ASSOCIATION BETWEEN EXPOSURE TO COMBAT AND BURDEN OF CORONARY HEART DISEASE, ISCHEMIC STROKE AND SUBCLINICAL ATHEROSCLEROSIS IN AGING MEN: THE ATHEROSCLEROSIS RISK IN COMMUNITIES (ARIC) STUDY

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ABSTRACT

ANNA M. JOHNSON**:** Association between Exposure to Combat and Burden of Coronary Heart Disease, Ischemic Stroke and Subclinical Atherosclerosis in Aging Men: The Atherosclerosis Risk in Communities (ARIC) Study
(Under the direction of Dr. Gerardo Heiss)

Studies of the long-term cardiovascular consequences of combat stress are few and inconclusive. We investigated the effect of combat on the incidence of coronary heart disease (CHD) and ischemic stroke (IS) and the burden of subclinical atherosclerosis—measured by carotid intima-media thickness (CIMT) and carotid plaque—among 5,347 black and white men from the Atherosclerosis Risk in Communities (ARIC) cohort study. Combat veterans and non-combat veterans were compared separately with non-veteran "controls" and with one another. Veterans were older, white and of higher socioeconomic status than non-veterans. Veterans were more likely to be current drinkers and heavy smokers but less likely to be current smokers and physically inactive. Combat veterans had the highest average systolic blood pressure and total cholesterol. Compared to non-veterans, combat veterans (Risk Ratio (RR): 1.19; 95% Confidence Interval (CI): 1.11, 1.28) and non-combat veterans (RR: 1.08; 95% CI: 1.01, 1.15) had higher risk of carotid plaque, and combat veterans (Risk Difference (RD): 28.6μm; 95% CI: 22.5, 34.6) and non-combat veterans (RD: 12.48μm; 95% CI: 2.64, 22.32) had higher average CIMT. Compared to non-combat veterans, combat veterans had higher risk of carotid plaque (RR: 1.11; 95% CI: 1.03, 1.19) and higher average CIMT (RD: 44.68μm; 95% CI: 32.47, 56.89). Differences remained when CIMT was dichotomized and when age was considered among men from the eras of World War II and

the Korean War but not the Vietnam Conflict. Combat veterans had higher CHD and IS incidence rates than non-combat veterans or non-veterans only among cohort members of the Korean War era. Incidence rate ratios (IRR) were statistically significant only in comparisons between combat and non-combat veterans for CHD (IRR=1.46; 95% CI=1.02, 2.07) and IS (IRR=1.81; 95% CI=1.01, 3.23). Results suggest that differences detectable at the subclinical level may not yet be manifest at the level of symptomatic disease. Interaction by era of service was noted in both analyses, with the most notable effects among men from the Korean War era. The findings in this study, if confirmed, have implications for our understanding of the lasting effects of traumatic stress on long-term cardiovascular health.

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LIST OF ABBREVIATIONS

AHA	American Heart Association
AMI	Acute myocardial infarction
APOE	Apolipoprotein E
ARIC	Atherosclerosis Risk in Communities
BMI	Body mass index
BP	Blood pressure
CAD	Coronary artery disease
CHD	Coronary heart disease
CHF	Congestive heart failure
CHS	Cardiovascular Health Study
CI	Confidence interval
CIMT	Carotid intima-media thickness
CPS	Current Population Survey
CSR	Chronic stress reaction
CT	Computed tomography
CV	Combat veteran
CVA	Cerebrovascular accident
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
ECG	Electrocardiographic
FEV	Forced expiratory volume
HDL	High density lipoprotein

HPA	Hypothalamic-pituitary-adrenal
HR	Hazard ratio
HVVP	Hawaii Vietnam Veterans Project
IAP	International Atherosclerosis Project
ICD-10	International Classification of Diseases
ICH	Intracerebral hemorrhagic strokes
IL-6	Interleukin 6
IR	Incidence rate
IRR	Incidence rate ratio
LC-SES	Life Course Socioeconomic Status, Social Context and Cardiovascular Disease
LDL	Low density lipoprotein
LVH	Left ventricular hypertrophy
MI	Myocardial infarction
MONICA	Monitoring Trends and Determinants in Cardiovascular Disease
MRFIT	Multiple Risk Factor Intervention Trial
MRR	Mortality rate ratio
NCV	Non-combat veterans
NIMH	National Institute of Mental Health
NLS	National Longitudinal Survey
NOS	Not otherwise specified
NSV	National Survey of Veterans
NV	Non-veteran
NVVRS	National Vietnam Veterans Readjustment Study

ONS	Office of National Statistics
PAD	Peripheral arterial disease
PDAY	Pathobiological Determinants of Atherosclerosis
POW	Prisoner of war
PTSD	Post-traumatic stress disorder
RD	Risk difference
RIND	Reversible ischemic neurological deficit
RR	Risk ratio
SAH	Subarachnoid hemorrhagic strokes
SBP	Systolic blood pressure
SCD	Sudden cardiac death
SD	Standard deviation
SES	Socioeconomic status
SMR	Standardized mortality ratio
TIA	Transient ischemic attacks
VES	Vietnam Experience Study
VHS	Veterans Health Study
WHO	World Health Organization
WSC	West of Scotland Collaborative

CHAPTER 1

INTRODUCTION

Stress is widely considered to have both psychological and physiological effects and is thought to influence the development of cardiovascular disease (CVD).[1, 2, 3] A primary mechanism through which stress may increase the risk of CVD is through an inflammatory or atherosclerotic process, involving neurological, endocrine, and immunological components.[4,5] Psychological, behavioral and other pathways have also been implicated.[6,7, 8] The psychosocial stress experienced by veterans who have engaged in active combat is a uniquely traumatic stressor that can have positive as well as negative consequences[9,10] and can have both short-term and long-term effects.[11,12] The effects of military service in general and military combat in particular are so pervasive yet so little studied that they have been termed the "hidden variable" in the aging of older American men.[13,14] Approximately 65% of American men over the age of 55 served in World War II or the Korean conflict. Further, about one quarter of all older American men were exposed to military combat at some time in their lives.[15,16]

The epidemiologic evidence supports a possible effect on increased cardiovascular risk from exposure to military combat, although the data are limited and to date have been inconclusive.[17,18,19] Exposure to combat has been associated with higher rates of behavioral problems,[20] psychological disorders,[21, 22] and self-reported health conditions[23, 24] Many studies have investigated the effects of military combat—typically depression or post-

traumatic stress disorder (PTSD)—rather than exposure to combat itself. Further, most studies have focused on psychological and short-term health outcomes rather than long-term physiological outcomes. Of the studies that have investigated long-term consequences of combat exposure, mortality has been the primary outcome. Studies of the long-term impact of combat on the incidence of CVD are few, and to date, no studies have directly assessed the association between exposure to combat and the prevalence of subclinical atherosclerosis. In this study, we took advantage of a unique opportunity to investigate the effect of combat on the incidence of coronary heart disease (CHD) and ischemic stroke (IS) and the burden of subclinical atherosclerosis in a large, community-based sample of men whose military service spanned World War II, the Korean War and the Vietnam Conflict. In the course of this study, the following two manuscripts were prepared:

Manuscript 1: The association between remote exposure to combat and subclinical atherosclerosis was assessed among 5,347 men in the Atherosclerosis Risk in Communities (ARIC) cohort. Coronary artery plaque and carotid intima-media thickness (CIMT) were compared between non-veterans and veterans with and without one or more self-reported combat exposures. Cardiovascular measurements were taken an average of 36 years after entry into military service. Descriptive statistics were calculated for baseline distributions of sociodemographic characteristics, risk factors and military and combat exposures. Statistical evaluation of differences in the distribution of carotid plaque and CIMT compared combat veterans and non-combat veterans separately with non-combat "controls" and also contrasted the two veteran groups: combat veterans with non-combat veterans. Linear regression was used to estimate risk differences (RDs) and 95% confidence intervals (CIs) for continuous

CIMT, averaged over Visits 1 and 2, while modified Poisson regression was used to estimate risk ratios (RRs) and 95% CIs for binary CIMT and plaque variables. Because age was not associated with the exposure in these data, it could not be treated as a typical confounder in statistical analyses. However, because it is strongly associated with the development of atherosclerosis, age at identification of subclinical atherosclerosis was accounted for by looking at age-specific values and ranges of each outcome. Results were stratified according to era of service (World War II, the Korean War or the Vietnam Conflict) and race (black or white) in order to assess potentially important heterogeneity in effects. This study addresses Aim 1 (see Section II).

Manuscript 2: The association between remote exposure to military combat and the risk of coronary heart disease (CHD) and ischemic stroke (IS) was assessed among 4,620 men in the Atherosclerosis Risk in Communities study. Descriptive statistics were calculated for baseline distributions of sociodemographic characteristics, risk factors and military and combat exposures. Ten-year predicted risks of CHD and IS associated with exposure to military service with and without combat were calculated independently using linear regression using published sex and race-specific parameter estimates. Incidence rates (IR) were calculated by dividing the number of events by the total time experienced for the participants followed. Incidence rate ratios (IRR) and 95% confidence intervals (CI) were calculated using Poisson regression. Combat veterans and non-combat veterans were compared separately with non-combat "controls," and the two veteran groups—combat veterans and non-combat veterans—were also compared with one another. Non-veterans were grouped into three age categories (<52, 52-59, 60+ years) that most closely mirrored the

age categories of veterans who served during the eras of World War II, the Korean War and the Vietnam Conflict, respectively. Results were stratified according to era of service (World War II, the Korean War or the Vietnam Conflict) in order to assess potentially important heterogeneity in effects. This study addresses Aim 2 (see Section II).

CHAPTER 2

SPECIFIC AIMS

In this study, we report on the long term association between exposure to military combat and the incidence of coronary heart disease (CHD) and ischemic stroke (IS) as well as the burden of subclinical atherosclerosis in a large, community-based sample of men whose military service spanned the eras of World War II, the Korean War and the Vietnam Conflict. Those with a history of military service who reported one or more combat-related stressors (combat veterans) were contrasted to those without a history of military service (non-veterans) as well as to those with a history of military service without combat (non-combat veterans). Results were stratified by era of service (World War II, the Korean War and the Vietnam Conflict) to detect differences in effect among veterans of different birth and service cohorts. We also examined the extent to which differences by combat exposure status, if extant, vary by differences in sociodemographic and cardiovascular risk factor profiles. To this end, we evaluated the following specific aims:

Specific Aim 1: To investigate the association between exposure to combat stress and the presence of subclinical atherosclerosis.

Hypothesis 1.1: Combat veterans have higher prevalence of subclinical carotid atherosclerosis (as measured by carotid intima media thickness (IMT) and the

presence of carotid artery plaque) than veterans without combat exposure or non-veterans.

Hypothesis 1.2: Associations between combat stress and subclinical carotid atherosclerosis remain after age is taken into account, both when combat veterans are compared with non-combat veterans and when combat veterans are compared with non-veterans.

Hypothesis 1.3: Associations between combat stress and subclinical carotid atherosclerosis differ by era of service, with the strongest associations among men of the Vietnam Conflict and Korean War eras and the weakest among men of the World War II era.

Hypothesis 1.4: Associations between combat stress and subclinical carotid atherosclerosis differ by race, with stronger associations among black men than among white men.

Specific Aim 2: To investigate the association between exposure to combat stress and the incidence of CHD and IS.

Hypothesis 2.1: Combat veterans have higher incidence of CHD and IS than veterans without combat exposure or non-veterans.

Hypothesis 2.2: Associations between combat stress and CHD and IS differ by era of service, with the strongest associations among men of the Vietnam Conflict and Korean War eras and the weakest among men of the World War II era.

Hypothesis 2.3: Associations between combat stress and CHD and IS differ by race, with stronger associations among black men than among white men.

CHAPTER 3

BACKGROUND AND SIGNIFICANCE

Cardiovascular disease (CVD) is the global term used to describe the major disorders of the heart and arteries supplying the heart, brain and peripheral tissues with blood.[25] CVD comprises many diseases and conditions that vary widely in their symptoms and effect on circulatory functioning and overall health. It has been estimated that CVD is responsible for 23% of all deaths the world, and 48% of deaths in industrialized countries.[26] Further, CVD is responsible for considerable disability, lowered quality of life and social and economic costs even when non-fatal. The major category of CVD, based on its widespread impact on health, is the category of atherosclerotic and hypertensive diseases, a distinct but closely related conditions that include coronary heart disease (CHD), stroke, peripheral arterial disease (PAD), aortic aneurysm, congestive heart failure (CHF) among others.

Atherosclerosis

Atherosclerosis refers to the lesions or plaques on the inner surface (lumen) and within the wall of large to medium-diameter arteries (macrovasculature) as well as to areas of the arterial wall that have been hardened (sclerosed) by lipid and calcium deposits, weakening the wall and intruding into the lumen, causing a partial or complete obstruction of blood flow. Atherosclerosis can occur in large or medium size arteries throughout the body, and thus it may affect blood flow differently based on the location of the lesions, including

flow to the heart, brain, lower extremities or abdominal aorta. Accordingly, atherosclerosis may contribute to a wide range of cardiovascular diseases, including hypertension, ischemic heart disease, pulmonary heart disease, cerebrovascular disease and diseases of arteries, arterioles and capillaries.[27]

The importance of blood cholesterol in the development of atherosclerosis has been recognized since the early 20th century when it was documented that even small changes in the amount of dietary cholesterol given to rabbits produced detectable changes in the likelihood of developing atherosclerosis. Further animal studies identified processes at the cellular level in which the arterial wall was affected by cholesterol-dense migrating cells. Human studies in the 1930s reinforced the cholesterol-atherosclerosis connection by finding that populations that consumed higher cholesterol diets were also those with higher rates of atherosclerosis. The process by which blood lipid levels lead to atherosclerosis is a complex one, involving both cellular and extracellular components. At the beginning of this process, cholesterol is transported via lipoproteins through endothelial cells into the intima of the artery. To counteract this influx, HDL removes some of this cholesterol from the intima. At the same time, oxidation of LDL may occur, a molecular process that can damage endothelial cells and convert migrating macrophages into cholesterol-laden "foam" cells. These foam cells can act to further damage endothelial cell functioning, promoting the adhesion of blood platelets and leading to the formation of a clot or thrombosis, adding to the size of the growing atherosclerotic plaque or completely occluding the vessel leading to ischemia. It must be emphasized that blood lipid concentrations are not the only crucial factor in this process, such that other factors which can affect the probabilities of oxidation or other

molecular changes can play an important role in the lipid-atherosclerosis relationship and attendant processes. [28]

Another distinct though complementary mechanism that is thought to underlie the atherosclerotic process is the response-to-injury hypothesis. Through this process, atherogenesis can also be viewed as an inflammatory response, as the autonomic nervous system, which is engaged in a period of stress, interacts directly with the immune system. [29,30, 31,32,33] Prolonged elevation of cortisol levels, as can occur through the autonomic nervous system's response to periods of stress, can inhibit proper functioning of the immune system, increase blood pressure and promote inflammatory vascular lesions. Such lesions can advance into a state of endothelial dysfunction, which is considered the first step in atherosclerosis, as described above.[34] In response to a stressor or injury, levels of endogenous IL-6 and other pro-inflammatory cytokines are elevated.[35, 36,37,38] The response-to-injury hypothesis of atherosclerosis is founded on the finding that an injury or stressor alters the homeostasis of the endothelium, leading to an increased adhesiveness of the endothelium to leukocytes and platelets, increased coagulation, increased migration and proliferation of smooth muscle cells at the area of inflammation, and increased permeability of the dysfunctional endothelial wall.[39] These inflammatory mechanisms act in concert to thicken the arterial wall, leading to dilation and, eventually, remodeling of the artery and restriction of the arterial lumen.[40] Specifically, the increased adhesion of platelets and leukocytes to the dysfunctional endothelium and to monocyte-derived macrophages that are assembled in response to injury accumulate on the arterial wall and further expand the lesion.[41] Monocyte-derived macrophages and T lymphocytes are key inflammatory cells and are key participants in the inflammatory response. Activated platelets also release cytokines and growth factors

that further call upon the migration and proliferation of smooth muscle cells and monocyte-derived macrophages.[42,43] Smooth muscle cells, further activated in the presence of pro-inflammatory cytokines,[44] migrate and proliferate at the site of inflammation to create an intermediate lesion, while monocyte-derived macrophages and T-lympocytes from the blood multiply within the lesion. These inflammatory cells, in turn, are activated to release cytokines, chemokines, and growth factors, which cause further damage that can lead to necrosis. At this point, the lesion has become advanced and may begin to narrow the lumen. Injury also acts to increase the permeability of the dysfunctional endothelial wall to LDL cholesterol.[45,46] Macrophages recruited to the site of inflammation oxidize LDL cholesterol and internalize the oxidized cholesterol. This process leads to further stimulation of the replication and recruitment of monocytes which, in turn, create macrophages to continue the inflammatory process. The inflammatory response can continue indefinitely if the offending agents are not effectively deactivated.[47]

A third mechanism through which atherosclerosis can be initiated or promoted is through viral[48] and bacterial[49] infection. Though less well studied, this mechanism has been observed in both animals and humans, particularly with infections involving the herpes viruses as well as bacterial infections with *Chlamydia pneumoniae* and *Helicobacter pylori* and the development of CHD. Additional mechanisms, including hormonal changes and other processes, leading to or furthering the atherosclerotic process are being studied.

Subclinical atherosclerosis

Even before clinical manifestations of atherosclerosis are observed, subclinical atherosclerosis may be present. The Cardiovascular Health Study (CHS) investigated a

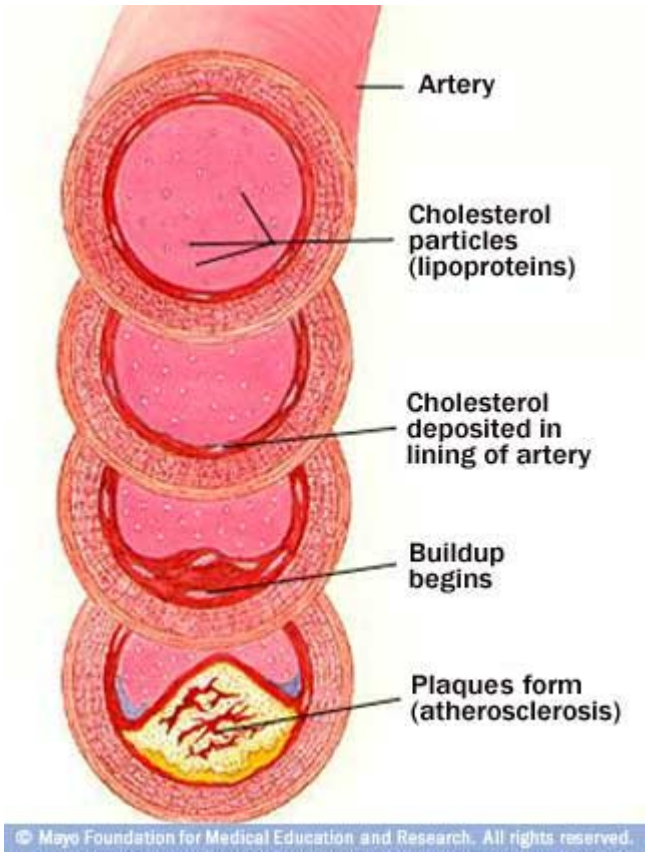
composite index of subclinical atherosclerosis in a population of adults aged 65 years and older, finding that while one quarter to one third of participants had clinical disease, more a third of participants had symptoms of atherosclerosis (via ultrasound, echocardiography (ECG) or self-reported impairment of coronary or lower extremity blood flow).[50] The prevalence of subclinical atherosclerosis in this study was approximately the same for men (39%) and women (36%), and the risk factors for subclinical disease were found to be similar to those for clinical disease—LDL and HDL cholesterol, SBP, blood glucose, smoking—though at younger ages. Individuals with subclinical disease are at very high risk for developing clinical atherosclerosis, particularly at older ages. Atherosclerotic changes, including cholesterol deposits known as fatty streaks, have been identified as early as childhood, suggesting atherosclerosis can have its origins early in life.[2]

Atherosclerotic Plaque

Plaque is a hallmark of either subclinical or clinical atherosclerosis. Atherosclerotic plaque refers to lesions on the lumen and within the wall of large to medium-diameter arteries where cholesterol deposits have become covered by a fibromuscular cap. Through the mechanisms outlined above, progression of atherosclerosis begins with the development of a fatty streak, becomes a transitional then advanced fibrolipid plaque and can become a complicated plaque. (Figure 1) Such advanced plaques can disrupt blood flow through the artery or, if ruptured, can cause occlusive thrombosis and, depending on the location of the plaque, lead to sudden cardiac death (SCD), myocardial infarction (MI), ischemic stroke (IS) or peripheral arterial disease (PAD). Advanced atherosclerotic plaques are known as atheromas, and due to chronic inflammation, may undergo changes that soften the material

within the fibrous cap, predisposing it to rupturing and potential formation of blood clots that can further enlarge the plaque and restrict or obstruct blood flow.

Figure 1. Atherosclerotic Progression.

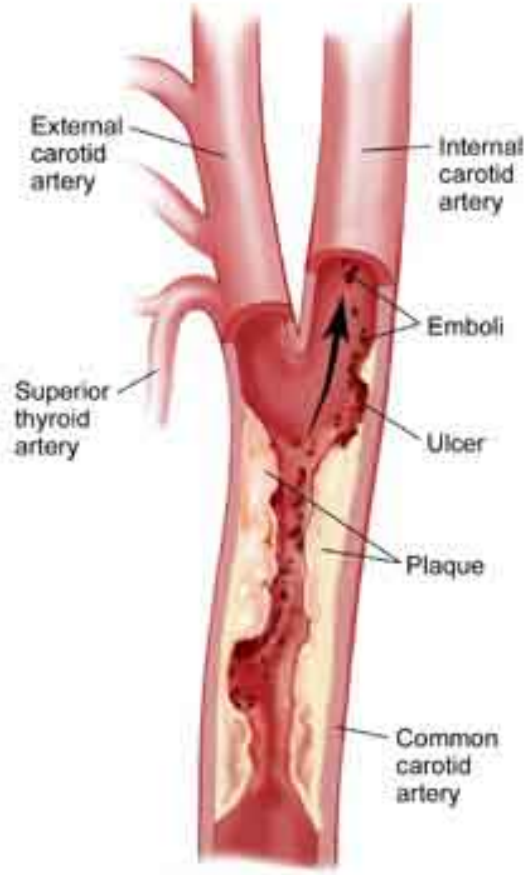


Source: Adapted from the Mayo Clinic, 2006. [51]

Although plaque can develop in large and medium sized arteries throughout the body, the carotid artery bifurcation, the location where the external and internal carotid arteries branch off from the common carotid artery, is the most common location of the development of atherosclerotic plaques in humans (Figure 2) The six carotid arteries (common carotid, internal carotid and external carotid on the left and right sides of the body) provide the main

blood supply to the brain and face. The common carotid artery is the blood vessel that supplies the head and neck with oxygenated blood, dividing in the neck to form the external carotid artery, which brings blood to the face and internal carotid artery, which brings blood to the brain. Blockage of blood flow to the carotid arteries can lead to a cerebral embolism or stroke. Specifically, carotid atherosclerosis is usually most severe within two centimeters of the bifurcation and most often involves the posterior wall of the artery.

Figure 2. Atherosclerotic Plaque and the Carotid Arteries.



Source: Adapted from Nott, 2007. [52]

Epidemiology of Atherosclerosis

Atherosclerosis has been recognized as a human disease since the 19th century. In the past 50 years, however, a great deal more about the pathology and epidemiology of atherosclerosis has been learned. Holman's autopsy studies in the 1950's of young persons (ages 1-40 years) discovered that fatty streaks appear commonly within the first ten years of life, and that these can progress into fibrous plaques and more advanced plaques with age. Holman also noted that progression of disease can occur at different rates in different population groups, and that progression occurs particularly quickly during puberty, suggesting hormonal involvement in the progression of the disease.[53] Further supporting the finding that considerable development of atherosclerosis occurs within the first twenty years of life, a series of autopsy studies of US military casualties reported visible lesions in the coronary arteries of 77% of the 300 Korean War casualties investigated[54] and the presence of coronary atherosclerosis in 45% of the 105 Vietnam Conflict casualties investigated by coronary angiography.[55]

The large-scale International Atherosclerosis Project (IAP), which investigated over 23,000 sets of coronary arteries in 14 countries in the 1960s, developed the standard of using the percentage of intimal arterial surface area that is covered by fibrous plaques and calcified lesions to measure the extent of atherosclerosis and discovered notable sex and race differences in the amount and location of atherosclerotic plaque development.[56] IAP investigators studied the arteries of decedents between the ages of 25 to 64 of different race groups and found that in a New Orleans population, white men had more than twice the surface area involvement (20%) of white women, while in a Durban, South Africa population the rates for black men and women were considerably lower (8%). Further, while the amount

of atherosclerosis in the aorta differed little between men and women, it was a considerably greater among men in the coronary arteries.

The notable progression of atherosclerosis by age was also highlighted in a World Health Organization (WHO) Study that looked at the presence and progression of atherosclerotic plaques in five European cities in the 1980s.[57] This WHO study noted an increase in the frequency of the population with atherosclerotic plaques by age, from less than 15% at age 20 to 100% for those ages 50 years and older. Another key study of changes in atherosclerosis with increasing age is the Bogalusa Heart Study.[58] Thirty years ago, investigators began following over 3,500 black and white, male and female school-age children to describe age trends and risk factors—including blood pressure, smoking, cholesterol, diet, anthropometric measurements—for the development and progression of atherosclerosis. Investigators noted the importance of controlling risk factors as early as childhood, as key risk factors such as blood lipids and blood pressure contribute prominently in the development of atherosclerosis early in life. These findings were supported in the Muscatine Study, a long-term prospective cohort study of Iowa children followed into their early 30s.[59]

The importance of blood lipid concentrations and smoking as risk factors for atherosclerosis were again highlighted in the US-based Pathobiological Determinants of Atherosclerosis (PDAY) Study, a post-mortem study of men ages 15 to 34 years. PDAY investigators reported considerably more atherosclerotic surface area involvement among smokers with unfavorable blood lipid profiles than among non-smokers with favorable blood lipids (30% *versus* 10% at age 15 and 50% *versus* 25% at age 34).[60] The PDAY study also

drew attention to sex differences in the location and extent of atherosclerosis, even as early as the teenage years, even after controlling for differences in smoking and blood lipid levels.

Marked differences in the rates of atherosclerosis among people from different industrialized countries have also been reported. Notably, a study comparing men ages 24 to 44 years from Tokyo, Japan with black and white men from New Orleans found little difference in the amount or location of fatty streaks but in the amount of surface area with raised lesions in the aorta and coronary arteries.[61] Further, this study brought to light the different importance of particular risk factors on the development of atherosclerosis in different anatomic locations. Specifically, while age, cholesterol and blood pressure were key risk factors for the degree of atherosclerosis in coronary arteries, blood pressure was most strongly related to the extent of disease in the cerebral arteries. Additional detail about the contribution of specific risk factors in the development of atherosclerosis, CHD and stroke are provided in section E below.

Coronary Heart Disease

A major disease of the heart, CHD is currently the leading cause of death in the United States[62] and accounts for 12.6% of deaths worldwide.[63] CHD, also known as ischemic heart disease, refers to atherosclerosis of the arteries supplying the myocardium or heart muscle. Because continuous supply of oxygen and nutrients is critical for the proper functioning of myocardial cells, insufficient blood supply to the myocardium (ischemia) can lead to injury and death in a matter of minutes.[64] The biological and clinical progression of CHD generally begins with a prolonged process of atherosclerosis, which leads to the development of advanced atherosclerotic plaques within the coronary arteries. Disruption or

enlargement of an advanced plaque can lead to acute symptoms (unstable angina), myocardial infarction (MI) or sudden death or to more chronic symptoms such as residual cardiac dysfunction or later onset of an event. Six major conditions are currently classified within CHD, according to the Tenth Version of the International Classification of Diseases (ICD-10), as shown in Figure 3 below.

Figure 3. Categories of Coronary Heart Disease.

ICD-10 Code	Diagnosis
I20	Angina pectoris
I21	Acute myocardial infarction
I22	Subsequent myocardial infarction
I23	Certain current complications following acute myocardial infarction
I24	Other acute ischemic heart disease
I25	Chronic ischemic heart disease

Source: Adapted from World Health Organization, 1992.[65]

The first of these conditions, angina pectoris, commonly known as angina, is defined as chest pain due to a transitory (15 seconds to 15 minutes) lack of blood flow (ischemia) of the myocardium due to obstruction or spasm of one or more of the coronary arteries and that fails to cause cellular death. Coronary artery disease (CAD), or atherosclerosis of the cardiac arteries, is the primary cause of angina.

Acute myocardial infarction (AMI or MI), commonly known as a heart attack, is the leading cause of death for both men and women throughout the world.[66] MI is caused by interruption of the blood supply to the myocardium resulting in necrosis of heart tissue. CAD is also the primary cause of MI, with the most common triggering event being the disruption of an atherosclerotic plaque in a coronary artery.

Sudden cardiac death (SCD) also falls under the general category of CHD and is defined by death resulting from sudden loss of heart function that occurs within one hour of the onset of acute symptoms. The majority of out-of-hospital cardiac-related deaths are due to SCD. The most common underlying cause of SCD is atherosclerosis; in 90% of adults with SCD, two ore more major coronary arteries are obstructed. The sudden cardiac arrest most commonly occurs when the electrical signals in the diseased myocardium become irregular (i.e., when there is an arrhythmia). This can occur when the impulses become too rapid, as occurs in ventricular tachycardia, too slow, in the case of bradycardia or irregular, as occurs in ventricular fibrillation. This arrhythmia can cause the heart to suddenly stop beating.[67]

Epidemiology of Coronary Heart Disease

Although CHD was recognized in clinical observation as early as ancient Greek and Egyptian times, it was not until the 19th century that progress was made toward a more advanced understanding of its pathology and epidemiology.[68] In the early 1900's the important link between acute occlusion of a coronary artery and the onset of MI was made,[69] as well as the recognition of CHD as a distinct, clinical entity and the development of key diagnostic procedures such as electrocardiography (ECG). Geographic variations in the prevalence of and mortality from CHD were noted early on with the Europe-based Seven Countries Study,[70] the Ni-Hon-San Study of Japanese men in Japan, Hawaii and San Francisco,[71] the Framingham Study of American men,[72] and other community-based studies. These studies were revolutionary in their design, providing for many years of follow-up, ancillary studies of both experimental and observational design, large-scale prevention

interventions and a wealth of information about the differences in risks among populations as well as the differences in risks within populations.

In the 1950s and 1960s, advancements were made in the standardization of definitions and classification systems; the interview methods for taking health histories (the London School of Hygiene or Rose questionnaire); and procedures for coding ECG findings (the Minnesota code), all of which were critical for comparison of data across studies.[73,74] As new diagnostic tools became available, such as troponin and other biomarkers for damaged cardiac cells, standardized definitions and classification systems have been updated accordingly. The algorithm for diagnosis and classification of acute CHD was initially developed by American Heart Association (AHA) investigators in the mid-1980s and, since its adoption by the WHO MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Project, the largest cardiovascular epidemiology study to date, this algorithm has become standard operating procedure in population studies. According to this diagnostic and classification system, fatal and nonfatal CHD events in population studies are classified according to the clinician's confidence in its occurrence (definite *versus* possible infarction), whether resuscitation from cardiac arrest was achieved, and, in the case of fatal events, whether sufficient information was available for classification as definite or possible infarction. Diagnosis of events is based on a composite picture including ECG findings, myocardial enzymes, history of chest pain and evidence of necropsy.[75]

Historically, population studies of CHD have measured its occurrence based on mortality (CHD deaths per 100,000 population per year), incidence (new fatal or non-fatal CHD cases per 1,000-100,000 population per year), case-fatality (the proportion of all CHD cases in the population that are fatal within 28 days of the onset of symptoms) and prevalence

(the proportion of the population living with identified CHD at any given time, reported as CHD cases per 1,000-100,000 population). Since the late-1950s, when standardized CHD mortality rates peaked in the US, rates have declined considerably.[76] Reasons for this decline are unclear, although it is thought that improvements in medical care, particularly in coronary intensive care units, as well as improved prevention efforts have reduced the incidence of CHD events.[77] Although mortality rates have declined over time for both men and women and for both black and white persons, race and sex-specific levels have consistently differed from one another over time. According to most recent estimates by the AHA, in 2004, CHD mortality rates per 100,000 population (using the year 2000 standard population for age adjustment) varied considerably, from 194.4 for white males, to 222.2 for black males, to 115.4 for white females and to 148.6 for black females.[78] International data on mortality from CHD comes primarily from the WHO MONICA Project, which found considerable variation in CHD mortality in the 21 countries studied, from nearly 500 CHD deaths per 100,000 men in Finland to 50 CHD deaths per 100,000 men in China and from 110 per 100,000 women in the United Kingdom to 11 per 100,000 women in Spain.[79]

Because of the many requirements needed for ascertainment of a CHD event, incidence, case-fatality and prevalence data are less available than mortality data. However, the WHO MONICA Project has been a fundamental source in providing this information internationally. According to data from this project, like CHD mortality rates, incidence rates vary widely among nations, from 915 per 100,000 men in East Finland to 76 per 100,000 men in China and from 256 per 100,000 women in the United Kingdom to 30 per 100,000 women in Spain. Incidence rates were consistently four to five times greater among men than women.

Differences in case definitions for case-fatality rates also complicate comparisons among studies and different populations. Regardless of the definition, case-fatality rates differed widely among nations studied, both for men—from 37% in Iceland to 81% in Poland—and women— from 31% in Canada to 69% in China—according to the definition that includes definite fatal events, possible fatal events, unclassifiable fatal events and definite nonfatal events. In the US, the Minnesota Heart Study has been a valuable source of information on CHD case-fatality rates and identified a 25% decrease in CHD mortality between 1985 and 1990 among both men and women and among both in-hospital and out-of-hospital cases, suggesting a combination of decreased incidence and decreased case-fatality rates.[80] Improvements in prevention and treatment have been credited for these reductions.

Persons included in the numerator of prevalence estimates include those who have survived past 28 days of the onset of a CHD event, those who have had a silent MI detected through screening, and those with a history of angina pectoris. In 1996, the prevalence of CHD in the US was estimated to be 5.23%, or about 13 million Americans.[81] Prevalence estimates are collected primarily through field surveys, and in developing countries with fewer resources estimates often do not follow standardized diagnostic criteria and methods.

In addition to studies designed to focus primarily on differences among cohorts of people, a number of large-scale community and employment studies have provided a wealth of information about factors that help explain differences in risk among persons within cohorts. In 1978 the AHA, in collaboration with the Heart Disease Control Program and the National Heart Institute, produced a Final Report of the pooled results of five such studies—the Albany civil Servants Study, the Chicago Gas Company Study, the Chicago Western Electric Company Study, the Framingham Study and the Tecumseh Study—and included a

total of 72,011 person-years and 658 incident CHD events before the age of 65 among a group of predominantly white men in the US.[82] This study determined that when persons are placed into quintiles of risk—defined by profiles of diastolic blood pressure (DBP), serum cholesterol concentration, smoking status and age—substantial CHD risk exists even well below the highest risk group. Another large-scale study of middle-aged American men, the Multiple Risk Factor Intervention Trial (MRFIT) prospectively followed 342,815 men free of disease at baseline and assessed the contribution of age, blood pressure, serum cholesterol concentration and cigarette smoking in the development of CHD. [83] This study found that persons in the highest risk levels for smoking, blood pressure and cholesterol were more than 20 times more likely to die of CHD than those in the lowest risk stratum for each of these risk factors. Additional detail about the contribution of specific risk factors in the development of atherosclerosis, CHD and stroke are provided in section E below.

Stroke

Cerebrovascular accident (CVA), commonly known as "brain attack" or stroke, is the third leading causes of death in the United States.[84] While CHD is the major class of atherosclerotic and hypertensive disease caused by a disorder in circulation to the heart, stroke is the major class of atherosclerotic and hypertensive disease caused by a disorder in circulation to the brain. Stroke generally begins with a sudden onset of symptoms, such as loss of consciousness or in function on one side of the body. Strokes are caused by a hemorrhage, or obstruction of a major artery by thrombosis (a clot near the brain) or embolism (a clot that formed elsewhere and traveled to the brain). While the onset of stroke symptoms is generally acute, the atherosclerotic or hypertensive condition preceding the

stroke is often a long-term process. Symptoms of stroke and its effects may disappear within minutes or houses or may persist ending in permanent disability or death.

Strokes are classified by whether symptoms resolved, the time in which symptoms resolved and whether the stroke was caused by a hemorrhage, thrombosis or embolism. Episodes that resolve within one hour are known as transient ischemic attacks (TIA). Previously, TIAs were defined as resolving within 24 hours, but this definition has recently been changed. TIAs that last more than one hour but less than 24 hours are known as reversible ischemic neurological deficit (RIND). Approximately 60% of persons who suffer a TIA or RIND have evidence of brain infarction. Strokes with symptoms that persist longer than 24 hours are referred to as completed strokes, and those that are followed by a death within 28 days are termed fatal strokes.

Strokes are commonly classified into ischemic or hemorrhagic strokes. Ischemic strokes account for 85% of all strokes and are caused by an interruption in cerebral circulation by occlusion of an artery near the brain. Ischemic strokes include TIAs, RINDs, thrombotic strokes (those in which an acute clot occludes an artery near the brain) and embolic strokes (those in which an acute clot that forms proximally separates from its source and travels to an artery near the brain). A ruptured plaque is the primary mechanism of most thrombotic and embolic strokes. Hemorrhagic strokes account for the remaining 15% of strokes and occur when a cerebral artery ruptures into the surrounding tissue. Brain cells can suffer direct trauma from the hemorrhage. Secondary damage also commonly occurs if the rupture leads to increased intracranial pressure, releases damaging mediators or causes decreased blood supply to the brain tissue downstream from the ruptured artery. Hemorrhagic strokes are further classified into intracerebral hemorrhagic strokes (ICH; when

blood ruptures directly into the brain parenchyma, most commonly from small intracerebral arterioles damaged by chronic hypertension)[85] and subarachnoid hemorrhagic strokes (SAH; when blood seeps into the subarachnoid space). SAHs are most commonly caused by aneurysms and can cause sudden and painful symptoms.[86] Proper classification of a stroke as a hemorrhagic or ischemic stroke is critical for treatment, as reperfusion therapy and fibrinolytic agents used to treat ischemic stroke can be fatal if given to a patient with a hemorrhagic stroke.

Epidemiology of Stroke

In the US, stroke morality and prevalence are approximately one quarter to one-third those of CHD. While stroke mortality rates vary widely among different populations, over the past few decades they have been decreasing in most of the countries in which trends have been described.[87] Between 1900 and 1960, stroke mortality in the US decreased continuously—from more than 125 to 75 or fewer deaths per 100,000 population[88]—and continued to decrease into the 1980s. However, this decline in mortality rates appears to be tapering off or ending.

Similar to CHD, case definitions for stroke for use in epidemiologic research were developed by the AHA in association with WHO and published through the WHO MONICA Project. According to this diagnostic system, stroke is defined as definite stroke, not stroke, definite stroke associated with definite MI or insufficient data to make a diagnosis. Classification is based on necropsy in fatal cases or computed tomography (CT) findings in nonfatal cases and include SAH, ICH, brain infarction due to occlusion of precerebral arteries, brain infraction due to cerebral thrombosis, or embolic brain infarction.[89] Ten major

conditions are currently classified within stroke, according to the Tenth Version of the International Classification of Diseases (ICD-10), as shown in Figure 4 below (Note that TIAs are not included in this list.) In order to ensure standardization, stroke type is based on CT findings in nonfatal cases and on postmortem examination in fatal cases.

Figure 4. Categories of Cerebrovascular Disease.

ICD-10 Code	Diagnosis
I60	Subarachnoid hemorrhage
I61	Intracerebral hemorrhage
I62	Other nontraumatic intracranial hemorrhage
I63	Cerebral infarction
I64	Stroke, not specified as hemorrhage or infarction
I65	Occlusion and stenosis of precerebal arteries, not resulting in cerebral infarction
I66	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction
I67	Other cerebrovascular diseases
I68	Cerebrovascular disorders in diseases classified elsewhere
I69	Sequelae of cerebrovascular disease

Source: Adapted from World Health Organization, 1992.[90]

It was not until the middle of the 20th century that stroke mortality rates were compared in different geographic locations.[91] Methodological challenges for epidemiologic study of stroke included difficulty in systematically distinguishing between different stroke types in death certificates and low event rates in young populations.[92] Despite these challenges, comparisons were made among a number of countries through death certificate studies, with mortality rates ranging from more than 150 to less than 40 cases per 100,000 population per year, and with the highest rates in Finland and Japan. Of special note was a study of men of Japanese descent by Gordon, in which he reported decreasing stroke mortality rates of men from Japan to Hawaii to California, a trend in distinct opposition to

the trend for CHD mortality rates.[93] Also of note was a study by Stallones that found no relation between the distributions of mortality from stroke and ischemic heart disease in US states, suggesting different mechanisms and disease processes. This study noted that Southeastern states had the highest stroke mortality rates, causing this region to be known as the "stroke belt." Although the prevalence of stroke has been declining in most developed nations, declines have been least marked in Russia and eastern European countries, where there is a higher prevalence of hypertension.[94]

Incidence rates for stroke, defined as the number of new or recurrent definite strokes per 100,000 population, also vary widely among nations, from 121 in Italy to 359 in Finland for men and from 58 in Germany to 294 in Russia for women.[95] Between 75% and 90% of these strokes were initial events. Case-fatality, defined as death within 28 days after the onset of symptoms, ranged from 15% to 49% for men and from 18% to 57% among women, with the highest case-fatality rates among both men and women in Poland.

Increased age is a strong risk factor for stroke, with two-thirds of strokes occurring in persons ages 75 years and older and with the incidence of stroke more than doubling with each progressive decade after the age of 55. Racial differences in stroke mortality rates have been noted in the US, with blacks at increased risk over whites. When gender is factored in, men are at increased risk of stroke among whites, while women are at increased risk of stroke among blacks, although gender differences have been decreasing since the 1950s. Age, race and gender differences are notable in comparison of stroke mortality rates (per 100,000 population) in the US. For example, in 1989 rates for black males, black females, white males and white females were 720, 706, 558 and 483, respectively, for persons ages 75-84 years and 1343, 1428, 1578 and 1706, respectively, for persons ages 85 years and older.[96]

Although many modifiable factors increase the risk of stroke, the strongest modifiable risk factor identified for stroke is high blood pressure. Hypertension can cause a thickening of the walls of cerebral arteries, causing decreased blood flow and predisposition to thrombosis. The major risk caused by chronic hypertension, however, is a hemorrhagic stroke. Another, major modifiable risk factor for stroke is smoking, which elevates blood pressure, accelerates the atherosclerotic process, releases toxic enzymes linked to the formation of aneurysms and affects platelet function.[97] Previous cardiovascular events and comorbidities such as previous TIA, prevalent CHD (particularly atrial fibrillation in the case of embolic stroke) and prevalent diabetes mellitus (which accelerates the atherosclerotic process) are also highly associated with future strokes. Other risk factors for stroke include alcohol and drug use, obesity, physical activity, poor diet, oral contraceptive use, inflammatory factors, subclinical disease, TIAs and other prevalent cardiovascular conditions.

Individual risk factors for stroke have been most widely studied in the Prospective Studies Collaboration, which reviewed 45 cohort studies of stroke, including a total of nearly 450,000 participants and over 13,000 stroke events, mainly deaths.[98] This study confirmed the importance of blood pressure in the risk of stroke, particularly among younger persons. The largest single cohort study of stroke mortality was of decedents of over 350,000 US men screened for the Multiple Risk Factor Intervention Trial (MRFIT) study.[99] This study reported higher mortality rates for different stroke subtypes among persons with higher values of systolic and diastolic blood pressure and among smokers. Serum cholesterol levels were modestly associated with an increased risk of death from nonhemorrhagic, SAH and ICH stroke subtypes, suggesting differences in the contribution of cholesterol as a risk factor

for different stroke subtypes. The Framingham Study was key in discovering the importance of hypertension, CHD and atrial fibrillation as risk factors for stroke.

Combat Exposure and Cardiovascular Disease

Advances in the prevention and treatment of CHD have resulted in a considerable decline in CHD mortality over the past four decades.[100,101] Despite continued reductions in traditional cardiovascular risk factors such as smoking, hypertension, and hypercholesterolemia in recent years,[102,103] the decline in CHD has begun to subside, and the incidence of myocardial infarction is on the rise.[104] Traditional risk factors—including high levels of total cholesterol and low-density lipoprotein (LDL), low levels of high-density lipoprotein (HDL) cholesterol, hypertension, smoking, diabetes, and a family history of coronary artery disease (CAD)—are estimated to predict only 58 to 75 percent of new cases of CAD.[105] Given the large amount still unknown about the causes of CVD, researchers have been exploring the contribution of nontraditional risk factors. Of these, psychosocial stress has emerged as a particularly promising potential risk factor.[106,107,108,109] Thus far, the literature has focused primarily on distinct areas of chronic life stress including generalized self-perceived stress, job stress, socioeconomic stress, marital strain and stress that results from exposure to traumatic events such as natural disasters. Epidemiological studies have demonstrated an association between these types of psychosocial stress and increased morbidity and mortality from CVD. However, less is known about the long-term effects of combat-related stress on cardiovascular health.[110,111]

The specific psychosocial stress experienced by veterans who have engaged in active combat is a unique stressor that includes psychological, moral, and physical components.[112]

The effects of military service in general and military combat in particular are so pervasive yet so little studied that they have been termed the "hidden variable" in the aging of older American men.[113,114] Among older American men, the prevalence of exposure to military service and military combat is high; according to the 2000 U.S. Census, over 26 million or 12.7% of the adult U.S. population served in the military at some time in their lives. Over 90% are men and 37% are over the age of 65 years.[115] According to results of the third Survey of Veterans, approximately 65% of men over the age of 55 served in World War II or the Korean War. Further, 52% of those who served in World War II and 35.3% of those who served during the Korean conflict were exposed to combat.[116] Accordingly, it is estimated that a quarter of all older American men were exposed to military combat.[117] Between 1990 and 2000, the number of veterans ages 65 years and older increased from six to nine million.[118]

Exposure to military service can have positive as well as negative consequences[119,120] and can both short-term and long-term effects[121] that act both directly and indirectly on servicemen's' lives.[122] Combat is typically the most traumatic or stressful aspect of military service.[123] Studies report higher rates of adverse behavioral risk profiles,[124,125] psychological conditions[126,127,128,129] and self-reported health conditions[130,131,132] among those exposed to military combat. Exposure to psychological stress has been linked with short-term increases in rates of coronary events.[133,134] Similarly, long term residence in a war zone has been linked to higher frequency of occurrence of CVD.[135] However, studies of the longer-term cardiovascular consequences of combat stress are limited, and to date have been inconclusive.[136,137]

Variation in the effect of war-related stress on cardiovascular mortality has been noted by the war theater in which veterans served.[138,139] For example, while a number of recent studies found that combat veterans who served during the eras of World War II and the Korean War have higher self-reported chronic health problems, more diagnosed illnesses, and are more likely to engage in adverse health behaviors such as smoking and drinking and have poorer self-rated health,[140,141,142,143] a study of Vietnam veterans that compared self-reported health with physical examinations did not find excess burden of physical illness among those exposed to combat.[144,145] The few studies that have assessed whether the association between cardiovascular mortality and war-related trauma varies by age or time since exposure have been inconsistent and based on limited samples.[146,147,148,149]

Epidemiologic Evidence

Most studies of the deleterious health effects of combat-related stress focus on short-term psychological, behavioral, and self-reported health symptoms. By contrast, relatively little attention has been given to the directly measured, long-term cardiovascular effects of military stress. Of the studies that have been conducted, many have investigated the effects of military combat—most commonly depression or PTSD—rather than exposure to combat itself. (Table 1) To date, the long-term physiological effects of military combat have been most thoroughly investigated in the Vietnam Experience Study (VES), a retrospective study of a random sample of all male US Army veterans who served during the Vietnam conflict. In VES studies of Vietnam theater veterans with PTSD and without, Boscarino and colleagues reported that theater veterans with PTSD were more likely to have clinically elevated leukocyte and total T-cell counts,[150] a higher prevalence of arrhythmias,[151] and a

higher lifetime prevalence of circulatory diseases[152] than those without PTSD twenty years after the conclusion of the conflict. PTSD-positive theater veterans seem to have a higher lifetime prevalence of CVD and a higher all-cause mortality rate as many as 30 years after military service.

The majority of studies that have investigated the effects of military combat itself, rather than PTSD, have been conducted in retrospective cohorts and have compared veterans who served in the primary theater of combat to veterans who served during the same era but outside the region of the major conflict. Therefore, the specific combat exposure of serving in a combat zone has been the primary focus of the current literature, although other combat exposures—such as seeing someone killed, killing another individual, and other traumas—could occur in either theater or era veterans. Overall and cause-specific mortality are the primary outcome measures in these studies, with results, on the whole, finding little difference between all-cause or cardiovascular mortality between theater veterans and era veterans. The most prominent of these studies are those conducted by VES investigators, who noted that Vietnam veterans had 45% higher all-cause mortality than veterans of World War II and the Korean conflict within five years after conclusion of service, although the largest increase in relative mortality was due to motor vehicle accidents and other external causes (suicide, homicide, poisonings).[153] Thereafter, mortality between Vietnam veterans and other veterans were similar, with the exception of drug-related deaths. Although authors reported a lower circulatory disease mortality rate among Vietnam theater veterans (standardized mortality ratio (SMR) = 0.48; 95% CI = 0.25, 0.85) compared to Vietnam era veterans (SMR = 0.87; 95% CI = 0.54, 1.34)), this finding was reversed in a later study.[154] In this follow-up study, conducted a 30-years after exposure, researchers still found no

difference in all-cause mortality between veterans of the Vietnam conflict and veterans of World War II and the Korean conflict, although increased mortality from drug-related deaths persisted.[155] Also, a small but not statistically significant increase in mortality fifteen years after discharge from circulatory diseases was noted among a subgroup of Vietnam veterans who discharged from active duty in 1970 or later. Although neither a non-combat nor a non-military comparison group was included in these analyses, the mortality rates were compared to those reported elsewhere for the US population.

Similarly, in a large-sample retrospective cohort study of US Marine veterans, Wantanabe and colleagues found that those who served in Vietnam had higher overall mortality, after 22 years of follow-up, compared to veterans who did not serve in Vietnam, even after adjustment for age and military rank.[156] Similar to VES findings, the elevated overall mortality was primarily due to excess deaths from external causes and was higher in the first five years of follow-up (rate ratio (RR)=1.26) than at the completion of the study (RR=1.14). Increased risk of death from cancer was elevated although not statistically significant. Mortality specifically from CVD was not assessed. Fett and colleagues reported comparable results, noting a significant increase in the rate of all-cause mortality among Australian veterans who served in Vietnam compared to those who served during the same period but in Australia (rate ratio (RR) = 1.0; 95% CI = 1.0, 1.4)[157] and an elevated but not significant difference in the rate of mortality from circulatory disease.[158] In a study of the effects of Vietnam theater exposure among women, Thomas and colleagues reported results similar to those of initial VES studies,[159] noting no significant differences found in all-cause or cancer-related mortality but moderately reduced circulatory disease mortality among theater era veterans. (mortality rate ratio (MRR) = 0.67; 95% CI = 0.38, 1.18). However,

because women are excluded from combat-related jobs and training, findings from this study are less informative for the research question at hand.

A similar pattern of results was obtained in a series of retrospective cohort studies of U.S. veterans of the Persian Gulf War. In 1996, Kang and colleagues reported that during the first 2.4 years after conclusion of the war, Gulf War theater veterans had mortality rates that were slightly but significantly elevated compared to era veterans in the National Guard and military reserves, after adjustment for age, sex, race and military variables.[160] Excess deaths were primarily due to those caused by external causes rather than disease. Theater veterans and controls did not have significantly elevated rates of circulatory disease. Further, compared to the U.S. population, both Gulf War theater and era veterans had significantly lower cause-specific standardized mortality ratios, after adjustment for age, sex, race and year of death, in line with the theory of the healthy veteran effect. In a 2001 follow-up study, the authors investigated differences in mortality after 7 years time.[161] As found in VES reports,[162] excess deaths among war theater veterans due to accidents and other external causes dissipated over time and no significant difference was found in mortality rates from cardiovascular disease. Significantly lower mortality from infectious diseases persisted among Gulf War theater veterans, primarily due to significant excess deaths among Gulf War era veterans from human immunodeficiency virus. Although these studies were retrospective and had only 2.4 and 7 years of follow-up time, these limitations were minimized by the very large sample of veterans included. However, neither study included measures of socioeconomic status. A study of post-war mortality of British Gulf War veterans reported similar results, finding no difference in all-cause mortality between Gulf War theater and era veterans.[163] Higher mortality from external causes and lower mortality from diseases of the

circulatory system were noted, although neither finding was statistically significant. However, this study was limited by the relatively young age of the cohort and the relatively small number of deaths.

VES investigators also studied the effects of varying levels of combat exposure on cardiovascular risk factors, finding that cortisol levels were inversely associated with combat exposure level among Vietnam theater veterans, with veterans exposed to heavy combat having the lowest plasma cortisol concentrations.[164] VES investigators also found a slight increased odds of left ventricular hypertrophy among Vietnam era veterans (OR=1.8; 95% CI = 1.0, 3.3) but few overall differences in the prevalence of any abnormal electrocardiograph findings of VES veterans. In terms of behavioral risk factors, Boscarino and colleagues found that while both Vietnam theater and era veterans had a higher adjusted prevalence of drug abuse[165] but not alcohol consumption[166,167,168] than non-veterans, combat exposure among veterans was not significantly associated with increased alcohol or drug abuse.[169] Although these studies did adjust for major demographic and risk factor covariates as well as education, participants were only from the Army branch of the US military and veterans from wars other than the Vietnam conflict were not studied.

Studies of combat exposures other than service in a combat zone are more limited. However, there is reason to believe that these additional exposures—such as whether or not they were ever under fire or fired at the enemy, saw others wounded or killed, or were ever wounded or missing in action—would have an effect beyond that of service in a combat zone. In a study of the prevalence of specific psychiatric disorders among Vietnam veterans and controls, Jordan and colleagues noted that although there were few differences between Vietnam theater and era veterans in the lifetime and current prevalence of depression and

other psychiatric diagnoses, there were striking differences in the rates for male theater veterans with high levels of war zone stress compared to other male veterans or civilians.[170]

Although the majority of studies to date have focused on mortality as the outcome, Gill and Bell studied the effects of being a prisoner of war (POW) during World War II on the prevalence of CHD forty years after the conclusion of military service. In this study, Gill and Bell compared the prevalence of self-reported CHD among ex-POWs to the prevalence among veterans who served during the same time but who were not captured.[171] The POWs had a slightly elevated prevalence of angina and history of MI compared to controls (21.7% *versus* 18.1%, respectively), although not statistically significant. Elder and colleagues studied the effects of military combat on both physical decline and mortality in male veterans of the Korean War and World War II in the Berkeley Growth Study, the Berkeley Guidance Study, and the Oakland Growth Study[172,173,174,] as well as in the Stanford-Terman Study.[175, 176,177] Findings from these studies include that the effect of exposure to combat significantly increased the odds of physical decline or all-cause mortality fifteen years after conclusion of World War II, even after adjustment for age, physical health at the conclusion of the war, military rank, branch and division of service, theater of engagement, and geographic region of combat exposure.

In the context of the current literature, the proposed study is unique in that it has a long average follow-up time, an older cohort (ages at the LC-SES interview range from 60 to 80 years), includes veterans who served during the eras of multiple conflicts (World War II, the Koran War and the Vietnam Conflict), and includes measures of specific combat exposures and both military and civilian controls. The contribution of a wide range of measures of behavioral risk factors, psychological measures and pre-conflict SES also sets

apart the proposed study from the extant literature. Further, the proposed study will assess not only mortality, but also incident cardiovascular event rates and the burden of subclinical atherosclerosis.

Table 1. Published Effects of Military Combat Exposure on Long-Term Physical Health and Mortality.

Author, Year	Comparison Groups	N	Follow-up time	Outcome(s)	Adjusted Effect Estimate (95% CI)	Covariates
Veterans with PTSD vs. Veterans without PTSD						
Boscarino, 1996[178]	Vietnam theater veterans with 4 levels of combat exposure (none-very heavy)	1971 (579 None/low; 542 Moderate; 711 Heavy; 650 Very heavy)	20 years	Plasma cortisol	*Adjusted Odds Ratio* Moderate *vs.* none/low: OR = 5.32 (2.0, 13.9) Heavy *vs.* none/low: OR = 10.00 (3.9, 25.1) Very heavy *vs.* none/low: OR = 24.75 (9.6, 62.4)	Age, income, education, race, pre-service, military adjustment, post-service adjustment
Boscarino, 1997[179]	Vietnam theater veterans with lifetime PTSD vs. no lifetime PTSD	1,399 (332 PTSD; 1,067 No PTSD)	20 years	Circulatory disorders Endocrine-nutritional –metabolic disorders Any chronic disease	*Adjusted Odds Ratio* OR = 1.64 (1.17, 2.30) OR = 1.75 (1.03, 2.97) OR = 1.72 (1.30, 2.27)	Intelligence, race, region of birth, enlistment status, volunteer status, Army marital status, Army medical profile, hypochondriasis, age, smoking history, substance abuse, education, income
Boscarino, 1999a[180]	Vietnam theater veterans with current PTSD vs. no current PTSD	2,490 (293 PTSD; 2,197 No PTSD)	20 years	Leukocyte T-cell lymphocyte CD8	*Adjusted Odds Ratio* OR = 1.83 (1.03, 3.25) OR = 1.82 (1.01, 3.26) OR = 1.80 (0.97, 3.35)	Intelligence, race, age, income, education, type of enlistment, Vietnam volunteer status, region of birth, cigarette smoking, illicit drug use, body mass index, and alcohol consumption

Author, Year	Comparison Groups	N	Follow-up time	Outcome(s)	Adjusted Effect Estimate (95% CI)	Covariates
Boscarino, 1999b[181]	Vietnam theater veterans with current PTSD vs. no current PTSD	4,462 (54 PTSD; 4408 No PTSD)	20 years	 Atrioventricular (AV) conduction defects AV infarctions	*Adjusted Odds Ratio* OR = 2.81 (1.03-7.66) OR = 4.44 (1.20-16.43)	Age, place of service, illicit drug use, medication use, race, body mass index, alcohol use, cigarette smoking, and education
Boscarino, 2006[182]	Vietnam *theater* veterans with current PTSD vs. no current PTSD	7,924 (214 PTSD; 7,710 No PTSD)	30 years	 All-cause mortality Cardiovascular mortality	*Adjusted Hazard Ratio* HR = 2.2 (1.7-2.7) HR = 1.7 (1.0-2.7)	Age, race, Army volunteer status, Army entry age, Army discharge status, Army illicit drug abuse, and intelligence
	Vietnam *era* veterans with current PTSD vs. no current PTSD	7,364 (836 PTSD; 6,528 No PTSD)		All-cause mortality Cardiovascular mortality	HR = 2.0 (1.3-3.0) HR = 1.2 (0.4-3.4)	
Theater vs. Non-theater veterans						
Boehmer, 2004[183]	Vietnam theater veterans vs. Vietnam era veterans	18,313 (9,324 theater veterans; 8,989 era veterans)	30 years	 All-cause All-cause Circulatory disease	*Adjusted Mortality Rate Ratio* MRR = 1.08 (0.97, 1.20) *Crude Mortality Rate Ratio* MRR = 1.07 (0.97, 1.18) MRR = 1.01 (0.82, 1.49)	Age, race, year of enlistment, enlistment status (volunteer *vs.* draftee), score on general technical test, primary military occupational specialty

Author, Year	Comparison Groups	N	Follow-up time	Outcome(s)	Adjusted Effect Estimate (95% CI)	Covariates
Boscarino, 1995[184]	Vietnam theater veterans with combat exposure vs. no combat exposure	4,462 (2,490 theater veterans; 1,972 era veterans)	20 years	 PTSD Generalized anxiety Depression Alcohol Dependency Drug Dependency	*Adjusted Odds Ratio* OR = 2.42 ($p < 0.001$) OR = 1.33 ($p < 0.001$) OR = 1.53 ($p < 0.001$) OR = 1.04 ($p > 0.05$) OR = 0.97 ($p > 0.05$)	Geographic region, army entry age, army enlistment status, Vietnam volunteer status
CDC, 1987[185]	Vietnam theater veterans vs. Vietnam era veterans	18,313 (9,324 theater veterans; 8,989 era veterans)	5 years 13.5 years	All-cause All-cause	*Adjusted Mortality Rate Ratio* MRR = 1.58 (1.16, 2.14) MRR = 1.04 (0.81, 1.33)	Age, race, Army General Technical score, pay grade at discharge, year of discharge
CDC, 1988b[186]	Vietnam theater veterans vs. Vietnam era veterans	4,462 (2,490 theater veterans; 1,972 era veterans)	13.5 years	 Hypertension Altered peripheral arterial hemodynamic finding Any abnormal electrocardiographic finding Any chest roentgenogram finding	*Adjusted Odds Ratio* OR = 0.8 (0.4, 1.7) OR = 1.2 (0.9, 1.7) OR = 1.1 (0.9, 1.3) OR = 1.1 (1.0, 1.4)	Age, race, year of enlistment, enlistment status (volunteer *vs.* draftee), score on general technical test, primary military occupational specialty
Fett, 1987a[187]	Australian Vietnam theater *vs.* era veterans	44,882 (19,205 theater veterans; 25,677 era veterans)	9-16 years	 All-cause mortality	*Adjusted Mortality Rate Ratio* MRR = 1.2 (1.0, 1.4)	Branch of the military

Author, Year	Comparison Groups	N	Follow-up time	Outcome(s)	Adjusted Effect Estimate (95% CI)	Covariates
Fett, 1987b[188]	Australian Vietnam theater *vs.* era veterans	44,882 (19,205 theater veterans; 25,677 era veterans)	9-16 years	 All circulatory disease All external causes	*Adjusted Mortality Rate Ratio* MRR = 1.6 (0.8, 3.2) MRR = 1.1 (0.9, 1.4)	Branch of the military
Jordan, 1991[189]	Male Vietnam theater veterans *vs*. era veterans *vs*. civilians	2,070 (1,200 theater veterans; 419 era veterans; 451 civilians)	11-24 years		*Summary measures not provided; Prevalence Rates contrasted*	Age, race/ethnicity
	Vietnam theater veterans with high *vs.* low levels of combat	887 (406 high-level combat veterans; 783 low to moderate-level combat veterans)				
Kang, 1996[190]	Gulf War theater veterans vs. Gulf War era veterans	1,441,807 (695,516 theater veterans; 746,291 era veterans)	2.4 years	 All cause Circulatory diseases	*Adjusted Mortality Rate Ratio* RR = 1.09 (1.01, 1.16) RR = 1.12 (0.90, 1.40)	Age, sex, race, branch of service, type of unit (Active; Reserve; National Guard)

Author, Year	Comparison Groups	N	Follow-up time	Outcome(s)	Adjusted Effect Estimate (95% CI)	Covariates
Kang, 2001[191]	Gulf War theater veterans vs. Gulf War era veterans	1,441,807 (695,516 theater veterans; 746,291 era veterans)	7 years	 All cause Circulatory diseases	*Adjusted Mortality Rate Ratio* MRR = 0.95 (0.92, 0.99) MRR = 0.90 (0.81, 1.01)	Age, sex, race, branch of service, type of unit (Active; Reserve; National Guard); marital status
Macfarlane, 2000[192]	UK Gulf War theater veterans vs. UK Gulf War era veterans	53,462 Gulf War theater veterans and 53,450 Gulf War era veterans	8 years	 All cause All disease-related All cancer All circulatory disease All external causes	*Adjusted Mortality Rate Ratio* MRR = 1.05 (0.91, 1.21) MRR = 0.87 (0.67, 1.11) MRR = 1.11 (0.73, 1.67) MRR = 0.74 (0.49, 1.12) MRR = 1.18 (0.98, 1.42)	Matched on age, sex, branch of military, rank (commissioned officer/other rank)
Thomas, 1991[193]	Female Vietnam theater veterans vs. Female Vietnam era veterans	4,644 Vietnam theater veterans and 6,575 Vietnam era veterans	16.5 years	 All cause Circulatory disease	*Adjusted Relative Risk* RR = 0.93 (0.74, 1.16) RR = 0.67 (0.38, 1.18)	Military rank, military occupation, duration of military service, age, race

Author, Year	Comparison Groups	N	Follow-up time	Outcome(s)	Adjusted Effect Estimate (95% CI)	Covariates
Visintainer, 1995[194]	Deceased male Vietnam veterans vs. deceased male non-Vietnam veterans	8,593 (5,229 theater veterans; 3,364 era veterans)	3-24 years	Endocrine, nutritional, metabolic, and immune diseases	*Proportionate Mortality Ratio* PMR = 1.56 (1.11, 2.13)	None
				Circulatory system	PMR = 1.00 (0.93, 1.07)	
Wantanabe, 1995[195]	Vietnam theater veterans vs. Vietnam era veterans	20,062 (10,716 theater veterans; 9,346 era veterans)	22 years	All-cause	*Adjusted Mortality Rate Ratio* RR = 1.15 (1.02, 1.29)	Age, rank in military
POW veterans vs. Non-POW veterans						
Gill, 1997[196]	World War II prisoners of war (POWs) *vs.* non-POWs	1,140 (635 POWs; 505 non-POWs)	39 years	Prevalent CHD	*Unadjusted OR* OR = 1.25 (p = 0.221)	None

Pathways and Mechanisms

The mechanisms through which psychosocial stress acts to affect physical health are still not well understood. Stress has been shown to have direct effects on cardiovascular risk, through neuroendocrine and immune functioning,[197, 198] as well as indirect effects, through unhealthy behaviors (e.g., smoking, alcohol and drug abuse).[199, 200,201] In addition, individual coping mechanisms may alter the way one individual responds to a psychosocial stressor, compared to another.[202, 203] Factors affecting the way an individual responds to stress may include psychological health factors (e.g., depression, hostility) as well as individual socioeconomic factors (e.g., income, education, employment) and community socioeconomic factors (e.g., mean neighborhood wealth, education, employment). Also, the timing of different stress exposure in an individual's life are thought to play a role in how an individual perceives and responds to that stressor.[204]

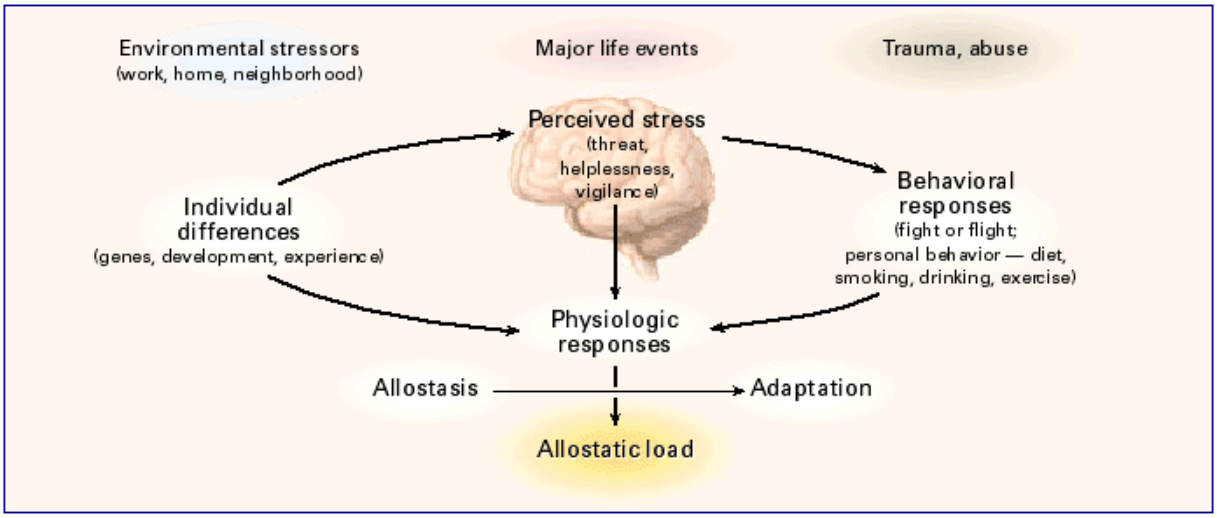
The process by which stress acts as an independent risk factor for atherogenesis involves behavioral, neurological, endocrine, and immunological components.[205206] Hypersecretion of cortisol in response to stress has been shown to play a role in the development of CHD.[207] Proinflammatory cytokines have been shown to be associated with both stress and the development of CHD,[208,209] and thus represent intermediate mechanisms through which stress can influence CVD. Because stimuli or events experienced as stressful trigger physiologic responses (cortisol, insulin, and catecholamine levels and their systemic effects), repeated or prolonged exposure to stress is thought to lead to elevations in cardiovascular risk factors and ultimately increased risk of CVD.[210, 211,212] Chronic stress is also associated with higher rates of behavioral risk factors such as smoking, higher fat and caloric intake, obesity, sedentary behavior, sleep disorders, and drug and alcohol use.[213,

[214,215] In turn, many of these behaviors have been associated with higher rates of hypertension, atherosclerosis, hypercholesterolemia, and diabetes.[216, 217] Importantly, individual personality traits and coping mechanisms can act as a "filters" for psychological exposures and partly determine the degree to which an exposure is experienced as a stressor.[218,219] Higher levels of risk factors and clustering of risk factors has been reported in numerous studies of the association between stress and cardiovascular risk factors assessed by a variety of measures.[220] This clustering of risk factors, through physiological, psychological and behavioral mechanisms, may work in concert to lead to elevated CVD risk. In addition to these factors, individual characteristics may alter how an individual recovers from a stressor, and may help explain why one individual returns to homeostasis and while another remains in a state of disequilibrium and carries an additional allostatic load.

One of the predominant conceptual frameworks used to describe the process through which stress affects physiological heath is the theory of allosatic load, which holds that stress causes a disruption in homeostasis and allostasis. Homeostatic theory was originally developed by 19th Century French physiologist and "father" of modern experimental physiology Claude Bernard in an effort to describe the fundamental principles of physiology. This theory was later promulgated and expanded into areas of social epidemiology by noted researchers including epidemiologist John Cassel, physiologist Walter B. Cannon (who coined the term "homeostasis"), and endocrinologist Hans Selye.[221, 222,223] According to homeostatic theory, when an individual is exposed to an environmental change, the body responds to the stressor and resists in an attempt to restore itself to its original state.[224] If the stress persists, it is thought that the body becomes exhausted and results in disordered

functioning of the homeostatic process.[225] An extension of this hypothesis, the allostatic load theory holds that chronic, repeated, or traumatic (i.e., perceived as potentially life-threatening) stress can disrupt the body's ability to maintain physiologic stability in a manner that promotes disease.[226] In this way, the nature of the stressor—its duration, severity, and persistence—affect how the stressor is perceived.[227] As shown in Figure 5, individual differences in genetics, development, and experiences throughout the life course further affect whether or not an event is perceived as stressful. The perceived stressor may then have a direct physiological response or act indirectly through changes in behavior such as smoking, alcohol drinking, diet, and physical activity. The sum of an individual's physiologic responses add to an individual's allostatic load, and, if too overwhelming, can lead to neuroendocrine and immune changes that adversely effect various organ systems and promote disease.[228]

Figure 5. The Stress Response and Development of Allostatic Load.



Source: Adapted from McEwen, 1998.[229]

Direct Physiolologic Mechanisms

There are a number of pathways through which a stressor directly affects physical functioning and cardiovascular health. One of the ways in which allostatic load is thought to be influenced is by a disturbance in the functioning of the neuroendocrine system, which regulates the functioning of the cardiovascular system.[230] According to both physiological and epidemiological evidence, the autonomic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis are critically involved in the mechanism through which chronic psychosocial stress affects cardiovascular functioning. Secretion of cortisol is one of the primary metabolic responses of the autonomic nervous system to the exposure to psychosocial stress.[231] A large part of the effect of chronic stress on the regulation of cortisol is mediated by an increase in the level of catecholamines and epinephrine (adrenaline) circulating in the plasma.[232, 233] When adrenaline and catecholamines are released, beta-adrenergic receptors stimulate the secretion of interleukin 6 (IL-6) and other inflammatory molecules.[234,235] This, in turn, leads to stimulation of the HPA axis, which transports cortisol from the adrenal glands back to the hypothalamus and other parts of the brain.[236,237,238] Exposure to chronic stress, during which there is a period of hypersecretion of cortisol, can cause a disruption in the HPA axis and lead to resistance and impaired feedback control.[239,240,241,242,243,244]

The process of atherogenesis can also be viewed as an inflammatory response, and the autonomic nervous system, which is engaged in a period of stress, interacts directly with the immune system.[245, 246,247,248] Prolonged elevation of cortisol levels, as can occur through the autonomic nervous system's response to periods of stress, can inhibit proper functioning of the immune system, increase blood pressure and promote inflammatory vascular lesions.

Such lesions can advance into a state of endothelial dysfunction, which is considered the first step in atherosclerosis.[249] The role of stress in this process has been recognized through the finding that levels of endogenous IL-6 and other pro-inflammatory cytokines are elevated during periods of acute and chronic stress, independent of the presence of smoking, hypercholesterolemia, and other established cardiovascular risk factors.[250, 251,252,253] The role of stress in the inflammatory process of atherogenesis is based on the definition of stress as "a state of threatened homeostasis provoked by a psychological, environmental, or physiologic stressor." [254,255,256,257] The response-to-injury hypothesis of atherosclerosis is founded on the finding that an injury or stressor alters the homeostasis of the endothelium, leading to an increased adhesiveness of the endothelium to leukocytes and platelets, increased coagulation, increased migration and proliferation of smooth muscle cells at the area of inflammation, and increased permeability of the dysfunctional endothelial wall.[258] These inflammatory mechanisms act in concert to thicken the arterial wall, leading to dilation and, eventually, remodeling of the artery and restriction of the arterial lumen.[259] Specifically, the increased adhesion of platelets and leukocytes to the dysfunctional endothelium and to monocyte-derived macrophages that are assembled in response to injury accumulate on the arterial wall and further expand the lesion.[260] Monocyte-derived macrophages and T lymphocytes are key inflammatory cells and are key participants in the inflammatory response. Activated platelets also release cytokines and growth factors that further call upon the migration and proliferation of smooth muscle cells and monocyte-derived macrophages.[261,262] Smooth muscle cells, further activated in the presence of pro-inflammatory cytokines,[263] migrate and proliferate at the site of inflammation to create an intermediate lesion, while monocyte-derived macrophages and T-lympocytes from the blood

multiply within the lesion. These inflammatory cells, in turn, are activated to release cytokines, chemokines, and growth factors, which cause further damage that can lead to necrosis. At this point, the lesion has become advanced and may begin to narrow the lumen. Injury also acts to increase the permeability of the dysfunctional endothelial wall to low-density lipoprotein (LDL) cholesterol.[264,265] Macrophages recruited to the site of inflammation oxidize LDL cholesterol and internalize the oxidized cholesterol. This process leads to further stimulation of the replication and recruitment of monocytes which, in turn, create macrophages to continue the inflammatory process. The inflammatory response can continue indefinitely if the offending agents are not effectively deactivated.[266]

Psychological Mechanisms

The effect of psychosocial stress in the development of atherosclerosis can be modified by individual personality traits and coping mechanisms. In other words, the physiological effect of a stressor on an individual may differ based on the psychological state of that individual. For example, the effect of exposure to an unstable social environment by cynomolgus monkeys (*Macaca fascicularis*) differs based on whether the animal presents a dominant or subordinate personality type.[267,268] In these studies, socially dominant monkeys exposed to periodic changing of the social structure of the group had a higher incidence of coronary artery disease than subordinate monkeys, both in the presence and absence of an atherogenic diet. In humans, the finding that traits such as hostility, aggression, and vital exhaustion (a condition of fatigue associated with depression) but not emotions such as anger or sadness, are associated with an increased expression of proinflammatory cytokines, suggests that there is a biological as well as contextual pathway in which the mechanisms

through which stress acts to increase cardiovascular risk.[269,270,271] Although few differences in the rates of psychiatric disorders between theater and era veterans have been noted, veterans have higher morbidity than non-veterans, and veterans with combat experience have significantly higher burden of psychiatric disorders compared to veterans without combat exposure and non-veterans.[272]

Alternatively, exposure to psychosocial stress may cause an individual to be more susceptible to the development of a psychological condition that leads to CVD. According to this mechanism, stress may interact with psychological distress to place an individual at higher risk of CVD. Still another mechanism through which psychological distress may act is by placing an individual at higher risk of engaging in atherogenic behaviors such as smoking, drinking alcohol, sedentary lifestyle, and high caloric intake.[273] For example, Beckham and colleagues found that Vietnam veterans with symptoms of post-traumatic stress disorder (PTSD) who smoked were more likely than veterans who did not smoke to report symptoms of depression trait anxiety.[274] These multiple potential mechanisms are not mutually exclusive and may act separately or in concert. The main psychological conditions and personality types that have been connected to the development of CHD and stroke are vital exhaustion and hopelessness (both associated with depression),[275, 276,277,278,279] anxiety,[280] trait anger and hostility.[281,282,283,284,285,286,287]

A number of systematic reviews suggest that depression is a prospective risk factor for coronary artery disease (CAD).[288, 289,290,291,292] According to these studies, individuals with depression are twice as likely to develop CAD as non-depressed individuals. In a prospective study of 2,397 persons without CAD at baseline, those with a diagnosis of major depressive disorder were 3.9 times more likely to die of cardiac causes compared to non-

depressed counterparts within four years of follow-up, even after adjustment for major risk factors.[293] Other prospective studies have reported rate ratios (RR) ranging from 1.6 to 3.45 for CHD or ischemic heart disease incidence and RRs ranging from 1.5 to 2.34 for CHD mortality.[294,295,296] In their 2003 systematic review, Wulsin and colleagues found that depression is a significant independent risk factor for the onset of CHD, and that it poses a greater risk than that of passive smoking but less than that of active smoking.[297] Further, there is a dose-effect relationship, whereby the more severe the depression the higher the risk of CAD (but not the more severe the disease).[298, 299] Physiologically, an elevated catecholamine response to stress has been observed among women with elevated depression scores.[300] In this way, depression may act directly to increase the inflammatory processes associated with development of atherosclerosis and CAD. Alternatively, a common factor such as chronic stress may result in an inflammatory process leading to both depression and CHD.[301] In addition, depression may increase CHD risk through increased adoption of intermediate, unhealthy lifestyles and behaviors such as smoking, atherogeneic diet and lack of physical activity. [302]

A similar construct as depression,[303] vital exhaustion has been found to be associated with a wider range of markers of inflammation than depression.[304, 305] Vital exhaustion has been has also been shown to be prospectively associated with risk of myocardial infarction, even after adjustment for major risk factors.[306] Among women ages 65 years and older, a one standard deviation (8.4 points) increase in the Maastricht Questionnaire of vital exhaustion was associated with a 53% increased risk of recurrent acute myocardial infarction (AMI).[307]

Like depression and vital exhaustion, anxiety is prospectively associated with risk for CHD.[308,309,310] Anxiety has been demonstrated to have a dose-response relationship with

development of sudden cardiac death (SCD).[311] Decreased heart rate variability has been noted in individuals with phobic anxiety[312,313] and is thought to play a role in the development of arrhythmia leading to SCD. A 2002 systematic review, however, found less conclusive evidence of an association between anxiety and nonfatal coronary events or CAD.[314]

A recent study of veterans of the first Gulf War found that 32% of surveyed veterans met the clinical criteria for a current or lifetime depressive disorder, including major depression, dysthymia, or depressive disorder—not otherwise specified (NOS).[315] In a prospective study of veterans of the US conflicts in Iraq, Hoge *et al* found that the proportion of study subjects who met clinical criteria for major depression or generalized anxiety was significantly higher after duty in Iraq than before deployment.[316] In a study of 6,903 male-male twins from the Vietnam Era Twin Registry, Scherrer and colleagues found that having one or more symptoms of depression was significantly associated with an increased prevalence of CHD and hypertension.[317] Similarly, vital exhaustion has been shown to be associated with higher odds of CVD. In a cohort study of 1955 World War II veteran twins, Fitzpatrick and colleagues found that prolonged fatigue is significantly associated with myocardial infarction or coronary artery surgery, even after adjustment for age, socioeconomic status, smoking, alcohol use and depression.[318]

Similarly, trait anger, hostility, and Type A personality type have been investigated for their association with the development of CHD and stroke. Although early evidence suggested that Type A personality (a combination of time urgency or compulsion and generalized hostility)[319] is an independent risk factor for CAD, more recent research is inconclusive.[320,321] Reanalysis of earlier data from large-scale studies of Type A

personality[322,323,324,325] and failure to replicate earlier findings in other large-scale cohort studies[326,327] suggest that the hostility component, rather than Type A personality as a whole, is associated with sudden death and myocardial infarction. Although other studies suggest that, after adjustment for other factors, hostility is only weakly associated with CHD or not associated at all,[328, 329,330,331,332] a 1996 45-study meta-analysis on the association between CHD and trait hostility, which includes "cynical mistrust, anger, and aggression"[333] concluded that hostility is an independent risk factor for CHD, even after adjustment for other risk factors.[334] A recent Framingham Offspring study found that, compared to men with low hostility scores, men with high hostility scores were 30 percent more likely to develop atrial fibrillation during a ten-year follow-up period, even after adjustment for traditional risk factors.[335]

Trait anger, however, has emerged as a more consistent predictor of CAD.[336,337] Results from a prospective Finnish study of middle-aged men found that men who were most likely to demonstrate anger outwardly were also had twice the risk of stroke as men where were least likely to openly demonstrate anger.[338] Results from a large-scale prospective study found a dose response relationship between trait and the risk of AMI, SCD, and angina,[339] and results from a longitudinal study of men found that anger is associated with a three-fold increase in the risk of premature CVD. According to the Framingham Offspring study, compared to men without trait anger, men with high trait anger scores had a 10 percent higher adjusted ten-year risk of developing atrial fibrillation.[340] A recent ARIC study found that angry temperament—but not anger in reaction to criticism, frustration, or unfair treatment—increases the risk of cardiac events among normotensive persons at a magnitude similar to that of hypertension.[341] Also in the ARIC study, trait anger was found to be

associated with an increased incidence of stroke,[342] CHD morbidity and CHD mortality independent of traditional risk factors.[343]

A review of the literature suggests that Vietnam veterans are both more likely than non-veterans to exhibit cynical hostility-like characteristics and more likely to develop cardiovascular disease.[344] In terms of biological mechanisms, anger-induced mental stress has been shown to induce myocardial ischemia in individuals with CAD both in the laboratory setting[345] and in populations.[346] Anger-induced hypertension is thought to be a likely mechanism for the trait anger-CVD association.[347, 348] Both chronic anger and hostility have been found to be independently associated with increases in plasma epinephrine and chronic sympathetic activation.[349,350]

Low social support has also been found to be associated with the development of CVD,[351, 352,353] as lack of social support can leave an individual less equipped to cope with stress.[354,355] For example, Russak and Schwartz noted that undergraduate students who rated their relationship with their parents as "cold and detached" had four times greater risk of developing depression and alcoholism as well as heart disease and diabetes 35 years later.[356] Similarly, in a prospective study of the effects of stressful life events on all-cause mortality, Rosengren and colleagues found that the association was present only among middle-age men who reported low emotional support.[357] In a systematic review by Kuper and colleagues, six of seven prospective etiologic studies reviewed reported showed increased risk of CAD among socially isolated persons.[358] In a systematic review of 15 studies, Rozanski *et al* reported a positive association between low social support and increased CVD risk in almost all cases.[359] It is estimated that persons with low social support have two to three times the CAD risk of persons with high social support, even after adjustment for traditional risk

factors.[360] Although clinical trials are not possible for the study of the association between social support and CVD, the finding of an inverse dose-response relationship between level of social support and cardiovascular risk further supports the role of social support in the development of cardiovascular disease.[361,362]

Conversely, positive parental relationships can act to reduce the effects of other less favorable factors and are associated with better resilience in the face of chronic stress.[363,364,365] For example, Conger and colleagues noted that the negative effects of poverty on child development were removed when the child had positive relationships with their parents.[366] With regard to veteran populations, researchers for the National Vietnam Veterans Readjustment Study (NVVRS)[367] and the Hawaii Vietnam Veterans Project (HVVP) concluded that one of the main predictors of the persistence of symptoms of PTSD is the level of social support and "emotional sustenance."[368] The primary mechanisms through which low social support is thought to modify the association between psychosocial stress and cardiovascular disease is through increased risk of hypertension and hyperlipidemia and through adverse health behaviors such as increased smoking and alcohol drinking.[369,370,371,372]

Social support is considered a potentially important coping strategy for veterans who were exposed to combat during the war. In a longitudinal study of veterans of World War II and the Korean conflict, combat veterans who reported having a supportive post-service social network also reported fewer stress symptoms forty years after conclusion of service.[373,374] Similar findings were reported in a study of the effect of social support on veterans who participated in the NVVRS study.[375] In accordance with Pennebaker and Susman's (1998) psychosomatic theory of inhibition,[376] social support is thought to mitigate the long-term effects of traumatic experiences by relieving the inhibition of "lingering

stresses and emotions of war" that "veterans learned to bury within their psyches."[377] In support of this theory, researchers who studied the unusually low PTSD rates (<10%) among Finnish veterans of World War II concluded that the community's acceptance of discussion of wartime experiences and the ability of Finnish veterans to speak freely about their experiences was noted as a potentially important factor in the high levels of well-being reported by survivors.[378] Further, different types of relationships may help veterans cope with traumatic experiences in different ways. Hunt and colleagues reported that while veterans rely on spouses and family members to help with physical and practical means of coping, they were more likely to discuss traumatic memories with fellow veterans.[379] However, the literature is not completely consistent on the strength of social support in the reduction of the long-term adverse effects of combat-related stress. For example, results from a study of participants in the Veterans Health Study (VHS), suggest that although social support is associated with abatement of the adverse effects of non-military traumatic events, a similar reduction in stress symptoms among those who experienced combat-related traumas was not observed.[380] The authors concluded that combat-related stressors may have an unusually strong and persistent effect on the health status of veterans.

Behavioral Mechanisms

Psychosocial stress may also affect cardiovascular risk indirectly, through behavioral mediators.[381,382] Chronic stress is associated with higher rates of smoking, diet (higher fat and calorie intake), obesity, sedentary behavior, sleep disorders, drug and alcohol use.[383] These behaviors, in turn, have been shown to be associated with higher rates of hypertension, atherosclerosis, hypercholesterolemia, and diabetes. Such unhealthy behaviors may be

associated with increased cardiovascular risk either directly or indirectly, through certain psychological conditions or profiles. For example, although hostility is associated with the development of myocardial infarction and sudden coronary death (SCD), its effect is weakened or even removed after adjustment for health behaviors such as fat and calorie intake, decreased physical activity, and alcohol and tobacco use.[384,385,386,387,388,389] Similarly, smokers and heavy drinkers are more likely to have symptoms of depression, anxiety, fatigue, and panic, worry and irritability, even after adjustment for gender, age, socioeconomic position, and geographic location in the United States.[390,391,392] In this way, stress and unhealthy behaviors may be associated with increased cardiovascular risk directly or may be modified by the effects of certain psychological conditions or profiles.

Smoking (compared to non-smoking) is strongly associated with incident acute myocardial infarction AMI, with a five-fold increase in risk among 30-49-year olds who smoke.[393] The association between psychosocial stress and smoking, however, is more complex. Nicotine is classified as a stimulant, as it increases heart rate and causes autonomic arousal,[394,395] and therefore acts as a stressor. However, a calming effect of smoking has been reported by smokers,[396] and individuals who are subject to increased psychosocial stress are more likely to engage in smoking in an effort to manage this stress.[397] This divergence has been the "physiological and subjective effects of smoking" has been termed the "nicotine paradox."[398] Current theory holds that although individuals experiencing psychosocial stress may engage in smoking in an effort to reduce this stress, its calming effects are transient as an effort to prevent developing nicotine withdrawal.[399, 400,401,402] Thus, although smoking may be initiated as a way to decrease psychosocial stress, its effects very likely increase physiological stress. In a recent study of the health behaviors of US veterans, Gizlice found

that veterans have significantly higher odds of current smoking, former smoking, and smokeless tobacco use compared to non-veterans, even after adjustment for age, race, education, and household income.[403] Other studies have reported similar results, finding that the prevalence of ever and current smoking is higher among US veterans compared to non-veterans.[404, 405,406] Studies of veterans from World War II, the Korean War[407] and the Vietnam conflict[408,409] found that combat veterans with symptoms of PTSD had significantly increased likelihood of former or current smoking. Thus, it appears that the adverse cardiovascular effects of smoking—as measured by higher diastolic blood pressure and higher mean arterial pressure—may be amplified in smokers with PTSD.[410] A study of Vietnam-era veterans found that the prevalence of smoking up to 35 years after exposure to combat increased with combat intensity.[411] The mechanisms through which smoking promotes CVD is well-studied; smoking damages the endothelium, promotes oxidation and thrombosis, increases the release of catecholamines and fibrinogen, causes the myocardium to work harder.[412,413]

Unhealthy diet (high caloric and fat intake) has been shown to be highly associated with increased cardiovascular risk.[414,415] Diets high in total calories, saturated fat, cholesterol, and sodium are associated with increased blood pressure, and may lead to the development of and destabilization of atherosclerotic plaques. Directly associated with energy balance, increased central and overall obesity are similarly associated with increase cardiovascular risk.[416]

Increased levels of psychosocial stress have also been associated with adverse changes in diet.[417] Behaviorally, stress has been shown to act either to increase or to decrease food intake in animal studies[418,419] and to be associated with a preference for diets high in

sucrose.[420] In humans, prospective survey studies have found that negative life events are positively associated with weight gain that was temporary in men and enduring in women.[421, 422,423,424] Similar to animal studies, a study of depression and dietary preferences found that individuals with depression show preference for diets with higher concentrations of sucrose.[425] The manner in which stress affects food intake has also been shown to vary based on the type of stressor (fear-inducing or ego-threatening)[426] as well as the individual (whether or not an individual is an "emotional eater").[427] However, studies on stress and eating behaviors in humans have been fraught with methodologic challenges, given the difficulty of measuring both food intake and psychosocial stress level.[428]

When psychosocial stress activates the sympathetic nervous system through mechanisms described above, a number of physiologic changes occur that affect food consumption, food preferences, and the digestive process. While mild or moderate and temporally limited stressors tend to produce an adaptive response of delaying or reducing food intake so that energy can be diverted away from digestion and towards coping mechanisms, chronic, frequent, or traumatic stressors tend to result in a disrupted response and, generally, increased rather than decreased intake.[429] For example, McCann et al found that increased job stress and workload was associated with higher self-reported total calorie intake and a higher percentage of calories consumed as fat.[430] Studies of stressors such as academic workload and examinations[431] have found similar results, while others found that academic workload was associated with a more unhealthy diet only among those with lower positive affect scores.[432] In a recent study of the health behaviors of US veterans, Gizlice found that veterans have significantly higher odds of being overweight compared to non-veterans, even after adjustment for age, race, education, and household income.[433]

In a typical physiologic response to a non-traumatic acute stressor, the HPA axis is engaged, leading to the release of corticotrophin releasing hormone which leads to hypophasia (the suppression of food intake).[434, 435,436,437] Reciprocally, in response to a traumatic, chronic, or periodic stressor, the functioning of the HPA axis is disrupted, leading to the release of corticotrophin antagonist and, consequently, leading to hyperphasia, or the increase of food intake. Additionally, the release of epinephrine (adrenaline) and norepinephrine (noradrenaline) in response to an environmental stressor stimulates lipolysis in adipose tissue and glycogenolysis in the liver thereby increasing the free fatty acid and glucose supply to muscles and other tissues.[438]

Physical activity is recognized as a protective factor against coronary heart disease.[439, 440,441,442] In 1992 the American Heart Association added physical inactivity as a primary risk factor for coronary heart disease, and the 1996 United States Surgeon General's Report concluded that regular physical activity decreases CHD mortality and is as important a risk factor as other behaviors such as smoking.[443] An inverse, dose-response association between level of physical activity and risk of CVD has been documented.[444,445,446,447] The association between physical inactivity and psychosocial stress is also recognized in the literature. A 1999 study of 194 men and women hospitalized for myocardial infarction found that patients with depression were less likely to adhere to a regimen of healthy diet and regular exercise.[448] In a 1984 consensus statement, the National Institute of Mental Health (NIMH) concluded that physical activity is associated with a reduced risk of mild to moderate depression and that exercise may be used as a collateral treatment for severe depression.[449] In a study of the effects of chronic social stress on physical activity in mice, Bartolomucci and colleagues found that intruders whose social position was changed to being subordinate had

marked reduced physical activity.[450] In humans, the psychosocial stress associated with lower job control was found to be associated with lower levels of physical activity.[451]

Consensus has not yet been reached as to the primary mechanism through which physical activity and psychosocial stress, together, act to reduce the risk of CVD, although a number of possible mechanisms have been identified.[452] Mechanisms include the release of endorphins, which causes a calmer mood known as "exerciser's euphoria;" a relaxation of muscles, an increase of Beta-endorphins; and an increase in corticotrophin and other hormones that counteract the effects of psychosocial stress.[453,454,455] Physical activity is also associated with decreased levels of a number of inflammatory markers.[456] Physical inactivity may also act indirectly, through the protective effects of lipid and blood pressure control, to reduce cardiovascular risk.[457] Physical activity has been shown to be directly associated with HDL levels and inversely associated with LDL and triglyceride levels in fasting plasma.[458, 459,460]

The association between average volume of alcohol consumed and CVD shows a U-shaped relationship in epidemiological studies in developed nations.[461] Heavy alcohol consumption has been found to be associated with increased cardiovascular risk; intake of more than two drinks per day may be associated with an increased risk of ischemic stroke.[462] However, light or moderate consumption is associated with decreased cardiovascular risk compared to non-drinkers.[463,464,465,466,467] The type of alcohol and the pattern of use also modify the effect of alcohol consumption on cardiovascular risk.[468] Binge drinking—drinking large amounts in a short period—has been found to be associated with increased platelet aggregation and a higher incidence of CVD.[469] In terms of the type of alcoholic beverage, regular, modest consumption of red wine, in contrast to other types of alcoholic

beverages, does not result in increased platelet aggregation, and is associated with a reduction of CVD.[470] Thus, while drinking one glass of red wine each day may be cardioprotective, drinking a week's worth of wine in one day may be damaging to the cardiovascular system.[471, 472,473] Although wine is most commonly associated with cardiovascular protection, most alcoholic beverages, in moderation, appear to be inversely associated with incidence of CHD.[474, 475,476,477]

Heavy alcohol consumption is also associated with increased levels of psychosocial stress.[478] Studies have also noted that found that the expectation of feelings of relaxation and reduced tension was the strongest predictor of problematic drinking among college students, even stronger than the expectation of physical or social pleasure.[479, 480] This expectation was also found to be associated with both quantity and frequency of drinking.[481] A 2003 study of job stress noted similar results, reporting that frequent overtime work was associated with heavy alcohol use 24 years later.[482] Similarly, Tsutsumi and colleagues noted that high psychosocial demands on the job and low job control were associated with a higher prevalence of current alcohol drinking.[483] In a study of Israeli witnesses of traumatic events, Hourani and colleagues noted a higher risk of heavy alcohol consumption among men but not women.[484] A study of US veterans from the first Gulf War found that deployed veterans were significantly more likely to have alcohol disorders than non-deployed veterans.[485] Similarly, Elder and colleagues found that Vietnam veterans who were exposed to combat were significantly more likely to be self-reported heavy or problem drinkers than non-combat veterans.[486]

Alcohol consumption and stress can work through multiple pathways to increase or decrease the risk for cardiovascular disease. In small amounts, alcohol consumption increases

beneficial high-density lipoprotein (HDL) concentrations,[487] which decreases the risk of carotid atherosclerosis, CHD and stroke.[488,489] It is thought that 40 to 50 percent of the protective effect of moderate alcohol consumption is attributable to this mechanism.[490, 491,492]

Small amounts of alcohol, particularly in red wine, also have the effect of inhibiting the adhesion of platelets to fibrinogen-coated surface under blood flow, presumably contributing to the cardioprotective effects of alcohol.[493] A meta-analysis of 42 published trials confirmed the contribution of both the influence of alcohol on lipids and on blood-clotting factors.[494] Limited alcohol consumption is also associated with increased insulin sensitivity[495] and lower central abdominal adiposity.[496,497] Moderate alcohol consumption may also reduce cardiovascular risk through anti-inflammatory pathways, as evidenced by the finding that, compared to non-drinkers, persons who consume moderate amounts of alcohol have lower levels of C-reactive protein (CRP), which is a circulating inflammatory marker.[498, 499,500,501,]Moderate alcohol consumption is also thought to reduce CHD risk through protective hormonal, specifically estrogenic, effects[502] and by promoting vasodilatation,[503] although fewer studies have been conducted in support of these hypotheses.

Conversely, heavy alcohol consumption acts to increase cardiovascular risk through the mechanisms of increased clotting and reduced threshold for ventricular fibrillation.[504] Heavy drinking, particularly in irregular patterns, has been shown to increase low-density lipoprotein (LDL) concentrations, which are associated with less favorable cardiovascular outcomes. These increases in unfavorable LDL levels do not come with the subsequent increases in favorable HDL and levels as found among persons who drink lightly or moderately on a regular basis.[505] Irregular, heavy drinking is also associated with an increased risk of thrombosis[506] and a predisposition to histological changes in the

myocardium and conducting system.[507] All of these pathways lead to an increased risk of sudden cardiac death and other unfavorable cardiovascular outcomes.[508,509,510]

Sociodemographic Factors

The association between combat-related stress and CVD risk may be affected by socioeconomic status, which refers distribution of wealth, power, status and opportunities. In other words, the association between combat-related stress and CVD risk may be different for persons based on their social, education, and economic backgrounds and current situations. In most industrialized countries today, the incidence of CHD[511] and stroke[512] is lowest among high SES groups. Inverse associations between socioeconomic status (SES) and CVD morbidity and mortality as well as mortality from other health related outcomes have been demonstrated repeatedly. This has been the case for individual[513,514] and neighborhood-level SES indices[515,516,517] as well as for SES measures assessing conditions in childhood,[518,519] adulthood[520,521] and across the life course.[522]

There are several mechanisms through which SES factors are thought to modify the stress-CVD association. Lower SES at the individual level is associated with increased risk of smoking, less healthy diet, less adequate housing, increased obesity, and reduced physical activity.[523, 524,525,526] In addition, persons from lower SES groups have less self-reported social mobility, increased financial strain and more stressful life events. In this way, the mechanisms through which SES act to increase risk for CVD are thought to be similar to those for other chronic psychosocial stressors.[527]

Overall, the education level of veterans has increased over time. As of 2001, approximately 89% of veterans had a high school diploma, up from 83% in 1992. In 2000,

55% of veterans were employed, 32% were retired, 4% were not working but were looking for a job, and 7% were disabled, differing little from veterans polled in 1992. More than one third of the veteran population polled in 2000 had a combined family income of over $50,000.[528]

Differences in the SES of veterans *versus* non-veterans as well as combat veterans *versus* non-combat veterans have been reported in the literature. In a study of Vietnam veterans up to 35 years after exposure to combat, Stellman and colleagues found that income was significantly lower among high-combat veterans compared to low- and medium-combat veterans.[529] In a study of British veterans from the Gulf War, Ismail and colleagues noted that military rank, used as a proxy for socioeconomic status, was positively associated with psychological and physical health.[530] Elder and colleagues found that the association between combat exposure and physical health did not differ by military rank among veterans of World War II.[531] However, according to results of the Veteran's Administration National Survey of Veterans (NSV), the sociodemographic profile and distribution of the veteran population has changed over time, this finding may or may not hold true for more recent cohorts of veterans.

Further, in a study of the role of SES in the effects of wartime stress on civilians, Sibai and colleagues reported that both the degree and type of wartime exposure as well as SES affects the strength of association between exposure to wartime stress and cardiovascular (CVD) risk.[532] In a longitudinal study of Vietnam era veterans and non-veterans, Cordray and colleagues noted that while PTSD is associated with military combat exposure, level of combat is related to pre-military SES.[533] In this study, the authors found that those from lower SES backgrounds were more likely to experience higher levels of combat, and those who experienced higher levels of combat were more likely to have PTSD

symptoms ten years after the war. An effect in the opposite direction has also been hypothesized, however, as described by the "healthy warrior effect." This hypothesis holds that those who are at higher SES are also healthier and thus more likely to be found fit for war. In the context of a military draft, such as occurred in Vietnam and Korea, this concept may be particularly relevant. Modification by SES was further investigated in the VES study by Bohemer and colleagues, who noted that the adjusted rate of mortality from cancer was elevated among Vietnam theater veterans compared to other veterans serving during the same era, but only among those at a low pay grade (MRR = 1.64; 95% CI = .0.94, 2.89).[534] Conversely, Vietnam theater veterans discharged at a high pay grade had lower adjusted cancer mortality rates compared to other high pay grade veterans who served during the Vietnam era. (MRR = 0.82; 95% CI = 0.63, 1.07) These findings support the theory that higher SES may provide protection against the effects of traumatic stress.

SES has the potential to influence the combat stress-CVD association at many levels.[535] One way the effect of SES on the combat stress-CVD association will be studied is within the framework of life course theory, which views life exposures in the context of timing, life events and life transitions. Life course theory views meaningful life exposures as changes that are rooted within dynamic trajectories of social roles and the events that give them meaning. In other words, the defining feature of life course theory—and the reason that it is used in this analysis—is that it holds that fundamental life experiences must be studied within the context of both social surroundings and changes over time.

The contribution of life course socioeconomic studies of long-term health outcomes has been assessed in three main studies. The National Longitudinal Survey (NLS) of Labor Market Experience of Mature Men is a panel survey of approximately 500 US men who were

between the ages of 45 and 59 in 1966.[536] During the 19-year follow-up period of this study, occupational, educational, and family history were recorded retrospectively, while mortality and other information was collected prospectively. A primary finding in this study was that the association between father's occupation and participant's mortality risk was eliminated after controlling for the participant's education, suggesting that the effect of childhood SES works through subsequent experiences such as educational attainment. The more favorable mortality rates experienced by those with higher educational attainment was further found to be attributable mainly to financial and occupational factors that come with advanced schooling. In addition to education, first occupation on entering the labor market was found to be independently associated with 25-year mortality in this cohort. The effects of first job were found to be attributable mainly to increased wealth and family assets associated with a managerial or professional occupation compared to other types of jobs.

Results from a Norwegian longitudinal data set linking decennial census information from 1960-1980 and vital registry statistics before 1985 are similar to those from the NLS.[537] In this study, the types, sequence, and timing of socioeconomic experiences were assessed in relation to approximately 180,000 deaths in the study population. The highest mortality was found among those with the lowest educational attainment, manual occupations, early retirement, and poor early-life housing conditions. Differences in the importance and effects of some socioeconomic factors were noted by gender, whereby high educational attainment and high-level employment conferred significant protective effects among men only.

The West of Scotland Collaborative (WSC) Study is a third source of information on the contribution of life course SES on health and mortality. In the early 1970's, approximately 5,500 male employees aged 35 to 64 years were screened for cardiovascular

risk factors and cardiovascular health. Early-life SES information was collected, and men were followed for 21 years. [538]Some of the main findings from this study include that while physiological risk factors such as diastolic blood pressure, serum cholesterol, and forced expiratory volume (FEV) are associated with both adulthood and childhood SES, behavioral risk factors such as recreational exercise and cigarette smoking are related to adult but not childhood SES. Results of this study were interpreted to mean that while physiological health is reflected in an accumulation of both past and present socioeconomic exposures, health and related behaviors are more heavily influence by the current social environment. When accumulated SES was measured by summing the number of times a non-manual occupation was held by the father, by the individual at first market entry, and by the individual during adulthood, authors reported that the most favorable health was found among those who held non-manual positions at all three time points.[539] Further, the authors noted a stepwise association between accumulated SES and a number of health outcomes as well as all-cause mortality, with each time point that included a manual labor position being associated with an additional reduction in health or longevity. Control of psychological and behavioral risk factors only modestly reduced the effect of cumulative SES on 21-year all-cause mortality.[540]

Subsequent WSC studies have found that life course SES does not related to specific causes of mortality in a consistent manner.[541] While most cancers are related to adult but not childhood SES, CHD, stroke, respiratory disease, lung cancer and stomach cancer are independently associated with both child and adulthood SES. Other more subtle differences have also been noted. For example, while control of adults SES and risk factors attenuates the association between childhood SES and CHD or respiratory disease mortality, it does not affect the particularly strong association between childhood SES and stroke or stomach

cancer mortality. In a systematic review of the effects of individual-level childhood SES on overall and cardiovascular mortality, Galobardes and colleagues concluded that the persistence of the effect of childhood SES over and above the effects of adult SES and traditional risk factors as an adult differed somewhat by study population. However, overall, the studies showed that individuals with lower childhood SES levels carried an elevated risk of both overall and cardiovascular mortality, independent of adult SES.[542]

The contribution of life course SES in the context of its effect on the association between military service and physiological health has been most extensively studied in the Standford-Terman study, a longitudinal study of the work and life histories of 1,500 men and women. Begun in 1922 when the participants were in elementary and secondary school, the Stanford-Terman study incorporated follow-up interviews every few years until 1992.[543] This longitudinal cohort study found that participation in military combat in World War II was associated with elevated physical decline or death 15 years after conclusion of the war, suggesting that this traumatic exposure had a notable effect on the course of men's lives.[544]

There are three main mechanisms through which social processes are thought to interact with health.[545] First, according to the cumulative disadvantage theory, the accumulation of even small differences in SES from childhood to adulthood is associated with a "chain of disadvantage" throughout life.[546] The example most commonly cited is the association between parental SES and birth weight as well as height in childhood and adolescence.[547,548] Disadvantage at birth and in childhood has also been shown to be associated with longer-term effects, such as increased risk of unemployment.[549] Mechanisms underlying these findings are thought to include financial difficulties, poor nutrition, disrupted sleep patterns, delayed growth and other social disadvantages. Slower childhood

growth is further associated with later educational disadvantages, which can, in turn, lead individuals to employment positions that are more hazardous and poorly regulated. These combined factors, over time, accumulate to form a "chain of disadvantage."

A second mechanism through which life course SES is associated with long-term health is that of social protection. According to this theory, previous socioeconomic conditions can act to either amplify the effects of new disadvantage in the case of previous disadvantage or attenuate these effects in the case of previous advantage.[550] Findings from the General Household Survey support this theory and further demonstrate that the effect of social protection increases as the magnitude of new disadvantage increases.[551] In this study it was found that men of working age with chronic illness and from a higher SES are more likely to be employed than chronically ill men from a lower SES, suggesting that social disadvantage is associated with protection from subsequent social disadvantage. Further, the finding that the positive association between SES and employment rates among the chronically ill suggests that socioeconomic disadvantage Inherent in this theory is that there are critical periods of development during which exposures have particularly long-lasting effects on future social status, health and well-being.[552] The primary critical period of susceptibility and development is that of in-utero growth, during which time environmental exposures to substances such as lead, thalidomide, hepatitis B, and other exposures influence future development and risk.[553, 554,555] Critical periods of social transition include the move from primary to secondary school, entry into the labor market, first residence, job changes, retirement, and onset of chronic illness.[556]

A third mechanism linking life course SES and health is that of social mobility. This mechanism highlights the contribution of young life SES on the probability and direction of

social mobility, and the contribution of this trajectory on subsequent health and wellbeing. Young life experiences associated with advantage or disadvantage such as childhood health and growth, education, number of siblings, family housing conditions are significantly and independently associated with adult SES.[557] The effect of social mobility on long-term morbidity[558] and mortality[559] has been studied most extensively in the Office of National Statistics (ONS) Longitudinal Study and the WSC Study.[560] Results from these studies show that upward mobility from a lower SES in childhood to a higher SES in adulthood is associated with more favorable health and advantage compared to those who remain stable at a lower SES in both childhood and adulthood, but not as favorable as those who remain stable at a higher SES. Reciprocally, those who are downwardly mobile and move from a higher SES in childhood to a lower SES in adulthood are more disadvantaged than those who remain at a higher SES but more advantageous than those who are stable at a low SES. Results from these studies are described in further detail in the next section of this proposal.

Life course theory in the context of this third mechanism is particularly applicable in the study of combat exposures. Life course socioeconomic exposures relate to changes in trajectories in two main ways. First, previously accumulated socioeconomic experiences of advantage or disadvantage influence whether or not particular transitions occur. For example, childhood SES is associated with the probability of attending college,[561] continued employment in a manual occupation,[562] and probability of disability in midlife.[563] In this way, those with a history of socioeconomic disadvantage are more likely to experience transitions such as loss of employment and physical disability and less likely to experience transitions such as enrollment in college and promotion into non-manual labor positions.

Life course socioeconomic exposures also relate to critical social transitions in that prior accumulated advantage or disadvantage can affect whether or not the transition results in a favorable outcome[564] For example, researchers for the General Household Survey reported that among men with chronic illness, those with a history of socioeconomic advantage were more likely to retain employment than those with a history of disadvantage.[565] Also, continuation in the same line of work over time is more commonly followed by unemployment or casual re-employment among persons with a history of disadvantage, who are more likely to work in more insecure and hazardous labor markets.[566]

In the context of military and combat exposures, war may act to either improve or deteriorate future social, psychological and physical health.[567] The socioeconomic position from which individuals enter the military may further affect the way in which this exposure affects their future trajectory. SES early in life may influence whether individuals enter the military, and also their rank and role in the military that, in turn, are associated with stress burden as well as with skills and resources to cope with such stress. For example, during the Vietnam conflict, sons of more highly educated fathers were disproportionately more both likely to enter the military and more likely to die in combat compared to sons of fathers with fewer years of education.[568] Between 1970 and 1973, priority for the draft into the military was randomly assigned to eligible men in a series of lotteries. However, many men avoided the draft by enrolling in school and obtaining educational deferment. According to a Current Population Survey (CPS) study, each additional year of schooling acquired in response to the draft is associated with a 6.6 percent increase in current weekly earnings.[569]

Further, attributes related to SES are also likely associated with the opportunities and resources available to individuals upon leaving the military, and possibly with the adoption

of unfavorable behavioral profiles (smoking, physical inactivity). It is thus plausible that the potential long-term cardiovascular sequelae of combat stress would be greater among individuals from lower SES groups. Similarly, SES in adulthood may in part be determined by participation in the military. Education received during the military or after service via the Montgomery G.I. Bill (which supplements educational costs) could lead to higher SES among those who served. Table 2 below lists the economic and educational benefits provided to veterans of World War II, Korean War, and Vietnam conflict era veterans. While some have theorized that the educational benefits provided by the military would be used disproportionately by those individuals who were at a higher SES at the outset and who could have funded additional education at their own expense,[570] a study by Mettler and Welch reported that use of the G.I. bill was not based on prior SES.[571] Thus, while some used these benefits to further their education in ways that they could have without them, others were able to gain access to education that they would not otherwise have been able. In 1999 Bound and Turner tested the hypothesis that the G.I. Bill increased educational attainment for returning World War II veterans. Using U.S. census data, Bound and Turner found that the educational benefits offered through the G.I. Bill did, in fact, lead to a modest gain in the postsecondary educational attainment of World War II veterans.[572] Results from a longitudinal study of Depression-era men suggest that the GI Bill allowed for veterans to keep pace with, but not exceed, non-veterans in terms of educational attainment.[573] Further, results from qualitative studies of veterans suggest that military service cultivates a stronger sense of self-efficacy, assertiveness, discipline, proclivity to teamwork, leadership, and positive self-image, which may be advantageous in future educational and occupational endeavors. [574,575]

Table 2. Economic and Educational Benefits Provided to US Veterans during the Eras of World War II, the Korean War and the Vietnam Conflict.

Servicemen's Readjustment Act of 1944 (Original World War II-era GI Bill of Rights)	
• Education and training: Paid tuition, books, fees, and other training costs and provided a monthly living allowance • Loan guarantees: For a home, farm, or business • Unemployment pay: $20 a week for up to 52 weeks • Job-search assistance	• Total educated: 7.8 million • Total cost: $14.5 billion • Expired: July 25, 1956
Veterans Readjustment Assistance Act of 1952 (Korean War GI Bill)	
• Education and training: Up to $110 per month • Loan guarantees: For a home, farm, or business	• Total educated: 2.4 million • Total cost: $4.5 billion • Expired: January 31, 1965
Veterans Readjustment Benefits Act of 1966 (Vietnam-era GI Bill)	
• Education and training: One month of coverage provided for each month of service, for a maximum of 36 months, later extended to 45 months; payment increased from $100 a month in 1966 to $376 per month in 1984 • Loan guarantees: For a home or farm • Job counseling: Employment placement service	• Total educated: 8.2 million • Total cost: $42 billion • Expired: December 31, 1989

Source: Adapted from the Raleigh News and Observer, 2004.[576]

Conversely, if psychological and physical conditions related to combat stress adversely affect access to or use of subsequent educational and occupational opportunities, a lower SES could result, with its attendant unfavorable CVD risk factor profile. For example, collaborators for the National Survey of the Vietnam Generation found that the adverse psychological sequelae of military service affects post-service employment and income. In this study, collaborators found that veterans who met clinical criteria for PTSD, anxiety disorders or major depression were significantly less likely to be employed and, if working, had significantly lower wage earnings than veterans without one or more of these diagnoses.[577] Such findings support the importance of considering SES, both prior to entry into the military and in subsequent civilian life.

Further, a number of differences in the timing of life events have been noted among American veterans. Results from longitudinal studies also suggest that compared to non-

veterans, veterans of World War II and the Korean War were more likely to have considerable delay in timing of school completion, marriage, full-time employment, and child-rearing.[578,579] Not only was military service associated with different timing of important life events, but it is also associated with different order of events. For example, Elder and colleagues found that marriage before finishing school is more common among veterans than non-veterans.[580] Although the additional effects of combat exposure among veterans was not able to be assessed in these studies, it was theorized that combat experience would play an important role in the timing and order of live events, particularly through the mechanisms of psychological health and impairment.[581]

Birth Cohort and Gender

The age of participants arose is also thought to affect the association between exposure to military combat and cardiovascular risk. Advanced age is associated with increased risk of CVD; however, categorization into birth cohorts rather than age in years allows for connections to be made between individual aging and historical period in which one lived. In descriptive analyses, acknowledgement of birth cohorts highlights the intersection of age, period, and cohort, which together act to produce different life patterns among different age groups or generations.

Although the U.S. is constantly engaged in some level military involvement, the prevalence of exposure to military combat in the U.S. population is not constant and changes with political climate. Many generational differences exist in both military service and combat exposures. Currently, the average age of the veteran population is increasing, as there are fewer military conflicts now than there were in earlier years and as veterans of World

War II, the Korean War and the Vietnam conflict continue to age. Between 1992 and 2001, the percentage of veterans under the age of 45 decreased from 32 to 21 percent, while the percentage of veterans over the age of 65 increased from 26 to 38 percent.[528] Currently, the average veteran is 58 years of age, employed, have completed high school and are enjoying a family income of more than $50,000 per year. [582] The proportion of veterans that is female has increased over time; currently 6 percent of veterans are female, compared to 4% in 1992. Female veterans tend to be younger, more highly educated, and include a greater proportion of minorities. These differences likely reflect the fact that few women entered the military before 1975.[583]

Male veterans are far more likely to have served in a combat or war zone compared to female veterans (40.6% *versus* 12.0%, respectively) and more likely to have been exposed to dead, dying, or wounded persons (37.2% *versus* 24.4%, respectively). (Table 3, below) A requirement for the receipt of disability compensation, service-related disability was reported by a slightly higher proportion of male veterans compared to female veterans (13.9% *versus* 12.7%, respectively). (Table 4, below) However, the proportion of veterans reporting any self-reported disabling condition incurred during active military service was similar for male and female veterans (13.8% and 13.5%, respectively).

Table 3. Percent Distribution of United States Veterans by Service in Combat or War Zone and Exposure to Dead, Dying or Wounded, by Gender.

	Total	Males	Females
Served in combat or war zone			
Yes	38.9	40.6	12.0
No	60.1	58.3	87.8
Unknown	1.0	1.1	0.2
Total	100.0	100.0	100.0
Exposed to dead, dying, or wounded people			
Yes	36.4	37.2	24.4
No	62.9	62.1	75.2
Unknown	0.7	0.7	0.4
Total	100.0	100.0	100.0
Number of veterans *	25,095,000	23,629,800	1,465,200

* Estimates of number of veterans are rounded to the nearest hundred.
Note: This table excludes veterans who received a medical discharge from the National Guard or Reserves but never served on active duty.
Source: Adapted from Department of Veterans Affairs, 2001.[528]

Table 4. Percent Distribution of United States Veterans with Service-Related Disability, by Gender.

	Total	Males	Females
Experienced a service-related disability			
Yes	13.8	13.9	12.7
No	16.6	16.8	12.0
Unknown	69.6	69.3	75.3
Total	100.0	100.0	100.0
Experienced a service-connected disability rating			
Yes	13.8	13.8	13.5
No	85.1	85.1	85.6
Unknown	1.1	1.1	0.9 †
Total	100.0	100.0	100.0
Number of veterans *	25,196,000	23,712,400	1,483,600

* Estimates of number of veterans are rounded to the nearest hundred.
† Low precision and/or sample size for the denominator between 30 and 59.
Note: This table excludes veterans who received a medical discharge from the National Guard or Reserves but never served on active duty.
Source: Adapted from Department of Veterans Affairs, 2001.[528]

Era of service

Exposure to combat and general military experiences further differed by era of service. Specifically, the probability of combat or war zone exposure decreased after World War II and increased again during the eras of the Vietnam conflict and the Gulf War. (Table 5) The highest percentage of veterans to report exposure to combat or war zones is among those who served during the World War II period, followed by veterans who served between World War II and the Korean conflict and those who served during the period of the Vietnam conflict. Because veterans polled by the National Survey of Veterans could indicate more than one period of service, the relatively high percentage of veterans reporting combat exposure who served between World War II and the Korean conflict may be due to veterans who experienced combat during the World War II era but continued to serve in the military after the conclusion of the war. Similarly, exposure to dead, dying or wounded persons was most commonly reported among veterans of WWII and the following period. The proportion of veterans who reported a service-related disability was highest during the Vietnam, Post-Vietnam, and Gulf War eras, compared to previous periods of service. However, as Veterans Administration researchers note, this finding may be an artifact reflecting the higher mortality among veterans from earlier periods of service.[584]

Table 5. Percent Distribution of United States Veterans by Service in Combat or War Zone; Exposure to Dead, Dying or Wounded Persons; Experience of a Service-Related Disability; or Experience of a Service-Connected Disability Rating, by Period of Service.

	Total	World War II	Between World War II and Korean War	Korean War	Between Korean Conflict and Vietnam War	Vietnam Conflict	Post-Vietnam Conflict	Gulf War
Served in combat or war zone								
Yes	38.9	60.3	52.8	42.4	31.9	48.1	31.5	38.1
No	60.1	38.7	46.5	56.9	67.1	51.1	67.3	60.7
Unknown	1.0	1.0	0.7	0.7	1.0	0.8	1.2	1.2
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Exposed to dead, dying, or wounded people								
Yes	36.4	49.7	42.9	34.8	30.0	45.9	32.3	31.7
No	62.9	49.2	56.3	64.6	69.4	53.5	67.0	67.6
Unknown	0.7	1.1	0.8	0.6	0.6	0.6	0.7	0.7
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Experienced a service-related disability								
Yes	13.9	13.6	14.0	11.7	12.5	18.5	19.6	22.5
No	16.5	28.6	25.1	22.7	18.8	11.6	7.4	3.0
Unknown	69.6	57.8	60.9	65.6	68.7	69.9	73.0	74.5
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Experienced a service-connected disability rating								
Yes	13.8	14.2	16.3	13.3	12.8	18.1	20.4	24.2
No	85.1	84.6	85.9	85.9	86.6	80.9	78.6	74.5
Unknown	1.1	1.2	1.1 *	0.8	0.6	1.0	1.0	1.3
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Number of veterans †	25,095,000	5,149,100	1,680,600	4,245,600	6,426,500	9,057,200	7,005,000	3,483,600

* Low precision and/or sample size for the denominator between 30 and 59.

† Estimates of number of veterans are rounded to the nearest hundred; the total estimate is smaller than the sum of the groups because veterans could indicate more than one period of service.

Note: This table excludes veterans who received a medical discharge from the National Guard or Reserves but never served on active duty.

Source: Department of Veterans Affairs, 2001.[528]

Notable differences exist, not only in post-military benefits, but also in the draft, the nature of the combat and the social and political context surrounding the conflicts.[585] Involuntary conscription was in effect when these men served, and it was not until the time of the Vietnam War when educational deferments were commonly granted and used as a means to avoid military service. Similarly, the lower rates of military service among blacks may reflect a lower demand or acceptance of black recruits, particularly prior to a racially integrated military (Korean War era). Also, Vietnam veterans are reported to have been subject to unusually high levels of "barbarity and moral ambiguity" while in the line of duty.[586, 587,588,589,590] Veterans of the Vietnam conflict also returned from war to a social and political environment that was particularly unsupportive of the US involvement in the conflict.[591,592] In contrast, World War II has been referred to as a "good" war that had overwhelming support of the American public.[593, 594,595] A 1994 study by Fontana and Rosenheck found that the manner in which solders were received at homecoming had a significant effect on the risk of developing PTSD and other psychiatric symptoms later in life.[596] The authors suggested that the more favorable homecoming experienced by World War II veterans may have mitigated the negative impact of combat experiences on psychological health. Alternatively, the greater stigma associated with mental illness during the era of the World War II generation may have led to underreporting of the presence or severity of symptoms. Further, World War II was a more traditional war with a clearly identified enemy. Like World War II, the Korean War was fought by defined armies for territory; however, civilians were also involved in the conflict. Unlike World War II, the Korean War lost support from the American public over the course of the war. Additionally, the nature of the combat experiences to which soldiers were exposed differed by conflict.

According to a findings from Fontana and colleagues' study of 5,138 war zone veterans who sought treatment from Veterans Affairs outpatient clinics, Vietnam veterans were more likely to have witnessed abusive violence or killings compared to veterans of World War II and the Korean War.[597] The confluence of divergent factors such as the clarity of identification of the enemy, involvement of civilians in combat, transparency of the goals of the war, and level of public support may result in different associations between combat-related stress and health among men from different eras.

Differences in effect by era may occur directly, due to differential socioeconomic, racial, sociopolitical or post-military readjustment stress, or indirectly, through differential adoption of resultant maladaptive health behaviors. In a study of Vietnam and World War II era veterans, Boscarino found that Vietnam era veterans had higher unadjusted alcohol consumption, binge drinking, and drug involvement, compared to both non-veterans and veterans of World War II.[598] Though considerably reduced, differences persisted even after adjustment for demographic variables. Adoption of atherogeneic behaviors such as smoking, drinking, and drug use may also have increased differentially during military service itself. During the Vietnam conflict, for example, drug use, alcohol consumption and smoking were particularly common. Although drug use declined sharply after conclusion of military service, high rates of drinking problems persisted.[599, 600,601]

Differences by era may also reflect different effects of military branch service. The proportion of veterans who served in the Army, compared to the Marines, Air Force, Navy, or Coast Guard has decreased over time, from 60% of veterans age 75 years and over to 43% of veterans less than 35 years of age. Conversely, the proportion of veterans who served in the Marine Corps has increased over time, from 6% among veterans age 75 years and over to

18% of veterans 35 years and under. Distributions of service in the other branches of the military have varied little over time.[602] Distribution of veterans by branch of service may impact probability of exposure to particular combat experiences. For example, those who served in the Marine Corps or Army have historically had a higher probability of incurring a service-related disability compared to those who served in the Navy, Air Force, or Coast Guard.[603] Unfortunately, rank and branch of service was not recorded during the LC-SES interview. Results from the Stanford Terman Study suggest no evidence of modification by rank or theater of engagement.[604]

Race and Ethnicity

Although race/ethnicity is commonly controlled for in epidemiologic studies,[605] the mechanism through which it acts in the development of disease is not well understood.[606] Currently it is thought that underlying gene-environment interactions and/or socioeconomic differences may explain differences that are found.[607, 608,609,610] However, even when the researcher controls for socioeconomic differences, residual confounding may persist due to the difficulty in measuring the complex schema of SES. Such residual confounding may subsequently and inappropriately be attributed to race.[611]Although considering race as a biological construct has been convincingly refuted,[612,613,614] it is still unclear whether race is indicative of a direct gene-environment interaction or, alternatively, whether it is instead a "broad indicator of risk factor status."[615]

Although U.S. veterans are a diverse group, the majority are white, non-Hispanic males. The proportion of non-white veterans has increased over time, and currently approximately 9 percent of veterans identify themselves as black and less than one percent of

veterans identify themselves as American Indian, Asian or Native Hawaiian, respectively. It follows then that although white veterans are most likely to have served during the Vietnam Era (35.9%), black veterans are most likely to have served during the Post-Vietnam era (45.8%). (Table 6) Similarly, while persons of Hispanic ethnicity were most likely to serve during the post-Vietnam era (35.9%), persons of non-Hispanic ethnicity were most likely to serve during the Vietnam era (36.1%). (Table 7)

Table 6. Percent Distribution of United States Veterans by Period of Service and Race.

Era of service		One race						Two or more races		Unknown race
	Total	Total one race	White	Black	American Indian or Alaska Native	Asian	Native Hawaiian or Other Pacific Islander	Total two or more races	American Indian or Alaska Native/White	
World War II	20.5	21.1	2.4	10.1	8.1	20.4	4.9*	11.1	12.0	9.7
Between World War II and Korean War	6.7	6.8	7.1	4.6	5.7*	9.8*	4.0*	5.7	7.2	3.5
Korean War	6.9	17.2	17.7	13.3	11.5	13.5*	18.0*	13.6	16.5	9.5
Between Korean War and Vietnam Conflict	25.6	26.0	26.8	18.8	18.9	24.1	27.0*	21.2	25.9	17.9
Vietnam Conflict	36.1	35.8	35.9	34.8	34.6	36.3	56.1*	44.2	45.0	38.2
Post-Vietnam Conflict	27.9	27.3	25.2	45.8	50.5	32.5	56.2*	39.1	34.1	37.7
Gulf War	13.9	13.3	11.9	26.4	19.6	32.0	16.6*	19.2	14.9	27.0
Number of veterans †	25,095,000	23,763,200	21,289,000	2,206,000	158,500	73,200	36,500	552,900	360,600	778,800

* Low precision and/or sample size for the denominator between 30 and 59.

† Estimates of number of veterans are rounded to the nearest hundred; only one sub-category of "Total Two or More Races" is shown because all other categories were too small to report; percent estimates sum to greater than 100% because veterans could indicate more than one period of service.

Note: This table excludes veterans who received a medical discharge from the National Guard or Reserves but never served on active duty.

Source: Department of Veterans Affairs, 2001.[528]

Table 7. Percent Distribution of United States Veterans by Period of Service and Ethnicity.

Era of service	Total	Spanish, Hispanic, or Latino/Latina	Not Spanish, Hispanic, or Latino/Latina
World War II	20.5	10.2	21.0
Between World War II and Korean War	6.7	3.1	6.9
Korean War	16.9	10.6	17.2
Between Korean War and Vietnam Conflict	25.6	17.9	26.0
Vietnam Conflict	36.1	34.9	36.1
Post-Vietnam Conflict	27.9	35.9	27.5
Gulf War	13.9	25.9	13.3
Number of veterans †	25,095,000	1,111,800	23,899,600

* Low precision and/or sample size for the denominator between 30 and 59.

† Estimates of number of veterans are rounded to the nearest hundred; the total estimate is larger than the sum of the groups because some veterans did not provide a category of Ethnicity; percent estimates sum to greater than 100% because veterans could indicate more than one period of service.

Note: This table excludes veterans who received a medical discharge from the National Guard or Reserves but never served on active duty.

Source: Department of Veterans Affairs, 2001.[528]

Female veterans are more likely than male veterans to be non-white; 17 percent of female veterans are non-white compared to 9 percent of male veterans. Approximately 4 percent of both male and female veterans identify themselves as Hispanic or Latino/Latina.[616] Compared to veterans of other races, black veterans have historically been more likely to serve in the Army and less likely to serve in the Navy than the other branches of the military. Conversely, white veterans have been more likely to serve in the Air Force compared to black veterans.

With regard to the particular association between combat stress and CVD, the literature is inconclusive on the effect of race and ethnicity. This area has been studied most extensively by NVVRS and its ancillary studies. For example, researchers with the HVVP, a congressionally-mandated follow-up study of NVVRS designed to assess current and lifetime prevalence of PTSD among male Vietnam veterans, noted significant differences in PTSD prevalence by race, whereby Hawaiian veterans of Japanese ancestry reported significantly lower prevalence of current full, current partial, and lifetime full PTSD compared to white veterans, even after adjustment for age and war zone.[617] In the NVVRS study, Kulka and colleagues also found that Hispanic veterans exhibited higher risk of developing PTSD compared to veterans of other racial and ethnic backgrounds.[618, 619] Similarly, NVVRS researchers Ortega and colleagues reported similar results, finding that Hispanic Vietnam veterans reported significantly more and more severe PTSD symptoms than non-Hispanic white veterans, even after adjustment for pre-military and military experiences. However, the authors conceded that differences in symptom reporting may reflect differences in expressive style rather than true differences in symptomology. Conversely, collaborators for the American Indian Vietnam Veterans Project and NVVRS found that adjustment for exposure

to war zone stress eliminated previously significant elevations in the prevalence of 1-month and lifetime PTSD among American Indian male Vietnam veterans compared to white Vietnam veterans.[620] Due to findings such as these, race will be assessed as a potential covariate.

Individual Susceptibility and Resilience

Although physiological, psychological and behavioral health factors play a strong role in an individual's susceptibility to both stress and cardiovascular disease, individual differences in susceptibility to and resilience in the face of stressors persist. McEwen and Stellar have described the additional individual factors as "cascading relationships" that begin in early life, between environmental and genetic factors that may or may not predispose an individual to susceptibility to both stress and cardiovascular disease.[621] According to Lazarus and Folkman, the way an individual assesses and responds to stress is based on not only on the level of the demand but also on the resources the individual has to cope with that demand.[622,623] Such individual traits favoring resilience include optimism, effective behaviors in spite of fear, adaptive social behavior and faith.[624,625] As described in the previous section, the contribution of individual factors and resilience will be assessed within the context of life course theory, which holds that the interaction of social processes with physiological health from childhood to adulthood creates cumulative advantage or disadvantage throughout life.[626]

Individual factors may also affect whether or not an individual perceives an event or situation as stressful and, further, may affect how an individual adjusts to or copes with a stressor. For example, family instability and childhood antisocial behavior have been found

to be associated with the development of post-service PTSD symptoms among Vietnam veterans.[627] In a study of patients with myocardial infarction (MI) and hospital controls with less serious illness, Byrne and colleagues found that although the two groups did not differ in the frequency of traumatic life events, individual impact scales of emotional distress were significantly higher among those who had suffered and MI.[628] Traumatic or stressful life events during the postwar period have been found to affect how an individual recovers from traumas experienced during military service.[629] In a recent study of the effect of factors that occur before, during, and after a traumatic event on recovery from PTSD, Schnurr and colleagues reported that failure to recover is related predominantly to experiences that occurred during or after, rather than before the event.[630]

A combination of familial and cultural factors may also play a role in an individual's susceptibility to psychosocial stress. For example, in a study of the effects on blood pressure of being exposed to an arithmetic test, Gerin and colleagues noted that parental history of hypertension was more common among those whose blood pressure remained elevated for several hours after taking the test.[631] However, a recent study of chronic fatigue and CVD in World War II veteran twins concluded that, although the association between chronic fatigue and CVD remains strong, genetics alone did not appear to play an important role.[632] Still, the effects of the combination of genetics and environmental factors such has psychosocial stress on the development of CAD has gathered much interest over the past decade.[633, 634] Such gene-environment interactions are thought to work through a process whereby genetic variation influences an individual's disease risk by affecting susceptibility to environmental risk factors. Such factors include behavioral factors such as smoking, alcohol use, poor diet, and physical inactivity.[635, 636] For example, individuals with the apolipoprotein E (APOE)

allele epsilon4, which is associated with an increased risk of CVD, experience a smaller cardioprotective increase in HDL associated with alcohol compared to those without the epsilon4 allele. (Djousse, 2004) Also associated with familial factors as well as behavioral and lifestyle choices, an individual's general physical health can affect how susceptible he or she is to the effects of psychosocial stress.[637, 638]

With regard to military combat stressors in particular, some, such as Hendin and colleagues hold that pre-military individual personality factors affect the way that individuals respond to traumatic events both psychologically and physiologically. This postulate is consistent with the finding that not all combat veterans develop PTSD. Further, among those who are diagnosed with PTSD, subgroup differences persist. The different ways that veterans respond to stressors associated with military combat was highlighted by a 2002 study of veterans of the Vietnam conflict and the Gulf War.[639] In this study, Glenn and colleagues identified subtypes of veterans that, despite similar exposures and common PTSD diagnosis, presented very different psychological profiles. While some veterans presented psychological profiles marked by distrust, anger, alienation and irregular or unusual thoughts, others had profiles dominated by anxiety, agitation, and irregular or unusual thoughts, and still others presented symptoms dominated by anxiety, worry and depression or symptoms primarily of depression, alienation, irregular or unusual thought processes and a history of odd or unusual experiences. A final group displayed symptoms of somatic complaints. When investigated as a single group, subgroup differences are obscured, highlighting the importance of individual differences in the reaction to a stressor.

Despite these differences in response, others maintain that pre-trauma personality factors or "predispositions" do not, in fact, modify the association between military combat

and later health.[640] This position is reinforced by studies of Vietnam veterans that found that pre-war personality factors were not predictive of subsequent PTSD scores, even after adjustment for military and combat exposures.[641, 642] This hypothesis is further supported by findings from Elder and colleagues' study of veterans of World War II that prewar psychological factors did not modify the association between overseas combat and rates of physical decline or all-cause mortality fifteen years after the conclusion of the war.[643] Others, however, maintain that individual personality factors or psychological profiles affect selection into the military. Research has shown that veterans with a history of difficulty with authority, academic problems, conduct disorders, unstable family life, and drug use were more likely to be exposed to heavier combat or more abusive combat during military service.[644,645,646]

Age at Entry into the Military and Duration of Service

Susceptibility to the adverse effects of military combat is further thought to differ by age at entry into the military. Earlier age at entry has been found to be associated with greater gains in psychological health from adolescence to midlife, compared to non-veterans.[647] In contrast, late entrance into the military has been found to be associated with higher negative trajectories on physical health compared to earlier entrants.[648,649] Because men who are mobilized later tend to carry more social obligations, particularly regarding family and work, their lives stand to be more disrupted upon entrance into the military compared to younger entrants with less experience and social responsibility.[650] Age at entry has also been shown to be associated with likelihood of developing PTSD, suggesting that the effects of traumatic military exposures may be modified by age at mobilization. Further, late entry into the

military was found to be positively associated with increased odds of physical decline or death in a cohort of World War II veterans.[651] Duration of service will be assessed as a potential covariate in the association between combat exposure and CVD risk, as it may alter the magnitude of the effect of exposure.

Public Health Significance

As a result of the Gulf War in the early 1990s and now the Iraqi occupation, younger cohorts of men and women have and are being exposed to combat related stress. Given the pervasiveness of combat exposure in our community, it is important that we explore and understand the long-term effects it has on the individuals who experience it. If deleterious effects are identified, evidence from studies like the one proposed could be used to help influence public health programs designed for veteran and active service populations and potentially reduce the burden of chronic disease in these populations in middle and older age.

From a more scientific perspective, this study of men with a history of distant military and combat exposure will contribute to the body of knowledge about the long-term effects of traumatic psychosocial stress. If an association is identified, this study could lead the way for future research aimed at elucidating the pathways—including biological, psychological, behavioral and lifestyle mechanisms—through which stress can place an individual at long-term risk for CVD. The findings in this study have implications for our understanding of the lasting effects of traumatic stress on long-term cardiovascular health.

CHAPTER 4

RESEARCH PLAN

Overview

In this study, we investigated the effect of military combat on the incidence of CHD and IS and the burden of subclinical atherosclerosis in a large, community-based sample of men whose military service spanned World War II, the Korean War and the Vietnam Conflict. Data were drawn from the cohort component of the ARIC Study, a prospective, community-based study that was designed to investigate the etiology and natural history of CVD and atherosclerosis. This study has both cohort and surveillance components; the current analyses include only members of the cohort study. At baseline (1987-1989), the cohort included 15,792 African-American and Caucasian men and women between the ages of 45 and 64 years, selected by probability sampling from four US communities: Minneapolis, MN; Washington County, MD; Jackson, MS; and Forsyth County, NC. Standardized interviews were conducted at baseline to establish health history and to obtain demographic, socioeconomic and behavioral risk data. Using standard protocols, trained and certified technicians performed physical exams and subclinical CVD procedures and collected fasting blood samples. After baseline, there were three triennial examinations, the last of which occurred in 1997-1999. In addition, approximately 94% of cohort survivors are successfully contacted and interviewed annually to ascertain vital status, health status and hospitalizations. Cardiovascular measurements were taken an average of 36 years after entry into military service.

For Manuscript 1, coronary artery plaque and carotid intima-media thickness (CIMT) were compared between non-veterans and veterans with and without one or more self-reported combat exposures. Linear regression was used to estimate risk differences (RDs) and 95% confidence intervals (CIs) for continuous CIMT, averaged over Visits 1 and 2, while modified Poisson regression was used to estimate risk ratios (RRs) and 95% CIs for binary CIMT and plaque variables. Results were stratified according to era of service and race.

For Manuscript 2, risk of coronary heart disease (CHD) and ischemic stroke (IS) were compared between non-veterans and veterans with and without one or more self-reported combat exposures. Incidence rates and incidence rate ratios were calculated using Poisson regression. Results were stratified according to era of service.

The ARIC Study

The Atherosclerosis Risk in Communities (ARIC) Study is a prospective, community-based study that was designed to investigate the etiology and natural history of CVD and atherosclerosis. This study has both cohort and surveillance components; the current analyses include only members of the cohort study. At baseline (1987-1989), the cohort included 15,792 African-American and Caucasian men and women between the ages of 45 and 64 years, selected by probability sampling from four US communities: Minneapolis, MN; Washington County, MD; Jackson, MS; and Forsyth County, NC. Participants from MN and MD were Caucasian, while African-American participants were sampled exclusively in MS. The NC center included both African-American and Caucasian participants, with African-Americans being over-sampled to assure a larger sample size.

Standardized interviews were conducted at baseline to establish health history and to obtain demographic, socioeconomic and behavioral risk data. Using standard protocols, trained and certified technicians performed physical exams and subclinical CVD procedures and collected fasting blood samples. A detailed account of the design and procedures has been published,[652, 653] and the study protocols and information on quality control and assurance can be found on the ARIC website (http://www.cscc.unc.edu/aric). After baseline, there were three triennial examinations, the last of which occurred in 1997-1999. In addition, approximately 94% of cohort survivors are successfully contacted and interviewed annually to ascertain vital status, health status and hospitalizations.

The LC-SES Study

The Life Course Socioeconomic Status, Social Context and Cardiovascular Disease (LC-SES) Study is an ancillary study to ARIC that was initiated in 2001 to examine the association between SES across the life course and adult cardiovascular conditions. Additional details about its design and procedures are published[654] and are available at the LC-SES website (http://www.lifecourseepi.info). After an average of fifteen years of follow-up, the ages of cohort participants ranged from 57 to 79 years. During this interview, 12,716 or 81% of the baseline ARIC participants (94% of cohort survivors) were interviewed by trained and certified interviewers who administered a telephone questionnaire that included 44 questions about parental and early adulthood occupational and educational exposures, place of residence during early childhood and earlier adulthood and military service and combat exposures. Mortality prior to participation in LC-SES varied considerably by race

and gender (22% for black men; 13% for white men; 13% for black women; 8% for white women).

Study Population

The study populations used for the two manuscripts included in this study were drawn from the LC-SES population. Female LC-SES Survey participants were excluded from this study, as only 49 reported a history of military service. Also, because their numbers were insufficient for analysis, men with a race other than African-American or Caucasian (n=14) and African-Americans from Washington County or Minneapolis (n=21) were excluded. Further excluded were men who had missing or unknown military service status (n=53), leaving a final study population of 5,347 men for the first manuscript. Further excluded for the second manuscript were 727 men who served outside the defined periods of conflict for World War II (1941-1945), the Korean War (1950-1953) and the Vietnam Conflict (1961-1975). After these exclusions, the study population for the second manuscript included 4,620 men.

Outcome Assessment

Prevalent Subclinical Atherosclerosis

Two measures of subclinical atherosclerosis were included: carotid intima-media thickness (CIMT) and carotid plaque. CIMT is a marker of subclinical atherosclerosis that has been validated by pathology[655] and that accurately predicts future cardiovascular events[656,657,,658, 659,660] The presence of carotid plaque by B-mode ultrasound measurement is

a significant predictor of advanced atherosclerosis,[661] incident CHD[662] and cardiovascular mortality.[663]

At each of the four ARIC visits, using a standardized protocol, B-mode ultrasound measurements were taken to measure CIMT and identify carotid plaque. Measurements were taken bilaterally at three specific 1-cm segments of the carotid artery located within the common carotid, the bifurcation and the internal carotid, for a total of six measurements. Readers measured the CIMT within these regions, reported whether they observed a plaque and reported whether acoustic shadowing was present. Plaques were defined as the presence of abnormalities in the arterial wall thickness, shape (protrusion into the lumen, rough or misaligned boundary with adjacent arterial wall) or texture (brighter echoes than adjacent wall boundaries).[662] Acoustic shadowing was defined as a dampened amplitude of echoes in the ultrasound. Images were video recorded at each study center, and tapes were read at a central ultrasound reading center. Further information about ultrasound scanning and reading have been published [664,665,655] A participant was categorized as having plaque if plaque with or without acoustic shadowing was found at one or more of the six sites at Visit 1 or Visit 2 *versus* no plaque at either visit.

For the purposes of the analyses presented here, CIMT was defined as the average far wall thickness across the six carotid sites. Adjustment for carotid site-specific reader differences and measurement drift across visits and imputation for missing sites was implemented using maximum likelihood techniques for linear mixed models.[666] Data from the six individual carotid sites were missing at random conditional on age, race, body mass and arterial depth. Methods used for the imputation of missing values use sex and race specific linear models developed for the ARIC Study and are published [667] Average values

from the mean CIMT measurements from Visits 1 and 2 were used in the following analyses in order to ensure consistent scanning technology and comparability with carotid plaque assessment. CIMT was assessed in two ways. First, it was assessed as a continuous measure. Second, it was assessed as a binary measure (≥1 mm *versus* < 1 mm), as this commonly-used cutpoint has been demonstrated reliable. [664]

Incident Coronary Heart Disease and Ischemic Stroke

Detailed descriptions of the methods of ascertainment of incident CHD and IS events have been provided in previous work.[668,669] Briefly, CHD and IS incidence were ascertained by annual follow-up interview and validated by review of hospital discharge records and death certificates.[670,671,672] Out-of-hospital deaths were ascertained through death certificates and, when available, coroner or autopsy reports. In the majority of out-of-hospital deaths, cause of death was further validated by an interview with one or more next of kin as well as by a questionnaire completed by the patient's treating physician. Incident events were included from enrollment in ARIC until December 31, 2002.

An incident CHD event was defined as: (a.) a validated definite or probable hospitalized myocardial infarction (based on a combination of chest pain symptoms, ECG changes, and cardiac enzyme levels); (b.) a definite CHD death (based on chest pain symptoms, underlying cause of death from death certificate, and other information from the hospital chart, medical history or ARIC visit); (c.) an unrecognized MI identified by ECG readings at one or more of the ARIC examinations (based on ECG readings with a major Q-wave or a minor Q-wave with ischemic ST-T changes, or an MI by computerized NOVA-

CODE criteria confirmed by a side-by-side visual comparison of baseline and follow-up ECGs); or (d.) a recorded coronary revascularization procedure.

An incident IS event was defined as a validated definite or probable hospitalized embolic or thrombotic stroke, classified according to symptom type, duration and severity as well as results of neuroimaging and other diagnostic procedures and autopsy evidence, when available.[673,674]

Exposure Assessment

Military service is based on self-report from the LC-SES follow-up interview. Participants who reported that they had served in the military were asked a series of questions detailing military experience, including: (1) age at entry into the service, (2) length of service, and whether they (4) served in a combat zone, (5) were ever under fire or fired at the enemy, (6) saw others wounded or killed or (7) were ever wounded or missing in action.[675] A copy of the LC-SES questionnaire, which contains the military service-related questions (items 37-44), can be found in Appendix B of this proposal. While history of military service was directly queried, exposure to combat was established based on a positive response to one or more of questions 4-7 above. In this way, a three-level exposure variable was derived: no history of military service (non-veterans), history of military service without exposure to combat stress (non-combat veterans) and history of military service with exposure to combat stress (combat veterans). Throughout these analyses, combat veterans and non-combat veterans are treated as two levels of exposure and are compared separately to non-veteran "controls."

Although it would be ideal to ascertain combat exposure concurrent with military service rather than relying on recall, to our knowledge, no cohorts exist that collected combat exposure during military service and which include long-term follow-up with a rigorous measurement of CVD outcomes. Use of recalled measures of combat stress has precedent[676,677,678] and has high validity and reliability.[679] Dr. Glen Elder, a renowned expert on the physiological health effects of military service and combat exposures over the life course,[680,681,682,683] developed the combat exposures questionnaire used in this study.

Assessment of Covariates

Era of Service

Era of military service was determined using information provided during the LC-SES interview on age at entry into the military and duration of service. Those exposed to combat served during the World War II (1941-1945), Korean (1950-1953) and Vietnam (1961-1975) eras. Men who served during multiple conflict eras (e.g., both World War II and the Korean War or both the Korean War and the Vietnam Conflict) were categorized according to their first era of service, as this was their initial military experience. Men who served between periods of defined conflict were not included in a separate category, as they were deemed too heterogeneous to provide results from which meaningful conclusions could be drawn.

For the second manuscript, veterans who served between periods of defined conflict were excluded from analysis. Non-veterans were placed into era of service categories according to the chronological age category into which they fell at Visit 1 (<52, 52-59 and 60+ years). These age categories matched up closely with era of service categories in this

study population, with 94% of World War II era veterans ages 60 years and greater, 89% of Korean War era veterans ages 52-59 years and 91% of Vietnam era veterans under the age of 52 years.

Assessed in both manuscripts were age at induction into service and duration of service in the military, both explicitly queried in the LC-SES interview and both measured in years. Although there is inadequate statistical power to formally address hypotheses about modification by age at entry and duration of service on the association between combat exposure and CVD risk, differences in the distribution of these variables by exposure status were explored in descriptive analysis.

Sociodemographics

Sociodemographic profiles were prepared and compared descriptively for men in the three exposure categories. Sociodemographic information was collected by standardized interviews at the baseline ARIC visit. Variables included in this study were mean age at baseline ARIC visit, race (black *versus* white), education (less than high school *versus* high school or greater), combined family income (less than $25,000 *versus* $25,000 or greater) and occupation (managerial/professional *versus* other occupations) Also included was father's education as a measure of childhood socioeconomic status (less than high school *versus* high school or greater).

Cardiovascular Risk Factors

Differences in the age-adjusted distribution of established biological and behavioral cardiovascular risk factors measured at the baseline assessment (Visit 1; 1987-1989) among

each of the three exposure groups were examined individually. Behavioral risk factors include current smoking status, self-reported pack years of cigarette smoking, alcohol intake (average number of drinks per week) and physical activity (sports activity index ranging from 1 to 5). Current cigarette smoking is defined as self-report of smoking one or more cigarettes per year at baseline (vs. former or never smoker). Pack years were categorized into four levels: heavy (660+), moderate (266-659), light (1-265) or none (0). The sports activity index was further collapsed into three levels of physical activity: inactive (1-1.9), moderate (2-2.9) or active (3-5).

Additional risk factors include overall and central obesity, measured by body mass index (BMI, kg/m^2) and waist circumference (cm), respectively, as well as self-reported health status, which was assessed on a 4-point scale ranging from poor to excellent. In addition, low density lipoprotein (LDL) cholesterol (mg/dL), high density lipoprotein cholesterol (HDL), as well as total cholesterol, triglycerides and systolic blood pressure (SBP, mmHg) were included. Prevalent left ventricular hypertrophy (LVH), prevalent diabetes mellitus, prevalent CHD, and blood pressure medication use were further assessed as covariates. For systolic blood pressure, three seated blood pressure measurements were taken with a random-zero sphygmomanometer, and the last two measurements were averaged. Plasma total cholesterol (mg/dL) and triglycerides were measured using an established enzymatic method,[684] and high density lipoprotein (HDL) cholesterol (mg/dL) was measured after dextran-magnesium precipitation of non-high density lipoproteins.[685] The presence of hypertension was defined as having a SBP of 140 mmHg or higher or a diastolic BP of 90 mmHg or higher or the self-reported use of hypertension-lowering medications in the last two weeks. Self-reported use of cholesterol-reducing medications in the past two

weeks was also assessed. Diabetes was defined as having a fasting glucose level of 126 mg/dL or higher, a non-fasting glucose level of 200 mg/dL or higher, or a self-reported diagnosis of diabetes or use of diabetic medication. Prevalent left ventricular hypertrophy was defined according to the Cornell definition. Coronary heart disease was defined as history of a myocardial infarction (MI), presence of an MI from adjudicated Visit 1 electrocardiographic (ECG) data, or history of heart or arterial surgery, coronary bypass surgery, balloon angioplasty or angioplasty of one or more coronary arteries. More details on the procedures used to obtain the risk factor data as well as the quality assurance procedures are published[686,687] and are detailed at http://www.cscc.unc.edu/aric.

An overall measure of predicted risk, composite CHD and IS risk scores optimized for race-gender groups within the ARIC population were also calculated using the ARIC risk equations for the second manuscript. Methods for calculating these risk scores and the parameter estimates used have been published.[688,689] The use of risk prediction equations has become increasingly common in both research and clinical applications.[690,691,692] Predicted CHD risk scores for men are stratified by race and incorporate baseline values for age in years, total and HDL cholesterol, SBP, prevalent diabetes, current smoking status and blood pressure medication use. Predicted IS risk scores incorporate age, race, current smoking status, SBP, prevalent diabetes, blood pressure medication use, LVH and prevalent CHD.

Statistical Analysis

SAS statistical software Version 8.02 was used for all analyses.[693] Descriptive statistics were calculated for baseline distributions of sociodemographic characteristics and military and combat exposures. Statistical evaluation of differences in risk factor

distributions compared combat veterans and non-combat veterans separately with non-combat "controls" and also contrasted the two veteran groups: combat veterans with non-combat veterans.

Analysis of Prevalent Carotid Intima Media Thickness and Plaque

Linear regression was used to estimate risk differences (RDs) and 95% confidence intervals (CIs) for continuous CIMT, averaged over Visits 1 and 2. Although the distribution of CIMT is right-skewed, a log transformation did not change the back-transformed RD more than 4%. Ordinary least squares regression has been shown to be robust to non-normality of the outcome variable distribution in large samples, and all subgroups in the current analysis are sufficiently large that there would be little benefit to transforming the outcome variable.[694] Modified Poisson regression using PROC GENMOD was used to estimate risk ratios (RRs) and 95% CIs for binary CIMT and plaque variables.[695,696]

Analysis of Incident Coronary Heart Disease and Ischemic Stroke

Incidence rates (IR) were calculated by dividing the number of events by the total time experienced for the participants followed. Incidence rate ratios (IRR) and 95% confidence intervals (CI) were calculated using Poisson regression[697] using PROC GENMOD with the log link and Poisson distribution options. In this way, CHD and stroke event rates were modeled on a logarithmic scale as a function of military and combat exposure status, and residuals followed a Poisson distribution. Combat veterans and non-combat veterans were compared separately with non-combat "controls," and the two veteran groups—combat veterans and non-combat veterans—were also compared with one another.

Assessment of the Role of Age

Because age is not associated with the exposure in these data, it could not be treated as a typical confounder in statistical analyses. However, because it is strongly associated with the outcomes, age at identification of the outcome was accounted for in the following ways. For the first manuscript, continuous CIMT was modeled linearly against age, and these residuals were used in linear regression to estimate RDs and 95% CIs for deviation from the average age-adjusted CIMT. Lack-of-fit tests using PROC RSREG could not be rejected, suggesting the data are appropriately fit by the linear model. For binary CIMT, age-specific cutpoints at the 85th percentile of CIMT at Visits 1, 2 or both were calculated and modeled against the exposure using modified Poisson regression to estimate RRs and 95% CIs. For plaque, the expected probability of having plaque at Visit 1 was calculated from a logistic regression equation modeling plaque against age at Visit 1 and was subtracted from the observed value (0 or 1) to obtain a value that measured the excess percentage of plaque for age at Visit 1. These values were then modeled against the exposure in linear regression to estimate RDs and 95% CIs.

For the second manuscript, results were stratified according to era of service (World War II, the Korean War or the Vietnam Conflict), which had the secondary effect of stratifying by age. Non-veterans were grouped into three age categories (<52, 52-59, 60+ years) that most closely mirrored the age categories of veterans who served during the eras of World War II, the Korean War and the Vietnam Conflict, respectively.

Assessment of Modification by Era of Service

Stratified results for era of service (World War II, the Korean War or the Vietnam Conflict) were presented in both manuscripts to assess potentially important heterogeneity in effects. Interaction by era was assessed using Wald chi-square tests for homogeneity of the effect measures using an *a priori* rejection level of 0.05. Due to generally low power to detect statistical interactions, a relatively stringent Type I error level such as $p<0.05$ yields a screen for interactions that is more specific and less sensitive. Therefore, interaction by race and era of service on the risk ratio and risk difference scales could not be confidently ruled out if $p>0.05$, due to elevated Type II error levels.[698]

Assessment of Modification by Race

Interaction by race (black or white) was also assessed using Wald chi-square tests for homogeneity of the RRs and RDs in the first manuscript using an *a priori* rejection level of 0.05. Although stratification by race was not conducted in the second manuscript, descriptive military, combat and sociodemographic profiles were presented in order to highlight differences by race among the three eras of service investigated.

Sample Size and Statistical Power

PS Software Version 2.1.31, available through Vanderbilt University, was used to calculate power for the proposed study.[699] To simplify presentation, we examples below are limited to a comparison of the combat veteran to the non-combat veteran groups. However, equivalent power is expected for the contrasts of the combat veterans to the non-veterans, as roughly the same number of persons is in each of the comparison groups. Also provided are figures stratified by era of service.

For continuous outcomes we present information on the mean detectable differences (MDD), calculated with a t-test (α=0.05 and β=0.20). (Table 8) Overall, power (1- β) is adequate to detect small differences in levels of predicted risk scores and risk factors. When stratified by era, the minimum detectable differences, though larger, are still modest.

Table 8. Minimal Detectable Differences (MDD) for Continuous Study Outcomes: Contrasting Combat Veteran to Non-combat Veteran Groups.[1]

	Predicted IS Risk Score[1] (0-1)	Predicted CHD Risk Score[1] (0-1)	CIMT (mm)
Mean (SD)[2]	0.03 (0.02)	0.11 (0.10)	0.79 (0.20)
Total [3]	0.01	0.01	0.02
By Era of Service			
World War II	0.02	0.01	0.04
Korean War	0.01	0.01	0.03
Vietnam Conflict	0.02	0.01	0.04

[1] MDD are rounded up to the next largest unit at which the attributes would typically be expressed.
[2] Standard deviations (SD) used in calculations were obtained from data available for men in the ARIC cohort.
[3] The ratio of unexposed to exposed used in the calculation of MDD is as follows: 1.8 total, 0.7 World War II, 1.5 Korean War, 2.1 Vietnam Conflict.

Table 9 below presents power calculations for a range of possible relative risks (RR) for binary outcomes. Calculations are based on chi-square and assume a Type I error probability for a two-sided test (α) of 0.05. For CHD, overall and within era subgroups, power is 0.80 or higher to detect a RR as small as 1.5 for the total population and white men and 1.8 for the World War II and Korean War eras; however, power is insufficient to test hypotheses among black men and men from the Vietnam Conflict era. Due to the low prevalence of IS, power is less than 0.80 to detect a RR of 1.8 or lower overall and within era and race subgroups. Power is adequate (>0.80) to detect differences as small as RR=1.3 for the outcome of carotid plaque both for the total population and within era and race subgroups but inadequate to detect differences even as large as RR=1.8 for the outcome of CIMT > 1mm, even in the total population.

Table 9. Power Calculations for Detecting Differences of Effect Overall and by Era of Service and Race (Binary Outcomes).

Outcome [1]	Probability of Outcome[1]			Power (1-β)													
				NCV vs. NV [2]					CV vs. NV					CV vs. NCV				
				n cases	Ratio of controls to cases	Power to detect RR=…			n cases	Ratio of controls to cases	Power to detect RR=…			n cases	Ratio of controls to cases	Power to detect RR=…		
	NV	NCV	CV			1.3	1.5	1.8			1.3	1.5	1.8			1.3	1.5	1.8
CHD																		
Total	0.2	0.18	0.2	601	0.96	0.70	0.98	>0.99	542	1.73	0.76	0.97	>0.99	483	1.81	0.67	0.97	>0.99
WWII[3]	0.28	0.23	0.21	132	NA	NA	NA	NA	162	NA	NA	NA	NA	174	0.66	0.25	0.55	0.91
Korea	0.18	0.2	0.22	258	NA	NA	NA	NA	211	NA	NA	NA	NA	223	1.66	0.40	0.79	0.99
Vietnam	0.13	0.13	0.11	211	NA	NA	NA	NA	169	NA	NA	NA	NA	86	2.56	0.15	0.31	0.60
Black	0.10	0.09	0.10	88	2.31	0.13	0.25	0.48	79	4.15	0.14	0.27	0.51	41	1.79	0.08	0.13	0.23
White	0.15	0.16	0.16	494	0.76	0.41	0.8	0.99	370	1.37	0.42	0.81	0.99	450	1.81	0.57	0.93	>0.99
IS																		
Total	0.04	0.04	0.05	123	0.96	0.07	0.11	0.19	143	1.73	0.94	0.16	0.29	124	1.81	0.09	0.15	0.27
WWII	0.05	0.06	0.05	30	NA	NA	NA	NA	35	NA	NA	NA	NA	43	0.66	0.05	0.07	0.09
Korea	0.04	0.03	0.06	51	NA	NA	NA	NA	53	NA	NA	NA	NA	46	1.66	0.07	0.08	0.12
Vietnam	0.03	0.02	0.01	42	NA	NA	NA	NA	55	NA	NA	NA	NA	35	2.56	0.07	0.09	0.12
Black	0.07	0.04	0.08	58	2.31	0.09	0.15	0.27	59	4.15	0.11	0.18	0.32	23	1.79	0.06	0.08	0.11
White	0.02	0.03	0.04	77	0.76	0.05	0.06	0.08	65	1.37	0.10	0.08	0.06	94	1.81	0.08	0.11	0.18
Plaque																		
Total	0.45	0.49	0.54	1828	0.96	>0.99	>0.99	>0.99	1453	1.73	>0.99	>0.99	>0.99	1565	1.81	>0.99	>0.99	>0.99
WWII	NA	0.58	0.63	N/A	NA	NA	NA	NA	N/A	NA	NA	NA	NA	450	0.66	>0.99	>0.99	>0.99
Korea	NA	0.53	0.56	N/A	NA	NA	NA	NA	N/A	NA	NA	NA	NA	552	1.66	>0.99	>0.99	>0.99
Vietnam	NA	0.37	0.33	N/A	NA	NA	NA	NA	N/A	NA	NA	NA	NA	238	2.56	0.84	>0.99	>0.99
Black	0.39	0.39	0.40	359	2.31	0.96	>0.99	>0.99	312	4.15	0.96	>0.99	>0.99	171	1.79	0.70	0.99	>0.99
White	0.43	0.47	0.52	1469	0.76	>0.99	>0.99	>0.99	1141	1.37	>0.99	>0.99	>0.99	1394	1.81	>0.99	>0.99	>0.99
CIMT>1mm																		
Total	0.06	0.07	0.12	264	0.96	0.13	0.26	0.51	266	1.73	0.16	0.34	0.64	286	1.81	0.20	0.41	0.74
WWII	NA	0.15	0.17	N/A	NA	NA	NA	NA	N/A	NA	NA	NA	NA	128	0.66	0.13	0.26	0.54
Korea	NA	0.08	0.12	N/A	NA	NA	NA	NA	N/A	NA	NA	NA	NA	103	1.66	0.11	0.20	0.40
Vietnam	NA	0.02	0.02	N/A	NA	NA	NA	NA	N/A	NA	NA	NA	NA	15	2.56	0.07	0.08	0.10
Black	0.05	0.05	0.09	44	2.31	0.08	0.11	0.18	44	4.15	0.09	0.13	0.22	28	1.79	0.07	0.09	0.13
White	0.07	0.07	0.13	220	0.76	0.11	0.22	0.44	222	1.37	0.15	0.30	0.58	258	1.81	0.18	0.38	0.70

[1] Based on prevalence rates among men in the LC-SES cohort; CHD = Coronary heart disease; IS = Ischemic stroke; Plaque = Carotid plaque; CIMT>1mm = Intima Media Thickness of Carotid Artery > 1 millimeter

[2] NV = Non-veteran; NCV = Non-combat veteran; CV = Combat veteran

[3] WWII = World War II

CHAPTER 5

RESULTS

Manuscript 1: Military Combat and Burden of Subclinical Atherosclerosis in Middle Aged Men: the Atherosclerosis Risk in Communities (ARIC) Study

Abstract

Studies of the long-term cardiovascular consequences of combat stress are few and inconclusive. The association between remote exposure to combat and subclinical atherosclerosis was assessed among 5,347 men in the Atherosclerosis Risk in Communities study. Coronary artery plaque and carotid intima-media thickness (CIMT) were compared between non-veterans and veterans with and without one or more self-reported combat exposures. Cardiovascular measurements were taken an average of 36 years after entry into military service. Combat veterans (n=1178) and non-combat veterans (n=2127) tended to be older, white and of higher socioeconomic status than non-veterans (n=2042). Veterans were more likely to be current drinkers and heavy smokers but less likely to be current smokers and physically inactive. Combat veterans had the highest average blood pressure and total cholesterol and were most likely to have coronary disease. Compared to non-veterans, combat veterans (Risk Ratio (RR): 1.19; 95% Confidence Interval (95% CI): 1.11, 1.28) and non-combat veterans (RR: 1.08; 95% CI: 1.01, 1.15) had a higher risk of carotid plaque, and both combat veterans (Risk Difference (RD): 57.2μm; 95% CI: 45.1, 69.2) and non-combat

veterans (RD: 12.48μm; 95% CI: 2.64, 22.32) had higher average CIMT. Compared to non-combat veterans, combat veterans had a higher risk of carotid plaque (RR: 1.11; 95% CI: 1.03, 1.19) and higher average CIMT (RD: 44.68μm; 95% CI: 32.47, 56.89). Differences remained when CIMT was dichotomized and when age was taken into account. Combat exposure may exert long-term adverse effects on the burden of subclinical atherosclerosis.

Introduction

Stress is widely considered to have both psychological and physiological effects and is thought to influence the development of cardiovascular disease (CVD).[1,2,3] A primary mechanism through which stress may increase the risk of CVD is through an inflammatory or atherosclerotic process, involving behavioral, neurological, endocrine, and immunological components.[4,5] Stress experienced by veterans who have engaged in active combat includes both psychological and physical components.[112]

The epidemiologic evidence supports a possible effect on increased cardiovascular risk from exposure to military combat, although the data are limited.[17] Exposure to combat has been associated with higher rates of behavioral problems, [20,112] psychological disorders,[21,22] and self-reported health conditions [23,24] Many studies have investigated the effects of military combat—typically depression or post-traumatic stress disorder (PTSD)—rather than exposure to combat itself. Further, most studies have focused on psychological and short-term health outcomes rather than long-term physiological outcomes. To date, no studies have directly assessed the association between exposure to combat and the prevalence of subclinical atherosclerosis. In this study, we take advantage of a unique opportunity to

investigate this association in a large, community-based sample of men whose military service spanned World War II, the Korean War and the Vietnam Conflict.

Methods

The Atherosclerosis Risk in Communities (ARIC) Study is a prospective, community-based study that was designed to investigate the etiology and natural history of CVD and atherosclerosis. This study has both cohort and surveillance components; the current analyses include only members of the cohort study. At baseline (1987-1989), the cohort included 15,792 African-American and Caucasian men and women between the ages of 45 and 64 years, selected by probability sampling from four US communities: Minneapolis, MN; Washington County, MD; Jackson, MS; and Forsyth County, NC. Participants from MN and MD were Caucasian, while African-American participants were sampled exclusively in MS. The NC center included both African-American and Caucasian participants, with African-Americans being over-sampled to assure a larger sample size. Standardized interviews were conducted at baseline to establish health history and to obtain demographic, socioeconomic and behavioral risk data. Using standard protocols, trained and certified technicians performed physical exams and subclinical CVD procedures and collected fasting blood samples. A detailed account of the design and procedures has been published,[652,653] and the study protocols and information on quality control and assurance can be found on the ARIC website (http://www.cscc.unc.edu/aric). After baseline, there were three triennial examinations, the last of which occurred in 1997-1999. In addition,

approximately 94% of cohort survivors are successfully contacted and interviewed annually to ascertain vital status, health status and hospitalizations.

The Life Course Socioeconomic Status, Social Context and Cardiovascular Disease (LC-SES) Study is an ancillary study to ARIC that was initiated in 2001 to examine the association between SES across the life course and adult cardiovascular conditions. Additional details about its design and procedures are published[654] and are also available at the LC-SES website (http://www.lifecourseepi.info). After an average of fifteen years of follow-up, the ages of cohort participants ranged from 57 to 79 years. During this interview, 12,716 or 81% of the baseline ARIC participants (91% of cohort survivors) were queried about socioeconomic conditions at various life stages, military service and combat exposures.

Female LC-SES Survey participants were excluded from this study, as only 49 reported a history of military service. Also, because their numbers were insufficient for analysis, men with a race other than African-American or Caucasian (n=14) and African-Americans from Washington County or Minneapolis (n=21) were excluded. Further excluded were men who had missing or unknown military service status (n=53), leaving a final study population of 5,347 men.

Military service is based on self-report from the LC-SES follow-up interview. Participants who reported that they had served in the military were asked a series of questions detailing military experience, including: (1) age at entry into the service, (2) length of service, and whether they (4) served in a combat zone, (5) were ever under fire or fired at the enemy, (6) saw others wounded or killed or (7) were ever wounded or missing in action.[675] Era of military service was determined using information provided on age at entry into the military and duration of service. Those exposed to combat served during the World

War II (1941-1945), Korean (1950-1953) and Vietnam (1961-1975) eras. Although it is possible that some veterans had their first exposure to combat in an era later than the first, men who served during multiple conflict eras (e.g., both World War II and the Korean War or both the Korean War and the Vietnam Conflict) were categorized according to their first era of service, as this was their initial—and possibly defining—military experience. Using this method to categorize veterans has precedents in the literature.[22]

A three-level exposure variable was derived: no history of military service (non-veterans), history of military service without exposure to combat stress (non-combat veterans) and history of military service with exposure to combat stress (combat veterans). While history of military service was directly queried, exposure to combat was established based on a positive response to one or more of questions 4-7 above. Throughout these analyses, combat veterans and non-combat veterans are treated as two levels of exposure and are compared separately to non-veteran "controls."

Two measures of subclinical atherosclerosis were included: carotid intima-media thickness (CIMT) and carotid plaque. CIMT is a marker of subclinical atherosclerosis that has been validated by pathology[655] and that accurately predicts future cardiovascular events[656,657,658,659,660] The presence of carotid plaque by B-mode ultrasound measurement is a significant predictor of advanced atherosclerosis,[661] incident CHD[662] and cardiovascular mortality.[663]

At each of the four ARIC visits, using a standardized protocol, B-mode ultrasound measurements were taken to measure CIMT and identify carotid plaque. Measurements were taken bilaterally at three specific 1-cm segments of the carotid artery located within the common carotid, the bifurcation and the internal carotid, for a total of six measurements.

Readers measured the CIMT within these regions, reported whether they observed a plaque and reported whether acoustic shadowing was present. Plaques were defined as the presence of abnormalities in the arterial wall thickness, shape (protrusion into the lumen, rough or misaligned boundary with adjacent arterial wall) or texture (brighter echoes than adjacent wall boundaries).[660] Acoustic shadowing was defined as a dampened amplitude of echoes in the ultrasound. Images were video recorded at each study center, and tapes were read at a central ultrasound reading center. Further information about ultrasound scanning and reading have been published[654,664,665] A participant was categorized as having plaque if plaque with or without acoustic shadowing was found at one or more of the six sites at Visit 1 or Visit 2 *versus* no plaque at either visit.

For the purposes of the analyses presented here, CIMT was defined as the average far wall thickness across the six carotid sites. Adjustment for carotid site-specific reader differences and measurement drift across visits and imputation for missing sites was implemented using maximum likelihood techniques for linear mixed models.[666] Data from the six individual carotid sites were missing at random conditional on age, race, body mass and arterial depth. Methods used for the imputation of missing values use sex and race specific linear models developed for the ARIC Study and are published.[667] Average values from the mean CIMT measurements from Visits 1 and 2 were used in the following analyses in order to ensure consistent scanning technology and comparability with carotid plaque assessment. CIMT was assessed in two ways. First, it was assessed as a continuous measure. Second, it was assessed as a binary measure ($\geq$1 mm *versus* < 1 mm), as this commonly-used cutpoint has been demonstrated reliable.[662]

Differences in the age-adjusted distribution of established biological and behavioral cardiovascular risk factors measured at the baseline assessment (Visit 1; 1987-1989) among each of the three exposure groups were examined individually. Behavioral risk factors include self-reported pack years of cigarette smoking, alcohol intake (average number of drinks per week) and physical activity (sports activity index ranging from 1 to 5). Pack years were categorized into four levels: heavy (660+), moderate (266-659), light (1-265) or none (0). The sports activity index was further collapsed into three levels of physical activity: inactive (1-1.9), moderate (2-2.9) or active (3-5).

Additional risk factors include overall and central obesity, measured by body mass index (BMI, kg/m^2) and waist circumference (cm), respectively, as well as self-reported health status, which was assessed on a 4-point scale ranging from poor to excellent. In addition, low density lipoprotein (LDL) cholesterol (mg/dL), as well as triglycerides and systolic blood pressure (SBP, mmHg) were included. Three seated blood pressure measurements were taken with a random-zero sphygmomanometer, and the last two measurements were averaged. Plasma total cholesterol (mg/dL) was measured using an established enzymatic method,[684] and high density lipoprotein (HDL) cholesterol (mg/dL) was measured after dextran-magnesium precipitation of non-high density lipoproteins.[685] The presence of hypertension was defined as having a SBP of 140 mmHg or higher or a diastolic BP of 90 mmHg or higher or the self-reported use of hypertension-lowering medications in the last two weeks. Self-reported use of cholesterol-reducing medications in the past two weeks was also assessed. Diabetes was defined as having a fasting glucose level of 126 mg/dL or higher, a non-fasting glucose level of 200 mg/dL or higher, or a self-reported diagnosis of diabetes or use of diabetic medication. Coronary heart disease was defined as

history of a myocardial infarction (MI), presence of an MI from adjudicated Visit 1 electrocardiographic (ECG) data, or history of heart or arterial surgery, coronary bypass surgery, balloon angioplasty or angioplasty of one or more coronary arteries. More details on the procedures used to obtain the risk factor data as well as the quality assurance procedures are published.[652,653]

SAS statistical software Version 8.02 was used for all analyses.[693] Descriptive statistics were calculated for baseline distributions of sociodemographic characteristics and military and combat exposures. Statistical evaluation of differences in risk factor distributions compared combat veterans and non-combat veterans separately with non-veteran "controls" and also contrasted the two veteran groups: combat veterans with non-combat veterans. Linear regression was used to estimate risk differences (RDs) and 95% confidence intervals (CIs) for continuous CIMT, averaged over Visits 1 and 2. Although the distribution of CIMT is right-skewed, a log
transformation did not change the back-transformed RD more than 4%. Ordinary least squares regression has been shown to be robust to non-normality of the outcome variable distribution in large samples, and all subgroups in the current analysis are sufficiently large that there would be little benefit to transforming the outcome variable.[694] Modified Poisson regression using PROC GENMOD was used to estimate risk ratios (RRs) and 95% CIs for binary CIMT and plaque variables.[695,696]

Because age is not associated with the exposure in these data, it could not be treated as a typical confounder in statistical analyses. However, because it is strongly associated with the outcomes, age at identification of the outcome was accounted for in the following ways. Continuous CIMT was modeled linearly against age, and these residuals were used in linear

regression to estimate RDs and 95% CIs for deviation from the average age-adjusted CIMT. Lack-of-fit tests using PROC RSREG could not be rejected, suggesting the data are appropriately fit by the linear model. For binary CIMT, age-specific cutpoints at the 85th percentile of CIMT at Visits 1, 2 or both were calculated and modeled against the exposure using modified Poisson regression to estimate RRs and 95% CIs. For plaque, the expected probability of having plaque at Visit 1 was calculated from a logistic regression equation modeling plaque against age at Visit 1 and was subtracted from the observed value (0 or 1) to obtain a value that measured the excess percentage of plaque for age at Visit 1. These values were then modeled against the exposure in linear regression to estimate RDs and 95% CIs.

Stratified results for era of service (World War II, the Korean War or the Vietnam Conflict) and race (black or white) are presented to assess potentially important heterogeneity in effects. Interaction by era and race was assessed using Wald chi-square tests for homogeneity of the risk ratios and risk differences using an *a priori* rejection level of 0.05. Due to generally low power to detect statistical interactions, a relatively stringent Type I error level such as $p<0.05$ yields a screen for interactions that is more specific and less sensitive. Therefore, interaction by race and era of service on the risk ratio and risk difference scales cannot be confidently ruled out if $p>0.05$, due to elevated Type II error levels.[698]

Results

Of the 5,347 men included, 38% reported no military service, 40% reported military service but no combat exposures and 22% reported both military service and exposure to one or more combat experiences. (Table 10) Of those who served in the military, 24% served

during the era of World War II, 33% served during the era of the Korean War, 21% served during the era of the Vietnam Conflict and 22% served between periods of defined conflict. Likelihood of reporting exposure to combat was greatest among World War II era combat veterans (41%) and least among those serving during the Vietnam Conflict (17%). Non-combat veterans were most likely to serve during the Korean War (32%) and least likely to serve during World War II (15%).

Mean age at induction into military service (19-20 years) differed little between combat and non-combat veterans, although induction ages increased slightly in later conflicts (Table 10). The average time elapsed between the time of induction into the service (i.e., the earliest time of exposure) and the date of ARIC Visit 1 (i.e., the time that the first outcomes were measured) differed somewhat between combat and non-combat veterans, with combat veterans having a slightly longer time since entry (mean of 38.2 *versus* 34.3 years), reflecting a population that served disproportionately in earlier conflicts. Combat veterans also tended to serve for longer periods of time compared to non-combat veterans (mean of 4.9 *versus* 3.1 years), and Vietnam era veterans tended to serve in the military for longer periods than other veterans. All four queried combat exposures were most commonly reported by World War II era veterans and least commonly reported by Vietnam era veterans. Service in a formally designated combat zone was the most commonly reported combat exposure (83%), and having ever been wounded or missing during the war was the least reported combat exposure (13%).

Veterans tended to be older, Caucasian and of higher SES compared to non-veterans (Table 11). Combat veterans tended to be slightly older than non-combat veterans or non-veterans, and both combat and non-combat veterans were less likely to be African-American

than non-veterans. Non-combat veterans were least likely to have less than a high school education than combat veterans or non-veterans, although there was little difference among the three groups in the proportion that reported having a father who had less than a high school education. Non-combat veterans were also least likely to have a combined family income below $25,000 or to work in a non-managerial or non-professional occupation.

Combat and non-combat veterans were more likely to be current drinkers and heavy smokers than non-veterans, but less likely to be current smokers and physically inactive (Table 12). Combat veterans and non-veterans were most likely to have prevalent diabetes, and combat veterans were most likely to have prevalent heart disease. The three exposure groups differed little on BMI or waist circumference, but compared to non-combat veterans or non-veterans, combat veterans had higher average SBP, total cholesterol and triglycerides (Table 13). Overall, men that participated in the LCSES survey had slightly more favorable behavioral and physical risk factor profiles at Visit 1 than the larger ARIC cohort from which they were drawn.

Little heterogeneity in the effect of combat by race was noted with the exception of heavy cigarette years of smoking (among blacks, combat veterans were least likely to smoke, while among whites they were most likely to smoke) and prevalent diabetes (among blacks, non-veterans had the highest rates, while among whites, combat veterans had the highest rates) (Table 12). Heterogeneity in effect by era of service was more notable (Tables 3 and 4). In particular, among World War II veterans, those exposed to combat were more likely to be current drinkers and heavy smokers, less likely to be physically inactive and less likely to have prevalent diabetes or CHD compared to non-combat veterans. Among Korean War veterans, combat veterans were more likely to be current and heavy smokers and more likely

to have diabetes or CHD, higher waist circumference, higher SBP and higher triglycerides compared to non-combat veterans. Among veterans of the Vietnam Conflict, those exposed to combat were less likely to be current or heavy smokers but more likely to have diabetes, higher waist circumference and higher triglycerides than non-veterans.

Combat veterans, followed by non-combat veterans, consistently had the least favorable carotid plaque and CIMT profiles (Table 14). Specifically, compared to either non-combat veterans or non-veterans, combat veterans were more likely to have plaque present at Visit 1 or Visit 2 (53.8, 48.5 and 45.1%, respectively). Excess burden of plaque at Visit 1 remained among combat veterans when observed percentages were compared to those expected for men their age. Combat veterans also had greater mean CIMT (802.4, 757.7 and 745.2 μm) and higher observed CIMT than expected for men their age. This finding held true when CIMT was assessed as binary variable: 12.3% of combat veterans had CIMT $\geq$ 1 μm, compared to only 6.7% of non-combat veterans and 6.1% of non-veterans, even when age was taken into account. In race and era stratified analyses these patterns tended to persist, with the exception of Vietnam era veterans, where the finding tended to be attenuated or reversed.

In comparative analysis, both combat and non-combat veterans had significantly less favorable plaque and CIMT profiles than non-veterans, although the relationship was more pronounced for combat veterans (Table 15). Compared to non-veterans, the relative risk of having carotid plaque at Visit 1 or 2 was 1.19 among combat veterans (95% confidence interval (95% CI): 1.11, 1.28) and 1.08 among non-combat veterans (95% CI: 1.01, 1.15). Results from analyses of continuous CIMT were similar: compared to non-veterans, combat veterans had an average of 57.2 μm thicker arterial wall (95% CI: 45.1, 69.2) and non-

combat veterans had an average of 12.5 μm thicker arterial wall (95% CI: 2.6, 22.3). A similar pattern was noted when CIMT was assessed as a binary variable and when age at identification was incorporated.

When combat and non-combat veterans were compared, combat veterans consistently had less favorable plaque and CIMT profiles (Table 14). Combat veterans had 1.11 times the risk of non-combat veterans of having plaque detected at Visit 1or 2 (95% CI: 1.03, 1.19) and an average excess of 10.8 percentage points of plaque compared to other men their age (95% CI: 7.0, 14.7). Combat veterans also had an average of 44.7 μm thicker arterial wall compared to non-combat veterans (95% CI: 32.5, 56.9), and an additional 14.9 μm (95% CI: 2.1, 27.8) CIMT than other men their age, compared to non-veterans. When CIMT was assessed as a binary variable, results were comparable, both unadjusted and using age-specific cutpoints of CIMT.

Interaction by race and era of service on the risk ratio and risk difference scales were found to be non-significant; however, due to low power, interaction could not be ruled out. Overall, findings held true for veterans of the World War II and Korean War eras but were attenuated for those from the Vietnam Conflict era. Results for white men were similar to overall results, while results for black men were weaker or absent.

Table 10: Profile of Recalled Military Service and Combat History Reported by Black and White Male Participants in the LC-SES Interview (2001-2002), by War/Conflict Era.

	Non-Combat Veteran *				Combat Veteran *			
	Total †	World War II	Korean War	Vietnam conflict	Total †	World War II	Korean war	Vietnam conflict
N	**2127**	**314**	**675**	**506**	**1178**	**478**	**407**	**198**
Mean (SD) Age in years at induction into service	19.8 (2.4)	17.9 (0.9)	19.7 (1.9)	21.2 (2.8)	19.1 (2.2)	18.0 (1.0)	19.4 (1.9)	20.9 (3.3)
Mean (SD) Years since inducted into service‡	34.3 (5.9)	43.6 (1.3)	36.6 (2.0)	27.0 (3.0)	38.2 (6.8)	44.5 (1.3)	37.3 (2.0)	26.7 (3.7)
Mean (SD) Years of service	3.1 (3.2)	2.5 (2.2)	3.5 (3.7)	4.0 (4.4)	4.9 (5.6)	4.2 (4.5)	5.2 (6.1)	7.2 (7.2)
n (%) Served overseas	1085 (51.0)	169 (54.2)	384 (56.9)	244 (48.2)	1108 (94.1)	460 (96.4)	392 (96.3)	182 (91.9)
n (%) Served in combat zone	N/A	N/A	N/A	N/A	975 (82.8)	430 (90.0)	339 (83.3)	163 (82.3)
n (%) Under enemy fire or fired at enemy	N/A	N/A	N/A	N/A	700 (59.7)	337 (70.7)	229 (56.8)	110 (55.6)
n (%) Saw wounded or killed during war	N/A	N/A	N/A	N/A	853 (72.7)	357 (74.8)	294 (73.0)	139 (70.2)
n (%) Ever wounded or missing during war	N/A	N/A	N/A	N/A	154 (13.1)	76 (15.9)	57 (14.1)	18 (9.1)

* Combat Veterans are identified by a summary variable based on whether or not the individual served in the military and, if so, whether hel (1) served in a combat zone, (2) was under enemy fire or fired at enemy, (3) saw wounded or killed during war, and/or (4) was ever wounded during war; Non-Combat Veterans are defined as those who served in the military but did not report any combat exposures (1-4).

† The 632 non-combat veterans and 95 combat veterans that served between periods of defined conflict are included in the totals but not as a distinct category in stratified results.

‡ Age at Visit 1 – self-reported age at entry into the military

Table 11: Sociodemographic Profile of Black and White Male Veterans at ARIC Baseline Examination (1987-1989), by Combat History and Era of Service.

	Non-Veteran	Non-Combat Veteran *				Combat Veteran *			
	Total	Total†	World War II	Korean War	Vietnam Conflict	Total†	World War II	Korean War	Vietnam Conflict
	2042	**2127**	**314**	**675**	**506**	**1178**	**478**	**407**	**198**
Mean (SD) Age at Baseline ARIC Visit in years	51.8 (5.2)	54.1 (5.1)	61.5 (1.6)	56.3 (2.4)	48.2 (2.5)	57.3 (5.8)	62.5 (1.5)	56.7 (2.2)	47.6 (2.6)
n (%) African-American	643 (31.5)	278 (13.1)	37 (11.8)	88 (13.0)	75 (14.8)	155 (13.2)	45 (9.4)	60 (14.7)	39 (19.7)
n (%) Education < High School	625 (30.7)	244 (11.5)	77 (24.5)	94 (14.0)	20 (4.0)	209 (17.8)	112 (23.4)	67 (16.5)	8 (4.1)
n (%)Father's Education < High School ‡	1010 (61.0)	1102 (59.4)	178 (63.1)	374 (64.0)	219 (50.9)	634 (61.4)	282 (64.7)	229 (65.4)	79 (48.2)
n (%) Combined Family Income < $25,000	625 (32.5)	368 (18.0)	81 (26.8)	135 (20.6)	63 (12.9)	284 (25.3)	163 (35.8)	74 (19.2)	26 (13.7)
n (%) Occupation Non-Managerial/ Professional	1446 (70.9)	1382 (65.0)	245 (78.0)	446 (66.1)	302 (59.7)	903 (76.7)	412 (86.2)	290 (71.3)	132 (66.7)

Note: columns may not sum to 100% due to rounding

* Combat Veterans are identified by a summary variable based on whether or not the individual served in the military and, if so, whether the individual (1) served in a combat zone, (2) was under enemy fire or fired at enemy, (3) saw wounded or killed during war, and/or (4) was ever wounded during war; Non-Combat Veterans are defined as those who served in the military but did not report any combat exposures (1-4).

† The 632 non-combat veterans and 95 combat veterans that served between periods of defined conflict are included in the totals but not as a distinct category in stratified results.

‡ 804 values missing information on natural father's education

Table 12: Risk Factor Profile of Black and White Men at ARIC Baseline Examination (1987-1989): LC-SES Participants (Overall and by Military/Combat Exposure) and All ARIC Participants, by Race and Era of Service (Binary Variables).

	LCSES men				ARIC men
	Total	**Non-Veteran**	**Non-Combat Veteran ***	**Combat Veteran ***	**Total**
N	**5347**	**2042**	**2127**	**1178**	**7030**
n (%) Current alcoholic drinking †					
Total (n=5347)	3528 (66.0)	1212 (59.7)	1492 (70.3)	824 (70.3)	4526 (64.7)
African-Americans (n=1076)	527 (49.6)	289 (45.7)	144 (52.2)	94 (61.4)	782 (49.5)
Caucasians (n=4271)	3001 (70.5)	923 (66.1)	1348 (73.1)	730 (71.6)	3744 (69.2)
World War II (n=792)	540 (68.5)	N/A	199 (63.6)	341 (71.8)	540 (68.5)
Korean War (n=1082)	727 (67.4)	N/A	455 (67.7)	272 (66.8)	727 (67.4)
Vietnam conflict (n=704)	524 (74.6)	N/A	380 (75.1)	144 (73.5)	524 (74.6)
n (%) Current smoking †					
Total (n=5347)	1261 (23.6)	541 (26.5)	473 (22.3)	247 (21.0)	1952 (27.8)
African-Americans (n=1076)	361 (33.6)	233 (36.2)	82 (29.5)	46 (29.9)	615 (38.4)
Caucasians (n=4271)	900 (21.1)	308 (22.0)	391 (21.2)	201 (19.7)	1337 (24.6)
World War II (n=792)	114 (14.4)	N/A	44 (14.0)	70 (14.6)	114 (14.4)
Korean War (n=1082)	247 (22.9)	N/A	139 (20.6)	108 (26.6)	247 (22.9)
Vietnam conflict (n=704)	180 (25.6)	N/A	136 (26.9)	44 (22.2)	18 (25.6)
n (%) Years of heavy smoking †					
Total (n=5347)	1351 (25.3)	438 (21.9)	545 (25.9)	368 (31.7)	2111 (30.6)
African-Americans (n=1076)	177 (17.07)	104 (16.8)	50 (18.5)	23 (15.7)	355 (23.1)
Caucasians (n=4271)	1174 (27.8)	334 (24.1)	495 (27.0)	345 (34.1)	1756 (32.7)
World War II (n=792)	257 (32.9)	N/A	94 (30.3)	163 (34.6)	257 (32.9)
Korean War (n=1082)	356 (33.3)	N/A	209 (31.2)	147 (36.8)	356 (33.3)
Vietnam conflict (n=704)	126 (18.1)	N/A	94 (18.8)	32 (16.4)	126 (18.1)
n (%) Physically inactive †					
Total (n=5347)	1131 (21.3)	616 (30.4)	843 (39.8)	515 (43.9)	1645 (23.5)
African-Americans (n=1076)	362 (34.0)	217 (34.2)	95 (34.3)	50 (32.7)	588 (37.1)
Caucasians (n=4271)	769 (18.1)	299 (21.5)	307 (16.7)	163 (16.0)	1057 (19.5)
World War II (n=792)	132 (16.7)	N/A	59 (18.9)	73 (15.3)	132 (16.7)
Korean War (n=1082)	226 (21.0)	N/A	142 (21.1)	84 (20.7)	226 (21.0)
Vietnam conflict (n=704)	128 (18.2)	N/A	90 (17.8)	38 (19.3)	128 (18.2)
n (%) Prevalent Diabetes					
Total (n=5347)	503 (9.4)	213 (10.6)	167 (7.9)	123 (10.5)	844 (12.1)
African-Americans (n=1076)	149 (14.2)	99 (15.9)	31 (11.4)	19 (12.5)	291 (18.6)
Caucasians (n=4271)	354 (8.3)	114 (8.2)	136 (7.4)	104 (10.2)	553 (10.2)
World War II (n=792)	96 (12.2)	N/A	40 (12.7)	56 (11.8)	96 (12.2)
Korean War (n=1082)	91 (8.4)	N/A	55 (8.2)	36 (8.9)	91 (8.4)
Vietnam conflict (n=704)	46 (6.6)	N/A	29 (5.8)	17 (8.6)	46 (6.6)
n (%) Prevalent CHD					
Total (n=5347)	311 (5.9)	107 (5.2)	117 (5.5)	94 (8.0)	574 (8.3)
African-Americans (n=1076)	37 (3.50)	20 (3.2)	9 (3.3)	8 (5.2)	93 (5.92)
Caucasians (n=4271)	274 (6.54)	85 (6.2)	105 (5.8)	84 (8.4)	481 (9.05)
World War II (n=792)	81 (10.41)	N/A	36 (11.6)	45 (9.6)	81 (10.41)
Korean War (n=1082)	79 (7.47)	N/A	42 (6.4)	37 (9.3)	79 (7.47)
Vietnam conflict (n=704)	16 (2.31)	N/A	12 (2.4)	4 (2.0)	16 (2.31)

Because of missing data, N differs for some variables.

Some columns may not sum to 100% due to rounding.

* Combat Veterans are identified by a summary variable based on whether or not the individual served in the military and, if so, whether the individual (1) served in a combat zone, (2) was under enemy fire or fired at enemy, (3) saw wounded or killed during war, and/or (4) was ever wounded during war; Non-Combat Veterans are defined as those who served in the military but did not report any combat exposures (1-4).

† Current alcohol drinking is defined as self-report of drinking any alcohol at baseline; Current cigarette smoking is defined as self-report of smoking one or more cigarettes per year at baseline; Heavy cigarette years of smoking is calculated by multiplying the number of cigarettes smoked per year by the number of years the individual has been smoking and is defined as having smoked 660 or more cigarettes; Physical inactivity is defined as having a sports activity index score less than 2.0.

Table 13: Risk Factor Profile of Black and White Men at ARIC Baseline Examination (1987-1989): LC-SES Participants (Overall and by Military/Combat Exposure) and All ARIC Participants, by Race and Era of Service (continuous variables).

	LCSES men				ARIC men
	Total	Non-Veteran	Non-Combat Veteran *	Combat Veteran *	Total
N	**5347**	**2042**	**2127**	**1178**	**7030**
Mean (SD) BMI (m/kg^2)					
Total (n=5347)	27.5 (4.1)	27.8 (4.4)	27.2 (3.8)	27.7 (4.0)	27.5 (4.2)
African-Americans (n=1076)	27.9 (4.7)	27.9 (4.6)	27.9 (4.9)	27.8 (4.7)	27.6 (4.9)
Caucasians (n=4271)	27.4 (3.9)	27.7 (4.3)	27.0 (3.6)	27.7 (3.8)	27.5 (4.0)
World War II (n=792)	27.3 (3.7)	N/A	27.4 (3.9)	27.3 (3.6)	27.3 (3.7)
Korean War (n=1082)	27.4 (4.0)	N/A	27.1 (3.8)	27.9 (4.2)	27.4 (4.0)
Vietnam conflict (n=704)	27.2 (4.0)	N/A	27.0 (3.9)	27.9 (4.1)	27.2 (4.0)
Mean (SD) Waist circumference (cm)					
Total (n=5347)	98.9 (10.7)	99.1 (11.6)	98.4 (10.0)	99.6 (10.3)	99.1 (11.1)
African-Americans (n=1076)	97.0 (12.3)	97.0 (12.3)	97.2 (12.2)	96.9 (12.1)	97.0 (12.9)
Caucasians (n=4271)	99.4 (10.3)	100.0 (11.2)	98.6 (9.6)	100.0 (9.9)	99.7 (10.5)
World War II (n=792)	99.4 (9.6)	N/A	99.7 (9.9)	99.3 (9.5)	99.4 (9.6)
Korean War (n=1082)	99.1 (10.2)	N/A	98.7 (9.9)	99.7 (10.6)	99.1 (10.2)
Vietnam conflict (n=704)	97.8 (10.5)	N/A	97.1 (10.3)	99.4 (10.8)	97.8 (10.5)
Mean (SD) Systolic BP (mmHg)					
Total (n=5347)	121.2 (16.9)	121.8 (17.6)	119.9 (16.3)	122.5 (16.7)	122.6 (18.1)
African-Americans (n=1076)	128.3 (19.9)	128.2 (20.2)	127.6 (19.5)	130.2 (19.2)	130.5 (21.7)
Caucasians (n=4271)	119.4 (15.6)	118.8 (15.4)	118.8 (15.4)	121.4 (16.0)	120.2 (16.2)
World War II (n=792)	125.6 (18.0)	N/A	125.7 (18.9)	125.6 (17.3)	125.6 (18.0)
Korean War (n=1082)	121.4 (16.2)	N/A	120.8 (16.3)	122.5 (16.0)	121.4 (16.2)
Vietnam conflict (n=704)	116.2 (14.6)	N/A	116.1 (14.6)	116.6 (14.5)	116.2 (14.6)
Mean (SD) Total cholesterol (mg/dL)					
Total (n=5347)	210.9 (39.2)	209.7 (39.8)	210.7 (37.9)	213.5 (40.4)	211.1 (40.0)
African-Americans (n=1076)	212.7 (43.3)	211.9 (43.3)	213.6 (41.9)	214.6 (45.4)	210.9 (44.1)
Caucasians (n=4271)	210.5 (38.2)	208.7 (38.1)	210.2 (37.2)	213.4 (39.6)	211.1 (38.7)
World War II (n=792)	213.4 (38.0)	N/A	212.0 (37.9)	214.3 (38.0)	213.4 (38.0)
Korean War (n=1082)	213.3 (39.3)	N/A	212.5 (37.3)	214.6 (42.6)	213.3 (39.3)
Vietnam conflict (n=704)	206.4 (39.6)	N/A	205.9 (39.0)	207.7 (41.0)	206.4 (39.6)
Mean (SD) LDL cholesterol (mg/dL)					
Total (n=5347)	139.6 (36.5)	138.3 (37.3)	139.6 (35.4)	141.9 (37.0)	139.4 (37.3)
African-Americans (n=1076)	140.0 (41.3)	138.7 (41.3)	141.2 (41.0)	142.7 (41.9)	137.4 (42.1)
Caucasians (n=4271)	139.5 (35.2)	138.0 (35.4)	139.4 (34.4)	141.7 (36.3)	140.0 (35.7)
World War II (n=792)	141.2 (35.1)	N/A	139.8 (35.0)	142.0 (35.1)	141.2 (35.1)
Korean War (n=1082)	142.2 (36.7)	N/A	141.5 (35.3)	143.4 (38.8)	142.2 (36.7)
Vietnam conflict (n=704)	135.4 (36.2)	N/A	134.9 (36.0)	136.5 (37.0)	135.4 (36.2)
Mean (SD) HDL cholesterol (mg/dL)					
Total (n=5347)	44.3 (13.2)	44.8 (13.5)	44.2 (13.2)	43.7 (12.8)	44.4 (13.9)
African-Americans (n=1076)	49.9 (15.5)	50.4 (15.9)	49.2 (14.9)	49.1 (15.2)	50.4 (16.9)
Caucasians (n=4271)	43.0 (12.2)	42.4 (11.5)	43.4 (12.8)	42.9 (12.2)	42.6 (12.4)
World War II (n=792)	44.3 (13.0)	N/A	44.7 (14.1)	44.1 (12.2)	44.3 (13.0)
Korean War (n=1082)	43.7 (13.0)	N/A	43.9 (12.8)	43.3 (13.2)	43.7 (13.0)
Vietnam conflict (n=704)	43.8 (13.0)	N/A	43.9 (13.0)	43.6 (13.1)	43.8 (13.0)
Mean (SD) Triglycerides (mg/dL)					
Total (n=5347)	140.8 (95.9)	137.0 (84.8)	140.3 (96.9)	148.1 (110.7)	142.1 (99.1)
African-Americans (n=1076)	118.0 (75.3)	117.1 (73.2)	115.7 (61.0)	125.7 (102.1)	120.1 (94.0)
Caucasians (n=4271)	146.3 (99.5)	145.8 (88.1)	143.9 (100.6)	151.4 (111.6)	148.3 (99.7)
World War II (n=792)	142.4 (80.0)	N/A	142.5 (92.0)	142.3 (71.1)	142.4 (80.0)
Korean War (n=1082)	143.6 (97.5)	N/A	139.3 (88.8)	150.8 (110.1)	143.6 (97.5)
Vietnam conflict (n=704)	146.9 (125.4)	N/A	141.7 (95.6)	160.2 (180.1)	146.9 (125.4)

Because of missing data, N differs for some variables.

* Combat Veterans are identified by a summary variable based on whether or not the individual served in the military and, if so, whether the individual (1) served in a combat zone, (2) was under enemy fire or fired at enemy, (3) saw wounded or killed during war, and/or (4) was ever wounded during war; Non-Combat Veterans are defined as those who served in the military but did not report any combat exposures (1-4).

Table 14: Observed Carotid Plaque and Carotid Intima-Media Thickness (CIMT), by Military Service and Combat History: Means (Standard Deviations) and Frequencies (Percentages).

	Non-Veteran	Non-Combat Veteran *	Combat Veteran *
N	**2042**	**2127**	**1178**
BINARY PLAQUE			
n (%) Plaque			
Total (n=5347)	858 (45.09)	970 (48.48)	595 (53.75)
African-Americans (n=1076)	250 (44.01)	109 (44.13)	62 (43.97)
Caucasians (n=4271)	608 (45.54)	861 (49.09)	533 (55.18)
World War II (n=792)	N/A	169 (58.08)	281 (62.86)
Korean War (n=1082)	N/A	340 (52.88)	212 (55.50)
Vietnam conflict (n=704)	N/A	177 (37.26)	61 (32.97)
Mean (SD) Excess % of plaque for age			
Total (n=5347)	-10.31 (52.29)	-2.84 (52.06)	7.97 (53.06)
African-Americans (n=1076)	-11.79 (51.91)	-7.16 (51.94)	-3.82 (53.08)
Caucasians (n=4271)	-9.69 (52.45)	-2.24 (52.06)	9.69 (52.87)
World War II (n=792)	N/A	19.59 (49.48)	26.14 (48.53)
Korean War (n=1082)	N/A	5.40 (50.20)	8.63 (50.26)
Vietnam conflict (n=704)	N/A	-24.30 (48.98)	-29.73 (47.77)
BINARY CIMT †			
n (%)CIMT ≥ 1 (µm)			
Total (n=5347)	122 (6.08)	142 (6.74)	144 (12.33)
African-Americans (n=1076)	30 (4.88)	14 (5.20)	14 (9.33)
Caucasians (n=4271)	92 (6.62)	128 (6.96)	130 (12.77)
World War II (n=792)	N/A	47 (15.06)	81 (17.02)
Korean War (n=1082)	N/A	53 (7.91)	50 (12.44)
Vietnam conflict (n=704)	N/A	11 (2.20)	4 (2.04)
n (%) Age-specific CIMT >85th percentile (µm) ‡			
Total (n=5347)	307 (15.03)	289 (13.59)	196 (16.64)
African-Americans (n=1076)	19 (12.26)	30 (10.79)	93 (14.46)
Caucasians (n=4271)	214 (15.30)	259 (14.01)	177 (17.30)
World War II (n=792)	N/A	46 (5.81)	80 (10.10)
Korean War (n=1082)	N/A	88 (13.04)	74 (18.18)
Vietnam conflict (n=704)	N/A	69 (13.64)	26 (13.13)
CONTINUOUS CIMT (µm) *			
Mean (SD) Average CIMT (µm)			
Total (n=5347)	745.2 (157.7)	757.7 (164.1)	802.4 (182.2)
African-Americans (n=1076)	745.7 (145.2)	742.9 (157.3)	774.9 (166.3)
Caucasians (n=4271)	745.0 (163.0)	749.6 (165.1)	806.5 (184.1)
World War II (n=792)	N/A	826.3 (202.4)	853.6 (192.1)
Korean War (n=1082)	N/A	779.7 (164.5)	799.2 (180.2)
Vietnam conflict (n=704)	N/A	701.0 (124.6)	698.9 (114.9)
Mean (SD) deviation from age-adjusted CIMT (µm)			
Total (n=5347)	2.74 (156.89)	-6.96 (165.02)	7.97 (189.81)
African-Americans (n=1076)	1.99 (145.43)	-0.90 (158.21)	-6.60 (157.58)
Caucasians (n=4271)	3.06 (161.68)	-7.81 (165.98)	10.11 (194.08)
World War II (n=792)	N/A	-12.70 (196.95)	3.67 (203.61)
Korean War (n=1082)	N/A	-7.53 (178.81)	13.51 (206.64)
Vietnam conflict (n=704)	N/A	-5.89 (130.27)	6.55 (125.28)

Because of missing data, N differs in some variables.

* Combat Veterans are identified by a summary variable based on whether or not the individual served in the military and, if so, whether the individual (1) served in a combat zone, (2) was under enemy fire or fired at enemy, (3) saw wounded or killed during war, and/or (4) was ever wounded during war; Non-Combat Veterans are defined as those who served in the military but did not report any combat exposures (1-4).

† Average far wall imputed CIMT over ARIC Visits 1 and 2

‡ Average far wall imputed CIMT over ARIC Visits 1 and 2; 85th percentile of CIMT for all African-American or Caucasian male ARIC participants; four separate age and race-specific 85th percentile cutpoints were used: Black men ages 45-54, Black men ages 55-65, White men ages 45-54 and White men ages 55-65.

Table 15: Observed Carotid Plaque and Carotid Intima-Media Thickness (CIMT), by Military Service and Combat History. Risk Ratios (RR) or Risk Differences (RD).

	Non-Combat Veteran vs. Non-Veteran*	Combat Veteran vs. Non-Veteran*	Combat Veteran vs. Non-Combat Veteran*
BINARY PLAQUE			
Plaque (RR (95% CI))			
Total (n=5347)	1.08 (1.01, 1.15)	1.19 (1.11, 1.28)	1.11 (1.03, 1.19)
African-Americans (n=1076)	1.00 (0.85, 1.19)	1.00 (0.81, 1.23)	1.00 (0.79, 1.26)
Caucasians (n=4271)	1.08 (1.00, 1.16)	1.21 (1.12, 1.31)	1.12 (1.04, 1.21)
World War II (n=792)	N/A	N/A	1.08 (0.96, 1.22)
Korean War (n=1082)	N/A	N/A	1.05 (0.93, 1.18)
Vietnam conflict (n=704)	N/A	N/A	0.88 (0.70, 1.12)
Excess % of plaque for age (RD (95% CI)) †			
Total (n=5347)	7.47 (4.18, 10.76)	18.28 (14.40, 22.16)	10.81 (6.96, 14.66)
African-Americans (n=1076)	4.63 (-3.15, 12.42)	7.97 (-1.63, 17.58)	3.34 (-7.49, 14.17)
Caucasians (n=4271)	7.45 (3.72, 11.18)	19.37 (15.03, 23.71)	11.92 (7.81, 16.03)
World War II (n=792)	N/A	N/A	6.55 (-0.67, 13.77)
Korean War (n=1082)	N/A	N/A	3.23 (-3.13, 9.59)
Vietnam conflict (n=704)	N/A	N/A	-5.43 (-13.70, 2.83)
BINARY CIMT			
CIMT ≥ 1 mm (RR (95% CI)) †			
Total (n=5347)	1.11 (0.88, 1.40)	2.03 (1.61, 2.55)	1.83 (1.47, 2.28)
African-Americans (n=1076)	1.07 (0.58, 1.98)	1.91 (1.04, 3.52)	1.79 (0.88, 3.66)
Caucasians (n=4271)	1.05 (0.81, 1.36)	1.93 (1.50, 2.49)	1.83 (1.46, 2.31)
World War II (n=792)	N/A	N/A	1.13 (0.81, 1.57)
Korean War (n=1082)	N/A	N/A	1.57 (1.09, 2.27)
Vietnam conflict (n=704)	N/A	N/A	0.93 (0.30, 2.88)
Age-specific CIMT >85thpercentile (RR (95% CI)) ‡			
Total (n=5347)	0.90 (0.78, 1.05)	1.11 (0.94, 1.30)	1.22 (1.04, 1.45)
African-Americans (n=1076)	0.75 (0.51, 1.10)	0.85 (0.53, 1.34)	1.14 (0.66, 1.95)
Caucasians (n=4271)	0.92 (0.77, 1.08)	1.13 (0.94, 1.36)	1.24 (1.04, 1.47)
World War II (n=792)	N/A	N/A	1.14 (0.82, 1.59)
Korean War (n=1082)	N/A	N/A	1.39 (1.05, 1.85)
Vietnam conflict (n=704)	N/A	N/A	0.96 (0.63, 1.47)
CONTINUOUS CIMT (µm)			
Mean CIMT in µm (RD (95% CI)) †			
Total (n=5347)	12.48 (2.64, 22.32)	57.16 (45.11, 69.21)	44.68 (32.47, 56.89)
African-Americans (n=1076)	16.03 (-5.31, 37.37)	29.15 (2.45, 55.85)	13.12 (-18.95, 45.19)
Caucasians (n=4271)	12.10 (0.65, 23.55)	61.43 (47.51, 75.35)	49.33 (36.16, 62.50)
World War II (n=792)	N/A	N/A	27.27 (-0.74, 55.28)
Korean War (n=1082)	N/A	N/A	19.51 (-1.58, 40.60)
Vietnam conflict (n=704)	N/A	N/A	-2.07 (-22.22, 18.08)
Deviation from age-adjusted CIMT in µm (RD (95% CI)) *			
Total (n=5347)	-9.69 (-20.23, 0.85)	5.23 (-7.26, 17.72)	14.92 (2.06, 27.78)
African-Americans (n=1076)	-2.89 (-25.33, 19.55)	-8.59 (-36.40, 19.22)	-5.70 (-38.45, 27.05)
Caucasians (n=4271)	-10.87 (-23.12, 1.38)	7.05 (-7.26, 21.36)	17.92 (4.00, 31.84)
World War II (n=792)	N/A	N/A	16.37 (-13.13, 45.87)
Korean War (n=1082)	N/A	N/A	21.04 (-3.36, 45.44)
Vietnam conflict (n=704)	N/A	N/A	12.43 (-9.35, 34.21)

Because of missing data, N differs in some variables.

* Combat Veterans are identified by a summary variable based on whether or not the individual served in the military and, if so, whether he (1) served in a combat zone, (2) was under enemy fire or fired at enemy, (3) saw wounded or killed during war, and/or (4) was ever wounded during war; Non-Combat Veterans reported military service but no combat exposures (1-4).

† Average far wall imputed CIMT over ARIC Visits 1 and 2

‡ Average far wall imputed CIMT over ARIC Visits 1 and 2; 85th percentile of CIMT for all African-American or Caucasian male ARIC participants; four separate age and race-specific 85th percentile cutpoints were used: Black men ages 45-54, Black men ages 55-65, White men ages 45-54 and White men ages 55-65.

Discussion

Men with distant military service, particularly when it included combat exposure, are more likely to have carotid plaque and increased CIMT than their non-veteran counterparts. These effects remain after age and race are taken into account. No prior studies have assessed the relationship between military or combat exposure and clinical or subclinical atherosclerosis. However, our findings are consistent with earlier studies that reported that combat veterans with post-traumatic stress disorder (PTSD) were more likely to have increased chronic cardiovascular arousal,[700] higher circulating catecholamines and other neuroendocrine agents implicated in arterial damage and a higher frequency of abnormal ECG readings.[151] In contrast to most previous studies, the current study investigated the effects of combat, rather than the clinically-defined chronic stress reaction (CSR) or PTSD diagnosis and incorporates both non-combat veteran and non-veteran "control" groups.

One possible explanation for our findings of higher rates of subclinical atherosclerosis in combat veterans is that the extreme trauma experienced set into motion a chronic stress response and a resultant inflammatory, atherosclerotic process that initiated the formation of plaque and the thickening of the arterial wall. Although the link between psychosocial stress and coronary events is well-established, [1,2,3] the mechanisms underlying these associations are not well understood. Specifically, the association between psychosocial stress and with subclinical atherosclerosis is not yet clear.[701] However, this theory is supported by findings in the ARIC study: lower SES, both early in life and cumulatively across the life course, is associated with elevated levels of inflammatory markers such as C-reactive protein, fibrinogen, white blood cell count and von Willebrand factor later in life.[702,703] Similarly, a small study of Croatian combat veterans with PTSD found that combat

veterans had higher lymphocyte counts than civilian controls, suggesting that the immune system was affected in the course of chronic PTSD.[704]

Both combat and non-combat veterans were more likely to be current drinkers and heavy smokers than non-veterans but less likely to be current smokers and physically inactive. Other studies have found that although men and women are selectively accepted into the military based on their good physical health, they tend to have higher alcohol and tobacco usage rates after participation in the military compared to the general population.[705,706,707] Given the strong link between smoking and atherosclerosis, smoking may be acting as a mediator in the effects found in this study. However, studies of veterans with and without combat-related PTSD have found that the association between PTSD and poor physical health persists even after controlling for smoking and alcohol consumption,[407,708] suggesting a more direct link between traumatic stress and subclinical disease or a role of psychological factors as mediators.

Psychological conditions such as CSR and PTSD have been associated with an increased burden of cardiovascular morbidity and mortality.[182,709] While it would have been of interest to provide results stratified on CSR or PTSD status, this information was not queried in the LC-SES interview. Psychological status would have been assessed as a potential effect measure modifier rather than as a confounder; consequently its exclusion does not detract from our findings. Our results support the conclusion that the effects of combat exposure extend beyond the narrow scope of these clinical diagnoses.[.594,700,710]

The association between combat-related stress and subclinical atherosclerosis may also differ by current and past social, educational and economic environments and opportunities. Inverse associations between SES and CVD as well as mortality from other

health related outcomes have been demonstrated repeatedly[511,512] and may work through a number of mechanisms. Lower individual SES is associated with increased risk of smoking, less healthy diet, increased obesity, and reduced physical activity[523,524] as well as lower self-reported social mobility, increased financial strain and more stressful life events.[709] SES may differentially affect how an individual responds psychologically and physically to other meaningful life events and stressors such as exposure to combat, both psychologically and physically, with higher SES providing protection.[22,567] In the current study, while non-combat veterans consistently have the most favorable SES profiles overall, combat veterans have more favorable levels of education and family income but less favorable early life SES (i.e., father's education and occupation) than did non-veterans. These differences may reflect the different age distributions in each exposure group, as the socioeconomic position of veterans has increased over time.[582] Alternatively, it may reflect the economic and educational opportunities such as the Montgomery GI Bill that have enabled veterans to keep pace with, though not exceed, non-veterans in terms of educational attainment.[647,572]

Because the combat exposure variables are based on self-report, recall bias may also affect results, such that men in worse health may differentially recall their military experiences. Although our outcome was subclinical disease, the status of which was likely unknown to participants at the time, combat veterans were more likely to have other known indicators of poor health such as hypertension, high cholesterol and CHD. Use of recalled combat exposures has precedent[676,677,678] and has high validity and reliability;[679] thus it is unlikely that differential recollection of past military experiences based on current health status was significant.

Age is a potent predictor of subclinical atherosclerosis; however, because age was not associated with the exposure in this study population, as evidenced by the similarities in the age at induction into the military, it could not be treated as a confounder in analysis. Still, participants' mean age at the time when CIMT and carotid plaque were measured differed sufficiently among the three exposure groups – with combat veterans averaging three years older than non-combat veterans and five years older than non-veterans – to raise the potential concern that age may be affecting results. Therefore, age was taken into consideration by assessing age and race-specific percentiles of carotid intima-media thickness. Although this data-driven method not ideal, it is a meaningful way of reflecting the age-dependent slope of vasculature. Even after using this method to consider age and race, combat veterans still had the highest risk of having carotid plaque and thickened carotid arterial walls.

The distribution of veterans by era of conflict differed substantially between combat and non-combat veterans. Combat veterans were more likely to serve during World War II and least likely to serve during the Vietnam Conflict, while non-combat veterans were most likely to serve during the Korean War and least likely to serve during World War II. Profiles of veterans from each era of service differ on factors such as age at entry, race, SES, type, duration and intensity of combat experienced and the sociopolitical atmosphere surrounding the conflict. Our results suggest heterogeneity in the effect of combat by era of service. In contrast to the higher prevalence of carotid plaque and thickened arterial walls among combat veterans compared to non-combat veterans of the World War II and Korean War eras, associations were weaker or even reversed among those who served during the era of the Vietnam Conflict.

The type and nature of combat experienced during each of these conflicts, as well as the social and political context surrounding them, differed.[585] Reports suggest that Vietnam veterans were subjected to unusually high levels of "barbarity and moral ambiguity" as well as chronic exposure to unpredictable and dangerous warfare environments, and were more likely to have witnessed abusive violence or killings compared to veterans of World War II and the Korean War.[711,712] Further, Vietnam veterans returned home to a social and political environment that was unsupportive of the US involvement in the conflict.[588] In contrast, World War II was a war with a clearly identified enemy, and returning soldiers had the overwhelming support of the American public.[595] Like World War II, the Korean War was fought by defined armies for territory; however, soldiers lost support from the American public over the course of the war. The manner in which soldiers were received at homecoming has been found to have a significant effect on the risk of developing PTSD and other psychiatric symptoms later in life.[596] The confluence of divergent factors such as the clarity of identification of the enemy, involvement of civilians in combat, transparency of the purported goals of the war, and level of public support could explain the different associations between combat-related stress and health among men from different eras. Given the particularly brutal nature of combat experienced during the Vietnam Conflict,[677] we might expect the effects of combat to be most pronounced among these veterans. Conversely, the negative sociopolitical atmosphere surrounding the Vietnam Conflict may have acted as a stressor among both combat and non-combat soldiers upon homecoming, attenuating differences.

The different demographic profile of the Vietnam Conflict cohort may also have contributed to differences in the effect of combat in this study. Members of this cohort tended

to be inducted into the military at a slightly older age and served for a longer period of time compared to those who served during the World War II or Korean War eras. They also tended to be of higher socioeconomic position, which, according to current theory, tends to be protective against the effects of traumatic stress.[22,511] Both older average age at induction and higher average SES among men in this cohort may be a reflection of secular trends in education or in the ability of affluent Vietnam draftees to postpone induction by enrolling in school and obtaining educational deferment.[713] Finally, the younger age at which Vietnam Conflict era veterans' outcomes were assessed in this study – an average of ten years younger than non-combat veterans and seventeen years younger than non-veterans – also may have contributed to the apparently weaker effect of combat exposure among these participants.

Heterogeneous behavioral and physical risk factor profiles among veterans by era may also have contributed to differences in effect by era of service. In line with results of a higher prevalence of carotid plaque and thickened arterial walls among combat veterans among World War II and Korean War era veterans but not Vietnam Conflict era veterans, results showed combat exposure was associated with higher rates of heavy lifetime smoking among World War II and Korean War era veterans, but not among Vietnam Conflict era veterans. However, combat exposure was associated with higher rates of diabetes, higher waist circumference and higher triglycerides only among veterans of the Korean War and Vietnam Conflict. Higher SBP and higher rates of CHD were found only among combat veterans who served during the era of the Korean War.

The effects of combat on subclinical atherosclerosis vary by race, consistent with other studies that have found that the composition and morphology of atherosclerotic plaque vary by ethnic and racial groups.[714,715] Whites tend to have plaque in larger arteries such as

the coronary arteries investigated in the present study, blacks typically develop plaques in smaller and more distal arteries.[716] Our results were in line with these findings, with a higher proportion of white men showing carotid plaque and a higher average carotid intima-media thickness measured at Visits 1 or 2 compared to black men, in each of the three exposure groups. These racial differences are consistent with our findings that the effect of combat on carotid plaque or CIMT was limited to white men. Combat-related effects noted in white but not black men may also be related to differences in baseline risk factor profiles. Most notably, white but not black combat veterans were most likely to be heavy smokers, a major risk factor for the development of subclinical atherosclerosis. Alternatively, the low sample size of black men may have masked an effect.

This study provided a rare opportunity to investigate the long-term association of combat exposure on levels of atherosclerosis and cardiovascular risk in a large community-based cohort. Average follow-up time was long and participants were of an age (60 to 80 years) where CHD is most likely manifest. Among veterans, periods of military service spanned from World War II through the Vietnam Conflict and includes measures of specific combat exposures and both military and civilian controls. Most previous studies have been based on retrospective cohorts and have investigated differences in CVD mortality comparing war theater veterans and non-theater veterans of the same era. Also a particular strength, this study included objective, standardized measures of cardiovascular outcomes. The wide range of physical and behavioral risk factor measures also allowed for a more extensive examination of the intermediate mechanisms through which the combat-subclinical atherosclerosis association potentially works. The availability of socioeconomic measures

from various life epochs further offered an unusual opportunity to investigate the role of SES in combat-cardiovascular associations.

As previously discussed, the use of self-reported combat exposures presents challenges. Although recalled exposure status is not ideal, to our knowledge, no cohorts exist that collected combat exposure during military service and included long-term follow-up with a rigorous measurement of cardiovascular outcomes. Further, defining combat as the exposure to one or more specific combat experiences can be viewed as a strength, as it is a more specific and meaningful definition than simply separating exposure groups into theater and non-theater veterans who served during the same era.

Combat exposure was not assessed until 12-14 years after baseline, at which time 17% of male baseline participants had expired. Thus, it is possible that selective survival may have biased our findings. We took two steps to address this concern. First, we conducted a pilot study on a subset of decedents from North Carolina for whom veteran status was recorded on death certificates. Briefly, we found a small (2%) but not statistically significant excess mortality among veterans, even after adjustment for age, race and education. Second, we conducted a sensitivity analysis to estimate the extent to which differential survival, if extant, may have influenced observed results by comparing observed RRs with those corrected for selection bias.[718] We applied the adjusted mortality rates obtained from the pilot study to hypothetical data with incident CHD as the outcome. Assuming that those who eventually had a CHD event were 1.5 times more likely to die before providing data on military history than those who did not go on to develop CHD, our odds ratio was underestimated by only 1.5%. Even under a more extreme scenario – where the difference in mortality was assumed to be higher than what we found in the pilot study (e.g., 14% for non-

veterans and 18% for veterans – a 29% difference in mortality) and assuming those who eventually go on to develop CHD were two times more likely to die prior to providing their military history – our observed effect estimate would still only differ from the corrected estimate by 7%. These results are reassuring as they suggest that both the potential magnitude of survivorship bias, if extant, would have been small in these data.

Finally, although this study includes a large population of men, it does not have adequate statistical power to formally address hypotheses about potential effect measure modification. In addition to era of service and race, of particular interest would be to see if there is interaction by age at entry, duration of service, psychological status and type of combat exposure.

Older male participants of the ARIC Study with a history of distant military and combat exposure had a higher burden of subclinical atherosclerosis than those not reporting military service. Thus, combat exposure may exert long-term adverse effects on subclinical atherosclerosis. A challenge for future studies is to elucidate the possible mechanisms through which stress can place an individual at long-term risk for atherosclerosis and CHD. With a focus on finding pathways for prevention, subsequent studies should assess whether psychosocial stress acts through mediational biological processes such as inflammatory markers as well as through psychological, behavioral or lifestyle changes. In addition, studies with larger sample sizes could better evaluate the potential role of service era, race, SES and other important modifiers of the association between combat and cardiovascular risk can be clarified. Ideally, studies should be population-based, so as to include both veteran and non-veteran controls. The findings in this study, if confirmed, have implications for our understanding of the lasting effects of traumatic stress on long-term cardiovascular health.

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Manuscript 2: Military Combat and Risk of Coronary Heart Disease and Ischemic Stroke in Aging Men: the Atherosclerosis Risk in Communities (ARIC) Study

Abstract

Studies of the long-term cardiovascular consequences of combat stress are few and inconclusive. The association between remote exposure to military combat and the risk of cardiovascular disease was assessed among 4,620 men in the Atherosclerosis Risk in Communities study. Predicted and observed risk of coronary heart disease (CHD) and ischemic stroke (IS), as well as key risk factors were compared between non-veterans and veterans with and without one or more self-reported combat exposures. Outcomes were assessed an average of 36 years after entry into military service during the eras of World War II, the Korean War and the Vietnam conflict. Veterans tended to be older, white and of higher socioeconomic status than non-veterans. Veterans were less likely to be current smokers than non-veterans. Combat veterans had higher average systolic blood pressure, lower average high density lipoprotein cholesterol and were more likely to be on hypertension medications and have prevalent CHD than either non-veterans or non-combat veterans. Combat veterans had higher CHD and IS incidence rates than non-combat veterans or non-veterans of the Korean War era; however, they had lower incidence rates than either comparison group for cohort members of World War II and the Vietnam Conflict eras. Incidence rate ratios (IRR) were statistically significant only in comparisons between combat and non-combat veterans for CHD (IRR=1.46; 95% CI=1.02, 2.07) and IS (IRR=1.81; 95% CI=1.01, 3.23). Results do not suggest that combat exposure exerts long-term adverse effects on cardiovascular risk among men; however, effects may differ by military conflict.

Introduction

Exposure to military service can have positive as well as negative consequences[9,10] and can have both short-term and long-term effects.[11,12] The psychosocial stress experienced by veterans who have engaged in active combat is a uniquely traumatic stressor that includes both psychological and physical components.[13,112] The effects of military service in general and military combat in particular are so pervasive yet so little studied that they have been termed the "hidden variable" in the aging of older American men.[10,13] Approximately 65% of American men over the age of 55 served in World War II or the Korean conflict. Further, about one quarter of all older American men were exposed to military combat at some time in their lives.[11,116]

Studies report higher rates of adverse behavioral risk profiles,[125] psychological conditions[128] and self-reported health conditions[130,131] among those exposed to military combat. However, studies of the long-term cardiovascular consequences of combat stress are limited, and to date have been inconclusive.[13,137] We report on the long term association between exposure to military combat and the incidence of coronary heart disease (CHD) and ischemic stroke (IS) in a large, community-based sample of men whose military service spanned the eras of World War II, the Korean War and the Vietnam Conflict.

Methods

Data for this investigation were collected in the cohort component of the Atherosclerosis Risk in Communities (ARIC) Study, a prospective, community-based study designed to investigate the etiology and natural history of cardiovascular disease (CVD) and

atherosclerosis. At baseline (1987-1989), the cohort included 15,792 African-American and Caucasian men and women between the ages of 45 and 64 years, sampled from four U.S. communities: Minneapolis, MN; Washington County, MD; Jackson, MS; and Forsyth County, NC. Participants from MN and MD were Caucasian, while African-American participants were sampled exclusively in MS. The NC center included both African-American and Caucasian participants with an over-sampling of African-Americans. At baseline, standardized interviews were conducted to establish health history and to obtain demographic, socioeconomic and behavioral risk data. Using standard protocols, trained and certified technicians performed physical exams and subclinical CVD procedures and collected fasting blood samples. A detailed account of the design and procedures has been published,[652,653] and the study protocols and information on quality control and assurance can be found on the ARIC website (http://www.cscc.unc.edu/aric). After baseline, three triennial examinations were given, the last of which occurred in 1997-1999. In addition, approximately 94% of cohort survivors are successfully contacted and interviewed annually to ascertain vital status, health status and hospitalizations.

An ancillary study to ARIC, the Life Course Socioeconomic Status, Social Context and Cardiovascular Disease (LC-SES) Study was initiated in 2001 to examine the association between SES across the life course and adult cardiovascular conditions. Additional details about its design and procedures are published[654] and are available on the LC-SES website (http://www.lifecourseepi.info). After an average of fifteen years of follow-up, the ages of cohort participants ranged from 57 to 79 years. During the LC-SES interview, 12,716 or 81% of the baseline ARIC participants (91% of cohort survivors) were queried about socioeconomic information, military service and combat exposures.

Because only 49 women who participated in the LC-SES Survey reported that they had served in the armed services, the current study was limited to men. Also, because their numbers were insufficient for analysis, men with self-reported race other than African-American or Caucasian (n=14) and African-Americans from Washington County or Minneapolis (n=21) were excluded. Further excluded were 53 men who had missing or unknown military service status and 727 men who served outside the defined periods of conflict for World War II (1941-1945), the Korean War (1950-1953) and the Vietnam Conflict (1961-1975). After these exclusions, the study population included 4,620 men for analyses.

Military service status is based on self-report during the LC-SES follow-up interview. Participants who reported that they had served in the military were further asked a series of questions detailing military experience, including: (1) age at entry into the service, (2) length of service, and whether they (4) served in a combat zone, (5) were ever under fire or fired at the enemy, (6) saw others wounded or killed or (7) were ever wounded or missing in action.[675] A three-level exposure variable was derived: no history of military service (non-veterans), history of military service without exposure to combat stress (non-combat veterans) and history of military service with exposure to combat stress (combat veterans). While history of military service was directly queried, exposure to combat was established based on a positive response to one or more of questions 4-7 above. Throughout the analyses, combat veterans and non-combat veterans are treated as two levels of exposure and are compared separately to non-veteran "controls."

Era of military service was determined using information provided on age at entry into the military and duration of service. Veterans served during the eras of World War II, the

Korean War and the Vietnam Conflict. Veterans who served during multiple conflict eras (e.g., both World War II and the Korean War or both the Korean War and the Vietnam Conflict) were categorized according to their first era of service, as this was their initial military experience. Veterans who served between periods of defined conflict were excluded from analysis, as they were deemed too heterogeneous to provide results from which meaningful conclusions could be drawn. Non-veterans were placed into era of service categories according to the chronological age category into which they fell at Visit 1 (<52, 52-59 and 60+ years). These age categories matched up closely with era of service categories in this study population, with 94% of World War II era veterans ages 60 years and greater, 89% of Korean War era veterans ages 52-59 years and 91% of Vietnam era veterans under the age of 52 years.

Differences in the age-adjusted distribution of established biological and behavioral cardiovascular risk factors measured at the baseline assessment (Visit 1; 1987-1989) among each of the three exposure groups were examined individually. Risk factors include current smoking status, total cholesterol, high density lipoprotein cholesterol (HDL), systolic blood pressure (SBP), prevalent left ventricular hypertrophy (LVH), prevalent diabetes mellitus, prevalent CHD, and blood pressure medication use. Current cigarette smoking is defined as self-report of smoking one or more cigarettes per year at baseline (vs. former or never smoker). Plasma total cholesterol (mg/dL) was measured using an established enzymatic method,[684] and HDL cholesterol (mg/dL) was measured after dextran-magnesium precipitation of non-high density lipoproteins.[685] For SBP measurements, three seated blood pressure measurements were taken with a random-zero sphygmomanometer, and the last two measurements were averaged. Prevalent left ventricular hypertrophy was defined according

to the Cornell definition. Diabetes was defined as having a fasting glucose level of 126 mg/dL or higher, a non-fasting glucose level of 200 mg/dL or higher, or a self-reported diagnosis of diabetes or use of diabetic medication. Prevalent CHD was defined as history of a myocardial infarction (MI), presence of an MI from adjudicated Visit 1 electrocardiographic (ECG) data, or history of heart or arterial surgery, coronary bypass surgery, balloon angioplasty or angioplasty of one or more coronary arteries. Blood pressure medication use was defined as self-reported use in the previous two weeks. Additional details of the procedures used to obtain the risk factor data as well as the quality assurance procedures are published[652,653] and are detailed at http://www.cscc.unc.edu/aric.

An overall measure of predicted risk, composite CHD and IS risk scores optimized for race-gender groups within the ARIC population were also calculated using the ARIC risk equations. Methods for calculating these risk scores and the parameter estimates used have been published.[668,669] The use of risk prediction equations has become increasingly common in both research and clinical applications.[690,691,692] Predicted CHD risk scores for men are stratified by race and incorporate baseline values for age in years, total and HDL cholesterol, SBP, prevalent diabetes, current smoking status and blood pressure medication use. Predicted IS risk scores incorporate age, race, current smoking status, SBP, prevalent diabetes, blood pressure medication use, LVH and prevalent CHD.

Detailed descriptions of the methods of ascertainment of incident CHD and IS events have been provided in previous work.[668,669] Briefly, CHD and IS incidence were ascertained by annual follow-up interview and validated by review of hospital discharge records and death certificates.[665,671,672] Out-of-hospital deaths were ascertained through death certificates and, when available, coroner or autopsy reports. In the majority of out-of-hospital deaths,

cause of death was further validated by an interview with one or more next of kin as well as by a questionnaire completed by the patient's treating physician. Incident events were included from enrollment in ARIC until December 31, 2002.

An incident CHD event was defined as: (a.) a validated definite or probable hospitalized myocardial infarction (based on a combination of chest pain symptoms, ECG changes, and cardiac enzyme levels); (b.) a definite CHD death (based on chest pain symptoms, underlying cause of death from death certificate, and other information from the hospital chart, medical history or ARIC visit); or (c.) an unrecognized MI identified by ECG readings at one or more of the ARIC examinations (based on ECG readings with a major Q-wave or a minor Q-wave with ischemic ST-T changes, or an MI by computerized NOVA-CODE criteria confirmed by a side-by-side visual comparison of baseline and follow-up ECGs).

An incident IS event was defined as a validated definite or probable hospitalized embolic or thrombotic stroke, classified according to symptom type, duration and severity as well as results of neuroimaging and other diagnostic procedures and autopsy evidence, when available.[671,674]

SAS statistical software Version 8.02 was used for all analyses.[693] Descriptive statistics were calculated for baseline distributions of sociodemographic characteristics and military and combat exposures. Ten-year predicted risks of CHD and IS associated with exposure to military service with and without combat were calculated independently using linear regression using published sex and race-specific parameter estimates. [668,669]

Incidence rates (IR) were calculated by dividing the number of events by the total time experienced for the participants followed. Incidence rate ratios (IRR) and 95%

confidence intervals (CI) were calculated using Poisson regression[697] using PROC GENMOD with the log link and Poisson distribution options. In this way, CHD and stroke event rates were modeled on a logarithmic scale as a function of military and combat exposure status, and residuals followed a Poisson distribution. Combat veterans and non-combat veterans were compared separately with non-combat "controls," and the two veteran groups—combat veterans and non-combat veterans—were also compared with one another.

Results were stratified according to era of service (World War II, the Korean War or the Vietnam Conflict) in order to assess potentially important heterogeneity in effects. Non-veterans were grouped into three age categories (<52, 52-59, 60+ years) that most closely mirrored the age categories of veterans who served during the eras of World War II, the Korean War and the Vietnam Conflict, respectively. Interaction by era was assessed using Wald chi-square tests for homogeneity of IRR using an *a priori* rejection level of 0.05. Although insufficient sample size prohibited further stratification by race, descriptive military, combat and sociodemographic were presented in order to highlight differences among the three eras of service investigated.

Results

A total of 4,620 men were included in this study: 2042 non-veterans, 1495 non-combat veterans and 1083 combat veterans. Among veterans, the most common period of service was during the Korean War (42%), and approximately equal proportions of veterans participated in World War II (31%) or the Vietnam conflict (27%) (Table 16). Combat veterans were more likely to have served during World War II and less likely to have served during the Vietnam conflict, compared to non-combat veterans. The mean age at induction

into the military was approximately one year younger for combat veterans compared to non-combat veterans, and the duration of service was approximately 1.5 years longer. Terms of service were longest for combat veterans who served during the Vietnam Conflict. The average time elapsed between induction into the military and enrollment in the ARIC study was 39 years among combat veterans and 35 years among non-combat veterans. Among combat veterans, service in a combat zone was the most commonly reported combat exposure, followed by having seen others wounded or killed during the war, and having been under fire or fired at the enemy. Only 14% of combat veterans reported having been wounded or missing during war. World War II era veterans were most likely to report each of the combat exposures assessed, while Vietnam Conflict era veterans were the least likely.

Veterans tended to be older, white and of higher SES compared to non-veterans (Table 17). A larger proportion of Vietnam Conflict era veterans were black (20%), compared to combat veterans of the World War II (9%) or Korean War eras (15%). Veterans consistently had more favorable socioeconomic profiles that non-veterans, with Vietnam veterans having the highest education, income and occupation levels.

When profiles were further broken down by race, a number of differences were noted among the three eras of service investigated (Table 18). White men were more likely to have served in the military than black men in each of the conflicts, although these differences were largest for the World War II era (83% vs. 55%) and smallest for the Vietnam Conflict era (44% vs. 42%). White veterans were more likely than black veterans to see combat during the World War II era, and less likely during the eras of the Korean War and the Vietnam Conflict. For each era of service investigated, black veterans served longer terms than their white counterparts. Black and white men differed little in their age at baseline. Black men

had lower adult SES, as measured by education, income and occupation at each combat level and during each era of service. However, measured by father's education level, childhood SES was higher for black men than white men during the World War II and Korean War eras and reversed for the era of the Vietnam Conflict.

Overall, veterans were less likely to be current smokers than non-veterans (Table 19). Combat veterans had higher average SBP, lower average HDL, and were more likely to be on hypertension medications and have prevalent CHD than either non-veterans or non-combat veterans (Tables 4 and 5). Non-combat veterans had the lowest prevalence of diabetes and the lowest average total cholesterol. When overall CHD and IS risk scores were calculated, the 10-year predicted CHD and stroke risk was highest for combat veterans and lowest for non-veterans. Current smoking rates were highest among Vietnam era men and lowest among World War II era men, while the reverse was true for hypertension medication use, LVH, CHD and diabetes rates. Similarly, men from the era of the Vietnam Conflict were most likely to have the lowest SBP, total cholesterol and predicted risks of CHD and IS. The association between combat and risk factors differed by era of service as well. In particular, among World War II era veterans, those exposed to combat were less likely to have prevalent diabetes or CHD compared to non-combat veterans. Among Korean War veterans, combat veterans were more likely to be current smokers and more likely to have diabetes or CHD and higher SBP compared to non-combat veterans. Among veterans of the Vietnam Conflict, those exposed to combat were less likely to be current smokers but more likely to have diabetes than non-veterans.

A total of 813 CHD events and 173 IS events occurred in this study population by December 31, 2002 (Table 21). Statistical interaction by era of service was detected on the

IRR scale (Wald chi-square $p<0.05$), supporting stratification of results into eras of service. Inter-era differences in the association between combat and the incidence of CHD and IS were notable. While combat veterans had higher CHD and IS incidence rates than either non-combat veterans or non-veterans for cohort members of the Korean War era, they had *lower* incidence rates than either comparison group for cohort members of World War II and the Vietnam Conflict eras. Even for cohort members of the Korean War era, however, IRRs were statistically significant only in comparison of rates between combat and non-combat veterans, both for CHD (IRR=1.46; 95% CI=1.02, 2.07) and IS (IRR=1.81; 95% CI=1.01, 3.23).

Table 16: Profile of Recalled Military Service and Combat History Reported During the LC-SES Interview, by War/Conflict Era.

	Non-Combat Veteran [1]	Combat Veteran
N		
World War II	314	478
Korean War	675	407
Vietnam Conflict	506	198
Mean (SD) Age at induction into service (years)		
World War II	17.9 (0.9)	18.0 (1.0)
Korean War	19.7 (1.9)	19.4 (1.9)
Vietnam Conflict	21.2 (2.8)	20.9 (3.3)
Mean (SD) Duration of service (years)		
World War II	2.5 (2.2)	4.2 (4.5)
Korean War	3.5 (3.7)	5.2 (6.1)
Vietnam Conflict	4.0 (4.4)	7.2 (7.2)
Mean (SD) Elapsed time since age at induction into service (years) [2]		
World War II	43.6 (1.3)	44.5 (1.3)
Korean War	36.6 (2.0)	37.3 (2.0)
Vietnam Conflict	27.0 (3.0)	26.7 (3.7)
n (%) Served in combat zone		
World War II	0	430 (90.0)
Korean War	0	339 (83.3)
Vietnam Conflict	0	163 (82.3)
n (%) Under enemy fire or fired at enemy		
World War II	0	337 (70.7)
Korean War	0	229 (56.8)
Vietnam Conflict	0	110 (55.6)
n (%) Saw wounded or killed during war		
World War II	0	357 (74.8)
Korean War	0	294 (73.0)
Vietnam Conflict	0	139 (70.2)
n (%) Ever wounded or missing during war		
World War II	0	76 (15.9)
Korean War	0	57 (14.1)
Vietnam Conflict	0	18 (9.1)

[1] Combat Veterans are identified by a summary variable based on whether or not the individual served in the military and, if so, whether the individual (1) served in a combat zone, (2) was under enemy fire or fired at enemy, (3) saw wounded or killed during war, and/or (4) was ever wounded during war; Non-Combat Veterans are defined as those who served in the military but did not report any combat exposures (1-4).

[2] Age at Visit 1 – self-reported age at entry into the military

Table 17: Sociodemographic Profile of Black and White Men at ARIC Baseline Examination (1987-1989): LC-SES Participants (Overall and by Military/Combat Exposure), by Era of Service.

	Non-Veteran	Non-Combat Veteran [1]	Combat Veteran
N			
World War II	217	314	478
Korean War	695	675	407
Vietnam Conflict	1130	506	198
Mean (SD) Age at Baseline ARIC Visit in years			
World War II	61.9 (1.5)	61.5 (1.6)	62.5 (1.5)
Korean War	54.9 (2.3)	56.3 (2.4)	56.7 (2.2)
Vietnam Conflict	47.9 (2.0)	48.2 (2.5)	47.6 (2.6)
n (%) Black			
World War II	68 (31.3)	37 (11.8)	45 (9.4)
Korean War	204 (29.4)	88 (13.0)	60 (14.7)
Vietnam Conflict	371 (32.8)	75 (14.8)	39 (19.7)
n (%) Education <High School			
World War II	113 (52.3)	77 (24.5)	112 (23.4)
Korean War	280 (40.4)	94 (14.0)	67 (16.5)
Vietnam Conflict	232 (20.6)	20 (4.0)	8 (4.1)
n (%) Father's Education <High School [2]			
World War II	108 (62.8)	178 (63.1)	282 (64.7)
Korean War	355 (63.6)	374 (64.0)	229 (65.4)
Vietnam Conflict	547 (59.1)	219 (50.9)	79 (48.2)
n (%) Combined Family Income <$25,000 [3]			
World War II	129 (62.3)	81 (26.8)	163 (35.8)
Korean War	229 (34.9)	135 (20.6)	74 (19.2)
Vietnam Conflict	267 (25.2)	63 (12.9)	26 (13.7)
n (%) Occupation Non-Managerial/Professional			
World War II	196 (90.3)	245 (78.0)	412 (86.2)
Korean War	512 (73.9)	446 (66.1)	290 (71.3)
Vietnam Conflict	738 (65.3)	302 (59.7)	132 (66.7)

Note: columns may not sum to 100% due to rounding

[1] Combat Veterans are identified by a summary variable based on whether or not the individual served in the military and, if so, whether the individual (1) served in a combat zone, (2) was under enemy fire or fired at enemy, (3) saw wounded or killed during war, and/or (4) was ever wounded during war; Non-Combat Veterans are defined as those who served in the military but did not report any combat exposures (1-4).

[2] 718 values missing information on natural father's education; Measured during LCSES Interview (2001-2002) and therefore not available on entire ARIC Study population.

[3] 220 values missing information on combined family income.

Table 18: Military, Combat and Sociodemographic Profile of Black and White Male LC-SES Participants (Overall and by Military/Combat Exposure), by Race and Era of Service.

	Black			White		
	Non-Veteran	Non-Combat Veteran [1]	Combat Veteran	Non-Veteran	Non-Combat Veteran	Combat Veteran
N (%) Military/combat status						
World War II	68 (45.3)	37 (24.7)	45 (30.0)	149 (17.4)	277 (32.3)	433 (50.4)
Korean War	204 (58.0)	88 (25.0)	60 (17.1)	491 (34.5)	587 (41.2)	347 (24.4)
Vietnam Conflict	371 (57.7)	75 (37.5)	39 (27.1)	759 (56.3)	431 (32.0)	159 (11.8)
Mean (SD) Duration of Service i						
World War II	0	2.9 (3.3)	6.3 (7.5)	0	2.5 (2.0)	4.0 (4.1)
Korean War	0	3.8 (4.4)	5.6 (6.8)	0	3.5 (3.5)	5.2 (6.0)
Vietnam Conflict	0	5.5 (6.8)	8.5 (8.2)	0	3.7 (3.7)	6.9 (6.9)
Mean (SD) Age at Baseline in years						
World War II	62.0 (1.6)	62.6 (1.2)	62.8 (1.5)	61.9 (1.5)	61.3 (1.6)	62.5 (1.5)
Korean War	54.8 (2.4)	56.8 (2.4)	57.1 (2.7)	55.0 (2.3)	56.3 (2.4)	56.6 (2.1)
Vietnam Conflict	47.8 (2.0)	47.7 (2.4)	47.5 (3.0)	48.0 (2.0)	48.3 (2.5)	47.6 (2.5)
n (%) Education <High School						
World War II	58 (85.3)	18 (48.7)	14 (31.1)	55 (37.2)	59 (21.3)	98 (22.6)
Korean War	147 (72.4)	15 (17.1)	9 (15.0)	133 (27.1)	79 (13.5)	58 (16.8)
Vietnam Conflict	134 (36.3)	4 (5.33)	2 (5.1)	98 (12.9)	16 (3.7)	6 (3.8)
n (%) Father's Education <High School [2]						
World War II	22 (51.2)	17 (58.6)	22 (64.7)	86 (66.7)	161 (63.6)	260 (64.7)
Korean War	76 (55.5)	40 (64.5)	38 (77.6)	279 (66.3)	334 (64.0)	191 (63.5)
Vietnam Conflict	173 (66.0)	34 (58.6)	19 (65.5)	374 (56.3)	185 (49.7)	60 (44.4)
n (%) Combined Family Income <$25,000 [2]						
World War II	59 (93.7)	21 (65.6)	28 (70.0)	70 (48.6)	60 (22.2)	135 (32.5)
Korean War	134 (71.7)	38 (46.3)	23 (44.2)	95 (20.2)	97 (16.9)	51 (15.3)
Vietnam Conflict	172 (53.4)	21 (31.3)	12 (34.3)	95 (12.9)	42 (10.0)	14 (9.0)
n (%) Occupation Non-Managerial/Professional						
World War II	67 (98.5)	30 (81.1)	41 (91.1)	129 (86.6)	215 (77.6)	371 (85.7)
Korean War	185 (90.7)	61 (69.3)	41 (68.3)	327 (66.9)	385 (65.6)	249 (71.8)
Vietnam Conflict	280 (75.5)	53 (70.7)	29 (74.4)	458 (60.3)	249 (57.8)	103 (64.8)

Note: columns may not sum to 100% due to rounding

[1] Combat Veterans are identified by a summary variable based on whether or not the individual served in the military and, if so, whether the individual (1) served in a combat zone, (2) was under enemy fire or fired at enemy, (3) saw wounded or killed during war, and/or (4) was ever wounded during war; Non-Combat Veterans are defined as those who served in the military but did not report any combat exposures (1-4).

[2] 718 values missing on natural father's education; 220 values missing information on combined family income.

Table 19: Risk Factor Profile of Black and White Men at ARIC Baseline Examination (1987-1989): LC-SES Participants (Overall and by Military/Combat Exposure), by Era of Service (Dichotomous Variables).

	Non-Veteran	Non-Combat Veteran [1]	Combat Veteran
N			
World War II	217	314	478
Korean War	695	675	407
Vietnam Conflict	1130	506	198
n (%) Current cigarette smoking status [2]			
World War II	42 (19.4)	44 (14.0)	70 (14.6)
Korean War	183 (26.4)	139 (20.6)	108 (26.6)
Vietnam Conflict	316 (28.0)	136 (26.9)	44 (22.2)
n (%) Used blood pressure-lowering medications in past 2 weeks			
World War II	77 (35.5)	118 (37.6)	139 (29.1)
Korean War	204 (29.4)	175 (25.9)	113 (27.9)
Vietnam Conflict	212 (18.8)	78 (15.4)	28 (14.1)
n (%) Prevalent left ventricular hypertrophy [3]			
World War II	8 (3.8)	10 (3.3)	7 (1.5)
Korean War	22 (3.3)	5 (0.8)	8 (2.0)
Vietnam Conflict	18 (1.6)	4 (0.8)	1 (0.5)
n (%) Prevalent diabetes			
World War II	36 (16.7)	40 (12.7)	56 (11.8)
Korean War	69 (10.1)	55 (8.2)	36 (8.9)
Vietnam Conflict	108 (9.7)	29 (5.8)	17 (8.6)
n (%) Prevalent coronary heart disease			
World War II	18 (8.5)	36 (11.6)	45 (9.6)
Korean War	45 (6.6)	42 (6.4)	37 (9.3)
Vietnam Conflict	42 (3.8)	12 (2.4)	4 (2.0)

Because of missing data, N differs for some variables.
Some columns may not sum to 100% due to rounding.

[1] Combat Veterans are identified by a summary variable based on whether or not the individual served in the military and, if so, whether the individual (1) served in a combat zone, (2) was under enemy fire or fired at enemy, (3) saw wounded or killed during war, and/or (4) was ever wounded during war; Non-Combat Veterans are defined as those who served in the military but did not report any combat exposures (1-4).

[2] Current cigarette smoking is defined as self-report of smoking one or more cigarettes per year at baseline; Heavy cigarette years of smoking is calculated by multiplying the number of cigarettes smoked per year by the number of years the individual has been smoking and is defined as having smoked 660 or more cigarettes; Physical inactivity is defined as having a sports activity index score less than 2.0.

[3] Presence of left ventricular hypertrophy was determined electrocardiographically using the Cornell criteria.

Table 20: Risk Factor Profile of Black and White Men at ARIC Baseline Examination (1987-1989): LC-SES Participants (Overall and by Military/Combat Exposure), by Era of Service (Continuous Variables).

	Non-Veteran	Non-Combat Veteran [1]	Combat Veteran
N			
World War II	217	314	478
Korean War	695	675	407
Vietnam Conflict	1130	506	198
Mean (SD) Systolic BP (mmHg)			
World War II	127.7 (20.5)	125.7 (18.9)	125.6 (17.3)
Korean War	123.5 (17.8)	120.8 (16.3)	122.5 (16.0)
Vietnam Conflict	119.5 (16.4)	116.1 (14.6)	116.6 (14.5)
Mean (SD) Total cholesterol (mg/dL)			
World War II	212.4 (38.8)	212.0 (37.9)	214.3 (38.0)
Korean War	212.6 (40.4)	212.5 (37.3)	214.6 (42.6)
Vietnam Conflict	207.4 (39.5)	205.9 (39.0)	207.7 (41.0)
Mean (SD) HDL cholesterol (mg/dL)			
World War II	46.7 (13.9)	44.7 (14.1)	44.1 (12.2)
Korean War	44.6 (13.5)	43.9 (12.8)	43.3 (13.2)
Vietnam Conflict	44.6 (13.5)	43.9 (13.0)	43.6 (13.1)
Mean (SD) 10-year predicted risk of coronary heart disease [2]			
World War II	0.1567 (0.0997)	0.1593 (0.0962)	0.1567 (0.0845)
Korean War	0.1283 (0.0797)	0.1325 (0.0792)	0.1456 (0.0853)
Vietnam Conflict	0.0788 (0.0561)	0.0805 (0.0589)	0.0766 (0.0491)
Mean (SD) 10-year predicted risk of ischemic stroke [2]			
World War II	0.0626 (0.0659)	0.0506 (0.0511)	0.0469 (0.0409)
Korean War	0.0299 (0.0308)	0.0275 (0.0292)	0.0316 (0.0293)
Vietnam Conflict	0.0149 (0.0155)	0.0117 (0.0100)	0.0114 (0.0102)

Because of missing data, N differs for some variables.

[1] Combat Veterans are identified by a summary variable based on whether or not the individual served in the military and, if so, whether the individual (1) served in a combat zone, (2) was under enemy fire or fired at enemy, (3) saw wounded or killed during war, and/or (4) was ever wounded during war; Non-Combat Veterans are defined as those who served in the military but did not report any combat exposures (1-4).

[2] Components of 10-year predicted risk score described in detail in *Methods* section; age is included in the risk prediction model and is centered at 55 years

Table 21: Observed Cumulative Incidence of Coronary Heart Disease (CHD) and Ischemic Stroke through 2002 by Military Service and Combat History.

	Non-Veteran	Non-Combat Veteran [1]	Combat Veteran
N			
World War II	217	314	478
Korean War	695	675	407
Vietnam Conflict	1130	506	198
CHD			
n (%) Events			
World War II	60 (27.7)	72 (22.9)	102 (21.3)
Korean War	123 (17.7)	135 (20.0)	88 (21.6)
Vietnam Conflict	147 (13.0)	64 (12.7)	22 (11.1)
Incidence rate (incident events per 10,000 person-years)			
World War II	38.9	32.5	29.6
Korean War	27.4	30.3	32.7
Vietnam Conflict	22.4	21.7	19.2
Incidence rate ratio (95% CI)			
World War II	REF	0.83 (0.59, 1.17)	0.77 (0.56, 1.06)
Korean War	REF	1.13 (0.89, 1.44)	1.22 (0.93, 1.61)
Vietnam Conflict	REF	0.97 (0.73, 1.30)	0.85 (0.55, 1.34)
Incidence rate ratio (95% CI)			
World War II		REF	0.93 (0.69, 1.26)
Korean War		REF	1.08 (0.83, 1.41)
Vietnam Conflict		REF	0.88 (0.54, 1.43)
ISCHEMIC STROKE			
n (%) Events			
World War II	11 (5.1)	19 (6.1)	24 (5.0)
Korean War	29 (4.2)	22 (3.3)	24 (5.9)
Vietnam Conflict	31 (2.7)	11 (2.2)	24 (1.0)
Incidence rate (incident events per 10,000 person-years)			
World War II	6.7	8.0	6.5
Korean War	6.0	4.0	8.3
Vietnam Conflict	4.4	3.5	1.6
Incidence rate ratio (95% CI)			
World War II	REF	1.19 (0.57, 2.51)	0.99 (0.49, 2.02)
Korean War	REF	0.78 (0.45, 1.36)	1.41 (0.82, 2.43)
Vietnam Conflict	REF	0.79 (0.40, 1.58)	0.37 (0.09, 1.54)
Incidence rate ratio (95% CI)			
World War II		REF	0.83 (0.45, 1.51)
Korean War		REF	1.81 (1.01, 3.23)
Vietnam Conflict		REF	0.46 (0.10, 2.10)

[1] Combat Veterans are identified by a summary variable based on whether or not the individual served in the military and, if so, whether the individual (1) served in a combat zone, (2) was under enemy fire or fired at enemy, (3) saw wounded or killed during war, and/or (4) was ever wounded during war; Non-Combat Veterans are defined as those who served in the military but did not report any combat exposures (1-4).

Discussion

This prospective study of aging men found that the association between exposure to military combat on the rate of CHD and IS later in life may not be consistent across military conflicts. While combat may be associated with increased CHD and IS rates among men who served during the era of the Korean War, combat exposure appears to have no effect or even a protective effect among men who served during the eras of World War II and the Vietnam Conflict.

To our knowledge, an association between exposure to military combat and incident CHD and IS has not previously been reported. However, our findings were in line with those from previous studies of veterans who served during the Vietnam Conflict that compared theater veterans to their non-theater veteran counterparts. These studies found no significant differences in all-cause or circulatory disorder mortality rates 20-30 years after participation in the military[154,157,158,194] or in relative risks of circulatory disease 16 after military service.[193] Although more limited, research on the long-term health effects of combat exposure among World War II and Korean War veterans parallels our findings for Korean War era veterans but not World War II era veterans. A study of former prisoners of war (POWs) of World War II and the Korean War reported higher risk of heart disease and stroke mortality among POWs compared to both non-POW veteran controls and US population controls 50 years after exiting the military.[147] Similarly, a study of World War II veterans found that combat was associated with higher prevalence of chronic illness and all-cause mortality 15 years after the end of the conflict[175] and all-cause mortality 50 years after exiting the military.[710] Heterogeneity in the effect of combat on carotid plaque and carotid artery wall thickness by era of service was noted in a previous analysis of ARIC men, which reported stronger

associations between combat and subclinical atherosclerosis among veterans of the World War II and Korean War eras than those who served during the era of the Vietnam Conflict.[717] Findings from this study are congruent with those from the present study for veterans of the eras of the Korean War and the Vietnam Conflict but not for those from World War II. The apparent disagreement of results among World War II era veterans—that combat is associated with higher rates of subclinical atherosclerosis but not CHD and stroke events—may be a result of the time that outcomes were measured, such that in this older cohort the majority of events may have already taken place regardless of combat or veteran status, masking differences.

Age is a potent predictor of CHD and stroke; however, because age was not associated with the exposure in this study population, as evidenced by the similarities in the age at induction into the military, it could not be treated as a confounder in analysis. Still, participants' mean age at the time when CIMT and carotid plaque were measured differed sufficiently among the three exposure groups – with combat veterans averaging three years older than non-combat veterans and five years older than non-veterans – to raise the potential concern that age may be affecting results. Although stratification of results by era of service limited the effects of age in these analyses, residual differences in age may still be playing a role in inter-era differences in effect. The older age of World War II era participants may mask effects in that the majority of events may have already taken place by the time that events were measured. Reciprocally, the younger age at which Vietnam Conflict era participants' outcomes were assessed in this study may have contributed to the apparently weaker effect of combat exposure among these participants,

Heterogeneous behavioral and physical risk factor profiles among veterans by era may also contribute to the apparent inter-era differences in the effect of combat. The finding of associations between combat and CVD among Korean War era veterans but not World War II and Vietnam Conflict era veterans mirrors findings that combat veterans were more likely to have higher rates of diabetes, higher waist circumference and higher triglycerides during the eras of the Korean War and Vietnam Conflict but not the World War II era, and that higher SBP and higher rates of CHD were found only among combat veterans who served during the era of the Korean War. Similarly, differences in the composite CHD and IS risk scores are in line with differences in the observed incidence rates of CHD and IS; the ten-year predicted risks of CHD and IS were highest for combat veterans during the Korean War era but not during the eras of World War II or the Vietnam Conflict. Some risk factor differences may be attributed, at least in part, to differences in the age at which risk factors were measured. The finding that Vietnam era men had higher smoking rates and lower hypertension medication use, SBP, total cholesterol, LVH, CHD and diabetes rates than members of the World War II and Korean War era cohorts is likely age-related, such that older men are more likely to have been diagnosed with health problems such as LVH, CHD, diabetes, high BP and high cholesterol that required them to quit smoking and be placed on hypertension medications.

Unmeasured psychological disorders such as post-traumatic stress disorder (PTSD) may also have acted as a mediator in the relationship between combat and cardiovascular morbidity and mortality.[182,709] The development and persistence of PTSD has been found to be directly associated with exposure to combat among veterans of all three conflicts,[10,595,710] as well as with plasma cortisol and other inflammatory markers[150,164] and circulatory

prevalence rates[408] among veterans of the Vietnam Conflict. While it would have been of interest to provide results stratified on PTSD status, this information was not queried in the LC-SES interview. Because PTSD status would have been assessed as a modifier rather than as a confounder, its exclusion does not detract from our findings. Our results support the conclusion that the effects of combat exposure extend beyond the narrow scope of these clinical diagnoses.[9,700,710]

The association between combat and CHD and IS may also differ by current and past socioeconomic environments and opportunities. Inverse associations between SES and CVD have been demonstrated repeatedly.[511,512] Lower individual SES is associated with increased rates of smoking, obesity and physical inactivity[523,524,525] as well as lower self-reported social mobility, increased financial strain and more stressful life events.[512] SES may differentially affect how an individual responds psychologically and physically to life events and stressors such as exposure to combat, both psychologically and physically, with higher SES providing protection.[567] In the current study, veterans consistently had the most favorable SES profiles overall, with Vietnam veterans having the highest education, income and occupation levels. Such differences may reflect the different age distributions in each exposure group, as the socioeconomic position of veterans has increased over time.[582] This finding is also likely a reflection of secular trends in education or in the ability of affluent Vietnam draftees to postpone induction by enrolling in school and obtaining educational deferment.[713] Alternatively, it may reflect the economic and educational opportunities such as the Montgomery GI Bill has enabled veterans to keep pace with, though not exceed, non-veterans in terms of educational attainment.[172,572]

Inter-era differences in the association between military and combat exposures with CHD and IS rates may also reflect differences in the type and nature of combat experienced during each of these conflicts as well as the social and political context surrounding them.[585] Although in the current analyses Vietnam Conflict era veterans were less likely to report combat exposure than other veterans, they served longer average terms, and the nature of the combat experienced may have differed. Reports suggest that Vietnam veterans were subjected to unusually high levels of "barbarity and moral ambiguity" as well as chronic exposure to unpredictable and dangerous warfare environments and were more likely to have witnessed abusive violence or killings compared to veterans of World War II.[711,712] Further, inter-era variations may also reflect differences in the social and political context surrounding the conflicts.[585] Vietnam veterans returned home to a social and political environment that was unsupportive of the US involvement in the conflict.[588] In contrast, World War II was a war with a clearly identified enemy, and returning soldiers had the overwhelming support of the American public.[595] Although the Korean War was fought by defined armies for territory, there were heavy military and civilian casualties, similar to the Vietnam Conflict. Further, soldiers left the war with no clear victor and little support or recognition and even condemnation from the American public, leading them to be known as the "forgotten" veterans.[727] The manner in which soldiers were received at homecoming has been found to have a significant effect on the risk of developing PTSD and other psychiatric symptoms later in life.[726] The confluence of divergent factors such as the clarity of identification of the enemy, involvement of civilians in combat, transparency of the purported goals of the war, and level of public support could explain the different associations between combat-related stress and health among men from different eras.

Given the particularly brutal nature of combat experienced during the Vietnam Conflict and the Korean War and the sociopolitical context in which their homecoming occurred,[588] we might expect the effects of combat to be most pronounced among these veterans. In fact, studies comparing postwar readjustment and psychological health among veterans of World War II, the Korean War and the Vietnam Conflict have found the highest rates of PTSD among Korean War and Vietnam Conflict veterans and the lowest among World War II veterans.[724] Once factors such as age, race, education and combat exposure were taken into account, symptoms of PTSD and psychiatric distress were found to be higher among Korean War Veterans than among either World War II or Vietnam Conflict veterans.[595,725] The stronger associations found in the present study between combat and cardiovascular morbidity and mortality are in line with such findings, in that the way that combat affected veterans was likely not the same in each conflict, and that the long-term psychological and physical health effects of such exposures may have been most damaging among veterans of the Korean War.

Inter-era differences in the effect of combat may also reflect differences in the racial composition of era of service cohorts. PTSD research suggests that different race groups may respond psychologically to combat in different ways. [142,617,619] Previous ARIC study results suggest modification by race, as an association between combat and subclinical atherosclerosis was noted in white but not black men.[717] However, these differences may have been attributable to differences in baseline risk factor profiles—white but not black combat veterans were most likely to be heavy smokers, a major risk factor for subclinical atherosclerosis—and the low sample size of black men may have masked an effect in this group. In the present study, a higher proportion of Vietnam Conflict era veterans were black

compared to those of the World War II or Korean War eras. Further, compared to black Korean War or Vietnam Conflict era veterans, black Vietnam Conflict era veterans were more likely to be involved in combat. Given these inter-era differences in racial composition, and because black men in the general population tend to have higher rates of both CHD and IS than white men, we might expect observed effects among the Vietnam era cohort to be inflated for CHD and IS. However, it is also foreseeable that the effect of race in the combat-CVD association may differ by era, as sociopolitical factors affecting participation of black men in the military and, specifically in combat, differed during the different eras of service investigated. Finally, racial differences are often difficult to disentangle from differences in SES. In the present study, black men had lower adult SES, as measured by education, income and occupation at each combat level and during each era of service. In previous studies, the effect of combat and other traumatic stressors on chronic disease and mortality has been found to be highest among low SES individuals, as these groups tend to have a higher overall stress burden as well as fewer skills and resources to cope with such stress.[10,135] Given these findings, we might expect the combat-CVD association to be higher among black men than white men. Future studies would benefit from large enough sample size to stratify results by both era and race.

This study provided a rare opportunity to investigate the long-term association of combat exposure on levels of cardiovascular risk in a large community-based cohort. Average follow-up time was long and participants were of an age (60 to 80 years) where CHD is most likely manifest. Among veterans, periods of military service spanned from World War II through the Vietnam Conflict and includes measures of specific combat exposures and both military and civilian controls. Most previous studies have been based on

retrospective cohorts and have investigated differences in CVD mortality comparing war theater veterans and non-theater veterans of the same era. Also a particular strength, this study included objective, standardized measures of cardiovascular outcomes and a wide range of physical and behavioral risk factor measures. The availability of socioeconomic measures from various life epochs further offered an unusual opportunity to investigate the role of SES in combat-cardiovascular associations.

The use of self-reported combat exposures presents challenges. Because the combat exposure variable used in this study is based on self-reported information, recall bias may affect results, such that men in worse health may differentially recall their military experiences. Even for participants whose CHD and stroke status was unknown at the time that military exposures were queried, participants may have been aware of their status on other health indicators such as hypertension and high cholesterol status. Although recalled exposure status is not ideal, to our knowledge, no cohorts exist that collected combat exposure during military service and included long-term follow-up with a rigorous measurement of cardiovascular outcomes. Further, defining combat as the exposure to one or more specific use of recalled combat exposures has precedent[676,677,678] and has high validity and reliability.[722,723] Therefore, it is unlikely that differential recollection of past military experiences based on current health status was significant. In fact, use of recalled combat experiences can be viewed as a strength, as it is a more specific and meaningful definition than simply separating exposure groups into theater and non-theater veterans who served during the same era.

As discussed in a previous study of combat veterans in the ARIC Study, men that participated in the LC-SES survey had slightly more favorable behavioral and physical risk

factor profiles at Visit 1 than the larger ARIC cohort from which they were drawn.[717] Combat exposure was not assessed until 12-14 years after baseline, at which time 17% of male baseline participants had expired. Thus, it is possible that selective survival may have biased our findings. We took two steps to address this concern. First, we conducted a pilot study on a subset of decedents from North Carolina for whom veteran status was recorded on death certificates. Briefly, we found a small (2%) but not statistically significant excess mortality among veterans, even after adjustment for age, race and education. Second, we conducted a sensitivity analysis to estimate the extent to which differential survival, if extant, may have influenced observed results by comparing observed RRs with those corrected for selection bias.[718] We applied the adjusted mortality rates obtained from the pilot study to hypothetical data with incident CHD as the outcome. Assuming that those who eventually had a CHD event were 1.5 times more likely to die before providing data on military history than those who did not go on to develop CHD, our odds ratio was underestimated by only 1.5%. Even under a more extreme scenario – where the difference in mortality was assumed to be higher than what we found in the pilot study (e.g., 14% for non-veterans and 18% for veterans – a 29% difference in mortality) and assuming those who eventually go on to develop CHD were two times more likely to die prior to providing their military history – our observed effect estimate would still only differ from the corrected estimate by 7%. These results are reassuring as they suggest that both the potential magnitude of survivorship bias, if extant, would have been small in these data.

Finally, although this study includes a large population of men, it does not have adequate statistical power to formally address hypotheses about potential effect measure modification. In addition to era of service and race, of particular interest would be to see if

there is interaction by age at entry, duration of service, psychological status and type of combat exposure.

Conclusions

These findings do not support the hypothesis that middle-aged men with a history of distant military and combat exposure are at increased long-term cardiovascular risk; however, effects may not be consistent across military conflicts. Specifically, combat veterans from the Korean War era—but not the eras of World War II or the Vietnam Conflict—had a higher risk of cardiovascular disease, primarily IS, than did those who did not report serving in this conflict. Given the inter-era differences noted, future studies should focus on which aspects of combat might help explain these differences would also be of benefit, including the role of specific combat exposures and other military factors as well as socio-political factors and homecoming experiences. Further, future studies should focus on elucidating possible mechanisms through which psychosocial stress can place an individual at long-term risk for CVD. In addition, studies with larger sample sizes could better evaluate the potential role of service era, race, SES and other important modifiers of the association between combat and cardiovascular risk can be clarified. Ideally, studies should be population-based, so as to include both veteran and non-veteran controls. The findings in this study, if confirmed, have implications for our understanding of the lasting effects of traumatic stress on long-term cardiovascular health.

Acknowledgements

The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by the National Heart, Lung and Blood Institute contracts R01-HL064142, No.T32-HL07055-27, N01-HC-55015, N01-HC-55016, N01-HC-55019, N01-HC-55020, N01-HC-55021, N01-HC-55022, and R21-HL080422-01. The authors thank the staff and participants of the ARIC study for their important contributions.

CHAPTER 6

CONCLUSIONS

Summary of Results

In this study we reported on the long term association between exposure to military combat and the burden of subclinical atherosclerosis (measured by carotid plaque and CIMT) as well as the incidence of CHD and IS in a large, community-based sample of men whose military service spanned the eras of World War II, the Korean War and the Vietnam Conflict. Those with a history of military service who reported one or more combat-related stressors (combat veterans) were contrasted to those without a history of military service (non-veterans) as well as to those with a history of military service without combat (non-combat veterans). Results were stratified by race as well as by era of service to detect differences in effect among veterans of different birth and service cohorts. We also examined the extent to which differences by combat exposure status, if extant, vary by differences in sociodemographic and cardiovascular risk factor profiles.

In the first manuscript we reported that men with distant military service, particularly when it included combat exposure, were more likely to have carotid plaque and increased CIMT than their non-veteran counterparts. These effects remained after age was taken into account. Overall, findings held true for veterans of the World War II and Korean War eras but were attenuated for those from the Vietnam Conflict era. Results for white men were similar to overall results, while results for black men were weaker or absent.

In the second manuscript we did not find the hypothesized association between combat exposure and risk of CHD or IS later in life; however, the effect of military combat on cardiovascular risk may not be consistent across military conflicts. Specifically, while modest associations were reported between combat exposure and increased CHD and IS rates among men who served during the era of the Korean War, combat exposure appeared to have no effect or even a protective effect among men who served during the eras of World War II and the Vietnam Conflict.

Sociodemographic and cardiovascular risk factor profiles were assessed in both manuscripts, with notable differences seen by combat exposure status. Veterans were more likely to be older and white compared to non-veterans, and veterans consistently had more favorable socioeconomic profiles than non-veterans, with Vietnam Conflict era veterans having the highest education, income and occupation levels. Combat and non-combat veterans were more likely to be current drinkers and heavy smokers than non-veterans but less likely to be current smokers and physically inactive. Combat veterans and non-veterans were more likely than non-veterans to have prevalent diabetes, but compared to either comparison group, combat veterans were most likely to have prevalent CHD, to be on hypertension medications and to have higher average SBP, total cholesterol and triglycerides and lower average HDL. When overall predicted CHD and IS risk scores were calculated, the 10-year predicted CHD and stroke risk was highest for combat veterans and lowest for non-veterans.

Overall Conclusions

To our knowledge, no prior studies have assessed the relationship between combat exposure and clinical or subclinical atherosclerosis or the relationship between combat exposure and incident CHD and IS. Our finding that combat is associated with carotid plaque and CIMT is consistent with earlier studies that reported that combat veterans with PTSD were more likely to have increased chronic cardiovascular arousal, higher circulating catecholamines and other neuroendocrine agents implicated in arterial damage and a higher frequency of abnormal ECG readings. Similarly, our finding of a lack of association between combat exposure and rates of CHD and IS are in line findings from previous studies comparing theater and non-theater Vietnam veterans that found no significant differences in all-cause or circulatory disorder mortality rates 20-30 years after participation in the military or in relative risks of circulatory disease 16 after military service. Our finding of heterogeneity in effect by era of service is also consistent with the current literature. Although more limited, research on the long-term health effects of combat exposure among World War II and Korean War veterans parallels our findings for Korean War era veterans but not World War II era veterans. A study of former POWs of World War II and the Korean War reported higher risk of heart disease and stroke mortality among POWs compared to both non-POW veteran controls and US population controls 50 years after exiting the military. Similarly, a study of World War II veterans found that combat was associated with higher prevalence of chronic illness and all-cause mortality 15 years after the end of the conflict and all-cause mortality 50 years after exiting the military.

As discussed in the Introduction, exposure to traumatic stress may affect cardiovascular processes through a variety of mechanisms. Although the link between

psychosocial stress and coronary events is well-established, the mechanisms underlying these associations are not well understood. One possible explanation for our findings of higher rates of subclinical atherosclerosis in combat veterans is that the extreme trauma experienced set into motion a chronic stress response and a resultant inflammatory, atherosclerotic process that initiated the formation of plaque and the thickening of the arterial wall. This theory is supported by ARIC study findings that lower SES, both early in life and cumulatively across the life course, is associated with elevated levels of inflammatory markers such as C-reactive protein, fibrinogen, white blood cell count and von Willebrand factor later in life. Similarly, a small-sample Croatian study found that combat veterans with PTSD had higher lymphocyte counts than civilian controls, suggesting that the immune system was affected in the course of chronic PTSD.

Our failure to find an association between combat exposure and rates of CHD and IS does not negate the possibility that combat stress causes a direct physiologic cardiovascular response; it may be that while differences are detectable at the subclinical level, they are not yet manifest at the level of symptomatic disease. The possibility that selection bias played a role in this discrepancy in results was also assessed. Men that participated in the LC-SES survey had slightly more favorable behavioral and physical risk factor profiles at Visit 1 than the larger ARIC cohort from which they were drawn.[717] Combat exposure was not assessed until 12-14 years after baseline, at which time 17% of male baseline participants had expired. Thus, it is possible that selective survival may have biased our findings. We took two steps to address this concern. First, we conducted a pilot study on a subset of decedents from North Carolina for whom veteran status was recorded on death certificates. Briefly, we found a small (2%) but not statistically significant excess mortality among veterans, even after

adjustment for age, race and education. Second, we conducted a sensitivity analysis to estimate the extent to which differential survival, if extant, may have influenced observed results by comparing observed RRs with those corrected for selection bias.[718] We applied the adjusted mortality rates obtained from the pilot study to hypothetical data with incident CHD as the outcome. Assuming that those who eventually had a CHD event were 1.5 times more likely to die before providing data on military history than those who did not go on to develop CHD, our odds ratio was underestimated by only 1.5%. Even under a more extreme scenario – where the difference in mortality was assumed to be higher than what we found in the pilot study (e.g., 14% for non-veterans and 18% for veterans – a 29% difference in mortality) and assuming those who eventually go on to develop CHD were two times more likely to die prior to providing their military history – our observed effect estimate would still only differ from the corrected estimate by 7%. These results are reassuring as they suggest that both the potential magnitude of survivorship bias, if extant, would have been small in these data.

Behavioral mechanisms may also be at work. Both combat and non-combat veterans were more likely to be current drinkers and heavy smokers than non-veterans but less likely to be current smokers and physically inactive. Given the strong link between smoking and atherosclerosis, smoking may be acting as a mediator in the effects found in this study. Still, studies of veterans with and without combat-related PTSD have found that the association between PTSD and poor physical health persists even after controlling for smoking and alcohol consumption.

Heterogeneous physical risk factor profiles among veterans by era may also act as mediators in the combat-CVD association and contribute to inter-era differences. In the study

of subclinical disease, associations were strongest among men who served during the World War II and Korean War eras and weakest among those who served during the era of the Vietnam Conflict. In the study of CHD and IS events, associations were present, though modest, among men from the Korean War era but not the eras of World War II or the Vietnam Conflict. These findings are compatible with those that found combat veterans more likely to have higher rates of diabetes, higher waist circumference and higher triglycerides during the eras of the Korean War and Vietnam Conflict but not the World War II era, and that higher SBP and higher rates of prevalent CHD were found only among combat veterans who served during the era of the Korean War. Similarly, differences in the composite CHD and IS risk scores are in line with inter-era differences in the effect of combat; the ten-year predicted risks of CHD and IS were highest for combat veterans during the Korean War era but not during the eras of World War II or the Vietnam Conflict.

The different social, educational and economic environments and opportunities to which combat veterans, non-combat veterans and non-veterans were exposed may also contribute to differences noted in the effect of combat on cardiovascular health. In the current study, while non-combat veterans consistently had the most favorable SES profiles overall, combat veterans had more favorable adult SES profiles but less favorable early life SES profiles than non-veterans. These differences may reflect the different age distributions in each exposure group, as the socioeconomic position of veterans has increased over time. Alternatively, they may reflect the economic and educational opportunities opened to servicemen through programs such as the Montgomery GI Bill. Given the inverse association between SES and CVD, the more favorable SES profiles of veterans in this study population may attenuate effect estimates if combat does, indeed, adversely affect cardiovascular health.

Reflecting secular trends, Vietnam veterans consistently had the highest education, income and occupation levels in each exposure group.

Interaction by Era of Service

As discussed in the manuscripts, inter-era differences in the association between military and combat exposures with CHD and IS rates may also reflect differences in the type and nature of combat experienced during each of these conflicts as well as the social and political context surrounding them. Given the particularly brutal nature of combat experienced during the Vietnam Conflict and the Korean War and the unfavorable sociopolitical context in which their homecoming occurred, we might expect the effects of combat to be most pronounced among these veterans. In fact, studies comparing postwar readjustment and psychological health among veterans of World War II, the Korean War and the Vietnam Conflict have found the highest rates of PTSD among Korean War and Vietnam Conflict veterans and the lowest among World War II veterans. In line with these findings, the manuscript investigating the association between combat and CHD and IS events reported that associations were present, though modest, among men from the Korean War era but not the eras of World War II or the Vietnam Conflict. While the study investigating the association between combat and subclinical disease also reported associations among men from the Korean War era, associations were also present among those who served during the World War II era but not the Vietnam Conflict era. The apparent disagreement of results among World War II era veterans—that combat is associated with higher rates of subclinical atherosclerosis but not CHD and stroke events—may be a result of differential survival, such

that in this older cohort the majority of events may have already taken place regardless of combat or veteran status, masking differences.

The lack of a finding of an effect of combat in either manuscript among men from the Vietnam Conflict era may reflect a number of factors. The negative sociopolitical atmosphere surrounding the Vietnam Conflict may have acted as a stressor among both combat and non-combat soldiers upon homecoming, attenuating differences. The different demographic profile of the Vietnam Conflict cohort may also have contributed to differences in the effect of combat in this study. Members of this cohort tended to be inducted into the military at a slightly older age than those who served during the World War II or Korean War eras and tended to be of higher socioeconomic position, which, according to current theory, tends to be protective against the effects of traumatic stress. Both older average age at induction and higher average SES among men in this cohort may be a reflection of secular trends in education or in the ability of affluent Vietnam draftees to postpone induction by enrolling in school and obtaining educational deferment. Finally, the younger age at which Vietnam Conflict era veterans' outcomes were assessed in this study, an average of 48 years old, was approximately ten years younger than Korean War era veterans and seventeen years younger than World War II era veterans, which may have contributed to the apparently weaker effect of combat exposure among these participants.

Interaction by Race

The effect of race on the combat-CVD association was assessed in both manuscripts—through stratification of results in the manuscript investigating subclinical disease and descriptively in the manuscript investigating CHD and IS. Consistent with

previous studies that have found that the topographic distribution of atherosclerotic plaque vary by ethnic and racial groups, the present study reported that the association between combat and subclinical atherosclerosis varied by race. Combat-related effects noted in white but not black men may also be related to differences in baseline risk factor profiles. Most notably, white but not black combat veterans were most likely to be heavy smokers, a major risk factor for the development of subclinical atherosclerosis. Alternatively, the low sample size of black men may have masked an effect.

Although results in the manuscript studying the association between combat and CHD and IS events were not stratified, demographic and risk factor profiles were created separately for black and white men. Because black men in the general population tend to have higher rates of CHD and IS than white men, given the larger proportion of black men that participated in the military in the Vietnam Conflict era, we might expect observed effects among the Vietnam Conflict era cohort to be inflated for CHD and IS. However, it is also foreseeable that the effect of race in the combat-CVD association may not be consistent across eras of service, as sociopolitical factors affecting participation of black men in the military and, specifically in combat, differed during the different eras of service investigated. Finally, racial differences are often difficult to disentangle from differences in SES. In the present study, black men had lower adult SES, as measured by education, income and occupation at each combat level and during each era of service. Thus, we might expect the association between combat and CHD and IS event rates to be higher among black men.

Strengths and Limitations

This study provided a rare opportunity to investigate the long-term association of combat exposure on levels of cardiovascular risk in a large community-based cohort. Average follow-up time was long and participants were of an age (60 to 80 years) where CHD is most likely manifest. Among veterans, periods of military service spanned from World War II through the Vietnam Conflict and includes measures of specific combat exposures and both military and civilian controls. Most previous studies have been based on retrospective cohorts and have investigated differences in CVD mortality comparing war theater veterans and non-theater veterans of the same era. Also a particular strength, this study included objective, standardized measures of cardiovascular outcomes and a wide range of physical and behavioral risk factor measures. The availability of socioeconomic measures from various life epochs further offered an unusual opportunity to investigate the role of SES in combat-cardiovascular associations.

The use of self-reported combat exposures presents challenges. Because the combat exposure variable used in this study is based on self-reported information, recall bias may affect results, such that men in worse health may differentially recall their military experiences. Even for participants whose CHD and stroke status was unknown at the time that military exposures were queried, participants may have been aware of their status on other health indicators such as hypertension and high cholesterol status. Although recalled exposure status is not ideal, to our knowledge, no cohorts exist that collected combat exposure during military service and included long-term follow-up with a rigorous measurement of cardiovascular outcomes. Further, defining combat as the exposure to one or more specific use of recalled combat exposures has precedent[719,720, 721] and has high validity

and reliability.[722, 723] Therefore, it is unlikely that differential recollection of past military experiences based on current health status was significant. In fact, use of recalled combat experiences can be viewed as a strength, as it is a more specific and meaningful definition than simply separating exposure groups into theater and non-theater veterans who served during the same era.

As discussed in both manuscripts, we were not able to assess the role of psychological mediators in the associations investigated. While it would have been of interest to provide results stratified on CSR or PTSD status, this information was not queried in the LC-SES interview.[724,725] Psychological status would have been assessed as a potential effect measure modifier rather than as a confounder; consequently its exclusion does not detract from our findings. Our results support the conclusion that the effects of combat exposure extend beyond the narrow scope of these clinical diagnoses.

Finally, although this study includes a large population of men, it does not have adequate statistical power to formally address hypotheses about potential effect measure modification for all of the outcomes assessed. In addition to era of service and race, of particular interest would be to see if there is interaction by age at entry, duration of service, psychological status and type of combat exposure.

Future Directions

Because this study is the first, to of our knowledge, to assess the relationship between combat exposure and clinical or subclinical atherosclerosis or the relationship between combat exposure and incident CHD and IS, the long-term effects of combat on cardiovascular health should be examined in other populations. Ideally, studies would be

population-based, so as to include both veteran and non-veteran controls, and would not include a gap in data collection between the time of exposure and the time of outcome assessment in order to minimize the potential impact of selective survival. Although this study offered a more meaningful measure of exposure than most studies of combat in the published literature, more information about the specific nature, duration and severity of combat would be of benefit in order to have a richer measure of exposure. If the association between combat and subclinical atherosclerosis is confirmed in other studies, whether this carries over into an increased risk of clinical disease and mortality should be investigated. Further, given the inter-era differences noted, future studies should focus on which aspects of combat might help explain these differences, including the role of specific combat exposures and other military factors as well as socio-political factors and homecoming experiences.[726,727]

If future studies support a connection between combat and CVD, an additional challenge will be to elucidate the possible mechanisms through which stress can place an individual at long-term risk for CVD. With a focus on finding pathways for prevention, subsequent studies should assess whether psychosocial stress acts through mediational biological processes such as inflammatory markers as well as through psychological, behavioral or lifestyle changes. In addition, studies with larger sample sizes could better evaluate the potential role of race, SES, pre- and post-military psychological status and other potentially important modifiers of the association between combat and cardiovascular risk. The findings in this study provide key groundwork for future opportunities into an important area of study that have implications for our understanding of the lasting effects of traumatic stress on long-term cardiovascular health.

APPENDICES

A. Institutional Review Board Certification.

Date: Fri, 15 Jun 2007 10:17:40 (EDT)
FROM: UNC-CH IRB
TO: Anne-Marie Johnson
SUBJECT: IRB Notice

TO: Anne-Marie Johnson
Epidemiology
545 Lakeside Dr. Statesville NC 28677

FROM: Public Health-Nursing IRB

_____
Authorized signature on behalf of IRB

APPROVAL DATE: 6/14/2007

EXPIRATION DATE OF APPROVAL: 6/12/2008

RE: Notice of IRB Approval by Expedited Review (under 45 CFR 46.110)
Submission Type: Renewal
Expedited Category: 5.Existing or non-research data
Study #: 05-1140 Also (05-2661)

Study Title: Association Between Exposure to Combat-Related Stress and Predicted Risk of CHD and Stroke in Aging Men: The Atherosclerosis Risk in Communities(ARIC) Study

This submission has been approved by the above IRB for the period indicated. It has been determined that the risk involved in this research is no more than minimal.

Federal regulations require that all research be reviewed at least annually. It is the Principal Investigator's responsibility to submit for renewal and obtain approval before the expiration date. You may not continue any research activity beyond the expiration date without IRB approval. Failure to receive approval for continuation before the expiration date will result in automatic termination of the approval for this study on the expiration date.

When applicable, enclosed are stamped copies of approved consent documents and other recruitment materials. You must copy the stamped consent forms for use with subjects unless you have approval to do otherwise.

You are required to obtain IRB approval for any changes to any aspect of this study before they can be implemented (use the modification form at ohre.unc.edu/forms). Should any adverse event or unanticipated problem involving risks to subjects or others occur it must be reported immediately to the IRB using the adverse event form at the same website.

Study Description:
This student project uses the ARIC data to study the association between exposure to combat stress and cardiovascular (CV) risk factors, sub clinical atherosclerosis, and the predicted risk of and morbidity from stroke and coronary heart disease. Confidentiality and privacy measures are in place. Data use agreement in provided. Criteria are satisfied for waiver of research consent [45 CFR 46.116(d)]. Documentation of education in human research ethics is provided. The risk is no more than minimal. This study is approved by expedited review per Category 5.

Submission Description:
With this renewal, dated June 5, 2007, this study, which has always involved only analysis of existing data or specimens, continues as previously approved.
No modifications are requested with this renewal.

The data use agreement with the ARIC Steering Committee is stated in the application to be valid for three years beginning on July 7, 2004. If the data use agreement needs renewal, it must be done before the current data use agreement expiration date.

Details:
Based on the information provided, the IRB has determined that HIPAA does not apply to this study.

This research meets criteria for a waiver of consent entirely according to 45 CFR 46.116(d).

Call the IRB at 966-3113 if you have any questions. You can now access IRB status information at https://my.research.unc.edu/.

This study was reviewed in accordance with federal regulations governing human subjects research, including those found at 45 CFR 46 (Common Rule), 45 CFR 164 (HIPAA), and 21 CFR 50 & 56 (FDA), where applicable.

The University of North Carolina at Chapel Hill holds a Federal Wide Assurance approved by the Office for Human Research Protections, Department of Health and Human Services (FWA # 4801).

CC: Gerardo Heiss, Epidemiology, CB# 8050 Bank of America Suite, Faculty Advisor

In addition:

CITI Human Subjects Approval was acknowledged on 7/6/05, 6/4/06 and 5/20/2007;

Data Use and Distribution Agreement of the ARIC data was entered into as of 5/31/2005;

Data Use and Distribution Agreement of the LC-SES data was entered into as of 7/5/2005;

ARIC Publications Committee accepted this study as manuscript proposal 1017 on 7/7/2004.

B. Annual Follow-up Interview Questions, 2001-2002 (Select Questions).

AFU RESIDENTIAL/OCCUPATIONAL HISTORY (SESB)

E. MILITARY SERVICE OR EXPOSURE TO WAR

Y = Yes
N = No
U = Unsure

37. Did you ever serve in the armed forces? …… Y N U
38. How old were you when you first entered? ……Y N U
39. For how many years all together did you serve in active duty? ……Y N U
40. While in the armed services, did you ever serve over-seas? ……. Y N U
41. Did you ever serve in a combat zone? ……... Y N U
42. Were you ever under enemy fire or did you ever fire at the enemy? …… Y N U
43. Did you ever see anyone wounded or killed during the war? …… Y N U
44. Were you ever wounded, or declared a prisoner of war or missing in action? .. Y N U

C. Supplemental Results, Manuscript 1.

Table 22. Wald Tests for Interaction on the Multiplicative Scale (Risk Ratio Using Modified Poisson Regression).

OUTCOME: Plaque		
Potential modifier	**Wald p-value ($p > \chi^2$)**	**Interpretation**
NCV v. NV		
Race	0.5672	No interaction
CV v. NV		
Race	0.2099	No interaction
CV v. NCV		
Race	0.4741	No interaction
Era of service	0.6207	No interaction
OUTCOME: Binary CIMT		
Potential modifier	**Wald p-value ($p > \chi^2$)**	**Interpretation**
NCV v. NV		
Race	0.9672	No interaction
CV v. NV		
Race	0.9810	No interaction
CV v. NCV		
Race	0.9543	No interaction
Era of service	0.2743	No interaction

H_0: OR are equal across strata. If $p<0.20$ then reject H_0.
NOTE: Tests are underpowered; i.e., cannot conclude that no interaction is present.

Table 23. Distribution of Age in Years (Categorized) by Era of Service.

	Age in years			
Era of Service N (%)	**44-49** (n=648)	**50-54** (n=768)	**55-59** (n=986)	**60-66** (n=903)
World War II (n=792)	0	0	48 (6.1)	744 (93.9)
Korean war (n=1082)	0	207 (19.1)	777 (71.8)	98 (9.1)
Vietnam conflict (n=704)	529 (75.1)	165 (23.4)	9 (1.3)	1 (0.1)
Between periods of defined conflict (n=727)	119 (16.4)	396 (54.5)	152 (20.9)	60 (8.3)

Table 24. Mean Age at Induction into the Military, by Era of Service, Including Men Who Served Between Periods of Defined Conflict.

	Non-Combat Veterans			Combat Veterans		
Era of Service N (%)	**N**	**Mean**	**SD**[1]	**N**	**Mean**	**SD**
World War II (n=792)	314	17.86	0.92	478	17.98	1.03
Korean war (n=1082)	675	19.70	1.88	407	19.35	1.86
Vietnam conflict (n=704)	506	21.16	2.79	198	20.87	3.31
Between periods of defined conflict (n=727)	621	19.93	2.31	92	19.50	2.42

[1] SD = Standard Deviation

Table 25. Observed Carotid Plaque and Carotid Intima-Media Thickness through 2002, Stratified by Education and Field Center.

	Non-Combat Veterans vs. Non-Veterans[1]			Combat Veterans vs. Non-Veterans		
	OR[2] Plaque	**OR CIMT**	**RD CIMT**	**OR Plaque**	**OR CIMT**	**RD CIMT**
Education						
< High school	1.645 (1.082, 2.501)	1.581 (0.986, 2.536)	0.0378 (0.0118, 0.0637)	2.301 (1.522, 3.480)	2.550 1.631, 3.987)	0.0394 (0.0251, 0.0536)
High school or equivalent	1.218 (0.851, 1.744)	0.921 (0.613, 1.383)	0.0050 (-0.0117, 0.0217)	1.841 (1.249, 2.713)	1.838 (1.212, 2.789)	0.0274 (0.0171, 0.0378)
> High school	1.792 (1.173, 2.737)	1.732 (1.065, 2.818)	0.0324 (0.0184, 0.0465)	2.877 (1.844, 4.487)	3.145 (1.910, 5.180)	0.0322 (0.0238, 0.0406)
Field Center						
Forsyth County, NC	1.226 (0.802, 1.876)	0.830 (0.537, 1.283)	0.0056 (-0.0139, 0.0250)	1.635 (0.986, 2.713)	1.363 (0.823, 2.257)	0.0259 (0.0123, 0.0395)
Jackson, MS	0.792 (0.405, 1.551)	0.874 (0.418, 1.830)	0.0084 (-0.0139, 0.0306)	1.502 (0.758, 2.978)	2.394 (1.222, 4.692)	0.0168 (0.0022, 0.0313)
Minneapolis, MN	1.370 (0.907, 2.069)	1.451 (0.897, 2.347)	0.0257 (0.0056, 0.0457)	2.231 (1.454, 3.423)	2.726 (1.679, 4.428)	0.0349 (0.0230, 0.0467)
Washington County, MD	1.176 (0.777, 1.781)	1.086 (0.638, 1.848)	0.0072 (-0.0120, 0.0263)	1.921 (1.270, 2.905)	2.348 (1.422, 3.876)	0.0297 (0.0191, 0.0404)

[1] Combat Veterans are identified by a summary variable based on whether or not the individual served in the military and, if so, whether the individual (1) served in a combat zone, (2) was under enemy fire or fired at enemy, (3) saw wounded or killed during war, and/or (4) was ever wounded during war; Non-Combat Veterans are defined as those who served in the military but did not report any combat exposures (1-4).

[2] OR = Odds ratio; RD = Risk Difference

Table 26: Observed Carotid Plaque and Carotid Intima-Media Thickness through 2002, Stratified by Race, Adjusted for Age.

	Non-Combat Veterans vs. Non-Veterans[1]	Combat Veterans vs. Non-Veterans	Combat Veterans vs. Non-Combat Veterans
Plaque (OR (95% CI)) [2]			
Unadjusted	1.15 (1.01, 1.30)	1.42 (1.22, 1.64)	1.24 (1.07, 1.43)
Age Adjusted	0.98 (0.86, 1.11)	0.92 (0.78, 1.09)	1.00 (0.85, 1.16)
Age-adjusted, by race			
African-Americans only	0.86 (0.63, 1.18)	0.74 (0.50, 1.11)	0.88 (0.57, 1.35)
Caucasians only	0.98 (0.85, 1.14)	0.93 (0.77, 1.13)	1.02 (0.86, 1.20)
Age-adjusted, by era of service			
World War II only	N/A	N/A	1.19 (0.87, 1.64)
Korean War only	N/A	N/A	1.10 (0.85, 1.42)
Vietnam conflict only	N/A	N/A	0.88 (0.61, 1.26)
Between periods of defined conflict only	N/A	N/A	0.78 (0.50, 1.22)
CIMT (µm) (RD (95% CI))			
Unadjusted	12.50 (2.6, 22.3)	28.6 (22.5, 34.6)	44.68 (32.47, 56.89)
Age Adjusted	-10.3 (-19.9, -0.8)	0.3 (-0.6.1, 6.6)	12.79 (0.72, 24.86)
Age-adjusted, by race			
African-Americans only	-8.51 (-29.13, 12.11)	-5.18 (-18.57, 8.21)	-7.08 (-37.40, 23.24)
Caucasians only	-9.88 (-20.99, 1.23)	0.65 (-6.72, 8.02)	15.89 (2.74, 29.04)
Age-adjusted, by era of service			
World War II only	N/A	N/A	16.66 (-12.86, 46.18)
Korean War only	N/A	N/A	16.89 (-4.14, 37.92)
Vietnam conflict only	N/A	N/A	4.22 (-15.56, 24.00)
Between periods of defined conflict only	N/A	N/A	10.64 (7.11, 14.17)
CIMT ≥ 1 mm (OR (95% CI))			
Unadjusted	1.115 (0.87, 1.43)	2.170 (1.685, 2.80)	1.95 (1.53, 2.48)
Age Adjusted	0.836 (0.65, 1.08)	1.080 (0.811, 1.44)	1.27 (0.97, 1.65)
Age-adjusted, by race			
African-Americans only	0.810 (0.41, 1.59)	1.273 (0.62, 2.61)	1.385 (0.62, 3.09)
Caucasians only	0.792 (0.60, 1.06)	0.975 (0.71, 1.34)	1.250 (0.95, 1.65)
Age-adjusted, by era of service			
World War II only	N/A	N/A	1.09 (0.72, 1.65)
Korean War only	N/A	N/A	1.63 (1.08, 2.45)
Vietnam conflict only	N/A	N/A	0.99 (0.30, 3.27)
Between periods of defined conflict only	N/A	N/A	1.51 (0.67, 3.40)

[1] Combat Veterans are identified by a summary variable based on whether or not the individual served in the military and, if so, whether the individual (1) served in a combat zone, (2) was under enemy fire or fired at enemy, (3) saw wounded or killed during war, and/or (4) was ever wounded during war; Non-Combat Veterans are defined as those who served in the military but did not report any combat exposures (1-4).

[2] OR = Odds ratio; RD = Risk Difference

Table 27: Profile of Recalled Military Service and Combat History Reported During the LC-SES Interview, by War/Conflict Era (Including Men Who Served between Periods of Defined Conflict).

	Non-Combat Veterans *					Combat Veterans *				
	Total	**World War II**	**Korean War**	**Vietnam Conflict**	**Between conflicts**	**Total**	**World War II**	**Korean War**	**Vietnam Conflict**	**Between conflicts**
N	**2127**	**314**	**675**	**506**	**632**	**1178**	**478**	**407**	**198**	**95**
Mean (SD) Age at induction into service (years)	19.8 (2.4)	17.9 (0.9)	19.7 (1.9)	21.2 (2.8)	19.9 (2.3)	19.1 (2.2)	18.0 (1.0)	19.4 (1.9)	20.9 (3.3)	19.5 (2.4)
Mean (SD) Elapsed time since age at induction into service (years) [3]	34.3 (5.9)	43.6 (1.3)	36.6 (2.0)	27.0 (3.0)	32.9 (3.5)	38.2 (6.8)	44.5 (1.3)	37.3 (2.0)	26.7 (3.7)	34.5 (4.5)
Mean (SD) Duration of service (years)	3.1 (3.2)	2.5 (2.2)	3.5 (3.7)	4.0 (4.4)	2.1 (1.1)	4.9 (5.6)	4.2 (4.5)	5.2 (6.1)	7.2 (7.2)	2.5 (1.1)
n (%) Served overseas	1085 (51.0)	169 (54.2)	384 (56.9)	244 (48.2)	288 (45.9)	1108 (94.1)	460 (96.4)	392 (96.3)	182 (91.9)	74 (77.9)
n (%) Served in combat zone	N/A	N/A	N/A	N/A	N/A	975 (82.8)	430 (90.0)	339 (83.3)	163 (82.3)	43 (45.7)
n (%) Under enemy fire or fired at enemy	N/A	N/A	N/A	N/A	N/A	700 (59.7)	337 (70.7)	229 (56.8)	110 (55.6)	24 (25.3)
n (%) Saw wounded or killed during war	N/A	N/A	N/A	N/A	N/A	853 (72.7)	357 (74.8)	294 (73.0)	139 (70.2)	63 (66.3)
n (%) Ever wounded or missing during war	N/A	N/A	N/A	N/A	N/A	154 (13.1)	76 (15.9)	57 (14.1)	18 (9.1)	3 (3.2)

[1] Combat Veterans are identified by a summary variable based on whether or not the individual served in the military and, if so, whether the individual (1) served in a combat zone, (2) was under enemy fire or fired at enemy, (3) saw wounded or killed during war, and/or (4) was ever wounded during war; Non-Combat Veterans are defined as those who served in the military but did not report any combat exposures (1-4).

[2] OR = Odds ratio; RD = Risk Difference

[3] Age at Visit 1 – self-reported age at entry into the military

Table 28: Sociodemographic Profile at Entry into the ARIC Cohort, by Military Service and Combat History, by War/Conflict Era (Including Men Who Served between Periods of Defined Conflict).

	NV Total	Non-Combat Veterans [1]					Combat Veterans				
		Total	World War II	Korean War	Vietnam Conflict	Between conflicts	Total	World War II	Korean War	Vietnam Conflict	Between conflicts
N	**2042**	**2127**	**314**	**675**	**506**	**632**	**1178**	**478**	**407**	**198**	**95**
Mean (SD) Age at Baseline ARIC Visit (years)	51.8 (5.2)	54.12 (5.1)	61.5 (1.6)	56.3 (2.4)	48.2 (2.5)	52.9 (3.6)	57.3 (5.8)	62.5 (1.5)	56.7 (2.2)	47.6 (2.6)	54.3 (4.7)
n (%) African-American	643 (31.5)	278 (13.1)	37 (11.8)	88 (13.0)	75 (14.8)	78 (12.3)	155 (13.2)	45 (9.4)	60 (14.7)	39 (19.7)	11 (11.6)
n (%) Education < High School	625 (30.7)	244 (11.5)	77 (24.5)	94 (14.0)	20 (4.0)	53 (8.4)	209 (17.8)	112 (23.4)	67 (16.5)	8 (4.1)	22 (23.2)
n (%) Natural Father's Education < High School [2]	1010 (61.0)	1102 (59.4)	178 (63.1)	374 (64.0)	219 (50.9)	331 (59.3)	634 (61.4)	282 (64.7)	229 (65.4)	79 (48.2)	44 (53.0)
n (%) Combined Family Income < $25,000	625 (32.5)	368 (18.0)	81 (26.8)	135 (20.6)	63 (12.9)	89 (14.8)	284 (25.3)	163 (35.8)	74 (19.2)	26 (13.7)	21 (22.8)
n (%) Occupation Non-Managerial/ Professional	1446 (70.9)	1382 (65.0)	245 (78.0)	446 (66.1)	302 (59.7)	389 (61.6)	903 (76.7)	412 (86.2)	290 (71.3)	132 (66.7)	69 (72.6)

Note: columns may not sum to 100% due to rounding

[1] Combat Veterans (CV) are identified by a summary variable based on whether or not the individual served in the military and, if so, whether the individual (1) served in a combat zone, (2) was under enemy fire or fired at enemy, (3) saw wounded or killed during war, and/or (4) was ever wounded during war; Non-Combat Veterans (NCV) are defined as those who served in the military but did not report any combat exposures (1-4).

[2] 804 values missing information on natural father's education

Table 29. Profile of Cardiovascular Risk Factors and Morbidity at Entry into the ARIC Cohort, by Military Service and Combat History, Means (Standard Deviations) or Frequencies (Percentages).

	Non-Veterans [2]	Non-Combat Veterans	Combat Veterans
N	**2042**	**2127**	**1178**
Behavioral Risk Factors [1]			
n (%) Current Alcoholic Drinking	1212 (59.73)	1492 (70.34)	824 (70.31)
n (%) Current Cigarette smoking status	541 (26.51)	473 (22.25)	247 (20.99)
n (%) Heavy Cigarette years of smoking	438 (21.85)	545 (25.93)	368 (31.72)
n (%) Physically inactive	616 (30.36)	843 (39.75)	515 (43.90)
Physical Risk Factors			
Mean (SD) BMI (m/kg^2)	27.8 (4.4)	27.2 (3.8)	27.7 (4.0)
Mean (SD) Waist circumference (cm)	99.1 (11.6)	98.4 (10.0)	99.6 (10.3)
Mean (SD) Systolic BP (mmHg)	121.8 (17.6)	119.9 (16.3)	122.5 (16.7)
Mean (SD) Diastolic BP (mmHg)	76.6 (11.6)	74.6 (10.3)	74.4 (10.2)
Mean (SD) Total cholesterol (mg/dL)	209.7 (39.8)	210.7 (37.9)	213.5 (40.4)
Mean (SD) LDL cholesterol (mg/dL)	138.3 (37.3)	139.6 (35.4)	141.9 (37.0)
Mean (SD) HDL cholesterol (mg/dL)	44.8 (13.5)	44.2 (13.2)	43.7 (12.8)
Mean (SD) Triglycerides (mg/dL)	137.0(84.8)	140.3 (96.9)	148.1 (110.7)
n (%) Hypertension	671 (32.9)	617 (29.0)	377 (32.0)
n (%) Prevalent Diabetes	213 (10.6)	167 (7.9)	123 (10.5)
n (%) Prevalent CHD	107 (5.2)	117 (5.5)	94 (8.0)

Because of missing data, N differs in some variables.

Some columns may not sum to 100% due to rounding.

[1] Current alcohol drinking is defined as self-report of drinking any alcohol at baseline; Current cigarette smoking is defined as self-report of smoking one or more cigarettes per year at baseline; Heavy cigarette years of smoking is calculated by multiplying the number of cigarettes smoked per year by the number of years the individual has been smoking and is defined as having smoked 660 or more cigarettes; Physical inactivity is defined as having a sports activity index score less than 2.0.

[2] Combat Veterans (CV) are identified by a summary variable based on whether or not the individual served in the military and, if so, whether he (1) served in a combat zone, (2) was under enemy fire or fired at enemy, (3) saw wounded or killed during war, and/or (4) was ever wounded during war; Non-Combat Veterans (NCV) are defined as those who served in the military but did not report any combat

Table 30. Frequencies and Percentages of Men Who Fall into the 85th and 90th Percentiles of Carotid Intima Media Thickness (CIMT) by Race and Age Category.

85th percentile	CIMT 85th percentile cutpoint by race and age category	n (%) total	> 85th percentile	≤ 85th percentile
By race/age category				
Black 45-54	0.8324	678 (100)	101 (14.9)	577 (85.1)
Black 55-65	0.9402	398 (100)	59 (14.8)	339 (85.2)
White 45-54	0.8289	2215 (100)	331 (14.9)	1884 (85.1)
White 55-65	0.9805	2056 (100)	308 (15.0)	1748 (85.0)
By combat exposure				
Non-veteran	N/A	2042 (100)	302 (14.8)	1740 (85.2)
Non-combat veteran	N/A	2127 (100)	293 (13.8)	1834 (86.2)
Combat veteran	N/A	1178 (100)	204 (17.3)	974 (82.7)
90th percentile	**CIMT 90th percentile cutpoint by race and age category**	**n (%) total**	**> 90th percentile**	**≤ 90th percentile**
By race/age category				
Black 45-54	0.8883	678 (100)	64 (9.4)	614 (90.6)
Black 55-65	0.9820	398 (100)	38 (9.6)	360 (90.4)
White 45-54	0.8730	2215 (100)	219 (9.9)	1996 (90.1)
White 55-65	1.0604	2056 (100)	204 (9.9)	1852 (90.1)
By combat exposure				
Non-veteran	N/A	2042 (100)	200 (9.8)	1842 (90.2)
Non-combat veteran	N/A	2127 (100)	193 (9.1)	1934 (90.9)
Combat veteran	N/A	1178 (100)	132 (11.2)	1046 (88.8)

Table 31: Observed Carotid Plaque and Carotid Intima-Media Thickness (CIMT) through 2002, by Military Service and Combat History, Means (Standard Deviations) or Frequencies (Percentages), LC-SES Men *versus* ARIC Men.

	LCSES men				ARIC men
	Total	**Non-Veterans** [2]	**Non-Combat Veterans**	**Combat Veterans**	**Total**
N	**5347**	**2042**	**2127**	**1178**	
n (%) Plaque	2423 (48.4)	858 (45.09)	970 (48.48)	595 (53.75)	3368 (51.96)
Mean (SD) 3-year average CIMT (μm)[1]	762.9 (167.3)	745.2 (157.7)	757.7 (164.1)	802.4 (182.2)	784.6 (186.1)
n (%) 3-year average CIMT ≥ 1 (μm)	408 (7.7)	122 (6.08)	142 (6.74)	144 (12.33)	719 (10.40)
n (%) CIMT > 85th percentile 3-year average CIMT (μm)	661 (12.4)	255 (12.49)	242 (11.38)	164 (13.92)	1052 (14.96)

NOTE: ARIC men have less favorable plaque and CIMT profiles, even after age and race-specific percentiles of CIMT are considered.

[1]Average far wall imputed CIMT over ARIC Visits 1 and 2; 85th percentile of CIMT for all African-American or Caucasian male ARIC participants; four separate age and race-specific 85th percentile cutpoints were used: Black men ages 45-54, Black men ages 55-65, White men ages 45-54 and White men ages 55-65.

[2] Combat Veterans (CV) are identified by a summary variable based on whether or not the individual served in the military and, if so, whether the individual (1) served in a combat zone, was under enemy fire or fired at enemy, (3) saw wounded or killed during war, and/or (4) was ever wounded during war; Non-Combat Veterans (NCV) are defined as those who served in the military but did not report any combat exposures (1-4).

Table 32: Profile of Behavioral Cardiovascular Risk Factors and Morbidity at Baseline, by Race and Era of Combat, Means (Standard Deviations) or Frequencies (Percentages).

	Non-Veterans [2]	Non-Combat Veterans	Combat Veterans
N	**2042**	**2127**	**1178**
n (%) Current alcoholic drinking [1]			
Total	1212 (59.7)	1492 (70.3)	824 (70.3)
By race			
African-American	289 (45.7)	144 (52.2)	94 (61.4)
Caucasian	923 (66.1)	1348 (73.1)	730 (71.6)
By era of service			
World War II	N/A	199 (63.6)	341 (71.8)
Korean War	N/A	455 (67.7)	272 (66.8)
Vietnam conflict	N/A	380 (75.1)	144 (73.5)
n (%) Current cigarette smoking status			
Total	541 (26.5)	473 (22.3)	247 (21.0)
By race			
African-American	233 (36.2)	82 (29.5)	46 (29.9)
Caucasian	308 (22.0)	391 (21.2)	201 (19.7)
By era of service			
World War II	N/A	44 (14.0)	70 (14.6)
Korean War	N/A	139 (20.6)	108 (26.6)
Vietnam conflict	N/A	136 (26.9)	44 (22.2)
n (%) Heavy cigarette years of smoking			
Total	438 (21.9)	545 (25.9)	368 (31.7)
By race			
African-American	104 (16.8)	50 (18.5)	23 (15.7)
Caucasian	334 (24.1)	495 (27.0)	345 (34.1)
By era of service			
World War II	N/A	94 (30.3)	163 (34.6)
Korean War	N/A	209 (31.2)	147 (36.8)
Vietnam conflict	N/A	94 (18.8)	32 (16.4)
n (%) Physically inactive			
Total	616 (30.4)	843 (39.8)	515 (43.9)
By race			
African-American	217 (34.2)	95 (34.3)	50 (32.7)
Caucasian	299 (21.5)	307 (16.7)	163 (16.0)
By era of service			
World War II	N/A	59 (18.9)	73 (15.3)
Korean War	N/A	142 (21.1)	84 (20.7)
Vietnam conflict	N/A	90 (17.8)	38 (19.3)

Because of missing data, N differs in some variables.
Some columns may not sum to 100% due to rounding.

[1] Current alcohol drinking is defined as self-report of drinking any alcohol at baseline; Current cigarette smoking is defined as self-report of smoking one or more cigarettes per year at baseline; Heavy cigarette years of smoking is calculated by multiplying the number of cigarettes smoked per year by the number of years the individual has been smoking and is defined as having smoked 660 or more cigarettes; Physical inactivity is defined as having a sports activity index score less than 2.0.

[2] Combat Veterans (CV) are identified by a summary variable based on whether or not the individual served in the military and, if so, whether he (1) served in a combat zone, was under enemy fire or fired at enemy, (3) saw wounded or killed during war, and/or (4) was ever wounded during war; Non-Combat Veterans (NCV) are defined as those who served in the military but did not report any combat exposures (1-4).

Table 33. Profile of Physical Cardiovascular Risk Factors and Morbidity at Baseline, by Race and Era of Combat, Means (Standard Deviations) or Frequencies (Percentages).

	Non-Veterans [1]	Non-Combat Veterans	Combat Veterans
N	**2042**	**2127**	**1178**
Mean (SD) BMI (m/kg^2)			
Total	27.8 (4.4)	27.2 (3.8)	27.7 (4.0)
By race			
African-American	27.9 (4.6)	27.9 (4.9)	27.8 (4.7)
Caucasian	27.7 (4.3)	27.0 (3.6)	27.7 (3.8)
By era of service			
World War II	N/A	27.4 (3.9)	27.3 (3.6)
Korean War	N/A	27.1 (3.8)	27.9 (4.2)
Vietnam conflict	N/A	27.0 (3.9)	27.9 (4.1)
Mean (SD) Waist circumference (cm)			
Total	99.1 (11.6)	98.4 (10.0)	99.6 (10.3)
By race			
African-American	97.0 (12.3)	97.2 (12.2)	96.9 (12.1)
Caucasian	100.0 (11.2)	98.6 (9.6)	100.0 (9.9)
By era of service			
World War II	N/A	99.7 (9.9)	99.3 (9.5)
Korean War	N/A	98.7 (9.9)	99.7 (10.6)
Vietnam conflict	N/A	97.1 (10.3)	99.4 (10.8)
Mean (SD) Systolic BP (mmHg)			
Total	121.8 (17.6)	119.9 (16.3)	122.5 (16.7)
By race			
African-American	128.2 (20.2)	127.6 (19.5)	130.2 (19.2)
Caucasian	118.8 (15.4)	118.8 (15.4)	121.4 (16.0)
By era of service			
World War II	N/A	125.7 (18.9)	125.6 (17.3)
Korean War	N/A	120.8 (16.3)	122.5 (16.0)
Vietnam conflict	N/A	116.1 (14.6)	116.6 (14.5)
Mean (SD) Diastolic BP (mmHg)			
Total	76.6 (11.6)	74.6 (10.3)	74.4 (10.2)
By race			
African-American	82.8 (12.3)	81.7 (11.8)	81.4 (12.2)
Caucasian	73.8 (10.0)	73.6 (9.6)	73.3 (9.4)
By era of service			
World War II	N/A	74.1 (10.6)	73.6 (10.1)
Korean War	N/A	74.8 (10.3)	74.9 (10.1)
Vietnam conflict	N/A	74.2 (11.0)	75.2 (10.6)
Mean (SD) Total cholesterol (mg/dL)			
Total	209.7 (39.8)	210.7 (37.9)	213.5 (40.4)
By race			
African-American	211.9 (43.3)	213.6 (41.9)	214.6 (45.4)
Caucasian	208.7 (38.1)	210.2 (37.2)	213.4 (39.6)
By era of service			
World War II	N/A	212.0 (37.9)	214.3 (38.0)
Korean War	N/A	212.5 (37.3)	214.6 (42.6)
Vietnam conflict	N/A	205.9 (39.0)	207.7 (41.0)

	Non-Veterans [1]	Non-Combat Veterans	Combat Veterans
Mean (SD) LDL cholesterol (mg/dL)			
Total	138.3 (37.3)	139.6 (35.4)	141.9 (37.0)
By race			
African-American	138.7 (41.3)	141.2 (41.0)	142.7 (41.9)
Caucasian	138.0 (35.4)	139.4 (34.4)	141.7 (36.3)
By era of service			
World War II	N/A	139.8 (35.0)	142.0 (35.1)
Korean War	N/A	141.5 (35.3)	143.4 (38.8)
Vietnam conflict	N/A	134.9 (36.0)	136.5 (37.0)
Mean (SD) HDL cholesterol (mg/dL)			
Total	44.8 (13.5)	44.2 (13.2)	43.7 (12.8)
By race			
African-American	50.4 (15.9)	49.2 (14.9)	49.1 (15.2)
Caucasian	42.4 (11.5)	43.4 (12.8)	42.9 (12.2)
By era of service			
World War II	N/A	44.7 (14.1)	44.1 (12.2)
Korean War	N/A	43.9 (12.8)	43.3 (13.2)
Vietnam conflict	N/A	43.9 (13.0)	43.6 (13.1)
Mean (SD) Triglycerides (mg/dL)			
Total	137.0 (84.8)	140.3 (96.9)	148.1 (110.7)
By race			
African-American	117.1 (73.2)	115.7 (61.0)	125.7 (102.1)
Caucasian	145.8 (88.1)	143.9 (100.6)	151.4 (111.6)
By era of service			
World War II	N/A	142.5 (92.0)	142.3 (71.1)
Korean War	N/A	139.3 (88.8)	150.8 (110.1)
Vietnam conflict	N/A	141.7 (95.6)	160.2 (180.1)
n (%) Hypertension			
Total	671 (32.9)	617 (29.0)	377 (32.0)
By race			
African-American	314 (58.9)	138 (49.8)	81 (52.26)
Caucasian	354 (25.4)	476 (25.9)	293 (28.90)
By era of service			
World War II	N/A	133 (42.6)	172 (36.3)
Korean War	N/A	212 (31.5)	132 (32.5)
Vietnam conflict	N/A	104 (20.7)	41 (21.1)
n (%) Prevalent Diabetes			
Total	213 (10.6)	167 (7.9)	123 (10.5)
By race			
African-American	99 (15.9)	31 (11.4)	19 (12.5)
Caucasian	114 (8.2)	136 (7.4)	104 (10.2)
By era of service			
World War II	N/A	40 (12.7)	56 (11.8)
Korean War	N/A	55 (8.2)	36 (8.9)
Vietnam conflict	N/A	29 (5.8)	17 (8.6)

	Non-Veterans [1]	Non-Combat Veterans	Combat Veterans
n (%) Prevalent CHD			
Total	107 (5.2)	117 (5.5)	94 (8.0)
By race			
African-American	20 (3.2)	9 (3.3)	8 (5.2)
Caucasian	85 (6.2)	105 (5.8)	84 (8.4)
By era of service			
World War II	N/A	36 (11.6)	45 (9.6)
Korean War	N/A	42 (6.4)	37 (9.3)
Vietnam conflict	N/A	12 (2.4)	4 (2.0)

[1] Combat Veterans (CV) are identified by a summary variable based on whether or not the individual served in the military and, if so, whether he (1) served in a combat zone, was under enemy fire or fired at enemy, (3) saw wounded or killed during war, and/or (4) was ever wounded during war; Non-Combat Veterans (NCV) are defined as those who served in the military but did not report any combat exposures (1-4).

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Table 34: Profile of Physical Cardiovascular Risk Factors and Morbidity at Baseline, by Race and Era of Combat, Means (Standard Deviations) or Frequencies (Percentages), LC-SES Men and ARIC Men.

	LCSES men				ARIC men
	Total	**Non-Veterans** [2]	**Non-Combat Veterans**	**Combat Veterans**	**Total**
N	**5347**				**7030**
n (%) Current drinking [1]					
Total	3528 (66.0)	1212 (59.7)	1492 (70.3)	824 (70.3)	4526 (64.7)
African-American	527 (49.6)	289 (45.7)	144 (52.2)	94 (61.4)	782 (49.5)
Caucasian	3001 (70.5)	923 (66.1)	1348 (73.1)	730 (71.6)	3744 (69.2)
World War II	540 (68.5)	N/A	199 (63.6)	341 (71.8)	540 (68.5)
Korean War	727 (67.4)	N/A	455 (67.7)	272 (66.8)	727 (67.4)
Vietnam conflict	524 (74.6)	N/A	380 (75.1)	144 (73.5)	524 (74.6)
n (%) Current smoking					
Total	1261 (23.6)	541 (26.5)	473 (22.3)	247 (21.0)	1952 (27.8)
African-American	361 (33.6)	233 (36.2)	82 (29.5)	46 (29.9)	615 (38.4)
Caucasian	900 (21.1)	308 (22.0)	391 (21.2)	201 (19.7)	1337 (24.6)
World War II	114 (14.4)	N/A	44 (14.0)	70 (14.6)	114 (14.4)
Korean War	247 (22.9)	N/A	139 (20.6)	108 (26.6)	247 (22.9)
Vietnam conflict	180 (25.6)	N/A	136 (26.9)	44 (22.2)	18 (25.6)
n (%) Years of heavy smoking					
Total	1351 (25.3)	438 (21.9)	545 (25.9)	368 (31.7)	2111 (30.6)
African-American	177 (17.07)	104 (16.8)	50 (18.5)	23 (15.7)	355 (23.1)
Caucasian	1174 (27.8)	334 (24.1)	495 (27.0)	345 (34.1)	1756 (32.7)
World War II	257 (32.9)	N/A	94 (30.3)	163 (34.6)	257 (32.9)
Korean War	356 (33.3)	N/A	209 (31.2)	147 (36.8)	356 (33.3)
Vietnam conflict	126 (18.1)	N/A	94 (18.8)	32 (16.4)	126 (18.1)
n (%) Physically inactive					
Total	1131 (21.3)	616 (30.4)	843 (39.8)	515 (43.9)	1645 (23.5)
African-American	362 (34.0)	217 (34.2)	95 (34.3)	50 (32.7)	588 (37.1)
Caucasian	769 (18.1)	299 (21.5)	307 (16.7)	163 (16.0)	1057 (19.5)
World War II	132 (16.7)	N/A	59 (18.9)	73 (15.3)	132 (16.7)
Korean War	226 (21.0)	N/A	142 (21.1)	84 (20.7)	226 (21.0)
Vietnam conflict	128 (18.2)	N/A	90 (17.8)	38 (19.3)	128 (18.2)
n (%) Used blood pressure-lowering medications in past 2 weeks					
Total	1289 (24.1)	493 (24.1)	495 (23.3)	301 (25.6)	1921 (27.4)
African-American	353 (32.8)	201 (31.3)	103 (37.2)	49 (31.6)	577 (36.1)
Caucasian	936 (21.9)	292 (20.9)	392 (21.2)	252 (24.7)	1344 (24.8)
World War II	257 (32.5)	N/A	118 (37.6)	139 (29.1)	257 (32.5)
Korean War	288 (26.7)	N/A	175 (25.9)	113 (27.9)	288 (26.7)
Vietnam conflict	106 (15.1)	N/A	78 (15.4)	28 (14.1)	106 (15.1)

	LCSES men				ARIC men
	Total	**Non-Veterans** [2]	**Non-Combat Veterans**	**Combat Veterans**	**Total**
n (%) Used cholesterol-lowering medications in past 2 weeks					
Total	151 (2.9)	53 (2.6)	64 (3.0)	34 (2.9)	216 (3.1)
African-American	15 (1.4)	7 (1.1)	7 (1.5)	4 (2.6)	22 (1.4)
Caucasian	136 (3.2)	46 (3.3)	60 (3.3)	30 (3.0)	194 (3.6)
World War II	25 (3.2)	N/A	10 (3.2)	15 (3.2)	25 (3.2)
Korean War	34 (3.2)	N/A	25 (3.7)	9 (2.2)	34 (3.2)
Vietnam conflict	19 (2.7)	N/A	13 (2.6)	6 (3.1)	19 (2.7)
n (%) Left ventricular hypertrophy present by Cornell definition					
Total	94 (1.8)	48 (2.4)	29 (1.4)	17 (1.5)	151 (2.2)
African-American	55 (5.3)	33 (5.35)	15 (5.6)	7 (4.6)	92 (6.0)
Caucasian	39 (0.9)	15 (1.1)	14 (0.8)	10 (1.0)	59 (1.1)
World War II	17 (2.2)	N/A	10 (3.3)	7 (1.5)	17 (2.2)
Korean War	13 (1.2)	N/A	5 (0.8)	8 (2.0)	13 (1.2)
Vietnam conflict	5 (0.7)	N/A	4 (0.8)	1 (0.5)	5 (0.7)
n (%) Prevalent Diabetes					
Total	503 (9.4)	213 (10.6)	167 (7.9)	123 (10.5)	844 (12.1)
African-American	149 (14.2)	99 (15.9)	31 (11.4)	19 (12.5)	291 (18.6)
Caucasian	354 (8.3)	114 (8.2)	136 (7.4)	104 (10.2)	553 (10.2)
World War II	96 (12.2)	N/A	40 (12.7)	56 (11.8)	96 (12.2)
Korean War	91 (8.4)	N/A	55 (8.2)	36 (8.9)	91 (8.4)
Vietnam conflict	46 (6.6)	N/A	29 (5.8)	17 (8.6)	46 (6.6)
n (%) Prevalent CHD					
Total	311 (5.9)	107 (5.2)	117 (5.5)	94 (8.0)	574 (8.3)
African-American	37 (3.50)	20 (3.2)	9 (3.3)	8 (5.2)	93 (5.92)
Caucasian	274 (6.54)	85 (6.2)	105 (5.8)	84 (8.4)	481 (9.05)
World War II	81 (10.41)	N/A	36 (11.6)	45 (9.6)	81 (10.41)
Korean War	79 (7.47)	N/A	42 (6.4)	37 (9.3)	79 (7.47)
Vietnam conflict	16 (2.31)	N/A	12 (2.4)	4 (2.0)	16 (2.31)

[1] Current alcohol drinking is defined as self-report of drinking any alcohol at baseline; Current cigarette smoking is defined as self-report of smoking one or more cigarettes per year at baseline; Heavy cigarette years of smoking is calculated by multiplying the number of cigarettes smoked per year by the number of years the individual has been smoking and is defined as having smoked 660 or more cigarettes; Physical inactivity is defined as having a sports activity index score less than 2.0.

[2] Combat Veterans (CV) are identified by a summary variable based on whether or not the individual served in the military and, if so, whether he (1) served in a combat zone, was under enemy fire or fired at enemy, (3) saw wounded or killed during war, and/or (4) was ever wounded during war; Non-Combat Veterans (NCV) are defined as those who served in the military but did not report any combat exposures (1-4).

Table 35: Profile of Recalled Military Service and Combat History Reported during the LC-SES Interview, Overall and by Race.

	Non-Combat Veterans[1]	Combat Veterans
N		
Total [2]	2127	1178
Black	278	155
White	1849	1023
Mean (SD) Age at induction into service (years)		
Total	19.8 (2.4)	19.1 (2.2)
Black	20.2 (2.3)	19.7 (2.5)
White	19.8 (2.4)	19.0 (2.2)
Mean (SD) Elapsed years since induction into service [3]		
Total	34.3 (5.9)	38.2 (6.8)
Black	34.0 (6.3)	36.5 (7.5)
White	34.3 (5.9)	38.5 (6.6)
Mean (SD) Duration of service (years)		
Total	3.1 (3.2)	4.9 (5.6)
Black	3.8 (4.7)	6.3 (7.3)
White	3.0 (3.0)	4.7 (5.3)
n (%) Served overseas		
Total	1085 (51.0)	1108 (94.1)
Black	164 (59.4)	151 (97.4)
White	921 (50.0)	957 (93.6)
n (%) Served in combat zone		
Total	N/A	975 (82.8)
Black	N/A	141 (91.0)
White	N/A	834 (81.6)
n (%) Under enemy fire or fired at enemy		
Total	N/A	700 (59.7)
Black	N/A	95 (62.1)
White	N/A	605 (59.3)
n (%) Saw wounded or killed during war		
Total	N/A	853 (72.7)
Black	N/A	93 (60.8)
White	N/A	760 (74.5)
n (%) Ever wounded or missing during war		
Total	N/A	154 (13.1)
Black	N/A	23 (15.0)
White	N/A	131 (12.8)

[1] Combat Veterans (CV) are identified by a summary variable based on whether or not the individual served in the military and, if so, whether he (1) served in a combat zone, (2) was under enemy fire or fired at enemy, (3) saw wounded or killed during war, and/or (4) was ever wounded during war; Non-Combat Veterans (NCV) are defined as those who served in the military but did not report any combat exposures (1-4).

[2] The 632 NCV and 95 CV that served between periods of defined conflict are included in the totals but not as a distinct category in stratified results as shown in the primary results reported in the manuscript.

[3] Age at Visit 1 – self-reported age at entry into the military

Table 36: Profile of Risk Factors and Morbidity at Entry into the ARIC Cohort (Dichotomous Variables), Overall and by Race.

	LCSES men				ARIC men
	Total	Non-Veterans [1]	Non-Combat Veterans	Combat Veterans	Total
N	**5347**	**2042**	**2127**	**1178**	**7030**
n (%) African-American					
Total [2]	1076 (20.1)	643 (31.5)	278 (13.1)	155 (13.2)	1602 (22.8)
n (%) Current cigarette smoking status [3]					
Total	1261 (23.6)	541 (26.5)	473 (22.3)	247 (21.0)	1952 (27.8)
Black	361 (33.6)	233 (36.2)	82 (29.5)	46 (29.9)	615 (38.4)
White	900 (21.1)	308 (22.0)	391 (21.2)	201 (19.7)	1337 (24.6)
n (%) Used blood pressure-lowering medications in past 2 weeks					
Total	1289 (24.1)	493 (24.1)	495 (23.3)	301 (25.6)	1921 (27.4)
Black	353 (32.8)	201 (31.3)	103 (37.2)	49 (31.6)	577 (36.1)
White	936 (21.9)	292 (20.9)	392 (21.2)	252 (24.7)	1344 (24.8)
n (%) Prevalent left ventricular hypertrophy [4]					
Total	94 (1.8)	48 (2.4)	29 (1.4)	17 (1.5)	151 (2.2)
Black	55 (5.3)	33 (5.35)	15 (5.6)	7 (4.6)	92 (6.0)
White	39 (0.9)	15 (1.1)	14 (0.8)	10 (1.0)	59 (1.1)
n (%) Prevalent diabetes					
Total	503 (9.4)	213 (10.6)	167 (7.9)	123 (10.5)	844 (12.1)
Black	149 (14.2)	99 (15.9)	31 (11.4)	19 (12.5)	291 (18.6)
White	354 (8.3)	114 (8.2)	136 (7.4)	104 (10.2)	553 (10.2)
n (%) Prevalent CHD					
Total	311 (5.9)	107 (5.2)	117 (5.5)	94 (8.0)	574 (8.3)
Black	37 (3.50)	20 (3.2)	9 (3.3)	8 (5.2)	93 (5.92)
White	274 (6.54)	85 (6.2)	105 (5.8)	84 (8.4)	481 (9.05)

NOTE: Because of missing data, N differs for some variables; Some columns may not sum to 100% due to rounding.

[1] Combat Veterans (CV) are identified by a summary variable based on whether or not the individual served in the military and, if so, whether the individual (1) served in a combat zone, (2) was under enemy fire or fired at enemy, (3) saw wounded or killed during war, and/or (4) was ever wounded during war; Non-Combat Veterans (NCV) are defined as those who served in the military but did not report any combat exposures (1-4).

[2] The 632 NCV and 95 CV that served between periods of defined conflict are included in the totals but not as a distinct category in stratified results as shown in the primary results reported in the manuscript.

[3] Current cigarette smoking is defined as self-report of smoking one or more cigarettes per year at baseline; Heavy cigarette years of smoking is calculated by multiplying the number of cigarettes smoked per year by the number of years the individual has been smoking and is defined as having smoked 660 or more cigarettes; Physical inactivity is defined as having a sports activity index score less than 2.0.

[4] Presence of left ventricular hypertrophy was determined electrocardiographically using the Cornell criteria.

Table 37: Profile of Cardiovascular Risk Factors and Morbidity at Entry into the ARIC Cohort (Continuous Variables), Overall and by Race.

	LCSES men				ARIC men
	Total	Non-Veterans [1]	Non-Combat Veterans	Combat Veterans	Total
N	**5347**	**2042**	**2127**	**1178**	**7030**
Mean (SD) Age (years)					
Total [2]	53.9 (5.7)	51.8 (5.2)	54.1 (5.1)	57.3 (5.8)	54.6 (5.8)
Black	52.9 (5.7)	51.5 (5.2)	54.2 (5.5)	56.2 (6.3)	53.9 (6.0)
White	54.2 (5.6)	51.9 (5.2)	54.1 (5.0)	57.5 (5.7)	54.8 (5.7)
Mean (SD) Systolic blood pressure (mmHg)					
Total	121.2 (16.9)	121.8 (17.6)	119.9 (16.3)	122.5 (16.7)	122.6 (18.1)
Black	128.3 (19.9)	128.2 (20.2)	127.6 (19.5)	130.2 (19.2)	130.5 (21.7)
White	119.4 (15.6)	118.8 (15.4)	118.8 (15.4)	121.4 (16.0)	120.2 (16.2)
Mean (SD) Total cholesterol (mg/dL)					
Total	210.9 (39.2)	209.7 (39.8)	210.7 (37.9)	213.5 (40.4)	211.1 (40.0)
Black	212.7 (43.3)	211.9 (43.3)	213.6 (41.9)	214.6 (45.4)	210.9 (44.1)
White	210.5 (38.2)	208.7 (38.1)	210.2 (37.2)	213.4 (39.6)	211.1 (38.7)
Mean (SD) HDL cholesterol (mg/dL)					
Total	44.3 (13.2)	44.8 (13.5)	44.2 (13.2)	43.7 (12.8)	44.4 (13.9)
Black	49.9 (15.5)	50.4 (15.9)	49.2 (14.9)	49.1 (15.2)	50.4 (16.9)
White	43.0 (12.2)	42.4 (11.5)	43.4 (12.8)	42.9 (12.2)	42.6 (12.4)

[1] Combat Veterans (CV) are identified by a summary variable based on whether or not the individual served in the military and, if so, whether the individual (1) served in a combat zone, (2) was under enemy fire or fired at enemy, (3) saw wounded or killed during war, and/or (4) was ever wounded during war; Non-Combat Veterans (NCV) are defined as those who served in the military but did not report any combat exposures (1-4).

[2] The 632 NCV and 95 CV that served between periods of defined conflict are included in the totals but not as a distinct category in stratified results as shown in the primary results reported in the manuscript.

Table 38: Observed Cumulative Incidence of Coronary Heart Disease through 2002 by Military Service and Combat History, Overall and by Race.

	Non-Veterans [1]	Non-Combat Veterans	Combat Veterans
N			
Total [2]	2042	2127	1178
Black	643	278	155
White	1399	1849	1023
CHD Events			
Total	330	382	235
Black	74	30	20
White	256	352	215
Mean (SD) time to event or censored in years			
Total	9.85 (1.81)	9.83 (1.94)	9.85 (2.05)
Black	10.00 (1.60)	9.78 (1.99)	9.98 (1.62)
White	9.78 (1.89)	9.84 (1.93)	9.83 (2.10)
Incidence rate (incident events per 10 person-years)			
Total	0.1627	0.1819	0.2000
Black	0.1151	0.1103	0.1293
White	**0.1871**	**0.1935**	**0.2138**
Incidence rate ratio (95% CI)			
Total	REF	1.11 (0.96, 1.29)	1.23 (1.05, 1.46)
Black	REF	0.96 (0.63, 1.46)	1.12 (0.69, 1.84)
White	REF	1.03 (0.88, 1.21)	1.14 (0.95, 1.37)

[1] Combat Veterans (CV) are identified by a summary variable based on whether or not the individual served in the military and, if so, whether the individual (1) served in a combat zone, (2) was under enemy fire or fired at enemy, (3) saw wounded or killed during war, and/or (4) was ever wounded during war; Non-Combat Veterans (NCV) are defined as those who served in the military but did not report any combat exposures (1-4).

[2] The 632 NCV and 95 CV that served between periods of defined conflict are included in the totals but not as a distinct category in stratified results as shown in the primary results reported in the manuscript.

Table 39: Observed Cumulative Incidence of Ischemic Stroke through 2002 by Military Service and Combat History, Overall and by Race.

	Non-Veterans [1]	Non-Combat Veterans	Combat Veterans
N			
Total [2]	2042	2127	1178
Black	643	278	155
White	1399	1849	1023
Ischemic stroke events			
Total	71	64	53
Black	47	11	12
White	24	53	41
Mean (SD) time to event or censored in years			
Total	14.11 (1.49)	14.22 (1.30)	14.18 (1.65)
Black	13.87 (1.99)	14.08 (1.56)	13.91 (1.79)
White	14.22 (1.18)	14.24 (1.26)	14.22 (1.63)
Incidence rate (incident events per 10 person-years)			
Total	0.0246	0.0212	0.0317
Black	0.0527	0.0281	0.0557
White	0.0121	0.0201	0.0282
Incidence rate ratio (95% CI)			
Total	REF	0.86 (0.61, 1.20)	1.29 (0.90, 1.83)
Black	REF	0.53 (0.28, 1.02)	1.06 (0.56, 1.98)
White	REF	1.67 (1.03, 2.70)	2.34 (1.42, 3.86)

[1] Combat Veterans (CV) are identified by a summary variable based on whether or not the individual served in the military and, if so, whether the individual (1) served in a combat zone, (2) was under enemy fire or fired at enemy, (3) saw wounded or killed during war, and/or (4) was ever wounded during war; Non-Combat Veterans (NCV) are defined as those who served in the military but did not report any combat exposures (1-4).

[2] The 632 NCV and 95 CV that served between periods of defined conflict are included in the totals but not as a distinct category in stratified results as shown in the primary results reported in the manuscript.

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