sensitivity than the comparison group consuming 0 grams of alcohol.[105] These studies suggest that improved metabolic factors may mediate part of the relationship between alcohol and stroke and cognitive decline.

Finally, there has been research to determine if effects of alcohol on CV risk factors are the result of ethanol per se or if they differ by beverage type. The meta-analysis results of Brien et al. were consistent across beverage types (wine, beer, spirits). While some evidence suggests that there are additional benefits of polyphenols, the observed effects of alcohol on biomarkers were

most likely the result of ethanol rather than other components found in red wine. It is possible that

the added benefit of polyphenols was not detectable in this analysis on top of the effect of ethanol.

There is evidence supporting an additional role for resveratrol, a polyphenolic antioxidant found at

highest concentration in red wine, and other phenolic compounds on disease risk.[73][74, 90, 106]

Experimental evidence in animal models, cell culture, and clinical studies suggests that polyphenols

in red wine (e.g. resveratrol, catechin, kaempferol, and tannic acid) can have anti-atherosclerotic,

anti-inflammatory, and antithrombotic effects.[74, 106] Namely, they improve endothelial function,

reduce susceptibility of LDL to oxidation, reduce oxidative stress by scavenging for free radicals and

interfering with free radical-producing systems, and reduce platelet aggregation.[74, 76, 90, 106] A

randomized trial testing the effects of red wine, ethanol, and dealcoholized red wine found both

ethanol and polyphenols had anti-inflammatory effects (most of these were non-additive), but that

only polyphenols modulated leukocyte adhesion molecules and only ethanol increased interleukin-

10.[107] The most likely mode of benefit from polyphenols may come from prevention of LDL

oxidation, which has been demonstrated *in vitro* as well as in some, but not all, human studies.[108]

C. Summary

The effect of alcohol on risk of stroke and cognitive decline is dose dependent. There is

convincing and well-established mechanistic support for a negative effect of heavy drinking on these

endpoints resulting from direct neurotoxic effects, increases in blood pressure, and adverse effects

on other CV risk factors. The precise threshold for negative effects is not well established, however.

Alcohol in moderate doses is a plausible beneficial factor for stroke and cognitive decline through its

well-established effect on CV biomarkers such as HDL, fibrinogen, and insulin. Effects of low-dose

alcohol on endothelial factors and blood pressure are less well-established, however. Whether the

effect of low-dose alcohol on biomarkers translates to improved clinical event rates is not fully

understood and warrants further research. The goal of this dissertation is to examine the dose-

dependent effects of alcohol on stroke and cognitive decline and to quantify the disease burden

attributable to heavy intake.

3.4 Measurement of Alcohol Consumption

A. Measurement Tools in Epidemiologic Research

Several measurement tools are available to research scientists to assess alcohol

consumption (Table 3).[109] The choice of which to use depends on its feasibility, cost, performance

characteristics, and the research goal (i.e. ranking individuals in categories of exposure vs.

estimating absolute levels of intake). Measurement tools may be subjective self-reports or objective

measures. Subjective measures are further classified as assessing 1) customary or 'usual' drinking,

in which the participant is required to average intake over a defined recall period; or 2) recent

drinking, which estimates both intake and within-person variability. Usual drinking measurement

tools are retrospective and subject to recall errors and reporting errors. Recent drinking approaches

can be either retrospective or concurrent, the latter being subject to measurement-induced

behavior change as well as reporting error.

Table 3. Tools for the measurement of alcohol consumption

Measurement Tool	Subjective vs. Objective	Type of drinking assessed	Timing	Primary Limitations
Single-item frequency	Self-report	Summary	Retrospective	Confounds Q and F and does not detect infrequent heavy drinking episodes
Quantity-frequency (QF)	Self-report	Summary	Retrospective	Does not capture heavy episodic drinking or beverage specific consumption
Indexed QF	Self-report	Summary	Retrospective	May over-estimate intake depending on algorithm
Extended QF	Self-report	Summary	Retrospective	May over-estimate intake if categories overlap
Graduated frequency	Self-report	Summary	Retrospective	May over-estimate intake if categories overlap

Most recent drinking occasion(s)	Self-report	Daily	Retrospective	Biased for irregular drinkers, may over-estimate frequency
Survey period recall	Self-report	Daily	Retrospective	Biased for irregular drinkers, may over-estimate abstention
Diaries	Self-report	Daily	Retrospective or Concurrent	High respondent burden; potential for behavior change
Blood alcohol content (serum, breath, urine, transdermal)	Objective	Recent exposure	Retrospective	Expensive; may not reflect usual drinking
Other biomarkers (e.g. GGT, CDT)	Objective	Recent (past 1-8 weeks)	Retrospective	Detects only chronic, heavy drinking; sensitivity may differ by gender

By far the most common measurement tools used in epidemiological studies are retrospective, self-reports to assess customary drinking habits. Modes of administration for these questionnaires include interviewer-administered (in person or over the telephone) and self-administered. A variety of measurement tools are available within this category including single-item frequency-based consumption measures, quantity-frequency (QF) measures, and graduated QF.[109-112]

In single-item frequency-based alcohol measures, respondents are asked to report the frequency (i.e. number of drinking days in a defined period) of alcohol consumption and are provided with response categories consisting of, for example, 'less than monthly', 'once per week', and 'one drink per day'. These questions are simple and rapidly administered, but are limited in that the response categories confound quantity and volume. Daily drinkers consuming large amounts would be captured as heavy drinkers, but not infrequent drinkers of large quantity. These questions thus differentiate better at the higher end of intake (i.e. with response options for once per day, twice per day, thrice per day, etc.), but are unable to differentiate between one drink once per week and 5 drinks once per week, because both would be categorized as drinking 'once per week'.[109]

QF measures, by far the most common in research, assess usual intake in 2 dimensions -

drinking frequency (number of drinking days over a reference period) and quantity (usual number of

drinks per occasion). Quantity and frequency are often collapsed into a 1-dimensional measure,

average volume, by multiplying QF responses. QF methods are simple to administer and easy to

compute, but can underestimate heavy drinking occasions. When compared with alcohol sales data,

QF methods have been shown to underestimate 23-77% of predicted intake.[113] Methods that

incorporate additional questions on binge drinking into standard QF measures yield higher levels of

reported intake. Reasons for underestimation from standard QF measures are two-fold. First,

respondents are typically not given enough time (or do not take enough time) to accurately

calculate average quantity per drinking occasion. Second, respondents are likely to misinterpret the

question as referring to the modal quantity or frequency and not the arithmetic mean. Because

individual intake distributions are typically right-skewed, the mode will underestimate the mean. As

a result of the underestimation of simple QF measures, the NIAAA Task Force recommends that

epidemiological research include at least 3 questions to measure alcohol intake: usual quantity,

usual frequency, and a third item for frequency of heavy drinking, referred to as binge drinking or

heavy episodic drinking. The latter question type typically asks the respondent for the number of

days over a reference period that he/she has consumed 5 or more drinks (a value of 4 or more is

sometimes used for women). Questions on heavy drinking enable researchers to measure drinking

patterns and may also be used to adjust average volume measures through an algorithm known as

indexing. Indexing methods adjust the average number of drinks per day based on the number of

reported heavy drinking days and the quantity consumed on these occasions. Standard QF

measures were compared with indexed QF methods in an analysis of 2003 BRFSS data.[113] The

authors reported that prevalence estimates of heavy drinking in the U.S. are higher when indexing

methods are used (6.8% vs. 8.1%) as is the average number of drinks per day (0.49 vs. 0.43).

Differences between these two calculation methods were larger for men and younger adults aged

18-34 years, groups in which heavy drinking is most common. Finally, extended QF measures have

been developed that capture drinking frequencies for different beverage types, in different

locations, or in different situations. These measures provide additional detail to researchers and

also are intended to reduce the respondent burden of averaging over different situations, reducing

variability.

A third measure is a derivative of the standard QF known as the graduated frequency (GF)

measure. This assesses the usual frequency of drinking at various quantity levels or 'bands'. The

first step is to establish the maximum number of drinks consumed in any day within the reference

period (usually chosen to be 1 year). Next, frequencies of drinking in the maximum band are

assessed; this process is repeated successively in lower quantity bands. The respondent burden of

averaging quantities is no longer required, but instead the respondent must accurately distribute

drinking days into categories of quantity. These question types are able to provide greater detail on

consumption, but are more time consuming for the respondent and therefore are infrequently used

in epidemiologic studies. In addition, because of their complexity, this measure typically collapses

all beverage types whereas QF methods are more easily able to incorporate separate questions on

beverage types such as wine, beer, and spirits. [109, 110, 112]

The second broad category of self-reported measurement tools are those that assess recent

drinking either retrospectively or prospectively. These include assessment of most recent drinking

occasion(s), fixed survey period recalls, and diaries. Most recent drinking occasion questionnaires

ask respondents to list all alcohol consumed on the last drinking occasion. Often the questionnaire

asks for the last two to four occasions to improve the measurement, but this method is still subject

to serious limitations. This technique tends to overestimate drinking frequency, particularly among

irregular drinkers, and therefore has differential validity according to drinking pattern.[109, 110, 112]

The survey period approach asks respondents to list all drinking occasions and quantities

consumed over a specified period, often one week in length. The advantage of this tool is that the

researcher may estimate within-person variability. Frequency is estimated based on the number of

drinking days in the reference period and quantity by averaging across all occasions. As with the

fixed-occasions assessment, this method is best used for populations with regular drinking

patterns.[109, 110, 112]

Finally, diaries can be used to capture recent drinking history or concurrent consumption.

These enable detailed data capture on type and quantity, but have high respondent burden and are

therefore best suited for short periods of time. A common method for measuring variability is to

use a series of 24-hour recalls. Concurrent records are subject to the respondent changing intake

behavior because of social desirability or to reduce recording burden. Advantages are that these

methods are likely subject to less reporting error from forgetting and averaging, and they provide

estimates of within-person variability.[109-112, 114]

Objective measures of alcohol consumption exist, though they have serious limitations for

use in large population-based studies.[109, 115, 116] Blood alcohol content is accurate and relatively

easily measured in breath, serum, urine or transdermally, but only reflects very recent intake and is

therefore not useful for assessing usual intake.[109] Gamma-glutamyl transferase (GGT) is one of the

most commonly used biomarkers for alcohol consumption and is elevated in the blood with chronic,

heavy consumption, typically 4 or more drinks per day for 4-8 weeks. Some evidence also suggests

that GGT is associated with moderate self-reported drinking.[117] Carbohydrate-deficient transferrin

(CDT) is a second blood protein that is elevated with heavy consumption and usually is detectible

prior to GGT (after 1-2 weeks of exposure). While elevated CDT has high specificity, the sensitivity is

lower than GGT and there is evidence that it performs less well among women. Interestingly,

elevations in GGT and CDT may indicate different drinking patterns. A study of outpatient alcoholics

found that among men, CDT was elevated more by drinking frequency (i.e. number of drinking days)

and GGT by drinking intensity (i.e. drinks per drinking day) while among women, both markers were more influenced by drinking intensity.[116] Numerous other biomarkers exist, but have similar limitations with low sensitivity, many sources of false positives including cardiovascular disease, diabetes, hypertension and obesity, and utility primarily for the detection of very heavy drinking (>40-60 grams per day).[118] While biomarkers may be useful in clinical practice to monitor a patient's adherence to treatment, they are impractical in large epidemiologic studies because of their high cost and ability to identify only recent drinking and those individuals who are chronic, heavy drinkers (a small proportion of most samples). However, these biomarkers may have utility for validation of self-reported heavy drinking (although this author is unaware of their use for this purpose in any longitudinal population-based study).

Epidemiologic studies usually measure alcohol consumption as part of food-frequency or diet history questionnaire. Most use a standard QF technique and many use extended QF measures, incorporating questions on heavy drinking episodes to capture additional detail. Some studies also include a series of 24-hour recalls or weighed food diaries in either the whole or often a sub-sample for validation purposes.

In the ARIC study, alcohol was measured using a single tool, precluding regression calibration correction for measurement error. The ARIC study does have multiple measures over time, however, which allows estimation of cumulative average and time-varying exposure with the caveat that measurement changes over time may also reflect measurement error . The QF measurement is vulnerable to under-reporting of heavy drinking episodes, as discussed above. However, separate questions for average quantity and frequency were included in questionnaires at visits 3-5, allowing for separate analysis of quantity and frequency (i.e. drinking pattern) in secondary analysis. Possible under-reporting of intake is a limitation of the measurement tool used in ARIC. While the degree of bias is unknown, simulation can be used to estimate this bias under

plausible misclassification scenarios.

B. Measurement Error and Validation Studies

The estimation of alcohol consumption is subject to measurement error that can be related to the instrument itself or to the individual. Instrument-related errors include collection mode, administration, question format, and reference period length.[109] Mode of data collection (telephone, mailed questionnaires, in-person) does not appear to affect measurement, although there is a tendency for response rates to be lower with mailed questionnaires.[119] Modes of administration include self- and interviewer-administered. Some evidence suggests that self-administered questionnaires yield higher alcohol intakes, purportedly because of increased sense of privacy and confidentiality relative to interviewer-administered surveys.[109, 120] Responses to self-administered questionnaires yielded higher alcohol levels than in telephone surveys likely because of reduced social desirability and interviewer effects.[119] However, interviewer administered surveys can result in high data quality because of greater control over data recording.[114] The question format can also be an important factor in alcohol measurement. Research indicates that open-ended questions elicit higher responses than closed-ended questions as does providing the respondent with a wide range of categories to reduce social desirability bias. Finally, the length of the reference period can impact measurement error. Shorter periods tend to over-estimate abstainers, while longer periods are subject to more forgetting error, particularly if drinking patterns are irregular. Longer recall periods, therefore, are theoretically less biased in estimating rank-order and distributions of drinking, but more subject to biases from forgetting. The better ranking in long versus short reference periods assumes that errors are linearly related to intake, i.e. that bias is similar across levels of intake. While no gold standard measure exists, the best administration mode is likely self-administration of a questionnaire that asks participants to report long-term

consumption and provides a wide range of response categories.

Individual related errors arise from recall errors of calculation, forgetting, and concealing. As discussed in the previous section, an individual's distributions of drinking frequency and quantity are highly right-skewed. When asked for the 'usual' value, respondents generally calculate the most common value, i.e. the mode. The mode will underestimate the mean of a right-skewed distribution. Some evidence suggests that the opposite effect can occur for reporting of frequency. For respondents with infrequent, periodic drinking, there may be a tendency to over-report frequency. Furthermore, because there is more individual variability in frequency than quantity, extended QF measures that ask about QF for different beverage types yield more valid estimates of average quantity. These methods minimize bias because the variability is decreased by asking separate questions on strata that account for individual variation in frequency, i.e. beverage type, location, etc. Many researchers collapse average quantity and frequency into average volume for analysis. The error in volume is directly related to errors in Q and F. While errors are compounded in the calculation of volume, rank order is maintained assuming that errors in Q and F are independent, i.e. that, for example, frequent drinkers do not have more bias in reporting quantity than infrequent drinkers. While some studies have found that frequent drinkers underestimate consumption and others that they overestimate consumption,[114] there is little convincing empirical support for dependent errors. For this reason, researchers assume that independence is achieved.[109] Finally, non-response bias in exposure measurement may result in selection bias, for example, if heavy drinkers are less likely to respond to alcohol consumption questionnaires than other drinkers. Interestingly, however, there is only mixed evidence in support of this hypothesis, with several studies reporting that heavy drinkers were equally likely to participate.[109, 112] The greater selection bias appears to arise from defining the sampling frame for study. Many sub-populations including institutionalized individuals, the homeless, and people without telephones are

not included in sampling frames for population-based studies and have a higher prevalence of heavy drinking than those living in households.

The above section summarized the mechanisms that can give rise to error in the estimation of alcohol consumption. Many studies have attempted to measure the magnitude of these errors and validate measurement tools. Validation of alcohol consumption is challenging given the lack of gold standard measurement and researchers have instead relied on relative validity studies that compare two or more different tools.[109, 112, 120] Relative validity studies have limitations, but are thought to be informative because the measurement errors between instruments are often independent and high correlations reflect stability of rank order.[121] Whether this is the case for alcohol is not fully understood. Validation studies have used a variety of designs to compare reports including collateral reports, official records, alcohol purchase and sales data, direct observations, self-report records, and biomarkers. Several of these designs are used in the clinical setting, namely collateral reports, official records, direct observation, and biomarkers, but are less useful for large epidemiologic settings. Below we will consider validation studies of alcohol in population-based studies, which typically compare self-reports (e.g. food frequency questionnaire [FFQ] and 24-hour recalls) and biomarkers.

Because there is no gold standard for measurement, validation studies tend to follow the assumption that greater reported consumption reflects higher instrument validity. One reason for this theory is that self-reports from national surveys vastly under-report consumption compared with sales data – to a degree beyond estimates of waste and sampling error. Another reason is that the 'more is better' philosophy aligns with the psychological mechanisms purported to underlie reporting errors. Forgetting drinking occasions and underreporting frequency and quantity because of social desirability would both lead to lower reported intake. However, there are situations that

can lead to over-reporting that should be considered when comparing instruments. These include

double counting consumption in GF methods and potential overlap in extended QF measures.[109, 120]

A review of 33 relative validity studies, primarily from the U.S. and Europe, found that

beverage-specific QF yielded 19% higher intake than other methods. After accounting for inclusion

of beverage-specific questions, the type of measurement tool was associated with reported intake;

retrospective diaries yielded intakes ~20% lower than QF and prospective diaries. Reference period

length and mode of administration were not predictors of intake level.   The authors also compared

mean intakes across measurement tools according to reported intake. There was some evidence for

non-proportional underreporting. Differences across measures were larger among individuals

reporting high intake (10 drinks per week) compared with individuals reporting low intake (4 drinks

per week). Finally, the authors assessed ranking of individual intake across the 33 studies using

relative validity and test-retest correlations (Table 4). Overall, the repeatability and relative validity

were good, particularly for QF methods. Test-retest correlations for volume of alcohol intake using

the extended QF method was 0.88 (range across studies from 0.83-0.98) and correlations between

extended QF methods and diaries were 0.66 and 0.73 (range of 0.57-0.89 across studies).[122] These

high correlations suggest that ranking of individuals is relatively accurate, although the possibility

that there is similar under-reporting in both instruments cannot be ruled out. True validity cannot

be assessed in the absence of gold standard measurements.

Table 4. Ranking of individuals according to alcohol intake: weighted averages of correlations (range across studies)[122]

Method	QF	Extended QF	Retrospective Diary	Prospective Diary
QF	0.88 (0.75-0.99)			
Extended QF	0.63 (0.59-0.90)	0.88 (0.83-0.98)		
Retrospective Diary	0.67 (0.66-0.74)	0.66 (0.66)	-	
Prospective Diary	0.71 (0.61-0.90)	0.73 (0.57-0.89)	0.65 (0.51-0.65)	0.84 (0.84)
24-hour Recalls	0.68 (0.32-0.90)	-	-	-

A validation study was conducted in the Nurses' Health and Health Professional Follow-up Studies that reported high correlation coefficients between 2 FFQs and multiple 1-week diet records for total alcohol; correlations ranged from 0.86-0.90 for women and 0.83-0.86 for men.[123] The correlation between 2 FFQs administered 1 year apart was 0.90 for women and 0.92 for men suggesting stability in reported consumption over a 1-year period. Correlations were not different for specific beverage types. Classification of individuals was also very similar between methods, with over 90% of individuals classified by FFQ within 1 quintile of their classification using diet records. Finally, the authors compared self-reported alcohol intake with serum HDL cholesterol levels. The relationships were roughly linear and consistent with controlled alcohol feeding studies, providing construct validity. Correlations ranged from 0.33-0.40 and were similar between diet records and FFQs. The primary source of potential correlated error between diet records and FFQ is intentional under-reporting of intake due to social desirability. This is most likely to affect heavy drinkers, as moderate drinking is not socially undesirable in U.S. culture. It is hypothesized, however, that heavy drinkers who are willing to participate in studies are also unlikely to conceal drinking. Differences in reported intake between frequency questionnaire and interview were unrelated to mean intake for beer, wine, and spirits in men and women in the Danish MONICA study.[124] In contrast, a study of 58 men in Finland found that, on a single drinking occasion, heavy drinkers (12-16 drinks) under-reported drinking compared with observation by an average 1.65 drinks (20%) compared with light drinkers (7-11 drinks) who under-reported drinking by 0.35 drinks (14%).[125]

More recent studies have found similar results to those described above. Women in Norway enrolled in the Norwegian Women and Cancer Study completed 2 FFQs 3 months apart. Test-retest correlation for alcoholic beverages was 0.76 and average within person difference was -9.1 (-11.5, -6.7) grams per day.[126] Regression calibration corrected results were away from the null

relative to naïve estimates. This suggested that, in their study, random error in measurement of

alcohol biased results toward the null. An analysis of FFQ versus 12 days of weighed food records

completed by Australian adults reported a Spearman correlation of 0.85 for alcohol intake.

Differences in the two measurement instruments were not related to participant characteristics of

age, sex, BMI, or occupation nor according to the level of alcohol intake (i.e. errors were relatively

proportional across alcohol intake).[127] A study of male and female German adults participating in

the European Prospective Investigation into Cancer and Nutrition Study compared relative validity of

3 24-hour recalls with a FFQ.[128] The mean difference was 0.9 grams, with the FFQ being slightly

lower. Correlations were highest of any nutrient, 0.86-0.88, and classification of individuals within 1

quintile of each other occurred in 87% of participants. Finally, while population-based studies have

not used biomarkers to validate alcohol intake, results from clinical populations suggest that self-

reports and biomarkers have modest agreement, but the generalizability of these results to non-

clinical populations is unknown.[120]

C. Challenges in the Operational Definition of Alcohol Exposure

Epidemiologic studies vary in how alcohol intake is represented in analysis and their ability

to differentiate effects of the components of intake. Alcohol consumption may be operationalized

in terms of average frequency, average quantity, average volume ('drinks' or grams of ethanol per

unit time), drinking patterns (e.g. number of binge drinking episodes), or combinations of these

components. By far the most common analytic approach is to calculate average volume and

estimate effects across categories. Operationally defining alcohol consumption in terms of volume

confounds effects of frequency and quantity.[129] This results in loss of information on drinking

pattern. Some researchers choose to separately estimate effects of frequency and quantity or to

estimate effects of drinking patterns on disease risk. In addition to choosing how to specify alcohol

consumption, researchers must also consider ethanol content, definition of cut-points for categorical analysis, and selection of reference group.

Error may be introduced in the calculation of average quantity or volume resulting from the variation in ethanol content according to beverage type, brand/manufacturer, glass size and shape, and percent alcohol.[77] Questionnaires ask about the number of drinks consumed and usually supply guidelines for the size of a typical drink (e.g. a 5-ounce glass of wine). However, respondents are likely to report in terms of the drink size they usually consume even if a quantity for typical drinks is provided as a reference.[110] Because drink size is the largest source of variation in ethanol content, some studies have provided individuals with pictures, observed pouring, and mailed standard size glasses with marks to more accurately measure quantity. These methods are less feasible for large population-based studies. When average volume is expressed as grams per unit time, there is an advantage of increased comparability across studies, particularly with international populations in which a 'drink' may be defined differently that in the U.S. Content of a 'standard' drink ranges from 8 grams in the United Kingdom to almost 20 grams in Japan (Figure 7A).[3] The standard drink measure used in the U.S. contains approximately 14 grams of ethanol and corresponds to 12 ounces of beer, 5 ounces of wine, and 1.5 ounces of distilled spirits or liquor (Figure 7B).[130]

Figure 7. Standard drink sizes in international populations[3] (A) and in the United States (B)[5]

A. Ethanol content of standard drinks by country   **B.** Ethanol content of US standard drinks by type
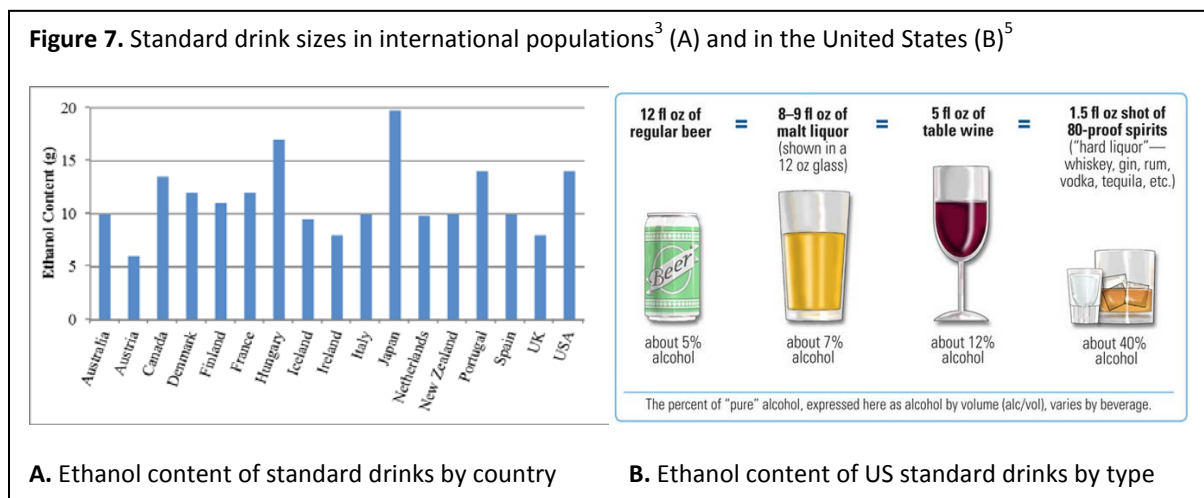
Selection of cut-points used for categorical analysis also varies greatly across studies, limiting their comparability. Current studies typically include categories for never drinkers, former drinkers, and current drinkers divided according to volume, e.g. <1/week, 1-7/week, etc.[93] There is some evidence that effects of drinking may differ by age, sex, or other individual-level factors. Categories need to be narrow enough to capture this potential modification so that definitions of 'moderate drinking' are sensitive to heterogeneity. Furthermore, care must also be used when estimating thresholds because the assessment of absolute intake is sensitive to measurement error. For example, if heavy drinkers underreport drinking, then the threshold of harm will be artificially elevated.[93]

Choice of reference group is also important for analysis. Many studies, particularly older ones, combined former, never, and occasional drinkers into the 'nondrinker' category and used this for reference group.[131, 132] Several authors have postulated that this categorization, known as 'abstainer error' or 'health selection', has biased effects of moderate drinking away from the null. Because sickness and old age are associated with reductions in drinking as well as with poor health, inclusion of these 'sick quitters' in the abstainer category would increase the risk in this group and therefore bias estimates of moderate vs. no drinking toward a protective effect. Inclusion of occasional drinkers in the abstainer category can also lead to error.[129, 132] For this reason, the use of a 'former drinker' and 'never drinker' category is preferred to a 'nondrinker' and 'occasional drinker' category. Researchers may also exclude early outcome events from analysis in case these were the result of pre-existing illness that had altered alcohol consumption. Finally, in their operational definitions of alcohol, researchers may choose to stratify by beverage type and consider the time-varying nature of alcohol consumption.

The measurement tool used by ARIC was similar to those used by many other population-based studies. The primary disadvantage is the absence of a second measurement tool such as 24-

hour recalls. There are several advantages, however. Questions were included on drinking history

that allow for differentiate of never and former drinkers. Response categories were narrow,

reducing reporting errors, enabling categorization of participants into groups with homogenous

disease risk, as well as generating categories similar to other research in order to compare study

results. Importantly, ARIC included questions on both frequency and volume (allowing for

calculation of quantity) for later study visits which may be useful in sensitivity analysis.

3.5 Outcome Measurement

A. Ascertainment and Definition of Stroke Events

Validity of stroke outcome measurement depends on the completeness of case

ascertainment, the accuracy of diagnosis, and correct differentiation between stroke types (i.e.

ischemic vs. hemorrhagic). Ascertainment of stroke events can be accomplished using a variety of

methods. Recommendations for stroke incidence studies were published by Malmgren[133] and later

refined by Sudlow and Warlow to incorporate more widely available imaging technologies.[134]

Recommended methods include self-reports; hospital and emergency department admission logs;

local physicians and outpatient clinic referrals; mortality databases and death certificates; follow-up

of TIA cases; and brain, carotid, and cerebral vascular imaging logs (Table 5).

Table 5. Methods of stroke case ascertainment recommended for use in community-based studies[134]

- General practitioners or primary healthcare physicians
- Other primary healthcare workers, e.g., district nurses, community physiotherapists, and occupational therapists
- Emergency services, e.g., ambulance coordination centers
- Nursing, residential, and rest homes
- Hospital admission lists, including patients presenting to casualty/emergency departments using a broad range of diagnostic labels
- Hospital discharge lists
- Computer-linked records systems
- Regular ward checks for cases occurring in patients already in the hospital

- Referrals to radiology departments for CT or MRI scans, carotid duplex studies, and cerebral angiography
- Death certificates
- Newspapers, e.g., news, obituaries, death announcements

Ascertainment is broadly classified as being passive (cold pursuit) or active (hot pursuit).[134, 135] In passive surveillance, cases are identified by searching hospital discharge lists or mortality databases for stroke-related discharge codes (often ICD-9 430-438 with some exclusions based on poor validity of individual codes). These are cost-effective and resource-conservative methods, but only capture hospitalized cases (which may be more severe) and rely on the accuracy of discharge diagnosis codes. Some studies adjudicate diagnosis with medical record review; this improves validity but does depend on record completeness and accuracy. In active surveillance, cases are identified by screening a variety of sources such as ED logs, out-of-hospital facilities, medical wards, and imaging centers. The advantage of this method is that non-hospitalized community cases are captured, but this method is time consuming and resource intensive. A relatively broad set of key diagnostic terms such as "dizziness", "visual disturbance", vertigo", "cerebrovascular accident", and "stroke" are used for screening.[135] Accuracy of active methods depends on several factors including the breadth of screening terms, the position and sets of ICD-9 codes used for identification, and completeness and accuracy of medical records. Much of the difference in case finding between active and passive surveillance is likely attributable to minor strokes that may not present to the hospital, may not be hospitalized, or may be incorrectly diagnosed as TIA. Routine clinical coding is known to underestimate the incidence of minor stroke because of misclassification as TIA.[136]

Several studies have compared ascertainment methods. Whether findings on the relative strengths of case ascertainment methods are generalizable across populations is unknown, given that populations differ with regard to healthcare systems, individual healthcare-seeking behavior, and access to care. For example, the proportion of stroke patients admitted to the hospital varies

widely across populations - from 40% in the Oxford Vascular Study to 95% in a Swedish cohort.

Hospitalization rates also vary within the United States. Out-of-hospital stroke cases (fatal and

nonfatal) comprised roughly 17% of all cases among Whites and 8% among Blacks in the Greater

Cincinnati/Northern Kentucky Stroke Study (GCNKSS) from 1993-2005 and 14% of strokes in the

Rochester Stroke Registry from 1970-1989.[137, 138] Below are described the findings from 3 different

population-based studies that compared ascertainment of stroke events with different methods.

They support the general conclusion of previous researchers that advocate for the use of multiple,

overlapping methods.

The Oxford Vascular Study authors defined a 'core' group of ascertainment methods that

included physician referral, hospital admission, ED, and discharge lists, case notes of in-hospital

deaths and acute medical wards, contact and case review of patients attending local clinics, and the

national death register. [134, 139] 'Supplemental' methods were follow-up of TIA patients and review of

referrals for brain carotid, or cerebral vascular imaging. 'Additional' methods included follow-up of

patients with any stroke-related discharge code in electronic medical records and follow-up of high-

risk patients (i.e. those hospitalized for cardiovascular disease in the past 6 months). 'Supplemental'

methods identified 15% more cases than core methods alone. Most of these cases were initially

identified as TIA by core methods, but were determined to be minor strokes. 'Additional' methods

of ascertainment identified only 2 additional cases, suggesting they have minimal benefit.

The Brain Attack Surveillance in Corpus Christi (BASIC) project is a population-based stroke

surveillance study in the U.S. that also used a combination of active and passive ascertainment

methods. Through active surveillance, researchers identified strokes that were admitted to the

hospital (82% of all validated cases), presented to the ED without hospital admission (16%), and

other out-of-hospital cases (2%; Figure 8).[135] Roughly half of the ED and out-of-hospital cases

identified only by active surveillance were TIAs. Passive surveillance alone identified 7% of cases

Figure 8. Sources of case identification in the BASIC project
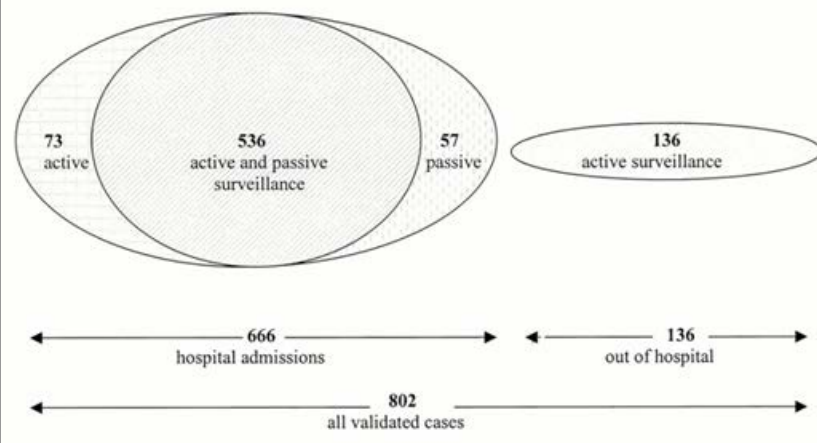
and failed to identify 11% of hospitalized cases, half of which were ischemic strokes. Overall, passive surveillance failed to capture 26% of cases, 46% of which were TIAs. If only active surveillance had been used, 7% of cases would have been missed. This study indicates that active surveillance was superior to passive surveillance alone for case ascertainment, but that an ideal study would use overlapping methods to capture stroke cases in the community as neither method by itself captured 100% of cases.

In the Cardiovascular Health Study (CHS), 3.5% of strokes and 0% of TIAs were ascertained using Medicare hospitalization data only, i.e. cases were not additionally identified through CHS assessment that included telephone calls, clinic visit interviews, and self-reports. In contrast, 15.5% of strokes and 30% of TIAs were identified by CHS ascertainment but not hospitalization data.[140] These study results support the need for supplementation of hospitalization records with other case ascertainment methods to identify non-hospitalized events and suggests that self-reports without passive surveillance of hospital logs does not capture a high proportion of cases.

In addition to missing cases, hospitalization and death certificates are subject false positives. The accuracy of death certificate cause of death (COD) was assessed in the Minnesota Heart Study compared with adjudicated cause of death from medical record review of in-hospital deaths. The positive predictive value (PPV), sensitivity (Se), and specificity (Sp) for ICH were 82%, 76%, and 95% and for non-hemorrhagic stroke were 97%, 58%, and 98%.[141] Analyses from the Framingham Study

were similar, with 78% sensitivity and 94% specificity for total stroke.[142] A study in Finland assessed the accuracy of ICD-9 codes listed in mortality records with physician review based on clinical signs and symptoms, neuroradiological findings, surgery, and autopsy. The proportions of correct diagnoses were 95% for SAH, 91% for ICH, 92% for IS. These values suggest reasonably high accuracy of codes; however, the generalizability of these findings is unknown particularly as the autopsy rate was high (39%).[143] Cardiovascular Health Study researchers compared death certificate cause of death with adjudicated cause of death and only 42% of true stroke deaths had a stroke-related COD and 62% of death certificates that listed stroke as the COD were adjudicated as stroke by the events committee.[140] In summary, death certificates have modest validity and it may be lower in the US than in Europe. Reliance only on death certificates will likely result in significant measurement error from missed cases and inclusion of non-strokes. Ideally, studies that include death certificates in case finding would include a validation step to remove false positives.

Accuracy of discharge codes is similar to death coding and varies widely depending on code groups used. The sensitivity of codes for stroke ranged from 72%-90% across several studies in the U.S. and Canada and PPV ranged from 47%-82%.[135] [137] [138] [140] [143, 144] The percentage of total correct code-based diagnoses have been reported as up to 90% in Canada and ~80% for SAH/ICH. [143] [144] Taken together, there is clear need for adjudication of cases that are identified using ICD codes to reduce outcome misclassification. Accuracy of diagnosis codes varies by their position and the code groups used, but is not adequate in any combination for identifying stroke events without bias.

Self-reported stroke had moderate positive predictive value in the British Heart Study when compared with medical record review (PPV=75%; Se=89%).[145] Most false positives were the result of TIA diagnosis that the patient reported as stroke, although there were cases of stroke-like symptoms being attributed to stroke by the patient. False positive rates of patient recall compared with medical record review from Norway, the Nurses' Health Study, and studies in the UK range

from 34-37% and false negative rates range from 5-66% suggesting that self-reports alone are not an adequate measure of stroke events.

Stroke diagnosis in epidemiological studies has typically been based on clinical presentation, with most studies using the World Health Organization definition of "rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin".[146] As discussed above, this definition is considered obsolete in favor of revised tissue-based criteria that also excludes global ischemia in stroke definition.[55] Table 6 shows minimal recommendations for diagnosis of stroke types that were common in the era during which most of the observational studies included in this proposal were designed and conducted. All depend on the availability of brain imaging for definite diagnosis.[93, 147]

Table 6. Standard definitions for comparing pathological types of stroke[148]

Definite Cerebral Infarction (CI)
- WHO-defined stroke *and*
- CT scan within 30 days of stroke (or MRI scan) shows infarct or no relevant lesion *and/or*
- Autopsy shows CI

Definite Primary Intracerebral Hemorrhage (PICH)
- WHO-defined stroke *and*
- CT (or MRI) scan shows PICH *and/or*
- Autopsy shows PICH

Definite Subarachnoid Hemorrhage (SAH)
- Appropriate clinical history *and*
- CT head scan shows subarachnoid blood *and/or*
- Lumbar puncture shows subarachnoid blood *and/or*
- Cerebral angiography shows source of subarachnoid bleeding *and/or*
- Necropsy shows SAH ± source

Probable CI
- WHO-defined stroke *and*
- Validated clinical score (Guy's Hospital Stroke Diagnosis Score or Siriraj Score) gives >90% likelihood of infarction

Probable PICH
- WHO-defined stroke *and*
- Validated clinical score gives >90% likelihood of hemorrhage

Undetermined pathological type
- WHO-defined stroke but not fulfilling above criteria for CI, PICH, or SAH

Researchers have developed a variety of clinical scores to differentiate ischemic and

hemorrhagic subtypes in the absence of brain imaging. These utilize patient signs, symptoms, and

medical history and in general have been found to have moderate accuracy. A study assessed the

Guys' Hospital Stroke score and the Siriraj Hospital Stroke score compared with computed

tomography (CT) and autopsy diagnosis. The Guys' Hospital Stroke (or Allen) Score diagnosis of

hemorrhage had Se, Sp, and PPV values of 31%, 95%, and 73% and ischemic stroke of 78%, 70%, and

86%, respectively.[147] The Se, So, and PPV of the Siriraj score for hemorrhage were 48%, 85%, and

59%, and for ischemic stroke were 61%, 74%, and 84%. Other studies have reported similar poor

accuracy of clinical scoring systems.[149] While these scores may be useful in estimating burden of

disease provided corrections are made for measurement error, they are inadequate for defining

stroke types and could result in considerable bias in etiologic studies.

Accurate classification of ischemic stroke, ICH, and SAH requires brain imaging results. Two

imaging modalities commonly used for diagnosis are CT and magnetic resonance imaging (MRI). CT

is more common than MRI diagnosis because it is less expensive, more widely available, and fast. It

is the standard for stroke detection and is useful for ruling out hemorrhage; however, it has limited

sensitivity for detection of early ischemia and can yield inconclusive results.[150, 151] The inter-rater

reliability is higher for MRI compared with CT in some studies, but lower in others.[150, 152] The

sensitivity of MRI compared with final clinical diagnosis for detecting acute ischemic stroke is higher

than for CT (83% vs. 16%), but the specificities were similar (96% vs. 98%) and the detection of

hemorrhages was similar.[150, 151] A third imaging technique, transcranial color-coded duplex

sonography, is widely available and is reasonably accurate in differentiating ischemic from

hemorrhagic stroke when compared with CT (Se=94%; Sp=95%).[151] This modality may offer an

alternative to CT/MRI when neither is available as it is easy to perform, mobile, and non-invasive.

Choice of imaging technique used for stroke diagnosis is not likely to result in misclassification when final clinical diagnosis also takes into consideration additional diagnostic tests and patient symptoms. Finally, there is some evidence that the physician specialty is important for diagnostic accuracy. Emergency department physicians in the BASIC study missed 11% of stroke cases compared with neurologist-validated diagnosis (Se=92%; PPV=89%).[153] As described in detail above, discharge codes and death certificates have limited ability to accurately identify strokes and to correctly distinguish subtype. For example, ICD-9 diagnosis of stroke type in the BASIC study was accurate for only 84.5% of hospitalized cases.[154] Ischemic strokes can be further classified according to their etiology and a common system was developed by the Trial of Org 10172 in Acute Stroke Treatment (TOAST) for this purpose. Subtypes include large-artery atherosclerosis, cardioembolism, small-artery-occlusion, and 'other' cause.

B. Summary

Epidemiologic studies wishing to study etiology of stroke need to include CT/MRI findings, when available, as part of case definition, and should not rely solely on administrative data for stroke ascertainment or diagnosis of stroke type. The ARIC study uses multiple, overlapping ascertainment methods and stroke events are validated by algorithm and physician review. Information used for validation is abstracted from medical records and includes evidence from brain imaging studies. Classification of events is based on the National Survey of Stroke criteria (Appendix 1), which were developed several decades ago and are currently dated compared with more recent classification systems such as TOAST and the AHA updated definitions. This is a potential limitation; however, the impact of using this outdated scheme is likely not significant because the criteria are roughly similar to more recent classification for the broad classification of ischemic stroke vs.

hemorrhage.

C. Measurement of Cognitive Function

Numerous neuropsychological assessment tools have been developed, standardized, and validated to assess cognitive function. These include both global and domain-specific tests and have varying applications to the clinical setting and in large research studies. Important considerations of test selection include the domain(s) of interest, floor and ceiling effects, and validity in the population of interest. Floor and ceiling effects occur when cognitive performance being assessed is outside the test range are therefore not measurable. Epidemiologic studies often utilize global cognitive tests as screening tools for dementia as well as domain-specific tests that are sensitive to changes at the higher end of cognitive function. For our study, which aims to estimate cognitive declines from mid-life into older age in a population with relatively high cognitive function at baseline, the best assessment tools will be reliable and valid tests in a bi-racial population, able to detect small changes over a broad range of cognition (i.e. without strong ceiling effects), and without strong practice effects because of their repeated administration over follow-up. In addition, practical considerations of administration time and cost are important for a large-scale study. Below are reviewed the most common neuropsychological assessments used in epidemiologic studies on cognitive decline, including those that are used by the ARIC study (see Appendix 3).

The **Mini-Mental State Examination (MMSE)**[155] was initially designed as a brief 11-item screening tool for cognitive loss in elderly patients and is now one of the most widely used screening tools for dementia. The test measures global cognition and captures several domains including orientation to space and time, language and comprehension, memory, attention, calculation, and praxis. Scores range from 0 to 30. Normal declines in MMSE reportedly range from 0.1-0.3 points per year for cohorts younger than 85 years of age.[60] Reliability of change estimates increases with

increasing duration of follow-up and time in between measurements.[60] Cut-points used for

MCI/dementia screening are often 23/24 or 24/25 and may vary by education level to minimize

misclassification. Sex-based differences are not seen for the MMSE, but age, race, and education

seem to affect scores. Reliability, both test-retest and inter-rater , is high (>0.8) in most reports.[156]

Content validity and concurrent validity (comparison with other global tests of cognition) are both

high, with correlations generally ranging from 0.6-0.8. Most research in MMSE validity has focused

on its ability to classify individuals with dementia, for which sensitivities and specificities are >80%.

Ability to classify patients correctly differs by education and in some studies age and race.

Advantages of the MMSE are that it can be administered by trained non-specialists, is brief in

duration, and has relatively high validity for detecting clinical impairments. Limitations include floor

and ceiling effects, low sensitivity to mild cognitive deficits when used as a screening tool, and poor

discrimination among degrees of dementia.[156] Of particular concern for population-based studies

that aim to detect changes across a wide range of cognition, including the higher end, is the strong

ceiling effect.[157] The MMSE is not an ideal tool for our aims.

       The **Telephone Interview for Cognitive Status (TICS-m)**[158] is a 13-item telephone-

administered test similar to the MMSE with scores ranging from 0 to 51.[59] It was later modified to

include an immediate and delayed recall of a 10-item word list. Telephone administration of the

test correlates well with face-to-face administration modes (r=0.85) and has high validity for

distinguishing dementia. In addition, research supports the absence of ceiling and learning effects

for the modified version.[159] The TICS-m, in contrast to the MMSE, may also be useful for

distinguishing MCI.[159] The primary advantages of the TICS-m are its administrative ease in large

population-based studies, lower concern for ceiling effects compared with the MMSE, good

performance as a screening tool, and enhanced assessment of memory compared with the MMSE.

Because of these factors it is better able to discriminate individuals with high levels of cognition.

Limitations include difficultly administering over the phone to individuals with hearing impairments and reliance on one primary domain (memory) to discriminate at higher levels of cognition. The memory component accounts for at least 50% of the variation in scores in a healthy adult population and therefore this test may detect declines in different cognitive domains (memory at higher end and global aspects at lower end).

The **Modified Mini-Mental State Test (3MS)**[160] assesses multiple domains including attention, concentration, orientation to time and space, memory, language ability, and abstract thinking. It contains the same items as the MMSE plus 4 additional items and adjusted scoring, which ranges from 0 to 100. Test-retest and inter-rater reliability are very high (>0.9) and the validity compared with other tests and as a screening tool for dementia are high.[156] Compared with the MMSE, the 3MS offers superior validity, covers more cognitive domains (i.e. verbal fluency and reasoning/judgment), has reduced floor and ceiling effects, and a larger scoring range. There is little added administration time and some increased complexity of scoring. Because of these factors the 3MS may offer a better assessment of cognition than the MMSE in a population of generally healthy adults.

The **Digit Symbol Substitution Test (DSST)**[161] measures 2 domains of cognition, attention and psychomotor speed, and is a component of the revised Wechsler Adult Intelligence Scale. Participants are given 90 seconds to fill in numbered blanks with corresponding symbols using a numeric key that links numbers 1 to 9 with a symbol. Scores can range from 0 to 93 and reliability is high (0.82-0.88).[59] Factors important for performance are motor persistence, attention, response speed, and visuomotor coordination. There is no apparent effect of intellectual ability, learning, or memory domains on scores. The test in insensitive to location of brain injury and thus is a good assessment for nonspecific brain dysfunction. Education accounts for roughly 30% of the variation in scores and age an additional 14%, though use of age and education norms are debated. A major

advantage to this test is that it does not display a ceiling effect (likely because of the speed

component of the test) and the relationship between the test score and its underlying construct is

linear for moderate to high cognition. Because of these properties, the DSST is very sensitive to

changes at high levels of cognition and is one of the first tests to show declines in dementia. In

contrast, at the impaired end of the spectrum, this test is nonlinear and is unable to detect changes

(i.e. has a strong floor effect).[157] For clinical use in measuring progression of dementia, this test

would not be very useful, but for our purposes is a good choice for neuropsychological assessment

of attention and speed. Another advantage for use in a study with repeated measures is the

apparent lack of practice effects. Limitations of this test include possible bias in test scores for

elderly individuals with physical impairments that limit speed and floor effects.

The Delayed Word Recall Test assesses verbal learning and short-term memory.[162]

Respondents are given a 10-word list and after a 5-minute interval are given 60 seconds to recall

these words. Scores range from 0 to 10 and the test has demonstrated high test-retest reliability

(r=0.75) in elderly individuals.[162] Age and sex appear to influence responses to word recall tests and

there is evidence of practice effects up to a year and beyond. The primary limitation of this test is

that 10 words is too low a ceiling for many participants of normal cognition.[59] Error types in this test

may help distinguish dementia types, with Alzheimer's and alcohol-related dementia patients

making the most false positive recognitions and forgetting the most words, and patients with

vascular dementia having fewer false positive recognitions and more repetitions.

The Word Fluency Test (WFT) is used as part of the Multilingual Aphasia Examination.[59] It

assesses language skills and short-term memory (to maintain the list of words already generated).

Participants are asked to record as many words as possible within a 60-second time interval that

begin with the letters 'F'. This is repeated for letters 'A' and 'S'. Scores are calculated as the total

number of words recorded for each trial. Scores are influenced by age, sex, and education and test-

retest reliability is high (r=0.82).[163] Individuals with ability to organize verbal output into meaningful clusters, for example words that start with the same phonological cluster such as 'con', are more successful. Verbal fluency impairments are seen with frontal lobe damage, particularly the left lateral front lobe. An advantage of this test is its sensitivity to early declines in cognitive functioning in older adults and a limitation is that it does not distinguish patients with depression and dementia.[59]

Operationally, many researchers will standardize raw test scores into z scores to make them comparable across tests or sub-groups.[59] The reasoning behind this approach is that the same raw score achieved by two individuals may not represent the same level of the underlying construct because of group-level differences in test performance (or norms). The z-score represents the raw score's placement on a standard normal curve with a mean of zero and a standard deviation of 1. There is debate in the literature as to what the standard population should be, but many researchers use some stratification of age, sex, race, or education. Education appears to influence performance on all tests while demonstration of race differences are mixed.[59] Use of standard scores is debated because when population means differ, for example by race, it is often difficult to determine if this is because of cultural preference of the testing instrument or a true difference due to differing prevalence of risk factors, underlying disease process, and genetic or biological factors. We will not use race-specific standard scores in primary analysis because there is no strong support for a racial difference and using different standards would bias estimates toward the null.

D. Summary

The best assessment of cognitive function is a standardized, reliable, and valid test that is tailored to its intended use and population. For our aim of studying changes over a long period from mid-life through older age, it is important to choose a test that is sensitive to early changes in

cognitive function and is not subject to strong practice effects. Tests without ceiling effects such as the DSST will be better able to discriminate early changes than tests with skewed distributions such as the MMSE. While there may be some practice effect for the DWRT and WFT, these are not likely to be strong in our study, which had visits separated by 3 and 14 years.

3.6 Studies Assessing the Relationship Between Alcohol and Stroke

A. Overview

The association between alcohol intake and stroke has been intensely studied for decades. Unlike in the area of coronary heart disease where there is a high degree of consistency in findings of a cardioprotective effect associated with moderate drinking, research in the area of stroke has been inconsistent. Early studies dating back to the 1980s often produced 'null' results and tended to have significant limitations. Many studies combined ischemic and hemorrhagic stroke types as an outcome, the etiologies of which differ as does the role of alcohol on disease risk. Combining a putative protective effect on ischemic stroke and harmful effect on hemorrhagic stroke could yield an overall lack of association depending on the magnitude of association and the proportion of each stroke type. Later studies that separated out stroke types in analysis tended to find a J-shaped relationship with ischemic stroke, but not for hemorrhagic stroke.

Stroke ascertainment may be incomplete in studies that relied on self-reports only or on administrative data. Methodological issues of exposure measurement have also plagued some cohort studies and could have yielded biased results. Several of these early studies used crude measures of alcohol consumption, sometimes categorizing individuals into broad categories of 'drinkers' and 'nondrinkers'. The chosen referent group sometimes was a combination of former and current non-drinkers as well as occasional drinkers, groups that are not likely to have homogeneous disease risk. While early studies suggested a particular beneficial effect of red wine

on atherothrombotic diseases, the majority of observational studies find reduced risk with all alcohol types. Many authors have concluded that there is currently no strong and convincing evidence that beverage type differentially affects risk, [93] while others maintain that there is good reason to recommend red wine consumption over other forms of alcohol for prevention of stroke and dementia.[72]

In this author's opinion, while there is reasonable biologic plausibility for independent effects of polyphenols above those of ethanol alone, the body of evidence from observational studies is not strong enough, nor consistent enough, to recommend red wine consumption in particular over other types of alcohol for the reduction of stroke risk. Additional limitations of prior studies include adjustment for possible causal intermediates such as blood pressure, lack of adjustment for confounding variables, and inability to account for time-varying exposure or patterns of alcohol consumption.

Below are summarized the findings from seven representative studies that assessed the alcohol-stroke relationship as well as three meta-analyses on the subject. The studies are arranged chronologically and were selected in part because they represent the state of the field at the time of their publication and because they have comparably robust methods. In general, there was an improvement in methods over time, with increasing attention paid to separating subtypes of stroke in analysis, validating exposure measurement, incorporating more sophistication in analysis (i.e. by adjusting for time-varying confounding and estimating effects for cumulative and time-varying exposure), increasing control for confounding bias, and assessment of population burden measures in addition to relative risk estimation. Appendix 2 summarizes these and other studies in terms of their study population and design, methods of exposure and outcome measurement, and results.

B. Description of Seven Key Studies

Key Study 1 – Physician's Health Study[164]

The Physicians Health Study was a randomized controlled trial of regular aspirin use among 21,071 male physicians aged 40-84 years at baseline in 1982.[164] Alcohol was assessed in terms of frequency (number of times per week) by mailed questionnaire at baseline, "How often do you usually consume alcoholic beverages?". Strokes were ascertained by self-report in annual follow-up questionnaires and adjudicated using medical records. Deaths were ascertained from family reports and postal authorities and stroke was assigned as the cause of death based on information from medical records, death certificates, and eye witness accounts. Cox proportional hazards models adjusted for age, systolic blood pressure, smoking, BMI, exercise, history or diabetes, current treatment for hypertension, and randomization group.

Over an average 12.2 years of follow-up there were 679 strokes, 557 ischemic, 88 hemorrhagic and 34 unknown type. Much of the analysis focused on total stroke and the authors report a reduced risk of all drinking frequencies compared with less than once per week. Stroke type specific analyses show similar results. The protective effect is relatively similar across drinking frequencies for ischemic and hemorrhagic stroke (Table 7).

Table 7. Relative risk of subtypes of stroke according to alcohol consumption[164]

Alcohol Consumption	Ischemic Stroke			Hemorrhagic Stroke		
	Cases	RR (95% CI)	p-value	Cases	RR (95% CI)	p-value
<1 drink/wk	168	1.00	0.10†	26	1.00	0.67†
1 drink/wk	54	0.73 (0.52-1.00)		13	1.17 (0.58-2.40)	
2-4 drinks/wk	91	0.74 (0.56-0.98)		14	0.70 (0.33-1.46)	
5-6 drinks/wk	68	0.81 (0.59-1.12)		11	1.00 (0.46-2.23)	
1+ drinks/d	176	0.79 (0.62-1.00)		24	0.90 (0.48-1.69)	

* Values are adjusted for age (in years), randomized treatment assignment (aspirin, yes or no; beta carotene, yes or no), systolic blood pressure (continuous variable), current treatment for hypertension, smoking (four categories), history of diabetes (yes or no), body-mass index (in quartiles), drink per week served as the reference category.

 † P-values are for linear trend across all categories of alcohol consumption.

A limitation of this study was the author's interpretation of their results given how alcohol was measured. The questionnaire assessed drinking frequency not quantity, but the authors interpreted these questions as reflecting average volume. As in other studies that rely on self-reported stroke, there is the potential for missed events. However, this bias is likely minimal given that the population consists entirely of physicians. Estimates were adjusted for the potential causal intermediate of blood pressure and dose-response was only assessed in category-by-category comparisons instead of in analysis that estimates the dose-response relationship. Category-by-category comparisons are sensitive to the choice of referent category and not ideal for estimation of dose-response. The referent category used in this study could contain a mixture of occasional, never, and former drinkers, the risks of which could differ. Exposure was measured only at baseline and potential confounders such as social support and exercise were not included. Finally, these results reflect a population of high-SES, male, nearly all-White physicians and included only a small number of hemorrhagic stroke events. Overall, this study design and methodology were not strong and several sources of bias exist. Effect estimates are likely biased, but the direction is unknown.

Key Study 2 – Northern Manhattan Stroke Study[39]

The Northern Manhattan Stroke Study (NOMASS) is a multiethnic population-based study among residents of northern Manhattan New York aged 40 years and older. A case-control study was conducted in this population the data of which were used to examine the alcohol-stroke relationship.[39] Stroke cases were identified from community surveillance in 1993-1997 from local hospital admission, discharge and neuroimaging logs; contact with local physicians; self-referral; and random-digit dialing. Strokes were adjudicated and subtyped using data from medical records; nearly all records (99%) included CT or MRI imaging. Controls were selected by random digit dialing of households in the study areas and were eligible if they had never had a stroke and were over age

40 years; the participation rate was 70%. Cases and controls were interviewed in person and

underwent physical and neurological exams. Alcohol consumption was measured using a beverage-

specific FFQ. Binge drinking and alcoholism (CAGE questionnaire) were also assessed. Alcohol was

operationally defined as categories of average drinks per unit time: no drinks in the past year,

moderate: >0-2 drinks/day, intermediate: >2-4 drinks/day, heavy: 5+ drinks/day. Covariates

included hypertension, cardiac disease, current smoking, education and BMI. There were 677 cases

of ischemic stroke included in analysis. Moderate and intermediate alcohol consumption were

associated with reduced odds of stroke (Table 8).

Table 8. Adjusted odds for ischemic stroke stratified by sex, age, and race/ethnicity.

Stratum	No. of Cases/Controls	Abstainer, 0 Drinks/ Past Year Prevalence in Controls	Moderate, ≤2 Drinks/d Prevalence in Controls	ORt (95% CI)	Intermediate, >2 to <5 Drinks/d Prevalence in Controls	ORt (95% CI)	Heavy, ≥5 Drinks/d Prevalence in Controls	ORt (95% CI)
Sex								
Men	299/447	37.8	49.7	0.54 (0.36-0.80)	8.7	0.72 (0.38-1.36)	3.8	1.33 (0.56-3.17)
Women	378/692	63.0	35.0	0.49 (0.34-0.71)	1.9	0.23 (0.05-1.08)	0.1	5.35 (0.51-56.67)
Age, y								
<65	212/333	46.3	45.4	0.44 (0.26-0.75)	6.3	0.70 (0.30-1.63)	2.1	2.39 (0.79-7.21)
≥65	465/806	56.0	38.8	0.53 (0.39-0.73)	3.9	0.43 (0.19-0.96)	1.4	1.13 (0.32-4.03)
Race/ethnicity								
White	132/256	44.5	50.4	0.51 (0.29-0.90)	4.3	0.31 (0.07-1.34)	0.8	1.49 (0.13-17.78)
Black	192/358	47.2	45.3	0.45 (0.28-0.73)	5.3	0.43 (0.14-1.30)	2.2	1.43 (0.37-5.49)
Hispanic	343/514	61.5	32.7	0.53 (0.35-0.81)	4.3	0.75 (0.35-1.63)	1.6	1.64 (0.52-5.10)

*Reference group is those not drinking during the past year. OR indicates odds ratio; CI, confidence interval.
†Matched for age, sex, and race/ethnicity and adjusted for hypertension, diabetes mellitus, cardiac disease, current cigarette use, education, and body mass index.

There were no significant interactions with sex, age, or race and results were similar by

beverage type. Effects appeared stronger in women

compared with men, but the confidence intervals were

wide and overlapped considerably. Heavy intake of ≥5

drinks per day was associated with increased risk of

stroke among all subgroups. In continuous analysis, the

lowest odds of stroke was observed at roughly 2-3

drinks per day, with increased odds beginning after 5

drinks per day (Figure 9).

Figure 9. Dose response relationship between alcohol and ischemic stroke
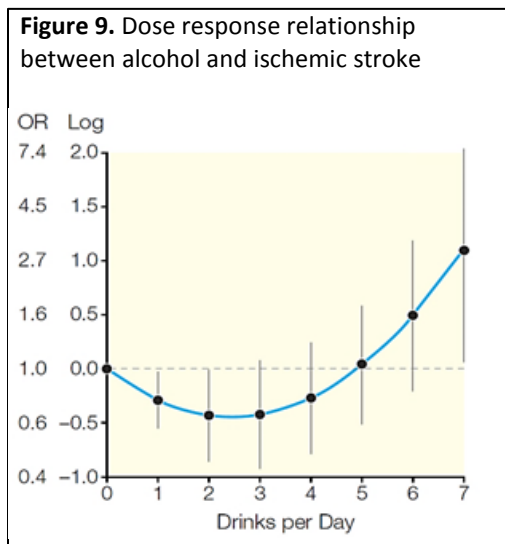
There were several strengths of this study. First, the authors assessed the reliability of alcohol measurement with test-retest methods and construct validity by comparing FFQ responses to the CAGE questionnaire. Other unique strengths include inclusion of minority populations (Blacks and Hispanics) and assessment of heavy drinking episodes (in sensitivity analysis former binge drinkers did not have an increased risk of stroke). Finally, the authors assessed potential bias that may have resulted from differential selection of control with respect to alcohol consumption. Bias-corrected estimates were similar for moderate and heavy drinking and slightly attenuated for intermediate drinking. Limitations include no adjustment for some potential confounders (diet, exercise, social support), adjustment for a potential causal intermediate (hypertension), and small numbers for subgroup analyses. Recall bias is possible among cases as is recall error due to stroke-related cognitive impairment. The temporality of alcohol exposure (i.e. the year prior to stroke) may not represent the period of effect. Finally, while the authors did attempt to address control selection bias, there remains potential for error, particularly if those heavy drinkers that participated are different from those that did not (i.e. were not adequate stand-ins for non-responding heavy drinkers). This study provides somewhat strong evidence for a relationship and is one of the most methodologically sophisticated studies of the alcohol-stroke relationship, limited primarily by its exposure measurement and selection bias as a consequence of the case-control design. White there were unaddressed methodological issues that may have biased the results, the authors performed several sensitivity analyses and were able to address many limitations of previous studies.

Key Study 3 – Framingham Study[165]

The Framingham study is a population-based cohort commenced in 1948. This analysis used data from the 5,209 participants in the original cohort who were re-examined biennially.[165] The average weekly number of drinks was collected at exams 2, 7, 9, 12, 15, and 17 and a standard drink

was defined as 360 mL of beer, 120 mL of wine or 37.5 mL of spirits. Exam 2 data were used to

identify former drinkers (nondrinker at exam 7 and a drinker at exam 2) and therefore follow-up

began at exam 7. In order to account for changes in alcohol consumption over time, the authors

divided the risk period into 3, 10-year periods in which alcohol was measured at each baseline

(examinations 7, 12, and 17). Alcohol consumption was categorized as never, 0.1-11, 12-23, ≥24

g/d, and former drinking of 0.1-11 and ≥12 g/d. Stroke events were detected at study examinations,

by daily surveillance of admissions to local hospitals, and outside hospital records. Adjudication of

strokes used information from medical records, radiographic images, medical history, and physical

examination findings. Because of the small numbers of hemorrhagic events, this analysis includes

only ischemic strokes. Cox proportional hazards models were run on the pooled 10-year risk sets

and adjusted for age, diabetes mellitus, and smoking.

Over the 30-year follow-up period, there were 441 ischemic strokes. There was a small

decreased risk of ischemic stroke for all current drinking categories relative to never drinking (Table

9). Results were largely similar for men and women.

Table 9. Risk and hazard ratio of IS according to total ethanol intake among participants of the Framingham Study

Ethanol, g/d	Case/Person-Years	Incidence Rate, Cases/1000 Person-Years	Age-Adjusted Hazard Ratio	Multivariate Adjusted Hazard Ratio*
Men				
Never	15/2300	6.5	1.0	1.0
0.1–11	59/10 035	5.9	1.0 (0.6–1.7)	0.8 (0.4–1.5)
12–23	24/4910	4.9	0.8 (0.4–1.6)	0.7 (0.4–1.4)
≥24	60/12 042	5.0	0.9 (0.5–1.6)	0.8 (0.4–1.5)
Former (0.1–11)	18/2703	6.7	0.8 (0.4–1.6)	0.8 (0.4–1.6)
Former (≥12)	20/1127	17.8	2.6 (1.3–5.1)	2.4 (1.2–4.8)
Women				
Never	54/9186	5.9	1.0	1.0
0.1–11	77/19 034	4.1	0.9 (0.6–1.3)	0.9 (0.6–1.3)
12–23	19/4670	4.1	0.8 (0.5–1.4)	0.8 (0.5–1.4)
≥24	28/6517	4.3	1.2 (0.7–1.9)	0.9 (0.5–1.5)
Former (0.1–11)	59/7151	8.3	1.1 (0.8–1.6)	1.0 (0.7–1.5)
Former (≥12)	8/1129	7.1	1.0 (0.5–2.0)	0.8 (0.4–1.7)

Values in parentheses are 95% CI.
*Adjusted for age, body mass index, smoking, and diabetes mellitus.

When authors stratified by age group (50-59, 60-69, and ≥70 y), there was a protective effect of current drinking at any level only among 60-69 year-olds. There is no convincing biological explanation for these age-specific results, but they could be due to chance or to different drinking patterns by age. Finally, no large differences in effect were seen by beverage type in analyses that compared current drinking with nondrinkers of each type. Relative risks were 0.8 (95% CI 0.6-1.0) for wine, 1.0 (0.8-1.4) for beer, and 0.9 (0.7-1.2) for spirits.

Ascertainment of strokes in this study was robust and the authors incorporated multiple exposure measurements into their analysis which are strengths relative to many other studies. Limitations include inability to assess drinking patterns, limited control of confounding, and a homogenous study population of primarily White individuals from a single geographic area. The effect estimates are likely biased from residual confounding and are imprecise due to low event numbers, limiting the strength of this study in assessing the relationship between alcohol and stroke.

Key Study 4 – Cardiovascular Health Study[166]

The Cardiovascular Health Study is a prospective study of 5,888 men and women aged 65 years and over from 4 U.S. communities starting in 1989. For the analysis of alcohol and stroke, 1,437 (24%) participants were excluded due to missing alcohol or pre-existing cardiovascular disease (MI, angina, TIA, stroke).[166] Alcohol consumption was measured at baseline and each subsequent year through 1999 using a beverage-specific quantity frequency questionnaire. Participants also reported whether they had recently changed drinking habits and whether they regularly consume 5 or more drinks per day. Incident ischemic strokes were ascertained by telephone calls and clinic visits that occurred every other 6 months over an average 9.2 years of follow-up. A panel of neurologists diagnosed stroke based on hospital medical records, test results, and imaging studies

using a definition of either a neurological deficit lasting at least 24 hours or imaging showing presence of a lesion.

In statistical analyses, alcohol was expressed as categories of drinks per week using long-term abstainers as the reference group. Models estimated relative risks of stroke in yearly increments using the previous alcohol exposure, thus allowing for changing drinking patterns over time. However, this approach assumes that the latency between consumption and stroke is one year in duration, which may not be appropriate. Models assessed individual effects of beverage types, modification by ApoE, and were adjusted for age, sex, race, marital status, smoking, depression, aspirin use, and BMI.

Light-to-moderate drinking was associated with reduced risk of ischemic stroke; heavy drinking was not associated with elevated risk (Table 10). Results were largely unchanged when assessing baseline alcohol consumption compared with updated alcohol exposure or across different beverage types. This suggests that changes in alcohol exposure late in life – after age 65 – are not contributing much to event risk and that the more important exposure period is mid-life.

Table 10. Relative risk of ischemic stroke according to usual alcohol consumption among CHS participants

| | Weekly Number of Drinks | | | | | | |
	None	Former	<1	1–6	7–13	≥14	P Value[‡]
Updated alcohol use							
Cases	179	90	68	45	22	30	
Person years	14 311	7950	7155	6030	2515	2795	
Basic model[*]	1	0.86	0.8	0.66	0.72	0.95	0.17 (0.02)
95% CI	…	0.66–1.11	0.60–1.06	0.47–0.92	0.45–1.13	0.63–1.43	
Full model[†]	1	0.87	0.85	0.75	0.82	1.03	0.52 (0.06)
95% CI	…	0.67–1.15	0.63–1.13	0.53–1.06	0.51–1.30	0.68–1.57	
Baseline alcohol use							
Cases	202	32	74	58	30	38	
Person years	16 409	3069	8017	7343	2540	3378	
Full model[†]	1	0.83	0.88	0.75	1.13	1.1	0.90 (0.05)
95% CI	…	0.55–1.25	0.66–1.16	0.55–1.03	0.74–1.72	0.76–1.61	

*The basic model adjusted for age, sex, race, education, marital status, and smoking;

† The full model adjusted for the covariates in the basic model and exercise intensity, depression score, frequent aspirin use, body mass index, and diabetes at baseline.

‡*P* values are derived from tests of linear (quadratic) trend.

ApoE genotype may be a modifier of the relationship between alcohol and stroke, with hazard ratios below the null among ApoE4 negative individuals, but over the null for higher levels of drinking among ApoE4 positive individuals (Figure 10). Results were highly imprecise and not greatly different in magnitude except for the high drinking categories. No significant interactions were found for sex, age, aspirin use, baseline hypertension, and atrial fibrillation.

Selection bias may be a concern in this study given the substantial portion of the cohort, almost one-quarter, that was excluded because of missing exposure or outcome data and from selection into the cohort (survival to age 65), which is likely related to both alcohol consumption and stroke risk. Another limitation was that exposure was assessed later

Figure 10.Risk of ischemic stroke according to baseline alcohol intake and ApoE genotype
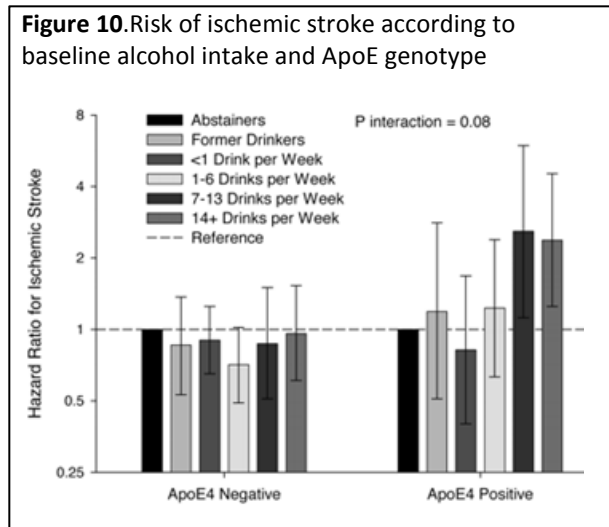
in life (age 65 or older) and may not represent the time period during which alcohol impacts risk. Finally, the prevalence of heavy drinking (2+ drinks/day) was low at 7%. In our proposed analysis of the ARIC study, missing data is much lower and alcohol is assessed at earlier ages; however, the prevalence of heavy drinking is similarly low (7.5%). Despite these limitations, this study provides supportive evidence for beneficial effects of moderate drinking but must be interpreted in light of the possibly large selection bias.

Key Study 5 – Health Professionals Follow-Up Study[167]

The Health Professionals Follow-up Study (HPFS) is a prospective cohort of 51,529 male health professionals aged 40-75 years at baseline in 1986.[167] Food frequency questionnaires captured beverage-specific alcohol quantity and frequency at baseline and at 3 additional occasions

roughly 4 years apart. A strength of the study was the assessment of the relative validity of FFQ self-reported alcohol compared with diet records and HDL-C. These validation results were discussed above in section 3.4.2; briefly, correlations were high for FFQ and diet records (0.79) and were as expected for HDL-C (0.31-0.35).   Non-fatal strokes were self-reported during follow-up questionnaires and confirmed by physician medical record review. Fatal strokes were ascertained from family reports and the National Death Index and confirmed with medical record review (84%), autopsy (2%), or using a combination of death certificate cause of death coding plus medical history and family reports (14%). Statistical analysis included a large number of potential confounders, updated as necessary over time, and included alcohol as a time-varying exposure. Potential causal intermediates such as blood pressure and HDL-C were not adjusted for in primary analyses.

There were 412 ischemic stroke events over 14 years of follow-up. Adjusted relative risks relative to no drinking were as follows: light drinking corresponding to ~<1 drink/day, RR=0.92, 95% CI 0.67-1.28; moderate drinking of roughly 1-2 drinks/day, RR=1.15, 0.82-1.61); heavy drinking ~2+ drinks/day, RR=1.22, 0.83-1.79). There was a slight trend for increased risk in the heavier drinking category; this was likely due to the wide range of drinking that comprised the heavy drinking category. There was no strong evidence that moderate drinking was associated with reduced risk of ischemic stroke. A second strength of this study design was the use of multiple measures of alcohol exposure. Interestingly, when results of updated alcohol analysis were compared with baseline only alcohol, there was an attenuation of the effect of heavy drinking, possibly because of averaging previous heavy drinking with later reductions in intake.

A third strength of the study methodology was the assessment of drinking pattern, which few studies have examined. Regular, moderate drinking defined as consumption of 1-2 drinks per day on 3-4 days per week was associated with a reduced risk of ischemic stroke (RR=0.68, 0.44-1.05) whereas drinking the same frequency, but more than 2 drinks per day was associated with an

increased risk (RR=1.47, 0.94-2.32; Table 11).

Table 11. Risk for ischemic stroke according to baseline frequency and quantity of alcohol consumption among 38,156 male health professionals.[167]

	Drinking Days per Week			
	0	**1-2**	**3-4**	**≥5**
Cases, n	93	101	57	161
Person years	123710	153326	83303	145564
Relative risk (95% CI)	1.00	0.87 (0.66–1.15)	0.87 (0.62–1.21)	1.14 (0.88–1.47)
Multivariate-adjusted RR (95% CI)	1.00	0.93 (0.70–1.24)	0.94 (0.66–1.32)	1.20 (0.91–1.58)

	Average Alcohol Use per Drinking Day						
	0	**< 30 g/d**	**≥30 g/d**	**< 30 g/d**	**≥30 g/d**	**< 30 g/d**	**≥30 g/d**
Cases, n	93	67	34	30	27	80	81
Relative risk (95% CI)		0.89 (0.65–1.22)	0.82 (0.55–1.21)	0.63 (0.42–0.96)	1.40 (0.91–2.16)	1.05 (0.77–1.42)	1.18 (0.87–1.60)
Multivariate-adjusted RR (95% CI)		0.95 (0.69–1.30)	0.89 (0.60–1.33)	0.72 (0.48–1.10)	1.47 (0.94–2.32)	1.17 (0.86–1.61)	1.25 (0.90–1.74)

* Relative risks are adjusted for age and smoking. Multivariate-adjusted relative risks are adjusted for age; smoking; body mass index; geographic region; parental history of myocardial infarction; physical activity; hypercholesterolemia; aspirin use; diabetes; and intake of vitamin E, folate, energy, saturated fat, trans fats, potassium, magnesium, omega-3 fatty acids, and dietary fiber.

The authors reported a somewhat stronger protective effect for red wine than for other beverage types. However, this analysis compared only 3 levels of drinking: none, <1 drink/day, and 1+ drinks per day. The apparent stronger effect of wine over other beverage types could reflect that the 1+ drinking category for wine contained fewer heavy drinkers than for other beverage types (because wine drinkers tend to be more moderate drinkers). Use of an open-ended category that could include both moderate and heavier drinkers severely limits the strength of these findings regarding beverage types.

Additional limitations of the study design and analysis include potential missed stroke cases that were not self-reported or correctly identified as the underlying cause of death on death certificates. While many potential confounders were available to the researchers, there was no adjustment for social support, which is associated with moderate alcohol consumption and

decreased stroke risk. Finally, there was no analysis of hemorrhagic strokes, low power for

subgroup analysis, only a minority of men were heavy drinkers (3.5% of men consumed >50 g/day),

and the results reflect a primarily white, high-SES population. Despite these limitations, this study is

one of the strongest published with careful attention to operational definition of the exposure and

analytic methods.

Key Study 6 – Nurses' Health Study & Health Professional Follow-Up[168]

The Nurses' Health Study (NHS) was established in 1976 as a prospective cohort of primarily

White women. Diet and alcohol intake were assessed at baseline and every 4 years thereafter

through 2002. This analysis was a pooled study using both the Nurses' Health Study and the Health

Professional Follow-Up Study, described above in 3.6.5.[168] Ascertainment of stroke in the NHS was

similar to the HPFS. Non-fatal events were ascertained from self-reports during follow-up and

confirmed with medical record review. Fatal cases were ascertained from next of kin, postal

authorities, and the National Death Index and confirmed using medical records, autopsy reports,

and death certificates with stroke listed as the underlying cause of death. The aim of this study was

to estimate effects of a low-risk lifestyle on incident stroke. 'Low-risk' for alcohol intake was defined

as consumption of 5-15 g/d of alcohol for women and 5-30 g/d for men. Additional stroke risk

factors included in analysis were smoking, exercise, healthy diet score, and BMI. Analyses were

adjusted for parental history of MI, regular aspirin use, vitamin E supplementation, and hormone

replacement therapy

Over follow-up there were 1,559 cases of stroke among women (853 IS, 278 HS, 428

unknown) and 994 among men (600 IS, 161 HS, 233 unknown). There was a protective effect of

light and moderate amounts of drinking for both ischemic and hemorrhagic stroke (Table 12).

Consumption over 30 grams per day (roughly 2 drinks) was associated with an increased risk of both

stroke types, except hemorrhagic events in men. These estimates must be interpreted with caution, however, as they are unadjusted for smoking, a strong confounder. Authors did conduct additional analyses for alcohol that were adjusted for smoking, BMI, diet, and daily exercise, but they report only relative effects of moderate drinking compared with other alcohol consumption levels. Slight reductions in the risk of ischemic stroke were found (RR=0.91, 95% CI 0.76-1.09 for women; RR=0.92, 0.77-1.09 for men). While analyses for the association of alcohol and stroke in this study were not as robust as other studies, the novel aspect of this study was the estimation of the population attributable fraction for low-risk lifestyle factors. More than half of ischemic strokes (54% in women and 52% in men) and a large portion of total strokes (47% in women and 35% in men) would have been prevented had all individuals in the population been shifted to the low-risk group that included not smoking, optimal BMI, daily exercise of at least 30 minutes per day, optimal diet score, and moderate alcohol intake.

Table 12. RR (95% CIs)* of Stroke by Categories of Alcohol Consumption (g/d) in Women and Men[168]

	Percent	Ischemic Stroke		Hemorrhagic Stroke		Total Stroke	
		Cases	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)
Women							
0	39	398	1.0 (Ref)	125	1.0 (Ref)	745	1.0 (Ref)
0.1–4.9	32	208	0.77 (0.65–0.92)	76	0.83 (0.62–1.10)	390	0.78 (0.68–0.88)
5–14.9	19	142	0.82 (0.68–1.00)	45	0.76 (0.54–1.06)	247	0.77 (0.66–0.89)
15–29.9	6	49	0.86 (0.64–1.16)	13	0.69 (0.39–1.23)	82	0.79 (0.63–0.99)
≥30	4	56	1.41 (1.07–1.88)	19	1.40 (0.86–2.28)	95	1.30 (1.04–1.61)
Men							
0	14	160	1.0 (Ref)	49	1.0 (Ref)	281	1.0 (Ref)
0.1–4.9	27	137	0.84 (0.67–1.06)	30	0.65 (0.41–1.03)	222	0.81 (0.68–0.97)
5–14.9	27	144	0.93 (0.74–1.17)	39	0.85 (0.55–1.30)	231	0.86 (0.72–1.03)
15–29.9	12	57	0.81 (0.60–1.10)	24	1.29 (0.78–2.13)	109	0.91 (0.73-1.15)
≥30	10	102	1.39 (1.08–1.79)	19	0.99 (0.58–1.71)	151	1.21 (0.99–1.49)

*RRs were estimated from Cox proportional-hazards models adjusted for age, calendar year, parental history of myocardial infarction at <60 years of age, regular aspirin use, and vitamin E supplementation, plus use of hormone therapy in women.

Possible sources of bias in exposure and outcome measurement are similar to those described for the HPFS above. Importantly, it appears that the risk estimates for alcohol consumption were unadjusted for other risk factors, i.e. smoking, physical activity, and diet, except in simple binary analysis of moderate intake vs. other intake. Finally, the population attributable fraction method used by the authors estimated a reduction in the event rate of strokes assuming a 100% shift in the population risk factor level to low-risk. Given that only 2% of women and 4% of men were classified as low-risk, this seems like an infeasible intervention. In the study population of NHS and HPFS, 19% of women and 38% of men were classified as moderate alcohol consumers, and therefore 'low-risk'. Furthermore, the intervention being considered was a shift in a combination of 5 risk factors and did not estimate effects of changing only alcohol consumption. For alcohol, assuming a 100% shift to moderate intake is improbable given that there are segments of the population that abstain for health-related or religious reasons or because of concerns of alcohol dependency. This study is not particularly useful in providing an unbiased estimate given the confounding bias, but is one of the few large cohort studies to publish recent analyses of attributable burden. The assumption of a complete elimination of harmful drinking is a major limitation to this methodology, however. Aim 2 of this proposal will extend these findings by using an approach to estimate effects of more moderate, achievable shifts in exposure.

Key Study 7 – Nurses' Health Study[169]

A recent publication on the association between alcohol and stroke is a re-analysis of the Nurses' Health Study.[169] The study population and methods of alcohol and stroke measurement were described above. This analysis improved on many of the limitations of that previous study. There were 2,171 strokes (1,206 ischemic, 363 hemorrhagic, and 602 probable strokes of unknown subtype) over a 26-year follow-up. Both baseline alcohol consumption and the cumulative average

exposure over follow-up were assessed. For the cumulative average exposure, alcohol was not

updated after development of disease. The authors adjusted for many confounders, particularly

those that few studies have considered such as diet scores, SES, and marital status (as a rough proxy

for social support). Finally, in addition to traditional categorical analysis, the authors estimated

dose-response relationships using nonparametric spline models.

There was a J-shaped relationship between alcohol and total stroke with minimal risk at

roughly 13 g/d and a threshold for harm beginning at approximately 30 g/d. Because of the low

drinking in this cohort, however, estimates at upper intakes are highly extrapolated and confidence

intervals are very wide. There was a reduced risk of ischemic and hemorrhagic stroke associated

with low-to-moderate intake compared with no intake (Table 13). No differences in effect estimates

were identified by beverage type.

Table 13. Multivariable association between alcohol and incidence of total, ischemic and hemorrhagic stroke

N=83 578		None	>0−4.9	5.0−14.9	15.0−29.9	30−45	P, Deviation From Linearity
				Alcohol Intake Categories, g/day			
Total stroke							
Events	2171	1045	552	341	131	102	
Smoking-adjusted	HR (95%CI)	1.00	0.74 (0.67–0.82)	0.66 (0.58–0.75)	0.71 (0.59–0.86)	0.94 (0.76–1.16)	<0.001
Multivariable model	HR (95%CI)	1.00	0.83 (0.75–0.92)	0.79 (0.70–0.90)	0.87 (0.72–1.05)	1.06 (0.86–1.30)	<0.001
Ischemic stroke							
Events	1206	566	318	196	65	61	
Smoking-adjusted	HR (95%CI)	1.00	0.78 (0.68–0.90)	0.71 (0.60–0.84)	0.67 (0.52–0.87)	1.06 (0.81–1.39)	<0.001
Multivariable model	HR (95%CI)	1.00	0.88 (0.76–1.02)	0.86 (0.72–1.02)	0.82 (0.63–1.07)	1.17 (0.89–1.54)	0.002
Hemorrhagic stroke							
Events	363	156	97	65	27	18	
Smoking-adjusted	HR (95%CI)	1.00	0.76 (0.59–0.98)	0.71 (0.53–0.96)	0.84 (0.55–1.27)	0.91 (0.55–1.49)	0.89
Multivariable model	HR (95%CI)	1.00	0.82 (0.63–1.06)	0.76 (0.56–1.03)	0.88 (0.58–1.35)	0.97 (0.58–1.60)	0.66

Multivariable model covariates: smoking, physical activity, body mass index kg/m², history of heart disease, family history of heart disease, history of diabetes, bilateral oophorectomy, postmenopausal status, use of hormone therapy, high cholesterol, multivitamin intake, aspirin intake, 6-nutrient diet score, highest level of education achieved, husband's level of education, and marital status.
CI indicates confidence interval; HR, hazard ratio.
*All models adjusted for age (mo).

The primary limitation of this study was the very low level of heavier drinking (65% of

women drank <½ glass/d and only 1% drank >45 g/d). Stroke ascertainment was from self-report or

death certificates, which are subject to error. Finally, there were few hemorrhagic stroke events,

minority individuals, and no assessment of drinking patterns. These limitations are relatively minor

compared with other studies and many are similar to those of other cohorts (low prevalence of

heavy drinking and few hemorrhagic events). While possibly not generalizable to all populations,

this paper was one of the stronger contributions to the literature when considering internal validity.

The authors paid careful attention to confounder selection, inclusion of multiple exposure

measurements, and assessment of dose-response. Our proposed study builds on these results by

including a bi-racial population of men and women thereby broadening its generalizability.

C. Meta-Analyses of the Association between Alcohol and Stroke[2, 6, 14]

A meta-analysis on the topic of alcohol and stroke was published by Reynolds et al. in 2003

and included all published English language papers from 1966 through April 2002 with relative risk

estimates comparing levels of alcohol consumption on the risk of total, ischemic, or hemorrhagic

stroke.[6] The authors identified 35 observational studies, 19 cohort and 16 case-control in design,

with sample sizes ranging from 1,621 to 107,137 and 89 to 677, respectively. Alcohol consumption

was standardized across studies and categorized as none, light (<12 g/d or <1 drink), light-to-

moderate (12-23 g/d or 1-2 drinks), moderate-to-heavy (24-60 g/d or 2-5 drinks), and heavy drinking

(60+ g/d or more than 5 drinks). Results are summarized in Table 14 and indicate that light-to-

moderate drinking was associated with lower risk of ischemic and hemorrhagic stroke relative to no

drinking while heavy drinking was associated with increased risk. Estimates for heavy drinking were

stronger for hemorrhagic than for ischemic stroke. Gender differences were noted, with women

experiencing stronger effects of both light and heavy drinking than did men for risk of total stroke.

The authors did not identify whether this gender difference in total stroke was present for both

ischemic and hemorrhagic strokes, nor were they able to assess race differences.

Table 14. Overall relative risk (95% confidence interval) of stroke associated with alcohol consumption and test for trend[6]

| | No. of Studies | Alcohol Intake, g/d | | | | P Value | |
		<12	12-24	24-60	>60	Test for Linear Association*	Test for Nonlinear Association
Overall	35	0.83 (0.75-0.91)	0.91 (0.78-1.06)	1.10 (0.97-1.24)	1.64 (1.39-1.93)		.002
Type of stroke							
Ischemic	15	0.80 (0.67-0.96)	0.72 (0.57-0.91)	0.96 (0.79-1.18)	1.69 (1.34-2.15)		.004
Hemorrhagic	12	0.79 (0.60-1.05)	0.98 (0.77-1.25)	1.19 (0.80-1.79)	2.18 (1.48-3.20)	.004	.17
Sex							
Men	27	0.89 (0.79-1.01)	0.94 (0.84-1.05)	1.08 (0.96-1.21)	1.76 (1.57-1.98)		<.001
Women	16	0.66 (0.61-0.71)	0.79 (0.56-1.11)	0.80 (0.49-1.30)	4.29 (1.30-14.14)		<.001
Study design							
Cohort	19	0.82 (0.73-0.92)	0.94 (0.84-1.05)	1.06 (0.90-1.23)	1.63 (1.49-1.79)		.02
Case control	16	0.80 (0.67-0.97)	0.65 (0.44-0.96)	1.12 (0.92-1.37)	1.98 (1.35-2.92)		.03

There was an apparent J-shaped curve for ischemic stroke, but a roughly linear association for hemorrhagic stroke in dose-response analysis (Figure 11). The J-shaped relationship between alcohol and total stroke was more pronounced for women than for men.

Figure 11. Scatterplot of log-RR and meta-regression curve of stroke associated with alcohol consumption by stroke subtype (top panel) and sex (bottom panel)
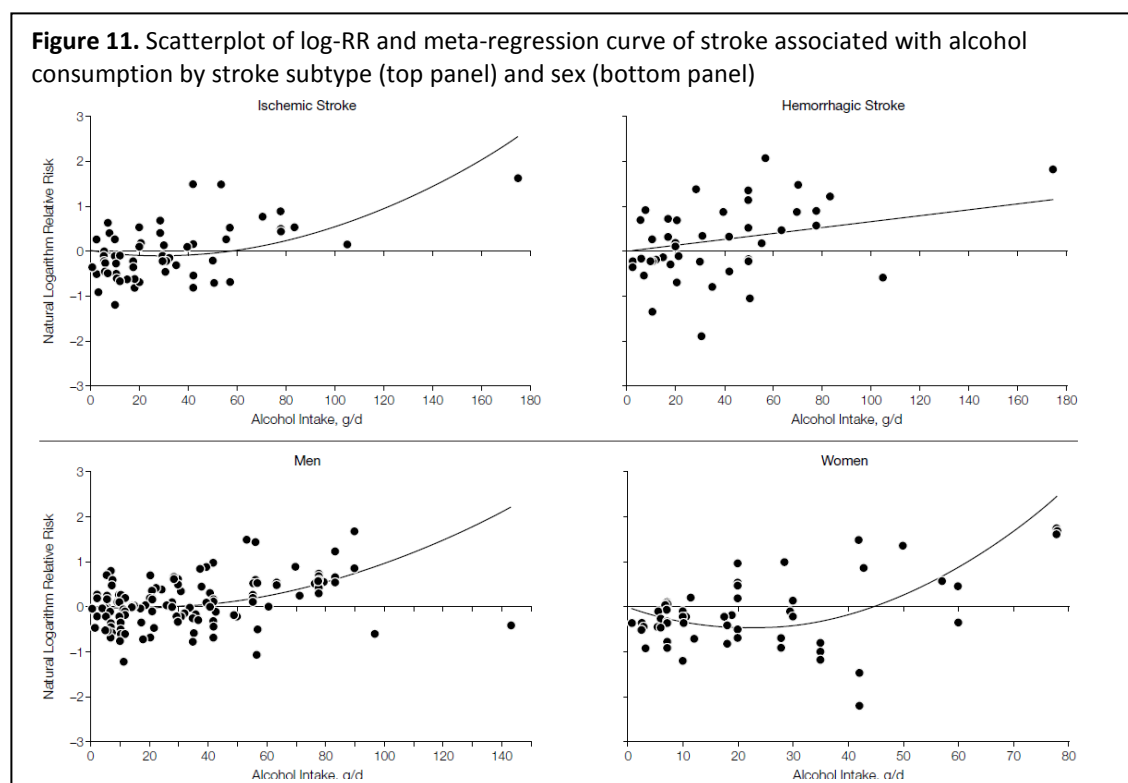
Results of this meta-analysis have limitations. The dose-response curve was highly extrapolated at higher alcohol consumption levels. The authors did not assess the separate effects of beverage type or drinking pattern on disease risk. There was no assessment of modification by

race-ethnicity and the analysis included point estimates that were adjusted for potential mediators as well as those whose referent groups included former drinkers. The authors did assess whether results were sensitive to the robustness of outcome ascertainment and adjustment for important confounders. Results were largely unchanged when restricted to studies using CT diagnosis of stroke, those controlling for important risk factors, and those excluding prevalent strokes at baseline. Finally, the authors found no evidence of publication bias in their analysis.

A second, more recent meta-analysis was published in 2010 by Patra et al. to assess the effect of alcohol on stroke subtypes and included 17 cohort and 9 case-control studies published from 1980 through June 2009.[2] All languages were included, but studies with fewer than 3 categories of alcohol consumption were excluded as were reports on total stroke only. Alcohol consumption was standardized across studies using country-specific ethanol content for standard drinks to convert results presented only as 'drinks per day'. Moderate alcohol intake was slightly protective for ischemic stroke for women and men while less so or not at all for hemorrhagic stroke (Figure 12). There was a tendency for light drinking of up to 3 drinks per day to reduce hemorrhagic stroke risk for women. Heavy drinking was associated with increased risk for both stroke types in men and women. There was suggestion that effects were stronger in women, but must be interpreted with caution as they are imprecise. The primary limitation of this meta-analysis is that many studies classified stroke type using death certificates or death registries as opposed to CT-based diagnosis. This could lead to considerable misclassification; however, the authors state that excluding these studies did not largely alter their results. The authors corrected for bias in the reference group (i.e., to have a uniform reference group of never drinkers) using statistical adjustment. This method corrected estimates with mixed reference groups based on results from effects among ex-drinkers compared with never drinkers and therefore may by subject to error.

Figure 12. Meta-analytic results of ischemic and hemorrhagic stroke incidence and mortality in women (panels A & C) and men (panels B & D)[2]
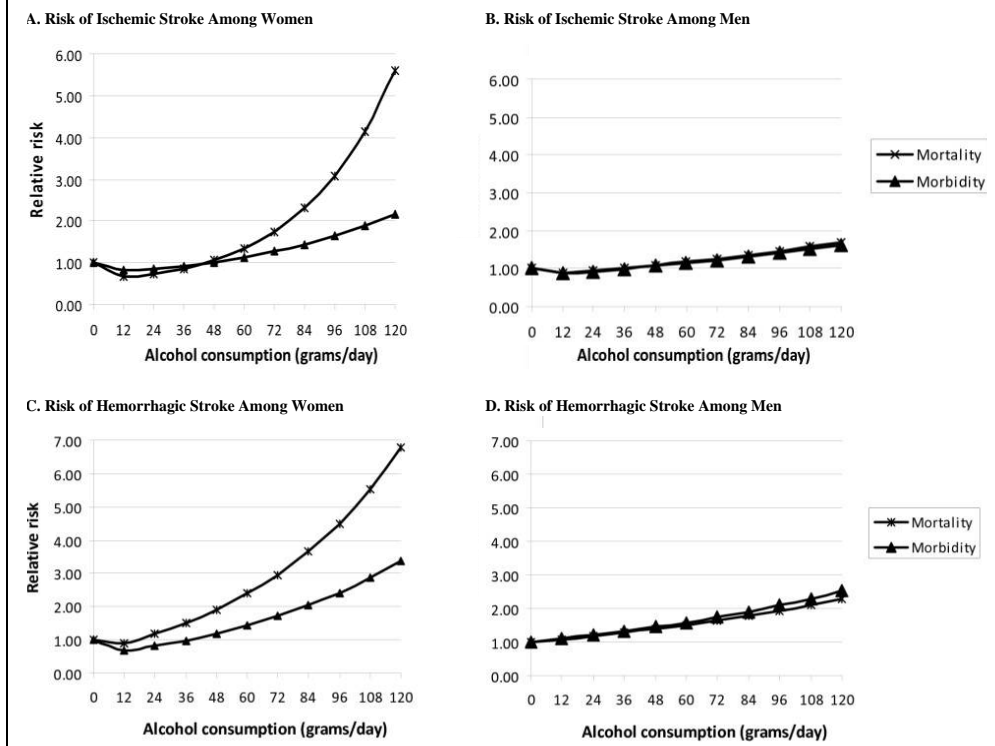
The most current meta-analysis was published by Ronksley et al. and included all prospective studies published from 1950 through September 2009 on the incidence and mortality from stroke.[14] There were a total of 10 studies of stroke mortality (sample size range from 286 to 89,299) and 17 of stroke incidence (N=427 to 128,934). Alcohol consumption was assessed according to average daily consumption, calculating grams as necessary using alcohol content in standard US drink portions. The pooled relative risk of incident stroke from 17 studies shows a reduced risk for light-to-moderate intake, with significant elevated risk evident at 60+ grams per day. For stroke mortality, a U-shape relationship was observed; the lowest risk occurred at 2.5-14.9 grams per day and was increased for 60+ grams per day (Table 15). The authors reported results by stroke type, but only comparing current drinkers with non-drinkers. For IS, the pooled relative risk (N=12 studies) was 1.14 (95% confidence interval 0.97-1.34) and for HS (N=8) was 0.92 (0.85-1.00). The primary limitation of this meta-analysis was that dose-response was assessed only for total

stroke and that the referent category of 'none' included studies that had combined never and former drinkers. Similar to the previous meta-analysis, the authors were unable to assess drinking pattern and beverage type and did not assess modification of the dose-response relationship between alcohol and stroke by sex or race.

Table 15. Stratified analyses of pooled relative risks (95% CI) for stroke outcomes.[14]

	Incident Stroke (n=17 studies; 458,811 subjects)	Stroke Mortality (n=10 studies; 723,571 subjects)
Active drinkers *v* lifetime abstainers	0.93 (0.85 to 1.02)	1.29 (1.09 to 1.53)
Former drinkers *v* non-drinkers	0.87 (0.72 to 1.07)	Not reported
Alcohol intake (g/day) *v* none		
<2.5	0.81 (0.74 to 0.89)	1.00 (0.75 to 1.34)
2.5–14.9	0.80 (0.74 to 0.87)	0.86 (0.75 to 0.99)
15–29.9	0.92 (0.82 to 1.04)	1.15 (0.86 to 1.54)
30–60	1.15 (0.98 to 1.35)	1.10 (0.85 to 1.45)
>60	1.62 (1.32 to 1.98)	1.44 (0.99 to 2.10)
Any current drinking *v* none		
Men	1.02 (0.92 to 1.13)	1.07 (0.89 to 1.28)
Women	0.87 (0.75 to 1.01)	0.81 (0.67 to 0.98)
Weak adjustment for confounding factors*	0.99 (0.86 to 1.13)	1.30 (1.11 to 1.52)
Strong adjustment for confounding factors	0.99 (0.89 to 1.09)	0.96 (0.81 to 1.14)
Short follow-up time†	0.98 (0.90 to 1.07)	1.01 (0.82 to 1.24)
Long follow-up time†	1.00 (0.88 to 1.13)	1.18 (1.02 to 1.37)

*Adjustment for confounding factors was dichotomized as weak (<median value) or strong (≥median value). Cut points: ≥5 for stroke mortality, ≥7 for incident stroke.

†Total follow-up time was dichotomized as short (<median value) or long (≥median value). Cut points: ≥12 for incident stroke, ≥14 for stroke mortality.

D. Gaps and Challenges for Future Research

While the meta-analyses above are able to address some limitations of previous individual studies, most notably small sample sizes and low power, they remain a summary of studies are subject to their same biases. Meta-analysis is particularly useful for obtaining more precise estimates of effect among heavy drinkers, a small proportion of most study cohorts, and for identifying potential sources of heterogeneity. It does not, however, ameliorate sources of bias in the parent studies. Some of the meta-analyses included older studies, which had more bias and

reflect experiences of populations that may have different drinking patterns from later cohorts.

Overall, the literature supports an increased risk of hemorrhagic stroke with heavy drinking, but varies as to the consumption level at which this increased risk begins. A J-shaped relationship between alcohol and ischemic stroke was found in many, but not all, studies. These inconsistencies may reflect heterogeneity in study populations, measurement of alcohol, ascertainment and validation of stroke events, and analytic methods.

Gaps in our knowledge and challenges in studying the alcohol-stroke relationship remain. Study designs to date have been observational cohort and case-control studies. While a randomized controlled trial would reduce the probability of confounding by design, it is infeasible for numerous reasons including ethical concerns of assigning individuals to alcohol consumption, lack of long-term compliance, and prohibitively long intervention and follow-up periods. Many cohorts in which the alcohol stroke relationship has been assessed include relatively high-SES, primarily White populations, with insufficient numbers of minorities. There is some evidence that effects may differ by race, particularly for Asian populations compared with Europeans;[170, 171] few studies exist to compare effects in U.S. Whites and African Americans and have had mixed findings.[39-41, 172] Selection bias is another concern of cohort studies. Heavy drinkers may be unlikely to be included in cohort sampling frames and to participate. It is uncertain if the heavy drinkers who do participate are representative of heavy drinkers overall and therefore whether the findings among heavy drinkers are generalizable.[131]

A primary limitation of all studies is exposure measurement error. Virtually all studies have used self-reported frequency and quantity measures as part of a food-frequency questionnaire. These are subject to reporting bias, particularly under-reporting by heavy drinkers, and do not adequately capture drinking patterns without supplemental questions. Under-reporting of heavy drinking may change the shape of the dose-response curve and suggest a lower threshold for safety

than is actually true (by moving higher-risk individuals to lower exposure levels and artificially elevating this group's risk). Biomarkers for validation of self-reports have limitations, but may be useful for validating heavy drinking in future studies. Validation studies to date rely primarily on instruments that may not have independent errors and therefore development of measures with independent errors would allow greater confidence in estimation of error. Assessment of drinking pattern (i.e. regular vs. episodic) is important for future studies and very few to date have examined consumption as anything other than average exposure.[167, 173, 174] Fewer still consider the time-varying nature of alcohol consumption. Drinking patterns and quantities change over the life course for many individuals. [69, 71] As such, a single measurement may not accurately reflect long-term exposure depending on the timing of measurement, i.e. if measured in older age as compared with mid-life. This is a particularly important consideration given that the biological mechanisms suggest many of the effects of alcohol on stroke risk accumulate over many years. Analysis of the effects of different beverage types was carried out by a fair number of studies.[165-167, 169, 175, 176] These analyses were under-powered and complicated by additional confounding; for example, wine drinkers tend to be healthier, non-smoking, female, and of higher SES and have different drinking patterns from beer drinkers.[131] Outcome measurement errors may be present in studies that had incomplete ascertainment (e.g. missing non-hospitalized cases), misclassification of diagnosis, and errors in classification of stroke type. These errors are particularly a concern for studies that use non-overlapping methods of ascertainment, do not adjudicate events, or rely solely on administrative data to ascertain events and determine stroke subtype. Separation of ischemic and hemorrhagic types in analyses is important given their different etiologies; however, many studies estimated effects of alcohol on total stroke.[174, 177-185]

Several analytic limitations exist among previous studies. Few have addressed the time-varying nature of alcohol consumption[165-167, 169, 186-188] and the separate effects of drinking pattern

and average quantity of consumption.[167, 173, 174] Most studies categorize alcohol consumption,

sometimes into broad categories. These categories often differ across studies, precluding easy

comparison of results. In addition, most studies assessed 'dose-response' relationships by way of

category-by-category comparisons to a single referent group using multiple significance tests

instead of estimating the dose-response with flexible models. Finally, early studies and some recent

ones included never and former drinkers in the referent group.[41, 42, 164, 168, 174, 176-179, 181-183, 185, 187-194]

Individuals with health problems may stop drinking, artificially elevating risk among the referent

group if combined with never drinkers.[131] Solutions are to separate ex-drinkers from never drinkers

and/or to exclude early outcomes that may result from pre-existing disease.[171] Residual

confounding is a concern in most previous studies, particularly from difficult to measure variables

such as SES and social support and strong confounders like smoking that were only crudely

operationalized (i.e. yes vs. no). Cardiovascular conditions such as hypertension, atrial fibrillation,

cardiomyophathy, and heart disease are affected by alcohol and may in turn affect risk of stroke.

Whether to treat these as confounders or causal intermediates depends on their temporal relation

with the exposure and outcome and is difficult to determine in many studies that do not have

multiple assessments over follow-up. Finally, most studies estimate relative effects of alcohol

consumption. Few report absolute measures, which are more easily interpreted and less likely

skewed by small baseline risks, or measures of population burden, which provide data on the

potential public health impact of interventions.

The study proposed herein will address several of the limitations of previous research. First,

stroke ascertainment and validation is robust and included multiple overlapping ascertainment

methods coupled with physician validation of suspected cases. Alcohol was measured at 4 time

points over follow-up, providing information about cumulative and time-varying exposure.

Questions were included in the alcohol survey to differentiate former and never drinkers, as well as

to separate effects of quantity and frequency at later visits. The statistical approach will include careful consideration of numerous confounders identified and analyzed using directed acyclic graphs as well as effect measure modifiers. This technique will minimize confounding bias and prevent inappropriate adjustment for causal mediators. Some limitations will remain; most notably exposure measurement error (i.e. under-reporting of consumption), survival bias, and under-representation of heavy drinkers in the study population.

3.7 Studies Assessing the Relationship Between Alcohol and Cognitive Decline

A. Overview

The body of literature on alcohol and cognitive decline is not as fully developed as for stroke and heart disease. There have been a number of studies that assessed the cross-sectional association between alcohol intake and cognitive function.[195-199] These have mixed findings, with several reporting a possible beneficial effect of moderate drinking. They are hardly conclusive, however, because of strong selection biases and potential for reverse causality. Other studies have examined the relationship between alcohol and dementia.[19, 20, 22-24, 26, 200, 201] There is good support for reduced risk associated with moderate intake, and some analyses identified a U-shaped dose response relationship similar to that reported in studies of alcohol and cardiovascular disease. A meta-analysis in 2008 reported that moderate alcohol intake was associated with reduced risk of dementia (RR=0.63, 95% CI: 0.53-0.75) and Alzheimer's disease (0.57, 0.44-0.74) and smaller reductions in risk of vascular dementia (0.82, 0.50-1.35) and cognitive decline (0.89, 0.67-1.17).[63] A major limitation of these studies is that many rely on prevalent cases of dementia and have significant survivor bias. Individual studies of cognitive function and dementia will not be reviewed in further detail as our focus is on cognitive decline.

Studies of alcohol and cognitive decline are relatively few in number and overall are methodologically weak, providing limited evidence for an association. As a whole, the body of literature is less strong and not as advanced as for alcohol and stroke. Very few studies have assessed the sensitivity of results to sample attrition (drop-out and death), which was considerable in most cohorts. Furthermore, few have long-term follow-up, utilize appropriate models to examine changes in cognition over time, or assess drinking patterns, beverage types, or time-varying alcohol exposure. Additional limitations include inclusion of mostly White populations, restriction to older adults at baseline, and infrequent cognitive assessments. Roughly a dozen papers examining alcohol and cognitive decline were identified (Appendix 3). Most measure cognitive decline using global cognitive measures including the MMSE, 3MS, and TICS. Many estimate mean changes in scores, but some estimate the odds of 'significant' decline, which results in loss of information. Below are described 4 studies that in this author's opinion represent the highest quality published reports.

B. Description of Four Key Studies

Key Study 1 – Women's Health Initiative Memory Study[21]

The Women's Health Initiative Memory Study (WHIMS) is an ancillary study of a randomized-controlled trial of hormone therapy that enrolled women aged 50-79 beginning in 1996. Alcohol consumption was assessed at baseline as part of a food frequency questionnaire. Beverage-specific usual consumption (drinks per day) was collected as was status as a former drinker or lifetime abstainer. Alcohol intake was broadly categorized as none, <1 drink per day, and 1 or more drinks per day. Global cognitive function was assessed at baseline and each year for 6 years using the 3MSE. Attrition was significant in this cohort, reaching 17% by Visit 4 and 98% by Visit 6. Logistic regression was used to estimate the association between baseline alcohol intake and a dichotomized outcome (≥8 point drop in 3MSE any time during follow-up).

Compared with no alcohol intake, consumers of either <1 drink per day or 1+ drinks per day had lower odds of cognitive decline of 8 points or more (Table 16).

Table 16. Odds ratios for occurrence of clinically significant declines of 8 or more units in 3MSE score from baseline, Women's Health Initiative Memory Study, 1996-2002[21]

Variable	Relative to no alcohol intake				*p* value (all pairwise differences)†
	<1 drink per day		≥1 drink per day		
	Odds ratio	95% CI*	Odds ratio	95% CI	
No additional covariates	0.56	0.41, 0.77	0.40	0.22, 0.72	<0.001
Adjusting for socioeconomic status/lifestyle‡	0.67	0.48, 0.95	0.51	0.27, 0.94	0.025
Adjusting for clinical characteristics§	0.58	0.42, 0.80	0.41	0.23, 0.74	<0.001
Adjusting for all covariates	0.69	0.49, 0.97	0.53	0.28, 0.99	0.042

* 3MSE, Modified Mini-Mental State Examination; CI, confidence interval.
† Results from analysis of covariance.
‡ Age, no. of years since menopause, education, ethnicity, family income, and smoking status.
§ Body mass index, hypertension status, prior cardiovascular disease, diabetes, prior hormone therapy, statin use, and aspirin use.

This study has several limitations that make conclusions difficult to draw regarding a causal effect of alcohol on cognitive decline. First, the follow-up time was short (mean 4.2 years) and alcohol was broadly classified and based on measurement at one point in time. The highest intake group was open-ended and could represent a heterogeneous mix of drinkers. More problematic is the analytic approach, which dichotomizes decline based on only 2 3MSE measurements instead of estimating mean declines over time in each group. Missing data and cohort attrition are not accounted for and could substantially bias results. Finally, the study population was highly selected, primarily high-SES White women participating in a clinical trial, which may both limit generalizability and represent a healthy selection bias.

While this study is stronger than many others of alcohol and cognitive decline, it has several major limitations such that it only provides modestly convincing evidence in support of an association between alcohol and cognitive decline.

Key Study 2 – Nurses' Health Study[1]

This analysis of the Nurses' Health Study (described in Section 3.6.6) included women aged 70+ years in 1995 with no history of stroke. Cognitive function was assessed using the Telephone Interview of Cognitive Status (TICS) and in 1997 included additional tests to assess verbal memory (East Boston Memory Test and delayed recall of the TICS 10-word recall), verbal fluency, and working memory and attention (digit span backward test). A global cognitive score was calculated by averaging all z-transformed test scores. Alcohol consumption was measured using the reported intake at the last visit that occurred before baseline cognitive assessment, 1994 for most women. Alcohol was categorized as none, 1.0-14.9 grams per day, and 15-30 grams per day. Analyses of cognitive decline used logistic regression to estimate effects of alcohol consumption on 'substantial decline', which was defined as a change in the lowest 10% of the distribution of decline. The mean duration of follow-up was short, only 1.8 years. Models were adjusted for baseline cognitive score to account for learning effects, ceiling effects, and within subject variability. Additional covariates are listed in Table 17.

Adjusted baseline scores for all tests were slightly lower for drinkers of 1-14.9 grams per day than nondrinkers and lower for drinkers of 15-30 grams per day. Odds of substantial decline in cognition over an average of 1.8 years were lower for both groups of drinkers compared with nondrinkers (Table 17).

Table 17. Relative risks of a substantial decline in cognitive function over a 2 year period, according to alcohol intake[1]

Measure of Substantial Cognitive Decline*	No. Who Completed Test	None†	1.0–14.9 g/day	15.0–30.0 g/day
			relative risk (95 percent confidence interval)	
TICS score for worst 10% of distribution of decline				
Adjusted for age and level of education	11,102	1.00	0.82 (0.72–0.95)	1.00 (0.74–1.35)
Multivariate-adjusted		1.00	0.85 (0.74–0.98)	1.04 (0.77–1.41)
Verbal memory score for worst 10% of distribution of decline	9,670			
Adjusted for age and level of education		1.00	0.82 (0.71–0.95)	0.78 (0.55–1.10)
Multivariate-adjusted		1.00	0.83 (0.72–0.97)	0.76 (0.54–1.09)
Global cognitive score for worst 10% of distribution of decline	9,661			
Adjusted for age and level of education		1.00	0.86 (0.74–0.99)	0.81 (0.58–1.13)
Multivariate-adjusted		1.00	0.89 (0.77–1.03)	0.82 (0.58–1.16)

* TICS denotes the Telephone Interview for Cognitive Status. The verbal memory score combines the results of immediate and delayed recall of both the TICS 10-word list and the East Boston Memory Test. The global cognitive score is the average of the results of all cognitive tests. Multivariate-adjusted relative risks were adjusted for age; level of education; the presence or absence of a history of hypertension, diabetes, high cholesterol levels, and heart disease; level of physical activity; age at menopause; use or nonuse of postmenopausal hormone therapy, aspirin and ibuprofen, and vitamin E supplements; body-mass index; smoking status; scores for the mental health and energy–fatigue indexes on the SF-36; score for the Berkman–Syme Social Network Index; and the interval between the most recent interview and the baseline cognitive assessment.
† Nondrinkers served as the reference group.

There were several sources of selection bias in this study that were not addressed in the analytic approach. Selection into the cohort, i.e. survival to age 70, is a large source of bias. Additionally, ~40% of eligible women did not participate in the baseline cognitive assessment and an additional 10% of participants were lost to follow-up through death or drop-out prior to the second cognitive assessment. Finally, missing data for individual tests resulted in a total attrition between baseline and follow-up of 23% of the sample for the global cognitive function measure. Alcohol exposure was defined using a single measurement taken immediately before cognitive assessment after age 70. It is possible that this exposure did not represent exposure over a longer period, particularly the period of critical effect and that it was affected by early cognitive changes. Given that the NHS collected alcohol at 5 times over a 15-year period prior to cognitive assessment, the authors could have operationally defined alcohol intake more rigorously. For example, by calculating cumulative average exposure, modeling time-varying intensity and duration independently, or by estimating trajectories of drinking patterns. Finally, the analytic approach did not estimate the degree of cognitive decline because the outcomes were dichotomized. While

results may be more easily interpreted in this manner, categorizing a continuous outcome results in loss of information and may be sensitive to cut-point selection. Models were adjusted for baseline cognition, which is controversial and may bias estimates.[202] No sensitivity analyses were presented comparing results with and without this adjustment.

This study has stronger measurement of exposure and outcome than many other studies in Appendix 3, but has significant limitations in its design - with only 1.8 years of follow-up – and the statistical approach. It provides only modest evidence of a beneficial effect of alcohol on cognitive decline. It provides no information on declines over longer periods of time, starting at younger ages, or among men or African American populations. Our study will build upon these results by including African Americans, having longer follow-up and estimating rates of decline.

Key Study 3 – Prospective Study of Pravastatin in the Elderly at Risk[32]

The Prospective Study of Pravastatin in the Elderly at Risk is a randomized trial of adults from Scotland, Ireland and the Netherlands aged 70-82 at baseline who had vascular risk factors or vascular disease. Alcohol intake over the last month was measured at baseline and categorized as usual intake per week according to data-driven cut-points. Cut-points were selected to provide equal sized groups (cutpoints: <3 units per week for women and <7 units per week for men). Cognitive function was assessed at baseline and at 9, 18, and 30 months and again at the end of the trial (~3 years). Cognitive tests included those for global cognition (MMSE), attention and processing speed (Stroop Color-Word test, Letter-Digit Coding test), and memory (Picture-Word Recall Test). Sex-stratified linear mixed models were used to estimate the rate of decline across alcohol categories adjusting for age, country, smoking status, BMI, body weight, education, incident stroke, history of vascular disease, and baseline cognitive score.

Cognitive scores over the length of follow-up were better for female drinkers compared

with nondrinkers for all tests, but not for male drinkers compared with male nondrinkers. Models

with time interactions showed that female non-drinkers declined faster than female drinkers on the

MMSE score but not on other tests (Table 18). No differences in cognitive decline were seen for

men across alcohol categories.

Table 18. Longitudinal analysis of cognitive decline and alcohol intake by sex[32]

	Annual Change	Mean Difference over Time Between Alcohol Groups		
	All Subjects	Moderate vs. None	Low vs. None	Trend
	Estimate (SE) p-value			
Women				
MMSE	−0.02 (0.01) .04	0.09 (0.02) <.001	0.07 (0.02) .001	0.05 (0.01) <.001
Stroop	0.60 (0.12) <.001	−0.13 (0.22) .56	−0.19 (0.23) .40	−0.08 (0.11) .46
LDCT	−0.32 (0.03) <.001	0.03 (0.05) .49	−0.06 (0.05) .24	0.01 (0.02) .73
PWRTi	−0.03 (0.01) .005	0.02 (0.02) .27	0.02 (0.02) .29	0.01 (0.01) .21
PRWTd	−0.07 (0.02) <.001	0.02 (0.03) .54	−0.02 (0.03) .60	0.01 (0.01) .66
Men				
MMSE	0.002 (0.02) .89	0.01 (0.02) .68	0.01 (0.02) .69	0.004 (0.01) .69
Stroop	0.90 (0.18) <.001	−0.28 (0.24) .24	−0.45 (0.24) .06	−0.13 (0.12) .28
LDCT	−0.37 (0.04) <.001	0.01 (0.05) .82	0.02 (0.05) .67	0.005 (0.03) .84
PWRTi	−0.01 (0.02) .53	−0.02 (0.02) .33	0.01 (0.02) .60	−0.01 (0.01) .33
PRWTd	−0.07 (0.02) .001	0.001 (0.03) .97	0.04 (0.03) .18	−0.001 (0.02) .94

A major advantage of this study over many others is the use of analytic methods that

incorporated all cognitive scores over follow-up. These models, however, adjusted for baseline

cognitive status and did not account for attrition and missing measurements (21% of the cohort).

Primary limitations included a short follow-up time (3 years) and broad grouping of alcohol

consumption based on sample size driven cut-points that do not necessarily reflect the underlying

dose-response relationship. In summary, this study is one of the stronger studies reviewed, with

more robust measurement of outcome and analytic techniques than others. The likely exposure

misclassification and error in exposure assessment is a serious limitation and renders the study of

modest overall quality.

Key Study 4 – The Northern Manhattan Stroke Study[34]

NOMAS (described in Section 3.6 Section B) included 3298 stroke-free participants at

baseline starting in 1993. A structured alcohol questionnaire assessed average consumption in the

past year as well as over the life course. In 2001, a follow-up questionnaire assessed intake over the

past 6 months, which was the measurement used to define alcohol exposure for this analysis. Also

in 2001, a telephone cognitive interview was conducted using the TICS-m on the ~80% surviving

cohort and was repeated annually thereafter. Forty-three percent of those who had an initial TICS-

m were lost to follow-up or died. Generalized estimating equations were used to assess change in

TICS-m over time, adjusted for the covariates shown in Table 19.

At baseline, the mean TICS-m score was 29 among never drinkers, 30 among past drinkers

and those consuming less than 1 drink per week, 33 among those drinking 1-14 drinks per week, and

35 among those drinking over 14 drinks per week. Over a mean follow-up of 2.2 years, the average

decline in TICS-m was slower among current drinkers than never drinkers. This was attenuated in

adjusted models, but the dose-response relationship was maintained (Table 19).

This study is similar in quality to Stott et al., reviewed above. The follow-up was short and

the assessment of exposure could have been improved. However, the study had unique strengths in

comparison to the majority of other studies by utilizing more appropriate analytic methods and

measuring cognitive status at multiple times over follow-up. The authors chose to condition on

several potential mediators (e.g., HDL-C, stroke, and hypertension), did not adjust for possible

confounders (e.g., social support), and did not account for attrition, all of which may have biased

estimates. Overall, this study provides modest support for a decrease in the rate of cognitive

decline associated with light to moderate alcohol consumption compared with abstention.

Table 19. Relation between reported alcohol intake and performance on repeated measures of TICS-m[34]

		Reported alcohol intake							
	Never	**Past**			**1 dk/m to < 1 dk/wk**		**1 dk/wk up to 2 dk/d**		**>2 dk/d**
		β (95% CI)	P	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P
Model 1	Ref	β[†] =0.6 (−0.2,1.3)	0.14	β =1.5 (0.5,2.5)	0.003	β =2.2 (1.3,3.0)	<0.0001	β =2.9 (1.4,4.4)	0.0002
Model 2	Ref	β =0.3 (−0.4,1.1)	0.40	β =1.0 (0.03,1.9)	0.04	β =1.6 (0.7,2.4)	0.0003	β =2.1 (0.6,3.6)	0.008
Model 3	Ref	β =0.4 (−0.4,1.2)	0.36	β =0.9 (-1.2,1.9)	0.09	β =1.5 (0.6,2.4)	0.001	β =2.4 (0.8,4.0)	0.003

[*]TICS-m – modified Telephone Interview for Cognitive Status.
[†]Beta coefficient represents the change in points on the TICS-m over time compared to never drinkers; positive denotes better scores.
Model 1 – Adjusted for age and education.
Model 2 – Model 1 + gender, race-ethnicity, and insurance status.
Model 3 – Model 2 + history of hypertension, diabetes, cardiac disease, physical inactivity, depression, current smoking, HDL-C level, and BMI.

C. Summary and Gaps in the Current Literature

There are several gaps in the literature on the association between alcohol and cognitive decline. In general, alcohol intake was measured at a single point in time - often late in life at the start of cognitive measurement – and was summarized as average consumption.[1, 21, 27-35] No study of which the author is aware assessed time-varying alcohol exposure or the effect of different drinking patterns on rate of cognitive decline. One study did categorize participants according to rough drinking patterns, such as 'habitual users' and 'social users', but this categorization utilized exposure data collected after measurement of cognitive function which may result in misclassification and immortal time bias. Putative effects of alcohol on cognition are cumulative and occur over decades of exposure. Baseline only definition of intake occurring relatively late in life is likely subject to misclassification. Furthermore, the referent group in some studies was mixed, including both former and nondrinkers and can result in biased estimates.[21, 28, 29, 31, 32, 35]

Sophisticated analytic approaches for modeling repeated outcome data were used by a few researchers,[27, 32, 34-36] and only one attempted to assess or correct for selection bias due to

attrition.[27] Cognitive decline was dichotomized in several of the analyses which is not as informative

for quantifying the degree of decline among alcohol groups.[1, 21, 28, 35] Another major limitation,

particularly in studying cognitive decline, is the short follow-up of these cohorts. Most were

followed for fewer than 5 years.[1, 21, 27-32, 34] Confounding bias may be a problem in many studies,

with some results not being adjusted for SES, smoking, social support, depression, diet or physical

activity,[1, 28-32, 34-37] and others adjusted for possible effect mediators including hypertension, HDL-C,

and incident stroke during follow-up.[1, 21, 27, 30-32, 34, 35] Finally, several studies only used the MMSE to

measure cognitive changes. This neuropsychological assessment is relatively insensitive to changes

at the higher end of cognition and is not the best tool for large population-based studies of

cognitively normal individuals, particularly with high levels of education.[28, 30, 31, 37]

The ARIC study shares some limitations with others including the small proportion of heavy

drinkers, high degree of participant attrition over time, and reliance on self-reported alcohol

consumption, which is subject to reporting errors and under-reporting of intake. The ARIC study

data are well suited to address many of the limitations of previous studies, however. First, there are

multiple measures of alcohol over a long period of follow-up that capture mid-life consumption.

Other unique strengths of the ARIC study design are long-term follow-up (20 years) with multiple

measurements of cognitive performance beginning at ages 48-67, assessment of many confounders

and effect measure modifiers, and inclusion of a biracial population. Not much is known about non-

White populations, with only a few studies examining effects in minority populations.[198]

Furthermore, the approach proposed herein will improve on previous research by estimating group

differences in the rate of decline using repeated measures and will include correction for selection

bias from drop-outs and deaths. Methods to account for attrition are critical because cognitive

impairment is known to be associated with drop-out and mortality.[60]

3.8 Public Health Significance

Stroke and cognitive decline are important targets for public health prevention. Both are associated with significant morbidity and heath care costs and are estimated to increase over the next few decades due to longer life expectancies and demographic population changes.[51, 52] Stroke is a leading cause of mortality in the US and worldwide. Approximately 1 in 3 Americans will have a stroke or develop dementia in their lifetime, underscoring the need for continued examination of potentially modifiable risk factors for these diseases.[9] Furthermore, given the current lack of treatments for dementia, understanding modifiable factors to prevent or delay cognitive decline and dementia onset is critical. One study estimated that delaying the onset of AD by 1 year would potentially prevent 12 million cases in 2050.

Alcohol has been studied as a potential factor in the etiology of both stroke and cognitive decline, with many studies reporting decreased risk associated with moderate intake and increased risks with high average intakes and harmful patterns of drinking. There are biologically plausible pathways to support the beneficial effects of moderate drinking including positive effects on HDL-C levels, platelet aggregation, fibrinogen levels, insulin sensitivity, antioxidant activity, and blood pressure. Harmful effects of heavy drinking include increased blood pressure, neurotoxicity, risk of atrial fibrillation and cardiomyopathy, decreased cerebral blood flow, elevated state of inflammation, and insulin insensitivity. Research to date, however has been inconsistent with regard to the effects of moderate intake and is subject to methodological limitations that preclude drawing strong conclusions about causal relationships. A comprehensive technical report from the US National Institutes of Health on evidence for the prevention of dementia and cognitive decline found that evidence supporting a beneficial role of alcohol is weak.[33, 203] The authors recommend additional research from rigorous population-based studies with careful control of confounding.

Estimating this association in a study with long-term follow-up, multiple measurements of alcohol intake and cognitive performance, will contribute additional knowledge to this topic.

With a large proportion of adults reporting current drinking (70%) and considerable numbers reporting heavy or episodic drinking (30% of adults; 20% of men >60 years) there could be significant impact on stroke and cognitive impairment burden by reducing harmful drinking behaviors.[68, 70] The total burden of stroke due to alcohol will depend on the prevalence of alcohol consumption, alcohol's effects on the two major stroke types, and their relative prevalence in a given population. Estimating impact fractions of changes to current alcohol consumption patterns in the US on stroke incidence has not been done to this author's knowledge and, if feasible, represents a novel component of the proposed study.

CHAPTER 4. RESEARCH METHODS

4.1 Study population

The ARIC cohort will serve as the study population for Specific Aims 1-3 and is described below in general terms. Inclusion and exclusion criteria specific to each Aim will be described in greater detail in future sections that delineate the research plans for each Specific Aim.

The ARIC study is a population-based cohort recruited using probability sampling of adults 45-64 years of age from four US communities: Forsyth County, NC; Jackson, MS; the suburbs of Minneapolis, MN; and Washington County, MD. Institutional review boards from each site approved the ARIC study and all participants provided written informed consent. The ARIC study design and rationale are described in detail elsewhere.[204] The racial distribution of the sample from Minneapolis and Washington County is primarily white and is representative of the area. Blacks were oversampled in Forsyth County and exclusively sampled in Jackson. The response rates were modest, 46% in Jackson and 65-67% for the other communities. A total of 15,792 participants were enrolled at visit 1 in 1987-1989 and underwent an in-home interview and physical examination. During annual follow-up telephone calls, ARIC investigators obtained information on hospitalizations and medical history over the preceding year. Four additional study visits consisting of an interview and physical examination occurred over the subsequent 25 years, with return rates of 91% at visit 2 to 70% at visit 4.   Much of the attrition at later visits is attributable to death (5% at visit 4) and visit nonattendance (14% at visit 4). Comparisons of responders and non-responders at visit 1 (based on data from the 75% of non-responders that completed the in-home interview) have been reported.[205] Briefly, white respondents were more highly educated, had higher incomes, reported better health status, and were less likely to be current smokers than white non-respondents. Black respondents

had more education and less current smoking than black nonrespondents. In general, differences by response status were smaller for blacks than for whites.

Table 20 below shows descriptive statistics for the ARIC cohort at baseline in terms of demographic characteristics, cardiovascular risk factors, prevalent disease, and self-reported alcohol consumption. Black participants comprised 27% of the sample and women 55%. Current alcohol consumption at baseline was reported by 25% of the sample, lifetime abstention by 19% and former drinking by 32%.

Table 20. Selected characteristics of ARIC cohort participants at Visit 1, 1987-1989

Characteristic	Proportion or mean (SD)
Age, years	54 (5.8)
Sex-Race Group	
White men	34.4
Black men	10.3
White women	38.3
Black women	16.7
Highest level of education	
Grade school	9.7
High school (no degree)	14.1
High school graduate/vocational school	40.6
College or higher	35.4
Body mass index, kg/m^2	27.7 (5.4)
HDL-cholesterol, mg/dL	37.3 (11.1)
Hypertension	35.0
Diabetes mellitus	12.0
Prevalent myocardial infarction	4.2
Smoking	
Never	41.7
Former	32.1
Current	26.2
Alcohol consumption	
Lifetime abstainer	19.0
Former drinker	55.5
Current drinker	25.0

4.2 Research Plan for the Assessment of Alcohol and Stroke (Aims 1 and 2)

A. Analytic Sample

The study population will exclude 1) participants not classified as white or black because of our interest in race as a potential modifier (N= 48); 2) participants missing alcohol at baseline visit

(N=106); and 3) participants with a history of stroke at baseline (N=284). Total participants excluded

were 434 individuals representing 2.7% of the cohort. After these exclusions, the total sample size is

15,358.

B. Exposure Assessment

Alcohol consumption was ascertained at all 5 study visits (see Appendix 4 for

questionnaires); for this analysis, only data from visits 1-4 will be used as visit 5 data were collected

after the last year for which we have validation of stroke events. During visit 1 (1987-1989) alcohol

intake was assessed using an interviewer-administered dietary questionnaire developed in

accordance with the validated Willett 66-item FFQ. Measurement of alcohol at visit 2 (1990-1992)

occurred as part of the health history questionnaire, at visits 3 (1993-1995) and 4 (1996-1998) as

part of the personal history questionnaire, and at visit 5 (2011-2013) with the alcohol use form.

Missing data patterns for alcohol intake across the first 4 study visits are summarized in Table 21

and show relatively small degrees of missing data, with <1% of cohort participants missing all 4

measurements. A large proportion (82%) have at least 3 measurements and 92% have at least 2

measurements.

Table 21. Percent missing alcohol intake data according to the cumulative number of missing measurements from Visit 1 through 4

Total number of missing alcohol measurements	0 (Complete data)	1 Missing	2 Missing	3 Missing	4 Missing
Percent of ARIC cohort	69%	13%	10%	7%	0.1%

Participants were first asked to report whether they currently consumed alcoholic

beverages. Nondrinkers were then asked if they had ever consumed alcohol and if so how long ago

they ceased drinking and for how many years they drank. Current drinkers were asked to report

their usual intake over the past 12 months in units of drinks per week. Later questionnaires (visits 3-

5) asked both average quantity per week (drinks per week) and frequency (number of drinking days

94

per week). Separate questions were asked at all study visits for wine, beer, and hard liquor

consumption with respective serving sizes for each specified as 4, 12, and 1.5 ounces. Calculation of

ethanol content was based on the following conversions: 4 ounces of wine contains 10.8 grams of

ethanol, 12 ounces of beer contains 13.2 grams, and 1.5 ounces of liquor contains 15.1 grams.

In dose-response analysis, alcohol exposure will be defined as baseline drinks per day. The

0-drink level includes never drinkers as well as current drinking reporting <0.5 glasses per week

(recorded as '0'). Polynomial and spline terms will be used to flexibly model the association with

stroke incidence.

In addition, exposure will be categorized to obtain estimates for calculation of impact

fractions. Categories will include former drinkers, never drinkers, occasional (<1 drink/week), light

(1.1-7 drinks per week), moderate (7.1-14 drinks/week), and heavier drinkers (>14 drinks per week).

The categories proposed herein are based on previous research and are in accordance with current

recommendations for intake by the USDA Dietary Guidelines for Americans. Further analysis will

assess the sensitivity of results to *a priori* defined cut-points by generating data-driven cut-points

based on observed dose-response patterns and possible sex-specific values. We will explore effects

specifying alcohol by cumulative dose or time-varying, but our primary goal is to estimate effects of

mid-life consumption as this is hypothesized to be the critical period for effect.

C. Outcome Assessment

Possible strokes were ascertained by self-report during in-home interviews, at study visits,

and during annual follow-up telephone calls. Additionally, ARIC study coordinators conducted

regular surveillance of local hospital discharge lists. Potential stroke hospitalizations were eligible

for further review if any of the following were found: 1) a cerebrovascular disease related discharge

code (*International Classification of Diseases, 9th Revision, Clinical Modification* 430-438); 2) at least

1 keyword listed in the discharge summary or nursing notes; 3) a diagnostic CT or MRI scan with cerebrovascular findings in the medical record; or 4) the patient had ever been admitted to the neurological intensive care unit. Keywords used to screen the discharge summary and nursing notes included 'stroke', 'transient ischemic attack', 'cerebrovascular disease', 'cerebral hemorrhage', 'cerebral infarction', 'subarachnoid hemorrhage', 'cerebral embolus', 'paralysis', 'aphasia', 'diplopia', 'lacunar infarction', 'dysarthria', 'cerebral angiography', 'carotid', and 'endarterectomy'. Out-of-hospital fatal strokes were also monitored but were not validated. These events, which are few in number, will be excluded.

Possible stroke events were further validated. Medical records were abstracted by a single trained nurse at the Minneapolis site. Abstracted elements included medical history, neurological symptoms and deficits, results of any procedures performed during the hospitalization (e.g. CT and MRI scans, carotid endarterectomy, B-mode and Doppler ultrasound), in-hospital therapies, and autopsy evidence in the case of death. All stroke diagnoses and classifications were conducted independently by a computer-derived algorithm and a physician medical record reviewer, with differences adjudicated by a second physician reviewer. Stroke classification was based on criteria adopted from the National Survey of Stroke[206] and required, at a minimum, evidence of sudden or rapid onset of neurological symptoms lasting >24 hours or leading to death, in the absence of evidence for a nonstroke cause. Strokes related to brain trauma, neoplasm, coma due to metabolic disorders or disorders of fluid or electrolyte balance, vasculitis involving the brain, peripheral neuropathy, hematologic abnormalities, or central nervous system infections were excluded. The presence of major symptoms (hemiparesis of ≥2 body parts, homonymous hemianopia, or aphasia) or minor symptoms (diplopia, vertigo or gait disturbance, dysarthria, dysphagia, dysphonia, or unilateral numbness of ≥2 body parts) were considered in subtype classification along with CT and MRI findings. Strokes were classified as ischemic (thrombotic brain infarction, lacunar infarction,

cardioembolic stroke), hemorrhagic (intracerebral hemorrhage [ICH], subarachnoid hemorrhage

[SAH]), possible stroke of undetermined type, no stroke, and fatal out-of-hospital stroke. Additional

details of these subtype classifications have been published.[207] Fatal out-of-hospital stroke

classification was based only on the underlying cause of death reported on the death certificate

without further validation. Deaths were discovered during annual phone calls and by searching

health department death certificate files. Instances of a case meeting 2 diagnostic criteria were

rare, but when they occurred a hierarchy was used to assign stroke type (ICH, SAH, cardioembolic

stroke, thrombotic brain infarction). As of December 31, 2010, there were 1,461 definite/possible

incident strokes (1,252 ischemic, 166 hemorrhagic, 24 possible strokes of undetermined type, 19

fatal out-of-hospital). Misclassification is possible as out-of-hospital stroke deaths are not validated

and there is a chance that cases were missed that either did not present to the hospital or presented

to hospitals outside the catchment area and were not reported at annual phone calls or study visits.

The probability of these occurrences is assumed to be low, a reasonable assumption. If we have no

false positives, missed cases would not bias effect estimates.

D. Confounder Selection and Assessment

Potential confounders were identified based on substantive knowledge of factors associated

with alcohol[129] and risk of stroke[7] and from existing literature on the association between alcohol

and stroke. Selection of confounders to include in primary analyses was based on directed acyclic

graph analysis (Figure 13) that included all potential confounders identified from the literature:

demographic characteristics (age, gender, race, SES), lifestyle factors (smoking, physical activity,

social support, marital status, diet), and medical history (myocardial infarction, heart failure, atrial

fibrillation, diabetes mellitus). Potential mediators include blood pressure, HDL-C level, and atrial

fibrillation. There was 1 minimally sufficient set of adjustment variables for the estimation of the

total effect of alcohol on stroke, which included age, sex, race, baseline comorbid conditions, diet,

SES, smoking, and social support.

Figure 13. Directed acyclic graph for the association between alcohol and stroke
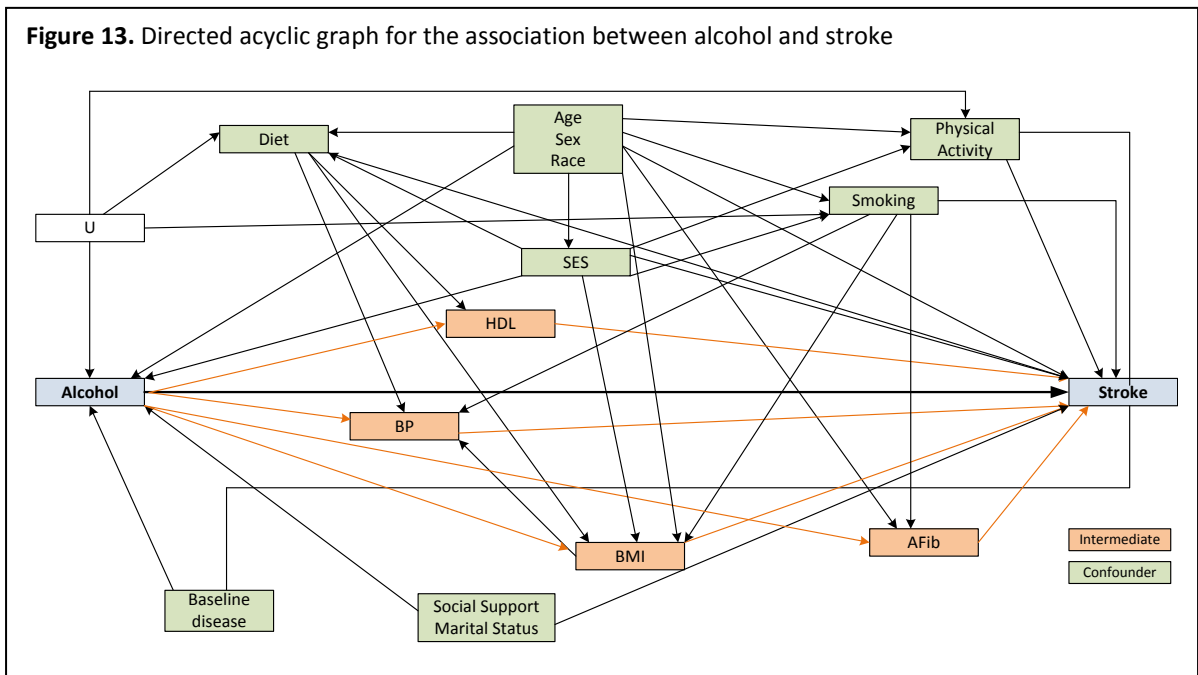
Information on covariates was obtained from home interviews and clinic visits.

Socioeconomic status was measured as the highest level of completed education and family income.

Dietary factors were assessed using the interviewer-administered 66-item FFQ administered at visits

1 and 3. Participants were asked to report their usual intake of foods over the past year according

to categories of intake ranging from 'never or less than once per month' to '>6 times per day'. Food

models were used by interviewers to convey portion sizes and nutrient content was calculated by

linking with the nutrient database developed by Willett et al.[208]

Anthropometric measurements (i.e. weight, height, waist circumference) were carried out

on participants while wearing light clothing and without shoes. Body mass index (BMI) was

calculated as weight (kg) divided by height squared (m^2). Blood pressure was measured using

standard methods, averaging the second 2 measurements of 3 following a 5-minute rest.

Smoking status was assessed at all 4 study visits (current, former, and never) and the total number of years of smoking was measured. Both continuous and categorical definitions of smoking will be assessed in analyses and the operationalization that best reflects the dose response relationship between smoking and stroke will be used in adjusted analyses. Physical activity was measured using the Baecke physical activity questionnaire that provides indices ranging from 1 to 5 for leisure, sport, and occupational activity.[209]

Social support was measured at visit 2 with the 40-item Interpersonal Support Evaluation List, which has high correlations with other social support scales, test-retest reliability, and internal consistency.[210] This tool assesses the perception of available support in four areas: tangible, belonging, self-esteem and appraisal. Six questions from the four subscales comprise the Perceived Social Support Scale. The questions asked whether social support (family and friends, helping with daily chores, dealing with personal problems, cooking and giving trustworthy advice) is available when needed. Scores ranged from 6 to 24, with lower scores indicating higher levels of perceived social support.

Finally, baseline medical history included myocardial infarction (self-reported physician diagnosis or positive ECG findings) and diabetes (self-reported physician diagnosis, fasting glucose >126 mg/dL, or self-reported pharmacologic treatment for diabetes). Hypertension was defined as any of the following: current use of antihypertensive medications, systolic blood pressure ≥140 mm/Hg, or diastolic blood pressure ≥ 90 mm/Hg. In primary analysis, we will consider covariates that could be both mediators and confounders as temporally after alcohol because we believe that baseline alcohol represents the long-term mid-life exposure.

E. Statistical Analysis

Cox proportional hazards regression will be used to estimate hazard ratios and 95% confidence intervals for the association between alcohol and incident total, ischemic, and hemorrhagic stroke. The time scale for these models will be time on study. Follow-up will continue until the earliest of stroke, death, loss to follow-up, or end of follow-up on December 31, 2011. The Cox proportional hazards method is semi-parametric and uses quasi-likelihood estimation. An advantage over parametric models is that the functional form of the baseline hazard does not need to be specified, but there is an assumption of proportionality over time. We will test the proportional hazards assumption by examining log-log survival plots and testing interactions of alcohol with time.

Another, stronger, assumption of this method is noninformative censoring. This is likely satisfied for loss to follow-up as the probability of dropping out was independent of reported alcohol consumption at baseline. Based on data through 2010, the proportions lost to follow-up were 2% for never drinkers, 0.7% for light drinkers, 0.2% for moderate drinkers, 0.2% for high drinkers, and 0.04% for heavy drinkers; p=0.3). However, censoring for death may violate this assumption as death is a common event in this population (31% by 2010) and may not be independent of the outcome conditional on covariates. Standard survival analysis, e.g. Cox PH regression, estimates cause-specific relative hazards in the hypothetical absence of competing risks.[211] There are several methods to address competing risks. One option is to estimate the risk of a combined endpoint, stroke + death, which has no competing risk. While the most straightforward, this option is not ideal given our study question. The resultant estimate would not necessarily reflect the etiological effect of alcohol on risk of stroke. A second option for addressing competing risks is to use inverse-probability of censoring weights in Cox models to account for death and loss to follow-up.[212-215] A third option is to estimate sub-distribution hazards, which reflect the likelihood

of the outcome given exposure while allowing competing risks to occur. The subdistribution HR may

not be generalizable to populations with different competing risk distributions, however. If

competing risks are deemed to be of concern, we will use the second or third options above in

sensitivity analyses.

Confounders will be operationalized in statistical models based on the confounder-outcome

relationship in the data. Therefore, unlike selection of confounders which is DAG-driven, the

modeling strategy will be data-driven. For continuous variables, we will explore linear, quadratic,

and spline terms as well as categorization in the prediction of the outcome of interest. The different

options for modeling confounders will be compared to each other based on the shape of the dose

response curve and precision of point estimates. Precision-validity tradeoff considerations balance

minimizing confounding bias and maximizing precision. The equation below represents the Cox

proportional hazards model for our study, where **Z** is used to represent the covariates.

Parameterization of covariates will be explored to best represent their relationship with the

outcome and will include exploration of disjoint indicator variables, polynomial, and spline terms.

$$log\ h_i(t) = \ h_0(t) + \beta_1 alcohol_i + \beta_2 alcohol_i(t) + \sum \beta \boldsymbol{Z}\ \ + \varepsilon$$

Effect measure modification by race-ethnicity and sex will be assessed using interaction

terms between alcohol and the modifier. Likelihood ratio tests comparing nested models with and

without interaction terms will be used to test interaction terms using a conservative p-value cut-

point of 0.2. A conservatively high p-value cut-point was chosen because of the low power of tests

of interaction and our interest in identifying heterogeneity in the dose-response relationship

between alcohol and stroke according to the selected characteristics. Stratified models will

estimate the dose-response patterns for subgroups separately if a meaningful interaction is present.

For Aim 2, we will investigate the feasibility of estimating proportional changes in total, ischemic, and hemorrhagic stroke incidence resulting from changes in the distribution of alcohol intake using generalized impact fraction methods.[216, 217] Feasibility will depend primarily on the number of confounders and the number of resultant strata within which point estimates must be calculated. If cells become too small and confidence intervals too wide, then our proposed method will not be feasible. Second, if our main effects are close to the null, we will not need to further calculate impact fractions, as these are only useful for exposures that are associated with the outcome of interest.

If deemed feasible, generalized impact fractions will be estimated within strata of age, sex, and race using effect estimates obtained from Cox regression models. Sex-race groups will include white men, white women, African-American (AA) women, and AA men. The impact fraction estimated by these methods accommodates proportionate changes in a polytomous exposure, for example, a 5% shift of the population from heavy to moderate drinking and 5% shift from never to moderate drinking. The formula below shows the calculation of GIF for a general scenario, where P_i represents the exposure prevalence in the population, P_i' represents the exposure prevalence after intervention, and RR_i represents the crude hazard ratio of exposure compared with referent group. We will calculate GIF within strata of strong confounders (hypothesized to be age, sex, and race) and use weighted case-load methods to combine estimates.

$$GIF = \frac{\sum P_i RR_i - \sum P_i' RR_i}{\sum P_i RR_i}$$

Bootstrapping methods will be used to estimate 95% confidence intervals for GIF estimates. We will consider several scenarios:

1) Achieving the Healthy People 2020 goal of a 3% reduction in heavy drinking. We will assume a shift to moderate drinking for these individuals.

2) Pricing policy: 10% relative increase. Based on published elasticity values for alcohol, this change in price will reduce consumption roughly 5%. We hypothesize based on published econometric data that light and moderate drinkers will be more inelastic to price change than heavy drinkers and therefore the relative reduction in consumption will be smaller in these groups than heavy drinkers.

3) Brief intervention in primary care setting of high-risk individuals. Based on a Cochrane review, this intervention is associated with risk differences of binge and heavy drinking of -11% and -15%, respectively.

F. Strengths and Limitations

Strengths of the ARIC data and this proposed study include multiple measurements of alcohol intake, a prospective study design with up to 23 years of follow-up, a racially diverse population, and robust ascertainment of stroke events. Strokes were ascertained using multiple overlapping methods and validated with medical record abstraction and physician review. Alcohol was measured at 4 time points, was beverage specific, reducing under-reporting. In addition, questions were asked that allow separate of nondrinkers into categories of lifetime abstainers and former drinkers.

There remain several limitations to the proposed study. First, selection bias is possible if heavy drinkers were less likely to participate in the study or to be lost to follow-up than moderate drinkers. As discussed above, we will perform several sensitivity analyses to assess possible selection bias in this study due to censoring and competing risks. Selection bias from loss-to-follow-up (censoring) is likely not a threat as it did not differ by alcohol consumption and was minimal (<5%). Data through 2010 suggest that drinking status at visit 1 is unrelated to loss-to-follow-up and therefore not a serious threat to validity (percent LTF by drinking category are as follows, 2% never

drinkers, 0.7% light drinkers, 0.2% moderate drinkers, 0.2% high drinkers, and 0.04% heavy drinkers; p=0.3). Second, while stroke ascertainment was thorough and utilized several capture methods, out-of-hospital events that were not reported by participants during study visits or at annual follow-up were not captured. Nor were out-of-hospital fatal stroke events for which the death certificate failed to list stroke as the underlying cause of death.

Exposure measurement error is one of the primary threats to validity in this study. Previous studies have supported the validity of FFQs, reporting high correlations between alcohol intake measured through diet records and FFQs (0.83-0.90) and modest correlations between FFQ and serum high-density lipoprotein levels (0.31-0.40).[123] Studies have reported that errors are generally linearly related to intake, which would result in incorrect absolute values of intake, but would provide reasonably reliable ranking of individuals.[122, 123] Without a gold standard measure of consumption, however, the true validity of self-reported consumption using FFQs is unknown. Greater under-reporting of alcohol by heavy drinkers is possible and may lead to underestimation of the effect in this group. The ARIC study does not have a second, independent measure of alcohol consumption with which to estimate error and calibrate effect estimates.

Confounding, either from failure to account for an important factor or through residual confounding, is a concern. The ARIC study collected data on several potential confounders that were unavailable in many previous analyses including SES, social support, smoking amount, and physical activity. Moderate drinking is associated with a general healthy lifestyle and we may not be able to fully account for this confounding with the selected covariates. Nor can we determine with certainty if confounders were perfectly measured and modeled. Finally, it is difficult to determine the temporal order at baseline of alcohol and prevalent diseases. Whether baseline diseases are true confounders, i.e. preceded alcohol, or as mediators, i.e. were the result of alcohol consumption, cannot be determined. In primary analyses we will treat these as confounders, as I

feel this is the most likely scenario. We will assess different causal relationships in sensitivity analysis.

Finally, the prevalence of heavy drinking is low in the ARIC cohort (6.3% consumed 24-60 g/d and 1.2% consumed >60 g/day at Visit 1). This may limit our ability to estimate effects with adequate precision in these groups. Furthermore, the heavy drinkers that participated in the ARIC study may not represent the larger population of heavy drinkers, limiting generalizability of study results.

4.3 Research Plan for the Assessment of Alcohol and Cognitive Decline

A. Analytic Sample

The sample for analysis will consist of all ARIC cohort participants without prevalent stroke at visit 2. Visit 2 will serve as study baseline because it was the first visit at which cognitive performance was assessed. Between visits 1 and 2, loss to follow-up was small, only 9%, resulting in a total of 14,348 participants. We will exclude non-white or black participants as well as those with missing alcohol exposure, visit 2 cognitive scores, or covariates. After these exclusions, there will be 13,704 participants for analysis.

B. Exposure Assessment

Assessment of alcohol consumption was described in section 4.2 B. For Aim 3, we will operationalize alcohol exposure as baseline (i.e. visit 2) average consumption. Participants will be categorized into groups because this will facilitate graphical presentation of cognitive declines (i.e. displaying slopes by alcohol consumption group). We will explore different categorizations to best capture the dose-response relationship between alcohol volume and cognitive decline. In secondary analysis, we will assess effects of alcohol consumption measured at visit 1 (closer to mid-

life exposure), cumulative average of visits 1 and 2, and according to different categorizations of light, moderate, and heavier consumption.

C. Outcome Assessment

Cognitive function was measured using 3 tests at visit 2 in 1990-1992, at visit 4 in 1996-1998, and at visit 5 in 2011-2013. There were 3 components to the cognitive testing: the Delayed Word Recall Test (DWRT), Digit Symbol Substitution Task (DSST), and the Word Fluency Task (WFT; Appendix 5). These tests have no ceiling effects, except possibly for the DWRT, which is an advantage in a relatively young population without frank dementia. The tests are summarized in Table 22 with regard to the cognitive domains they assess, the task involved, and the theoretical score range.

Table 22. Neuropsychological assessments in the ARIC study

Neurocognitive Assessment	Domains	Task	Score Range
Delayed Word Recall Test	Verbal learning Short-term memory	Learn 10 common nouns, use each in 2 sentences, recall the words after a 5 minute delay during which another task is performed	0-10
Digit Symbol Substitution Test	Executive function Processing speed	Participants are provided with a key that links different symbols with numbers 1 through 9 and asked to write out symbols corresponding to a series of numbers in 90 seconds	0-93
Word Fluency Test	Executive function Expressive language	Generate as many words as possible that start with a given letter (F, A, S) within 3 60-second trials	0-X

Tests were administered by trained and certified staff in a quiet environment without distraction. Administrators were re-certified annually and both technique and protocol adherence were monitored over the study. The scores for the DWRT and WFT are recorded by the test administrator, while the DSST is recorded by the participant and scored by the staff member.

We will calculate Z-scores for each test at each study visit for analysis. These scores will be standardized to the population mean and standard deviation at Visit 2. A global cognitive score will be calculated by averaging the 3 test-specific z scores at each visit; these global scores will be standardized to the visit 2 global mean and standard deviation.

D. Confounder Selection and Measurement

Potential confounders were identified based on substantive knowledge of factors associated with alcohol[129] and risk of cognitive decline[33, 203] and from existing literature on the association. Selection of confounders to include in primary analyses was based on directed acyclic graph analysis (Figure 14) that included all potential confounders identified from the literature: demographic characteristics (age, gender, race, SES), lifestyle factors (smoking, physical activity, social support, marital status, omega-3 fatty acid intake), and medical history (CAD, diabetes mellitus, depression). Potential mediators include blood pressure, HDL-C level, atrial fibrillation, fibrinogen, and platelet concentrations. ApoE alleles have been implicated in risk of cognitive decline (ApoeE4) and atherosclerosis (ApoE2 and ApoE4) and will be considered as potential covariates. Allele status is not a confounder of the relationship according to the DAG analysis as there are no backdoor paths from alcohol to ApoE, but many researchers adjust for this variable because it is highly predictive of the outcome. There was 1 minimally sufficient set of adjustment variables for the estimation of the total effect of alcohol on cognitive decline, which included age, sex, race, education, income level, diet (i.e. omega-3 fatty acid consumption), physical activity, social support, and history of stroke, diabetes, and depression. In later analysis, income level and depression were not included because 1) income had a high degree of missing data and it is hypothesized that education adequately captures the SES effect on cognition; 2) depression has not yet been validated in ARIC data and we believe that adjustment for social support and network size will serve as an adequate proxy for depression. Furthermore, omega-3 fatty acid level was adjusted for as part of a comprehensive diet quality score.

Figure 14. Directed acyclic graph for the relationship between alcohol and cognitive decline
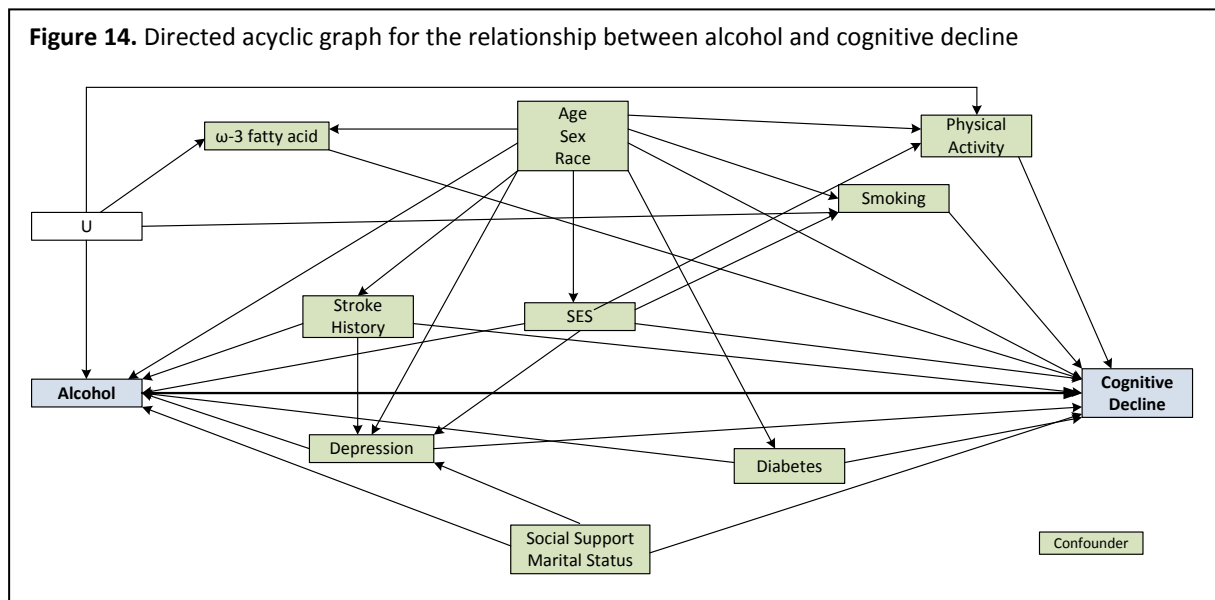
Information on covariates was obtained from home interviews and clinic visits. Collection

and operationalization is described in more detail in Section 4.2.4 for those covariates in common

with Aim #1. As discussed above, questions have unknown validity in these data for diagnosis of

depression and may potentially reflect symptoms of early dementia instead of depression.

Furthermore, depression is relatively common in the stages of cognitive impairment. Adjustment

for factors reflecting early cognitive decline would bias results toward the null. For these reasons,

they will not be used in primary analysis. Current work in the ARIC study is being done to generate

and validate a depression diagnosis using items from the Vital Exhaustion Scale, a 21-item

questionnaire that assesses fatigue lack of energy, and feelings of hopelessness.[218]

E. Statistical Analysis

Linear regression models with generalized estimating equations (GEE) will be used to

estimate rates of cognitive decline by alcohol consumption status and additional changes in

cognitive scores relative to never drinkers. GEE is an alternative estimating technique to maximum

likelihood that is appropriate for longitudinal data analysis with correlated responses. These models

are marginal (i.e. population-averaged, with effects contrasting outcomes of a randomly selected exposed individual to a randomly selected unexposed individual) and therefore allow for group-level inferences.[219] This is in contrast to mixed modeling approaches in which estimates relate to inferences about the subject-specific likelihood of an outcome given exposure (i.e. the effect on an outcome for an individual selected at random if they experience a change in exposure status). Marginal models are well suited for our scientific aim of comparing cognitive decline patterns between sub-populations defined by alcohol consumption level. Another reason they are well-suited is that GEE is best for data that have large sample size, but relatively small number of repeated observations within a subject, which is satisfied by our data.

GEE models are robust to misspecification of the correlation structure of repeated observations within a subject because the mean response is conditional only on covariates and not within subject correlation.[219] Valid standard errors are obtained with the "sandwich" estimator and higher precision is achieved with correct specification of the working correlation matrix. A limitation of GEE as compared with mixed models is its stricter assumptions for missing data. In GEE, outcome data are assumed to be missing completely at random, dependent on covariates but not observed or unobserved outcomes. This assumption may be violated. Mixed models assume missingness at random and therefore missing data can be associated with both covariates and observed outcomes. Potential bias from missing data will be explored in sensitivity analysis using inverse-probability weights or other methods (see Section 4.4). In addition, we will estimate effects using mixed models to assess the robustness of our estimates obtained from GEE compared with mixed models with random intercepts and with both random intercepts and slopes.

The proposed model for our analysis is shown below, where u represents the mean response (cognitive score) and the matrix **Z** represents the covariates identified in Section 4.3.4 and study center. We will model the working correlation matrix using unstructured correlation, as this is

flexible and can be fit with our large sample size. Exposure will be included as a class variable, with

lifetime abstainers serving as the reference group. Time on study will be represented by linear

spline variables with a knot at 6 years as recommended by the NCS analytic team. This

parameterization will allow estimation of mean changes from years 1 to 6 and from 6 to 20.

Interactions between all covariates and time will be included unless not statistically significant at

alpha=0.2. Our primary interest is on the parameter estimate for the interaction between alcohol

and time, β_3. This estimate reflects how the average rates of cognitive decline differ between

groups, for example moderate drinkers compared with lifetime abstainers.

$$u_{ij} = \beta_0 + \beta_1 alcohol + \beta_2 time + \beta_3 alcohol * time + \sum \beta \mathbf{Z} \ + \sum \beta \mathbf{Z} * time + \varepsilon$$

Effect measure modification of alcohol consumption by sex-race and ApoE ε4 allele status

will be assessed using interaction terms as well as by comparing stratum-specific effect estimates.

Finally, models will be re-fit in sensitivity analysis using a re-weighted sample or multiple imputation

of missing data to correct for subject attrition over time. Selection of the methodological approach

to account for attrition and additional details of this analysis are described in Section 4.4.

F. Strengths and Limitations

Strengths of the ARIC data and this proposed study include its prospective study design with

20 years of follow-up, a racially diverse population, and multiple measurements of cognitive

function over time. The cognitive assessments used are sensitive to changes at higher levels of

cognition unlike in many other studies that relied solely on MMSE scores. Alcohol consumption was

measured mid-life with a further 20 years for outcome follow-up. Finally, we will utilize the richness

of the ARIC data to build predictive models for attrition that will allow us to correct for selection

bias.

There remain several limitations to the proposed study. First, in-selection bias is possible if heavy drinkers were less likely to participate in the study or to be lost to follow-up than moderate drinkers. As discussed above, drinking at baseline was not associated with attrition by Visit 2 and total attrition prior to Visit 2 was small. The greater concern for selection bias is out-selection bias occurring after Visit 2 by way of drop-out or death. This bias may remain even after we correct for attrition in sensitivity analyses. There is potential for floor and practice effects in cognitive assessments.

As in Aim #1, exposure measurement error and confounding are threats to validity. While relative validity studies support FFQ measurement of alcohol, there is no gold standard for true validation. Under-estimation of consumption by heavy drinkers is possible and would result in misclassification. Confounding, either from failure to account for an important factor or through residual confounding, is a concern. The ARIC study collected data on several potential confounders that were unavailable in many previous analyses including SES, social support, and physical activity. Moderate drinking is associated with a general healthy lifestyle and we may not be able to fully account for this confounding with the selected covariates (diet, smoking, physical activity). Finally, the prevalence of heavy drinking is low in the ARIC cohort and may limit our ability to estimate effects with adequate precision in these groups. Furthermore, the heavy drinkers that participated in the ARIC study may not represent the larger population of heavy drinkers, limiting generalizability of study results.

4.4 Sensitivity Analyses

A. Alternative Approaches of Specifying Alcohol Exposure

Alcohol is a complex exposure variable, with multiple dimensions including quantity, frequency, duration, and type. It is also non-monotonic with respect to disease risk. Time

permitting, we will consider several alternative approaches to operationalizing exposure including

assessing independent effects of quantity and frequency if feasible (and possible cross-classifications

of these) and cumulative intake metrics to capture duration effects. We will consider calculating

average intake over follow-up using reported intake at all study visits prior to the outcome (i.e. visit

immediately prior to the date of first stroke or censored date for Aim #1 and visit 2 for Aim #3).

Finally, we will compare our effect estimates in categorical analysis (based on data-driven cut-

points) to a variety of different definitions for light, moderate, and heavier drinking used in the

literature and in guideline recommendations for alcohol consumption.

B. Accounting for Informative Visit Nonattendance and Death

Sample weighting is a method that can be used to correct for selection bias from missing

data, in our case from visit nonattendance and death in Aim #3. The method proposed herein has

been guided by work done by the Neurocognitive Study Analysis Workgroup.[220] We will assume a

monotone drop-out model as opposed to an intermittent missingness model because it requires

fewer assumptions and is appropriate for the majority of attrition in our study. We will therefore

consider an individual as exiting the study at the time of their first missing cognitive score regardless

of subsequent non-missing scores. If intermittent missingness is common, which we assume is not

the case, we will consider using multiple imputation to predict these intermittent missing values.

We will calculate observation-specific weights that are the inverse cumulative probability of

death as estimated using logistic regression. First, we will fit logistic regression models to predict

being alive at a study visit conditional on being observed at the previous visit. Second, we will

calculate conditional probabilities for non-dropout conditional on being alive. Third we will

calculate joint probabilities of being alive and observed at each visit as the product of probabilities in

Steps 1 and 2. Fourth, we will calculate cumulative probabilities as the product of joint probabilities

at each previous visit. Fifth, we will calculate weights as 1/cumulative probability. Weights will be

stabilized if there is instability defined as a maximum weight that is more than 20 times the

minimum weight.

IPW analysis will be carried out assuming an independent correlation structure, which is the

more conservative option without a large penalty of increasing standard errors. We will calculate

bootstrapped standard errors, which are more precise than model-derived standard errors. As our

analysis will include correction for both death and dropout, it will provide estimates of etiologic

associations between alcohol and cognitive decline with inference to a hypothetical population in

which death is related only to the exposure. This approach will be unbiased assuming the models

for death and dropout are correctly specified. Covariates to be included in these models will include

observed outcomes at previous visits, main model covariates, additional variables from annual

follow-up data including disease status (incident stroke, MI), and interactions between these

variables.

Since the initial proposal of this method, simulation results from models estimating

cognitive decline with other exposures has shown IPW methods ineffective at modeling the drop-

out and death in the population. An alternative method, multiple imputation with chained

equations, was identified, tested, and found to be superior. Unlike with IPW, MICE-corrected

estimates differed from complete case analysis and changed in the hypothesized direction.

Therefore, we opted to use the MICE method instead of IPW for our sensitivity analysis.

MICE is a method to handle missing data that generates multiple imputations for variables

of interest and therefore is able to incorporate uncertainty in the imputation process into the final

variance of point estimates from analysis models.[221, 222] The assumption of this method is that the

data are missing at random, i.e. on observed values only. We will use MICE to impute missing

covariates and missing cognitive scores at visits 4 and 5. A set of chained equations is used whereby

each successive variable is imputed, beginning with those with the least amount of missing data. The link function of a given imputation model depends on the variable type, e.g. logit for binary data, identity for continuous variables. Because the proportion missing alcohol exposure is very low (0.3%), we will not impute missing exposure. The imputation process will be repeated 24 times so that a total of 25 datasets with 'complete' data are generated. Analysis models will be run, using GEE and mixed models, on each of the 25 datasets to obtain estimates for the alcohol-cognitive decline relationship. These points estimates are then combined into a single estimate with variance calculated to account for the uncertainty in the imputations (between variance) as well as the within dataset variance. The covariates for the imputation models will include all covariates in the analysis model, alcohol, as well as predictors of missingness. These latter variables include: self-reported outcomes on annual follow-up (stroke, CHD, diabetes, hypertension, lung disease), nursing home residence, proxy respondent on annual follow-up, functional status, hospitalizations, previous measured cognitive scores, clinical dementia rating score, Mini Mental State Exam score, TICS score, suspected dementia based on ICD-9 hospitalization codes, and APOE allele status.

Diagnostics of imputed data will be performed by examining descriptive statistics for observed and imputed variables, identifying outlying values, and graphical representations. The MICE procedure will be carried out using code provided by the ARIC Neurocognitive Study working group using STATA. Analysis models will be run on 1) complete data, 2) data with imputed covariates only, 3) data with imputed covariates and outcomes for alive persons, and 4) imputed covariates and outcomes for the living and the dead. Because we will be imputing cognitive scores for participants that die 6 months prior to their date of death, the study design becomes unbalanced with regard to timing of cognitive measurements. As such, GEE models may not be appropriate and therefore we will also estimate effects using mixed models.

C. Additional Sensitivity Analyses

Several other sensitivity analyses will be performed for Aims #1 and #3. In particular these include:

1) Comparing points estimates and 95% confidence intervals from Cox models in Aim #1 with and without adjustment for baseline factors that could act as confounders or mediators (i.e. hypertension and body mass index).

2) Investigate possible floor effects in cognitive scores that may prevent measurement of declines in z scores over time. This will be achieved by dropping participants in the lowest 5% of a given z score and re-running linear regression models to estimate additional cognitive changes. These points estimates and confidence intervals will be compared to those from models without dropping low baseline scores.

3) Assessing the stability of the MICE models by repeating the imputation procedure and comparing point estimates and their confidence intervals between the two sets of imputations. If similar, this will be taken as evidence of stability. If they differ, we will investigate using more imputations or altering the MICE models to achieve stability.

4) Re-running MICE models with a 20% validation sample. We will compare the ('true') scores of this 20% sample with the imputed scores using regression, the R-squared statistic, and plots showing Lowess fit curves. We will also compare the performance of the imputation by education, sex-race, and alcohol intake category.

CHAPTER 5. MANUSCRIPT #1: MIDLIFE ALCOHOL CONSUMPTION AND THE RISK OF STROKE IN THE ATHEROSCLEROSIS RISK IN COMMUNITIES STUDY

5.1 Overview

Background: Alcohol consumption is common in the U.S. and may confer beneficial cardiovascular effects at low-to-moderate doses. The alcohol-stroke relationship remains debated. We sought to estimate the relationship between mid-life, self-reported alcohol consumption and ischemic stroke (IS) and intracerebral hemorrhage (ICH) in a biracial cohort.

Methods: We examined 12,433 never and current drinkers in the Atherosclerosis Risk in Communities Study, aged 45-64 at baseline. Participants self-reported usual drinks/week of beer, wine, and liquor at baseline. We used multivariate Cox proportional hazards regression to assess the association of alcohol with incident IS and ICH and effect modification by sex-race group. We modeled alcohol intake with quadratic splines to further assess dose-response relationships.

Results: One-quarter of participants self-reported abstention, 33% and 20%, respectively, consumed ≤3 and 4-17 drinks/week, and only 4% reported heavier drinking. There were 773 IS and 81 ICH over follow-up (median ~22.6 years). Light and moderate alcohol consumption were not strongly associated with IS (HR_{Light}=0.98, 95% CI 0.79-1.21; HR_{Mod}=1.06, 0.84-1.34) while heavier drinking was associated with a 31% increased rate relative to abstention. There was no support for a J-shaped curve; rather we noted a roughly linear relative increase across intake. Moderate (2.07, 1.10-3.87) and heavy (1.48, 0.47-4.63), but not light, consumption tended to increase the rate of ICH.

Conclusion: Self-reported light-to-moderate alcohol consumption at mid-life was not associated with reduced stroke risk compared with abstention over 20 years of follow-up in the ARIC study. Heavier consumption increased the risk for both outcomes as did moderate intake for ICH.

5.2 Introduction

Stroke is a leading cause of mortality and disability worldwide, a major contributor to U.S. health care costs, and is projected to increase in burden as the population ages.[7, 9, 223] Given the high burden of stroke, continued examination of modifiable risk factors and behaviors that may prevent disease occurrence is needed. One such factor may be alcohol, a prevalent exposure both in the U.S. and worldwide. Seventy percent of U.S. adults report current drinking and more than one-quarter report excessive drinking (either heavy episodic or average consumption). [50, 67]

The relationship between alcohol intake and stroke has been widely studied, yet uncertainties remain; results from observational studies are inconsistent and randomized trials are infeasible. Light-to-moderate alcohol consumption may reduce the risk of stroke, but some studies, particularly older ones, have not found beneficial effects. Current meta-analyses suggest that moderate intake is protective for ischemic stroke (IS), but not intracerebral hemorrhagic (ICH), with possible differential dose-responses between women and men.[2, 6, 14] Limitations of our understanding stem from 1) the assessment of alcohol intake late in life, a period that may not reflect the most critical exposure window for disease risk and that may be influenced by other medical conditions developing in later life; 2) alcohol measurement errors and misspecification due to variations in drinking patterns; and 3) limited generalizability.[2, 6, 14, 39, 164, 166, 167, 169, 186, 190] Furthermore, some studies do not adjust for lifestyle and socioeconomic factors that may account for protective effects in light drinkers or combine never and former drinkers into a single referent group. In contrast to the evidence on effects of light-to-moderate intake, consistent and convincing

evidence supports the harmful effects of heavy consumption on stroke risk. The precise dose-response relationship, however, is unclear.

Despite the large body of work on alcohol and stroke, few studies have included substantial numbers of minority populations. Blacks have higher stroke incidence and different drinking patterns from whites and therefore warrant investigation.[7] In addition, studies to date have not accounted for the competing risk of mortality, which may be substantial in prospective studies. Subdistribution hazard estimation may be particularly useful to public health scientists interested in assessing risks and benefits of alcohol in a population in the presence of competing risks.[224] In our study, we estimated the dose-response relationship between usual, mid-life alcohol consumption and incident stroke among black and white adults in the Atherosclerosis Risk in Communities (ARIC) study, a population-based cohort drawn from 4 U.S. communities.

5.3 Methods

Study Population

The ARIC study is a population-based cohort recruited using probability sampling of adults aged 45-64 years from 4 U.S. communities: Forsyth County, NC; Jackson, MS; suburbs of Minneapolis, MN; and Washington County, MD. The ARIC study design and rationale are described in detail elsewhere.[204] A total of 15,792 participants were enrolled at Visit 1 (1987-1989) and underwent an in-home interview and physical examination. Four additional study visits consisting of an interview and physical examination occurred over the subsequent 25 years. The study population for analysis excluded participants not classified as white or black (N= 48), blacks from Minnesota or Washington County (N=55), missing alcohol intake at baseline (N=106), and those with a history of stroke at baseline (N=284). After these exclusions, the analytic cohort totaled 15,305. We further limited our population to current or never drinkers (N=12,433) because of the

heterogeneity in exposure among former drinkers in our population with regard to duration and quantity of consumption and time since cessation.[167]

Alcohol Assessment

Alcohol consumption was measured at baseline using an interviewer-administered dietary questionnaire developed in accordance with the validated Willett 66-item food frequency questionnaire (FFQ).[208] Participants were asked to report whether they currently consumed alcoholic beverages and if so, their usual intake over the past 12 months in units of drinks per week. Separate intake frequency questions were asked for standard drinks of wine (4-oz), beer (12-oz), and hard liquor (1.5-oz).

Stroke Definition

Suspected stroke hospitalizations were ascertained by self-report during in-home interviews, at study visits, and during annual follow-up as well as through surveillance of local hospital discharge lists. Validation of suspected events and determination of stroke diagnosis were conducted independently by a computer-derived algorithm and a physician reviewer using data abstracted from the medical record; differences were adjudicated by a second physician reviewer. Strokes were classified using criteria adopted from the National Survey of Stroke[206] and required, at a minimum, evidence of sudden or rapid onset of neurological symptoms lasting >24 hours or leading to death in the absence of evidence for a nonstroke cause. Out-of-hospital fatal strokes (N=19) were not validated and are not included. Additional details of stroke subtype classification have been published.[207]

Covariates

Confounders were identified based on substantive knowledge and from existing literature. Directed acyclic graph analysis was used to obtain a minimally sufficient set of adjustment variables: age, sex, race, study center, baseline comorbid conditions, diet score, low-density lipoprotein cholesterol, education, smoking status, and marital status. Mediators included blood pressure, high-density lipoprotein cholesterol, and atrial fibrillation.

Dietary factors were assessed using an interviewer-administered 66-item FFQ measuring usual intake of foods over the past year. Food models were used by interviewers to convey portion sizes and nutrient content was calculated through linkage with the nutrient database developed by Willett et al.[208] We calculated a diet score as described elsewhere[225] based on quintile values for 6 dietary components: percent energy from trans-fatty and omega-3 fatty acids, fiber, folate, glycemic load, and polyunsaturated:saturated fatty acid ratio. Physical activity was measured using the Baecke physical activity questionnaire.[209] Baseline medical history included diabetes (self-reported physician diagnosis, fasting glucose ≥126 mg/dL, or self-reported pharmacologic treatment) and coronary artery disease (electrocardiogram-adjudicated or self-reported myocardial infarction or any of self-reported heart/arterial surgery, coronary bypass, or angioplasty).

Statistical methods

Descriptive statistics for participant characteristics were calculated according to categories of alcohol intake and weighted according to the person-time in each exposure group. Cox proportional hazards regression was used to estimate hazard ratios and 95% confidence intervals for the association between alcohol and incident IS, ICH, and total stroke. Participants contributed person-time until the earliest of: incident stroke, death, loss to follow-up, or end of follow-up on

December 31, 2011. The proportional hazards assumption was tested using interaction terms

between exposure and time.

Alcohol consumption was categorized as drinks per week by examining the dose-response

relationship as well as using *a priori* values selected to align with prior research and recommended

intake guidelines. Results were similar for both sets of cut-points and are presented herein as <0.5-

3, 4-17, and 18 or more drinks per week. In secondary analyses, we assessed possible non-linear

relationships using quadratic splines. Knots were selected based on AIC values compared across

models with 2, 3, and 4 knots located at percentile values.[226, 227] Secondary models for IS were

stratified by sex-race group.

Finally, in sensitivity analysis, we estimated sub-distribution hazard ratios to assess the risk

of stroke given the relatively high proportion of death (26%) over follow-up. Censoring for death, as

in cause-specific hazards models, yields estimates that reflect the relative *rate* of stroke. Sub-

distribution hazards ratios, on the other hand, reflect the relative *risk* over a period of time.[224]

These were obtained using the SAS macro PSHREG based on the proportional sub-distribution

hazards model proposed by Fine and Grey.[228] All analyses were conducted using Statistical Analysis

Software Version 9.2 (SAS Inc., Cary, N.C.).

5.4 Results

Nearly one-third of the cohort were light alcohol drinkers, consuming ≤3 drinks/week (Table

23). Twenty percent were moderate drinkers of 4-17 drinks/week, and only 4% consumed >18

drinks/week. A quarter of participants reported lifetime abstention from alcohol. Women

comprised the largest proportion of abstainers and white men accounted for nearly three-quarters

of heavier drinkers. Light-to-moderate drinkers were of higher socioeconomic status – in the form

of greater educational attainment, more managerial occupations, and higher family income - than

heavier drinkers and lifetime abstainers. Current smoking was reported by 46% of heavier drinkers

but only 23% of light drinkers. The prevalence proportion of diabetes was low overall (8.6%) and

was roughly twice as high in abstainers compared with current drinkers. Finally, blood pressure and

HDL-C increased across alcohol consumption level.

Table 23. Characteristics of ARIC participants according to self-reported usual alcohol consumption at baseline.*

	Alcohol consumption, drinks per week			
	Lifetime abstainer	≤3	4-17	18+
Number of participants	3851	4876	3042	664
Person-years	76974.8	99125.5	60479.2	11947.2
Alcohol consumption, median (25th-75th)				
Grams ethanol per week		0 (0-24)	95 (68-151)	317 (277-415)
Glasses per week		0 (0-2)	7 (5-11)	24 (20-30)
Age, years	54.6 (5.7)	53.7 (5.8)	53.8 (5.7)	53.9 (5.8)
Sex-race group				
White men	14	34	50	71
White women	40	55	34	11
Black men	8	4	11	17
Black women	38	7	5	2
Educational attainment				
<High school	30	13	14	19
High school or vocational	41	45	38	43
College degree or higher	29	43	49	38
Occupation				
Managerial	18	29	34	25
Non-managerial	69	59	53	57
Retired	13	13	14	19
Income				
<$12,000	22	7	7	10
$12,000-$49,999	65	60	52	60
$50,000+	13	34	41	30
Physical activity index score	2.2 (0.7)	2.5 (0.8)	2.6 (0.8)	2.4 (0.8)
Diet score	12.3 (3.8)	11.8 (3.9)	12.0 (3.8)	12.0 (3.7)
Cigarette smoking				
Current	13	23	30	46
Former	16	33	43	43
Never	71	44	27	12

	Lifetime abstainer	≤3	4-17	18+
Blood pressure, mmHg				
Systolic	124.0 (19.9)	117.9 (17.3)	120.9 (18.4)	127.1 (18.8)
Diastolic	74.5 (11.5)	72.2 (10.6)	74.3 (11.2)	77.0 (11.5)
LDL-c, mg/dL	139.4 (40.7)	136.3 (38.1)	135.3 (39.7)	132.4 (39.8)
HDL-c, mg/dL	37.8 (10.7)	37.0 (10.9)	39.4 (11.7)	40.5 (12.1)
Body mass index, kg/m^2	29.0 (6.1)	27.1 (4.9)	26.6 (4.5)	26.7 (4.5)
Coronary artery disease	2	3	3	4
Diabetes	13	7	7	7

* Population includes never and current drinkers (N=12,799), excluding participants with history of stroke, not of white or black race, blacks from Washington County or Minnesota, and missing alcohol information (N=366). Proportions reflect person-time distributions of covariates. Values are presented as %, or mean (SD), unless otherwise specified

Over a median follow-up of 22.6 and 22.7 years, respectively, there were 773 IS and 81 ICH. Ischemic stroke incidence rates per 100,000 person-years increased across alcohol intake categories: 251 for ≤3/wk, 313 for 4-17/wk, 435 for ≥18/wk, and 368 for abstainers (Table 24). After adjustment, light and moderate drinking were not associated with IS (HR=0.98, 95% CI 0.79-1.21; 1.06, 0.84-1.34, respectively; Table 24). Heavier drinking was associated with a 31% relative increase (HR=1.31, 0.92-1.86).

Table 24. Hazard ratios and 95% confidence intervals (CI) for the association of alcohol consumption and IS and ICH

	Alcohol Consumption, drinks per week				N	Events
	Lifetime abstainer	≤3	4-17	18+		
Ischemic stroke						
Events	283	249	189	52		
Person-years	76,975	99,126	60,479	11,947		
Incidence rate per 100,000 PY (95% CI)	367.7 (324.8-410.5)	251.2 (220.0-282.4)	312.5 (268.0-357.1)	435.2 (316.9-553.6)		
Hazard ratio (95% CI)						
Unadjusted	1	0.68 (0.57-0.81)	0.85 (0.71-1.02)	1.22 (0.91-1.64)	12,433	773
Model 1*	1	0.90 (0.74-1.10)	0.97 (0.78-1.20)	1.17 (0.84-1.63)	12,407	771
Model 2**	1	0.98 (0.79-1.21)	1.06 (0.84-1.34)	1.31 (0.92-1.86)	11,452	684

	Lifetime abstainer	≤3	4-17	18+	N	Events
Intracerebral hemorrhage						
Events	31	20	26	4		
Person-years	78,599	100,456	61,415	12,296		
Incidence rate per 100,000 PY (95% CI)	39.4 (25.6-53.3)	19.9 (11.2-28.6)	42.3 (26.1-58.6)	32.5 (0.7-64.4)		
Hazard ratio (95% CI)						
Unadjusted	1	0.50 (0.29-0.89)	1.08 (0.64-1.81)	0.85 (0.30-2.40)	12,433	81
Model 1[*]	1	1.03 (0.55-1.93)	2.07 (1.10-3.87)	1.48 (0.47-4.63)	12,407	81

[*]**Model 1** is adjusted for age (linear), center-race interaction (5 levels), sex, educational attainment (<high school, high school, college or higher), and cigarette smoking (current, former, never).
[**]**Model 2** is additionally adjusted for marital status (married, divorced/separated, widowed, never married), LDL-C (quadratic), diet score (linear; comprised of % energy from trans-fatty acid and ω-3 fatty acid, fiber (g), folate (mg), glycemic load, and polyunsaturated:saturated fatty acid ratio), physical activity at work, leisure, sports (continuous), and prevalence of coronary artery disease (binary) and diabetes (binary) at baseline.

Associations of light drinking compared with abstention were close to the null and largely similar across sex-race sub-groups, though whites had lower HRs compared with blacks (Figure 15). Moderate drinking estimates differed somewhat across subgroups, although confidence intervals overlapped considerably: there was a protective effect among white women (HR=0.63, 0.39-1.02), effects closer to the null in white men and black women, and increased risk among black men.

Figure 15. Associations of midlife alcohol consumption and IS by sex-race group

Diamonds and whiskers represent hazard ratios with 95% confidence intervals, respectively. The left panel compares effects by race among women; the right panel compares effects by race among men.
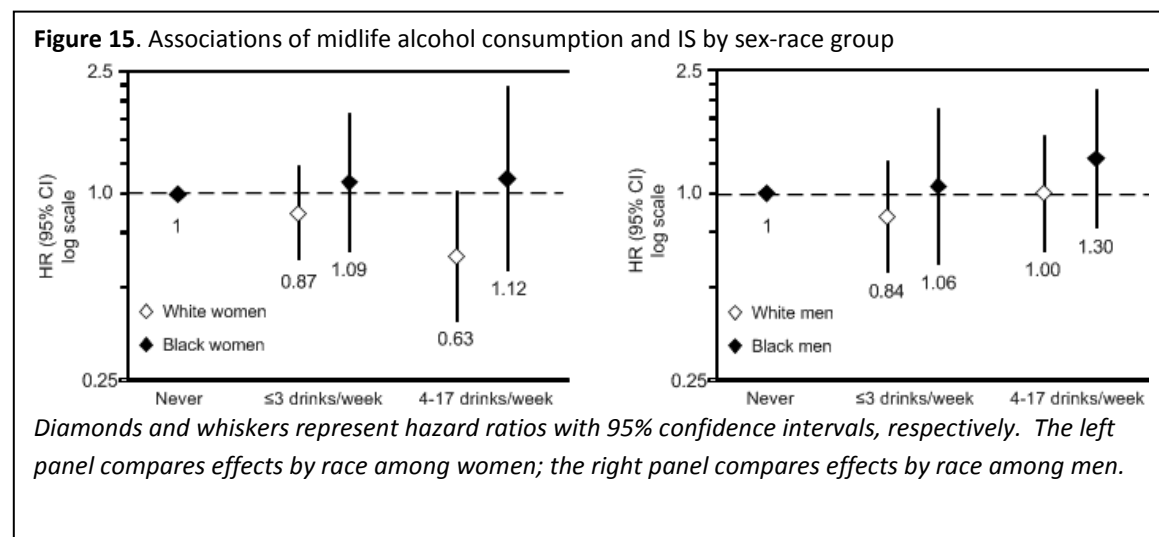
ICH incidence rates ranged from 20 per 100,000 person-years among light drinkers to 42 among moderate drinkers. We found no association with light drinking (HR=1.03, 0.55-1.93) after adjustment for age, race, sex, smoking status and education (Table 24). Both moderate and heavy drinking, however, were associated with higher ICH rates compared with abstention (HR$_{moderate}$=2.07, 1.10-3.87; HR$_{heavy}$=1.48, 0.47-4.63). The precision of these estimates was low because of small numbers of events, which also precluded adjustment for additional lifestyle factors. Effect estimates for total stroke (IS+ICH) were similar to those for IS alone: HR$_{light}$=0.98, 0.80-1.20; HR$_{moderate}$=1.13, 0.91-1.42; and HR$_{heavy}$=1.36, 0.97-1.91.

Results from Cox models with quadratic spline for alcohol intake did not support a J-shaped relationship (Figure 16). Furthermore, the log-hazard ratio of IS was roughly linear across intake (β=0.06 for a 1 drink-per-week increase; HR=1.06, 0.99-1.13). Additional quadratic (p=0.3) and cubic terms (p=0.9) were not statistically significant compared with the linear model.

Figure 16. Dose-response relationship between midlife alcohol consumption and IS estimated with quadratic splines.

Shading indicates 95% confidence bands. Knots were placed at 0.5, 3, and 17 drinks/week. Point estimates and 95% confidence intervals from categorical analysis are overlaid at the median of each category.
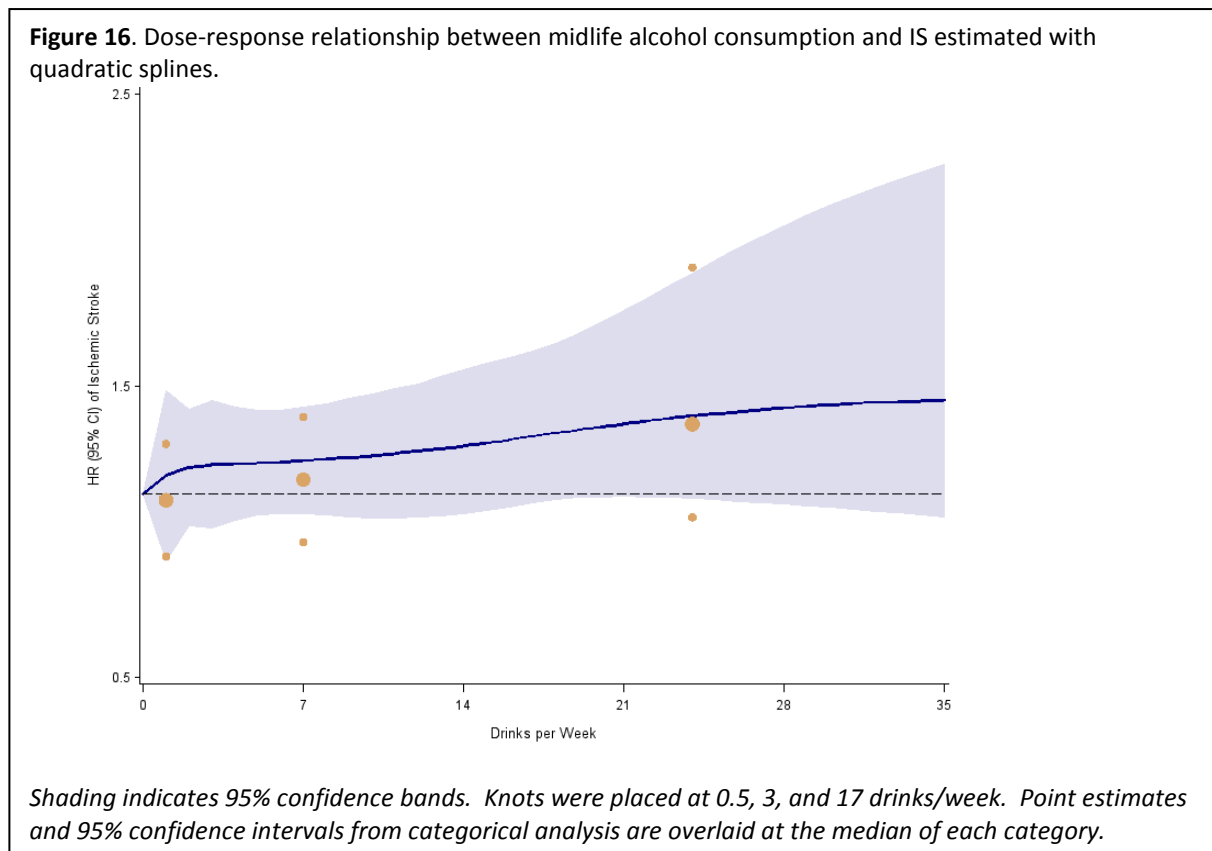
More than one-quarter of the participants died over follow-up, ranging from 24% in light to 42% in heavier drinkers. In sensitivity analyses, we estimated sub-distribution hazards models that account for this underlying risk of mortality to produce HRs that reflect the relative cumulative incidence – or risk - in our population. As expected, effect estimates were attenuated slightly for heavy drinkers, but conclusions were largely unchanged; light and moderate alcohol consumption were not associated with reduced IS risk compared with abstention and may increase ICH risk (Table 25).

Table 25. Cause-specific and subdistribution hazard ratios and 95% confidence intervals (CI) for the association of alcohol consumption and IS and ICH

	Alcohol Consumption, drinks per week			
	Lifetime abstainer	≤ 3	4-17	18+
Ischemic stroke[*]				
Hazard ratio (95% CI)				
Unadjusted	1	0.68	0.85	1.22
		(0.57-0.81)	(0.71-1.02)	(0.91-1.64)
Cause-specific	1	0.98	1.06	1.31
		(0.79-1.21)	(0.84-1.34)	(0.92-1.86)
Subdistribution	1	0.97	1.06	1.19
		(0.79-1.21)	(0.84-1.35)	(0.83-1.72)
Intracerebral hemorrhage[**]				
Hazard ratio (95% CI)				
Unadjusted	1	0.50	1.08	0.85
		(0.29-0.89)	(0.64-1.81)	(0.30-2.40)
Cause-specific	1	1.03	2.07	1.48
		(0.55-1.93)	(1.10-3.87)	(0.47-4.63)
Subdistribution	1	1.07	2.13	1.37
		(0.55-2.05)	(1.07-4.23)	(0.43-4.40)

[*] IS models are adjusted for covariates listed in Model 2 of Table 2.
[**] ICH models are adjusted for covariates listed in Model 1 of Table 2.

5.5 Discussion

We did not find support for a J-shaped relationship between mid-life alcohol consumption

and IS in this study of a bi-racial population-based cohort of U.S. adults. There was little effect of drinking on rates of IS until heavier drinking levels. ICH rates were increased even at moderate levels of drinking compared with lifetime abstention, though strict monotonicity was not observed and confidence intervals were wide. Sex-race stratified results suggest a possible protective effect of light-to-moderate drinking on IS among white women, but not other groups. Heterogeneity by sex-race may reflect different drinking patterns, lifestyle and socio-cultural factors, measurement error, or imprecision in our estimates.

Alcohol consumed moderately in mid-life has been suggested to reduce IS risk through its chronic anti-thrombotic, anti-inflammatory, and anti-atherogenic effects. It beneficially alters several vascular risk factors including high-density lipoprotein cholesterol, fibrinogen, blood pressure, platelet aggregation, inflammatory markers and insulin sensitivity compared with no drinking.[6, 42-44] In contrast, high doses of alcohol have well-established deleterious effects mediated through elevations in blood pressure, reduction in cerebral blood flow, and development of atrial fibrillation and cardiomyopathy that in turn increase stroke risk.[18] Alcohol at lower doses may also increase the risk for hemorrhage through hemostatic changes that promote bleeding. Biological mechanisms may differ by sex. Women attain higher blood alcohol levels than men because of higher body fat percentages, lower water concentrations, and slower alcohol metabolism.[49]

A J-shaped relationship between alcohol consumption and ischemic stroke is frequently reported.[6, 14, 39, 166, 169] For example, consumption of ≤1 drink/d was associated with a 20% reduced risk of ischemic stroke and 1-2 drinks with a 28% reduced risk in pooled data analysis.[6] Pooled hazard ratio estimates may be limited by inclusion of non-validated stroke events, lack of adjustment for lifestyle factors such as physical activity and diet, and inclusion of causal intermediates (e.g. blood pressure and HDL-C) in regression models. Our results, based on well-validated stroke events, were controlled for important confounders and suggest no clear J-shaped

relationship. The dose-response relationship we estimated was imprecise, but was approximately

linear and above the null across alcohol intake.

Stronger protective effects of low-dose alcohol may be present among women compared

with men.[6, 14] Meta-analyzed hazard ratios comparing light drinking with abstention are 0.66, 95% CI

0.61-0.71 for women and 0.80, 0.67-0.96 for men, consistent with our results for white women, but

not men, in the ARIC Study.[6] Women who consumed less than ~2 drinks/d in the Nurses' Health

Study had a 12-18% lower risk of IS compared with non-drinkers.[169] The Nurses' Health Study

population was almost exclusively white and our results align with these, showing similar effects of

moderate drinking in white, but not black, women in the ARIC study. Our results for men were

similar to those reported by the Health Professionals Follow-up Study that found no association for

<1 drink/d and slightly elevated risk at ≥1 drinks/d.[167] In addition to sex differences, we noted

possible differences by race such that blacks had higher HRs than whites. These differences may be

explained by different drinking patterns between whites and blacks.[229] Interactions between

quantity and volume may exist such that moderate drinking is beneficial when consumed at

moderate but not high frequency.[167] One of the few studies to report race-specific results found

similar protective effects of light drinking in both blacks and whites. Differences between these and

our study results may reflect the timing of alcohol measurement (mid-life at baseline in ARIC vs.

post-stroke self-report) and our adjustment for diet and physical activity.[39]

ICH risk appears to increase log-linearly with increasing alcohol consumption based on

current literature. Consumption of 2 or fewer drinks per day compared with abstention was

associated with a 12-24% reduced risk of hemorrhagic stroke in the Nurses' Health Study. We found

no evidence of a protective effect of light drinking in our population. Rates increased even at

moderate drinking levels (4+ drinks/wk). Our results, however, were limited by small numbers of

events.

In sensitivity analysis, we assessed whether alcohol increases the risk of experiencing stroke – as opposed to the rate of disease – as this is a relevant question for population scientists estimating disease burden. The results of sub-distribution hazards models were unchanged for light and moderate drinking categories and attenuated slightly for heavier drinking compared with cause-specific hazards.

Our results should be interpreted in light of several limitations. Participants may under-report alcohol consumption. While we were unable to quantify errors or calibrate effect estimates, construct and rank-order validity of our measure was supported by positive correlations of alcohol with both HDL-C and blood pressure. Selection bias from loss to follow-up is unlikely as it was rare (<5%) and independent of alcohol consumption conditional on model covariates. Residual confounding is possible, although we adjusted for many important confounders to minimize bias. The prevalence of heavy drinking was low (7.5% consumed >2 drinks/d) and limited our ability to estimate the impact of heavier drinking. Finally, race-specific results may not generalize to the U.S. population outside of the ARIC communities.

Strengths of our study include a prospective study design with ~23 years of follow-up, a bi-racial population, and robust ascertainment of stroke events. Alcohol consumption was assessed using a validated instrument with beverage-specific questions (thus reducing under-reporting) that differentiated never from former drinkers. We had rich covariate data, allowing adjustment for lifestyle factors, smoking, and SES.

Public health recommendations on alcohol consumption must consider both its associated benefits and risks. While light-to-moderate intake may reduce the risk of some cardiovascular outcomes, harmful effects may exist even at low doses (e.g., dependency, cancer, medication interaction). As such, the American Heart Association does not recommend initiation of drinking for

disease prevention.[47] Our results support this recommendation. We found no risk reduction for IS

or ICH with light-to-moderate mid-life alcohol consumption and increased risks at heavier intake

levels. Our observed sex-race differences, limited by sample size, warrant further investigation in

other cohorts. Understanding the alcohol-stroke relationship would also be advanced by assessing

dose-dependent exposure measurement errors and estimating their impact on effect estimates.

CHAPTER 6. MANUSCRIPT #2: MIDLIFE ALCOHOL CONSUMPTION AND COGNITIVE DECLINE IN THE ATHEROSCLEROSIS RISK IN COMMUNITIES STUDY

6.1 Overview

Background: The effect of alcohol at low-to-moderate doses on cognitive aging trajectories is uncertain. Identifying modifiable factors that may delay or prevent cognitive impairments is critical given the high burden on patients, their caregivers, and the healthcare system. We estimated additional 20-year cognitive changes according to self-reported alcohol consumption.

Methods: We analyzed 13,704 Black and White adults in the Atherosclerosis Risk in Communities Study with median age of 57 years at baseline in 1990-1992. Alcohol consumption was self-reported as usual drinks per week and categorized as never, former, light (≤3), moderate (4-17), and heavier (≥18) drinking. Cognitive status was assessed thrice over follow-up using 3 tests of executive function, memory, and processing speed. Linear regression with generalized estimating equations was used to estimate the difference in rates of decline according to alcohol intake. In sensitivity analysis, we used multiple imputation methods to address informative attrition by imputing outcome and covariate data.

Results: Over 20 years of follow-up, light and moderate drinkers compared with abstainers had similar additional changes of 0.019 and -0.002 global z score units (95% CIs: -0.032 to 0.070 and -0.066 to 0.061, respectively) while heavier and former drinkers had 0.041 and 0.035 more decline (95% CIs: -0.152 to 0.070 and -0.096 to 0.026). Patterns were similar across specific tests, with some suggestion that light drinkers had slower cognitive changes in verbal fluency (DWRT and WFT).

Conclusion: Self-reported light and moderate alcohol consumption at mid-life were not associated with additional 20-year cognitive changes compared with no drinking. Heavier consumption as well

as former drinking, however, were associated with slightly accelerated declines.

6.2 Introduction

Cognitive aging is not uniform across the population; some individuals experience very little decline well into their 80s while others exhibit varying degrees of decline beginning in their 60s.[59] Slowing cognitive decline is important for increasing quality of life and for reducing the lifetime risk of developing dementia, currently estimated at 1 out of 5 to 6 adults.[9] Alcohol consumption has been associated with cross-sectional differences in cognitive function,[197] but its effect on cognitive aging trajectories is unknown.[33] Estimating these effects may lead to additional avenues for preventing or delaying the onset of cognitive impairments and dementia.

Seventy percent of U.S. adults report current drinking and more than one-quarter report excessive drinking (either heavy episodic or average consumption).[50, 67] Although heavier alcohol intake is known to damage the brain and may increase the risk of vascular disease, [72, 76] other studies have actually suggested that *modest* alcohol consumption might be protective against cognitive decline, although this concept remains controversial.[1, 18, 20-26, 33] Hypothesized mechanisms include reduction in vascular disease risk as well as increases in cerebral blood flow and facilitation of memory.[18, 44, 72, 98] A meta-analysis reported ~11% lower relative risk of dementia and Alzheimer's disease, and to a lesser degree vascular dementia and 'significant' cognitive decline in light-to-moderate drinkers compared with nondrinkers.[230] Examining the effects of alcohol on rates of cognitive decline as opposed to risk of clinical endpoints has advantages; it does not rely on prevalent cases (minimizing survivor bias), can inform as to the etiology of small, pre-clinical changes in cognition, and is less influenced by confounding factors.[231] Among studies with repeated cognitive measures, only one corrected for attrition,[27] and there were the following additional limitations: combining never and former drinkers into a single referent group,[19, 21, 22 21, 28, 29, 31, 32, 35]

short (<5-year) follow-up periods,[20, 21, 23, 25 1, 21, 27-32, 34] lack of confounder adjustment, [1, 19, 20, 24-26, 28-32, 34-37]and adjustment for mediators (e.g., HDL-C).[1, 19, 21, 22, 24-27, 30-32, 34, 35]

In our study, we estimated the association between self-reported, usual mid-life alcohol consumption and 20-year cognitive decline in a biracial population-based cohort drawn from 4 US communities, the Atherosclerosis Risk in Communities (ARIC) study. We use multiple imputation with chained equations (MICE) to correct for selection bias due to visit nonattendance and death.

6.3 Methods

Study Population

The ARIC study is a population-based cohort recruited using probability sampling of adults aged 45-64 years from 4 US communities: Forsyth County, NC; Jackson, MS; the suburbs of Minneapolis, MN; and Washington County, MD. The ARIC study design and rationale are described in detail elsewhere.[204] The racial distribution of the sample from Minneapolis and Washington County is primarily White, whereas Blacks were oversampled in

Figure 17. The ARIC study timeline and number of participants attending visits 1-5

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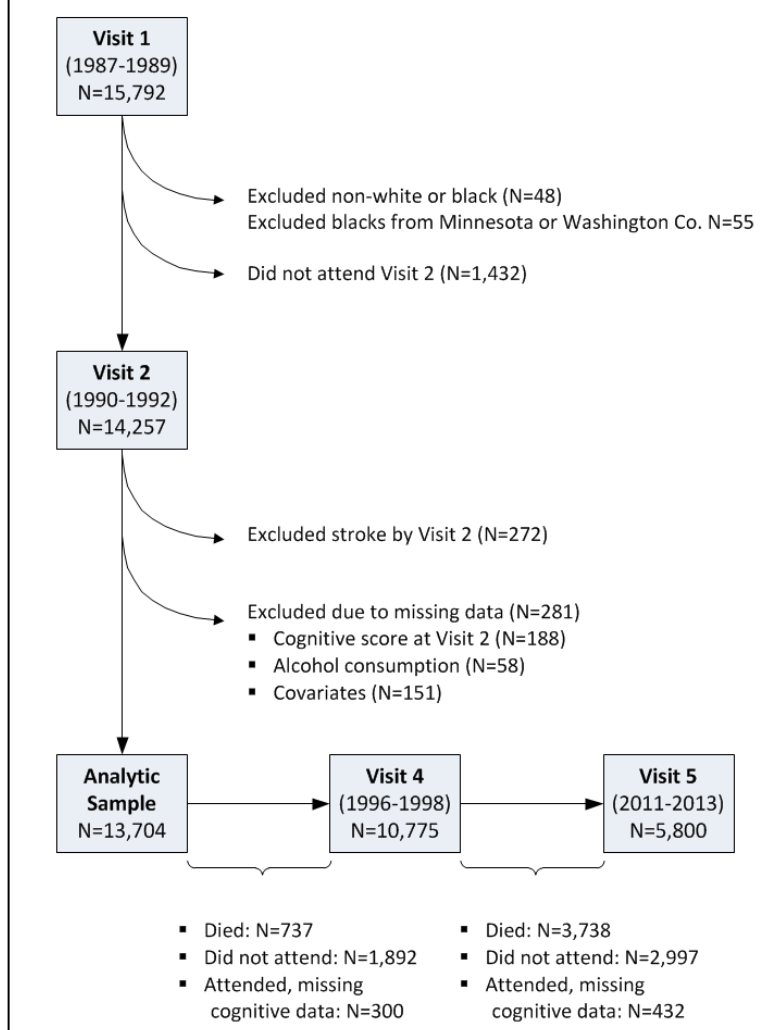
Forsyth County and exclusively sampled in Jackson. A total of 15,792 participants were enrolled at visit 1(1987-1989) and underwent an in-home interview and physical examination. During annual telephone follow-up, ARIC investigators obtained information on hospitalizations and medical history over the preceding year. Four additional study visits consisting of an interview and physical examination occurred over the subsequent 25 years (Figure 17). The population for analysis included participants attending visit 2 (baseline for this analysis). Exclusions included participants not classified as white or black (N=48); blacks from Minnesota or Washington County (N=55); prevalent stroke at visit 2 (N=272); missing data for alcohol consumption, baseline cognitive score, or covariates (total N=281). After these exclusions, the analytic cohort totaled 13,704, 87% of the initial cohort.

Alcohol Assessment

Alcohol consumption was measured using an interviewer-administered dietary questionnaire developed in accordance with the validated Willett 66-item food frequency questionnaire (FFQ).[208] Participants were asked at visit 2 to report whether they currently consumed alcoholic beverages and if so, their usual intake over the past 12 months in units of drinks per week. Separate intake frequency questions were asked for standard drinks of wine (4-oz), beer (12-oz), and hard liquor (1.5-oz).

Measurement of Cognition

Cognitive function was measured at visits 2 (1990-1992), 4 (1996-1998), and 5 (2011-2013) using three tests: the Delayed Word Recall Test (DWRT), the Digit Symbol Substitution Task (DSST), and the Word Fluency Task (WFT). These tests measured several cognitive domains including short-term memory, verbal learning, processing speed, executive function, and expressive language. Tests were administered by trained and certified staff in a quiet environment without distraction.

Administrators were re-certified annually, and both technique and protocol adherence were monitored over the study. We generated z scores for each test at each study visit standardized to the population mean and standard deviation at visit 2. A global score was calculated as the average of the three test-specific z scores and standardized to the global mean and standard deviation at the second study visit.

Covariates

Confounders were identified based on substantive knowledge of factors associated with alcohol[129] and risk of cognitive decline.[33, 203] Covariates to include in regression models were identified with directed acyclic graphs[232]: demographic characteristics (age, gender, race-center, education), lifestyle factors (smoking, physical activity, social support, diet), and medical history (diabetes mellitus, coronary artery disease [CAD]). Apolipoprotein E ε4 alleles have been implicated in risk of cognitive decline and were included as an important predictor of the outcome.

Age, sex, race, and education (<high school; high school or vocational school; some college or more) were self-reported at visit 1 as was usual dietary intake, measured with a FFQ.[208] We calculated a diet score, as described elsewhere, based on quintile values for 6 dietary components: percent energy from trans-fatty acid, percent energy from omega-3 fatty acid, fiber (g), folate (mg), glycemic load, and polyunsaturated:saturated fatty acid ratio.[225] At visit 2, smoking status was self-reported (never; current; former), physical activity was measured using the Baecke questionnaire,[209] and social support was measured with the 40-item Interpersonal Support Evaluation List and the Lubben Social Network Scale.[233] Medical history at visit 2 included diabetes (self-reported physician diagnosis, fasting glucose >126 mg/dL, or self-reported pharmacologic treatment for diabetes) and CAD (electrocardiogram-adjudicated myocardial infarction [MI] or any of self-reported: MI, heart/arterial surgery, coronary bypass, or angioplasty).

Statistical Analysis

Linear regression models fit with generalized estimating equations (GEE) were used to estimate rates of cognitive decline by category of alcohol consumption.[219] Valid standard errors were obtained with the "sandwich" estimator and we assumed an unstructured correlation matrix. Time since visit 2, our study baseline, was modeled with linear splines (knot at 6 years) and all models were adjusted for the covariates listed above and their interactions with time. Twenty-year declines at each level of alcohol intake were estimated for all covariates after centering to represent the 'average' ARIC participant and interactions between alcohol and time were used to estimate additional 20-year declines compared with lifetime abstainers. Effect estimates represent changes in z score units and were scaled to represent additional years of aging by dividing the 20-year adjusted differences by the annual average population change. In secondary analyses, we tested for differences in effect estimates by sex-race and APOE ε4 using stratified models and tests of interaction terms between sex-race or APOE and exposure by time. We also estimated trends in additional changes in 20-year z scores across continuous alcohol drinks per week among current drinkers and lifetime abstainers. Finally, we repeated analyses using the cumulative average alcohol consumption (from measurements at visits 1 and 2) and compared these results to those of primary analysis of baseline (visit 2) alcohol consumption.

Sensitivity Analysis

Missing outcome data in GEE models are assumed to be missing completely at random, an assumption likely to be violated in our data as both visit attendance and death were associated with baseline cognition and alcohol consumption. We accounted for this informative missingness using multiple imputation with chained equations (MICE).[221, 222] Missing data at visits 4 and 5 were imputed with 25 iterations. GEE analysis models were run on each of the 25 datasets and combined into a single estimate with variance calculated to account for the uncertainty in the imputation

process as well as the within-dataset variance. Covariates used in the imputation models included

all covariates in the analysis model, as well as predictors of missingness: self-reported outcomes on

annual follow-up (stroke, CAD, diabetes, hypertension, lung disease); nursing home residence; proxy

respondent on annual follow-up; functional status; hospitalizations; measured cognitive scores;

clinical dementia rating score; Mini Mental State Exam (MMSE) and telephone interview for

cognitive status (TICS) scores; and suspected dementia based on prior hospitalization with an ICD-9

code for dementia or need for proxy interview on annual calls.

Additional sensitivity analyses were conducted to test for floor effects by dropping

participants in the lowest 5% of the global z score distribution s at visit 2. In addition, we assessed

the sensitivity of our results to the selection of exposure cut-points by comparing our results with

those obtained using alternative cut-points from other studies and in alcohol consumption

guidelines. We used Statistical Analysis Software Version 9.2 (SAS Inc) and STATA 13.0 (StataCorp)

for analyses.

6.4 Results

Participant characteristics

Over one-third of the ARIC participants were light drinkers, consuming 3 or fewer glasses of

alcohol per week (Table 26). Roughly one-fifth of participants each were moderate drinkers of 4 to

17 drinks per week, lifetime abstainers, and former drinkers and only 4% consumed 18 or more

drinks per week. Women comprised the largest proportion of abstainers and light drinkers, and

white men accounted for nearly three-quarters of heavier drinkers. Light-to-moderate drinkers had

higher educational attainment than heavier drinkers, abstainers and former drinkers. High

perceived social support and large social network size were less common for heavier and former

drinkers. Current smoking was reported by 42% of heavier drinkers but only 22% of light drinkers.

Diabetes was more than twice as prevalent in abstainers compared with current drinkers. Finally,

blood pressure and HDL-cholesterol increased across alcohol consumption level.

Table 26. Characteristics of ARIC Participants at Visit 2 (1990-1992) According to Self-Reported Usual Mid-Life Alcohol Consumption*

	Alcohol Consumption, usual drinks per week				
	Abstainers	**≤3**	**4-17**	**≥18**	**Former**
Number of participants	3073	4942	2335	510	2844
Ethanol intake, g/week	0	0 (0-15)	98 (72-151)	318 (277-423)	
Drinks per week, median (IQR)	0	0 (0-1)	7 (5-11)	24 (20-31)	
Age, years	57.6 (5.7)	56.6 (5.7)	56.6 (5.7)	57.2 (5.8)	57.3 (5.7)
Sex-race group					
White men	16.2	35.9	51.5	72.4	37.0
White women	46.4	50.8	34.0	11.2	27.5
Black men	5.5	5.4	9.9	14.5	14.2
Black women	31.8	7.9	4.6	2.0	21.4
Educational attainment					
Less than high school	28.6	12.4	12.1	19.0	35.1
High school or vocational	43.1	44.7	38.7	42.6	37.7
College degree or higher	28.3	42.9	49.2	38.4	27.2
Large social network	80.4	78.3	76.2	69.8	73.7
High perceived social support	80.1	81.3	81.0	77.7	76.4
Sports physical activity index	2.3 (0.7)	2.5 (0.8)	2.6 (0.8)	2.5 (0.9)	2.4 (0.8)
Diet score	12.4 (3.8)	11.9 (3.9)	12.1 (3.8)	12.0 (3.7)	11.9 (3.9)
Cigarette smoking status					
Current	11.6	22.0	29.3	42.4	24.2
Former	17.7	39.9	47.7	44.7	47.0
Never	70.7	38.1	23.1	12.9	28.8
Apolipoprotein E ε4 alleles					
0	68.8	70.1	69.1	71.8	68.2
1	28.1	27.3	28.4	27.2	29.2
2	3.1	2.6	2.5	1.0	2.6
Coronary artery disease**	3.4	4.4	5.1	6.3	9.1
Diabetes mellitus	17.6	8.8	7.2	6.9	20.4
Systolic blood pressure, mmHg	123 (19)	119 (18)	122 (18)	128 (19)	122 (19)
Visit 5 (2011-2013) status					
Attended	44.4	50.7	48.0	35.1	37.2
Died	30.4	28.0	31.4	48.4	41.5
Alive, did not attend	25.2	21.3	20.6	16.5	21.3

* Includes 13,704 white and black participants attending study visit 2 without history of stroke or missing exposure, covariates, or baseline cognitive score. Values indicate % of mean (SD) unless otherwise indicated

Univariate associations between alcohol and cognitive decline

Baseline cognitive z scores were considerably lower for abstainers and former drinkers compared with current drinkers (Table 27). Among current drinkers, there was a tendency for heavier drinkers to have lower cognitive scores on all tests, but differences were small. Average unadjusted 20-year declines in global z scores were largest for heavier drinkers (-0.85) and smallest for abstainers (-0.76). This trend was relatively consistent across the specific tests; however, light drinkers had the largest decline on the DSST and the least decline on the WFT of any group.

Table 27. Mean Global and Test-Specific z Scores at Visits 2 (1990-1992), 4 (1996-1998), and 5 (2011-2013) by Alcohol Intake in the ARIC study

	Alcohol Consumption, usual drinks per week				
	Abstainers	≤3	4-17	≥18	Former
Global z score					
Visit 2	-0.22	0.23	0.23	0.00	-0.34
Visit 4	-0.22	0.16	0.17	-0.07	-0.36
Visit 5	-0.78	-0.43	-0.42	-0.69	-0.91
20-year decline[*]	-0.76	-0.80	-0.82	-0.85	-0.80
Delayed word recall test					
Visit 2	-0.07	0.12	0.08	-0.08	-0.17
Visit 4	-0.07	0.07	0.02	-0.14	-0.22
Visit 5	-0.98	-0.82	-0.91	-1.14	-1.14
20-year decline[*]	-0.94	-0.98	-1.02	-1.11	-1.02
	Abstainers	≤3	4-17	≥18	Former
Digit symbol substitution task					
Visit 2	-0.26	0.28	0.22	-0.06	-0.38
Visit 4	-0.29	0.15	0.11	-0.16	-0.43
Visit 5	-0.70	-0.31	-0.33	-0.57	-0.81
20-year decline[*]	-0.64	-0.73	-0.72	-0.66	-0.65
Word fluency test					
Visit 2	-0.19	0.14	0.24	0.15	-0.25
Visit 4	-0.16	0.14	0.24	0.11	-0.21
Visit 5	-0.27	0.09	0.19	0.01	-0.29
20-year decline[*]	-0.21	-0.16	-0.17	-0.22	-0.20

* Mean 20-year declines in z scores were estimated from unadjusted linear models fit with GEE that included time splines and alcohol intake category

Effect of alcohol on additional adjusted 20-year changes in cognition

After adjustment for covariates, compared to abstainers, light and moderate drinkers had similar 20-year rates of decline (0.019 z score units; 95% CI -0.032, 0.070 and -0.002; -0.066, 0.061; Table 28). Both heavier (-0.041; 95% CI -0.152, 0.070) and former drinkers (-0.035; -0.096, 0.026) had somewhat steeper declines compared with abstainers. To provide context for these z score changes, we estimated the population decline in z score and scaled the effect estimates to represent additional years of cognitive aging. Light consumption was associated with approximately 0.5 years less aging over 20 years than the average ARIC participant (95% CI -1.8 to 0.8) and heavier and former drinking with 1 (-1.8 to 3.8) and 0.9 (-0.7 to 2.4) years, respectively, of additional aging compared with the overall population decline. The trend in additional cognitive change across drinks per week mirrors the findings from categorical analysis; there was little additional change at lower levels of consumption and small, non-significant acceleration of decline roughly around 14 drinks per week (Figure 18).

Table 28. Estimated Average 20-Year Cognitive Decline and Additional Adjusted 20-Year Cognitive Change Associated with Alcohol Consumption Category in the ARIC study, Complete Case Analysis compared with MICE-Corrected Analysis

	Global z score		Delayed Word Recall Test z score	
	Complete Case	MICE Imputed	Complete Case	MICE Imputed
20-Year Average Decline (SD)				
Abstainers (ref)	-0.89 (-0.94, -0.85)	-0.97 (-1.03, -0.91)	-1.13 (-1.20, -1.05)	-1.18 (-1.27, -1.08)
Light (≤3 drinks/week)	-0.88 (-0.91, -0.84)	-0.93 (-0.98, -0.88)	-1.09 (-1.15, -1.03)	-1.13 (-1.20, -1.05)
Moderate (4-17 drinks/week)	-0.90 (-0.95, -0.85)	-0.99 (-1.05, -0.92)	-1.12 (-1.19, -1.04)	-1.19 (-1.30, -1.09)
Heavier (≥18 drinks/week)	-0.94 (-1.04, -0.83)	-1.01 (-1.13, -0.88)	-1.19 (-1.35, -1.02)	-1.26 (-1.44, -1.07)
Former	-0.93 (-0.98, -0.88)	-0.99 (-1.06, -0.92)	-1.17 (-1.25, -1.09)	-1.21 (-1.30, -1.12)
20-Year Additional Decline (SD)				
Light vs. Abstainers	0.019 (-0.032, 0.070)	0.036 (-0.027, 0.099)	0.037 (-0.047, 0.121)	0.049 (-0.055, 0.153)
Moderate vs. Abstainers	-0.002 (-0.066, 0.061)	-0.017 (-0.090, 0.056)	0.012 (-0.090, 0.114)	-0.019 (-0.134, 0.097)
Heavier vs. Abstainers	-0.041 (-0.152, 0.070)	-0.035 (-0.164, 0.093)	-0.060 (-0.238, 0.119)	-0.080 (-0.265, 0.105)
Former vs. Abstainers	-0.035 (-0.096, 0.026)	-0.024 (-0.093, 0.046)	-0.040 (-0.140, 0.059)	-0.034 (-0.133, 0.066)
	Digit Symbol Substitution Test z score		**Word Fluency Test z score**	
20-Year Average Decline (SD)				
Abstainers (ref)	-0.74 (-0.77, -0.71)	-0.77 (-0.81, -0.73)	-0.26 (-0.30, -0.22)	-0.29 (-0.34, -0.24)
Light (≤3 drinks/week)	-0.75 (-0.78, -0.73)	-0.77 (-0.81, -0.74)	-0.22 (-0.25, -0.19)	-0.23 (-0.28, -0.19)
Moderate (4-17 drinks/week)	-0.77 (-0.81, -0.74)	-0.81 (-0.86, -0.76)	-0.23 (-0.27, -0.18)	-0.26 (-0.32, -0.20)
Heavier (≥18 drinks/week)	-0.77 (-0.85, -0.70)	-0.77 (-0.85, -0.69)	-0.25 (-0.35, -0.16)	-0.29 (-0.41, -0.17)
Former	-0.78 (-0.81, -0.75)	-0.80 (-0.84, -0.76)	-0.24 (-0.28, -0.20)	-0.27 (-0.33, -0.21)
20-Year Additional Decline (SD)				
Light vs. Abstainers	-0.013 (-0.049, 0.024)	-0.005 (-0.049, 0.040)	0.041 (-0.005, 0.088)	0.056 (0.007, 0.105)
Moderate vs. Abstainers	-0.029 (-0.075, 0.016)	-0.040 (-0.098, 0.019)	0.034 (-0.023, 0.091)	0.026 (-0.038, 0.090)
Heavier vs. Abstainers	-0.033 (-0.114, 0.048)	-0.006 (-0.083, 0.072)	0.008 (-0.096, 0.111)	-0.006 (-0.130, 0.118)
Former vs. Abstainers	-0.039 (-0.081, 0.003)	-0.030 (-0.074, 0.015)	0.020 (-0.033, 0.072)	0.017 (-0.042, 0.076)

Models are adjusted for age, age^2, sex, race-center (whites in NC, MN, and MD; blacks in NC and MS), education (<high school; high school, GED, vocational school; college and above), smoking status (never; former; current), prevalent diabetes, prevalent CAD, physical activity (continuous), apolipoprotein E ε4 genotype allele number (0; 1; 2) social support (continuous), diet score (continuous), time since visit 2 as a linear spline with a knot at 6 years, and all interactions between covariates and time. Values are presented as z score, or change in z score, (95% confidence intervals)

Figure 18. Adjusted additional 20-year cognition change in global and test-specific z scores according to alcohol intake category
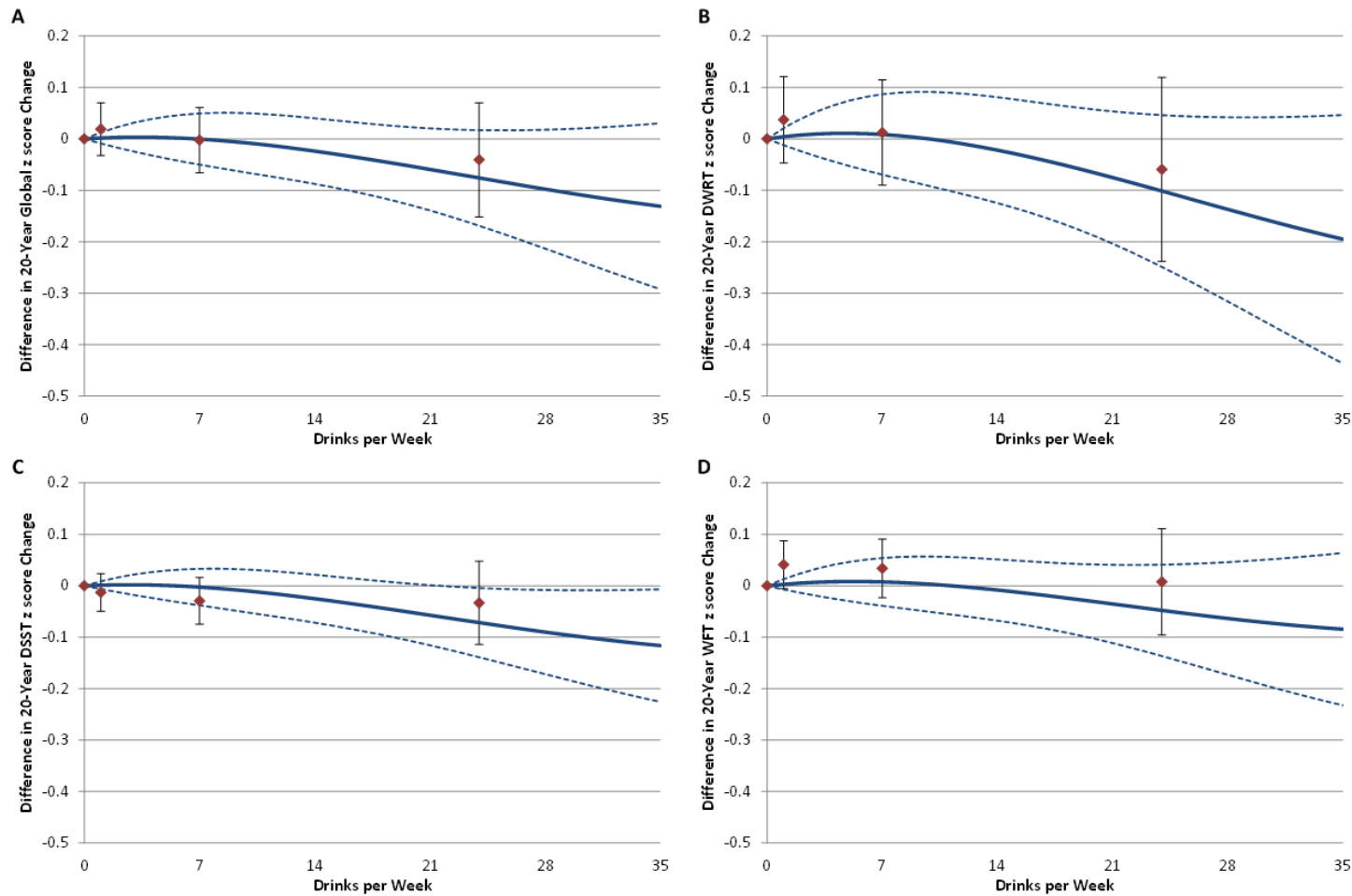
Estimates were obtained from linear models fit with GEE on complete case data and were adjusted for covariates. Data markers and error bars indicate categorical point estimates and 95% confidence intervals; lines represent curvilinear trend for drinks per week with corresponding 95% confidence intervals shown with dotted lines. A. Global z score; B. Delayed Word Recall Test (DWRT); C. Digit Symbol Substitution Test (DSST); D. Word Fluency Test (WFT)

Twenty-year changes in the DWRT and DSST z scores followed a roughly similar pattern by alcohol group as for the global z score, although effect estimates were small and confidence intervals overlapped the null (Table 28). Both heavier and former drinkers compared with abstainers had steeper declines. The largest difference was for heavier drinkers on the DWRT (-0.060; -0.238, 0.119), which is equivalent to ~1.2 years additional aging. Light drinking versus abstention was associated with small decreases in additional decline on the DWRT (0.037; -0.047, 0.121) and little effect was seen on the DSST. Moderate drinking was not strongly associated with additional change on the DWRT or DSST. The largest test-specific effects for light and moderate drinking were observed for the WFT. Light and moderate drinkers had slower declines, equivalent to 4.6 and 3.8 fewer years of aging, respectively (0.041; -0.0058, 0.088 and 0.034; -0.023, 0.091). Trend analysis complemented the results of categorical analysis; 20-year additional declines accelerated at higher numbers of drinks per week, and for DWRT and WFT, the trend suggests slight, non-significant inverse U-shapes (Figure 18).

Analyses using MICE

Missing cognitive scores were associated with alcohol intake; non-attendance at visit 5 ranged from 17% among heavier drinkers to 25% among abstainers and mortality by visit 5 from 28% among light drinkers to 48% among heavier drinkers (Table 26). In models that included MICE-imputed scores to correct for this informative missingness, the estimated average decline increased for all exposure groups, as expected. Effect estimates for additional change were very small and moved away from the null for light and moderate drinking by approximately 0.016 global z score units and toward the null by ~0.01 z score unites for heavier and former drinkers. Differences between MICE models and complete case analysis were similarly small for test-specific z score changes. Overall, inferences were not changed by our sensitivity analysis.

Sensitivity analyses

Results were unchanged (not shown) in sensitivity analyses testing for "floor effects" of cognitive scores, which may occur if baseline scores are so low that additional decline is not measurable. We also found no differences in results when testing for effect modification by sex-race or when specifying alcohol intake as the cumulative average of visits 1 and 2. Finally, we assessed the sensitivity of our results to choice of cut-points and found nearly identical results when compared with alternative cut-points for defining light, moderate, and heavier intake (e.g., ≤7; 8-14; ≥15 drinks per week).

6.5 Discussion

We found no meaningful association between light-to-moderate alcohol consumption at mid-life and 20-year rates of global cognitive decline in this analysis of a bi-racial population-based cohort. There was some evidence for slower declines in verbal fluency (DWRT and WFT z scores) with light drinking, but effects were small, roughly equivalent to 0.75 and 4.6 years of additional aging, respectively. Heavier and former drinkers had slightly accelerated rates of decline compared with never drinkers in global cognition and the DWRT and DSST, equivalent to approximately 1 additional year of aging.

We noted fairly large baseline differences in cognitive scores between abstainers and light-to-moderate drinkers consistent with other reports.[1, 21, 34] Longitudinal studies suggest that light drinking may also be associated with lower risk of dementia or cognitive decline,[230, 234] but many are limited by short follow-up and survivor bias given the relatively older ages at baseline. Moderate alcohol intake was associated with 11% reduced risk of cognitive decline (RR=0.89, 0.67-1.17) in meta-analysis results.[230] Specifically, the Women's Health Initiative and Nurses' Health Study both

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reported lower relative odds of 'substantial' cognitive decline among light-to-moderate drinkers compared with abstainers on measures of global cognition (the 3MSE and TICS, respectively).[21] These populations were older at baseline, follow-up was short (6 and 1.5 years, respectively), effect estimates were not corrected for attrition, and rates of decline were not estimated. Our results build on these by estimating differences in the rate of cognitive decline over longer follow-up in a diverse population. We also employed test-specific measures that are less subject to the ceiling effects of global measures. Our results suggest that protective effects of light-to-moderate drinking on the rate of cognitive decline are small at most and that cognitive patterns in these persons may not differ substantially from never drinkers. These small effects may possibly reflect the timing of exposure measurement (mid-life in this study); earlier alcohol exposures may have larger effects on cognitive aging.

Rates of change in global measures of cognition have been estimated in a small number of studies. Declines in the MMSE were 0.05 points per year less for female low-to-moderate drinkers compared with women reporting non-drinking at baseline; no differences across alcohol intake levels were found for men.[32] The average change in TICS-m over ~2.2 years of follow-up in the Northern Manhattan Stroke Study was higher for all levels of drinking compared with never drinkers; 0.9 (95% CI -1.2, 1.9) for light drinkers, 1.5 (0.6, 2.4) for moderate drinkers, and 2.4 (0.8-4.0) for heavier drinkers. Most recently, men consuming ~3 or more drinks per day compared with <1 had faster 10-year declines in cognition, equivalent to 1.5-5.7 additional years of aging in the Whitehall II cohort; no differences were observed between lower levels of drinking and abstention.[235] For women, abstention was associated with faster decline than light drinking (additional decline in z-scores of -0.21(-0.37, -0.04) for global cognition and -0.17 (-0.32, -0.01) for executive function. Overall, our effect sizes were smaller in magnitude than those in the Whitehall cohort, possibly because of differences in population characteristics and drinking habits,

measurement and specification of the exposure and outcomes, or selection factors. In addition, light-to-moderate drinking may serve as a marker for better health that is not fully accounted for by covariates. To provide additional context for the magnitude of our estimates, rates of decline for hypertension versus no hypertension in the ARIC study are reported to range from -0.008 on the DWRT to -0.079 on the DSST, with -0.056 for the global z score.[236]

Heavier drinking has been implicated in increased risk of dementia, significant cognitive declines, and faster rates of cognitive decline in several studies,[230, 234] but others have found no association or even improved scores with heavier drinking.[30, 34, 234] Our estimates were relatively small and overlapped the null, but are consistent with an increased rate of decline relative to abstainers among both heavier and former drinker, particularly in tasks requiring psychomotor speed. Lack of associations with some measures of cognition in our and other studies may reflect the relatively small proportion of heavier drinkers in these studies (several reports do not estimate effects of heavy drinking), survivor biases, and attenuation of effect estimates from cohort attrition.

Test-specific results suggested a possible reduced rate of decline for WFT, but not the DSST for light and moderate drinkers. These tests measure different cognitive domains; verbal fluency and executive function versus processing speed and visuospatial ability, respectively, and suggest that light-to-moderate intake may have greater effects on executive functions, which are often the first to be impaired in vascular dementia. Others have reported a specific effect of light drinking on verbal fluency compared with other tests of verbal memory, visuospatial ability, or global cognition,[237, 238] while others report effects for memory and executive function.[235]

Light-to-moderate alcohol consumption is hypothetically associated with reduced cognitive decline through its putative effects on vascular risk factors (i.e. chronic anti-thrombotic, anti-inflammatory, and anti-atherogenic effects) that in turn preserve neurovasculature.[72] For example, moderate alcohol consumption is associated with higher HDL-C, lower fibrinogen levels and

decreased platelet aggregation.[13] In addition, there is evidence that alcohol increases acetylcholine

and therefore may facilitate learning and memory. Heavier consumption of alcohol has direct

neurotoxic effects on the brain. [72, 76] Additional adverse effects include elevations in blood pressure,

small-vessel disease, infarcts and bleeds, white matter lesions, and alcohol-related dementias.

Our study results should be interpreted in light of several limitations.   First, alcohol was self-

reported and therefore may be under-reported. We were unable to quantify measurement errors

or calibrate effect estimates; however, construct and rank-order validity of our measure was

supported by positive correlations of alcohol with both HDL-C and blood pressure and relative

validity studies report high reliability of alcohol self-reports by FFQ (REF). Second, residual

confounding is possible, although the ARIC study collected data on myriad confounders including

social support, physical activity, and diet quality. Third, the prevalence of heavy drinking was low

and limited our ability to estimate the impact of heavier drinking. Furthermore, the heavier drinkers

that participated in the ARIC study may not represent the larger population of heavy drinkers,

limiting generalizability of study results. Fourth, selection bias induced by informative

nonattendance at study visits and deaths is likely, and would tend to attenuate our estimates as we

hypothesize that non-attenders would have lower cognitive scores. We attempted to mitigate this

selection bias using MICE methods. Fifth, there is potential for floor and practice effects in cognitive

assessments; however, we conducted sensitivity analyses that suggested floor effects were minimal.

Strengths of our study include a prospective study design with over 20 years of follow-up, a

bi-racial population, and repeated measures of 3 cognitive tests over time that are sensitive to

changes at higher levels of cognition - unlike the MMSE - and allow differentiation of cognitive

domains. Alcohol consumption was assessed using a validated instrument with beverage-specific

questions (thus reducing under-reporting) that differentiated never from former drinkers.

Our study results suggest that the putative beneficial effects of mid-life light-to-moderate drinking on cognitive decline are, at most, quite small, and may affect verbal fluency more than other domains. Consumption of alcohol in moderation does not appear to adversely affect aging trajectories, consistent with other findings but neither should it be recommended for slowing cognitive aging based on these and other studies. Consumption of 18 or more drinks per week was associated with accelerated decline on global function and delayed word recall in particular, though all estimates were imprecise. The potential harmful effects of heavier intake on cognitive aging is consistent with public health recommendations to moderate alcohol consumption.[47] Understanding the alcohol-cognitive decline association would be further advanced by continued development of methods to correct for cohort attrition, measurement of drinking patterns and consumption over the life course including in younger adulthood, and by estimating dose-dependent exposure measurement errors for effect estimate calibration.

CHAPTER 7. CONCLUSIONS AND PUBLIC HEALTH IMPLICATIONS

Stroke and cognitive impairment represent a significant health burden. The prevalence of these conditions is projected to increase dramatically as the population demographic shifts to a greater proportion of older adults.[51, 52] Identifying modifiable risk factors to prevent or delay disease - such as the consumption of alcoholic beverages - is necessary to reduce disease burden, its high economic cost, care giver burden, and negative impact on quality of life. This research is further motivated by the high prevalence of alcohol exposure (70% of adults report drinking alcohol), which could result in a large impact on disease in the population even with small effects on disease risk. Specific aims of this dissertation research were to 1) estimate the dose-response relationship between usual alcohol consumption and incidence of ischemic and hemorrhagic stroke; and 2) to estimate the additional change in 20-year cognitive decline according to alcohol intake.

The literature on alcohol and stroke is expansive, has grown in methodologic rigor over the past few decades, and yet is inconsistent with regard to effects of light-to-moderate consumption. There is still debate as to whether light-to-moderate alcohol intake protects against cardiovascular disease, stroke in particular. Biological mechanisms include changes in HDL-cholesterol, clotting and platelet aggregation, blood pressure, and insulin sensitivity that depend on alcohol dose and may have different impacts on ischemic and hemorrhagic stroke etiologies. Meta-analyses report J-shaped relationships between alcohol and ischemic stroke.[2, 6, 14] The pooled hazards ratio comparing drinkers with nondrinkers for ischemic stroke were 0.92 (95% CI: 0.85-1.00) and 1.04 (1.02-1.06) and for hemorrhagic stroke was 1.14 (0.97-1.34); these results were largely similar for men and women.[2, 14] Alcohol and cognitive decline research is comparatively much younger, less robust, and far from conclusive. Studies report varying results from no differences across intake, to reduced

declines in global cognition for women but not men at low levels of drinking, faster decline for men consuming heavy alcohol but no differences at lower intakes, and slower declines at all levels of drinking compared with abstention.[32, 34, 235]

Effect estimates for both outcomes are subject to several biases. Primary among these are exposure measurement error, confounding by healthier lifestyles of light-to moderate drinkers, and selection bias from cohort attrition. The ARIC study and our analytic approach were unique in their ability to address several of these important limitations. While measurement error in our study is a possibility, we have comparatively strong measurement of beverage-specific alcohol consumption assessed with a validated FFQ. Our data were obtained from a large, racially-diverse middle-aged population-based cohort with ~25 years of follow-up, robust stroke ascertainment, rich covariate data, and repeated assessment of cognitive function. Our findings suggest little support for a protective effect of self-reported light-to-moderate drinking of 0.5 to 17 drinks per week compared with lifetime abstention and either stroke or cognitive decline. Increased risk of ischemic stroke and faster rates of decline were found for consumption of 18 or more drinker per week compared with abstention, although confidence intervals were wide and overlapped the null. Increased risk of hemorrhagic stroke was present for moderate drinking.

The null association between light drinking and stroke and cognitive decline may reflect mis-measurement of alcohol that attenuated effect estimates, attrition that was not captured in MICE models for cognitive decline, or imprecision in our estimates. It may also reflect the true relationship between alcohol and these outcomes despite the underlying plausible biological mechanisms. For example, HDL-C (a major pathway through which alcohol may influence disease risk) is a weaker predictor of stroke than heart disease. Previously reported protective effects may have been confounded by lack of adjustment for socioeconomic status, smoking, or former drinking. Finally, additional characteristics of alcohol consumption such as drinking patterns, life-course

trajectories, and cumulative effects may modify results across studies, few of which are able to examine these factors.

Our findings are consistent with the American Heart Association recommendations that adults moderate their alcohol consumption (≤2 drinks per day for men; ≤1 for women) and that individuals should not initiate drinking for the purposes of reducing cardiovascular disease risk.[47] These recommendations were made primarily based on cardioprotective effects observed in studies of coronary heart disease as well as the known risks of alcohol consumption even at lower doses including dependency, interactions with medications, and increased cancer risk. Our study results suggest that there is no benefit from light drinking on vascular-related diseases of the brain and likely harm from higher intake. The definition of moderate consumption in clinical guidelines may need continued scrutiny and modification as data from other cardiovascular disease outcomes – such as stroke and cognitive changes – becomes available.

This dissertation research and its extensive review of the literature and limitations, has brought to attention areas for advancement in future research. First, dose-dependent errors in self-reported alcohol are largely unexplored. Studies are needed that measure alcohol intake with multiple, independent measurement tools and that compare validity across intake levels. This information will be useful not only in quantifying the magnitude of error across intake, but also for calibration to obtain bias-corrected effect estimates. Furthermore, epidemiologic studies should include separate questions to assess the frequency and quantity of alcohol intake as well as the frequency of heavy-drinking episodes. Identification of valid biomarkers for usual alcohol intake is needed to validate self-reported alcohol intake. Second, additional research is needed that examines sex-race effects. We noted no differences in associations by sex-race, but were limited by sample size. Third, continued methodological development and refinement of existing methods for correcting attrition will be useful in estimating rates of cognitive decline in cohorts with a high

degree of death or drop-out. These are essential for cognitive decline research because cognition must be repeatedly assessed through older age, a time at which mortality and non-attendance will be high and are likely associated with exposures of interest. Fourth, large pooling studies that include only high-quality studies are needed to achieve Aim #2 in this dissertation of estimating the population impact of changes in alcohol consumption. Quantifying the change in rates of disease is important for policy makers and public health researchers and should be done using precise and minimally biased effect estimates.

The research herein has added data from a major U.S. cohort study with minimal bias in stroke measurement to the alcohol-stroke relationship and has added substantially to the cognitive decline literature as one of the first studies to correct for attrition and to have long follow-up beginning in mid-life. Our study will contribute additional data for future meta-analyses and systematic reviews that in turn will be useful for population scientists and clinicians judging the risk-benefit tradeoff of alcohol consumption for individual patients. We found no support for a protective effect of light-to-moderate alcohol intake and risk of stroke or rate of cognitive decline. Consistent with existing knowledge, heavier intake likely increases the risk of these outcomes. Public health recommendations should continue to encourage reduction of excessive drinking and should not issue population-wide recommendations for initiation of light drinking. Effective strategies for reducing excess drinking could involve pricing policies and brief interventions in high-risk groups.

Addendum A

CLINICAL ALGORITHM

Definition of Stroke

Stroke will be defined as a clinical syndrome consisting of a constellation of neurological findings, sudden or rapid in onset, which persist for more than 24 hours, and whose vascular origins will be limited to:

1. Thrombotic or embolic occlusion of a cerebral artery resulting in infarction, or
2. Spontaneous rupture of a vessel resulting in intracerebral or subarachnoid hemorrhage.

This definition excludes occlusion or rupture due to traumatic, neoplastic, or infectious processes which produce vascular pathology.

Procedure for Case Ascertainment

A. Out-of-Scope Cases

Cases falling into one of the following groups are excluded from the study:

1. Error in Diagnostic Indexing

Diagnosis in the discharge summary is not related to stroke and review of clinical record discloses no evidence suggesting an acute stroke.

2. Diagnostic Term Properly Indexed But Not Related to an Acute Stroke

Diagnosis in the discharge summary is properly indexed but review of clinical record discloses no evidence suggesting an acute stroke.

3. Autopsy Findings Only Related to Stroke

Diagnosis of stroke is derived from autopsy findings only and review of the clinical record discloses no evidence suggesting an acute stroke.

4. Hospital Admission More than 30 Days After Onset

Patients initially admitted to a hospital more than 30 days after onset of the stroke. Such stroke patients are presumed to be "non-hospitalized" during their acute phase. A stroke patient admitted by transfer to a study hospital from another short-term general hospital will not be excluded from the study if the date of initial hospital admission is less than 30 days after onset of the acute stroke.

5. A Patient With a Discharge Diagnosis of SAH Who Had Clear Spinal Fluid in Spinal Tap Within Two Weeks of Stroke Onset

Patient will either be reclassified, or excluded from study, unless the diagnosis of SAH is "confirmed" by cerebral angiography (showing an aneurysm or arteriovenous malformation), computerized tomography (showing a blood clot), or by findings of a bleeding aneurysm at surgery or at autopsy.

B. In-Scope Patients

Patients who are not considered to be out-of-scope will be classified into one of the following five broad diagnostic categories on the basis of clinical, diagnostic and autopsy findings; within each diagnostic category, patients will be further classified as definite, highly probable, probable or possible based on the degree to which the discharge diagnosis is confirmed by diagnostic or autopsy findings:

1. Subarachnoid hemorrhage
2. Intraparenchymal hemorrhage
3. Thrombotic infarction of brain
4. Embolic infarction of brain
5. Stroke of undetermined type

Criteria for Diagnostic Categorization

I. Subarachnoid Hemorrhage (SAH)

A. *Definite**. Must meet the criteria specified under at least *one* of the four paragraphs below:

1. Angiographic identification of a saccular aneurysm or arteriovenous malformation (AVM) as the source of the bleeding (e.g., demonstration of a clot adjacent to aneurysm or AVM, or reduced caliber of otherwise normal vessels),

OR

2. Demonstration by computerized tomography of a blood clot in Fissure of Sylvius, between the frontal lobes, in basal cisterns, or within a ventricle,

OR

3. Demonstration at surgery of a bleeding saccular aneurysm or arteriovenous malformation,

OR

4. Demonstration at autopsy of recent bleeding of a saccular aneurysm or arteriovenous malformation.

B. *Highly Probable*. Must meet all of the following criteria:

1. A patient whose discharge diagnosis of SAH is supported by evidence in the patient's clinical record that meet both criteria (a) and (b) below:

(a) Two or more of the following symptoms or

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*Includes the diagnostic reclassification of patients whose discharge diagnosis was *other than* SAH, and who meet the specified criteria for a "Definite" case of SAH.

signs occurred within minutes or a few hours after onset;

- Severe headache at onset, or severe headache when first conscious after hospital admission;
- Depression of state of consciousness;
- Evidence of meningeal irritation;
- Retinal (subhyaloid) hemorrhages;
- Weakness on one side;
- Disturbance of vision caused by palsy of the iii cranial nerve;

AND

(b) Bloody (not traumatic) tap or xanthochromic spinal fluid.

C. *Probable.* Must meet all of the following criteria:
1. A patient whose discharge diagnosis of SAH is supported by evidence in the patient's clinical record that meet *both* criteria (a) and (b) below:

(a) One or more symptoms or signs listed above for a "Highly Probable" case must be documented,

AND ALSO

(b) A spinal tap was either not done, *or* was a traumatic tap, *or* was done and the spinal fluid was clear but the tap was done more than two weeks after onset of the stroke.

D. *Undocumented.* Must meet the following criterion:
1. A patient whose discharge diagnosis of SAH is not sufficiently supported by evidence in the patient's clinical record to meet the criteria set forth above for a "Definite," "Highly Probable" or "Probable" case of SAH.

Note

A patient with a discharge diagnosis of SAH who had clear, colorless spinal fluid in a spinal tap made within two weeks of the onset of the stroke will be considered for *reclassification,* or for *exclusion* from the study, *except* when the diagnosis of SAH is *confirmed* by cerebral angiography, computerized tomography, or findings of a bleeding aneurysm at surgery or at autopsy. (See paragraph I-A above).

II. Intraparenchymal Hemorrhage (IPH)

A. *Definite.** Must meet the criteria specified under at least *one* of the four paragraphs below:

1. Demonstration of an intracerebral hematoma by

computerized tomography, e.g., an area of increased density, such as seen with blood,

OR

2. Surgical evacuation of a hematoma,

OR

3. Demonstration at autopsy of intracerebral hemorrhage,

OR

4. Evidence in the patient's clinical record that meet criteria (a), (b) and (c) below:

(a) One or more of the following neurological signs or symptoms that lasted at least 24 hours or until the patient died:
- Depression of state of consciousness;
- Disturbance of vision;
- Paresis (weakness) or paralysis of one side of body, or bilateral, as might occur in brain stem lesions;
- Unilateral diminution of sensation;
- Speech impairment;
- Dysphagia;
- Ataxia;
- Sudden, severe headache;

AND ALSO

(b) Bloody (not traumatic tap) or xanthochromic spinal fluid,

AND ALSO

(c) Cerebral angiography demonstrates an avascular mass effect and no evidence of aneurysm or arteriovenous malformation.

B. *Highly Probable.* Must meet all of the following criteria:
1. A patient whose discharge diagnosis of IPH is supported by evidence in the patient's clinical record that meet *both* criteria (a) and (b) below:

(a) One or more of the neurological signs or symptoms listed in paragraph A-4 above that lasted at least 24 hours or until the patient died,

AND ALSO

(b) Bloody (not traumatic) tap or xanthochromic spinal fluid.

C. *Probable.* Must meet all of the following criteria:
1. A patient whose discharge diagnosis of IPH is supported by evidence in the patient's clinical record that meet *both* criteria (a) and (b) below:

(a) One or more of the neurological signs or symptoms listed in paragraph A-4 above that lasted at least 24 hours or until the patient died,

*Includes the diagnostic reclassification of patients whose discharge diagnosis was *other than* an IPH but who meet the specified criteria for a "Definite" case of IPH.

AND ALSO

(b) A spinal tap was either not done, *or* was a traumatic tap, *or* was done more than two weeks after onset of the stroke.

D. *Undocumented.* Must meet the following criterion:

1. A patient whose discharge diagnosis of IPH is not sufficiently supported by evidence in the patient's clinical record to meet the criteria set forth above for a "Definite," "Highly Probable" or "Probable" case of IPH.

Note

If spinal fluid examined within two weeks of onset is clear, an IPH case can be classified as "Definite" *only* when confirmed by computerized tomography, surgical evacuation of a hematoma or autopsy findings; otherwise, case should be classified as "Undocumented."

III. Thrombotic Infarction of Brain (TIB)

A. *Definite.** Must meet the criteria specified under at least *one* of the two paragraphs below:

1. Demonstration at autopsy of nonhemorrhagic infarct in brain,

OR

2. Evidence in the patient's clinical record that meet criteria (a), (b) and (c) below:

(a) One or more of the following neurological signs and symptoms that either lasted at least 24 hours or until the patient died:
- Depression of state of consciousness;
- Disturbance of vision;
- Paresis (weakness) or paralysis of one side of body, or bilateral, as might occur in brain stem lesions;
- Unilateral diminution of sensation;
- Speech impairment;
- Dysphagia;
- Ataxia;

AND ALSO

(b) Spinal fluid is clear and colorless, if obtained,

AND ALSO

(c) One or more of the following diagnostic procedures support the diagnosis of TIB:
- Angiography reveals severe stenosis or obstruction of one or more major

cerebral arteries or their branches, or of the carotid or vertebral arteries,

OR

- Brain scan shows an uptake consistent with an infarction, and presence of a brain tumor is ruled out,

OR

- Computerized tomography shows an area of decreased density which may indicate edema or ischemia, with no evidence of hemorrhage.

B. *Highly Probable.* Must meet all of the following criteria:

1. A patient whose discharge diagnosis of TIB is supported by evidence in the patient's clinical record that meet both criteria (a) and either (b) or (c) below:

(a) One or more of the neurological signs and symptoms listed in paragraph A-1 above that lasted at least 24 hours or until the patient died,

AND EITHER

(b) Spinal fluid is clear and colorless,

OR

(c) Brain scan shows an uptake consistent with an infarction, but brain tumor is *not* ruled out.

C. *Probable.* Must meet the following criterion:

1. A patient whose discharge diagnosis of TIB is supported by evidence in the patient's clinical record of:

(a) One or more of the neurological signs and symptoms listed in paragraph A-2 above that lasted at least 24 hours or until the patient died.

D. *Undocumented.* Must meet the following criterion:

1. A patient whose discharge diagnosis of TIB is not sufficiently supported by evidence in the patient's clinical record to meet the criteria set forth above for a "Definite," "Highly Probable" or "Probable" case of TIB.

IV. Embolic Infarction of Brain (EIB)

A. *Definite.** Must meet the criteria specified under at least *one* of the two paragraphs below:

1. Demonstration at autopsy of:
(a) An infarcted area in the brain,

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*Includes the diagnostic reclassification of patients whose discharge diagnosis was *other than* TIB (except for EIB), but who meet the specified criteria for a "Definite" case of TIB.

*Includes the diagnostic reclassification of patients whose discharge diagnosis was *other than* EIB (except for TIB), but who meet the specified criteria for a "Definite" case of EIB.

AND ALSO

(b) A source of emboli in a vessel of any organ, or an embolus in the brain,

OR

2. Evidence in the patient's clinical record that meet criteria (a), (b), (c) and (d) below:
    (a) One or more of the following neurological signs or symptoms that began abruptly and lasted at least 24 hours or until the patient died:
    - Depression of state of consciousness;
    - Disturbance of vision;
    - Paresis (weakness) or paralysis of one side of body, or bilateral, as might occur in brain stem lesions;
    - Unilateral diminution of sensation;
    - Speech impairment;
    - Dysphagia;
    - Ataxia;
    - Seizures (one or more seizures, not necessarily lasting more than 24 hours);

AND ALSO

(b) Spinal fluid is clear or is blood tinged, if obtained,

AND ALSO

(c) Establishment of a likely source for cerebral embolus, e.g.:
    - Valvular heart disease;
    - Atrial fibrillation;
    - Myocardial infarction with mural thrombus;
    - Cardiac operation;
    - Air embolism;
    - Fat embolism;
    - Cardiac myxoma;
    - Ulcerating atherosclerotic plaque in carotid artery;
    - Bacterial endocarditis;

AND ALSO

(d) Demonstration of infarction by special tests such as angiography, brain scan or computerized tomography (as specified above for a "Definite Case" of TIB). Note: Angiography may show luxury perfusion, or brain scan rules out presence of tumor in the brain, or CT may show hemorrhagic infarction).

B. *Highly Probable*. Must meet all of the following criteria:
1. A patient whose discharge diagnosis of EIB is supported by evidence in the patient's clinical record that meet criteria (a), (b) and either (c) or (d) below:
    (a) One or more neurological signs or symptoms listed in paragraph A-2 above, that lasted at least 24 hours or until the patient died,

AND ALSO

(b) An identifiable source for the cerebral embolus as specified in paragraph A-2(c) above,

AND EITHER

(c) Spinal fluid is clear or is blood tinged,

OR

(d) Brain scan shows uptake consistent with infarction but brain tumor was not ruled out.

C. *Probable*. Must meet the following criterion:
1. A patient whose discharge diagnosis of EIB is supported by evidence in the patient's clinical record of:
    (a) One or more of the neurological signs or symptoms listed in paragraph A-2 above that lasted at least 24 hours or until the patient died.

D. *Undocumented*. Must meet the following criterion:
1. A patient whose discharge diagnosis of EIB is not sufficiently supported by evidence in the patient's clinical record to meet the criteria set forth above for a "Definite," "Highly Probable" or "Probable" case of EIB.

V. Stroke of Undetermined Type

A. *Probable*. Must meet the following two criteria:

1. A patient whose discharge diagnosis is non-specific as to type of stroke, e.g., acute cerebrovascular disease, cerebrovascular accident, or stroke, and there is supported evidence in the patient's clinical record of at least one neurological sign or symptom that lasted more than 24 hours or until the patient died,

AND ALSO

2. Clinical history, signs, symptoms and findings from diagnostic tests and/or autopsy are *not* sufficient to meet the criteria for classifying the case as a "Definite" case of one of the four specific diagnostic categories of stroke. (Case is not reclassified if it only meets the criteria for a "Highly Probable," "Probable" or "Undocumented" case of one of the four specific diagnostic categories of stroke).

B. *Undocumented*. Must meet the following criterion:

1. A patient whose discharge diagnosis is non-specific as to type of stroke, e.g., acute cerebrovascular disease, cerebrovascular accident, or stroke, *and* there is *no evidence* in the patient's clinical record of a neurological deficit that lasted more than 24 hours or until the patient died.

APPENDIX 2: ALCOHOL AND STROKE LITERATURE REVIEW TABLES

A. Part 1: Population, Study Design, and Measurement

Author (Year)	Population	Baseline Calendar Year	N	Follow-up (y)	Stroke Ascertainment	Stroke Events, N	Alcohol Measurement	Analysis Included Multiple Exposure
Berger (1999)	**Physicians' Health Study** Prospective cohort of male physicians, aged 40-84	1982	22,071	12.2	Medical record review, clinician adjudication		**Frequency:** Self-reported number of drinks per unit time	No
Djousse (2002)	**Framingham Study** Population-based cohort of adults aged 28-62	1948-1952	5209	3 pools of 10-y	Review of interim exams, surveillance of hospital admissions, medical record review and review	441	In-person interview Average number of drinks per week; alcohol consumption in past 12 years	Yes, follow-up divided into 3 10-yr periods with alcohol re-assessed at each starting point
Djousse (2009)	**Framingham Study** Population-based cohort of adults aged 28-62 at baseline in 1948 and Offspring cohort in 1971	1948-1952; 1971	7676	2 pools of 8-yr	Review of interim exams, surveillance of hospital admissions, medical record review and review	222	In-person interview Average number of drinks per week; alcohol consumption in past 12 years	Yes, follow-up divided into 2 8-yr periods with alcohol re-assessed at each starting point
Chiuve (2008)	**Health Professionals Follow-up Study & Nurses' Health Study** Prospective cohorts of men 40-75 and women 34-59,	1986; 1976	43, 685 men; 71,243 women	18; 20	Self-reported with medical record review. Death certificates		FFQ-based QF ~ every 2 years	Yes, cumulative average

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respectively

Elkind (2006)	**The Northern Manhattan Study** Prospective cohort of adults ≥40 years residing in northern Manhattan	1993	3176	5.9 y	Self-report with further evaluation, surveillance of area hospital admissions. Defined based on WHO criteria		Interviewer administered FFQ, quantity per day	
Bazzano (2007)	**China National Hypertensive Survey** Prospective cohort of men aged ≥40 years	1991	83533	9	Self-reported with verification by medical record review or death certificates. Diagnosis made by neurologist using criteria from ARIC study	3434	Interviewer administered questionnaire asking 6 questions on frequency, amount, and type	
Donahue (1986)	**Honolulu Heart Program** Prospective study of men of Japanese ancestry aged 45-69 residing in Oahu	1965-8	8006	12	Surveillance of hospital discharges, death certificates, autopsy records. Neurologist diagnosis based on WHO definition, records, clinical findings	190	In-person interview recording usual monthly intake of beer, wine, and liquor	No
Drogan (2012)	Case cohort nested in the European Prospective Investigation into Cancer and Nutrition	1994-8	2558	8.2	Self-report or death certificate	246	Self-administered FFQ	No

	(EPIC)-Potsdam, a general population cohort of 27548 adults aged 35-65 year							
Gaziano (2000)	**Physicians' Health Study** Prospective cohort of male physicians, aged 40-84	1982	89299	5.5	Death certificate	150 deaths	Brief diet questionnaire asking combined question of FQ	No
Goldberg (1994)	**Honolulu Heart Program** Prospective study of men of Japanese ancestry aged 45-69 residing in Oahu who survived to second examination in 1971	1971-4	6069	12	Surveillance of hospital discharges, death certificates, autopsy records. Neurologist diagnosis based on WHO definition, records, clinical findings	70 deaths; # events NR	In-person interview recording usual monthly intake of beer, wine, and liquor	No
Gorelick (1989)	Case control study of ischemic stroke patients and general outpatient controls	1984	615	NA		205	Frequency of usual weekday and weekend alcohol intake and usual amounts in the past yr	No
Hansagi (1995)	**Swedish Population-based Twin Register** National register of the Swedish population born between 1886 and 1925	1967-1968	15077	19	National death register, ICD-9 codes 430-438. Authors cite validity of codes to be 97%	769 deaths	Self-administered questionnaire asking current and former intake, current QF and binge drinking	No

Hart (1999)	Prospective cohort study of employed men aged 35-64 residing in Scotland	1970-3	5766	21	Death certificates, ICD codes 430-438)	133 deaths	Self-reported weekly alcohol consumption	No
Ikehara (2009)	**Japan Public Health Center-Based Prospective Study Cohort II** Adults aged 40-69 residing in 5 regions in Japan	1993	19356	9.9	Self-reported stroke with medical record confirmation, surveillance of hospital records and death certificates. Dx based on criteria from National Survey of Stroke	629	Self-administered questionnaire, QF	No
Iso (1995)	**Japan Public Health Center-Based Prospective Study Cohort I** Adults aged 40-59 residing in 4 regions in Japan	1990	27063	11	Self-reported stroke with medical record confirmation, surveillance of hospital records and death certificates. Dx based on National Survey of Stroke	694	Self-administered questionnaire asking frequency, amount, and type of alcohol	Sensitivity analysis updated exposure
Jakovljevic (2004)	Cohort study of middle-aged residents of Serbia	1974	500	20	Death certificate	7 deaths	Self-administered multiple choice questionnaire to assess drinks per day	No

Jimenez (2012)	**Nurses' Health Study** Female nurses aged 30-50 years in 11 US states	1976	121700	26	Self-report on follow-up questionnaires; stroke deaths through National Death Index searches and next of kin. Included adjudication with medical records, death certificates	2171	Food frequency questionnaire every 4 years assessed beverage specific QF	Cumulative average alcohol in secondary analysis
Jousilahti (2000)	**WHO MONICA** Prospective study of adults aged 25-64 in Finland from 2 samples	1982, 1987	15658		Administrative data on hospital discharges and deaths. Diagnosis based on ICD-9 codes.	470	Self-administered questionnaire assessing number of drinks per week	No
Kiyohara (1995)	**Hisayama Study** Prospective study of Japanese adults aged 40+	1961	1621	26	Self-report, confirmed with exam and record review, surveillance		Interview-administered questionnaire asking usual weekly intake of alcohol	No
Klatsky (1989)	**Kaiser Permanente** Adults <age 50 y receiving health examinations in prepaid health plan	1978	101137	max 6	Hospital discharge records. Dx based on ICD-8 codes	361	Self-administered Questionnaire, details of administration unclear, asking for average amount per day	No

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Klatsky (2002)	**Kaiser Permanente** Adults <age 50 y receiving health examinations in prepaid health plan	1978	128934	8.5	Hospital discharge records. Dx based on ICD-8 codes	2494	Health examination questionnaires assessing number of days per week and amount usually consumed	No
Kono (1986)	Cohort of Japanese male physicians	1965	5477	18	Death certificate	230 deaths	Self-administered questionnaire assessing past and current alcohol intake	No
Leppälä (1999)	**Alpha-Tocopherlo Beta-Carotene Cancer Prevention Study** Male cigarette smokers aged 50-69 residing in Finland enrolled in an RCT	1985	26556	6.1	National hospital discharge and death registers. Diagnosis based on ICD diagnosis codes	960	Self-administered diet history questionnaire including questions about amount and frequency of consumption	No
Maskarinec (1998)	Population-based prospective cohort of Hawaiians older than 30 years of age from one of 5 ethnicities	1975-80	27678	15.3	Death from death certificate ICD-9 codes 430-438		Questionnaire asking type and usual QF. Self-administered (maybe proxy?)	No

Mukamal (2005a)	**Cardiovascular Health Study** Prospective study of community-dwelling adults ≥65 years of age from 4 U.S. communities	1989	5888	9.2	Surveillance of hospitalizations reported by participants at 6-month interval telephone calls or clinic exams. Neurologist review of medical charts for hospitalizations and deaths. Dx based on neurological deficit lasting 24 hours, typing based on imaging test results etc	434	Questionnaire on usual frequency of consumption and number of drinks. Also asked about past exposure and episodes of heavy drinking (≥5 drinks/d)	Yes
Mukamal (2005b)	**Health Professionals Follow-up Study** US male health professionals aged 40-75	1986	51529	14	Medical record review of self-reported stroke and deaths	412	FFQ in previous 12 months average frequency of drinking a specified amount of alcohol.	Yes
Romelsjo (2012)	Cohort study of Swedish conscripts from 1969-1970 born from 1949-1951	1969	49411	34	National Cause of Death Register (ICD-9 430-438)	72	Questionnaire on Q and F of alcohol; measure of binge drinking	No
Romelsjo (1999)	Cohort study of Swedish conscripts from 1969-1970 born from 1949-1952	1949	49618	25	Unclear, death register and inpatient care register	233	Questionnaire on Q and F of alcohol	No

Sacco (1999)	Case control study embedded in **Northern Manhattan Stroke Study** Cases were >39 years of age and resident of Northern Manhattan	1993	1816	-	Self-report with further evaluation, surveillance of area hospital admissions. Defined based on WHO criteria	677	In-person interview adapted from the National Cancer Institute Block FFQ	No
Sankai (2000)	Prospective cohort of adults aged 40-69 years in 6 communities in Japan	1975	12372	9.4	Insurance claims, local physician reporting, ambulance records, death certificates, CV risk surveys	71	Interviewer questionnaire assessing usual weekly intake of alcohol in standard unit	No
Shaper (1991)	**British Regional Heart Study** Cohort of men aged 40-59 randomly selected from general practices in 24 English towns	1978-80	7735	8	Death certificates, nonfatal events based on presence of neurological deficit for >=24 hours	110	Nurse administered questionnaire on average intake	No
Stampfer (1988)	**Nurses' Health Study** Female nurses 34-59 years	1980	87526	4		120	Self-administered questionnaire	No
Truelson (1998)	**Copenhagen City Heart Study** Adult residents of Denmark aged 45-84 years	1976	13329	16	Self-reported stroke ascertained upon examination, Danish National Patient register, and death register. Identification based on ICD codes with validation using	833	Questionnaire on weekly intake of beer, wine, and spirits	No

medical records

Yuan (1997)	Prospective study of men aged 45-64 in Shanghai	1986-1989	18244	6.7	Death certificates	269	Interviewer-administered questionnaire to assess drinks per week	No
Woo (1990)	Cohort of Chinese adults aged 60 years and over living independently	1986	427	2.5	Self-reported stroke with confirmation from medical record review	7	Questionnaire	No
Yang (2012)	Population-based cohort of 220,000 men aged 40-79 years randomly selected from 45 regions in China	1990-1	218189	15	Death certificate	4644	Questionnaire assessed amount consumed in a typical week of each beer, wine, and spirits	No

B. Part 2: Analysis and Ischemic Stroke Results

Author (Year)	Operation Definition of Alcohol Consumption	Covariates	Ischemic Stroke		
Berger (1999)	<1 drink/week vs. ≥1 drink/week; more categories evaluated for total stroke	Age, SBP, smoking, BMI, exercise, diabetes, current HTN tx, randomization assignment	0.77 (0.63-0.94)		
Djousse (2002)	Never, 0.1-11 g/d, 12-23 g/d, ≥24 g/d, former drinker of 0.1-11 g/day, former drinker of ≥12 g/d	Age, diabetes, smoking, BMI, BP, left ventricular hypertrophy, AF, antihypertensive tx, CHD		**Men**	**Women**
			Never	1.00	1.00
			0.1-11 g/d	1.0 (0.6-1.7)	0.9 (0.6-1.3)
			12-23 g/d	0.8 (0.4-1.6)	0.8 (0.5-1.4)
			≥24 g/d	0.9 (0.5-1.6)	0.9 (0.5-1.5)
			Former (0.1-11)	0.8 (0.4-1.6)	1.0 (0.7-1.5)
			Former (≥12)	2.6 (1.3-5.1)	0.8 (0.4-1.7)
Djousse (2009)	None vs. any current drinking	Age, sex, SBP, treatment for hypertension, cigarette smoking, diabetes, CHD		**Apo E4 neg**	**Apo E4 pos**
			Age < 65 years		
			Never	1.00	1.00
			Any	0.50 (0.24-1.07)	0.70 (0.24-2.05)
			Age 65+		
			Never	1.00	1.00
			Any	0.88 (0.62-1.25)	1.40 (0.83-2.77)
Chiuve (2008)	Grams per day: 0, 0.1-4.9, 5-14.9, 15-29.9, ≥30	Age, calendar year, parental history of MI before age 60, aspirin use, vitamin E supplementation, HRT for women		Men	Women
			0 g/d	1.00	1.00
			0.1-4.9 g/d	0.84 (0.67-1.06)	0.77 (0.65-0.92)
			5-14.9 g/d	0.93 (0.74-1.17)	0.82 (0.68-1.00)
			15-29.9 g/d	0.81 (0.60-1.10)	0.86 (0.64-1.16)
			≥30 g/d	1.39 (1.08-1.79)	1.41 (1.07-1.88)

Elkind (2006)	<1 drink per month, 1 drink per month - 2 drinks per day, >2 drinks/day - <5 per day, 5 or more per day	Age, sex, race-ethnicity, hypertension, diabetes, AF, HDL, smoking	<1 drink/month	1.0	
			1 drink/m - 2 drinks/d	0.67 (0.46-0.99)	
			>2 drinks/d	1.30 (0.69-2.45)	
Bazzano (2007)	Nondrinkers, 1-6 drinks/week, 7-20, 21-34, >35.	Age, BMI, physical activity, urban residence, geographic region, smoking, diabetes, education	Nondrinkers	1.0	
			1-6 drink/w	0.95 (0.77-1.16)	
			7-20 dk/w	0.88 (0.76-1.01)	
			21-34 dk/w	0.87 (0.73-1.05)	
			>=35 dk/w	0.99 (0.83-1.19)	
Donahue (1986)	Nondrinkers, light (1-14 oz/m), moderate (15-39 oz/m), heavy (40+ oz/m)	Age, hypertension, cholesterol, BMI, smoking, uric acid, glucose, hematocrit	Nondrinkers	1.0	
			1-14 oz/m	1.0 (0.7-1.4)	
			15-39 oz/m	1.2 (0.8-1.8)	
			40+ oz/m	1.1 (0.7-1.7)	
Drogan (2012)	Average grams per day: Non-drinker, >0-6, >6-12, >12-24, >24-60, 60+	Age, BMI, waist circumference, smoking status, education, physical activity, non-alcohol energy intake, hypertension, diabetes, total cholesterol, past alcohol intake, ADH polymorphism		**Women**	**Men**
			0 g/d		
			>0-6 g/d	1.00	1.00
			>6-12 g/d	1.28 (0.71-2.31)	1.01 (0.47-2.17)
			>12-24 g/d	1.11 (0.53-2.30)	1.07 (0.51-2.25)
			>24-60 g/d	0.52 (0.14-1.87)	1.68 (0.85-3.32)
			60+		1.01 (0.41-2.46))
Gaziano (2000)	Rarely/never, 1-3/month, 1/wk, 2-4/wk, 5-6/wk, 1/d, 2+/d	Age, smoking, diabetes, exercise, BMI	-		
Goldberg (1994)	Nondrinkers, light (1-14 mL/d), moderate (15-39 mL/d), heavy (40+ mL/d)	Age, SBP, serum cholesterol, triglycerides, uric acid, smoking, coffee intake, calorie intake	**Fatal + Nonfatal stroke**		
				50-64 years	**65-75 years**
			Abstainer	1.0	1.0
			Light	0.84	1.12
			Moderate	1.44	1.64

				Heavy	0.66	0.70
Gorelick (1989)	Grams per week: 0, 1-99, 100-299, 300+	Age, race, sex, hospital payment method, smoking, hypertension			Men	Women
			0		1.00	1.00
			1-99 g/wk		2.20 (0.95-5.13)	1.06 (0.23-4.86)
			100-299 g/w		1.86 (0.89-3.92)	2.70 (0.75-9.77)
			300+ g/w		1.68 (0.79-3.56)	1.77 (0.23-13.45)
Hansagi (1995)	Assessed average intake, quantity, frequency, and binge drinking	Age, smoking			Men	Women
			0 g/d		1.00	1.00
			0.01-4.99 g/d		1.3 (0.9-2.0)	0.6 (0.5-0.8)
			5.00-14.9 g/d		1.3 (0.8-2.0)	0.9 (0.5-1.8)
			15+ g/d		1.1 (0.6-2.0)	1.7 (0.5-5.8)
Hart (1999)	Drinks per week (0, 1-7, 8-14, 15-21, 22-34, 35+)	Age, smoking, cholesterol, BMI, adjusted FEV, social class, father's social status, education, care use, siblings, deprivation, angina, ischemia on electrocardiogram, bronchitis	-			
Ikehara (2009)		Age, smoking, BMI, hypertension, diabetes, leisure time sports, mental stress level, flushing, employment, marital status, medical checkup, region	Never	1.00		
			Former	0.78 (0.47-1.28)		
			Occasional	0.86 (0.52-1.42)		
			1-149 g/wk	0.93 (0.68-1.26)		
			150-299 g/w	1.07 (0.79-1.44)		
			300-449 g/w	1.35 (0.97-1.88)		
			450+ g/w	1.13 (0.76-1.68)		

Iso (1995)	Weekly intake in grams per week	Age, smoking, BMI, diabetes, education, leisure time sports, dietary intake of fruits, vegetables, and fish.	Nondrinker 0.72 (0.47-1.09) Occasional 1.00 1-149 g/wk 0.61 (0.39-0.97) 150-299 g/w 0.97 (0.65-1.47) 300-449 g/w 1.00 (0.65-1.55) 450+ g/w 1.12 (0.74-1.70)
Jakovljevic (2004)	Rare/never, moderate (1-2 drinks/day), heavy (3+ drinks per day)	Gender, smoking, BMI, BP	-
Jimenez (2012)	Grams per day (0, >0-4.9, 5-14.9, 15-29.9, 30-45)	Age, smoking, physical activity, BMI, family history of heart disease, history of heart disease, diabetes, hypertension, oophorectomy, post-menopausal status, hormone therapy, high cholesterol, multivitamin intake, aspirin, diet score, education level, husband's education level, marital status	None 1.00 >0-4.9 0.88 (0.76-1.02) 5.0-14.9 0.86 (0.72-1.02) 15-29.9 0.82 (0.63-1.07) 30-45 1.17 (0.89-1.54)
Jousilahti (2000)	Drinks per week	Age, study year, smoking, serum total cholesterol, SBP, DBP, BMI	-
Kiyohara (1995)	Nondrinker, light (<34g/d), heavy (34+ g/d)	Age, sex, BP, heart rate per minute, ECG abnormalities suggesting left ventricular abnormality or ischemic changes, glucose intolerance, serum cholesterol, BMI, smoking	Figure only: No diff between 0 and light, heavy has higher risk

Klatsky (1989)	Abstainers, former drinkers, <1 drink/d, 1-2 drinks/day, 3+ drinks per day	Age, sex, race, coffee, smoking, Quetelet index, restricted to no history of CVD	Abstainers	1.00
			Former	1.05 (0.49-2.24)
			<1/day	0.61 (0.37-1.00)
			1-2/day	0.73 (0.41-1.28)
			3+/day	0.62 (0.29-1.31)
Klatsky (2002)	Abstainers, former drinkers, <1 drink/d, 1-2 drinks/day, 3-5 drinks per day, 6+ drinks per day	Age, sex, race, BMI, education, smoking	Abstainers	1.0
			Former	1.0 (0.8-1.3)
			<1/mo	0.9 (0.8-1.0)
			<1/d	0.8 (0.7-1.0)
			1-2/day	0.8 (0.6-0.9)
			3-5	1.0 (0.8-1.2)
			6+/day	1.0 (0.7-1.5)
Kono (1986)	Non-drinker, ex-drinker, occasional drinker, daily drinker (<2/day and >=2 per day)	Age, smoking	Nondrinker	1.0
			Ex-drinker	3.2 (1.9-5.4)
			Occasional	1.0 (0.6-1.7)
			Daily, <2	1.4 (0.8-2.3)
			Daily, 2+	1.8 (1.0-3.2)
Leppälä (1999)	Mean daily alcohol intake. Nondrinkers, light (≤24 g/d), moderate (24.1-60.0 g/d), heavy (>60.0 g/d)	Age, BMI, total cholesterol, smoking, education, leisure-time physical activity, diabetes, heart disease, randomization group	None	1.00
			Light	0.91 (0.72-1.14)
			Moderate	1.17 (0.91-1.51)
			Heavy	1.54 (1.08-2.19)
Maskarinec (1998)	drinks per week	Age, ethnicity, smoking, BMI, years of education	-	

Mukamal (2005a)	Average weekly consumption. None, former, <1 drink, 1-6 drinks, 7-13 drinks, ≥14 drinks	Age, sex, race, smoking, marital status, education, exercise intensity, diabetes, depression score, aspirin use, BMI	None 1.00 Former 0.87 (0.67-1.15) <1/wk 0.85 (0.63-1.13) 1-6/wk 0.75 (0.53-1.06) 7-13/wk 0.82 (0.51-1.30) ≥14/wk 1.03 (0.68-1.57)
Mukamal (2005b)	Average grams per day of ethanol. Abstainer, light (0.1-9.9), moderate (10-29.9), and heavier (≥30)	Age, smoking, BMI, aspirin use, diabetes, hypercholesteroliemia, daily exertion, energy intake, parental history of MI before age 60, saturated fat, trans fat, folate, vitamin E, dietary fiber, geographic region, magnesium, potassium, omega-3 fatty acids	0 g/d 1.00 0.1-9.9 g/d 0.99 (0.72-1.37) 10.0-29.9 g/d 1.26 (0.90-1.76) 30+ g/d 1.42 (0.97-2.09)
Romelsjo (2012)	Average grams of ethanol per day (0, 0.1-10, 10-30, 30-60,60+)	None	
Romelsjo (1999)	Average grams of ethanol per day (0, 0.1-14.9, 15-30, 30+)	BP, BMI, father's social status, running away from home, poor school wellbeing, parental divorce, poor emotional control, few friends, unemployment, poor health, smoking	-
Sacco (1999)	Average daily consumption in past year	Age, sex, race-ethnicity, hypertension, diabetes, cardiac disease, smoking, education, BMI	None 1.00 1 drink/y-2 drinks/d 0.55 (0.42-0.72) 3-4 drinks/d 0.77 (0.44-1.34) 5+ drinks/d 1.55 (0.70-3.43)

Sankai (2000)	Lifetime abstainer, former, current drinker (<69g/d vs. 69+ g/d)	Age, smoking, blood pressure, total cholesterol, BMI, diabetes	-	
Shaper (1991)	Never/occasional, light (1-20 drinks/week), 21-42 drinks/week), heavy >42 drinks/week)	Age, SBP	-	
Stampfer (1988)		Age, parental history of infarction before age 60, menopausal status, HRT in women, study period, smoking, hypertension, diabetes, cholesterol level, obesity, exercise, cholesterol intake, saturated fat intake, polyunsaturated fat intake	0 <1.5 g/day 1.5-4.9 g/d 5-14.9 g/d ≥15 g/d	1.0 0.7 (0.4-1.6) 0.4 (0.2-0.9) 0.3 (0.1-0.7) 0.5 (0.2-1.1)
Truelson (1998)	Total weekly intake (# beverages) of alcohol: <1, 1-7, 8-14, 15-21, 22-41, 42+	Age, sex, smoking, BMI, physical activity in leisure time, Cholesterol, antihypertensive treatment, triglycerides, education, diabetes	<1 drink/d 1-7 8-14 15-21 22-41 42+	1.17 (0.96-1.43) 1.0 1.02 (0.82-1.26) 1.02 (0.76-1.37) 0.93 (0.68-1.26) 1.35 (0.99-1.86)
Yuan (1997)	Non-drinker, drinks per week(<=7, 8-14, 15-21, 22-28, 29-42, 43+)	Age, smoking, education	-	
Woo (1990)	Yes vs. no	none	-	

Yang (2012)   Average grams per week   Region, age, smoking, education   -

C. Part 3: Hemorrhagic and Total Stroke Results

Author (Year)	Hemorrhagic Stroke			Total Stroke		
Berger (1999)	0.92 (0.55-1.54)			<1 drink/wk 1.00		
				1 drink/wk 0.78 (0.59-1.04)		
				2-4 drinks/wk 0.75 (0.58-0.96)		
				5-6 drinks/wk 0.83 (0.63-1.11)		
				≥1 drink/day 0.80 (0.64-0.99)		
Djousse (2002)	-			-		
Djousse (2009)	-			-		
Chiuve (2008)		Men	Women		Men	Women
	0 g/d	1.00	1.00	0 g/d	1.00	1.00
	0.1-4.9 g/d	0.65 (0.41-1.03)	0.83 (0.62-1.10)	0.1-4.9 g/d	0.81 (0.68-0.97)	0.78 (0.68-0.88)
	5-14.9 g/d	0.85 (0.55-1.30)	0.76 (0.54-1.06)	5-14.9 g/d	0.86 (0.72-1.03)	0.77 (0.66-0.89)
	15-29.9 g/d	1.29 (0.78-2.13)	0.69 (0.39-1.23)	15-29.9 g/d	0.91 (0.73-1.15)	0.79 (0.63-0.99)
	≥30 g/d	0.99 (0.58-1.71)	1.40 (0.86-2.28)	≥30 g/d	1.21 (0.99-1.49)	1.30 (1.04-1.61)
Elkind (2006)	<1 drink/month	1.0		<1 drink/month	1.0	
	1 drink/m - 2 drinks/d	1.17 (1.46-2.97)		1 drink/m - 2 drinks/d	0.68 (0.47-0.98)	
	>2 drinks/d	2.27 (0.60-8.64)		>2 drinks/d	1.28 (0.71-2.32)	
Bazzano (2007)	Nondrinkers	1.0		Nondrinkers	1.0	
	1-6 drink/w	0.76 (0.55-1.06)		1-6 drink/w	0.92 (0.80-1.06)	
	7-20 dk/w	1.06 (0.86-1.30)		7-20 dk/w	1.02 (0.93-1.13)	
	21-34 dk/w	0.90 (0.68-1.19)		21-34 dk/w	1.22 (1.07-1.38)	
	>=35 dk/w	1.23 (1.00-1.58)		>=35 dk/w	1.22 (1.08-1.37)	

Donahue (1986)	Nondrinkers	1.0			Nondrinkers	1.0	
	1-14 oz/m	2.3 (1.2-4.3)			1-14 oz/m	1.2 (0.9-1.6)	
	15-39 oz/m	2.5 (1.2-4.2)			15-39 oz/m	1.3 (0.9-1.9)	
	40+ oz/m	2.9 (1.4-6.0)			40+ oz/m	1.5 (1.1-2.2)	

Drogan (2012)	-					**Women**	**Men**
					0 g/d	1.71 (0.67-4.38)	3.48 (1.10-10.95)
					>0-6 g/d	1.00	1.00
					>6-12 g/d	1.24 (0.71-2.13)	0.94 (0.45-1.94)
					>12-24 g/d	1.00 (0.50-1.99)	1.54 (0.80-2.95)
					24+ g/d	1.03 (0.41-2.56)	1.46 (0.65-3.28)

Gaziano (2000)	-				Rarely/never	1.00	
					1-3/month	0.95 (0.49-1.83)	
					1/week	0.62 (0.30-1.28)	
					2-4/week	0.59 (0.30-1.15)	
					5-6/week	1.10 (0.58-2.11)	
					1/d	1.21 (0.76-1.94)	
					2+/d	0.84 (0.34-2.04)	

Goldberg (1994)	**Fatal + Nonfatal stroke**				**Fatal + Nonfatal stroke**		
		50-64 years	**65-75 years**			**50-64 years**	**65-75 years**
	Abstainer	1.0	1.0		Abstainer	1.0	1.0
	Light	4.02	1.70		Light	1.17 (0.71-1.91)	1.27 (0.71-2.25)
	Moderate	1.86	0.01		Moderate	1.43 (0.72-2.86)	1.19 (0.45-3.18)
	Heavy	4.59	3.86		Heavy	1.35 (0.71-2.55)	1.00 (0.37-2.75)

Gorelick (1989)	-				-		

Hansagi (1995)		Men	Women			Men	Women
	0 g/d	1.00	1.00		0 g/d	1.00	1.00
	0.01-4.99 g/d	0.8 (0.4-1.5)	0.7 (0.5-1.1)		0.01-4.99 g/d	1.2 (0.8-1.6)	0.6 (0.5-0.8)
	5.00-14.9 g/d	0.8 (0.4-1.7)	0.8 (0.3-2.2)		5.00-14.9 g/d	1.1 (0.8-1.7)	0.9 (0.5-1.5)

Study						
	15+ g/d	1.1 (0.5-2.7)	1.2 (0.2-9.6)	15+ g/d	1.1 (0.7-1.9)	1.6 (0.5-4.6)
Hart (1999)	-			None	1.00	
				1-7 units/wk	0.98 (0.57-1.69)	
				8-14	1.08 (0.63-1.85)	
				15-21	1.53 (0.87-2.68)	
				22-34	1.59 (0.89-2.82)	
				35+	1.98 (1.09-3.59)	
Ikehara (2009)	Never	1.00		Never	1.00	
	Former	1.26 (0.64-2.50)		Former	0.90 (0.60-1.34)	
	Occasional	1.41 (0.79-2.54)		Occasional	1.04 (0.72-1.52)	
	1-149 g/wk	0.68 (0.41-1.12)		1-149 g/wk	0.83 (0.64-1.08)	
	150-299 g/w	0.93 (0.58-1.48)		150-299 g/w	1.02 (0.79-1.31)	
	300-449 g/w	1.39 (0.86-2.26)		300-449 g/w	1.37 (1.04-1.79)	
	450+ g/w	1.80 (1.10-2.97)		450+ g/w	1.36 (1.01-1.85)	
Iso (1995)	Nondrinker	1.49 (0.85-2.63)		Nondrinker	1.09 (0.80-1.49)	
	Occasional	1.00		Occasional	1.00	
	1-149 g/wk	1.83 (1.03-3.24)		1-149 g/wk	1.04 (0.75-1.44)	
	150-299 g/w	2.52 (1.45-4.36)		150-299 g/w	1.46 (1.08-1.99)	
	300-449 g/w	2.09 (1.17-3.73)		300-449 g/w	1.31 (0.94-1.81)	
	450+ g/w	2.51 (1.43-4.41)		450+ g/w	1.64 (1.20-2.24)	
Jakovljevic (2004)	-			RR=1.138 (0.207-6.268) for moderate vs. rare/never		

Jimenez (2012)	None	1.00		None	1.00	
	>0-4.9	0.82 (0.63-1.06)		>0-4.9	0.83 (0.75-0.92)	
	5.0-14.9	0.76 (0.56-1.03)		5.0-14.9	0.79 (0.70-0.90)	
	15-29.9	0.88 (0.58-1.35)		15-29.9	0.87 (0.72-1.05)	
	30-45	0.97 (0.58-1.60)		30-45	1.06 (0.86-1.30)	

Jousilahti (2000)	-				Women	Men
				Abstainer	1.00	1.00
				1-3/wk	0.64 (0.39-1.06)	1-5/wk 0.96 (0.71-1.30)
				4-6/wk	0.93 (0.49-1.80)	5-10 0.94 (0.65-1.37)
				7+/wk	1.22 (0.57-2.64)	10+ 0.96 (0.67-1.40)

| Kiyohara (1995) | Figure only: ~ linear increase in RR | | | - | | |

Klatsky (1989)	Abstainers	1.00		-		
	Former	1.47 (0.28-7.83)				
	<1/day	1.02 (0.39-2.65)				
	1-2/day	0.94 (0.28-3.17)				
	3+/day	3.85 (1.19-12.41)				

| Klatsky (2002) | - | | | - | | |

Kono (1986)	Nondrinker	1.0		Nondrinker	1.0	
	Ex-drinker	1.0 (0.4-2.4)		Ex-drinker	2.3 (1.5-3.5)	
	Occasional	1.2 (0.7-2.2)		Occasional	1.1 (0.7-1.6)	
	Daily, <2	0.9 (0.5-1.8)		Daily, <2	1.2 (0.8-1.8)	
	Daily, 2+	1.6 (1.0-3.2)		Daily, 2+	1.7 (1.1-2.6)	

Leppälä (1999)		**SAH**	**ICH**	None	1.00	
	None	1.00	1.00	Light	0.90 (0.74-1.10)	
	Light	1.00 (0.47-2.13)	0.83 (0.46-1.50)	Moderate	1.12 (0.89-1.39)	
	Moderate	1.33 (0.59-2.99)	0.64 (0.31-1.35)	Heavy	1.52 (1.12-2.08)	
	Heavy	1.58 (0.54-4.63)	1.77 (0.73-4.31)			

Study						
Maskarinec (1998)	-				Men	Women
				0	1.00	1.00
				1-7	0.89 (0.58-1.36)	1.04 (0.59-1.83)
				8-14	1.03 (0.60-1.78)	0.83 (0.30-2.29)
				15-28	1.12 (0.86-1.47)	
				15-35		2.38 (1.07-5.30)
				29-42	1.00 (0.40-2.47)	
				43-70	0.54 (0.07-3.88)	
				70+	0.65 (0.09-4.71)	
Mukamal (2005a)	-			-		
Mukamal (2005b)	-			-		
Romelsjo (2012)	-			0 g/d	1.00	
				0.1-10	1.32 (0.41-4.27)	
				10-30	1.91 (0.58-6.34)	
				30-60	2.10 (0.42-10.40)	
				60+	3.62 (0.61-21.68)	
Romelsjo (1999)	-			0 g/d	1.00	
				0.1-14.9	1.59 (0.64-3.92)	
				15-30	1.52 (0.57-4.00)	
				30+	2.30 (0.81-6.43)	
Sacco (1999)	-			-		
Sankai (2000)		**SAH**		-		
	Lifetime abstainer	1.00				
	Former drinker	-				
	<69 g/d	1.0 (0.5-2.3)				
	69+ g/d	3.9 (1.4-10.6)				
Shaper (1991)	-			Age, BP, smoking adjusted incidence per 100 PY		
				None/occasional : 1.9		

			Light: 1.9 Moderate: 1.7 Heavy: 2.4	
Stampfer (1988)	0	1.0	-	
	<1.5 g/day	2.4 (0.5-12.1)		
	1.5-4.9 g/d	2.9 (0.7-11.5)		
	5-14.9 g/d	3.7 (1.0-13.8)		
	≥15 g/d	2.6 (0.7-10.3)		
Truelson (1998)	-		-	
Yuan (1997)	-		Nondrinker	1.00
			1-28 drinks/w	1.02
			20+ drinks/w	1.65 (1.12-2.44)
Woo (1990)	-		RR=1.9 (0.01-11.6)	
Yang (2012)	-		Non-drinker	1.00 (0.96-1.05)
			<140 g/wk	0.99 (0.88-1.12)
			140-279 g/wk	1.12 (1.01-1.24)
			280-419 g/wk	1.14 (1.03-1.26)
			420-699 g/wk	1.21 (1.07-1.37)
			700+ g/wk	1.55 (1.37-1.75)

APPENDIX 3: ALCOHOL AND COGNITIVE DECLINE LITERATURE REVIEW TABLES

A. Part 1: Population, Study Design, and Measurement

Author (Year)	Population	Baseline Calendar Year	N	Follow-up (y)	Attrition (%)	Alcohol Measurement	Analysis Included Multiple Exposure	Frequency of cognitive assessments	Assessment of Cognitive Status
Bond (2004)	Pooled prospective cohort of **The Kame Project**, population-based study of community-dwelling Japanese Americans 65+ years of age and **The Adult Changes in Thought (ACT) study**	1994	4,191	Max 4	NR, at least 11%	Structured interview asking about alcohol consumption ever, formerly or currently (within the last year)	No	3 total, every 2 years	CASI (assessment of 9 cognitive domains)
Dufouil (2000)	**Epidemiology of Vascular Aging (EVA) Study** Population-based prospective study of adults aged 59-71 y in western France.	1991	1,389	4	21.0%	Self-reported, beverage-specific number of glasses of alcohol consumed at 6 different times throughout the day.	No	Twice, 4 years apart	Global cognition: MMSE

Espeland (2005)	**Women's Health Initiative Memory Study (WHIMS)** Randomized controlled trial of estrogen and progestin in postmenopausal women aged 50-79 years	1996	4,461	4.2	2% missing any follow-up visit. Participation at V1-6 were 96%, 92, 91, 83, 39, and 2%	Beverage-specific FFQ assessing past 3 months of intake	No	Annually	Global cognitive function: Modified Mini-Mental State Examination (3MSE)
Ganguli (2005)	**Monongahela Valley Independent Elders Survey (MoVIES)** Prospective cohort of rural-dwelling blue collar workers in PA aged 65+	1987-9	1,681	7.3	Not reported	Baseline QF measure, with F over follow-up	Yes, trajectory of frequency	Every 2 years	MMSE, Trailmaking Test, Word List Learning and Delayed Recall, Story Immediate and Delay Recall, Boston Naming Test, Clock Drawing, etc
Herbert (1993)	**Established Populations for Epidemiologic Studies of the Elderly**, non-institutionalized persons aged 65+ in East Boston, MA	1982	3,809	3	15.0%	Interview-administered questionnaire assessing alcohol consumption in past year (yes or no) and amount consumed in past month (# of	No	2 total, 3 years apart	Memory test (story recall), digit span test, and orientation

drinks)

Leroi (2002)	**Baltimore arm of Epidemiologic Catchment Area program** prospective study of adults 18+ from 5 sites	1981	3,481	12.5	57.3%	QF of alcohol consumption at 3 waves	No, subject to immortal person-time	2; 1 and 11 years	MMSE
Lobo (2010)	**ZARADEMP Project** Prospective, population-based study of adults 55 and older in Spain	1994	4,803	4.5	41.0%	Beverage-specific usual daily intake (Q only)	No	2; ~2 years apart	MMSE
Peters (2009)	**The Hypertension in the Very Elderly Trial (HYVET)** Randomized trial of antihypertensive treatment among older adults aged 80 and over from Europe, China,	2005	3,336	2	NR	Consumption of alcohol at baseline	No	Annually	MMSE

and Australia

Stampfer (2005)	**Nurses' Health Study** Female nurses aged 30-55 years in 11 US states	1995	12,480	1.8	11% (~3% died, 7% LTF or declined)	Food frequency questionnaire every 4 years beginning in 1980 assessed beverage specific QF	No, restricted to women with stable drinking over time and used measurement immediately prior to cognitive assessment	1.8 years apart	Baseline: Telephone Interview of Cognitive Status (TICS) Follow-up: TICS, East Boston Memory Test, 10-Word List, verbal fluency, digit span backward test
Stott (2008)	**Prospective Study of Pravastatin in the Elderly RISK (PROSPER)** RCT of adults aged 70-82 years with vascular risk factors or disease in Ireland, the Netherlands, and Scotland	~1998	5,804	3.2	20.8%	Self-reported usual intake during previous month	No	5; baseline and 9, 18, 30 months, final visit	MMSE, Stroop Color-Word test, Letter-Digit Coding Test (LDCT), Picture Word Recall Test (PWRT)

Wright (2006)	The Northern Manhattan Stroke Study Residents of Northern Manhattan >39 years of age with no history of stroke at baseline	2001	2,631	2.2	46.0%	In-person interview adapted from the National Cancer Institute Block FFQ to assess beverage-specific average consumption in past 6 months	No	Annually	TICS-m
Yaffe (2009)	Health, Aging, and Body Composition (Health ABC) study Prospective cohort of community-swelling residents of Memphis, TN and Pittsburgh, PA aged 70-79	1997	3,075	Max 7 years	NR, at least 20%	Interviewer administered questionnaire to assess usual weekly consumption over 12-month period	No	Years 1, 3, 5, 8	3MS

B. Part 2: Analysis and Results

Author (Year)	Operation Definition of Alcohol Consumption	Operation Definition of Cognitive Status	Covariates	Statistical Analysis	Results		
Bond (2004)	Current (5+ drinks per year) Former (drinking but not in past year) Abstainer	Mean CASI score as a function of time	Age, BMI, education, income, smoking, stroke history, HTN, CHD, depression, DM	Mixed-effects hierarchical linear models with multiple imputation for missing data generated through death, LTF, refusals	**Alcohol** Current Not current	**Intercept, B(SE);p** 1.36 (0.26); <0.001 0.89 (0.33); <0.01	**Slope, B(SE);p** 0.17 (0.08); <0.05 0.02 (0.11); NS
Dufouil (2000)	Usual daily intake in drinks per day. Never, <2, 2-5, 5+	Categorized MMSE change score as 1) Deterioration (3+ point drop) or 2) No deterioration (drop less than 3 points)	None	Logistic regression	**Daily Alcohol** 0 <2 glasses 2-5 glasses 5+ glasses	**RR (95% CI)** APOE e4+ 1.0 1.9 (0.7-5.0) 2.7 (0.9-8.4) 8.3 (1.0-66.00	**RR (95% CI)** APOE e4- 1.0 0.7 (0.5-1.1) 0.6 (0.4-1.1) 0.3 (0.1-1.3)
Espeland (2005)	Drinks per day: none, <1, 1+	Baseline 3MSE, continuous Decline of 8+ points vs not	Age, years since menopause, education, family income, use of tobacco, BMI, HTN, CVD, DM, statin therapy,	Analysis of variance (cross-sectional analysis), logistic regression (drop in score of 8 or more points vs.	No alcohol <1 drink/d 1+ drink/d p-value	**Baseline score** 95.28 95.63 96.00 <0.001	**OR (8pt drop)** 1.0 0.69 (0.49-0.97) 0.53 (0.28-0.99)

		aspirin use, HRT, intervention assignment	not)		
Ganguli (2005)	Drinking frequency trajectory PROC TRAJ identified 1) no drinking, 2) minimal drinking (1/mo or less), 3) moderate drinking (>1/mo)	Global (MMSE score) and domain specific (learning, memory, visuospatial, fluency, trailmaking, naming)	Age, sex, education level, smoking, depressive symptoms, self-reported HD, DM, stroke, neurologic disease, peptic ulcer disease, nervous/emotional conditions, baseline MMSE score, incident dementia	Latent class analysis	Baseline scores were higher and declines were slower among minimal and moderate drinkers compared with nondrinkers. When models were compared with nondrinkers broken out as quitters and abstainers, find most of the effect is due to quitters
Herbert (1993)	Average ounces per day 1) None in previous year 2) V. light < 0.5 oz per day 3) Light 0.1-1 oz per day 4) Moderate 1+ oz	Normal score transformation within strata of baseline scores	Age, sex, education, income, presence of any chronic condition (self-reported stroke, MI, cancer, DM, or HTN), baseline score.	Linear regression	(see below)

Normal Score Change (95% CI)

Alcohol	Orientation	Digit-span	Memory
None	0	0	0
V. light	0.10 (-0.03, 0.23)	0.09 (0.02, 0.16)	0.03 (-0.10, 0.16)
Light	0.17 (-0.03, 0.37)	0.06 (-0.05, 0.17)	0.05 (-0.16, 0.25)
Mod.	-0.001 (-0.20, 0.19)	0.07 (-0.04, 0.18)	0.18 (-0.02, 0.38)

Leroi (2002)	Categorized as the highest reported intake over the 3 waves 1) Nonuser 2) Mild/Moderate: <5 drinks/day on <20 d/m 3) Habitual: <5 drinks/day on 20+d/m 4) Heavy infrequent: >4 drinks/d on <20 d/m 5) Heavy frequent: >4 drinks/d on 20= d/m	Mean change in MMSE between waves 2 and 3	Age, sex, race, education	Analysis of covariance		**Men**	**Women***
					Nonusers	-1.25	-1.75
					Social users	-1.23	-1.50
					Habitual users	-1.34	-1.10
					Binge users	-1.06	-1.56
					Heavy, frequent users	-1.29	-0.86
					* F-test significant differences, p<0.0001		
Lobo (2010)	Abstainers, former drinkers, grams/day: <12, 12-24, >24 for women and <12, 12-24, 24-40, and >40 for men	Annual change in MMSE from the first and last measurements.	Age, marital status, education, smoking (yes, no), HTN, depression, use of psychotropic drugs, disability index	Simple linear regression		**Men**	**Women**
					Abstainer	0	0
					<12 g/day	-0.09 (-0.23,-0.05)	-0.55 (-0.25,-0.14)
					12-24 g/day	0.09 (-0.07,0.25)	0.29 (-0.02,0.61)
					24-40 g/day	-0.06 (-0.23,0.11)	
					40+ g/day	-0.01 (-0.21,0.20)	
					Former	0.04 (-0.09,0.18)	-0.06 (-0.30, 0.19)
Peters (2009)	Consumption of alcohol (yes vs. no)	Mean annual change in MMSE score	Age, sex, current smoking, lives alone, BMI (underwt, overwt, obese), education,	Simple linear regression	Alcohol (yes vs. no) -0.01 (-0.25,0.23)		

use of piraetam,
treatment arm.
Hypertension, by
design

					OR for Substantial Decline		
						TICS	Global Cog Score
Stampfer (2005)	Grams per day: 0, 1.0-14.9, 15.0-30.0	Global cognition: average of z scores from all tests Mean scores on individual tests Change: substantial decline (bottom 10t percent of decline) vs. not	Age, highest educational degree, HTN, cholesterol, DM, heart disease, physical activity, age at menopause, HRT, vitamin E, BMI, smoking status (former, never, current), aspirin use, mental health index, energy-fatigue index, SF36, social integration, baseline cognitive score	Cross-sectional: linear regression, logistic regression Longitudinal: Logistic regression	No alcohol 1.0-14.9 15.0-30.0	1.00 0.85 (0.74-0.98) 1.04 (0.77-1.41)	1.0 0.89 (0.77-1.03) 0.82 (0.58-1.16)
Stott (2008)	Units per week. Women categorized as 0, <3 units per week, 3+; men 0, <7 units per week, 7+	Mean test score	Age, country, edu. level, baseline cognitive status, smoking, BMI, weight, incident stroke, history of vascular disease, test version	Linear mixed models estimating rate of decline and mean decline	Mean differences were smaller for female drinkers compared with nondrinkers for all tests except PWLT. No differences for men. Rate of decline similar for all cognitive domains. MMSE decline was less in female drinkers vs. nondrinkers (0.05 points per year, p=0.001)		

Wright (2006)	Average daily consumption in past year categorized as: never, past, <1 drink/wk, 1-14 drinks/wk, >14 drinks/week	Mean change in TICS-m	Age, education, sex, race, insurance status, HDL-C, BMI, HTN, DM, cardiac disease, current smoking, depression, physical inactivity, time between TICS-m administration	Generalized estimating equations. Accounts for correlation among change scores	**Alcohol Intake category** Never Former 0-7 drink/wk 7-14 drinks/w >14+ drinks/w		**Change in TICS-m over referent** 1.00 0.4 (-0.4, 1.2) 0.9 (-1.2, 1.9) 1.5 (0.6, 2.4) 2.4 (0.8, 4.0)
Yaffe (2009)	Current drinking (>1 drink/day vs. ≤ 1 drink/day)	Trajectory of cognitive decline categorized based on participant-specific slopes: 1) Maintainers, slope ≥0; 2) Minor decliners, slope <0 and > (mean decline - 1SD); 3) Major decliners, slope > 1SD below mean decline	Age, race, education, employed, social support, lives alone, self-rated health, exercise, current smoking, CED-D, BMI, HTN, DM, stroke history, APOE, CRP, IL-6, TG, fasting glucose	Linear mixed model with random intercepts and slope to categorize outcome. Logistic regression to estimate association of alcohol with cognitive trajectory.	≤1 drink/day >1 drink/day	**Maintainer vs. minor decline** 1.0 1.33 (0.91-1.93)	**Major vs. minor decline** 1.0 0.67 (0.36-1.27)

DIETARY INTAKE FORM (screen 16 of 18)

I. ALCOHOL

"I am going to ask you about wine, beer, and
drinks made with hard liquor because these are
the three major types of alcoholic beverages."

90. Do you presently drink
    alcoholic beverages? .... Yes   Y

        ┌─────────────────┐
        │ Go to Item 96, │   No   N
        │   Screen 17   │
        └─────────────────┘

91. Have you ever consumed
    alcoholic beverages? .... Yes   Y

                                    No   N
        ┌─────────────────┐
        │ Go to Item 101, │
        │   Screen 18   │
        └─────────────────┘

92. Approximately how many years
    ago did you stop drinking? .... ☐☐

95. What was the usual number of drinks
    you had per week before you stopped
    drinking alcoholic beverages? .... ☐☐
    {One drink means 1 beer or 1 glass
    of wine or 1 shot of liquor or 1 mixed drink.
    Record 0 if less than one drink per week.}

    ┌──┐
    │ After completing item 95, go to item 101 │
    └──┘

96. How many glasses of wine do
    you usually have per week? .... ☐☐
    {4 oz. glasses; round down}

97. How many bottles or cans of beer
    do you usually have per week? .... ☐☐
    {12 oz. bottles or cans; round down}

93. For how many years did you
    drink alcoholic beverages? .... ☐☐

94. In the past, which types of alcoholic
    beverages did you ordinarily drink?
    {Circle Y or N for each type below}   Yes   No

    a. Wine ....   Y   N

    b. Beer ....   Y   N

    c. Drinks made with hard liquor ....   Y   N

    d. Other ....   Y   N

    e. Specify: ☐☐☐☐☐☐☐☐☐☐

98. How many drinks of hard liquor
    do you usually have per week? .... ☐☐
    {1 1/2 oz. shots; round down}

99. During the past 24 hours, how
    many drinks have you had? .... ☐☐

        ┌──────────────────────┐
        │ If "0", go to item 101 │
        └──────────────────────┘

100. Were these: {Circle Y or N for each}
                                            Yes   No

    a. Wine? ....   Y   N

    b. Beer? ....   Y   N

    c. Liquor? ....   Y   N

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APPENDIX 5: COGNITIVE FUNCTION ASSESSMENTS USED IN THE ARIC STUDY

ʟ-70

ARIC
Atherosclerosis Risk in Communities

Appendix 2.4a

COGNITIVE FUNCTION FORM

ID NUMBER: ☐☐☐☐☐☐☐ CONTACT YEAR: ☐1☐ ☐0☐ FORM CODE: ☐C☐N☐F☐ VERSION: C 01/30/96

LAST NAME: ☐☐☐☐☐☐☐☐☐☐☐ INITIALS: ☐☐

PART A: DELAYED WORD RECALL

PLACE A CHECK IN THE COLUMN TO THE RIGHT OF EACH WORD AFTER THE PARTICIPANT HAS READ IT ALOUD AND USED IT IN A SENTENCE.

PLACE A CHECK IN THE 2ND COLUMN TO THE RIGHT OF EACH WORD AFTER THE PARTICIPANT HAS READ IT ALOUD AND USED IT IN A SENTENCE THE SECOND TIME.

AFTER THE COMPLETION OF THE DIGIT SYMBOL TEST, ASK THE PARTICIPANT TO RECALL THE 10 WORDS ORIGINALLY GIVEN:

CHECK OFF ALL THE WORDS RECALLED WITHIN 60 SECONDS.

	FIRST TIME	SECOND TIME		DELAYED WORD RECALL
chimney	_____	_____	book	_____
salt	_____	_____	button	_____
harp	_____	_____	chimney	_____
button	_____	_____	finger	_____
meadow	_____	_____	flower	_____
train	_____	_____	harp	_____
flower	_____	_____	meadow	_____
finger	_____	_____	rug	_____
rug	_____	_____	salt	_____
book	_____	_____	train	_____

PART B: DIGIT SYMBOL SUBSTITUTION (DSS) TASK

10. DIGIT SYMBOL

1	2	3	4	5	6	7	8	9	SCORE
—	⊥	⊐	L	U	O	∧	X	=	

SAMPLES

1	3	7	2	4	8	2	1	3	2	1	4	2	3	5	2	3	1	4	5	6	3	1	4

1	5	4	2	7	6	3	5	7	2	8	5	4	6	3	7	2	8	1	9	5	8	4	7	3

6	2	5	1	9	2	8	3	7	4	6	5	9	4	8	3	7	2	6	1	5	4	6	3	7

9	2	8	1	7	9	4	6	8	5	9	7	1	8	5	2	9	4	8	6	3	7	9	8	6

PART C: WORD FLUENCY TASK

START THE STOPWATCH. RECORD VERBATIM. DO NOT CORRECT ERRORS. IF THE PARTICIPANT STOPS, ENCOURAGE FURTHER RESPONSES. ALLOW 60 SECONDS FOR EACH LETTER. THE NEXT LETTER IS NOT GIVEN UNTIL THE ENTIRE 60-SECOND PERIOD HAS PASSED.

	F	A	S
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			
10.			
11.			
12.			
13.			
14.			
15.			
16.			
17.			
18.			
19.			
20.			

CNF SCORING SUMMARY

PART A: DELAYED WORD RECALL

ADD UP THE CHECK MARKS IN COLUMN 3, PART A AND ENTER THE TOTAL NUMBER OF RECALLED WORDS BELOW:

1.   TOTAL WORDS RECALLED (CNFC, Part A):   []

PART B: DIGIT SYMBOL SUBSTITUTION

APPLY THE DSS SCORING TEMPLATE TO THE RESPONSES ON PART B AND ENTER THE NUMBER OF CORRECT SYMBOLS BELOW:

2.   TOTAL CORRECT SYMBOLS (CNFC, Part B):   []

APPLY THE DSS SCORING TEMPLATE TO THE RESPONSES ON PART B AND ENTER THE NUMBER OF INCORRECT SYMBOLS BELOW:

3.   TOTAL INCORRECT SYMBOLS (CNFC, Part B):   []

PART C: WORD FLUENCY

ADD UP THE TOTAL NUMBER OF WORDS LISTED IN COLUMNS F, A, AND S ON PART C, AND ENTER THAT TOTAL BELOW:

4.   TOTAL WORDS LISTED (CNFC, Part C):   []

PART D: ADMINISTRATIVE INFORMATION

5.   DATE OF DATA COLLECTION: [/ /]
                                 month   day   year

6.   INTERVIEWER CODE NUMBER: []

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